Local Protocol #: *Please insert your local protocol # for this study.*

TITLE:

A single-arm, Phase II study of thoracoscopic lung cancer staging with the use of Intraoperative Ultrasound at the time of definitive resection

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University of Kentucky

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SCHEMA

All patients undergoing video-assisted thoracoscopic (VATS) resection of lung cancer will receive standard therapy including lobectomy or sub-lobar resection and mediastinal lymph node dissection. After completion of the standard of care, intraoperative ultrasound will be used to evaluate lymph node stations for the presence of any missed lymph nodes with particular focus on lymph nodes which may appear pathologic on ultrasound evaluation.

Additional lymph nodes which are found by ultrasound evaluation will be resected and sent with the standard specimen for evaluation of presence of tumor.

Patients will receive standard-of-care treatment in the postoperative period, including adjuvant therapy as dictated by final pathologic stage.

Data will be reviewed for rates of pathologic upstaging, and sensitivity and specificity of ultrasound as an additional diagnostic tool in the operating room will be evaluated.

Patients with NSCLC appropriate for
VATS lung resection

Successful surgical procedure including standard mediastinal lymph node dissection)

Intraoperative U/S evaluates nodal stations
for presence of additional and possibly pathologic nodes

Resection of U/S identified nodes

Pathologic evaluation of both standard resection and U/S-guided resected nodes

TABLE OF CONTENTS

1. OBJECTIVES

Hypothesis: Intra-operative thoracoscopic ultrasound following standard video-assisted thoracoscopic (VATS) dissection will increase the rate of pathologically staged in N2 nodes in non-small cell lung cancer patients undergoing definitive surgical resection. (H_0: upstaging rate of 2% vs H_1: upstaging rate of 8%)

1.1 Primary Objectives

To determine the rate of detection of occult pathologic N2 lymph nodes with the addition of intra-operative ultrasound to VATS.

1.2 Secondary Objectives

- Evaluate surgical complication rate
- Measure time to perform the evaluation and effects on overall operative time
- Rate of detection of additional lymph nodes by ultrasound
- Sensitivity of VATS ultrasound related to lymph nodes harvested after standard dissection: does ultrasonography reveal any additional pathologically positive lymph nodes over standard techniques.

2. BACKGROUND

2.1 Lung Cancer

Lung cancer is the leading cause of cancer deaths in the United States and worldwide. About 228,190 new cases of lung cancer (both small cell and non-small cell) and about 159,480 deaths from lung cancer are predicted in the US for 2013.(1) Non-small cell lung cancer (NSCLC) represents about 85% of all lung cancer and frequently has a dismal outcome. The 5-year survival rate for late-stage (stages III and IV) patients is less than 10%. Survival is directly

related to stage. As such, treatment of lung cancer is stage-based.(2)

2.2 Lung Cancer Staging

The evaluation of N2 disease in NSCLC represents an important decision point. In patients who present with N2 positive disease based on imaging, and confirmed by tissue diagnosis, treatment is primarily systemic. A small subset of stage I-II patients, who have been evaluated prior to resection and are found at the time of surgery to have microscopic metastases to their N2 nodal stations, are upstaged to IIIA and receive postoperative systemic therapy. Although the incidence of pathologic upstaging is low (7.6% for standard thoracotomy with lobectomy), if these patients are not detected at the time of surgery they will be misclassified as stage I-II based on tumor size and may not receive any additional therapy after surgery. This will result in the increased risk of nodal and systemic recurrence, with impact on the stage-based survival.(3, 4)

2.3 Surgical Therapy

Lung cancer surgery has been traditionally performed by open thoracotomy. The thoracotomy incision is associated with significant pain which places patients at risk for postoperative pulmonary complications, delays recovery, and can hinder compliance with adjuvant therapy regimens.(5)

Advances in minimally invasive surgery have allowed for the safe performance of a thoracoscopic (VATS) lobectomy which is associated with vastly improved postoperative pain control. As such, patients have shorter lengths of stay, increased postoperative mobility with decreased rates of postoperative complications, and importantly have improved compliance with adjuvant therapy regimens.(5)

Despite this, there has been slow adoption of VATS. Nationally, only 30% of lung cancer resections are performed using minimally invasive techniques. Critique of the technique has included difficulty with the learning curve, and the debate regarding lymph node yield and the oncologic equivalency continues.

