AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6685

A MULTICENTER TRIAL OF FDG-PET/CT STAGING OF HEAD AND NECK CANCER AND ITS IMPACT ON THE N0 NECK SURGICAL TREATMENT IN HEAD AND NECK CANCER PATIENTS

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CONFIDENTIAL

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LIST OF ABBREVIATIONS AND ACRONYMS

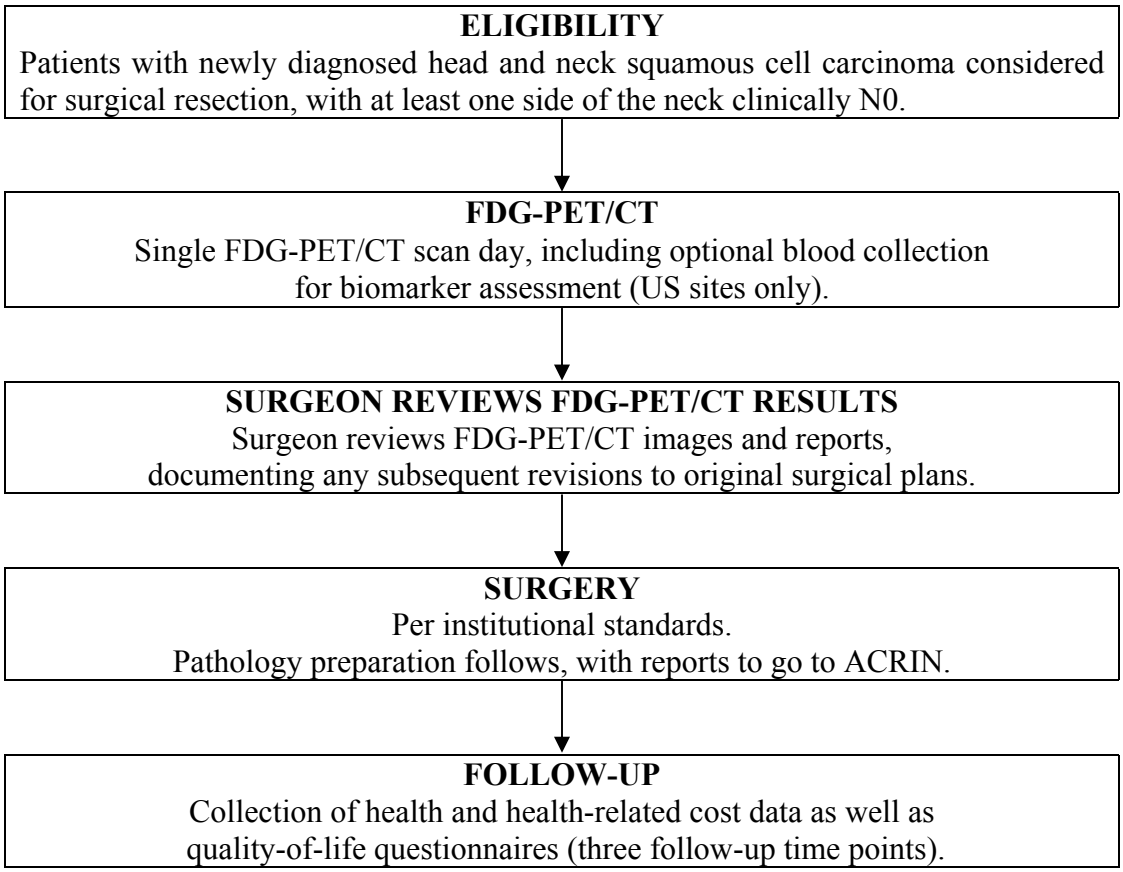
ACR	American College of Radiology
ACRIN	American College of Radiology Imaging Network
AE	Adverse Event
AICP	ACRIN Imaging Core Panel
BC	Biostatistics Center
BDMC	Biostatistics and Data Management Center
CD	Compact Disk
CEA	Cost-Effectiveness Analysis
CIP	Cancer Imaging Program
cm	Centimeter
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	CTEP Adverse Event Reporting System
DICOM	Digital Imaging and Communications in Medicine
DMC	Data Management Center
DMCC	Data Management Coordination Center
DSMC	Data and Safety Monitoring Committee
DVD	Digital Video Disk *or* Digital Versatile Disk
EC	Ethics Committee
FDA	Food and Drug Administration
FDG	[^{18}F]-fluorodeoxyglucose
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FDG-PET/CT	Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography
FOV	Field of View
FWA	Federal Wide Assurance (number)
GCP	Good Clinical Practice
GQA	General Qualifying Application
HIPAA	Health Insurance Portability and Accountability Act
HUI	Health Utilities Index
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
IPC	(ACRIN) Institutional Participants Committee
IRB	Institutional Review Board
ISP	Internet Service Provider
ITW	Imaging transmittal Worksheet
IV	Intravenous
kV	Kilovolt
mAs	Milliampere Seconds
mL	Milliliter
mm	Millimeter
mSv	Millisievert
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
N/A	Not Applicable

NCI	National Cancer Institute
N/D	Not Done
NIH	National Institutes of Health
NPV	Negative Predictive Value
OHRP	Office for Human Research Protections
PACS	Picture Archive and Communication System
PDRC	Protocol Development and Regulatory Compliance
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography/Computed Tomography
PSA	Protocol Specific Application
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QC	Quality Control
QoL	Quality of Life
RA	Research Associate
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SUV	Standardized Uptake Value
US	Ultrasound *or* United States
UW-QoL	University of Washington Quality of Life Scale

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6685: A Multicenter Trial of FDG-PET/CT Staging of Head and Neck Cancer and its Impact on the N0 Neck Surgical Treatment in Head and Neck Cancer Patients

SCHEMA



STUDY OBJECTIVES/SPECIFIC AIMS

Determine the negative predictive value of PET/CT for the N0 neck based upon pathologic sampling of the neck lymph nodes and determine PET/CT's potential to change treatment of the N0 neck.

ELIGIBILITY *(see Section 5.0 for details)*

Patients with newly diagnosed head and neck squamous cell carcinoma being considered for surgical resection, with at least one side of the neck planned for dissection clinically N0, and at risk for occult metastasis (when risk based on clinical data is felt to be greater than 30%).

SAMPLE SIZE

Total of 292 participants will be enrolled into this study. Minimum of 10 ACRIN-approved institutions will be enrolling participants for approximately 24 months.

1.0 ABSTRACT

Head and neck cancer is the sixth most common cancer worldwide and many patients with head and neck squamous cell carcinoma (SCC) present with locoregionally advanced disease. When properly diagnosed, early stage head and neck cancer is curable; however, those patients who develop local and/or distant metastases to cervical lymph nodes have poor prognoses. Different head and neck cancer treatment regimens have been shown to be effective in certain subgroups of patients: concurrent chemoradiotherapy is widely accepted treatment, but long-term survival remains unchanged and the need for subsequent neck dissection remains controversial. Neck dissections are performed often because clinical examination and structural imaging do not reliably identify residual disease.[1–4] Radical resection is associated with multiple functional and cosmetic deformities. The current paradigm comprises neck dissection only in high risk patients and clinical follow-up with close observation in the majority of cases.[5]

Patients with head and neck cancer and a clinically-defined negative neck (N0 neck) pose a different challenge to the treating surgeon. Approximately 25% to 30% of these patients are found to have metastatic neck nodes at surgery. Nodal involvement in head and neck cancer decreases the overall survival by almost 50%.[6,7] The prognosis depends on the number of nodes involved, with early resection improving outcome. This finding means that the majority of patients with N0 necks who will eventually undergo a neck dissection are unlikely to have a therapeutic effect from this procedure. The cosmetic morbidity associated with neck dissection, however, can be significant; patients face cosmetic stigma even from selective or modified radical neck dissections. Risk for other morbidities, such as paralysis of the trapezius muscle, have been greatly reduced by limited use of radical neck dissection and may occur in fewer than 2% of patients undergoing functional neck dissection.[8]

Imaging modalities, such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) have been used to determine the extent of metastatic disease to the neck. The advent of positron emission tomography (PET) has improved the staging, treatment evaluation, and detection of recurrent disease in patients with head and neck SCC[1]. With added anatomical information from CT, PET/CT has demonstrated the ability to identify metastatic head and neck malignancies in cases where the other imaging techniques have failed. Several studies have evaluated fluorodeoxyglucose (FDG)-PET in this setting, attempting to identify the patients who need radical neck dissection.[9–12] A large scale clinical trial that shows accurate characterization of disease stage will impact treatment success by potentially identifying true N0 necks without invasive therapeutic treatment and subsequent morbidity while recognizing the most appropriate clinical management.

In this study, participants with newly diagnosed head and neck SCC will undergo a FDG-PET/CT scan prior to surgical resection. The surgeon will have access to the FDG-PET/CT results prior to the surgical procedure. The data will demonstrate how the inclusion of the FDG-PET/CT imaging will impact the determination of extent of disease, disease characterization and prognosis, and the surgical plan originally devised from clinical nodal assessment and CT and/or MRI results. Quality of life (QoL) assessments and cost-effectiveness analysis (CEA) will be included in the study to determine the impact of FDG-PET/CT inclusion relative to surgical assessment of the N0 neck. QoL results will be used to evaluate reduction in morbidity associated with potentially more-definitive targeting of metastatic disease; CEA targets potential reductions in costs from identifying a truly N0 neck and reducing need for therapeutic dissection,

follow up, subsequent re-dissection from missed disease, etc. Prior to imaging, blood samples will be collected at US sites to explore serum biomarkers as they correspond to prognosis, staging, and FDG-PET/CT findings. Future correlation between blood and imaging biomarkers may strengthen clinical confidence in defining the N0 neck. Ultimately, the study may show that FDG-PET/CT images will improve the characterization of the N0 neck by accurately diagnosing N0 necks, better defining extent of primary disease, discovering unappreciated distant metastasis, reducing morbidity, and representing cost-effective value to society.

2.0 BACKGROUND AND SIGNIFICANCE

Many different head and neck cancer treatment regimens have been investigated in the past few decades in attempts to improve survival among this patient cohort. Chemoradiotherapy regimens have been increasingly successful in inducing response in advanced disease, but long-term survival has remained unchanged. Sometimes patients are under- or over-treated because of a lack of precision in appreciation of the extent of their cancer.[13] As more options in the armamentarium of head and neck cancer treatment are available, better characterization of disease stage may help improve survival by leading to increased understanding of appropriate, disease stage- and subsite-specific treatments.

2.1 Imaging Studies for Head and Neck Cancers

The choice of treatment of head and neck cancer and its results can differ substantially depending upon the extent of the disease. Determining the extent of disease is a challenge. CT, MRI, and FDG-PET/CT are used to determine the extent of disease, but no large studies have evaluated the benefits of these tests in relationship to stage characterization and how improved characterization could impact clinical management. Consequently, some patients may be over-treated (unnecessary neck[s] treatment) while others are given insufficient treatment to their regional lymphatics, which places them at increased risk of failure. This therapeutic challenge is the result of limits in the sensitivity and negative predictive value of our current diagnostic imaging.[14]

2.2 PET/CT Imaging Studies for Head and Neck Cancers

Among CT, MRI, and PET/CT, PET/CT is the most recent imaging method to come into the clinical algorithm for evaluating head and neck malignancy disease stage. It has been demonstrated that PET/CT can identify metastatic head and neck malignancy in some cases where it is not discovered by the other two imaging techniques.[15–19] In such cases, one could expect that disease classification and treatment plans could be modified appropriately to account for this increase in disease burden. This could potentially lead to better outcomes.

Treatment modification would be able to address the above clinical dilemma if PET/CT scans were able to predict more accurately when there is not metastatic disease in the neck of patients with head and neck cancer. Importantly, while metastatic disease to the neck is the most significant staging criteria related to survival, noninvasive methods to determine the presence of metastatic neck disease remain elusive. A patient staged as N0 in the neck by standard physical exam and CT has about a 22% to 42% chance of having pathologically proven metastatic disease in the neck at the time of surgery.[20] There is also evidence, in the cases of some advanced staged primaries, of a significant chance of clinically occult contralateral neck metastases.[14, 21–24] For this reason, many advocate dissection of any N0 neck if the risk of metastasis based on tumor stage and location is greater than 30%. Single institution studies and modeling paradigms have intimated that PET/CT may be better able to characterize the “N0” neck in such situations

although there is clearly disagreement in the published literature.[25–30] None of the studies performed to date have sufficient sample size to provide adequate confidence intervals (CIs) on their results; many included varied patient groups, with both untreated and recurrent disease, as well as various tumor types, such as melanoma and SCC of the skin.

2.3 Quality-of-Life and Cost-Effectiveness Analyses

Approximately 50,000 new head and neck cancer patients are diagnosed annually. About half of these patients have cervical nodal disease. The other half are clinically free of neck disease, some of which have sub-clinical metastasis (approximately 30%) ipsilateral to their primary tumor. The frequency of sub-clinical metastasis presents a conundrum: Do we treat all of these patients—thereby over-treating 70% of these patients (17,000)—or are these patients observed (under-treated), risking recurrence in 8,000 patients? There is even a more compelling reason to identify which clinically N0 patients have occult nodal disease, as a significant percentage (as discussed above) may have positive nodes contralaterally or bilaterally. Currently, patients may be treated unnecessarily or not treated when necessary, or disease may be caught appropriately.

Although medical tests, including imaging tests and pathologic sampling, are never 100% accurate, one could consider that a test with a 90% negative predictive value (NPV) for determination of the N status of metastatic neck disease could lead to more appropriate treatment considerations.[31] However, no large or multicenter, prospective studies have been performed to provide data regarding the performance of PET/CT as it may be applied to disease treatment planning. Therefore, in this study, we propose to study PET/CT staging of SCC of the head and neck and how it might alter treatment specifically as it relates to the N0 neck in head and neck cancers.

We plan to assess the findings' impact on patient management and QoL and to conduct a CEA of PET/CT in this indication. Greater understanding of when FDG–uptake negative necks are pathologically negative, and vice versa, could potentially benefit head and neck patients presenting with clinically N0 necks, offering some patients the opportunity to forgo unneeded neck treatment.

It would be difficult to predict how neck treatment could be more appropriately used by having a precise means to detect occult cervical disease. We do not possess the necessary data to make estimates of operations saved, complications avoided, or economic impact to present them here. It would be reasonable to conclude, however, that thousands of patients annually could have their treatment confirmed as appropriate or modified based on PET/CT results of their regional nodal status.[30]

CEA is used to evaluate medical and surgical interventions and provide information to make decisions based on the relative value of the interventions. Value is fundamentally about the trade-off between cost and quality. The argument for fundamental value is obvious in some cases. For example, no rational decision maker will accept an intervention that is more costly and less effective. Similarly, no rational decision maker will reject an intervention that is less costly and more effective. The most interesting cases are those where the intervention is more costly but also more effective, or less costly but less effective. In these cases, the interventions may represent good value if they provide enough benefits to offset the additional costs. CEA provides a methodology that enables decision makers to make this determination.

CEA is inherently comparative, that is, it necessarily involves comparing one treatment strategy to another, even if the alternative strategy is to do nothing. The fundamental metric of all CEA is

the incremental cost-effectiveness ratio (ICER). The ICER takes estimates of the costs of the two strategies and the effectiveness of the two strategies, and summarizes the relative value by quantifying how much must be incurred in additional costs to obtain one additional unit of benefit. For example, if we are interested in the cost-effectiveness of a surgical procedure relative to medical management of a particular condition, CEA would first estimate the cost of administering the surgical procedure, C_S, and the cost of the medical treatment, C_M. Then it would estimate the benefits, or effects, in terms of the most important clinical outcomes for the surgical procedure, E_S, and the medical treatment, E_M. CEA is flexible in terms of effectiveness. Effectiveness may be defined as whatever is the most important outcome for a given intervention. It may be, for example, infections avoided, reductions in mortality, increases in life expectancy, increases in quality adjusted life years (QALY) or some other outcome depending on the context of the question. The cost-effectiveness ratio is computed as:

$$\text{ICER} = \frac{C_S - C_M}{E_S - E_M}$$

This cost-effectiveness ratio tells how much additional costs must be incurred to achieve one more unit of benefit using the surgical approach. For example, if our outcome measure was QALYs and the ICER was $63,000, this would be interpreted to mean that it would cost $63,000 for each additional QALY saved if all patients were treated with the surgical rather than the medical approach. The decision maker then compares this amount to the amount she is willing to pay for the outcome. If the decision maker is willing to pay more than $63,000, then the surgical approach is cost-effective relative to medical management. If the decision maker is not willing to pay $63,000 per QALY then the surgical procedure is not cost-effective relative to medical management. The term cost-effective is often misused in casual conversation. Cost-effective does not mean cheap or less costly. In fact, many therapies that are cost-effective are more expensive than their alternatives. Cost-effective means that the incremental cost-effectiveness ratio is low enough that the intervention represents good value for the resources spent.

