

Near-Infrared Intraoperative Imaging Can Successfully Identify Malignant Pleural Mesothelioma After Neoadjuvant Chemotherapy

Jarrold D. Predina, MD, MTR^{1,2}, Andrew Newton, MD^{1,3}, Greg Kennedy, BA¹, M. Kenneth Lee, MD, PhD³, and Sunil Singhal, MD^{1,2}

Abstract

Malignant pleural mesothelioma is a deadly disease. Complete surgical resection provides patients with the best opportunity for long-term survival. Unfortunately, identification of disease during resection can be challenging. In this report, we describe successful intraoperative utilization of the near-infrared imaging agent, indocyanine green, to help the surgeon identify malignant disease in a patient with malignant pleural mesothelioma who had previously received neoadjuvant chemotherapy. This technology may ultimately enhance the thoracic surgeon's ability to identify small disease deposits at the time of resection.

Keywords

malignant pleural mesothelioma, inflammation, surgery, intraoperative imaging

Introduction

Treatment of malignant pleural mesothelioma (MPM) remains a clinical dilemma. Median survival is under 2 years despite aggressive multimodal treatment protocols that incorporate chemotherapy, radiation, and surgery.¹ A number of modifications to this treatment paradigm have been proposed to improve local control rates, for example, neoadjuvant hemithoracic radiation,² intraoperative hyperthermic chemotherapy,³ or postresection photodynamic therapy.⁴

Several groups have alternatively proposed utilization of near-infrared (NIR) fluorescent contrast agents for real-time intraoperative imaging to enhance debulking for abdominal disease; however, this has not been explored for pleural-based diseases. Our group is investigating the NIR probe, indocyanine green (ICG), which exploits vascular abnormalities found in malignancies.⁵ This probe has previously demonstrated excellent in vivo efficacy in pulmonary-based malignancies and has a favorable side-effect profile.⁵ In this report, we detail the first human experience utilizing a NIR intraoperative imaging agent, ICG, in a patient with MPM who received neoadjuvant chemotherapy.

Clinical Summary

A 67-year-old male was seen in our multidisciplinary pleural-based disease clinic for the management of a recently diagnosed

left-sided pleural neoplasm. Briefly, a preoperative computed tomography (CT) demonstrated a 5.0 cm × 2.5 cm mass of the left anterolateral pleura (Figure 1A) and an ipsilateral 1.0 cm × 0.9 cm transdiaphragmatic pleural nodule (Figure 1B). There was no suspicious lymphadenopathy by positron emission tomography (PET)/CT. A transthoracic core needle biopsy of the anterolateral pleural mass was suggestive of epithelioid MPM. The patient was initially enrolled in a clinical trial of cisplatin/pemetrexed with LY3023414 (dual PI3k/mTOR inhibitor). The patient completed 6 cycles of treatment with strong response and was subsequently transitioned to maintenance therapy with LY3023414. After approximately 5 weeks of LY3023414 monotherapy, the patient was reevaluated in our surgical clinic for resection. Given continued favorable

¹ Center for Precision Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

² Division of Thoracic Surgery, Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

³ Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Submitted: 07/03/2017. Revised: 01/06/2017. Accepted: 04/07/2017.

Corresponding Author:

Sunil Singhal, 6 White Building, 3400 Spruce St, Philadelphia, PA 19104, USA.
Email: sunil.singhal@uphs.upenn.edu



