



Intraoperative near-infrared molecular imaging for diagnostic thoracoscopy in difficult clinical scenario

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ABSTRACT

Precise diagnosis in intrathoracic malignancies is paramount for adequate treatment planning. Standard approach is histologic analysis from targeted biopsy obtained with different invasive procedures. Rarely, in difficult clinical scenarios, even gold standard diagnostic procedures can be ineffective in obtaining a satisfying result. Procedural developments and technological improvements applied to the chosen technique can be helpful to deal with such situation. We present two clinical cases of suspected intrathoracic malignancy in which repeated unsuccessful diagnostic procedures had already been attempted. We adopted a protocol based on intraoperative fluorescence during diagnostic thoracoscopy to increase diagnostic efficacy. In both cases we obtained a precise pathological diagnosis.

Key words: diagnostics; diffuse large B-cell lymphoma; malignant pleural mesothelioma

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Introduction

Most intrathoracic malignancies require precise pathologic diagnosis in order to design an adequate treatment. Moreover, suitable histological specimens are often needed in several clinical scenarios. For instance, the wide spectrum of oncological treatment available today for non-small-cell lung cancer requires thorough molecular analysis that could only rarely be obtained from cytology. Similarly, intrathoracic lymphoproliferative disease is another well-known scenario in which abundant histologic material is necessary.

Common diagnostic methods involve non-invasive and invasive procedures, the latter usually

being the ones with the higher diagnostic yield. Fibre-optic bronchoscopy, CT or ultrasound-guided needle biopsy and diagnostic thoracoscopy are frequently applied for most intrathoracic tumors. Nevertheless, even optimal procedures sometimes could not provide a precise histological diagnosis. When this happens, to repeat the procedure is a common approach. However, a simple second attempt of the same technique might lead to a second non-diagnostic result. Indeed, this could be a consequence of underlying clinical and pathological features of the specific case, often unveiled only when final diagnosis is obtained, and which can affect the effective diagnostic yield of the procedure of choice. It is advisable to set out techni-

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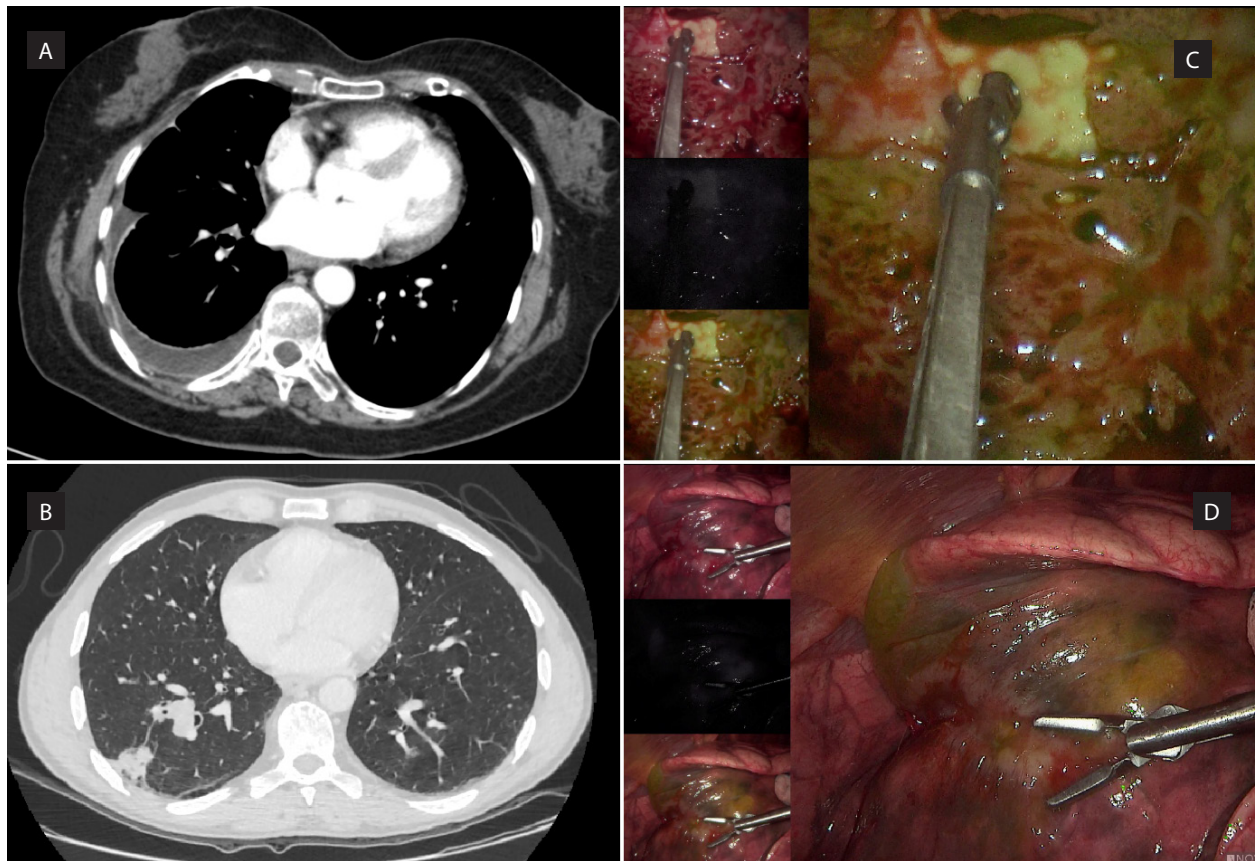


Figure 1. Preoperative CT scan of first (A) and second (B) patient are showed on figure's left side; corresponding intraoperative appearance with fluorescence (C, D)

cal improvement of the applied procedure to raise its diagnostic efficacy. Moreover, delayed diagnosis means a consequent delay in treatment, with possible negative effect on patient's final prognosis.