The use of QALYs in cost-effectiveness is ubiquitous, largely because by putting the ICER in common units (i.e. incremental cost per QALY) it facilitates comparisons across disparate treatment options. QALYs capture the fact that one year of perfect health is better than one year of life spent in poor health. They are computed by multiplying life expectancy by utility, which is a number between 0 and 1 that represents patient preferences for different health states. Zero represents death and 1 represents perfect health. Utilities are estimated by giving surveys to patients and healthcare providers that are designed to elicit preferences for different health states.

In this study, we will use modeling to estimate the cost-effectiveness of the PET/CT strategy relative to treatment with unilateral neck dissection and treatment with bilateral neck dissection. The rationale is that if PET/CT can better characterize the N0 neck, costs will be avoided in patients who do not need treatment, and QoL and utility will be improved in patients who receive treatment when necessary. Effectiveness in this study will be measured as QALYs, and we will administer survey instruments to measure QoL and utilities in order to estimate QALYs. QoL will be assessed using the 36-Item Short Form Survey Instrument (SF-36, version 2), the Health Utilities Index (HUI), and the University of Washington Quality of Life Scale (UW-QoL).

QoL will also be measured separately as a secondary outcome in this study. The rationale is that better staging will alter treatment plans and have implications for QoL. For example, a patient who has subclinical nodal metastases that are detected by PET/CT will lead to a more aggressive

surgical approach—with serious implications for breathing, swallowing, communication, and daily activities—in the future.

2.4 Clinical Biomarkers: Blood and Tissue Specimens

While it appears that PET/CT has the potential to improve the characterization of the N0 neck, other noninvasive methods of determining such risk may be preferable. In order to explore non-imaging predictive markers for advanced disease, serum biomarkers will be evaluated as a component of this study for prediction of disease. No commonly accepted clinical biomarker test (other than evidence of virus exposure like HPV)[32] has been identified, or at least none has been found significantly better than others assessed in patients with head and neck cancer.

It may be that while no single biomarker is an obvious choice at this time in head and neck cancer, multiple biomarkers used in combination could be powerful predictors of disease. Interestingly, such a biomarker panel of multiplexed cytokine profiles used by Linkov et al using the Luminex multianalyte profiling technology (xMAP™), has recently been described and is intriguing.[33] This multiplex platform demonstrated 84.5% sensitivity and 98% specificity in detecting head and neck cancer when normal patients were compared to patients with head and neck cancer. It would be interesting to evaluate such a multiplex serum assay in its ability to predict not just the presence of disease, but the disease's potential to metastasize. The use of the multiplex platform for serum is similar to using DNA microarray technology to uncover changes in gene expression.

PET/CT is relatively expensive compared with blood tests; Medicare charges for PET/CT presently fall in the $1000 range. If serum biomarkers of disease were just as predictive at identifying patients at low risk for neck metastasis, significant cost savings could be achieved. It would be very important to have the correlative science of the PET/CT and biomarker data in the same patient group, as it would standardize the dataset from which the findings from all testing are acquired. Similarly, an assessment of complementary contributions of the imaging and serum tests in the determination of metastatic disease can be performed. This may be particularly important considering the likely limitations of each method. Therefore, a multiplex biomarker panel, Luminex xMAP™, as described by Linkov et al,[33] will be included in this trial so that the relationship with the PET/CT results in this population can be evaluated. As the specimens can be collected at the time of imaging, there will be little additional infrastructure required for collection and storage of these specimens.

2.5 ACRIN 6685 FDG-PET/CT Trial

This protocol is a prospective, multicenter trial using FDG-PET/CT to assess patients with newly diagnosed head and neck SCC, who are being considered for surgical resection, with at least one side of the neck planned for dissection clinically N0.

Participants with newly diagnosed head and neck SCC will undergo a FDG-PET/CT scan prior to surgical resection. The surgeon will have access to the PET/CT results prior to the surgical procedure. The study will collect data on how the inclusion of the PET/CT results impact the determination of extent of disease, disease characterization and prognosis, and the surgical plan originally devised from clinical nodal assessment and CT and/or MRI results. Radiation risk from the FDG-PET/CT scan is not expected to exceed 30% of annual allotment for imaging technicians.

QoL assessments and CEA will be included in the study to determine the impact of PET/CT inclusion relative to treatment of the N0 neck. A blood collection at US sites will explore biomarkers as they correspond to prognosis, staging, and PET/CT findings.

Ultimately, we hope this screening study will show that PET/CT images will improve the characterization of the N0 neck—potentially reducing morbidity, upstaging perceived N0 necks, better defining extent of primary disease, uncovering unappreciated distant metastasis, and representing cost-effective value to society.

3.0 STUDY OBJECTIVES/SPECIFIC AIMS

3.1 Primary Endpoint

Determine the negative predictive value (NPV) of PET/CT for staging the N0 neck based upon pathologic sampling of the neck lymph nodes and determine PET/CT's potential to change treatment of the N0 neck.

3.2 Secondary Endpoints

3.2.1 Estimate the sensitivity and diagnostic yield of PET/CT for detecting occult metastasis in the clinically N0 neck (both by neck and lymph node regions) or other local sites;

3.2.2 Determine the effect of other factors (e.g., tumor size, location, secondary primary tumors, or intensity of FDG uptake) that can lead to identification of patient subsets that could potentially forego neck dissection or provide preliminary data for subsequent studies;

3.2.3 Analyze cost-effectiveness of using PET/CT for staging of head and neck cancer versus current good clinical practices;

3.2.4 Evaluate the incidence of occult distant body metastasis discovered by whole body PET/CT;

3.2.5 Correlate PET/CT findings to CT/MRI and biomarker results;

3.2.6 Evaluate QoL, particularly in participants whose patient management could have been altered by imaging results;

3.2.7 Evaluate the PET/CT and biomarker data for complementary contributions to metastatic disease prediction;

3.2.8 Compare baseline PET/CT and biomarker data to 2-year follow up as an adjunct assessment of their prediction of recurrence, disease-free survival, and overall survival;

3.2.9 Determine the proportion of neck dissections that are extended—additional levels clinicians intend to dissect beyond the initial surgery plan—based on local-reader PET/CT findings shared with the surgeon prior to dissection;

3.2.10 Estimate the optimum cutoff value of standardized uptake values (SUV) for diagnostic accuracy of PET/CT test;

3.2.11 Evaluate the impact of PET/CT on the N0 neck across different tumor subsites (defined by anatomic location).

3.3 Clinical Implications from the Objectives

3.3.1 We will evaluate the potential impact on patient management of PET/CT in staging head and neck cancer. The primary, implied management change will be

in treatment of the clinically N0 neck. For example, if PET/CT has a high NPV in the N0 neck, this would imply that observation only of the neck could be entertained.

3.3.2 We will assess the potential impact of PET/CT, if found to have high sensitivity for identifying neck disease, to estimate the potential for influencing changes in neck dissection strategies from standard selective neck dissection to standard plus targeted neck dissection or radiotherapy.

3.3.3 Newly-identified biomarkers may provide additive predictive ability to PET/CT in the risk assessment of advanced disease/metastasis. We will evaluate the ability of serum biomarkers to predict disease at the time of presentation and in follow up within 2 years.

3.3.4 We will be able to estimate the clinical impact of detecting distant metastases using PET/CT.

3.3.5 We will be able to estimate the cost-effectiveness of these strategies employed to evaluate N0 neck status.

3.3.6 We will assess QoL among participants, and apply it to those whose clinical strategy could have been adjusted based on information from the PET/CT.

3.4 Hypotheses

3.4.1 PET/CT can more accurately identify head and neck cancer—or the absence thereof—at primary, nodal, or distant sites than clinical exam, CT, or MRI.

3.4.2 This additional PET/CT imaging information will lead to important changes in patient care, patient QoL, costs, and cost-effectiveness, specifically as relate to treatment of the N0 neck. These changes may result from upstaging an N0 neck to N+, better defining extent of primary disease, or uncovering unappreciated distant metastasis.

3.4.3 Other biomarkers may correspond to FDG-PET/CT findings, clinical stage, and patient outcomes. These findings may reflect the aggressiveness of the clinical course, which in turn may direct the patient towards more or less aggressive modality therapy.

4.0 STUDY OVERVIEW

This prospective, multicenter trial will recruit approximately 292 eligible participants with newly diagnosed head and neck SCC being considered for surgical resection, with at least one side of the neck planned for dissection clinically N0 according to physical examination and MRI and/or CT evaluation, who are at risk for occult metastasis (when risk based on clinical data is felt to be greater than 30%).

In this study, participants with newly diagnosed head and neck SCC will undergo an FDG-PET/CT scan prior to surgical resection. Blood specimens are an optional component for US sites only, to be collected at the time of imaging for biomarker analysis. The surgeon will be provided with the PET/CT results prior to the surgical procedure, and any revisions to the surgical plan based on FDG-PET/CT results will be collected. Pathology reports from surgical biopsy will be collected, and specimens (slides and reports) will be requested for quality assessment purposes.

QoL assessments and CEA are included in the study to determine the impact of FDG-PET/CT results on the surgical outcomes of the N0 neck. QoL questionnaires focused on morbidity associated with surgery will be completed at four (4) different time points of the trial for each participant—at the initial screening visit after consenting to the trial, about 30 to 60 days after surgery, about year 1 after surgery (6 weeks before through 6 weeks after), and about year 2 after surgery (6 weeks before through 6 weeks after). QoL questionnaires will take approximately a half hour to complete at each time point. The participants will be followed for up to 2 years after the surgical resection, unless death occurs first. The cost-effectiveness model will estimate cost-effectiveness over the course of the trial and also over the projected lifetime of the participant.

5.0 PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

Patients with newly diagnosed head and neck SCC being considered for surgical resection, with at least one side of the neck planned for dissection clinically N0, and at risk for occult metastasis (when risk based on clinical data is felt to be greater than 30%) will be assessed for eligibility.

5.1 Inclusion Criteria

5.1.1 Participant ≥ 18 years of age;

5.1.2 Participant with histologic confirmation of newly diagnosed SCC of the head and neck;

5.1.3 Participant with unilateral or bilateral neck dissection planned for care. An N0 neck must be planned to be dissected for the patient to be eligible. The N0 neck can be either ipsilateral to the head and neck tumor or the contralateral N0 neck if a bilateral neck dissection is planned;

5.1.3.1 Surgery and pathology will be defined as described in Appendix III;

5.1.4 Participant with confirmed head and neck SCC;

5.1.4.1 CT and/or MR imaging has been completed within six (6) weeks prior to enrollment, even if the SCC diagnosis has been made via other methods, and will be submitted to ACRIN;

5.1.4.2 Simultaneous diagnostic CT with PET will not be excluded, but in such cases PET cannot be used as part of the criteria to define the N0 neck as required for entrance to the trial;

5.1.4.3 If sites received CT and/or MR images from institutions other than their own, ACRIN recommends a re-read by a local neuroradiologist to ensure compliance with protocol eligibility requirements.

5.1.5 Participant with at least one neck that is clinically N0 as defined by clinical exam (physical exam with CT and/or MRI as the gold standard of the N0 neck); Stages T2, T3, or T4. N0–N3, excluding N2c for bilateral disease based on criteria from the American Joint Commission on Cancer[34] (available through the National Comprehensive Cancer Network www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf; web site registration required);

5.1.6 Participant in whom it may be considered a viable clinical option to perform neck dissection when primary cancers are at high risk for neck metastasis (see definition above);

5.1.6.1 These will include: 1) oral cavity cancer; 2) oropharynx cancer, including base of tongue and tonsil cancers; 3) larynx cancer; or 4) supraglottic cancer.

5.1.7 Participant willing to provide a written informed consent.

5.2 Exclusion Criteria

5.2.1 Patient who is pregnant and/or breastfeeding;

5.2.2 Patient with sinonasal carcinoma;

5.2.3 Patient with tumors in the head and neck that are not SCC;

5.2.4 Patient with salivary gland malignancies;

5.2.5 Patient with thyroid cancers;

5.2.6 Patient with advanced skin cancers;

5.2.7 Patient with nasopharyngeal carcinoma;

5.2.8 Patient with poorly controlled diabetes (defined as fasting glucose level > 200 mg/dL; optimally participants will have glucose < 150 mg/dL) despite attempts to improve glucose control by fasting duration and adjustment of medications;

5.2.9 Patient not a candidate for surgery (neck dissection) because of an underlying medical condition;

5.2.10 Patient who weighs more than the weight limit for the PET table.

5.3 Recruitment and Screening

A minimum of 10 ACRIN-approved institutions across the country will be participating in the clinical trial. For this protocol, a total of 146 participants will be accrued per year to the study, which has a projected 24-month accrual period. Should fewer than 50 participants be accrued in one year, the study will be re-assessed.

ACRIN will develop a trial communications plan that will describe the production of materials to aid participant recruitment. All materials used for participant recruitment will be reviewed and approved by each institution's Institutional Review Board (IRB).

5.4 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993, with regard to inclusion of women and minorities in clinical research, the projected gender and minority accruals are shown in Table 1:

Table 1. Gender and Minority Accrual Estimates

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	15	30	0	45
Not Hispanic or Latino	82	165	0	247
Ethnic Category: Total of all participants	**97**	**195**	0	**292**
Racial Category				
American Indian or Alaskan Native	1	2	0	3
Asian	4	9	0	13
Black or African American	25	49	0	74
Native Hawaiian or other Pacific Islander	2	4	0	6
White	65	131	0	196
Racial Category: Total of all participants	**97**	**195**	0	**292**

6.0 SITE SELECTION

6.1 Institution Requirements

All sites either must have been previously approved to participate in ACRIN clinical trials, by having an ACRIN Institutional Participants Committee (IPC)-approved General Qualifying Application (GQA) on file, or must submit a GQA for IPC review. The GQA application can be found on the ACRIN web site at www.acrin.org/6685_protocol.aspx. In addition, each institution must submit a Protocol Specific Application (PSA) that documents sites have the necessary personnel, equipment, and referral base to carry out the requirements specific to the ACRIN 6685 protocol. In particular, the site principal investigator must confirm on the PSA that patients who present with head and neck SCC are typically provided a primary surgical treatment option and must identify a lead referring oncologist.

Sites also must obtain PET/CT qualification for the scanner(s) that will be used for scanning trial participants. In addition, test images of the PET/CT scan per protocol specifications (see Section 9.0) must be reviewed and approved prior to participate enrollment. All scanner and image qualification materials are available at www.acrin.org/6685_protocol.aspx, and Section 9.0 provides detailed information regarding the FDG-PET/CT imaging protocol and related procedures.

6.2 Regulatory Requirements

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on CTEP Web site: http://ctep.cancer.gov/investigatorResources/investigator_registration.htm

or by calling the PMB at (240) 276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must also obtain IRB approval for this protocol and submit IRB approval and the supporting documentation listed in the previous paragraph to the CTSU Regulatory Office before they can enroll patients.

All forms and documents required for this study can be downloaded from CTSU members' area of the website (https://www.ctsu.org). Patients can be registered only once all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

All institutions must have study-specific Institutional Review Board (IRB) approval for the protocol and informed consent form (ICF), which is included in this protocol as Appendix I. The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB at the institution.

Requirements for ACRIN 6685 site registration:
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Pre-study requirements for patient enrollment on ACRIN 6685
- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- Site must meet institution requirements as noted in section 6.1

6.3 Accrual Goals and Monitoring

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Total target accrual for this study is 292 participants. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving any recruitment barriers. If a site's actual accrual falls below 60% of what is reported in the PSA, the Protocol Support Enrollment Committee (PSEC), comprised of the trial PI and his or her designees, will determine a follow-up action plan to identify site accrual barriers and develop strategies to support the site in meeting accrual goals. Should fewer than 50 participants be recruited within one year, the study will be re-assessed.

The ACRIN Steering Committee regularly reviews the overall trial accrual and may request information about a trial's accrual performance to better understand general accrual barriers or issues. Accrual and safety information will be presented to the ACRIN Data and Safety Monitoring Committee (DSMC) at regularly scheduled meetings thereof; the DSMC may, at its discretion, re-evaluate the study with respect to feasibility or the need for additional participating institutions.

7.0 DATA MANAGEMENT/ONLINE REGISTRATION

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 BDMC of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the DMC is located at ACRIN in Philadelphia, PA. A DMC contact list is located on the ACRIN web site (www.acrin.org) for each protocol.

7.1.3 Participant registration and data entry are available to clinical sites 24 hours a day, seven days a week. Participant registration occurs through Oncology Patient Enrollment Network (OPEN).