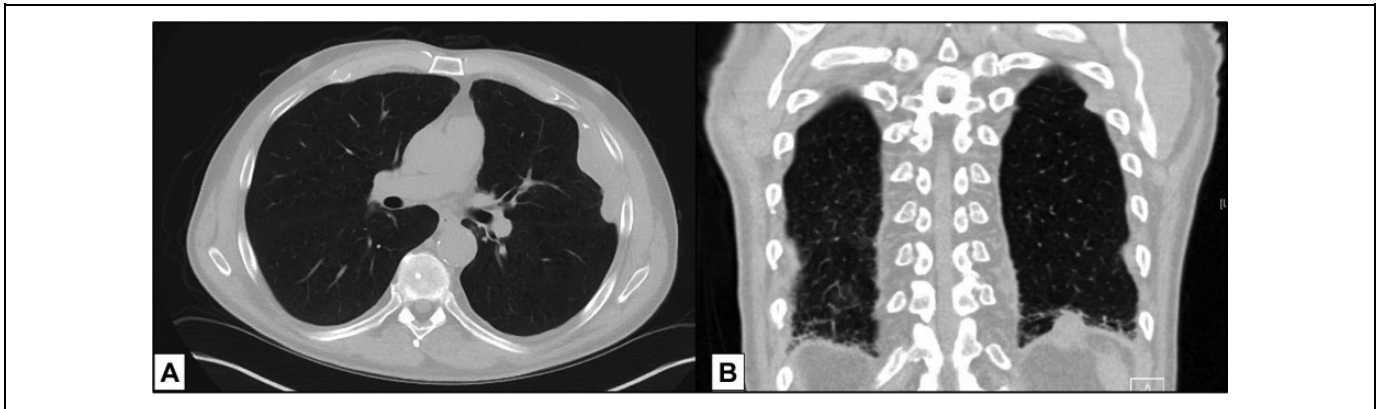


Figure 1. Preoperative computed tomography demonstrating (A) an anterolateral pleural nodule and (B) a transdiaphragmatic implant in the left hemithorax.

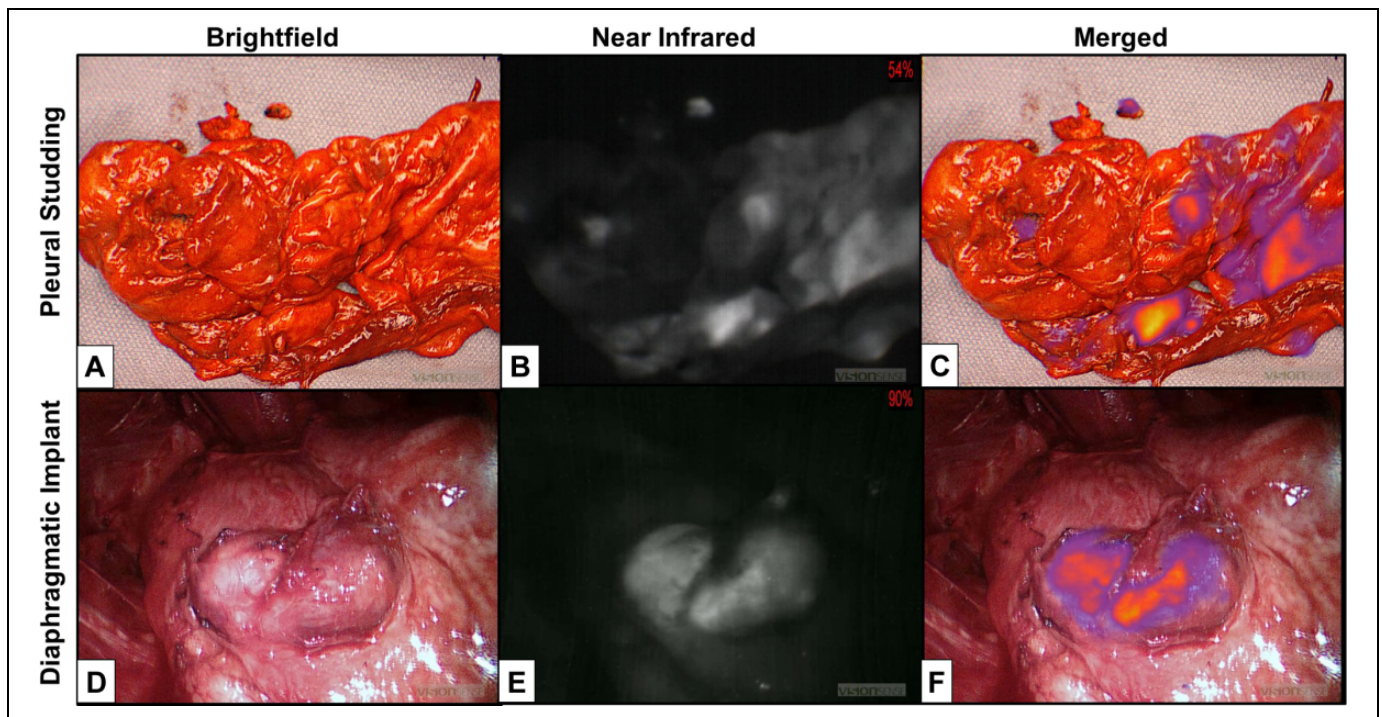


Figure 2. Near-infrared imaging at the time of pleurectomy and decortication: (A) brightfield view, (B) near-infrared view, and (C) merged view of pleural specimen with multiple subcentimeter pleural nodules. (D) Brightfield view, (E) near-infrared view, and (F) merged view of in situ diaphragmatic implant.