Small-volume randomized controlled trials performed by centers routinely employing the technique have failed to demonstrate issues from an oncologic standpoint. However, a large review of national data demonstrates a significant rate of upstaging of patients when a thoracotomy is performed as compared with VATS. A limitation of VATS, as in all minimally invasive surgery, is the inability to palpate the tissues and this may be a factor. This was also recently replicated in a national study published in Denmark this year.(3, 4, 6)

2.4 Intraoperative Ultrasound

Intraoperative ultrasound is routinely used in laparoscopic cases and has added significant value in terms of ability of the surgeon to determine anatomic boundaries and assess for metastatic disease.(7-9) To date, this modality has seen limited utilization in VATS and in particular there are no reports of use of the technology being used to assess lymph nodes at the time of surgery. Given its ability to objectively assess tissue beyond simple visual inspection this should help to identify pathologic lymph nodes in these patients if indeed they are present.

2.5 BK Medical ApS Ultrasound transducer system

BK Medical ApS, Peabody MA, manufactures an FDA-approved ultrasound transducer/system for use during minimally invasive surgery. (8666-RF, 10-5MHz ultrasound transducer). This system is routinely used at the University of Kentucky in general surgery, hepatobiliary surgery, gynecologic oncology, and neurosurgery to assist the surgeon with intraoperative decision making.

The system has not been used in thoracic applications at the University of Kentucky. The laparoscopic probe would be introduced into the chest at the time of VATS through the pre-

existing incision to allow for an evaluation of lymph node stations after performing a standard lung cancer resection and lymph node dissection.

http://www.bkmed.com/8666RF_en.htm

2.6 Rationale

Standard approaches have been developed to lung cancer resections using VATS. This includes a standard sampling of lymph node stations to obtain an accurate pathologic staging. However evaluation of these nodes is limited by the reliance of the surgeon on conventional 2-dimensional video imaging of anatomy and does not allow for palpation of abnormal tissues.

VATS lobectomy is associated with potentially missed N2 nodal disease during surgical resection of presumed early-stage lung cancer. Pathologic false negative evaluation will result in patients who are truly stage III being misclassified as stage I-II and as such missing the opportunity to benefit from adjuvant therapy. Recent review of national data demonstrates the occurrence of pathologic upstaging during standard thoracotomy in 7.6% of resections, compared with 2.3% of VATS cases. Limitations incurred by minimally invasive surgery may be responsible for this differential rate.

Intraoperative ultrasound adds an additional dimension to the evaluation of lymph nodes and abnormal tissue. If there are additional lymph nodes present, which have not been resected by standard techniques, they should be detected by an intraoperative ultrasound scan.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have potentially resectable non-small cell lung cancer by VATS as determined by a multidisciplinary team review. This primary should not have undergone any neoadjuvant chemo- or radiation therapy.

3.1.2 Age ≥18 years.

3.1.3 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.4 Life expectancy of greater than 3 months

3.1.5 Patients be able to undergo VATS resection as defined below:

- Preoperative FEV1 ≥ 40% predicted
- OR
- Post-operative predicted FEV1 ≥ 0.8 l
- Hg ≥ 8.0
- No evidence of coronary ischemia on stress evaluation

3.1.6 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients with surgery for a prior ipslilateral lung cancer are excluded

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. (Patients with HIV are not excluded from this study)

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. As such, no particular accrual targets are pre-defined with plans to accrue consecutive patients during the enrolment period.

4. REGISTRATION PROCEDURES

4.1.1 Protocol Review and Monitoring Committee and Institutional Review Board Review

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the Markey Cancer Center's Protocol Review an Monitoring Committee and the University of Kentucky Institutional Review Board (IRB). A signed and dated statement that the protocol and informed consent have been approved by the IRB must be maintained in the Markey Cancer Center Clinical Research and Data Management Shared Resource Facility (MCC CRDM SRF) regulatory binder. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the study sponsor and the UK IRB.