7.2 Clinical Data Submission

7.2.1 **Registration**: All site staff (Lead Group) will use OPEN to enroll participants to this study. OPEN can be accessed at https://OPEN.ctsu.org or from the CTSU members' web site OPEN tab. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All participants have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. Information on establishing a CTEP-IAM account can be found at https://www.ctsu.org/readfile.aspx?fname=public/ctep-iam_factsheet.pdf

  This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent “Registrar” role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under Regulatory Support System (RSS) on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

7.2.2 To submit data via the ACRIN web site, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The

user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, data that are out of range, and data that are in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the "Complete Form Submission" button is depressed.

7.2.3 Once data entry of a form is complete, and the summary form is reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form Submission" button on the form summary screen and the data are transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data generated and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the DMC for resolution of the submission.

7.2.4 If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site research associate (RA) or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACR can serve as an ISP.

7.3 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

7.4 Electronic Data Management

7.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Brown BC and the DMC. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and the more thorough checks. Data elements that fail validation are followed up by the DMC. The validation program generated by BC produces a log of errors, which is sent to the DMC for resolution. The program is frequently updated to incorporate exceptions to rules

so that subsequent validity checks minimize the time the DMC needs to spend resolving problems. Additional data review will take place once the data are transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC for resolution. All BDMC communication with the participating sites is normally done through the DMC.

7.4.2 If checks at DMC or BC detect missing or problematic data, the DMC personnel assigned to the protocol sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DMC updates the participant's data submission calendar with the due date for the site RA or investigator's response.

7.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Due Forms Report may be sent on an as needed basis in addition to past due reports. The site investigator or RA may use the Forms Due and Future Due Reports as a case management tool.

7.6 Data Quality Assurance

7.6.1 The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the DMC. The transfer of data between the DMC and the BC has been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. 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.

7.6.2 A goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the BDMC will apprise the ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance (PDRC) department, until the problem has been resolved. If the BDMC, along with the PDRC, cannot find a resolution to the problem, it will be brought to the ACRIN Quality Assurance (QA) Committee for further discussion and resolution.

8.0 STUDY PROCEDURES

The primary study procedure is FDG-PET/CT. Details of the study imaging procedures can be found in Section 9.0. Blood samples and tissue specimens will be collected as part of the trial for

analysis; foreign sites will be exempt from blood collection and submission. Tissue samples will not be collected from foreign sites for quality assessment (i.e., Section 8.8).

8.1 Visit 1: Screening/Eligibility Visit

At the registration visit, the potential participant will be screened and confirmed for eligibility by the appropriate study-team designee prior to electronic registration:

8.1.1 Obtain a signed, IRB-approved informed consent prior to conducting any study-related procedures;

8.1.2 Have participant complete a detailed Contact Information Worksheet following informed consent. This form collects information used to maintain contact with the participant over the course of the trial. This form is retained at the site and is not submitted to the ACRIN master database. The site RAs will contact the participant for completion of the QoL forms at approximately 30 days, 1 year, and 2 years post-surgery;

8.1.3 Screen and confirm eligibility, which includes:

8.1.3.1 Review and confirmation of inclusion and exclusion criteria (see Section 5.0);

8.1.3.2 Review of localized CT and/or MR images per institutional standards—obtained within six (6) weeks prior to registration—to confirm N0 disease in at least one neck planned for dissection (see www.acrin.org/6685_protocol.aspx for preferred imaging parameters). If sites received CT and/or MR images from institutions other than their own, ACRIN recommends a re-read by a local neuroradiologist to ensure compliance with protocol eligibility requirements;

8.1.3.3 Submit CT and/or MR images to ACRIN for central reader study review;

8.1.3.4 Review medical history and records for confirmation of pathologically-proven disease, diagnostic and treatment planning details, and endoscopy results;

8.1.3.5 Conduct clinical examination of the nodal basins by the site investigator or investigator designee;

8.1.4 Conduct a standard pregnancy test per institutional standard practices if the participant is unsure of her pregnancy status prior to any imaging;

8.1.5 Administer the quality-of-life (QoL) questionnaire by the site investigator-designee. The QoL forms contain the SF-36, HUI, and UW-QoL.

8.2 Visit 2: FDG-PET/CT Imaging Day Within 14 Days Prior to Surgery Visit 3

Within 14 days prior to the day of surgery Visit 3, the participant must undergo a single session of whole-body FDG-PET/CT imaging (see Section 9.0 for preparation and imaging details).

8.2.1 Insert one (1) intravenous catheter placed in a vein in the arm to check serum glucose and to inject the FDG agent (see Section 9.0);

8.2.2 Check glucose levels immediately prior to FDG injection to confirm fasting blood glucose level is not greater than 200 mg/dL at maximum; optimally participants will have glucose lower than 150 mg/dL. Participants with diabetes will preferably be scheduled in the morning and instructions for fasting and use of

medications will be provided in consultation with the participants' primary physicians;

8.2.3 Collect 10 mL of peripheral blood in about one (1) red top tube (serum collection tube) prior to injection of FDG to be prepared for storage and subsequent shipment and analysis, **if participant consents to the blood collection**. Foreign sites are exempt from blood collection and submission;

NOTE: The blood draw should be performed on the Visit 2 PET/CT imaging day, prior to the FDG administration. However, if a blood draw is part of the routine clinical evaluation, it can be used for research as long as the participant signs the consent form agreeing to the blood collection component and has enrolled in the trial. The blood draw for the trial must be collected prior to surgery, or it will be a protocol violation.

8.2.4 Serum samples will be sent at the end of the study or when a site is closed. Serum samples will be kept prior to shipping at –70°C without a freeze/thaw cycle (see serum instructions in Section 10.2). **Specimen collection and shipping instructions are available on the ACRIN 6685 protocol web page (**www.acrin.org/6685_protocol.aspx**);**

8.2.5 Inject FDG into the IV approximately 60 minutes (± 10 minutes) prior to the PET/CT scan;

8.2.6 Perform the PET/CT scan;

8.2.7 Assess for adverse events (AEs) prior to the participant's departure from the PET suite. Assessment to be completed by site investigator or investigator-designee;

8.2.8 Submit PET/CT radiology report to ACRIN and ensure it is available for surgeon on the day of surgery.

8.3 Visit 3: Day of Surgery (Pathology Preparation)

8.3.1 Obtain PET/CT image and results for review prior to surgery and for reference during surgery. Neck dissection is to be performed with knowledge of PET/CT results to guide inclusion of any additional suspected nodal disease in the dissection (see Appendix III). Revisions to the surgical plan based on PET/CT imaging will be documented. The reading pathologist should be "blind" to the PET/CT results prior to rendering a pathology interpretation;

8.3.2 Conduct the surgical resection according to institutional standard of care. Neck dissection performed as select neck dissection to include zones I, II, and III or II, III, and IV at a minimum. Bilateral or unilateral planned neck dissection is acceptable as long as one neck planned for dissection is clinically N0. Clear margins should be 2 mm at minimum;

8.3.3 Submit surgical report to ACRIN;

8.3.4 Obtain and prepare the pathology sampling (preparation instructions can be found in Section 10.0, in Appendix III, and on the ACRIN 6685 protocol web page, www.acrin.org/6685_protocol.aspx);

8.3.5 Tissue specimens will be held by the enrolling institution and may be requested for QA purposes (from US sites only; foreign sites are exempt from submission for quality assurance purposes).

NOTE: Surgical follow up after Visit 3 (Day of Surgery) will be conducted per institutional standard of care at time points that may not coincide with the follow up described for the purpose of this study.

8.4 Visit 4: Thirty (30) Day Quality-of-Life Follow Up After Surgery (30 to 60 Days Post-Op)

8.4.1 Participant will be mailed QoL forms, with additional follow up by telephone if necessary (see Section 11.1.2 below). QoL questionnaires should be completed within the 30-to-60 day period following surgery.

8.5 Visit 5: One (1) Year Follow Up After Surgery

8.5.1 Conduct surgical follow-up timeline per institutional standard of care;

8.5.2 Collect details of subsequent treatment (radiation and/or chemotherapy);

8.5.3 Collect/abstract recurrence and survivorship data from the treating physician;

8.5.4 A minimum of 3 attempts must be made by the site to contact the treating physician for follow-up information (recommend that site research associate visit the treating physician's office to obtain and abstract information from the participant's medical chart). Participant may be contacted for an update of treating physician contact information if necessary;

8.5.5 Participant will be mailed QoL forms, with additional follow up by telephone if necessary (see Section 11.1.2 below). QoL questionnaires should be completed within the 6 weeks prior to and the 6 weeks after the 1-year post-op anniversary.

8.6 Visit 6: Two (2) Year Follow Up After Surgery

8.6.1 Conduct surgical follow up timeline per institutional standard of care;

8.6.2 Collect details of subsequent treatment (radiation and/or chemotherapy);

8.6.3 Collect/abstract recurrence and survivorship data from the treating physician;

8.6.4 A minimum of 3 attempts must be made by the site to contact the treating physician for follow up information (recommend that site research associate visit the treating physician's office to obtain and abstract information from the participant's medical chart). Participant may be contacted for an update of treating physician contact information if necessary;

8.6.5 Participant will be mailed QoL forms, with additional follow up by telephone if necessary (see Section 11.1.2 below). QoL questionnaires should be completed within the 6 weeks prior to and the 6 weeks after the 2-year post-op anniversary.

8.7 Off-Study Criteria

Participants will not continue with the study, and will need to be replaced, based on the following criteria. The study will continue to accrue until complete imaging data are collected for 292 participants.

8.7.1 Participant withdraws from the study before imaging and surgery are completed;

8.7.2 Participant goes to surgery prior to FDG-PET/CT or prior to surgeon's review of FDG-PET/CT results, in which case the participant will be removed from the trial and another participant will need to be recruited;

8.8 Quality Assessment and Submission Guidelines for Blood and Tissue Specimens

Foreign sites are exempt from blood collection and submission. Tissue samples will not be collected from foreign sites for quality assessment.

8.8.1 Blood Specimens Collection: Quality Assessment and Close of Study

8.8.1.1 Sites consenting patients to optional blood collection must submit all specimens to an ACRIN-designated central laboratory upon request for quality assessment (foreign sites are exempt from collection and submission);

8.8.1.2 Quality assessment will comprise a review of appropriate hematolyzation, freezing compliance, labeling, and volume—repeat assessment may be necessary based on results of the 6-month quality assessment;

8.8.1.3 All study specimens collected after the quality assessment will be shipped overnight delivery to the ACRIN-designated central laboratory at the close of study once all participants have completed their PET/CT scans;

8.8.1.4 ACRIN will inform sites of the appropriate time points and will provide additional submission details to sites collecting blood specimens.

8.8.2 Tissue Specimens Quality Assessment: Coordinated With Futility Analyses

8.8.2.1 Sites must submit pathology reports and slides from all nodal tumor tissue biopsy specimens to ACRIN for quality assessment at an ACRIN-designated central pathology laboratory (foreign sites are exempt from submission of tissue specimens for quality assessment);

8.8.2.2 Initial quality assessment will be conducted at the same time as the first futility analysis (once 50 participants with negative PET/CT results are accrued, see Section 17.4) on reports and slides from completed biopsies; a random sample of up to 25 cases (at least one from each participating site) will be reviewed by the central pathologist;

8.8.2.3 Quality assessment will comprise a review of appropriate preparation, storage compliance, labeling, and pathologists' interpretation;

8.8.2.4 A second quality assessment of local pathology reports and slides will be conducted at the same time as the second futility analysis (once 100 participants with negative PET/CT results are accrued); a random sample of up to 25 additional cases (at least one from each participating site) will be reviewed by the central pathologist;

8.8.2.5 Additional quality assessment may be conducted for sites joining the trial after the second futility analysis has been completed;

8.8.2.6 ACRIN will request overnight shipment of select additional specimens to an ACRIN-designated pathology laboratory **only** if a repeat quality assessment is necessary or pathology and PET/CT results conflict;

8.8.2.7 ACRIN will inform sites of the appropriate time points/specimens requested for central review and will provide additional submission details to all sites.

8.9 Study Procedures Table

Study Procedure	VISIT 1: Screening and Eligibility	VISIT 2: FDG-PET/CT Imaging Day Within 14 Days Prior to Visit 3	VISIT 3: Day of Surgery	VISIT 4: Thirty (30) Day Telephone Follow Up After Surgery	VISIT 5: Year One (1) Follow Up After Surgery	VISIT 6: Year Two (2) Follow Up After Surgery
Informed Consent Form	X					
Screening/Eligibility	X					
Medical History	X					
Medical Record	X					
CT and/or MR Images	X					
Physical Examination	X					
Urine Pregnancy Test[1]	X	X				
Quality of Life Questionnaire[2]	X			X	X	X
Web Registration	X					
Intravenous Catheter (IV)		X				
Glucose Levels		X				
Blood Collection (If Performed)[3]		X				
FDG Administration		X				
FDG-PET/CT (Submit Images and Report)		X				
Collect Surgical Plans from Prior to and Following FDG-PET/CT Images Review			X (prior to Visit)			
Review FDG-PET/CT Images and Report, Prior to and During Surgery			X (prior to Visit)			
Surgery per Institutional Standard of Care (Submit Report)			X			
Tissue Specimen Reports and Slides[4]			X			
Participant Mail and/or Telephone Contact[2]				X	X	X
Follow Up with Physician per Institutional Standard of Care					X	X
Physician Telephone Contact/Visit (Medical Record Extraction)					X	X
AE Assessment		X				

[1] To be conducted prior to any imaging scans if a female participant is unsure of her pregnancy status.

[2] See Section 11.1.2 for details of QoL questionnaire procedures. Timelines for completion of QoL forms are as follows: 30 to 60 days post-op for the 30-day time point; between 6 weeks before through 6 weeks after the 1-year post-op anniversary for the 1-year time point; and between 6 weeks before through 6 weeks after the 2-year post-op anniversary for the 2-year time point.

[3] Blood samples will be delivered upon request for a quality assessment to determine sufficient preparation and storage. Blood samples will be collected again at study closure once all participants have completed Visit 2 imaging time points. Additional details for processing and delivery will be provided to sites participating in the blood samples collection. Foreign sites are exempt from blood collection and submission.

[4] Tissue specimen reports and slides will be collected at two time points: at the first analysis (see Section 17.4) after 50 participants with negative PET/CT results are accrued and at the second futility analysis after 100 participants with negative PET/CT results have been accrued. Additional tissue specimens will be shipped from the enrolling institution only if additional quality assessment is needed. Sites accruing to the trial after both futility analyses have been completed may be asked to submit tissue specimen reports and slides for quality assessment. Foreign sites are exempt from tissue submission for quality assessment. See Section 8.8 for details.

9.0 IMAGING PROTOCOL: FDG-PET/CT SCAN

The study imaging modality is FDG-PET/CT performed per the parameters presented here and detailed on the protocol-specific page for ACRIN 6685 at www.acrin.org/6685_protocol.aspx. Neck dissection is to be performed with knowledge of FDG-PET/CT results to guide inclusion of any additional suspected nodal disease in the dissection (see Section 8.3 and Appendix III). See Section 3.3 for the clinical implications of the study's objectives.

9.1 Methods Overview

- FDG-PET/CT imaging performed in accordance with ACRIN quality control and acquisition standards;
- Local image reads;
- Centralized, multiple, blinded image readings (used for primary objective standard);
- Centralized statistical analysis—FDG-PET/CT uptake measures (SUV);
- Centralized statistical analysis—visual assessment.

9.2 Baseline Neck Assessment: Physical Examination and CT/MRI

9.2.1 Clinically N0 neck will be determined by physical examination and standard-of-care CT and/or MRI. The N0 neck will be defined by non-palpable nodes and by CT and/or MRI results where node sizes: are < 1 cm; are < 1.5 cm for jugular digastric nodes (IIa), spinal accessory (IIb), or submental-submandibular nodes (Ia and Ib); or show lack of central lymph node necrosis.

9.3 Overview of Study PET and CT Data Acquisition

9.3.1 Qualification

The participant must be scanned on PET/CT scanners that have been qualified by the ACRIN PET Core Laboratory per the protocol-specific instructions posted on the ACRIN web site at: www.acrin.org/CORELABS/PETCORELABORATORY/PETQUALIFICATION/tabid/485/Default.aspx.

9.3.2 Mandatory, Dedicated Hybrid Scanner

A dedicated hybrid PET/CT scanner is mandatory. The PET/CT scanner must be capable of performing both emission and CT transmission images in order to allow for attenuation corrected PET/CT scan images. The ability to calculate SUVs is also mandatory.