disease response by PET/CT and improvements in performance status, the patient was consented for a left-sided pleurectomy and decortication with NIR intraoperative imaging using ICG. LY3023414 was stopped 3 weeks prior to resection. Twenty-four hours prior to resection, the patient received intravenous ICG (5 mg/kg) uneventfully. Of note, ICG was initially reconstituted in water, then further diluted with saline as previously described.⁵

The patient was taken to the operating room for a left-sided visceral and parietal pleurectomy via left thoracotomy. Obvious inflammation and pleural studding (all less than 1

cm in size) were noted. Utilization of intraoperative imaging enhanced the surgeon's ability to discriminate benign inflammatory processes from malignant foci on the pleural surface (Figure 2A-C). The diaphragmatic implant was also clearly delineated with fluorescent imaging and resected (Figure 2D-F). Fluorescent portions were analyzed by a certified pulmonary pathologist, and the diagnosis of MPM was confirmed in 91% of nodules. Of note, there were no MPM deposits identified in nonfluorescent areas in specimen (negative predictive value = 100%). The patient ultimately recovered without signs of study drug toxicity.

Discussion

In this report, we demonstrate safety and feasibility of intraoperative imaging for a patient with MPM using the NIR contrast agent, ICG. Traditionally, ICG has been utilized to evaluate perfusion and assess vascularity.^{6,7} When used as a perfusion assessing agent, ICG is typically delivered at a dose of 0.2 to 0.4 mg/kg with fluorescent imaging shortly following (within 30-60 minutes).^{6,7} In contrast, in the presented case, ICG was utilized as a tumor-mapping agent and delivered at a higher dose of 5 mg/kg with imaging occurring at 24 hours. When implementing these delivery parameters, ICG functions by exploiting abnormally leaky capillaries and increased pressure gradients (also known as the enhanced permeability and retention effect), which are found in most solid malignancies, including MPM.⁸ Using a commercially available imaging system capable of NIR detection (Visionsense, Philadelphia, Pennsylvania), we observed that optical properties of ICG ($\lambda_{\text{ex}} = 805$ and $\lambda_{\text{em}} = 825$) were optimal for intrathoracic imaging given low levels of autofluorescence.

Although additional data are currently being accumulated, these initial results are nonetheless encouraging. First, no toxicity was observed, which is consistent with the low toxicity profile reported with other targeted NIR imaging probes. Second, we found that the addition of intraoperative imaging was feasible and added only 5 minutes to the case duration. Third, the subcentimeter sensitivity suggests that this technology may improve MPM resection and potentially improve local control rates. Lastly, we found intraoperative imaging effective after neoadjuvant chemotherapy, a paradigm commonly employed for the patient with MPM. We are currently further evaluating this technology (NCT02280954).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: J.D.P. was supported by a grant from the American Philosophical Society, the NIH (F32 CA210409), and the Association for Academic Surgery Research Grant. S.S. was supported by the NIH (R01 CA193556).

References

1. van Meerbeeck JP, Scherpereel A, Surmont VF, Baas P. Malignant pleural mesothelioma: the standard of care and challenges for future management. *Crit Rev Oncol Hematol*. 2011;78(2):92–111.
2. de Perrot M, Feld R, Leigh NB, et al. Accelerated hemithoracic radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg*. 2016;151(2):468–473.
3. Rusch VW, Figlin R, Godwin D, Piantadosi S. Intrapleural cisplatin and cytarabine in the management of malignant pleural effusions: a Lung Cancer Study Group trial. *J Clin Oncol*. 1991;9(2):313–319.
4. Ris HB. Photodynamic therapy as an adjunct to surgery for malignant pleural mesothelioma. *Lung Cancer*. 2005;49(suppl 1):S65–S68.
5. Keating J, Newton A, Venegas O, et al. Near-infrared intraoperative molecular imaging can locate metastases to the lung. *Ann Thorac Surg*. 2017;103(2):390–398.
6. Alander JT, Kaartinen I, Laakso A, et al. A review of indocyanine green fluorescent imaging in surgery. *Int J Biomed Imaging*. 2012;2012:940585.
7. Boni L, David G, Mangano A, et al. Clinical applications of indocyanine green (ICG) enhanced fluorescence in laparoscopic surgery. *Surg Endosc*. 2015;29(7):2046–2055.
8. Jiang JX, Keating JJ, Jesus EM, et al. Optimization of the enhanced permeability and retention effect for near-infrared imaging of solid tumors with indocyanine green. *Am J Nucl Med Mol Imaging*. 2015;5(4):390–400.