4.1.2 Enrollment Guidelines

Eligible patients will be identified by the principal investigator and co-investigators of this study. Potentially eligible patients will be screened in the University of Kentucky Markey Cancer Center clinics by the investigators, study personnel, and the Principle Investigator (PI). Upon obtaining proper consent, patients will be enrolled into the study.

4.1.3 Informed Consent

The goal of the informed consent *process* is to provide people with sufficient information so they can make informed choices about whether to begin or continue participation in clinical research. The process involves a dynamic and continuing exchange of information between the research team and the participant throughout the research experience. It includes discussion of the study's purpose, research procedures, risks and potential benefits, and the voluntary nature of participation.

The informed consent document provides a summary of the clinical study and the individual's rights as a research participant. The document acts as a starting point for the necessary exchange of information between the investigator and potential research participant. Also, research participants and their families may use the consent document as an information resource and reference throughout participation in the trial. The informed consent document is often considered the foundation of the informed consent process; it does not, however, represent the entirety of the process. Nor is the informed consent document a risk-management tool for the investigator and/or institution.

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with the protocol at the time of IRB review.

4.1.4 **Compliance with Laws and Regulations**

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board

(IRB) requirements. The PI or designee will be responsible for obtaining continuing and not less than annual IRB re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB and copies of the IRB continuance of approval must maintained by the MCC CRDM SRF. The PI or designee is also responsible for notifying the Data and Safety Monitoring Committee of the MCCC and the UK IRB of any significant adverse events that are serious and/or unexpected, as per SOP's of those entities. DSMC will review adverse events of this IIT as per its SOP.

5. TREATMENT PLAN

5.1 Enrollment and Screening Process

Prior to any study-required tests, subjects must first provide written informed consent to participate in this study. All lab tests and radiographic studies should be completed prior to surgery. Preoperative evaluation will include:

- Complete history, physical examination, and evaluation of Zubrod Performance Status.
- Multidisciplinary review of case presentation: Either Pathological (biopsy) or cytologically proven non-small cell lung cancer, or patients suspected of having early stage NSCLC are enrolled.
- CT with contrast or PET/CT (preferred)of chest and upper abdomen to include the liver and adrenals
- Baseline brain MRI or CT scan.
- Bone scan, only if the patient has bone pain and/or and elevated alkaline phosphatase > 1.5 x ULN.
- Pulmonary function tests - including FEV1
- CBC; serum chemistry tests to include creatinine, and electrolytes.

5.2 Surgery

Surgery will occur on an inpatient basis.

