



CURRENT POSTGRADUATE STUDENT

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PROGRAM	PhD in Surgery	
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FIELD OF RESEARCH / INTENDED THESIS TITLE	Pattern-specific protein analysis of lung adenocarcinoma subtypes in the development of rapid diagnostic tool to guide surgical therapy	
KEYWORDS FOR RESEARCH	Lung cancer; surgery; adenocarcinoma; subtypes; diagnosis	
RESEARCH STUDY:		
Background With increasing use of high-resolution computer tomography (CT) scan for screening of lung cancer, more and more pulmonary lesions are being detected. Some of the small lesions have a ground-glass opacity (GGO) appearance, which is defined as a hazy increased attenuation with the preservation of bronchial and vascular margins on CT. Increasing evidence suggest the solid part of a GGO (consolidation/tumour ratio) could represent the invasive growth of the tumour. Lung cancer patients with dominant GGO component on CT scan are more likely to have the non-invasive adenocarcinomas, namely adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA), whose 5-year recurrence-free survival rate are near 100%. Therefore, for such patients it may not be necessary to receive a radical lobectomy and they may be suitable for sublobar (tissue-sparing) resection procedure, for example segmentectomy, especially if the tumours are relatively small. On the other hand, for patients with a higher consolidation/tumour ratio (greater than 0.25 to 0.5 or more), more invasive adenocarcinomas could be present. Invasive lung adenocarcinomas can be classified into five major growth patterns: lepidic (LEP), acinar, papillary, micropapillary (MIP), solid (SOL) and other variants according to the 2011 new the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) classification system. Currently, two large randomized trials that mainly recruiting part-solid GGO (JCOG0802 and CALGB 140503) comparing lobectomy to sublobar resection for early-stage lung cancer are ongoing (the former excluded consolidation/tumour ratio ≤ 0.25 and the latter excluded pure GGO lesions). However, a major problem is that subgroups within invasive adenocarcinoma differs regarding to clinical outcome, of which LEP indicates the best, acinar/papillary growth indicates the moderate and MIP/SOL growth pattern indicates the worst prognosis regardless of TNM stage. And meanwhile nearly over 80 %		



of the lung adenocarcinomas had a mixed growth pattern. For invasive adenocarcinoma, in particular those subtypes with poor prognosis, a more radical surgical resection by lobectomy is more appropriate.

Fundamentally, we are still unable to distinguish the subtypes of invasive adenocarcinomas intraoperatively by frozen section with high sensitivity. The accurate identification of adenocarcinoma subtypes intraoperatively is important to guide surgical approach, since the presence of invasive adenocarcinoma MIP/SOL patterns are associated with greater recurrence potential, which warrant a lobectomy rather than sublobar resection even when harbouring a part-solid GGO appearance. The semi-dry dot-blot (SDB) method that based on the dot-blot method developed by Hirakawa et al is reported to be a substitutable tool for intraoperative frozen section diagnosis to detect lymph node metastasis in breast or lung cancer. In brief, such technique could visualizes the presence of metastasis in lymph nodes by washing the sectioned lymph nodes with anti-pancytokeratin antibody and chromogen on a dot-blot membrane. The advantage of such technique, in addition to its high sensitivity to detect as little as 0.01 mg/ml of protein extracted from cancer tissue, is the short detection time it requires (around 40 minutes), making it applicable for rapid intraoperative diagnosis and guide on-table surgical approach.

By identifying proteins or protein patterns specifically expressed by MIP/SOL growth pattern adenocarcinomas, the SDB method based on antigen-antibody reaction could be used to diagnose the existence of such components intraoperatively to guide surgical resection. In contrast to non-invasive adenocarcinoma, invasive lung adenocarcinoma is expected to have characteristics of and express a variety of proteins associated with cancer invasion. Adhesion molecules disassembling as well as apoptosis resistance had been found to be engaged in the aggressive and metastatic behavior of MIP/SOL growth adenocarcinoma. However, precise proteomic differences between the various invasive and non-invasive forms of lung adenocarcinoma by high throughput technique as antibody array have not been properly explored.

