Prospective Randomized Study on Video Double-Lumen Tube versus Double-Lumen Tube

Principal Investigator: Dr. Jagtar Singh Heir
Co-Investigator: Dr. Juan Cata
Collaborators: Drs. Reza Mehran, David Rice, Kazim Mirza, Piotr Kwater, Ron Purugganan, Tim Jackson, Teresa Moon, Shital Vachhani, Javiar Lasala, Elena Potylchansky, Dilip Thakar, January Tsai, Peter Norman, Shu-Lin Guo
Bio-statistician Collaborator: Lei Feng

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1.0 Background

1.1 Lung Isolation For Thoracic Surgery

In the 1930's, lung isolation became possible with the introduction of single lumen endobronchial tubes, as well as endobronchial blockers. Thereafter, Carlens invented a double lumen tube (DLT) with a carinal hook in 1949, to assist in bronchial placement so that proper lung isolation could be maintained.[1] This landmark development in lung isolation allowed placement of the endotracheal tube without necessitating a rigid bronchoscopy, which had always been previously required. However, this type of equipment essentially required significant experience in order to achieve successful lung isolation.

Furthermore, this carinal hook was also the source of increased airway trauma, as the hook could potentially break off in the airway leading to malposition, as well as a foreign body in the airway. However, White then modified the Carlens tube by creating a right-sided version, also with a carinal hook, which was easier to place. Thereafter in 1962, Robertshaw introduced a reusable red rubber DLT without a carinal hook.[2] In addition

to the reusability component, the right-sided red rubber Robertshaw DLT had a larger 22mm slotted endobronchial cuff for improved right upper lobe (RUL) ventilation.

Subsequently, in the 1970's the primary airway device used for lung isolation in the United States was the DLT. However, the Robertshaw DLTs had their own unique problems: small internal channels, which made suction difficult as well as low volume-high pressure bronchial cuffs, which could lead to tracheal mucosa ischemia via compression. In the 1980's, disposable polyvinylchloride (PVC) DLTs were created, which remain the mainstay of DLTs used currently for lung isolation. These PVC DLTs have the advantage of high volume-low pressure tracheobronchial cuffs which inflate more evenly thus significantly decreasing the chances of mucosal ischemia. Furthermore, these PVC DLTs are easier to manipulate and place, while also offering larger internal lumens for suction and fiberoptic (FOB) scope placement, which is used to verify correct placement.

Throughout the development of DLTs and other lung isolation devices, the capability for direct visualization to insure correct placement of these devices has always been a major limiting factor for their use. Proper placement is paramount to patient safety and device effectiveness. The development and refinement of flexible fiberoptic bronchoscopes offered an alternative, more reliable method than auscultation for proper placement of airway isolation devices.

1.2 Impact on Patient Outcomes

The use of a pediatric FOB scope was only first described in 1982 by Watson, as practitioners had noted improper placement could still occur despite inspection and auscultation. Hence in the United States, FOB verification is considered the current standard of care. There are multiple studies that support the use of FOB to confirm DLT placement.
For example, one study found that despite normal findings on auscultation and inspection, 39% (79) of these patients had DLT malposition diagnosed by FOB.[3] Moreover, of the 79 patients with malposition, 25 were critical malpositions. Additionally, DLTs were malpositioned as often after positioning the patient for lateral thoracotomy (46%) as they were after intubation (53%). Similarly, yet another study found that auscultation failed to confirm accurate tube position in 28% of L DLT patients. 78% of left DLT patients and 83% of right DLT patients, who were intubated blindly, required repositioning with FOB.[4] Likewise, a third study found 44% of DLTs required position readjustments using FOB during initial intubation and 30% required FOB readjustments during the operation.[5]