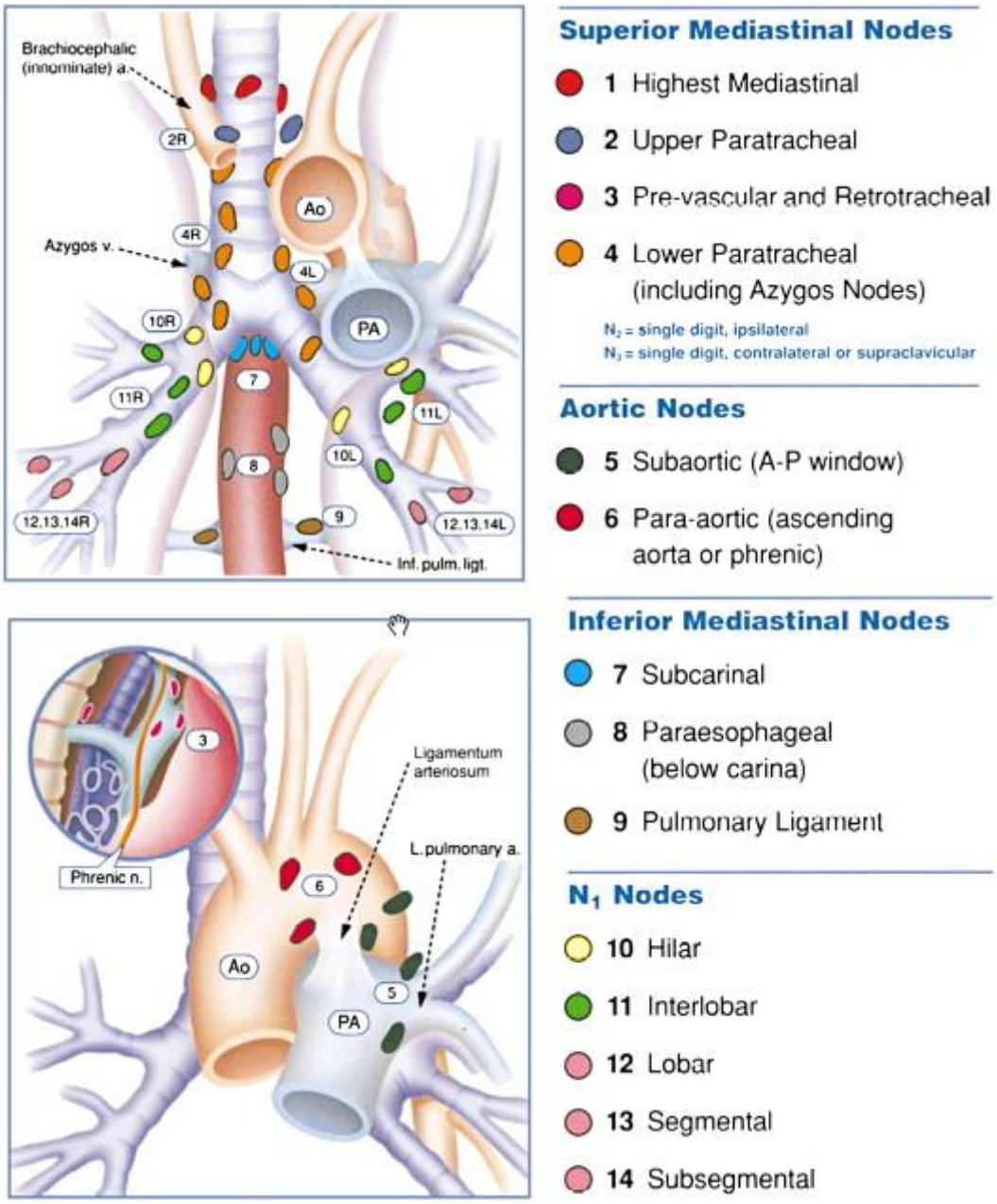
Intraoperative monitoring will consist of standard intravenous access, arterial line and EKG monitoring.

Lung isolation will be performed under general anesthesia in standard manner with the use of dual lumen endotracheal intubation or bronchial blocker at the discretion of the cardiothoracic anesthesiologist.

The chest will be accessed using standard thoracoscopic (VATS) techniques. The operating surgeon will assess resectability, and perform the definitive operation. In the case of those patients who have a suspicion of, but do not have a diagnosis of cancer prior to surgery, a wedge resection or intraoperative core biopsy will be performed with pathology confirming the presence of NSCLC with frozen section.

The resection will include the standard mediastinal lymph node dissection as routinely performed by the operating surgeon. At a minimum, these stations will include:

1) Right Upper/Middle Lobe – R4, 7
2) Right Lower Lobe – 7, R8/9
3) Left Upper Lobe – 5, 7
4) Left Lower Lobe – 7, L8/9



(Figure 1, IASLC mediastinal lymph node map)(10)

At the conclusion of the thoracoscopic lung cancer resection, the BK 8666-RF ultrasound transducer will be introduced through the existing operating ports and used to evaluate all lymph node stations evaluable from the ipsilateral thorax. Additional lymph nodes identified in the defined stations above will be resected, and imaging characteristics noted. Image-capture will be

used to document the appearance of lymph nodes which are identified for resection to allow for clinico-pathologic correlation.

Reported adverse events and potential risks are described in Section 7. Appropriate therapy modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.3 Intraoperative Ultrasound Examination

Intraoperative ultrasound will be performed at the completion of the standard lung cancer resection with mediastinal lymph node dissection. This evaluation will be performed by a different surgeon from the primary surgeon (either JM or AM) performing the operation to minimize operator variability with the ultrasound system and help control for bias. Additional lymph nodes identified will be resected and sent for pathologic evaluation. It is anticipated that this additional evaluation and treatment should take no more than 30 minutes and as such a time limit of 30 minutes from introduction of the ultrasound probe into the surgical field will be set.

5.4 Duration of Therapy

Treatment will occur at the time of surgery and subjects will be followed for 30-days post operatively or until resolution of all study related adverse events < grade 2.

