Pafolacianine: A Diagnostic Agent to Identify Lung Cancer Lesions in Adults with Known or Suspected Lung Cancer

Linda Martin
Department of Surgery, Thoracic Surgery Division, University of Virginia School of Medicine, VA, USA

DOI: https://doi.org/10.17925/OHR.2023.19.1.2

Linda Martin
Linda Martin is Associate Professor at the University of Virginia, Chief of Thoracic Surgery and leads the Thoracic Oncology Tumor Board, in addition to co-leading the Enhanced Recovery Program for Thoracic Surgery. She leads multiple committees for the Alliance for Clinical Trials, and also serves as principle investigator of a stage 3 lung cancer trial. She has authored over 50 articles and has been an associate editor for the Annals of Thoracic Surgery, and an editor for Clinical Lung Cancer.

Keywords
Lung cancer, pafolacianine, diagnosis

Disclosures: Linda Martin is a member of the advisory board for AstraZeneca, on the steering committee for ELUCIDATE trial, a consultant for Ethicon/Johnson and Johnson and part of the speakers bureau for Genentech.

Acknowledgements: Medical writing assistance was provided by Alex Lowe on behalf of Touch Medical Media, and was supported by Touch Medical Media.

Review process: This is an expert interview and as such has not undergone the journal's standard peer-review process.

Compliance with ethics: This article is an expert interview and does not report on new clinical data, or any studies with human or animal subjects, performed by the author.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this article.

Authorship: The named authors meet the criteria of the International Committee of Medical Journal Editors (ICMJE) for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Received: 21 March 2023

Published online: 14 April 2023

Citation: *touchREVIEWS in Oncology & Haematology*. 2023;19(1):2–3

Corresponding author: Linda Martin, Department of Surgery, Thoracic Surgery Division, University of Virginia School of Medicine, 1340 Jefferson Park Ave, Charlottesville, VA 22903, USA. E: LM6YB@uvahealth.org

Support: No funding was received in the publication of this article.

Accurately detecting lung tumours and their margins is important for disease outcomes.[1,2] However, detection is challenging due to the use of minimally invasive surgery and current localization techniques, such as computed tomography (CT)-guided and endobronchial interventions, which add significantly to procedure time and risk of complications.[3] Intraoperative imaging using a targeted agent to optically fluoresce cancerous cells may address these problems, in addition to locating previously unknown tumours and determining tumour margins.[4]

The fluorescent imaging agent pafolacianine binds and accumulates in folate receptor-positive tissues, visually highlighting these tissues intraoperatively when under a near-infrared lighting system.[5] As the majority of pulmonary malignancies continue to express the folate receptor after chemotherapy,[6,7] the phase 3 ELUCIDATE trial (ClinicalTrials.gov identifier: NCT04241315) investigated the use of pafolacianine in detecting lung tumours.[8] In this expert interview, Professor Linda Martin discusses challenges in intraoperative imaging of lung nodules, and the ELUCIDATE trial of pafolacianine.

Q. What are the challenges in intraoperative imaging of lung nodules?

Some of the challenges come from the desire to make surgery even more minimally invasive, which makes it harder for the surgeon to feel or palpate nodules within the lung to help localize them and determine the margins. So, we were looking for ways to improve our technology so that we can accurately find and remove small nodules while maintaining a minimally invasive surgical approach.

Q. Following approval in ovarian cancer, what was the rationale for investigating pafolacianine in lung cancer detection?

The idea for intraoperative imaging is based on previous practice. In the past, when looking for a small nodule, patients would be sent for an additional invasive procedure to inject a dye or a tracer, allowing for imaging of the nodule during surgery. However, this meant additional risk and cost, as well as introducing a human element into the imaging. The pulmonologist or radiologist was required to estimate where to inject the dye or tracer, which would sometimes result in the dye ending up in the wrong place, for example in the pleural space, or result in the patient getting a pneumothorax. Additionally, this method would not allow for the estimation of nodule margins because it was just an estimate of the location of the nodule. The novel idea was to take this previous imaging practice but use intraoperative molecular imaging, where a tracer is given intravenously and only accumulates in cancerous tissue. This provides an accurate location of the nodule, and in a substantial number of patients, second and even third nodules that were previously unknown are also located. Overall, this provides much more information at the time of surgery.