Although the FOB has become the standard of care for confirmation of DLT, unfortunately many anesthesiologists lack the training and familiarity of tracheobronchial anatomy for adequate application of this technique,

leading to a high incidence (38%) of malposition despite the use of FOB.[6] Furthermore, a limitation common to existing comparative studies is that all these studies were conducted by anesthesiologists with particular interest and expertise in thoracic anesthesia, who perform lung isolation procedures on a routine basis. However, in many practices, lung isolation is an uncommon procedure and is performed by anesthesiologists who do not specialize in thoracic anesthesia. In addition, lung isolation is needed for many procedures performed outside of the regular thoracic surgical suite and hence is performed by clinicians with less experience. Therefore, potentially the results of malposition and incorrect placement could conceivably be higher in the practices of these non-thoracic anesthesiologists.

Yet, another issue that limits the use of fiberoptic bronchoscopy is availability. Fiberoptic bronchoscopes are precision instruments that are costly to acquire and maintain. Because of the expenditure involved, smaller community health care centers and/or poorly funded hospitals may lack funding to acquire fiberoptic bronchoscopes. As there is an increasing demand for one-lung ventilation in both thoracic surgery and other procedures (i.e. spine surgery, cardiac surgery), identifying the most effective technique of lung isolation for anesthesiologists with limited experience in lung isolation techniques, would benefit to improve the safety for patients.

One such technologic advance has been in video camera and light source miniaturization, which may offer a novel solution to this problem. The VivasightTM (ET ViewLtd,Misgav,Israel)DLT is a video double-lumen tube(VDLT) that has an embedded camera and light source between the tracheal and bronchial cuffs, enabling continuous airway visualization on a portable external proprietary monitor that is connected via a mini-USB adapter. Heir and colleagues evaluated whether the use of a VDLT reduced the need for fiberoptic bronchoscopy for (1) verification of initial tube placement and for (2) reverification of correct placement after repositioning for thoracotomy.[7] The study found that for 93.2% of patients, the use of FOB was not needed either for initial placement or for verification of correct VDLT placement upon final positioning of the patient. This study demonstrated that the VDLT requires significantly less (6.8%) FOB use for both initial placement and verification of final position, in stark contrast to standard practice in which bronchoscopy is always used to verify final positioning of the double-lumen tube.

Furthermore, the authors also noted that the continuous real time monitoring allowed for greater measure of safety, as they were able to forewarn the surgeon when aggressive manipulation would otherwise have led to a malposition. Furthermore, the real time image provided by the embedded camera, could potentially allow for quick diagnosing of the

problem, hence enabling the provider to institute proper therapy in more timely fashion. Likewise, VDLT could provide an additional measure of safety in procedures such as pneumonectomies, where it is desired to move the DLT before the surgeon clamps the bronchus, allowing visualization of the stapling that avoids inadvertent stapling of the tube into the bronchial stump or rupturing of the endobronchial cuff of the DLT.

Although the FOB remains the gold standard for examination of the tracheobronchial tree, the embedded camera view can be used as an adjunct to teach trainees to recognize and become more familiar with the anatomy via direct visualization. This concept could also be useful for the anesthesiologist who does not use DLTs on a regular basis and is more likely to employ the blind advancement technique when placing a DLT.

1.3 Current Standard of Care

In centers across North America, FOB use is employed as the current standard for verification of DLT placement. However, there are institutions, which still promote auscultation as viable method of DLT placement confirmation, as FOB may not always be available and trainees need to be able to properly position a DLT in less than ideal circumstances (off-site locations, broken equipment, etc). However, even in most of these cases, this does not preclude that the tube position cannot then be confirmed with FOB, after the staff and/or resident have checked initially with auscultation.

Furthermore, consideration has to be given to the fact that even with the use of FOB, correct tube position is not always obvious. There is a considerable learning curve to bronchoscopic positioning of double-lumen tubes, particularly when there are anatomic distortions because of tumor masses or previous surgery; analogous to anesthesiologists examining hundreds of routine airways to become comfortable with the airway anatomy. Therefore, correct placement of a DLT can be challenging and hence lung isolation may become difficult to achieve. Novel intubation devices like the VDLT have been developed that offer real-time continuous observation of the trachea and carina, thus allowing the anesthesiologist to confirm continuous correct placement and also recognize dislodgement.