5.5 Duration of Follow Up

Patients will be followed for 30 days after their operation or until resolution of all greater than grade 2 adverse events that are possibly, probably or definitely related to study intervention as

determined by the treating physician. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event to ≤ grade 2.

5.6 Criteria for Removal from Study

The possibility exists that a patient who has been screened and enrolled for the study, was taken to the operating room without a definitive diagnosis. At the time of surgery, if a diagnosis of non-malignancy, or tumor other than NSCLC is rendered, then the patient will be removed from the study.

6. DOSING DELAYS/DOSE MODIFICATIONS

N/A

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via AdEERS) **in addition** to routine reporting.

7.1 Expected Toxicities

Ultrasound represents a non-invasive, atraumatic method of evaluation of tissues. The performance of the exam itself should not incur adverse events. The following adverse conditions may be related directly or indirectly to the use of ultrasound in this setting:

- **Injury during introduction/operation of the ultrasound probe**
  The ultrasound transducer is a firm object, used in contact-evaluation. It is unlikely, but possible, that traumatic injury to any intrathoracic structure may occur during conduct of an examination.
- **Injury to recurrent laryngeal nerve**
  Extensive dissection in the paratracheal region, where level 2 and 4 nodes are located, may result in injury to the recurrent laryngeal nerve. This would manifest as postoperative hoarseness.
- **Chylothorax / Lymphatic leak**
  Lymph leak may occur during a more extensive lymph node dissection
- **Extended operating time**
  Ultrasonographic screening will add additional time to the operation that would otherwise be completed. Additional time under general anesthetic is associated with increased risks due to infection. As such, additional time for this procedure will not exceed 30 minutes and postoperative complications will be monitored as defined above.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment 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/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 For MCC Investigator-Initiated Trials (IITs), investigators **must** report to the Overall PI any serious adverse event (SAE) on the local institutional SAE form. This applies to the following categories:

- **Grade 2 (moderate) and 3 (severe) Events** – Only events that are Unexpected and Possibly, Probably or Definitely Related / Associated with the Intervention.
- **ALL Grade 4 (life threatening or disabling) Events** – Unless expected AND specifically listed in protocol as not requiring reporting.
- **ALL Grade 5 (fatal) Events** regardless of study phase or attribution

Note: If subject is in Long Term Follow Up, death is reported at continuing review.

7.3.2 The following table outlines the required forms and reporting structure for this clinical trial.

Study type	Expedited reporting to MCC	Expedited reporting to External Agency	Non-expedited AE	Form	IRB
IIT where MCC investigator holds the IDE or IND	• Grade 2 and 3 – Unexpected AE PLUS Possibly, Probably or Definitely Related • ALL Grade 4 Unless expected AND listed in protocol as not requiring reporting. • ALL Grade 5 (fatal) Events	FDA: Suspected AE that is serious and Unanticipated (not listed in IB or consent)	OnCore and DSMC reporting only	Mandatory Medwatch 3500a for Serious and unanticipated OnCore for all others	Yes if it meets the IRB reporting requirements: Unanticipated Problem and/or Serious AE (use IRB AE reporting form for all correspondence with IRB)

7.3.3 MCC Expedited Reporting Guidelines for MCC IITs

Investigators within MCC will report SAEs directly to the MCC DSMC per the MCC DSMC SOP and the University of Kentucky IRB reporting policy.

Attribution	MCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

7.4 Expedited Reporting to External Agencies

The Overall PI will comply with the policies of all external funding agencies and the UK IRB regarding expedited reporting, as per the UK IRB's SOP: http://www.research.uky.edu/ori/SOPs_Policies/C4-0150-Mandated_Reporting_to_External_Agencies_SOP.pdf.

7.4.1 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.4.2 Expedited Reporting to Hospital Risk Management

Participating investigators will report to the UK Office of Risk Management any participant safety reports or sentinel events that require reporting according to institutional policy.

7.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the OnCore case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

N/A

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

N/A

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 4 weeks prior to start of protocol therapy. Scans and x-rays must be completed ≤4 weeks prior to surgery. Routine postoperative evaluation includes a first postop visit at 2 weeks post discharge, and a 30 day (post-surgery) follow-up visit to complete the study follow-up period.

