

Are frozen sections of mediastinoscopy samples as effective as formal paraffin assessment of mediastinoscopy samples for a decision on a combined mediastinoscopy plus lobectomy?

Saina Attaran*, Gentjan Jakaj, Metesh Acharya and Jon R. Anderson

Department of Cardiothoracic Surgery, Hammersmith Hospital, Imperial College, London, UK

* Corresponding author. 46 Queen of Denmark Court, Finland Street, London SE16 7TB, UK. Tel: +44-7973435452; fax: +44-2072314421; e-mail: saina.attaran@nhs.net (S. Attaran).

Received 5 November 2012; received in revised form 19 December 2012; accepted 3 January 2013

Abstract

A best evidence topic in cardiothoracic surgery was written according to a structured protocol. The question addressed was 'Are frozen sections of mediastinoscopy samples as effective as formal paraffin assessment of mediastinoscopy samples for a decision on a same-day lobectomy?'. Five papers were found using the reported search that represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. These studies compared the efficacy and accuracy of frozen sections (FSs) from mediastinal lymph nodes for staging of patients with lung cancer to determine whether a combined procedure can be planned based on these results and to proceed to thoracotomy and lung resection in cases of negative mediastinal nodes diagnosed by FS. These studies unanimously showed that FS of mediastinal nodes are as accurate as permanent section results and definite histology diagnosis with a sensitivity of >94% and specificity of 100% with no false-positive results. They also confirmed that even in benign lung conditions and other malignancies of the mediastinum, the results of FS are compared with the histology of the node. Based on the current reports, a combined procedure (staging mediastinal nodes by FS and planning for thoracotomy or abandoning thoracotomy) is a safe approach to treat non-small-cell lung cancer (NSCLC). From the patients' point of view, this approach is superior to the staged procedure (mediastinoscopy followed by lung resection at a later date based on the histology of mediastinal nodes) due to single hospitalization and anaesthesia, however whether it is cost effective or not is debatable. It is also labour-intensive and operator-dependant. In conclusion, the current evidence in the literature suggests that a combined procedure of mediastinal node FS followed by lung resection can be a safe alternative to a staged approach to this disease.

Keywords: Lung cancer • Mediastinal lymphadenopathy

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In [Patients undergoing mediastinoscopy as part of lung cancer staging] is [Frozen section] as effective as [paraffin sections] for the identification of [Mediastinal involvement].

CLINICAL SCENARIO

You are a visiting surgeon in a North American hospital and watch a US surgeon performing a VATS lobectomy. Prior to this, he always performs a mediastinoscopy with frozen section (FS) and then continues with the lobectomy if the results of FS are negative. You are surprised by this as you had always assumed

that you had to wait for a week for the results from paraffin section to come back, and wonder if FS ever gives a false-negative result that may put the patient through an unnecessary lobectomy. You decide to check the evidence.

SEARCH STRATEGY

Medline 1950 to September 2012 using OVID interface [exp frozen section mediastinal nodes/OR.mp] AND [exp same day lung resection/OR single procedure mediastinoscopy/lung resection.mp].

SEARCH OUTCOME

We excluded non-English papers, case reports and those that did not compare FS with definite histology of mediastinal nodes. Of five papers that were identified, three were retrospective

Table 1: Papers comparing results of mediastinal frozen sections with formal paraffin embedded histopathology results

Author, year, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments and limitations
Gephardt and Rice (1990), J Thorac Cardiovasc, USA [2], Retrospective (level III)	122 consecutive patients	FS of mediastinal nodes is reliable and accurate with high degree of sensitivity Lower cost with one stage	False-negative = 1.6% Sensitivity = 94.6% NPV = 97.7% False-positive = 0% Specificity = 100% PPV = 100%	Cases of known bronchogenic carcinoma only Retrospective study
Clarke <i>et al.</i> (1994), Ann Thorac Surg, USA [3] Randomized (level I)	Group 1: 38 patients for IC Group 2: 36 patients for FS (128 samples in each group)	FS and IC are both effective and sensitive tests for mediastinal lymph nodes	False-negative = 1% Sensitivity = 94% NPV = 99% False-positive = 0% Specificity = 100% PPV = 100% Efficacy = 99.2%	Disadvantages of FS compared with IC was that IC is less time consuming
de Montpréville (1997), Eur J Cardiothorac Surg, France [4] Retrospective (level III)	420 consecutive patients	FS is effective in staging and single stage procedure in lung cancer but less valuable in other mediastinal pathologies	Sensitivity = 99% Specificity = 97% Efficacy = 99.4%	Retrospective Different approaches to the mediastinal nodes Different pathologies
Sanli <i>et al.</i> (2008), Adv Ther, Turkey [6] Prospective observational (level II)	136 patients	FS is a sensitive and specific tool in determining malignant as well as benign tumours of the mediastinum	False-negative = 3.6% Sensitivity = 94% NPV = 90% False-positive = 0% Specificity = 100% PPV = 100% Morbidity = 1.5%	Observational study
Kim <i>et al.</i> (2004), J Thorac Cardiovasc Surg, USA [7] Retrospective (level III)	57 staged procedures 286 combined procedures Cases of induction chemotherapy were excluded	No FS result was reversed by further histological evaluation	Accuracy = 95% 7% FS showed N2/N3 Similar results with combined and staged procedures	Retrospective study A full staging (radiology/lung cancer histology) will facilitate the combined approach

NPV: negative predictive value; PPV: positive predictive value; FS: frozen section; IC: imprint cytology.

reports, one prospective observational study and only one randomized trial. These studies are presented in Table 1.