In addition, displacement and dislodgement of DLT is common and repeated checks for correct positioning with a FOB are often necessary. In some cases these frequent checks can interfere with oxygenation and ventilation, which may pose a considerable risk to the patient. This potentially may be detrimental, as this can lead to hypoxemia and prolongation of the surgical procedure. Thus these newer intubation devices can offer continuous observation of the trachea and carina and

thereby reduce the need for a FOB during tube placement and subsequent airway monitoring.

2.0 VDLT and DLT Information

2.1 Description of VDLT

2.1.1 The VDLT is essentially a FDA approved disposable, single use left-sided double lumen endobronchial tube with an embedded video imaging device and light source at its distal tip and integrated cable with connector. The device is compatible with ETview's displays and with medical grade NTSC video monitors. The VDLT projects images of the airway onto the monitor screen during intubation and for as long as the device remains within the patient's airway. (See Appendix 3)

2.1.2 The VDLT is made of PVC transparent material, with two low-pressure cuffs and two color-coded, corresponding pilot balloons. The tracheal cuff with clear pilot balloon and the bronchial cuff with blue pilot balloon. The valves are intended for Luer and Luer-lock syringe tips. It also comes with a stylet, which can be fixed to maintain the shape of the tube, as well as radiopaque intubation depth markers, which run along the tube's wall. Additionally, it has a red injection port leading to two lumens running along the tube's wall that open distal to the lens of the optics which can be used for cleaning the lens with air, saline or prescribed medications.

2.1.3 Accessories: The VDLT comes with a Y-piece plastic connector intended to connect to the breathing circuit. A small malleable metal stylet is also provided with the VDLT. It also comes with two suction catheters, which can be inserted in the tracheal or bronchial lumens to clear secretions.

2.1.4 Thermal qualities: The VDLT should not be used in surgical procedures that involve the use of a LASER beam near the VDLT. The VDLT should not be stored at temperatures greater than 42 degrees Celsius.

2.2 Description of DLT

2.2.1 The DLT is a double lumen endobronchial tube that allows the anesthesiologist to preferentially ventilate one or both lungs, enabling lung isolation for the proposed surgery. The device comes in both left and right-sided versions. (See Appendix 4)

2.2.2 The DLT is also made of PVC transparent material, with two low-pressure cuffs and two color-coded, corresponding pilot balloons. The tracheal cuff with clear pilot balloon and the bronchial cuff with blue pilot balloon. The valves are intended for Luer and Luer-lock syringe tips. It also comes with a stylet, which can be fixed to maintain the shape of the tube, as well as radiopaque intubation depth markers, which run along the tube's wall.

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3.0 Study Endpoints

3.1 Primary endpoint

3.1.1 Determine the rate of fiberoptic use with the VDLT during surgeries requiring lung isolation and to compare to the rate of FOB use with the conventional DLT.

3.2 Secondary Objectives

3.2.1 Determine any potential reduction of cost: VDLT vs. acquisition, use, maintenance, and repair of FOB systems

3.2.2 Determine the incidence of malposition: VDLT vs. DLT

3.2.3 Compare quality of view provided by the VDLT (embedded camera) vs. DLT (FOB) using grading system: (See Appendix 1 attached)

3.2.4 Determine the number of times secretions need to be cleared/flushed for either VDLT (embedded camera) and DLT (FOB)

3.2.5 Determine the efficacy of technique used for clearing secretions for VDLT (embedded camera) and DLT (FOB): Yes or No

3.2.6 Determine difficulties when inserting the VDLT or DLT (See Appendix 2 attached)

3.2.7 Determine the number of times anesthesiologist was able to forewarn/ anticipate dislodging or malposition

3.2.8 Assess the times from initiation of intubation to ready to position, and ready for surgical intervention

4.0 Patient Eligibility

4.1 Inclusion Criteria

To be eligible for participation in the study patients must meet all of the following criteria