	Pre-Study	Admission	2 week post discharge	30 day post surgery Off Study[c]
Ultrasound / Surgery		A		
Informed consent	X			
Demographics	X			
Medical history	X			
Physical exam	X	X		X
Vital signs	X	X		X
Height	X			
Weight	X	X		X
Performance status	X	X		X
CBC w/diff, plts	X	X	X	X
Serum chemistry[a]	X	X	X	X
EKG (as indicated)	X			
Adverse event evaluation		X----------	----------	----------X
Tumor measurements	X			
Radiologic evaluation	X			

S: *[Ultrasouond/Surgery]*:

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

c: Off-study evaluation.

11. MEASUREMENT OF EFFECT

11.1 Evaluation of intraoperative ultrasonography

For the purposes of this study, patients will be evaluated at the time of surgery for potentially occult pathologic involvement of N2 nodes. Evaluation will be undertaken for determination of sensitivity, specificity and false positive rate for lymph nodes evaluated by VATS ultrasound. Intraoperative evaluation will determine the appearance of standard mediastinal lymph node stations as defined in section 5.2. Appearance of lymph nodes found during imaging will be documented, and additional nodes sampled will be labeled as such to determine whether or not ultrasound allowed the detection of additional pathologic nodes and therefore contributed to upstaging.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will require data submission and reporting via the OnCore Database, which is the official database of the Markey Cancer Center Clinical Research and Data Management Shared Resource Facility (CRDM SRF). Instructions for submitting data is listed in Study-Specific Data Management Plans created by CRDM SRF staff.

12.1.2 Responsibility for Data Submission

Study staff are responsible for submitting study data and/or data forms to OnCore as per

the Markey Cancer Center CRDM SRF SOP's. This trial will be monitored by the MCC Data and Safety Monitoring Committee (DSMC) on a schedule determined by the Protocol Review and Monitoring Committee at the initial PRMC review. THE CRDM SRF staff is responsible for compiling and submitting data for all participants and for providing the data to the Principal Investigator for review.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a single-arm, two-stage, Phase II trial of intraoperative ultrasound in thoracoscopic surgery (VATS) with the primary goal of testing the upstaging rate of patients with presumed clinically N2 negative disease, to N2 positive disease. Secondary study endpoints include complication rate (see Section 1.2 above), length of surgical time, lymph nodes detected by ultrasound and estimation of sensitivity, specificity and false positive rate for lymph nodes evaluated by VATS ultrasound.

13.2 Sample Size/Accrual Rate

A Simon's two-stage optimum design is employed to test the null hypothesis that upstaging rate is equal to 2% versus an alternative equal to 8% (11). A sample of 34 patients will be enrolled in the first stage. The trial will be terminated if none of the first 34 patients were upstaged; otherwise, an additional 36 patients will be enrolled in the second stage (for a total of 70 patients). If the intervention is actually not effective at detecting N2 pathologic nodes, there is a 0.049 probability of concluding that it is (alpha error rate of 5%) while if it effective, there is a 0.198 probability of concluding that it is (for 80% power). Based on the hypothesized upstaging rate above, if the total number of upstaged patients detected is less than equal to 3, then the intervention will be rejected.

In order to account for at most a 10% drop-out rate, a total of 78 patients will be enrolled into the trial. The projected accrual rate is 30 – 40 patients per year (about 3 per month). We expect to accrue patients into the study within 2 years.

13.3 Stratification Factors

Not Applicable for this trial

13.4 Analysis of Primary and Secondary Endpoints

Estimate of upstaging rate will be calculated along with exact 95% binomial confidence interval. The estimate will be adjusted given the two-stage nature of the study design. Descriptive statistics including median, inter-quartile range, etc. will be calculated to summarize length of surgical time and number of lymph nodes detected. False positive rate, sensitivity and specificity of ultrasound evaluation of additional lymph nodes regarding upstaging compared with pathology evaluation will be calculated. All patients who received study intervention will be included in safety analysis including estimation of overall complication rate and rates for each complication event mentioned in section 7.0 above using frequencies and proportions (See section 13.7.1 below).

