

Near-infrared intraoperative imaging during resection of an anterior mediastinal soft tissue sarcoma

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Abstract. Sarcomas are rare malignancies that are generally treated with multimodal therapy protocols incorporating complete local resection, chemotherapy and radiation. Unfortunately, even with this aggressive approach, local recurrences are common. Near-infrared intraoperative imaging is a novel technology that provides real-time visual feedback that can improve identification of disease during resection. The presented study describes utilization of a near-infrared agent (indocyanine green) during resection of an anterior mediastinal sarcoma. Real-time fluorescent feedback provided visual information that helped the surgeon during tumor localization, margin assessment and dissection from mediastinal structures. This rapidly evolving technology may prove useful in patients with primary sarcomas arising from other locations or with other mediastinal neoplasms.

Introduction

Primary mediastinal sarcomas are rare (1). Similar to other primary sarcomas, achieving long-term survival often requires multimodal therapy including complete local resection, chemotherapy, and radiation (2). Accomplishing complete resection of anterior mediastinal sarcomas poses challenges given proximity to critical mediastinal structures such as the phrenic nerve, heart, and great vessels. Accurate tumor identification and margin assessment during mediastinal dissection is further complicated when occurring after neoadjuvant chemotherapy, an approach commonly implemented for sarcomas.

Our group has previously reported successful utilization of near-infrared (NIR) fluorescent, real-time intraoperative

imaging to improve pulmonary metastasectomy (3). In this report, we detail successful utilization of this approach to enhance accurate identification of malignancy during resection of a thymic carcinosarcoma in a patient that previously underwent neoadjuvant chemotherapy. This report highlights how this approach can improve a surgeon's ability to identify disease and safely obtain adequate margins during resection of primary mediastinal sarcomas and, perhaps more broadly, other solid tumors located near critical structures.

Case report

A 59-year-old male was seen in our multi-disciplinary thoracic oncology institute for management of an incidentally identified 5.7x7.5x8.4 cm anterior mediastinal mass (Fig. 1A). This mass was abutting the left pulmonary artery without obvious vascular invasion. Metastatic work-up revealed no suspicious metastases. A transthoracic needle biopsy was suspicious for a thymic carcinosarcoma with rhabdomyosarcomatous elements. Six rounds of neoadjuvant chemotherapy with Adriamycin, Ifosfamide and Vinorelbine. After completing neoadjuvant treatment, the patient was consented for resection via left thoracosternotomy with NIR intraoperative imaging.

Twenty-four hours before resection, intravenous indocyanine-green (ICG) was delivered (5 mg/kg). During resection, the tumor displayed high levels of fluorescence (tumor-to-background signal ratio of 3.6) (Fig. 1B and C). Real-time fluorescent feedback aided the surgeon when during dissection from critical mediastinal structures including the phrenic nerve, pulmonary artery and aorta. After resection, negligible residual fluorescence (tumor-to-background signal ratio of 1.2) was appreciated within the operating field which increased the surgeon's confidence of complete resection (Fig. 1D).

On backtable evaluation, tumor samples were obtained from 4 quadrants (Fig. 1C and E) and fluorescence was evaluated using a macroscopic NIR fluorescence system (Visionsense®, Philadelphia, PA) (Fig. 1F). Specimen were then evaluated using a microscopic NIR fluorescent imaging system (LiCor Odyssey, Lincoln, NE) and by H&E staining (Fig. 1G and H). Margins were clear thus confirming findings of intraoperative fluorescent imaging. Of note, utilization of intraoperative imaging added 11 min to the case duration.