4.1.1 Patients need lung isolation for purposed surgery

4.1.2 18 years or older

4.1.3 All patients to give written informed consent to participate

4.2 Exclusion Criteria

Patients with any of the following will not be eligible for enrollment

4.2.1 Patients with known tracheobronchial anatomical anomalies

4.2.2 Patients requiring emergency operations

4.2.3 Patients with known difficult airways

4.2.4 Patients where other lung isolation devices may be warranted (tracheostomy, nasal intubation)
4.2.5 Patient requiring sizes not available in DLT or VDLT
4.2.6 Patients requiring a right sided VDLT or DLT

5.0 Treatment Plan

5.1 **Design:** 2-arm, randomized prospective trial

5.2 **Randomization:** Patients will be randomized in a group that utilizes either a conventional DLT or VDLT for lung isolation for the purposed surgery. Patients will undergo surgical procedure after lung isolation is acquired with VDLT or DLT. The patients will undergo surgical procedures that are part of their medical treatment and will not undergo any diagnostic or extra laboratory work as a result of participating in this study

5.3 **Explanation of Thoracic Anesthesia Intervention**
One of the collaborating thoracic anesthesiologists will explain the procedure prior to obtaining consent. Consent and randomization will occur at minimum one hour prior to surgery. Randomization will be done after consent and by a computerized system.

5.4 **Withdrawal of individual subjects:**
Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

5.5 **Specific criteria for withdrawal (if applicable)**
Not applicable

5.6 **Replacement of individual subjects after withdrawal**
Not applicable

5.7 **Follow-up of subjects withdrawn from treatment**
Not applicable

5.8 **Premature termination of the study**
Not applicable

5.9 **Post discharge Dosing**
Not applicable

5.10 **Intraoperative and Postoperative Anesthesia Care**
In the preoperative holding area, patients will receive intravenous midazolam if clinically indicated according to the anesthesiologist's judgment. Prophylactic antibiotics will be given per surgical routine. A balanced anesthetic technique comprising of narcotics, muscle relaxants, inhalational will be utilized to induce and maintain general anesthesia for all patients undergoing thoracic surgery.

General anesthesia will be induced with fentanyl or sufentanil and propofol intravenously according to the anesthesiologist's clinical judgment. Tracheal intubation will be facilitated by succinylcholine or a nondepolarizing muscle relaxant. Anesthesia will be maintained with

desflurane, sevoflurane or isoflurane in (50%–100%) oxygen or propofol infusion according to the anesthesiologist's clinical judgment. Intraoperative analgesia will be obtained by the intravenous administration of sufentanil, fentanyl or hydromorphone.

Alternatively, an epidural can also be utilized intraoperatively, according to the anesthesiologist's clinical judgment if an epidural has been placed. Hemodynamics will be maintained according to the clinical anesthesiologist's judgment. Normothermia will be maintained with forced-air warming. Antiemetics will be given according to the anesthesiologist's clinical judgment. In those patients deemed to be awakened from general anesthesia when surgery is complete, muscle relaxation will be reversed and the trachea extubated.
At the end of surgery, hydromorphone or fentanyl will be given intravenously if considered necessary for pain control. In the postoperative care unit, patients may receive intravenous boluses of fentanyl, hydromorphone, or boluses of epidural infusion for postoperative pain control. In those patients for whom sedation and admission to the intensive care unit is necessary, intravenous propofol will be given continuously during transport.

With respect to achievement of lung isolation for the proposed thoracic surgeries, patients will either be randomized to the DLT or VDLT group. In either scenario, the DLT or VDLT will be inserted with conventional laryngoscopy or video-laryngoscopy by a member of the thoracic anesthesia team. Once correct placement has been thought to be achieved, the final position will be verified confirmed in the following ways: in the DLT group, final position will be verified with FOB and in the VDLT group, the final position will be verified with the embedded camera, however, at the discretion of the anesthesiologist the FOB may be used to also verify final position, as long it is recorded in the chart.