Materials and methods

As general thoracic department, we have experienced this problem first-hand. We present our current surgical practice to face these scenarios. As examples, we report two clinical scenarios we have faced. Written informed consent was obtained from the patient for case report and any accompanying image publication. The first patient is a 68-year-old woman with a lifelong asbestos exposure, presenting with right-sided pleural effusion and diffuse thickening (Fig. 1A) with focal pleural uptake on PET/CT scan; she had already undergone medical thoracoscopy, but final pathology provided inconsistent results (necrosis and mesothelial hyperplasia). The second patient is a 36-year-old male with history of primitive mediastinal B-cell lymphoma,

presenting with enlarging a solid PET positive lung lesion in a clinical situation of otherwise treatment-responsive disease (Fig. 1B); two CT-guided core needle biopsies and a fibre-optic bronchoscopy provided no diagnosis (blood cell aggregates with scattered lymphocytes). Therefore, we decided to perform diagnostic thoracoscopy with the aid of intraoperative fluorescence. We employed preoperative indocyanine-green (ICG) intravenous administration (5 mg/kg of body weight) and near-infrared (NIR) spectroscopy intraoperatively (i.e. 1688 Advanced Imaging Modalities (AIM) 4K Platform, Stryker Corporation®, USA).

Results

Intraoperative imaging system showed focal uptake of fluorescent dye, which guided surgeon's choice in biopsies harvesting (Fig. 1CD). Areas with abnormal morphology but lesser fluorescence display were avoided, presumed to be mostly necrotic or fibrotic. No early or delayed side effect

presented after ICG systemic administration. The patients had no complications related to surgical procedures nor from ICG administration. Final pathology proved consistent in both cases, resulting in malignant pleural mesothelioma in the first case and lung localization of primary mediastinal lymphoma in the other one. Histopathology showed morphologic heterogeneity in specimens from both patients: the first patients had pleural surface with sclero-hyaline changes and mesothelial malignant transformation; the other patient had extensive necrosis and fibrosis with focal infiltration by lymphoid elements. Further medical treatment based on these results was started for these patients.

Discussion

Intraoperative NIR imaging with ICG dye is currently used in thoracic surgery for different purposes [1]. Okusanya et al. [2] first described intraoperative lung nodules identification by means of intraoperative NIR imaging after ICG administration. They also described how neoplastic tissues are more prone to show intraoperative NIR fluorescence than non-neoplastic lesions. Thorough analysis of biomarker retention timing and capability of displaying fluorescence in time eventually led to development of the TumorGlow® technique [3]. This technique consists in high-dose ICG systemic intravenous administration (5 mg/kg) prior to surgery and intraoperative use of NIR spectroscopy imaging for identification of malignant tissue within the thorax. It is hypothesized that solid tumors have peculiar biological features and cytoarchitecture that determines different pattern of permeability and retention of ICG molecules compared to healthy tissue [4, 5]. Optimal timing to detect intraoperative ICG fluorescence for solid tumors was found to be after 24 hours from administration [6]. Main applications of these technique are in lung nodule detection, lung metastasectomy, identification of sentinel lymph nodes, assessment of resection margins [3]. ICG adverse effects include liver toxicity caused by excessive dosage and allergic reactions [7].

We applied the cited protocol in both patients presented above. Both patients had strong diagnostic suspect, the first being malignant pleural mesothelioma and the other being localization of persistent lymphoproliferative disease. Nevertheless,

they still required a precise diagnosis for adequate treatment planning and judicial issues (especially for malignant pleural mesothelioma, which is considered a professional disease in our country). In both cases, invasive diagnostic procedure had been attempted (in the second case even two times) without satisfying results. We believe that histopathologic heterogeneity reflected the different intraoperative fluorescent appearance in different areas within the same macroscopically abnormal tissue. We also believe that intraoperative fluorescence helped to raise thoracoscopy's diagnostic yield in the presented scenarios and lessened the chance of further delay in diagnosis and, consequently, appropriate treatment.

The cases reported have a major limitation: intraoperative fluorescence detection was purely empirical and not quantitative; furthermore, we could not determine whether surgical biopsy alone without intraoperative fluorescence would have equally led to an adequate diagnosis or not. It has been reported in literature that intraoperative fluorescence is able to identify focal lung neoplastic localization (primary or metastatic) that could be overlooked with optic visualization alone [2, 8]. On the other hand, there are no reported studies about the capability of intraoperative fluorescence to discern between diagnostic and non-diagnostic areas within a single inhomogeneous lesion, such as lymphoproliferative disease localizations could be. Future cohort studies aimed at this purpose are needed to clarify this aspect.

Conclusions

Intraoperative fluorescence with ICG pre-operative administration and NIR spectroscopy can be a valuable tool for intrathoracic malignancy diagnostics; it can be especially helpful to approach difficult scenarios like the ones presented in this work.

Conflict of interest

The authors have nothing to disclose.

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