RESULTS

The combined procedure was first proposed by Gephardt and Rice [2] who reported the results of FS with histology from 122 consecutive patients with a history of bronchogenic carcinoma and showed no false-positive results and only 1.6% false-negative in the samples. Their study also showed a 15% lower cost with a single-stage procedure.

Their findings were strongly supported by Clarke *et al.* [3] with no false-positive results and only 1% false-negative samples. In his study, he randomized patients with enlarged mediastinal lymph nodes to undergo imprint cytology (IC) (Group 1) or FS (Group 2). Both techniques were found to be equally sensitive for the evaluation of mediastinal lymph nodes, however, the authors concluded that IC was superior to FS as it is less time

consuming compared with FS; with FS each specimen is separately embedded, frozen, sectioned and stained resulting in a longer process and artifactual changes, however, these changes did not affect the efficacy of FS.

Despite the high efficacy of the FS of mediastinal lymph nodes in lung cancer, its sensitivity and specificity for other cancers involving mediastinum are also assessed; de Montpréville *et al.* [4] retrospectively examined the results of mediastinal node FS against the results from permanent section from 420 consecutive patients; they confirmed that in 99% of the cases, FS confirms the involvement of mediastinal nodes with malignant cells. For conditions such as sarcoidosis sensitivity was as high as 100%. In 1 patient with lymphoma, however, a second mediastinal operation was required for a precise subtyping. Four of five cases of thymoma were correctly diagnosed with FS, and in the patient with false-negative results delay in treatment resulted. With regard to lung cancer, FS was confirmed to be a useful, easy and sensitive technique to determine whether the surgeon should proceed to thoracotomy or not. The risk of false-negative is only limited to

the cases of micrometastasis, and a limited mediastinal involvement does not prevent the patient from benefiting from resection [5]. An observational study on 136 patients also confirmed no false-positive samples with 100% specificity of FS and 94% specificity [6]. They also assessed the value of FS in all types of enlarged mediastinal nodes and found similar sensitivity and specificity with benign as well as malignant lesions.

A retrospective observational study, which was based on the registry database, by Kim *et al.* [7] compared the outcome of staged with combined procedures; they showed no difference in the outcome of treatment between the two groups before and after propensity matching. No FS diagnosis was reversed by a further routine histological evaluation. Although the combined procedure was favoured by the patients, there was an unsuspected 7% N2/N3 nodes in whom thoracotomy was not performed, therefore the operative time was not utilized.

CLINICAL BOTTOM LINE

FS of mediastinal lymph nodes is as sensitive and specific as histological evaluation of these samples. Therefore, a combined procedure of mediastinal lymph node biopsy ± lung resection should be considered where FS facilities are available. This approach is preferred by the patients due to single hospitalization and single anaesthesia. The rate of false-positive with FS was found to be 0% by all the studies, therefore the risk of abandoning lung resection in a resectable lung cancer is expected to be

zero. Only a small percentage of FS were false-negative, which resulted in lung resection, however, this may be due to micrometastasis and limited mediastinal lymph node involvement in which lung resection remains beneficial.

Conflict of interest: none declared.

REFERENCES

- [1] Dunning J, Prendergast B, Mackway-Jones K. Towards evidence-based medicine in cardiothoracic surgery: best BETS. *Interact CardioVasc Thorac Surg* 2003;2:405-9.
- [2] Gephardt GN, Rice TW. Utility of frozen-section evaluation of lymph nodes in the staging of bronchogenic carcinoma at mediastinoscopy and thoracotomy. *J Thorac Cardiovasc Surg* 1990;100:853-9.
- [3] Clarke MR, Landreneau RJ, Borochovitz D. Intraoperative imprint cytology for evaluation of mediastinal lymphadenopathy. *Ann Thorac Surg* 1994; 57:1206-10.
- [4] de Montpréville VT, Dulmet EM, Nashashibi N. Frozen section diagnosis and surgical biopsy of lymph nodes, tumors and pseudotumors of the mediastinum. *Eur J Cardiothorac Surg* 1998;13:190-5.
- [5] Pearson FG. Staging of the mediastinum. Role of mediastinoscopy and computed tomography. *Chest* 1993;103:346S-8S.
- [6] Sanli M, Isik AF, Tuncozgun B, Akar E, Deniz H, Bakir K *et al.* The reliability of mediastinoscopic frozen sections in deciding on oncological surgery in bronchogenic carcinoma. *Adv Ther* 2008;25:488-95.
- [7] Kim K, Rice TW, Murthy SC, DeCamp MM, Pierce CD, Karchmer DP *et al.* Combined bronchoscopy, mediastinoscopy, and thoracotomy for lung cancer: who benefits? *J Thorac Cardiovasc Surg* 2004;127:850-6.