6.0 Other Data to be Collected

Research staff will collect demographic and clinical information from the patient's medical record. Demographic data to be collected may include such items as birth date and race/ethnicity. Examples of clinical information that may be collected at one or more time points during the study include height and weight, disease information (e.g., cancer site/stage), treatment information (e.g., type of surgery, postsurgical status, current medications), comorbidities, and performance status.

7.0 Statistical Considerations

The primary objective is to determine the rate of FOB use with the VDLT during surgeries requiring lung isolation and to compare to the rate of FOB use with the conventional DLT. The rate of FOB use with the conventional double lumen tube

is known to be 100%. We plan to enroll 80 patients for the study with 40 patients each arm. The study will have 99% power (Scenario #1 in the table below) to detect the difference in the rate of FOB use between 20% for the new video double lumen tube arm and 99% for the conventional double lumen tube arm, assuming a two-sided type error rate of 0.05 (nQuery Advisor 7.0).

Power calculations based on different scenarios of rate of FOB use are provided in the table below.

Assumption: two-sided α=0.05, and the rate of FOB use with the conventional double lumen tube=0.99 (the software requires the rate to be less than 1).

Scenario	Rate of fiberoptic use with VDLT	power
1	0.20	99%
2	0.30	99%
3	0.40	99%
4	0.50	99%
5	0.60	99%
6	0.70	96%
7	0.80	80%

Frequency counts and percentages will be reported for categorical variables (such as gender, race, device used for intubation, and incidence of malposition). Summary statistics such as number of non-missing observations (N), mean, median, standard deviation (std. dev), and range will be provided for continuous variable (such as age, time measured in minutes from intubation to ready to position, and time from intubation to ready for surgical intervention). The rate of FOB use and its 95% confidence interval for the new video double lumen tube arm and the conventional double lumen tube arm will be calculated. Fisher's exact test or Chi-square test will be used to evaluate the difference in the rate of FOB use between the two arms. Logistic regression may be used to assess the association between FOB use and other patient demographic and surgical characteristics.

Analysis results in an aggregated format will be provided to Dr. Shu-Lin Guo, one of the study collaborators. Dr. Guo will use the aggregated information to assist with manuscript writing and review.

8.0 Adverse Events and Reporting

8.1 Definitions

Adverse Event: Any symptom, illness or experience that develops or worsens in severity and/or frequency during the course of the study (i.e. any change from baseline. Intercurrent illnesses or injuries should be

regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality results in study withdrawal, is associated with clinical signs or symptoms, leads to treatment or to further diagnostic tests, or is considered by the investigator to be of clinical significance.

8.2 **Eliciting Adverse Event Information**

Adverse events will be elicited post surgery, after the patient has been extubated. All adverse events that are directly observed and all adverse events that are spontaneously reported by the patient are to be documented by the investigator.

8.3 **Grading/Rating Scale**

All adverse events reported during the study will be evaluated and graded on a scale of 1-4. The graded toxicity scale used in this study is the CTC version 4.0 for toxicity and Adverse Event reporting. A copy of the CTC version 4.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

For adverse events not covered by the CTC, the following definitions will be used:

Grade	Rating	Description
1	Mild	Adverse event is transient and easily tolerated by the patient; asymptomatic
2	Moderate	Adverse event causes the patient discomfort and interrupts the patients usual activities; symptomatic but does not interfere with function
3	Severe	Adverse event causes considerable interference with the patients usual activities
4	Life-threatening	Adverse event is incapacitating or life-threatening

8.4 **Reporting of Adverse Events**

All adverse events relating to the placement of the DLT or VDLT during the study period will be reported. Potential adverse events include tube dislodgement or ineffective ventilation.