9.3.3 Scanner Calibration

The PET/CT scanner must be kept calibrated in accordance with the manufacturer's recommendations. The scanner should routinely be assessed for quantitative integrity and stability by being tested using various imaging protocols on a standard phantom. For SUV measurements, this assessment should include a comparison against a dose calibrator to ensure accuracy; that is, a comparison of the absolute activity measured versus the measured activity injected, should be performed.

The PET/CT scanner calibrations should be routinely verified according to manufacturer recommendations. The scanner should be assessed regularly for quantitative integrity and stability by scanning a standard quality control phantom with the same acquisition and reconstruction protocols used for study participants.

The SUV verification measurements must include the dose calibrator used to measure the doses of study participants to ensure that the dose calibrator and PET/CT scanner are properly cross calibrated, i.e., the dose measured in the dose calibrator and injected into the phantom matches the results obtained from analysis of the phantom images.

9.3.4 Routine Quality Control (QC)

A daily QC check must be performed at the beginning of the day, including PET/CT scanner and dose calibrator, in accordance with the manufacturer recommendations. If any of the QC results are outside of the manufacturer's guidelines, the study must be rescheduled and the problem rectified before scanning any participants.

9.4 FDG-PET/CT Imaging Procedures

9.4.1 Participant Preparation

9.4.1.1 Participants must fast for a minimum of 4 hours prior to the injection of FDG for the PET/CT scan. However, they will be encouraged to drink water to ensure adequate hydration.

9.4.1.2 Upon arrival to the PET/CT facility, the participant's height and weight must be measured using calibrated and medically approved devices (not verbally relayed by the participant). Serum glucose should be measured to determine that the blood glucose concentration is within the normal range.

9.4.1.3 If the serum glucose concentration is found to be greater than 200 mg/dL, the study should be rescheduled. The referring oncologist or the primary physician of the patient will be contacted to optimize blood glucose control.

9.4.1.4 The participant should be placed in a comfortable position, either supine or semi-recumbent. A large-bore intravenous line (21-gauge or greater) should be placed in an arm or hand vein. The room should be kept warm to avoid shivering and temperature effects that may increase muscular or fat uptake. The participant should move as little as possible and should not talk more than necessary in the first 30 minutes following FDG injection.

9.4.1.5 Prior to positioning the participant on the PET/CT scanner the participant should be asked to urinate.

9.4.2 Injection of Fluorodeoxyglucose (FDG)

9.4.2.1 The dose of FDG to be administered should be 10 to 20 millicuries (mCi), adjusted according to weight or as per institutional norm within this range.

9.4.2.2 FDG will be synthesized and prepared in accordance with United States Pharmacopeia (USP) compendial reference standards.

9.4.2.3 The exact time of calibration of the dose should be recorded and the exact time of injection (approximately 60 minutes prior to imaging) noted to permit correction of the administered dose for radioactive decay. In addition, the dose remaining in the tubing or syringe, or that

was spilled during injection should be recorded. The injection should be performed through an IV catheter.

9.4.3 FDG-PET/CT Imaging Sequence

9.4.3.1 PET/CT scanning must begin 60 +/- 10 minutes after FDG injection.

9.4.3.2 It is strongly recommended that participants should be imaged from the orbits through the upper thigh. PET/CT's from institutions that perform whole body imaging from clavicle through the upper thigh will be accepted.

Under certain circumstances, institutions that perform head and neck-only PET/CT scans as standard practice may be approved to participate in this trial. A formal request along with proof of head and neck only PET/CT as standard practice **MUST** be submitted to ACRIN for review and approval (submit request to the ACRIN 6685 Project Manager). Requesting institutions may be required to provide additional information to process the request. With ACRIN approval, an institution can participate and perform head and neck-only PET/CT for the duration of the trial.

9.4.3.3 A dedicated head and neck imaging acquisition (orbits to upper thorax) with arms down is required given the higher sensitivity of this exam.

The remainder of the body is to be scanned with the arms raised over the patient's head. If participants cannot tolerate these exams for the FDG-PET/CT study, different participant positioning may be chosen.

9.4.3.4 A low-dose CT scan will be acquired for attenuation correction and anatomical localization of findings in the PET scan.

9.4.3.5 The acquisition parameters for the dedicated head and neck CT, low-dose CT scan should be approximately: kV = 120; effective mAs = 90-150 (patient dependent, auto current modification acceptable); gantry rotation time < 0.5 sec; maximum reconstructed slice width = 2.5 mm (overlap acceptable); standard reconstruction algorithm, maximum reconstruction diameter = 30 cm; and without iodinated contrast.

The acquisition parameters for the low-dose CT scan for attenuation correction should be approximately: kV = 120; effective mAs = 30–80 (patient dependent, auto current modification acceptable); gantry rotation time < 0.5 sec; maximum reconstructed width = 3–5 mm without overlap; standard reconstruction algorithm, minimum reconstruction diameter = outer arm to outer arm; and without iodinated contrast.

9.4.3.6 The axial field of view of the CT scan for attenuation correction will range from the mid thighs to the base of the skull. Arm positioning will be the same as for the PET scan.

9.4.3.7 The CT scan will be performed during normal breathing. No respiratory gating will be applied.

9.4.3.8 After the CT scan, a PET scan covering the same axial field of view will be performed. This scan will start at the upper thighs. The number of bed positions and the acquisition time per bed position will be scanner

specific. Typical parameters are 6 bed positions and an acquisition of 2 to 5 minutes per bed position. The dedicated head and neck PET/CT will typically follow the body exam. Two bed positions will often suffice for orbits to upper thorax (top of aortic arch) and acquisitions should at a minimum be 6 minutes per bed position and be reconstructed into a 30 cm FOV (field of view) with a 256 x 256 matrix.

9.4.4 Image Reconstruction

9.4.4.1 The FDG-PET/CT data will be corrected for dead time, scatter, randoms, and attenuation using standard algorithms provided by the scanner manufacturers. For the dedicated head and neck views, a post-filter with a FWHM (full-width at half maximum) in the range of 5 mm is recommended.

9.4.4.2 Image reconstruction will be performed as specific in the ACRIN certification of the PET/CT scanner.

9.5 Methods of Image Evaluation and/or Analysis

9.5.1 Image Evaluation Dynamics

Following the completion of PET/CT imaging at the study site, images will be sent to the ACRIN Core Laboratory. Digital images will be sent via TRIAD or media to the ACRIN core lab as described in Section 9.6. Following receipt, all PET/CT studies will be reviewed for diagnostic acceptability. If studies are found to be technically insufficient, problems will be resolved prior to presentation to the core reading panel.

PET/CT images will be interpreted by an ACRIN Imaging Core Panel (AICP) of expert PET/CT readers who will have no involvement or knowledge of the participant's clinical care and who will be blinded to the participant's diagnosis, local PET/CT scan results, and clinical history. No AICP readers can be site investigators at the site producing the PET/CT scans. AICP readers will be shown a group of 10 cases for training purposes. Feedback on each of these cases will be provided prior to reading the study participants' PET/CT scans.

AICP readers will be provided with a case report form (CRF) that details—in a standardized manner—basic patient demographics that include age, gender, height, and weight. Readers will be instructed to characterize the participant's primary malignancy and lymph node metastasis. They will be told to evaluate the PET/CT scans for distant metastasis. Diagnosis of the primary mass, lymph nodes, and distant disease will be made using a five-point ordinal scale ranging from "Definitely Benign" to "Definitely Malignant." SUV values will be determined at the ACRIN Imaging Core Lab using an automated region detection program. This will allow determination of SUV values for primary and lymph nodes sites in a standardized fashion. An SUV_{max} value of $\geq$ 2.0 will be considered positive. The SUV value will be provided to the reader in their assessment of the PET/CT scan to aid in their interpretation.

Each PET/CT scan will be read independently by two AICP PET/CT readers. AICP reader pairs will be alternated so that the two readings of each PET/CT scan is not performed by the same pair of readers for more than 30% of the entire PET/CT data set.

9.5.2 FDG Uptake Analysis

"Positive" nodal uptake of FDG is defined as uptake visually greater than background and more than that activity seen in the blood pool. Local blood pool reference can be the carotid or the aortic arch. To increase standardization and reproducibility of the analysis, the SUV_{max} value will be calculated and a cutoff of 2.0 will be used to define the positives (i.e., $SUV_{max} \geq 2.0$), which is primarily based on the findings from case reviews from Mayo Clinic (unpublished data, Mayo Clinic Rochester) and previous studies.[35,36] Also in the literature, no SUV cutoff value for head and neck cancer adenopathy has been previously shown to have greater accuracy than visual analysis. Therefore, ROC curve analysis will be performed post hoc to determine the optimum cutoff SUV value to separate benign from malignant lymph nodes.

9.5.3 Visual Assessment

The qualitative assessment from readers' visual impression will also be collected and be compared with the quantitative assessment using PET SUV_{max}.

9.6 Image Submission

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

9.6.1 TRIAD Access Requirements

Site radiology staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account.

To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

9.6.2 TRIAD Installations

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/. This process can be done in parallel to obtaining your CTEP-IAM account username and password. If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

9.6.3 For Submission Via Media:

In the event that the transfer of image data is not available via TRIAD, images may also be sent on a CD/DVD-ROM to the ACRIN core lab for transfer to the image archive. All image data submitted to the ACRIN core lab must be in DICOM format.

Images and the ITW may be mailed to:

American College of Radiology Imaging Network
Core Laboratory
Attn: ACRIN 6685
1818 Market Street, Suite 1720
Philadelphia, PA 19103

10.0 TISSUE AND BLOOD SPECIMEN COLLECTION AND PATHOLOGY ANALYSIS

10.1 Tissue Collection and Pathology Analysis

Tissue collection and pathology analysis must be conducted at the ACRIN-qualified participating site. Slides and specimen storage and pathology reports will be delivered to the University of Arkansas, an ACRIN-designated pathology laboratory, as described in the ACRIN 6685 Pathology Manual, posted online at www.acrin.org/6685PathologyLabMaterials.aspx. Foreign sites are exempt from tissue submission for quality assessment purposes (i.e., Section 8.8).

10.1.1 Tissue Collection Process

For each participant, the tumor tissue obtained from the diagnostic surgery performed after the study FDG-PET/CT will be collected and stored on site; tissue slides, specimen-storage reports, and pathology reports will be submitted to ACRIN when requested to coincide with the two stages of futility analysis as outlined in Sections 8.8.2 and 17.4 (first futility analysis after 50 participants with negative PET/CT results accrued; second futility analysis after 100 participants with negative PET/CT results accrued). Depending on the outcome of the quality assessment, additional tissue specimens may be requested via overnight delivery to an ACRIN-designated pathology laboratory for additional quality assessment. Subsequent tumor tissue specimens will be banked locally to be shipped overnight for central review at an ACRIN-designated pathology laboratory upon request. Sites will be provided with specific detailed collection instructions and shipment information in the ACRIN 6685 Pathology Manual (www.acrin.org/6685PathologyLabMaterials.aspx). Specimens not collected for central review at the ACRIN-designated pathology laboratory should be destroyed at the end of the study unless otherwise directed by ACRIN or mandated per institutional standards.

Each institution will have one pathologist designated as the lead pathologist. This person would not, however, be limited as the only site pathologist able to read out study specimens. The lead pathologist would be the institutional "go to" person and would ensure quality control of the readings from his/her institution.

Neck dissection specimens will be submitted in specific nodal levels using the AAO-HNS/AHNS node level designations. Each nodal level will be passed from the operative field by the surgeon in a labeled container (i.e., right level I); formalin solution will be added and the specimen will be sent to the pathology department for analysis. However, institutional standard practice (e.g., delivery of the intact specimen from surgery to pathology for processing) is allowable if approved by the site PI; should the site PI approve an alternative process, a Note to File should detail the site's procedures and be signed by the site PI to inform ACRIN auditors of the process distinction. A surgeon's data sheet will accompany the pathology nodal specimens to reconcile the tissue removed from

each study participant and to provide an inventory for the pathology department.[37,38]

10.1.2 Local Tissue Pathology Analysis

Pathology specimens will be received and logged into the hospitals' electronic medical record (EMR) as per local practice. The attending pathologist will process or supervise the processing of the nodal specimen into paraffin block for conventional Histologic interpretation.

Special processing instructions for this study include:

- Lymph nodes less than 5 mm in smallest diameter must be bisected perpendicular to the smallest diameter and submitted *in toto* for histology.
- Lymph nodes greater than 5 mm and less than 1.5 cm in smallest diameter must be trisected perpendicular to the smallest diameter and submitted *in toto* for histology section in the minimum cassettes required with appropriate documentation in the gross description. If a cross section is too big to fit in a cassette, it may be subdivided to fit. No cassette should contain the contents of more than one lymph node.
- Lymph nodes greater than 1.5 cm in smallest diameter should be have 4 representative cross sections taken at equal distances along the perpendicular axis made up by the smallest dimension and submitted for histologic section in the minimum number of cassettes required with appropriate documentation in the gross description. If a cross section is too big to fit in a cassette, it may be subdivided to fit. No cassette should contain the contents of more than one lymph node.
- Any lymph node which is grossly positive for tumor should have the metastasis grossly measured and documented in the gross description and then a single representative section showing the gross tumor should be submitted. This supersedes the sectioning guidelines detailed above. If the lymph node proves to be histologically negative, additional sections should be taken to fulfill the sectioning guidelines.

All slides will be processed with conventional hematoxylin and eosin stain and read at low and high magnification. The pathologist will read out presence or absence of SCC. The amount of carcinoma also will be reported, including greatest dimension if possible. Features such as extra-capsular spread and perineural invasion should be commented upon if present.

Pathology data from local site assessment will be submitted by the sites to ACRIN. Only local diagnosis will be performed. Upon central review of local pathology data, individual case blocks or slides may be requested for central interpretation or additional quality control review.

10.2 Blood Serum Collection and Analysis (Optional)

Serum samples will be collected and frozen from consenting participants at US sites only at the time of placement of their IV for their PET/CT scan. Foreign sites are exempt from blood collection and submission. These samples, along with their clinical data, will be sent in batches by clinical sites to a central laboratory for analysis at specific time points or at the request of ACRIN. Serum biomarker analysis will follow the technique of Linkov et al[33] (see below) as this

serum analysis technique demonstrated good accuracy in detection of the presence of head and neck cancer.

10.2.1 Blood Serum Collection and Storage

Ten (10) mL of peripheral blood, drawn from consenting study participants during placement of an IV catheter for ^{18}FDG infusion procedures, will be allowed to clot. Handling and processing is similar for all groups of participants. Sera will be separated by centrifugation within 2 hrs, and all specimens are immediately aliquoted into 1 mL (preferred) or 2 mL cryovials and stored in a –70°C freezer until shipment to the ECOG-ACRIN CBPF at M. D. Anderson Cancer Center. Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at M. D. Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be provided in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org.

Shipping Address:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

An STS shipping manifest form must be generated and shipped with all sample submissions.

10.2.2 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest form should be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

10.2.3 Storage and Shipping Instructions

These samples will be held in storage at the participating institution and sent to a central laboratory when requested for a quality assessment, and at the end of the trial, or when a site is closed, for processing and analysis (see Section 8.8.1). Only the analyses described in this protocol will be conducted on the blood serum specimens, and any remaining samples will be destroyed per institutional standard upon completion of the required trial analysis.

Serum samples will be kept prior to shipping at –70°C without a freeze/thaw cycle (see serum instructions at www.acrin.org/6685_protocol.aspx). Specimens will be packed on dry ice and shipped by overnight priority delivery with a tracking number.

10.2.4 Multiplex Serum Analysis

The Luminex xMAP™ serum assays will be performed in 96-well microplate format. Analytes are chosen based on knowledge of pathophysiology of malignancy and markers reported in the literature.33 Multiplex bead-based immunoassays for cytokines will be purchased from Invitrogen.

Other assays for proteins have been developed in the Luminex Core Facility of University of Pittsburgh Hillman Cancer Center, Pittsburgh, PA, USA, according to the protocol by Luminex Corporation.

Potential analytes may include: Eotaxin-1, IFN- α (Interferon-alpha), IFN-γ (Interferon-gamma), IL (Interleukin) 10, 12 p40, 13, 15, 17, 1 α, 2, 4, 5, 6, 7, 8, IP-10 (Interferon gamma inducible protein 10), MCP-1 (Monocyte Chemotactic Protein alpha), MIG (Monocyte Induced Gamma interferon), MIP-1 α (Macrophage Inflammatory Protein 1-alpha), MIP-1β (Macrophage Inflammatory Protein 1-beta), RANTES (Regulated upon Activation, Normally T-Expressed and presumably Secreted), TNF- α (Tumor Necrosis Factor alpha), TNF-RI (Tumor Necrosis Factor Receptor I), TNF-RII (Tumor Necrosis Factor Receptor II), DR5 (Death Receptor 5), EGF (Epithelial Growth Factor), bFGF (Basic Fibroblast Growth Factor), G-CSF (Granulocyte Colony Stimulating Factor), GM-CSF (Granulocyte Monocyte Colony Stimulating Factor), HGF (Hepatocyte Growth Factor), VEGF (Vascular Endothelial Growth Factor).