13.5 Interim Analyses

As indicated in sections 13.1 and 13.2 above, an interim analysis of upstaging rate will be performed after 34 patients have been accrued into the study based on a Simon's two-stage optimum design.

13.6 Data Management

The study statistician and staff from the Biostatistics Shared Resource Facility (BSRF) of the Markey Cancer Center will work closely with the study PI and the Clinical Research and Data Management (CRDM SRF) at Markey in the development of eCRFs for the study. Specifically,

the statisticians will attend several meetings including the Protocol Initiation Meeting (PIM) to address all statistical considerations for this protocol including incorporation of interim monitoring plans to assess upstaging rate, appropriate and accurate collection of primary and secondary study endpoints and inclusion of valid values and range checks for data fields. The OnCore clinical trial management system, managed by Markey's CRDM SRF, will be the primary database repository of clinical data from all patients enrolled into this trial. Data will be accessed by the study statistical on a regularly-scheduled basis to perform statistical programming for conduct of data quality control, data management, generation of interim reports and statistical analysis. The BSRF has developed an automated mechanism for generating the interim trigger for assessment of upstaging rates as indicated in section 13.2 and 13.5 above. In collaboration with the study team, procedures will be developed for timelines for data quality control, resolution of data queries, interim reporting and final data analysis,

13.7 For phase 2 protocols only: Reporting and Exclusions

13.7.1 Evaluation of Toxicity/Safety

All enrolled patients will be included in the safety analysis. Specifically, the following safety parameters will be evaluated: Any occurrence of injury related to VATS ultrasound, incidence of hoarseness attributable to recurrent laryngeal nerve injury, incidence of chylothorax. In addition, any evaluation which has not been completed within 30 minutes will be noted as a safety issue due to prolonging operative time. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event and incidence of serious adverse events. The total number of episodes for each event reported (Frequency Table), the severity and attribution to study intervention of each episode reported (Severity Table and Attribution Table) will also be displayed. Listings of adverse events by patients will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study intervention, whether it was a serious event, and whether it caused withdrawal. Toxicities will be graded according to Common Toxicity Criteria (CTCAE) v4.0.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B CASE RECORD FORM

A single-arm, Phase II study of thoracoscopic lung cancer staging with the use of Intraoperative Ultrasound at the time of definitive resection

1. **Preoperative**
    a. Name / MRN _____
    b. Age _____
    c. Gender M / F
    d. ECOG status ____
    e. Physiologic parameters
        i. ECHO: Ejection Fraction (EF) ___ %
    f. PFTs
        i. FEV1 (% predicted) ____ %
        ii. DLCO if done ____ %
    g. Clinical Stage:
        i. CT data – nodule size ___ mm
        ii. PET data – nodule size / nodes _____
        iii. Brain MRI – done, positive / negative _____
        iv. Discussed at Multi-Disciplinary conference Y/N – outcome
    h. Planned resection:
        i. Lobectomy / Wedge / Other
        ii. Surgeon : _____
        iii. Surgeon for Ultrasound: _____

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2. **Intraoperative**
    a. Surgeon : _____
    b. Operative time (exclusive of ultrasound time) : _____
    c. Blood loss: _____ ml
    d. Surgical approach : _____
    e. Surgeon comments about the case : _____

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3. **Intraoperative Ultrasound**
    a. Sonographer: _____
    b. Ultrasound time: _____
    c. Lymph node stations examined
        i. Paratracheal ___
        ii. Subcarinal ___
        iii. Prevascular ___
        iv. Infrahilar ___
    d. Ultrasound findings
        i. Number of suspicious nodes identified : _____
        ii. Number of nodes retrieved : _____
        iii. Maximal size of additional lymph node by ultrasound criteria: _____

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4. **Postoperative, inpatient**
    a. Length of stay : _____d
    b. Chest tube duration : _____ d
    c. Chest tube daily drainage (daily)
        i. ___ ___ ___ ___ ___
    d. Need for any additional procedures : _____
    e. Surgeon comments on postoperative stay: _____

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5. **Postoperative, followup**
    a. Final pathologic staging : _____
    T, N, M
    b. Was N staging affected by the Ultrasound screening? : _____
    c. Postoperative comments, concerns, complications. : _____
    _____
    _____