Specific Aims & Significance

To study specific proteomic expression pattern among subtypes of lung adenocarcinoma by antibody array, and to prospectively establish diagnostic tool based on SDB and protocol that enable surgeons to identify specific adenocarcinoma subtypes (namely, MIP and SOL) with unfavorable clinical outcome on the surgical table.

The translational study will record:

- 1) The results and success of high throughput antibody array in providing characteristic proteomic differences between subtypes of lung adenocarcinoma in Asian population;
- 2) The feasibility, accuracy and sensitivity of such an intraoperative diagnostic tool and protocol for identifying MIP/SOL component of lung adenocarcinoma using the SDB method compared with conventional pathological diagnosis.



CONFERENCE TITLE / ABSTRACT / POSTER:

Publications

1. Zhao ZR, Xi SY, Li W, Situ DR, Chen KM, Yang H, Su XD, Lin YB, Long H. Prognostic impact of pattern-based grading system by the new IASLC/ATS/ERS classification in Asian patients with stage I lung adenocarcinoma. *Lung Cancer* 2015;90:604-9.
2. Zhao ZR, Ng CSH. The Road to Ultimate Minimal Invasiveness. *J Vis Surg* 2016;2:29
3. Zhao ZR, Lau RWH, Ng CSH. Hybrid theatre & Alternate Localization Techniques in Single Port VATS. *J Thorac Dis* 2016 Mar; 8(Suppl 3):S319-27. doi: 10.3978/j.issn.2072-1439.2016.02.27
4. Zhao ZR, Li Z, Situ DR, Ng CSH. Recent Clinical Innovations in Thoracic Surgery in Hong Kong. *J Thorac Dis* [in press 3-2016] doi: 10.21037/jtd.2016.03.93
5. Zhao ZR, Lau RWH, Ng CSH. Non-intubated video-assisted thoracic surgery: The final frontier? *Eur J Cardiothorac Surg* 2016 [in press 4-2016]
6. Zhao ZR, To KF, Mok TSK, Ng CSH. Is there significance in pre- and intraoperative identification of micropapillary or solid growth patterns in early-stage lung adenocarcinoma. *Interact Cardiovasc Thorac Surg* [submitted 5-2016 ICVTS]
7. Zhao ZR, Situ DR, Lau RWH, Mok TSK, Chen GG, Underwood MJ, Ng CSH. Segmentectomy leads to survival equivalent to that of lobectomy for stage IA lung adenocarcinomas >1 and ≤2 cm in size: a population-based study. *J Thorac Cardiovasc Surg* [submitted 4-2016] No. JTCVS-16-759
8. Zhao ZR, Ng CSH. Statistical modelling for thoracic surgery by nomogram based on logistic regression. *J Thorac Dis* [in prep]
9. Zhao ZR, Ng CSH. Image-guided localization of small lung nodules in VATS. *J Thorac Dis* [in prep]

Chapters

1. Zhao Zerui, Ng CSH. Hookwire localization of Pulmonary Nodules in Uniportal VATS. In: Diego Gonzalez-Rivas, Calvin Sze Hang Ng (Corresponding), Gaetano Rocco, Thomas A D'Amico (eds). *Atlas of Uniportal Video Assisted Thoracic Surgery*. Springer Science Publishing 2017. Complete: July 2016 [in prep]
2. Zhao Zerui, Ng CSH. Image Guided Uniportal VATS in the Hybrid Operating Room. In: Diego Gonzalez-Rivas, Calvin Sze Hang Ng (Corresponding), Gaetano Rocco, Thomas A D'Amico (eds). *Atlas of Uniportal Video Assisted Thoracic Surgery*. Springer Science Publishing 2017. Complete: June 2016 [in prep]

Grants

- 1) Principal Investigator : Calvin SH Ng. Co-Investigator: Zhao Zerui, To Ka Fai, Chen Gong George, Underwood Malcolm. Title: Pattern-specific protein analysis of lung adenocarcinoma subtypes in the development of rapid diagnostic tool to guide surgical therapy. Department of Surgery and Department of Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong. Project Ref No.: 2015.1.087. Direct Grant 2015/16. Amount : HKD 25,000. Start Date: 30-6-2016, End date: 29-6-2017