Internal (spiked) control analytes will be included for validation and standard curves. For intra-assay precision, coefficients of variation (CVs) will be calculated from 6 replicates of a control serum run on a single plate. For inter-assay precision, CVs will be calculated from at least 5 separate experimental runs of the same control serum.

10.2.5 Statistical Analysis

Reference normal samples (healthy donor serum bank) will be compared to study participants' specimens. Univariate and multivariate analyses will be performed. Panels of markers, based on initial results, will be developed to increase the sensitivity and specificity of diagnosis of the presence and/or stage of head and neck SCC with specific attention to neck metastasis. To simulate each panel's large-scale diagnostic use, we will average together the results of training and testing the classifier on a large number of training and test sets randomly

generated with permutation re-sampling. The re-sampling algorithm will consist of the following steps for each factor panel examined: (1) randomly divide data into training and test sets, (2) train the classifier on the training set, (3) apply the trained classifier to the test set, (4) store test-set prediction probabilities, and (5) repeat.

Ten thousand iterations will ensure every sample would be randomized into a test set at least two thousand times. Specification of a positive-valued seed for the pseudorandom number generator ensures that the different factor panels are compared on the same 10,000 data-set partitions. Each sample's collection of test-set prediction probabilities will be averaged across iterations to yield a robust, randomization-independent estimate of how the factor panel classifies that sample when it's in a test set. Samples' average test-set prediction probabilities will be used to construct an empirical (non-parametric) and binormal (parametric) ROC curve for each factor panel.

10.3 Tumor Markers

Multiplex serum analysis will be evaluated using multiple markers, based initially on the 25 markers found to be most predictive by Linkov's group. Reference normal samples (healthy donor serum bank) will be compared to study participants. Univariate and multivariate analyses will be performed. Panels of markers, based on initial results, will be developed to increase the sensitivity and specificity of diagnosis of the presence and/or stage of head and neck SCC with specific attention to neck metastasis. Multivariate logistic regression will then be used to study the multimodality biomarkers (serum and imaging). Stepwise procedure will be applied to select the minimal number of predictive serum markers. ROC curves based on logistic regression models will be compared to see how well the multimodality biomarkers can stage patients. As an exploratory analysis, we will also fit a semiparametric logistic regression model where imaging features are modeled parametrically and serum biomarkers are modeled nonparametrically. ROC curves based on this semiparametric model will also be compared. To study the additive predictive ability of biomarkers, we will use the approach of the optimality of the risk score (defined as the conditional probability of disease given the biomarker status) to combine the biomarker and PET/CT in the binary regression analysis.[39,40] We refer to McIntosh and Pepe[39,40] for detailed discussion.

10.4 Standards of Reference

Pathology from neck dissection, surgical resection of primary sites, and 2-years' clinical follow up in all participants.

10.4.1 Tumor Biomarkers

Multiplex cytokine profile serum analysis

10.4.2 Methods

- Local collection of tissue;
- Local processing of specimens;
- Local reading of lymph node specimens by protocol;
- Centralized collection of pathology CRFs, institutional path reports, and glass slides (at futility analysis time points and then as requested);
- Serum biomarker collection and analysis to follow the technique of Linkov et al[33];

- Centralized statistical analysis.

11.0 QUALITY OF LIFE AND COST-EFFECTIVENESS

11.1 Quality of Life Assessment

In our preliminary CEA, two of the most important input variables were the patient utilities following unilateral versus bilateral neck dissection, which can be correlated with QoL measures. However, the most reliable estimates we could obtain for these variables were based on a questionnaire study of patients receiving unilateral or bilateral neck dissections conducted in England between 1995 and 2000. Furthermore, the instrument used to assess QoL, the University of Washington Quality of Life (UW-QoL) questionnaire, was disease-specific and obtained scores that are not directly related to the utilities that are needed for CEA. Therefore, we intend to assess utilities in our participants directly using several standard instruments for measuring preferences: the 36-Item Short Form Survey Instrument, version 2 (SF-36 v2), the Health Utilities Index (HUI), and the UW-QoL.

11.1.1 The SF-6D is an algorithm for reliably converting SF-36 scores to utilities. By using the SF-6D we will be able to report patient functional status measures as well as utilities. One drawback to the SF-36 is that there are specific health domains that are not measured, such as speech and communication. Thus, the SF-36 may not be sensitive to some dimensions of QoL that will be affected by treatment decisions guided by FDG-PET/CT. The HUI is a generic, preference-scored survey instrument for measuring health-related QoL. It also provides an algorithm for producing utility scores. HUI has the advantage of including domains for speech, mobility, emotion, and pain, all of which will be relevant to QoL in patients with head and neck cancer. Finally, we will administer the UW-QoL. Although this instrument does not provide an algorithm for utility estimates, it is an important disease-specific QoL instrument for head and neck cancer. By administering this survey now we will be able to develop utility crosswalks in the future for this instrument. The total time to complete all three questionnaires is approximately 30 minutes.

11.1.2 The QoL questionnaires will be collected at four (4) different time points throughout the trial for all consenting participants. Initial QoL will be collected prior to surgery at Visit 1 of the study. Subsequent QoLs will be collected about 30 days after surgery (between 30 and 60 days post-op), about year 1 after surgery (the 6 weeks before through the 6 weeks after the 1-year post-op anniversary), and about year 2 after surgery (the 6 weeks before through the 6 weeks after the 2-year post-op anniversary). A protocol deviation occurs should a participant be unable to complete the initial QoL questionnaire at baseline, but the participant does not become ineligible for the trial; however, subsequent QoL questionnaires will not be administered for these participants.

11.1.2.1 Collection of Baseline Information on QoL

To establish a baseline for the QoL assessment, all participants who consent and can read or understand English, Spanish, or other languages based on international site participation will be asked to independently complete the SF-36 v2, HUI, and UW-QoL. International sites will be responsible for the translation of appropriate materials for their

participants. Sites will complete English-based electronic CRFs to report results.

When participants are completing the QoL forms, the site RA will facilitate the completion of the forms as necessary, but will not respond to queries that attempt to interpret the meaning of questions. During trial-specific training sessions and routine conference calls devoted to operational aspects of the trial, all RAs will receive training as to the appropriate approaches to assisting participants with QoL forms completion.

11.1.2.2 Management of Contact Information for QoL Study and Administration of QoL Tools at Follow Up

Administration of the QoL tools will be coordinated by the participating sites. Site RAs who have completed training to facilitate QoL forms completion will conduct the QoL questionnaire administration. Participant contact information for mail correspondence will be documented on the 'Participant Contact Information Worksheet' at the time of registration. Only participants who completed the baseline questionnaire will be asked to complete the QoL instruments at approximately 30 days, 1 year, and 2 years post-operative (see Section 11.1.2 for time point variables).

Mailing: The site RA will mail copies of QoL tools to participants along with pre-addressed, stamped envelopes for return mailing to the site. The questionnaire mailing will include a cover memo with contact information and a telephone number for the site RA should the participant require assistance with reading the questionnaires. If the questionnaires are not received at the site within 10 working days of the date of the mailing, the site RA will telephone the participant to determine whether the questionnaires were received and completed. Participants who did not receive the questionnaires will have additional questionnaires sent by mail after confirming the correct mailing address.

Telephone contact: If questionnaires were received by the participant but never completed, the site RA will make telephone contact to urge the study participant to complete and return the questionnaire. If questionnaires are not returned within 20 working days thereafter, the site RA will attempt to complete the questionnaires in a telephone interview. Telephone interviews will be conducted only as a final measure to avoid any biases introduced by differences in the method of administration of the questionnaires, and the mode of administration of all such questionnaires will be documented in the trial database. The site RAs will not attempt to interpret a question; training will be provided to help ensure site RAs facilitate completion of the QoL questionnaires in a standardized fashion.

11.2 Cost-Effectiveness Assessment

We will perform a CEA comparing three strategies: 1) treatment with unilateral neck dissection; 2) treatment with bilateral neck dissection; and 3) treatment based on results of PET/CT. The

CEA will assume a societal perspective and a lifetime time horizon.[41] Main endpoints will include effectiveness, reported in terms of QALYs, costs reported in terms of U.S. dollars, and cost-effectiveness reported in terms of ICER. We will use commercially available software (TreeAge Pro Suite 2008, Release 1.5.1) to construct a Markov model[42] and perform the CEA. In addition to analyzing the base case, we will perform sensitivity analyses on several key variables, including the pretest probability of contralateral lymph node metastases, the sensitivity and specificity of PET/CT, the effectiveness of lymph node dissection, QoL after surgery, and various costs.

12.0 ADVERSE EVENTS REPORTING

Prompt reporting of AEs is the responsibility of each investigator, clinical RA, and/or nurse engaged in clinical research. Anyone uncertain about whether a particular AE should be reported should contact the ACRIN headquarters at 215-574-3150 for assistance.

Adverse events (AEs) meeting the criteria in the tables below, including all serious adverse events (SAEs) will be reported to the CTEP Adverse Event Reporting (CTEP-AERS) and Cancer Imaging Program (CIP) as directed in this section.

CTEP-AERS is an electronic, internet based expedited Adverse Event reporting system operated by NCI/CTEP. It is generally used to capture and disseminate information on relatively significant Adverse Events, based upon trial stage, expectedness, severity, and attribution. However, it may be used to report adverse events of all types if CTEP-AERS reporting is required per protocol.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497, or 301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

12.1 General Definitions

Adverse Event (AE): For the purpose of this study, an Adverse Event is an untoward medical condition experienced by a study participant during the Adverse Event reporting period as defined in Section 12.7 Table A of the protocol, or by applicable guidance, regulation, or policy. An AE is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with participation in the study, regardless of exposure to an agent or procedure, and regardless of whether it is considered to be caused by the agent, device, or process under investigation. If there is any uncertainty, concerns, or questions, consult the CIP Clinical Trials Branch. If a decision must be made pending final clarification, the stricter requirement should be applied.

Life-Threatening Adverse Event: A life-threatening AE is any adverse event that places the study participant, in the clinical opinion of the investigator, at immediate risk of death.

Serious Adverse Event (SAE): An SAE is defined as any untoward medical occurrence that meets any one of the following criteria:

- Results in death or is life-threatening at the time of the event;
- Requires inpatient hospitalization, or prolongs hospitalization;

  NOTE: Hospitalization for expedited AE reporting purposes is a medically required inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should be reserved for situations where

the adverse event truly fits this definition, and not for hospitalizations associated with less serious events. For example, a hospital visit where a subject is admitted for observation or minor treatment (e.g., hydration), and released in less than 24 hours, generally is not intended, in and of itself, to qualify as an SAE. Furthermore, hospitalization for pharmacokinetic sampling, is not an AE, and therefore is not to be reported either as a routine AE or in an expedited report. As in all cases, if there is any doubt as to reporting an event, the CIP SAE reporting desk help line is to be consulted promptly.

- Results in a persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect (in a participants offspring);
- Requires intervention to prevent any of the above, per the investigator/sponsor.

All SAEs are to be followed by the investigator until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology or until subject is lost to follow up.

Adverse Event Expedited Reporting System (CTEP-AERS): CTEP-AERS is a web-based system created by NCI for electronic submission of SERIOUS and/or UNEXPECTED AE reports & is to be used in this study. All CIP trials must use CTEP-AERS for expedited reporting of AEs.

Commercial Agent: A commercial agent is any agent marketed and obtained from a commercial source, and used under approved label indication. For example, the gadolinium contrast agent used in this study is commercial agent.

12.2 AE Reporting Requirements

For this protocol, AEs with the grades of 3, 4, and 5 and attribution of possible, probable and definite to the study procedures will be recorded and reported. Refer to Reporting Requirements Table in 12.7 for timelines. The list of AEs, and the characteristics of an observed AE [see "Adverse Event Characteristics - Definitions" in Section 12.4] will determine whether the event requires expedited (via CTEP-AERS) reporting **in addition** to routine reporting. For this study CTEP-AERS reporting will be done electronically.

12.3 Adverse Event List(s) for Study Procedures

12.3.1 Expected Adverse Events Associated With Standard of Care Practice

Any AE that is a result of standard-of-care practice will be reported and managed per the institution's policies and procedures.

12.3.2 Expected Adverse Events Associated With the Intravenous (IV) Catheter Placement for Blood Collection and Injection of FDG:

- Dizziness/lightheadedness from blood collection;
- Hemorrhage (hematoma at the injection site);
- Infection (catheter related infection) at the injection site;
- Minor discomfort;
- Bleeding;
- Infection;
- Bruising.

12.3.3 Expected Adverse Events and Potential Risks Associated with FDG:

- Allergic-type or other adverse reaction to FDG.

12.3.4 Expected Adverse Events from PET Scan:

- Discomfort;
- Claustrophobia.

12.3.5 Expected Adverse Events from CT Scan:

- Discomfort;
- Claustrophobia;
- Malfunction of implanted electronic medical devices, e.g., pacemakers, neurostimulators, insulin pumps (see note below).

NOTE: As of July 14, 2008, FDA released a preliminary public health notification of possible malfunction of electronic medical devices caused by CT scanning. Site should use CT scout views to determine if implanted or externally worn electronic medical devices are present and if so, their location relative to the programmed scan range. Refer to the FDA web site for the notification (www.fda.gov/cdrh/safety/071408-ctscanning.html) and their recommendations.

12.3.6 Radiation Risk from the FDG-PET/CT Scan:

This research study involves exposure to radiation from one FDG-PET/CT scan. The radiation exposure is equal to a uniform whole-body exposure of approximately 14 mSv—approximately 11 mSv from the injected radioactive FDG and 3 mSv from the CT component—equaling approximately 30% of the allowable annual dose of 50 mSv for radiation workers. The overall radiation exposure will be specific for each site's machine; these numbers are general guidelines.

12.4 Adverse Event Characteristics

Expected Adverse Event: An expected AE is an event that is listed in the protocol or the Investigator's Brochure.

Unexpected Adverse Event: An unexpected AE is an event that is NOT listed in the protocol or the Investigator's Brochure.

Attribution: Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

- **Definite:** The AE is **clearly related** to a treatment or procedure
- **Probable:** The AE is **likely related** to a treatment or procedure
- **Possible:** The AE **may be related** to a treatment or procedure
- **Unlikely:** The AE is **likely unrelated** to a treatment or procedure
- **Unrelated:** The AE is **clearly not related** to a treatment or procedure

Note: For this study, attributions are in terms of the study related procedures (i.e. study imaging, contrast injection, etc.).

Grade: Grade denotes the **severity** of the AE. An AE is graded using the following categories:

- **Mild**
- **Moderate**
- **Severe**
- **Life-threatening or disabling**
- **Fatal**

Note: Severity is graded on a NCI Common Terminology Criteria for Adverse Events (CTCAE) based scale for each CTCAE event. For example, an abnormal hemoglobin

value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal Hemoglobin values. "Severity" is NOT the same as "Seriousness," which is an overall assessment that determines reporting requirements.

12.5 CTCAE Term (AE Description and Grade)

The descriptions and grading scales found in the NCI CTCAE version 4.0 will be utilized for AE reporting. All appropriate clinical areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).]

12.6 Expedited Adverse Event Reporting

24 Hour Telephone Reporting Instructions

Any AE/SAEs that require 24-hour notification are reported as follows:

12.6.1 CIP–SAE Reporting Line: (301) 897-7402

- The CIP-SAE reporting line is staffed Monday through Friday from 7:30am – 7:30pm ET (Eastern Time).
- AE/SAEs may be reported via voicemail during off hours.
- A TRI contact for AE/SAE reporting will return your call within 24 hours.

Generally the following details are essential to initiate an AE/SAE report:

- Name of person reporting the AE/SAE and telephone number
- Institution name and institution number
- Protocol title and number
- Participant's case number and initials
- Site principal investigator name and telephone number
- Date and time of the AE/SAE
- Date and time you learned of the AE/SAE
- Brief description of the AE/SAE
- Site principal investigator's assignment of the grade of the adverse event
- Site principal investigator's assignment of the attribution of the adverse event (do not delay initial report if not available)

12.6.2 ACRIN–AE/SAE Reporting Line: (215)717-2763

- The ACRIN–AE/SAE reporting line is monitored by the ACRIN AE Coordinator: Monday through Friday from 8:30am – 4:30pm ET.
- AE/SAEs may be reported via voicemail during off hours.
- The ACRIN AE Coordinator will return your call within 24 hours.