Q. What were the aims, design and inclusion criteria of the phase 3 ELUCIDATE trial?

The ELUCIDATE trial aimed to confirm the efficacy of intraoperative molecular imaging with pafolacianine to localize lung nodules, identify additional tumours and assess tumour margins during pulmonary resection. The trial had a phase 3 design, where all patients received a single intravenous infusion of pafolacianine (0.025 mg/kg) 24 hours before surgery. Patients were randomized 1:10 to intraoperative molecular imaging using an infrared camera or traditional methods of white light and palpation of nodules. The primary study endpoint was to assess the number of clinically significant events, defined in the following three ways: 1. Did we identify the nodule in question? 2. Did we find a second nodule? 3. Were we able to assess the nodule margins based on this technology? Overall, rather than assess longer-term outcomes such as survival following the procedure, this study just aimed to test the technology.

Q. Could you give us an overview of the clinical data supporting the approval of pafolacianine in this indication?

Patients eligible for the ELUCIDATE trial included those with diagnosed or suspected lung cancer. In total, 54% of patients in the intraoperative molecular imaging group (n=100) had at least one clinically significant event. This included 19 patients whose tumour could not be located by white light, 9 patients who had additional previously unknown nodules identified, and 38 patients who had close (≤10 mm) margins. There were no drug-related serious adverse events. Based on these results, pafolacianine is now approved by the US Food and Drug Administration to assist in the identification of known or suspected lung tumours.[9]

Q. What impact will this approval have on the treatment paradigm for thoracic surgery, and in which patients will pafolacianine be considered?

In my opinion, this study will have a large impact, as it expands our ability to safely perform surgery with fewer steps and interventions for patients with small lung nodules of unclear origin. This is particularly important given the increased adoption of lung cancer screening, which has created a conundrum in instances where we find small lung nodules. In these instances, the malignancy of nodules is unknown, locating them is very challenging, and there is a need to remove them in an as minimally invasive manner as possible. Intraoperative molecular imaging with pafolacianine provides a technique for greater accuracy in determining margins, with the added benefit of finding unknown nodules and without the need for a separate invasive procedure. ❑

1. Chang YL, Wu CT, Lee YC. Surgical treatment of synchronous multiple primary lung cancers: Experience of 92 patients. *J Thorac Cardiovasc Surg*. 2007;134:630–7. DOI: 10.1016/j.jtcvs.2007.06.001
2. Mohiuddin K, Haneuse S, Sofer T, et al. Relationship between margin distance and local recurrence among patients undergoing wedge resection for small (≤2 cm) non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2014;147:1169–75. DOI: 10.1016/j.jtcvs.2013.11.056
3. Keating J, Singhal S. Novel methods of intraoperative localization and margin assessment of pulmonary nodules. *Semin Thorac Cardiovasc Surg*. 2016;28:127–36. DOI: 10.1053/j.semtcvs.2016.01.006
4. Okusanya OT, DeJesus EM, Jiang JX, et al. Intraoperative molecular imaging can identify lung adenocarcinomas during pulmonary resection. *J Thorac Cardiovasc Surg*. 2015;150:28–35. DOI: 10.1016/j.jtcvs.2015.05.014
5. Shum CF, Bahler CD, Low PS, et al. Novel use of folate-targeted intraoperative fluorescence, OTL38, in robot-assisted laparoscopic partial nephrectomy: Report of the first three cases. *J Endourol Case Rep*. 2016;2:189–97. DOI: 10.1089/cren.2016.0104
6. Crane LMA, Arts HJG, van Oosten M, et al. The effect of chemotherapy on expression of folate receptor-alpha in ovarian cancer. *Cell Oncol (Dordr)*. 2012;35:9–18. DOI: 10.1007/s13402-011-0052-6
7. Predina JD, Newton AD, Xia L, et al. An open label trial of folate receptor-targeted intraoperative molecular imaging to localize pulmonary squamous cell carcinomas. *Oncotarget*. 2018;9:13517–29. DOI: 10.18632/oncotarget.24399
8. ClinicalTrials.gov. ELUCIDATE: Enabling lung cancer identification using folate receptor targeting (ELUCIDATE) ClinicalTrials.gov Identifier: NCT04241315. Available at: https://clinicaltrials.gov/ct2/show/NCT04241315 (Date last accessed: 1 March 2023)
9. US Food and Drug Admnistration. FDA approves imaging drug to help identify lung lesions during surgery. Available at: www.fda.gov/drugs/news-events-human-drugs/fda-approves-imaging-drug-help-identify-lung-lesions-during-surgery (Date last accessed: 1 March 2023)