8.4.1 Reporting of Serious and/or Unexpected Events

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must by reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy ". SAEs must be reported to the IRB and the Sponsor (Safety Project Manager) regardless of attribution.
- **All life-threatening or fatal events** occurring during the study period will have a written report faxed within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the Office of Research Education and Regulatory Management (ORE&RM) (fax 713-563-5468). The sponsor representative should be notified by phone at 713-563-0379 to confirm receipt of the fax.
- The MDACC Internal Adverse Event Reporting Form will be used for reporting to the IRB and the Sponsor (Safety Project Manager ORE&RM).
- **It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**
- One of the following individuals should be contacted if a patient on this trial is known or suspected to have experienced an adverse event:
  Jagtar Singh Heir, D.O. phone: 713-792-6911
- At the time of the initial report the following information should be provided if possible: protocol number, study site, patient number, study phase during which the event occurred, description of the event, date of onset and current status, start date of treatment, whether treatment has been discontinued, reason why the event is classified as serious, and the investigator's current assessment of the relationship between the event and study treatment.

8.5 **In Case of Death**

Where feasible and appropriate, an autopsy will be requested on patients who die while on study

9.0 Data Confidentiality Plan

All patient-reported outcomes, laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

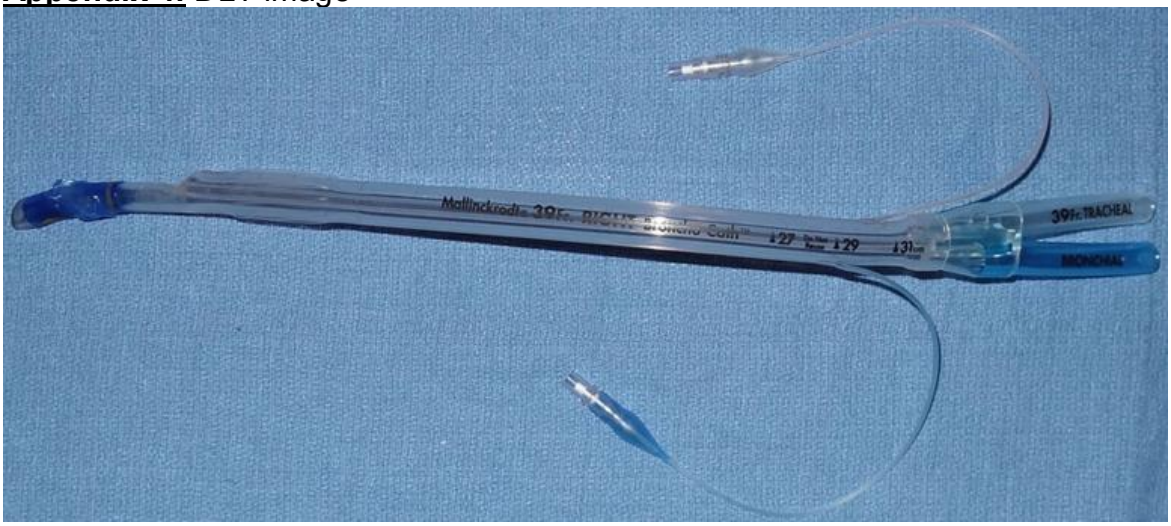
10.0 Appendix

Appendix 1: Grading system for quality of view provided by VDLT
Good: defined as right mainstem bronchus clearly visualized, hint of bronchial cuff seen in left mainstem bronchus (slight blue seen)
Adequate: defined as proper positioning of endobronchial cuff noted, however right mainstem bronchus not visualized well/partially
Poor: defined as unable to recognize anatomy, necessitating FOB to verify confirmation of placement

Appendix 2: Potential problems encountered inserting VLDT or DLT
Difficulties including ruptured cuff, not able to pass vocal cords, not able to occlude bronchus for lung isolation

Appendix 3: Close up image of embedded camera within VDLT

Appendix 4: DLT image



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