Generally the following details are essential to initiate an AE/SAE report:

- Name of person reporting the AE/SAE, telephone number
- Institution name and institution number
- Protocol title and number
- Participant's case number and initials
- Site principal investigator's name and telephone number
- Date and time of the AE/SAE
- Date and time you learned of the AE/SAE
- Brief description of the AE/SAE
- Site principal investigator's assignment of the grade of the adverse event
- Site principal investigator's assignment of the attribution of the adverse event (do not delay initial report if not available)

IMPORTANT: After the 24 hour contact to CIP and ACRIN-AE/SAE reporting lines, an electronic Adverse Event Expedited Report (CTEP-AERS) must be submitted per the protocol-specific requirements or the regulatory reporting timelines, if not specified in the protocol.

12.7 Expedited Reporting Guidelines

Expedited AE reporting for this study must use electronic CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). Expedited reporting is defined as the immediate notification of ACRIN and electronic submission of an CTEP-AERS) report per Section 12.6. Routine reporting requirements will also apply. All serious AEs (SAEs) will be documented in the study participant's chart and AE CRFs, in addition to meeting all study-specific reporting requirements of ACRIN, NCI, and the local IRB (per local IRB policy).

NOTE: In addition to documentation listed above, the AE must also be documented in the participant's chart and an AE CRF in order to satisfy routine reporting requirements.

TABLE A: CTEP-AERS reporting requirements for AEs occurring within 30 Days of the last study procedure

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Un-expected and Expected	Unexpected		Expected	Unexpected		Expected		Un-expected	Expected	Un-expected	Expected
		with Hospital-ization	without Hospital-ization		with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization				
Unrelated Unlikely	**Not Required**	**Not Required**	**Not Required**	**Not Required**	**Not Required**	**Not Required**	**Not Required**	**Not Required**	**Not Required**	**Not Required**	**Not Required**	**Not Required**
Possible Probable Definite	**Not Required**	**Not Required**	**Not Required**	**Not Required**	**10 Calendar Days1**	**Not Required2**	**Not Required2**	**Not Required2**	**24-Hour; 5 Calendar Days1**	**10 Calendar Days1**	**24-Hour; 5 Calendar Days1**	**10 Calendar Days1**

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

All SAEs are to be followed by the investigator until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology or until subject is lost to follow up.

Adverse events that occur more than 30 days after the last study procedure and have an attribution of possible, probable, or definite require reporting as follows:

CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 Unexpected Events

CTEP-AERS 10 calendar day report:

- Grade 3 Unexpected Events with Hospitalization
- Grade 5 Expected Events

[1]AEs reported through CTEP-AERS must also be reported in routine study data submissions (i.e. ACRIN AE case report form).
[2] These AEs will require routine reporting (refer to Section 12.8).

Expedited AE Reporting Timelines Defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via a telephone report to NCI/CIP and ACRIN within 24 hours of learning of the event,

followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.

- "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

  Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

12.8 Routine Adverse Event Reporting

The following adverse events **must** be reported in routine study data submissions (i.e. ACRIN AE case report form):

- Grade 3 Expected and Unexpected AEs with an attribution of **possible, probable or definite** require routine reporting. [See Section 12.7 Table A for CTEP-AERS reporting requirements].
- Grade 4 Expected and Unexpected AEs with an attribution of possible, probable or definite require routine reporting. [See Section 12.7 Table A for CTEP-AERS reporting requirements].
- Grade 5 Expected and Unexpected AEs with an attribution of possible, probable or definite require routine reporting. [See Section 12.7 Table A for CTEP-AERS reporting requirements].

AEs reported through CTEP-AERS must <u>also</u> be reported in routine study data submissions.

12.9 Local Institutional Review Board (IRB) Reporting

Refer to the IRB policies and procedures for AE reporting.

13.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference of Harmonisation [ICH] guidelines), applicable government regulations, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB) for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to ACRIN before implementation of the study.

The investigator will provide ACRIN with the institution's Federalwide Assurance (FWA) number, along with the IRB approval letter and copy of the IRB-approved ICF. The investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

All study participants in this study will be given an IRB-approved, site-specific ICF describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix I for an ICF template). The ICF will be submitted along with the protocol for review and approval by the EC/IRB. The study participant MUST be consented with the EC/IRB-approved ICF before the participant is subjected to any study procedures. The approved ICF MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent.

Any revisions to the ICF at any time during the trial will need to be submitted to the IRB for approval and submission to ACRIN PDRC.

14.0 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with ACRIN Conflict of Interest policies and applicable federal, state, and local laws and regulations.

15.0 PUBLICATION POLICY

Neither complete nor any part of the results of the study obtained under this protocol, nor any information provided to the investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of ACRIN, the Study Chairs, and/or the ACRIN Publication Committee. Any investigator involved in this study is obligated to provide ACRIN with complete test results and all clinical data obtained from the participants in this protocol. Investigators will follow the ACRIN Publication Policy (available online at www.acrin.org/PublicationsPolicy.aspx).

16.0 INSTITUTIONAL MONITORING AND AUDITS

The investigator will permit study-related auditing and inspections of all study-related documents by the EC/IRB, government regulatory agencies, and ACRIN. The investigator will ensure the capability for inspection of all participating sites' study-related facilities (e.g. imaging centers, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits.

Oversight for this study at all sites will be provided by the investigator with delegation of appropriate responsibilities to sub-investigators and designated study personnel. They will ensure all entry criteria are met prior to the initiation of the protocol and all study procedures and reporting of adverse events are performed according to the IRB-approved protocol.

16.1 Monitoring

Monitoring ensures data quality and the rights, safety, and well-being of the participants are protected. Monitoring also makes certain that the trial is in compliance with the currently approved protocol/amendments, with GCP and applicable regulatory requirements. It will provide the site an opportunity to verify that reported trial data are accurate, complete and verifiable from source documents. Institutional monitoring will be implemented at several different time points during the conduct of the study.

Monitoring instructions will be sent to the site prior to the implementation of monitoring to aid in preparation for the review. The instructions will specify regulatory documents and participant case records scheduled to be monitored. CRFs and source documents of selected study participants enrolled at each site will be reviewed. In addition, the initial regulatory documents and any revised regulatory documents will also be monitored.

16.2 Audits

All participating institutions that enroll participants will be audited. The timing of the initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site-specific), the number of evaluable participants enrolled at an individual site, the status of the

protocol and pending amendments, and monitoring status. Generally, audits will be conducted after the number of evaluable participants reaches 20% of targeted accrual, either study-wide and/or site-specific. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate immediate auditing. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited. Additionally, site-specific circumstances may prompt an audit at any time.

Subsequent audits will be scheduled per the outcome of the initial audit. Audits can be conducted more frequently at the discretion of the protocol team. The audits will be conducted per procedures established by the Cancer Imaging Program (CIP) of the NCI. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. These instructions will specify which participant case records will be reviewed during the audit. On-site records will be verified against the submitted form, and the findings will be recorded on specially-prepared audit reports. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and ICFs will also be reviewed at the time of the audit visit. The ACRIN Audit Manual is available online at www.acrin.org/pdrc.aspx.

To help sites prepare for monitoring and audits and to assure that the investigator and the research staff maintain records appropriately, ACRIN Headquarters will offer training to sites. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial.

16.3 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ACRIN.

Source documents must verify the eligibility criteria and data submitted on all CRFs. If an item is not mentioned (e.g., history and physical examination alluding to a condition, but no mention of a psychological condition), it will be assumed it is not present.

Research records for each case should contain copies of the source documents for the data collected and reported to ACRIN. If data are abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. Every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol. This will prevent any discrepancies and the inability to verify the document and the data reported.

16.4 Case Report Forms (CRFs)

CRFs, both web-based and paper forms, are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank on paper CRFs because the procedure was not done or the question was not asked, “N/D” must be noted. If the item is not applicable to the individual case, “N/A” must be noted. All entries on paper CRFs must be printed legibly in black ink on the paper CRFs. In the event of any entry errors, corrections must be made by drawing a **single straight line** through the incorrect entry, writing **the initials of the person making the**

correction, recording the date when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser. Please refer to ICH Good Clinical Practice Guidelines.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be reviewed against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires must be available for review. Required study image interpretation data that are more detailed in information than the image and not typically documented in the standard radiology report may be documented on the CRF and are acceptable source documentation **if signed by the Investigator**. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date of the exam(s) from the medical record(s). Any use of approved CRFs as source documentation require a signature and date on the CRF with a reference to the information source (participant questionnaire, CT, MR, etc.). Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a major protocol deficiency.

16.5 Institutional Review Board

Sites must obtain initial local IRB approval to participate in ACRIN trials. Prior to participant registration, a copy of the IRB approval letter for the protocol and the ICF must be sent to ACRIN, along with a copy of the IRB-approved, site-specific ICF. Investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

17.0 STATISTICAL CONSIDERATIONS

17.1 Specific Aims and Analysis Plan

17.1.1 Primary Endpoints

Determine the NPV of PET/CT for staging the N0 neck based upon pathologic sampling of the neck lymph nodes, and determine PET/CT's potential to change treatment of the N0 neck.

To determine the NPV of PET/CT for staging the N0 neck, we will first dichotomize PET/CT test results according to the definition as described in Section 9.5. Then we will identify the true negative cases using the reference standard, determined by histopathology reports. The NPV will be estimated using the binomial distributed sample. The exact method will be used to construct the 95% CI.

17.1.2 Secondary Endpoints

17.1.2.1 *Estimate the sensitivity and diagnostic yield of PET/CT for detecting occult metastasis in the clinically N0 neck (both by neck and lymph node regions) or other local sites.*

Using the dichotomized PET/CT test results and the reference standard as defined above, we can estimate the sensitivity and construct the 95% CI. The diagnostic yield, defined as the ratio of cancers to total screened, will be estimated as a binomial proportion, and CI will be developed using appropriate asymptotic theory results.

17.1.2.2 *Determine the effect of other factors (e.g., tumor size, secondary primary tumors, location, or intensity of FDG uptake) that can lead to*

identification of patient subsets that could potentially forego neck dissection or provide preliminary data for subsequent studies.

Two approaches will be considered for this aim: (i) stratification, if the sample size permits, and (ii) regression modeling in which the various factors are entered as covariates in appropriately constructed regression models for binary outcomes.

17.1.2.3 *Analyze cost-effectiveness and cost-benefit of using PET/CT for staging of head and neck cancer versus current good clinical practices.*

To estimate cost-effectiveness we will estimate the ICER and compare it to standard reference values (e.g. $50,000/QALY to $100,000/QALY). Since the foundation of the CEA is a model, this is not a statistical test. We will explore the amount of uncertainty in the model through sensitivity analyses. For this aim, all patients with PET/CT imaging will be included in the analysis dataset.

17.1.2.4 *Evaluate the incidence of occult distant body metastasis discovered by whole body PET/CT.*

The incidence of occult distant body metastasis will be estimated using binomial distribution and the 95% CI will be constructed with the exact method. For this aim, all patients with PET/CT imaging will be included in the analysis dataset.

17.1.2.5 *Correlate PET/CT findings to CT/MRI and biomarker results.*

McNemar's test will be used to compare the paired proportions of dichotomized PET/CT and CT/MRI test results. The regression model will be used to evaluate the relationship between PET/CT findings and biomarker results. For this aim, all patients with PET/CT imaging will be included in the analysis dataset.

17.1.2.6 *Evaluate quality of life, particularly in participants whose patient management could have been altered by imaging results.*

QoL will be compared between treatment groups using tests that are appropriate to each instrument. Because their support is the positive real line, SF-36 scores, non-utility HUI scores, and UW-QoL scores will be compared using Student's t tests. The support for utility scores derived from the SF-6D and the HUI is the unit space and their difference will be evaluated using a two-proportion t test assuming unequal variances. For this aim, all patients with PET/CT imaging will be needed in the analysis dataset.

17.1.2.7 *Evaluate the PET/CT and biomarker data for complementary contributions to metastatic disease prediction.*

Logistic regression will be used to model the complementary effects of PET/CT and biomarker data, while the metastatic disease status is the response variable and PET/CT test results and biomarker data are predictors. For this aim, all patients with PET/CT imaging will be included in the analysis dataset.

17.1.2.8 *Compare baseline PET/CT and biomarker data to 2-year follow up as an adjunct assessment of their prediction of recurrence, disease-free survival, and overall survival.*

Cox regression will be used to model the associations of PET/CT test results and biomarker data (predictors) to recurrence, disease-free survival, and overall survival (censored responses). For this aim, all patients with PET/CT imaging will be included in the analysis dataset.

17.1.2.9 *Determine the proportion of neck dissections that are extended—additional levels clinicians intend to dissect beyond the initial surgery plan—based on PET/CT findings shared with the surgeon prior to dissection.*

One sample binomial proportion will be estimated and the exact method will be used for the construction of 95% CI.

17.1.2.10 *Estimate the optimum cutoff value of SUV for diagnostic accuracy of PET/CT scan.*

ROC method will be used to estimate the optimum cutoff value of SUV for diagnostic accuracy of PET/CT on N0 neck.[24]

17.1.2.11 *Evaluate the impact of PET/CT on the N0 neck across different tumor subsites (defined by anatomic location).*

NPV, sensitivity, diagnostic yield of PET/CT on the N0 neck will be calculated by tumor subsite—defined by anatomic location—using the same techniques as described above. The post-hoc stratification trend will be explored to determine if the staging of PET/CT on the N0 neck is dependent on tumor subsite.

17.2 Sample Size Consideration

Since the primary objective of this study is to estimate the NPV of PET/CT for staging the N0 neck, the sample size consideration has been primarily based on binding the half-length of the 95% CI of NPV. The desired half-length for this analysis is set at 0.05. At the same time, we also consider the effect of the proposed sample size on the half-length of 95% CI of PET/CT sensitivity. The desired half-length for this analysis is set at 0.1. The prevalence of true nodal positives after clinical diagnosis is assumed to be 25%.

We hypothesize that the proportion of negative test results of PET/CT is around 80%; and the NPV of PET/CT is at least 90%. Under this assumption, Table 3 shows that a sample of 250 participants would provide an exact half-length of 95% CI shorter than the target value 0.05. In case the proportion of negative PET/CT is different from 80% or the true NPV is different from 90%, we conducted a sensitivity analysis on the effect of the proposed sample size on half-lengths of CIs under various assumptions of true NPV and proportion of negative PET/CT. Under the proposed sample of 250 participants found in Table 3, all half-lengths of 95% CIs are shorter than 0.05, the desired half-length for this analysis.

Table 3. Half-length of exact 95% CI of NPV

P(Y=0)	N	NPV					
		0.90	0.91	0.92	0.93	0.94	0.95
0.9	200	0.0465	0.0446	0.0424	0.0401	0.0376	0.0348
	250	0.0414	0.0396	0.0377	0.0356	0.0334	0.0309
0.8	200	0.0495	0.0474	0.0452	0.0428	0.0401	0.0372
	250	0.0440	0.0421	0.040	0.0379	0.0355	0.0329
0.7	200	0.0532	0.0509	0.0485	0.0459	0.0431	0.0400
	250	0.0472	0.0452	0.0431	0.0407	0.0382	0.0354

Table 4 lists the half-length of 95% CI of PET/CT specificity. It is clear that when the true specificity is above 80%, the half-length is always shorter than 0.06.

Table 4. Half-length of 95% CI of PET/CT specificity

N	Spe=0.75	Spe=0.8	Spe=0.85	Spe=0.9
200	0.072	0.066	0.059	0.050
250	0.064	0.059	0.053	0.044

Table 5 lists the half-length of 95% CI of PET/CT sensitivity. For the proposed sample of 250 participants, when the true sensitivity is above 75%, the half-length is always shorter than 0.1—the target value for one of the secondary aims.

Table 5. Half-length of 95% CI of PET/CT sensitivity

N	Sen=0.75	Sen=0.8	Sen=0.85	Sen=0.9
200	0.110	0.101	0.090	0.076
250	0.098	0.091	0.081	0.068

Table 6 assumes that 80% of all cases will turn out negative by PET/CT and shows the exact 95% CIs. These are exact intervals that will be obtained if the observed values of NPV are as specified in the second column. Even if the observed NPV is 98%, the two sided interval will still touch the value of 95%.