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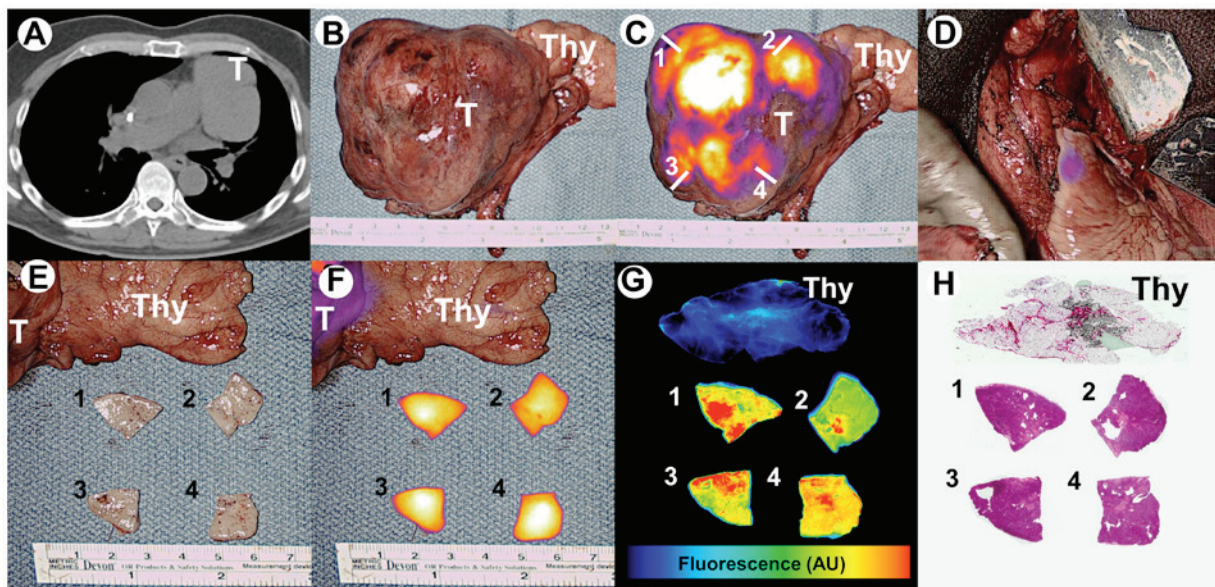


Figure 1. Preoperative and intraoperative NIR imaging of thymic carcinosarcoma: (A) preoperative CT demonstrating 4.6x7.6 cm anterior mediastinal mass, (B) white-light imaging of en bloc resection involving 10.0x9.0x3.7 cm tumor with benign thymic tissue, (C) fluorescent imaging of en bloc resection with denotation of breadloaf sections (labeled 1-4), (D) post-resection wound bed with negligible fluorescence, (E) White-light views of breadloaf sections and benign thymus, (F) macroscopic fluorescent imaging of breadloaf sections and thymus, (G) microscopic fluorescent imaging of specimens, (H) H&E microscopy of specimens. T-tumor; Thy-thymus; 1-4 breadloaf sectioning of tumor; AU-arbitrary units.

Histopathologic analysis revealed a biphasic tumor, composed of spindle and rhabdoid morphology cells along with epithelioid cells in other regions. Upon immunohistochemical analysis, spindle and rhabdoid cells stained positive for desmin, myogenin, smooth muscle actin, HHF-35, and INI-1; patchy weak positivity for S100 and MelanA was also noted. Epithelioid cells were noted to be positive for AE1/3, CAM5.2, CK5/6, and p40; weak positivity for PAX8 was also found. Overall, this morphology and immunohistochemical staining pattern was consistent with thymic carcinosarcoma with rhabdomyosarcomatous elements.

The subject recovered uneventfully without drug toxicity and remains disease free after 1 year of follow-up.

Discussion

In this report, we provide preliminary evidence suggesting safety and feasibility of NIR intraoperative imaging with ICG for anterior mediastinal sarcomas after neoadjuvant therapy. Real-time fluorescent feedback provides additional visual information that can help the surgeon during tumor localization, margin assessment and dissection from nearby vital structures.

ICG has traditionally been utilized by clinicians to assess perfusion and determine vascularity (4). Our group has recently described ICG as a tumor mapping agent (3). For tumor mapping, ICG is delivered at a dose of 5 mg/kg with imaging occurring 24 h later. Under these dosing parameters, ICG functions by exploiting abnormally leaky capillaries and increased pressure gradients (the Enhanced Permeability and Retention Effect) which are found in most solid malignancies, including sarcomas (5). In this report, we found optical properties of ICG to be excellent for intrathoracic imaging. One reconcilable drawback, however, was persistent low

levels of background fluorescence from the aorta, which is likely due to low levels of circulating albumin bound ICG. Nevertheless, accurate tumor identification was feasible given significantly higher levels of tumor-specific signal.

Although additional studies are needed, these initial findings remain encouraging. First, delivery of this dosage of ICG was well tolerated, which is consistent with our previous experiences with ICG (3). Second, we found that the addition of intraoperative imaging was efficient and added only several minutes to the case duration. Third, reliable real-time fluorescent feedback (100% accuracy) assisted the surgeon during dissection from critical mediastinal structures and suggested complete resection. Lastly, we found high levels of fluorescence after neoadjuvant chemotherapy, an approach that is applied to a variety of solid tumors, including sarcomas. Further investigation of this approach in patients with primary sarcomas and other mediastinal neoplasms, such as ectopic parathyroid adenomas and thymoma, is ongoing (NCT02280954). In the future, this technology may be a reliable tool to enhance a surgeon's ability to perform a variety of oncologic procedures including tumor localization, margin assessment and intraoperative staging.

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