Table 6. 95% CI for NPV greater than 90%

N of PET Negative Cases	Sample Proportion of True Negatives	95% CI Lower Limit for NPV	95% CI Upper Limit for NPV	95% CI Length for NPV
200	0.900	0.850	0.938	0.088
200	0.910	0.861	0.946	0.084
200	0.920	0.873	0.954	0.080
200	0.930	0.885	0.961	0.076
200	0.940	0.898	0.969	0.071
200	0.950	0.910	0.976	0.066
200	0.960	0.923	0.983	0.060
200	0.970	0.936	0.989	0.053
200	0.980	0.950	0.995	0.045

Based on all of these factors, we believe that a sample of 250 participants would be sufficient for both the primary analysis and part of the experimental analysis. Due to the random nature of the observed number of negative PET/CTs, a sample size correction technique attributed to Pepe[39] needs to be applied. Our calculation shows that after adding 15 extra participants, the chance of having at least 200 PET/CT negative tests is greater than 95%, which is good enough to guarantee that recruited participants will include the desired number of negative PET/CT test results.

After an additional 10% inflation to account for potentially incomplete data, we arrive at an overall sample size of 292 participants.

17.3 Sample Size/Accrual Rate

The planned sample size is 292 participants at a minimum of 10 institutions, to be accrued over 2 years. Should fewer than 50 participants be accrued in one year, the trial will be re-assessed.

17.4 Methods for Futility Analysis

We will carry out two (2) futility analyses in the middle of the study, using the first 50 or 100 PET/CT negative patients identified, to decide if the study should be stopped based on evidence that the NPV is too low to be clinically useful. The hypothesis testing will be used for this purpose and can be formulated as follows:

H_0 (null hypothesis): $p \geq 0.90$
H_A (alternative hypothesis): $p < 0.90$

p stands for the true NPV. The significance level (α) is set at 0.01. If H_0 is rejected, then we will stop the study.

Table 7 lists the power that can be achieved at different proportions given H_A. Specifically, out of the first 50 PET/CT negatives, if we observe no more than 39 truly negative N0 neck patients, we will reject the null hypothesis and stop the study; out of the first 100 PET/CT negatives, if we observe no more than 81 truly negative N0 neck patients, we will reject the null hypothesis and stop the study.

Table 7. Power calculation at different proportions given HA

Power	N	Proportion Given H_0	Proportion Given H_A	Significance Level (α)	Reject H_0 if R* ≤ This
0.7378	50	0.9000	0.7500	0.0100	39
0.6822	50	0.9000	0.7600	0.0100	39
0.6210	50	0.9000	0.7700	0.0100	39
0.5552	50	0.9000	0.7800	0.0100	39
0.4864	50	0.9000	0.7900	0.0100	39
0.4164	50	0.9000	0.8000	0.0100	39
0.3473	50	0.9000	0.8100	0.0100	39
0.2813	50	0.9000	0.8200	0.0100	39
0.2203	50	0.9000	0.8300	0.0100	39
0.1661	50	0.9000	0.8400	0.0100	39
0.1199	50	0.9000	0.8500	0.0100	39
0.9370	100	0.9000	0.7500	0.0100	81
0.9038	100	0.9000	0.7600	0.0100	81
0.8585	100	0.9000	0.7700	0.0100	81
0.7991	100	0.9000	0.7800	0.0100	81
0.7252	100	0.9000	0.7900	0.0100	81
0.6379	100	0.9000	0.8000	0.0100	81
0.5403	100	0.9000	0.8100	0.0100	81
0.4374	100	0.9000	0.8200	0.0100	81
0.3359	100	0.9000	0.8300	0.0100	81
0.2424	100	0.9000	0.8400	0.0100	81
0.1628	100	0.9000	0.8500	0.0100	81

17.5 Reporting Guidelines

Routine reports for this protocol will be included in the ACRIN BC Mid-Year and Year End Updates and will be provided to oversight bodies, including DSMC for review during each of its twice-yearly meeting.

Routine reports will include:

- Accrual and participant characteristics;
- Timeliness and completeness, eligibility and protocol compliance, and outcome data;
- All reported adverse events.

REFERENCES

1. Schoder H, Yeung HW. Positron emission imaging of head and neck cancer, including thyroid carcinoma. *Sem Nucl Med*. 2004;34(3):180–197.
2. McHam SA, Adelstein DJ, Rybicki LA, et al. Who merits a neck dissection after definitive chemoradiotherapy for N2-N3 squamous cell head and neck cancer? *Head Neck*.. 2003;25:791–798.
3. Sanguineti G, Corvo R, Benasso M, et al. Management of the neck after alternating chemoradiotherapy for advanced head and neck cancer. *Head Neck*.1999;21:223–228.
4. Frank DK, Hu KS, Culliney BE, et al. Planned neck dissection after concomitant radiochemotherapy for advanced head and neck cancer. *Laryngoscope*. 2005;115:1015–1020.
5. O'Brien C, Smith J, Soong S, et al. Neck dissection with and without radiotherapy—prognostic factors, patterns of recurrence and survival. *Am J Surg*. 1986;152:456-463.
6. Leemans CR, Tiwari R, Nauta JJ, et al. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. *Cancer*. 1994;73:187-190.
7. Velazquez RA, McGuff HS, Sycamore D, Miller FR. The role of computed tomographic scans in the management of the N-positive neck in head and neck squamous cell carcinoma after chemoradiotherapy. *Arch Otolaryngol Head Neck Surg*. 2004;130:74–77.
8. Prim MP, De Diego JI, Verdaguer JM, et al. Neurological complications following functional neck dissection. *Eur Arch Otorhinolaryngol*. 2006:263(5): 473-476. Epub Dec 2005.
9. Schoder H, Yeung HW, Gonen M, Kraus D, Larson SM. Head and neck cancer: clinical usefulness and accuracy of PET/CT image fusion. *Radiology*. 2004;231:65–72.
10. Branstetter BF IV, Blodgett TM, Zimmer LA, et al. Head and neck malignancy: Is PET/CT more accurate than PET or CT alone? *Radiology*. 2005;235:580–586.
11. Connell CA, Corry J, Milner AD, et al. Clinical impact of, and prognostic stratification by, F-18 FDG PET/CT in head and neck mucosal squamous cell carcinoma. *Head Neck*. 2007;29:986–995
12. Patel SG, Shah JP. TNM staging of cancers of the head and neck: striving for uniformity among diversity. *CA Cancer J Clin*. 2005;55:242–258.
13. Song T, Bi N, Gui L, Peng Z. Elective neck dissection or "watchful waiting": optimal management strategy for early stage N0 tongue carcinoma using decision analysis techniques. *Chin Med J (Engl)*. 2008;121(17):1646-1650.
14. Gourin CG, Conger BT, Porubsky ES, et al. The effect of occult nodal metastases on survival and regional control in patients with head and neck squamous cell carcinoma. *Laryngoscope*. 2008;118(7):1191-1194.
15. Laubenbacher C, Saumweber D, Wagner-Manslau C, et al. Comparison of fluorine-18-fluorodeoxyglucose PET/CT, MRI and endoscopy for staging head and neck squamous-cell carcinomas. *J Nucl Med*. 1995;36(10):1747-1757.

16. Adams S, Baum RP, Stuckensen T, Bitter K, Hör G. Prospective comparison of 18F-FDG PET/CT with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. *Eur J Nucl Med*. 1998;25(9):1255-1260.

17. Sigg MB, Steinert H, Grätz K, et al. Staging of head and neck tumors: [18F]fluorodeoxyglucose positron emission tomography compared with physical examination and conventional imaging modalities. *J Oral Maxillofac Surg*, 2003. 61(9):1022-1029.

18. Ng S-H, Yen T-C, Liao C-T, et al. 18F-FDG PET/CT and CT/MRI in oral cavity squamous cell carcinoma: A prospective study of 124 patients with histologic correlation. *J Nucl Med*. 2005;46(7):1136-1143.

19. Kyzas PA, Evangelou E, Denaxa-Kyza D, Ioannidis JP. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. *J Natl Cancer Inst*. 2008;100(10):712-720.

20. Persky MS, Lagmay VM. Treatment of the clinically negative neck in oral squamous cell carcinoma. *Laryngoscope.*1999;109(7 Pt 1):1160-1164.

21. Aluffi P, Pisani P, Policarpo M, Pia F. Contralateral cervical lymph node metastases in pyriform sinus carcinoma. *Otolaryngol Head Neck Surg*. 2006;134(4):650-653.

22. Lim YC, Lee JS, Koo BS, et al. Treatment of contralateral N0 neck in early squamous cell carcinoma of the oral tongue: elective neck dissection versus observation. *Laryngoscope*. 2006;116(3):461-465.

23. Lim YC, Lee SY, Lim JY, et al. Management of contralateral N0 neck in tonsillar squamous cell carcinoma. *Laryngoscope*. 2005 Sep;115(9):1672-1675.

24. Gallo O, Fini-Storchi I, Napolitano L. Treatment of the contralateral negative neck in supraglottic cancer patients with unilateral node metastases (N1-3). *Head Neck*. 2000;22(4):386-392.

25. Ng SH, Yen T-C, Chang JT, et al. Prospective study of [18F]fluorodeoxyglucose positron emission tomography and computed tomography and magnetic resonance imaging in oral cavity squamous cell carcinoma with palpably negative neck. *J Clin Oncol*. 2006;24(27):4371-4376.

26. Schroeder U, Dietlein M, Wittekindt C, et al. Is there a need for positron emission tomography imaging to stage the N0 neck in T1-T2 squamous cell carcinoma of the oral cavity or oropharynx? *Ann Otol Rhinol Laryngol.* 2008;117(11):854-863.

27. Schoder H, Carlson DL, Kraus DH, et al. 18F-FDG PET/CT for detecting nodal metastases in patients with oral cancer staged N0 by clinical examination and CT/MRI. *J Nucl Med.* 2006;47(5):755-762.

28. Nahmias C, Carlson ER, Duncan LD, et al. Positron emission tomography/computerized tomography (PET/CT) scanning for preoperative staging of patients with oral/head and neck cancer. *J Oral Maxillofac Surg.* 2007;65(12):2524-2535.

29. Hafidh MA, Lacy PD, Hughes JP, Duffy G, Timon CV. Evaluation of the impact of addition of PET to CT and MR scanning in the staging of patients with head and neck carcinomas. *Eur Arch Otorhinolaryngol.* 2006;263(9):853-859.

30. Lowe VJ, Hollenbeak CS, Stack, Jr. BC. Decision tree analysis in the treatment of the N0 neck. *Cancer*. 2001;92:2341-2348.

31. Curtin HD, Ishwaran H, Mancuso AA, et al. Comparison of CT and MR imaging in staging of neck metastases. *Radiology.* 1998;207(1):123-130.

32. Fakhry C, Westra W, Li S, et al. Prognostic significance of human papillomavirus (HPV) tumor status for patients with head and neck squamous cell carcinoma (HNSCC) in a prospective, multi-center phase II clinical trial. *J Clin Onc*; 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 6000

33. Linkov F, Lisovich A, Yurkovetsky Z, et al. Early detection of head and neck cancer: development of a novel screening tool using multiplexed immunobead-based biomarker profiling. *Cancer Epidemiol Biomarkers Prev*. 2007;16(1):102-107.

34. Green FL, Page DL, Fleming ID, et al (eds): *AJCC Cancer Staging Manual* (ed 6). New York, NY, Springer-Verlag, 2002.

35. Murakami R, Uozumi H, Hirai T, et al. Impact of FDG-PET/CT imaging on nodal staging for head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2007;68(2):377-382.

36. Schmidt M, Schmalenbach M, Jungehülsing M, et al. ^{18}F-FDG PET for detecting recurrent head and neck cancer, local lymph node involvement and distant metastases. Comparison of qualitative visual and semiqualitative analysis. *Nuklearmedizin*. 2004;43(3):91-101; quiz 102-104.

37. Lester SC, ed. *Manual of Surgical Pathology*. Chapter 27: Lymph nodes, spleen, and bone marrow. Philadlephia: Churchill Livingstone. 2001;293-296.

38. Westra WH, Hruban RH, Phelps TH, Isacson C, eds. *Surgical Pathology Dissection. An Illustrated Guide*. Chapter 5: Lymph Nodes. Second Edition. New York: Springer. 2002;34-36.

39. Pepe, MS. *The Statistical Evaluation of Medical Tests for Classification and Prediction*. Oxford University Press. 2003.

40. McIntosh MW, Pepe MS. Combining several screening tests: optimality of the risk score. *Biometrics*. 2002; 58(3):657-664.

41. Gold MR, Siegel JE, Russell LB, Weinstein MC (eds). *Cost-effectiveness in health and medicine.* New York:Oxford University Press, 1996.

42. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13(4):322-338.

APPENDIX I: INFORMED CONSENT FORM TEMPLATE

ACRIN 6685

A MULTICENTER TRIAL OF FDG-PET/CT STAGING OF HEAD AND NECK CANCER AND ITS IMPACT ON THE N0 NECK SURGICAL TREATMENT IN HEAD AND NECK CANCER PATIENTS

[Note: The American College of Radiology Imaging Network (ACRIN) complies with the privacy measures put forth by the Health Insurance Portability and Accountability Act (HIPAA). However, ACRIN does not monitor compliance with HIPAA; that is the responsibility of the local institutions and their Institutional Review Boards (IRBs). Local IRBs may choose to combine the authorization elements in the informed consent.]

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. You are being invited to participate in this research study. Clinical trials include only people who choose to take part. Please take your time in deciding whether you want to be involved in the clinical trial. You are encouraged to discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you should ask your study doctor for more explanation.

This document is to help you to understand what will happen in the study, why the study is being done, and what risks or benefits might be involved in the study as you talk with your study doctor. If you decide to volunteer for this study, you will be asked to sign and date this form. This form must be signed before you can participate in the study and before any study procedures are performed.

If you want more information about being a part of clinical trials, ask your study doctor for a copy of the National Cancer Institute (NCI) booklet *Taking Part in Cancer Treatment Research Studies*. You can learn more about clinical trials at http://cancertrials.nci.nih.gov or by calling the NCI's help line at 1-800-4-CANCER (1-800-422-6237 or TTY: 1-800-332-8615).

You are being asked to be in this trial because you have been newly diagnosed with head and neck cancer. This clinical trial for head and neck cancers involves FDG-PET/CT. FDG stands for fluorodeoxyglucose, a radioactive drug/tracer. PET stands for positron emission tomography and CT stands for computed tomography. PET/CT is a unique imaging technology that combines two imaging modalities, PET images and CT images, into one image.

WHY IS THIS STUDY BEING DONE?

Today, treating doctors diagnose a person with neck cancer by a physical examination and MRI (magnetic resonance imaging) or CT scans then decide whether a patient needs surgery. This purpose of this study is to see if doctors can use a different technology to look inside the neck—by using FDG-PET/CT—to learn more about cancers in the neck. They hope to see if the FDG-PET/CT will clearly show whether there is cancer in the lymph nodes in the neck and if surgeons may change their treatment plans for surgery because of the FDG-PET/CT scan.

FDG-PET/CT is technology that uses an injection of a small amount of a radioactive drug/tracer (a chemical similar to sugar which is called FDG). The PET/CT can pick up where this imaging

agent creates "hot spots" from within cancer cells. Some doctors believe PET/CT of the neck and the rest of the body may be able to tell doctors when the neck has no cancer or may catch more cancer in the neck than can be found by physical examination, MRI and/or CT scans, and surgery alone.

General Information about the Types of Scans

About FDG-PET Scan

PET is a nuclear medicine medical imaging technique that produces a 3-D image of functional processes in the body.

About CT Scan

A CT scanner is a special kind of X-ray machine. Instead of sending out a single X-ray through your body as with ordinary X-rays, several beams are sent simultaneously from different angles. The computer processes the results, displaying them as a two-dimensional picture shown on a monitor.

About FDG-PET/CT Scan

Many PET scanners also include a CT scanner. This allows images of both anatomy (CT) and function (PET) to be taken during the same examination. The FDG-PET/CT scan has the benefit of combining the PET scan information about cell function with the CT scan information about the size and shape of abnormal cells. Alone, each test has its limitations but when the results of the scans are fused together they provide the most complete information on cancer cell function and location.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 292 people with head and neck cancer will take part in this study from across the country.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you agree to take part in this study and are determined to be eligible by your study doctor, you will be asked to read and sign this consent form before you are enrolled to participate in this trial and before any study procedures are performed. After you are enrolled into the study, you will have the following tests and procedures.

<<Foreign sites are exempt from submitting tissue samples for the study. Site-specific informed consent forms should be adjusted accordingly.>>

As part of this study, reports and slides from your biopsy tissue samples will be sent to ACRIN for quality review at a central pathology laboratory. Samples of your tumor tissue may be obtained from a biopsy or from surgery for analysis as part of this study. You will not need to have any additional biopsies to participate in the study.

See the Study Chart at the end of this section for a visit-by-visit outline of what will be expected of you if you decide to participate in this trial.

Standard medical procedures that are part of regular cancer care and would probably be done even if you do not join the study:

- Medical history;
- Physical examination;
- Diagnostic MRI and/or CT scan(s);
- Surgery to remove lymph nodes from your neck;
- Pregnancy test (if applicable).

Standard medical procedures that are being done specifically because you are in this study (these may or may not be done if you were not in this study):

- One (1) PET/CT scan with FDG before your surgery;
- Glucose levels checked before the PET/CT scan;
- Questionnaires—you will be asked to complete questionnaires four (4) times, before and after surgery (after 30 days, year 1, and year 2 after surgery) to help study doctors understand your quality of life. The questionnaires should take you about 30 minutes total each time you complete them. You will be contacted via mail and/or telephone to complete the questionnaires;
- ***Optional:*** About one (1) tube of blood taken (10 mL, which is less than 2 teaspoons).

<<Foreign sites should remove reference to blood sample collection from local informed consent form versions as they are exempt from blood collection and submission.>>

Blood sample collection—this is an optional procedure:

Your study doctors would like to collect, ship, and store your blood at MD Anderson Cancer Center in Houston, TX, USA, until it is transferred to the University of Pittsburgh for analysis according to the protocol by Luminex Corporation. This is an optional procedure in this study, so you may choose to be in the study but not to have the blood sample collection. If you agree, the blood specimens will be collected, stored, and used for this study to learn more about this and other diseases. All your personal information will be removed from the sample before it is shared and stored.

If you agree, you will have about one (1) tube of blood (10 mL, which is less than 2 teaspoons) taken from the IV catheter placed in your arm for the FDG administration.

The blood sample will be given only to the approved researchers and will not be sold. The research done with your blood will probably not help you but it may help other people with cancer in the future. Reports about the research done with your blood will not be given to you or your treating doctor. No genetic testing will be conducted with these blood samples. These reports will not be put into your medical records and it will not have an effect on your care.

I agree to participate in the blood sample collection and storage for this study.

☐ **YES** ☐ **NO** _____ **Participant's Initials**

Before surgery: You will be asked to have one (1) FDG-PET/CT scan before you have your neck surgery.

If you have had a PET/CT scan has previously been performed outside of *<<this institution>>*, a repeat scan will be performed at *<<this institution>>* at no additional cost to you. This repeat scan will include: One FDG-PET/CT scan and sedation before the scan if appropriate.

Preparation for a PET/CT scan: On the day of the FDG-PET/CT scan, do not eat for 4 to 6 hours before your appointment time and drink only water. You will be given details of what to do to prepare for your PET/CT scan.

During the exam: On the day of your FDG-PET/CT scan, you first will be given an injection of a small amount of a radioactive drug/tracer (a chemical similar to sugar which is called FDG) into a vein in your arm or hand. The amount of radiation from the FDG and from the CT scan is each small, no more than what you would have during a normal x-ray. It only stays in your body for a few hours. The FDG will travel to particular parts of your body. It travels to places where glucose is used for energy. It can show cancer because the cancer cells use glucose in a different way from normal tissue.

The PET/CT scanner is a large machine with a hole in the middle. It looks like a donut with a table in the middle. Approximately 30 to 60 minutes after the injection of FDG, you will be asked to go to the bathroom (urinate) and then lie on a partially enclosed scanning table. The table will slide into the scanning machine. You will be asked to remain still during the scan. You will hear buzzing or clicking sounds during the scan. You will need to lie still for about 20 to 60 minutes before coming off of the scanning table.

The size of the scanner opening is 27 to 30 inches. How much space you feel you have around you will depend on your body size and the scanner type. If you feel any anxiety over being in enclosed spaces, let your study doctor know. A mild sedative may help you feel more comfortable during the exam.

Time required: The entire FDG-PET/CT scan procedure is expected to take no more than 2 hours.

Follow up: Within two weeks after you have had your FDG-PET/CT scan, you will undergo neck surgery. The surgery is part of the usual treatment for your neck cancer. The FDG-PET/CT image taken as part of the study will be given to your surgeon prior to surgery and may change your surgeon's decision about the extent of your surgery.

Your treating doctor will be asked to inform the study doctors about your health, including any radiation or chemotherapy that you undergo, and your disease status until the end of the study. You will follow up with your treating doctor at regular intervals according to her/his recommendations and usual practice. Information gathered by your treating doctor as part of your normal follow-up visits will be given to your study doctors for two (2) years so they can find out more about your health and costs related to your health care. Your follow-up care will be decided between you and your treating doctor.

Study follow up will include a series of three (3) quality of life questionnaires, which will be mailed to you at 30 days, 1 year, and 2 years after your surgery. You should expect it will take you about a half an hour (30 minutes) to complete the questionnaire each time. You will be asked

to supply contact information so that research staff can mail the forms to you for completion and call you if they do not receive the forms or if you need help completing them.

STUDY CHART

VISIT 1: Screening/Eligibility	• Sign this informed consent form; • Provide medical history; • Have a physical examination; • Complete a quality-of-life questionnaire; • Provide CT and/or MR images taken within the six (6) weeks prior to enrollment; • Have a pregnancy test, if applicable.
VISIT 2: FDG-PET/CT Imaging Within 14 Days Prior to Surgery	• Have an intravenous (IV) catheter placed in a vein in your arm; • Have your blood sugar checked; • If you agree, have one (1) tube of blood (10 mL, which is less than 2 teaspoons) drawn *<<US sites only>>*. • Have the FDG agent injected into the IV; • About an hour (60 minutes) after the FDG is injected, have the PET/CT scan; • Tell your study doctor how you feel after and/or throughout the imaging scan.
VISIT 3: Day of Surgery	• Your surgeon will have the FDG-PET/CT scan images available prior to surgery. Your surgical treatment plan will be determined by your surgeon; • Reports and slides from samples of the tissue removed from your neck, called an "excision," will be collected (slides from US sites only).
VISIT 4: Thirty (30) Day Telephone Follow Up After Surgery	• Receive quality-of-life questionnaire in the mail to complete and return to the study doctors (if you do not complete and return the questionnaire, research staff will contact you to remind you or to complete the questionnaire with you).
VISIT 5: One (1) Year Follow Up After Surgery	• Follow up with your treating doctor per his/her recommendation; • Receive quality-of-life questionnaire in the mail to complete and return to the study doctors (if you do not complete and return the questionnaire, research staff will contact you to remind you or to complete the questionnaire with you).
VISIT 6: Two (2) Year Follow Up After Surgery	• Follow up with your treating doctor per his/her recommendation; • Receive quality-of-life questionnaire in the mail to complete and return to the study doctors (if you do not complete and return the questionnaire, research staff will contact you to remind you or to complete the questionnaire with you).

HOW LONG WILL I BE IN THE STUDY?

You will be actively involved in the study for more than two (2) years. The study FDG-PET/CT imaging for the study will happen in one (1) day, but your study doctors would like to know about how you are doing, your quality of life, and if you incurred more health-related costs after your neck surgery.

This study is expected to end after all study participants have completed the visits and all the information has been collected. This study may be stopped at any time by your study doctor, ACRIN, Food and Drug Administration (FDA), or National Cancer Institute (NCI) without your consent because:

- Your health or safety may be at risk;
- You have not been following study instruction;
- New information becomes available that might change your mind about participating in the trial;
- A study administrative decision made by the study doctor, ACRIN, FDA, or NCI.

These actions do not require your consent, but you will be informed of any of these decisions if such a decision is made.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your treating doctor first. Withdrawal will not interfere with your future care. There will be no penalty for deciding not to participate.

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS OF THE STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the FDG-PET/CT scan. In some cases, side effects can be serious, long lasting or may never go away.

Risks Associated with Intravenous Catheter Placement:

Likely

- Minor discomfort;
- Pain in the injection site.

Less Likely

- Bleeding;
- Infection;
- Bruising.

Risks Associated with FDG:

Rare

- An allergic-type.

Risks Associated with PET/CT Scans:

- Discomfort;
- Claustrophobia.

Other Risks Associated with CT Scans:

Rare
Malfunction of worn or implanted electronic medical devices. If you wear or have electronic medical devices implanted, such as a pacemaker or a drug pump, please make sure you tell your study doctors and research staff. It was recently reported by the FDA that the CT scan may cause problems for electronic medical devices.

Risks Associated with Radiation Exposure from FDG-PET/CT Scans:

<<Each site may need to modify this section to quote the correct CT dosimetry for its own PET/CT and CT scanners in accordance with its own institutional policies and procedures.>>
For example:
This research study involves exposure to radiation from *1* FDG-PET/CT scan. The radiation exposure you will receive is equal to a uniform whole-body exposure of approximately *14* mSv (a measure of radiation exposure), with approximately *11* mSv from the injected radioactive FDG and *3* mSv from the CT component. This is about *30%* of the allowable annual dose of 50 mSv for radiation workers (for example, x-ray technicians). The risk from this level of radiation exposure is too small to be measured and is small when compared with other everyday risks.

If you would like more information about radiation exposure associated with the PET and CT scans, please speak with your study doctor.

Reproductive Risks:

Because the radiation from PET/CT scans can damage an unborn baby, you should not become pregnant or father a baby while on this study. These days, some doctors tell patients undergoing PET scans that they should not have close contact with pregnant women, babies, and young children for a few hours after their scan. If you are breast feeding, you have to express enough milk beforehand to get your baby through the first 6 hours after the scan. This is not because there will be radiation in the milk. It is because the mother should not be holding the baby closely during the time the radiation is in her body. Some doctors recommend you get someone else to feed the baby for 24 hours, although it is safe for you to express more milk for those feeds from 6 hours after the scan.

If you are a woman who can become pregnant, you must agree to a pregnancy test (blood test) before becoming part of the study. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study.

For more information about risks and side effects, ask your study doctor.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. The PET/CT imaging results may impact the surgery you need to remove possible cancers from your neck. Your PET/CT

imaging results will be given to your surgeon prior to surgery, but how the imaging results will effect his or her decisions is unknown. The information and knowledge from this study could help doctors decide on the best treatment for people with neck cancer in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO PARTICIPATE?

You may choose not to take part in this study. If you choose not to participate, there will be no penalty or loss of benefits to which you are otherwise entitled. You can choose not to have a PET/CT done for this study. If you choose not the have a PET/CT with this study, you can still be treated per standard of care at this institution. You can have surgery as originally planned. Please talk with your treating doctor about your options.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that your personal information will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. Records of your participation on this study, your progress, blood specimens (from US sites only), tissue specimens (from US sites only), and images submitted (such as CT and/or MRI and PET/CT scans) while you are on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia, and at the University of Arkansas for blood and tissue specimens (de-identified prior to delivery). Your personal information may be given out if required by law.

Authorized representatives of ACRIN, Center for Statistical Sciences at Brown University, the Food and Drug Administration (FDA), the National Cancer Institute (NCI) and its agents and contractors, the Institutional Review Board (IRB) of *<<Institution>>*, and other groups or organizations that have a role in this study may, without obtaining additional consent from you, have inspect and/or copy both your medical and research records, including the results of your participation in this study. This access is necessary to ensure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner in which you cannot be identified.

Your research records and images will be kept permanently on file at ACRIN and may be used for future research. It may also be used as the basis for publications by investigators deemed qualified by ACRIN. However, all tissue and blood collected for this trial will be studied as described in the protocol and then will be destroyed. No future research will be conducted on these specimens. All data sent to ACRIN over the Internet will be coded so that other people cannot read it. All personal identifiers will be removed and replaced with a unique identifying number to protect your identity. The research that may be done with the information will not specifically help you. But, it might help people who have cancer and other diseases in the future.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Taking part in this study may lead to added costs to you or your insurance company. FDG-PET/CT scans for neck cancer are usually covered by most insurance companies, but this is not guaranteed. The study will reimburse for the FDG-PET/CT if it is a repeat at baseline, such as if you have had a previous FDG-PET/CT scan and need to have another for the trial. The study also

will pay for all blood collection and biomarker assessment costs without charge to you. Please ask your study doctor(s) about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, *<<insert name>>*, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at *<<insert telephone number>>*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is your choice. You may choose to take part or not to take part in the study. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you decided to participate, you are free to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not interfere with your future care. You can still get your medical care from our institution.

During the study, we may find out more information that could be important to you. We will tell you about new information or changes in the study that may affect your health or your willingness to continue with the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

This document explains your rights as a study participant. It you have any questions regarding your participation in this research study or you have any questions regarding your rights as a research participant, do not hesitate to speak with your study doctor or anyone listed below.

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, *<<insert name>>*, at *<<insert telephone number>>*.

For questions about your rights while taking part in this study call the *<<insert name IRB contact person>>* at *<<insert name of the IRB>>* Institutional Review Board (a group of people who review the research to protect your rights) at *<<insert telephone number>>*.

(Provide the name of a local IRB contact person)

_____	_____
Name	Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

Visit the NCI's Web sites for clinical trials information http://cancertrials.nci.nih.gov**,** or for cancer information visit http://cancernet.nci.nih.gov. ACRIN's Web site is www.acrin.org.

ACKNOWLEDGEMENT

When you sign this document, you are agreeing to take part in this study. This means you have read all the above information, asked questions regarding your participation, and received answers that you understand to all your questions. You have also had the opportunity to take this consent form home for review or discussion if you want to. A copy of the signed consent will be given to you.

You willingly give your consent to participate in this study.

_____	_____	_____
Printed Name of Study Participant/ Legal Representative	Signature	Date

<Insert other signature and date lines as appropriate per local IRB policies and procedures>

APPENDIX II: SUPPLEMENTAL MATERIALS AVAILABLE ONLINE

ACRIN 6685

Supplemental materials that support the conduct of the trial are available on the ACRIN Web site at the ACRIN 6685 Protocol Web page (www.acrin.org/6685_protocol.aspx). Types of materials posted include:

- Application and protocol activation documents (General Qualifying and Protocol Specific Applications, protocol activation checklist, etc.);
- Data forms;
- Imaging materials (Image Transmittal Worksheet, imaging parameter charts, and scanning and image qualification instructions);
- Quality assessment submission details, provided in the ACRIN 6685 Pathology Manual (instructions for submitting tissue specimen slides and reports, available online at www.acrin.org/6685PathologyLabMaterials.aspx);
- Blood collection, processing, and shipping instructions provided in the ACRIN 6685 Blood Collection Manual are available online at www.acrin.org/6685PathologyLabMaterials.aspx;
- Recruitment and education materials;
- Regulatory resources;
- Participating site list.

For more information related to the trial, contact the ACRIN 6685 Contact Personnel link on the above-mentioned Web page for a list of protocol team members at ACRIN Headquarters and their roles.

APPENDIX III: SURGERY AND PATHOLOGY DEFINITIONS AND GUIDANCE QUICK SHEET

ACRIN 6685

Neck Dissection Specimens Surgery

- This protocol does not proscribe the type of neck dissection performed other than it must include either zones I, II, and III **or** zones II, III, and IV and in some cases I (floor of mouth and anterior tongue) to be dissected. However, a minimum of 2 mm margins are requested for standardization across participating sites.
- Surgeons will have knowledge of PET/CT results to guide inclusion of any additional suspected nodal disease in the dissection, and will need to report revisions to surgical care as ordinarily practiced based on knowledge of the PET/CT results.
- Surgeons are responsible for identification of discrete nodal levels, and side of neck from whence they were dissected, for pathology submission and processing.
- Definition of nodal levels:
    - I: submandibular triangle. If level Ia is dissected, it must be indicated on the case report form. It is optional to submit these nodes separately.
    - II: jugulodigastric. These are defined as the jugular chain from the skull base to the level of the greater cornu of the hyoid. If level IIb is dissected, this must be indicated on the case report form although it is optional to submit these nodes separately. Level "IIb" nodes are defined as: nodal tissue between the 11^{th} cranial nerve and the anterior border of the trapezius muscle.
    - III: mid jugular chain. From the cornu to the omohyoid muscle.
    - IV: jugular chain below the omohyoid.
    - V: posterior triangle.
    - VI: tracheoesophageal groove, midline tissue from the hyoid to the innominate artery (on the right) or the level of the clavicle (on the left).

Pathology

- Each level is submitted in a separate, marked specimen container for permanent pathology indicating its side of origin.
- Marked fresh tissue specimens are then to be sent to pathology.
- Formalin fixed tissues will be imbedded in paraffin blocks. A slice will be taken through each node in the nodal level specimen. Each slice will be stained for hematoxylin and eosin (H&E) and read out by the local pathologist.
- The final pathology report will contain a list of nodal levels submitted, total number of nodes found in each level, and number of nodes positive for metastatic SCC. Comments regarding extra-capsular spread, maximum size of tumor deposit, and necrosis when present, are required.
- Pathology reports will be submitted along with a pathology transmittal form to the ACRIN central site.
- The slice adjacent to all positive node slices will be mounted, unstained, and sent for central archive and possible interpretation. If a slice is unavailable due to complete processing of the nodal specimen, an extra slide may be submitted.