Does the sequence of pulmonary vasculature ligation have any oncological impact during an anatomical lung resection for non-small-cell lung cancer?

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Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was ‘in patients with primary lung carcinoma, does the sequence of pulmonary vasculature ligation during anatomical lung resection influence the oncological outcomes?’ A total of 48 papers were found using the reported search, of which 7 represented the best evidence to answer the question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. Among six prospective studies included, five of them randomized patients to either pulmonary vein or artery occlusion first during anatomical lung resection, while one study was retrospective. Two reports did not find any difference between pulmonary vein and artery occlusion first during long-term follow-up in terms of either disease recurrence (51 vs 53%, P = 0.7), or 5-year overall survival (54 vs 50%, P = 0.82). One report did not find any difference with regard to circulating tumour cells either after thoracotomy (5.0 vs 3.9, P = 0.4), or after the completion of lobectomy (38.0 vs 70.0, P = 0.23). One report found a higher expression of CD44v6 (P = 0.008) and CK19 (P = 0.05) in patients undergoing pulmonary arterial occlusion first. One report found that pulmonary vein occlusion before that of the pulmonary arterial branches has a favourable outcome on circulating carcino-embryonic antigen (CEA) mRNA in the peripheral blood, while another one did not find a significant difference in circulating levels of CEA mRNA (P = 0.075) and CK19 mRNA (P = 0.086) with either method. Another study reported no correlation between circulating pin1 mRNA levels in peripheral blood after the completion of the resection and the sequence of ligation of pulmonary vessels (9.95 ± 0.91 vs 14.71 ± 1.64, P > 0.05). Based on the two studies assessing the long-term outcome of patients with primary lung cancer undergoing anatomical curative resection, the sequence of ligation of pulmonary vessels does not seem to influence the oncological outcomes or survival. However, the other studies focusing on the influence of these techniques on circulating tumour cells or their molecular products report conflicting results the clinical consequences of which cannot be predicted.

Keywords: Non-small-cell lung carcinoma • Surgery • Pulmonary artery • Pulmonary vein • Circulating neoplastic cells • Survival

INTRODUCTION

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

THREE-PART QUESTION

In [patients undergoing anatomic lung resection for non-small cell lung carcinoma], does [the sequence of pulmonary vasculature occlusion] has any [oncologic impact]?

CLINICAL SCENARIO

A 68-year old male patient has been diagnosed with non-small-cell lung cancer (NSCLC) of the right upper lobe. After the preoperative work-up and a negative distant and mediastinal metastatic staging, you decide that the most appropriate therapeutic approach would be a right upper lobectomy along with mediastinal lymph node dissection. Before surgery, a discussion with your assistant raises the issue whether dissecting and individually ligating the pulmonary artery (PA) branches to the upper lobe before doing so for the upper lobe branch of the superior pulmonary vein (PV) might affect the oncological outcome of the procedure. You resolve to check the literature yourself.

SEARCH STRATEGY

Ovid MEDLINE(R) 1946 to July 2014 was searched using the following search terms: [exp Lung Neoplasms/] AND [surgery.mp] AND [pulmonary vessels.mp].

SEARCH OUTCOME

Forty-eight studies were identified using the reported search criteria and 7 were selected as the best evidence on the topic (Table 1).
<table>
<thead>
<tr>
<th>Author, date, journal and country</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Refaeli et al. (2003), J Thorac Cardiovasc Surg, Israel [2]</td>
<td>Entire cohort: 279 patients undergoing anatomical lung resection for NSCLC divided in two groups: - interruption of the PV before the artery (V-first), n = 133 - interruption of PA first (A-first), n = 149</td>
<td>Disease recurrence in correlation with the sequence of vessel interruption for a mean follow-up of 22.6 months (range 0.16-106 months)</td>
<td>‘V-first’ group n = 68 (51%) ‘A-first’ group n = 78 (53%) P = 0.7</td>
<td>Results suggest that the sequence of vessel interruption during anatomical lung resection for NSCLC is not a risk factor for disease recurrence, while lung manipulation (forceful retraction prior to vessel interruption) might cause tumour cell dissemination</td>
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<td>Kozak et al. (2013), Adv Med Sci, Poland [3]</td>
<td>Patients undergoing anatomical lung resection (lobectomy, bilobectomy, pneumonectomy) were randomized in two groups: - ligation of the PA branches first (Group A), n = 215 - ligation of the PV first (Group V), n = 170</td>
<td>5-year overall survival in relation with sequence of pulmonary vessel ligation</td>
<td>Group A: 50% Group V: 54% P = 0.82</td>
<td>Long-term survival does not seem to be influenced by the sequence of vessel ligation during anatomical lung resections in patients with NSCLC</td>
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<td>Hashimoto et al. (2014), Interact CardioVasc Thorac Surg, Japan [4]</td>
<td>30 consecutive patients undergoing lung resection for primary lung cancer: - ligation of the PA first and the PV last (PA group), n = 21 - ligation of the PV first (PV group), n = 9</td>
<td>Incidence of blood-related metastasis in relation with sequence of pulmonary vessel ligation</td>
<td>Group A: 20.5% Group V: 14.7% P = 0.18</td>
<td>Ligation of the PV first may reduce the rate of haematogenous cancer cell dissemination and the occurrence of distant metastasis (statistically not significant difference)</td>
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<tr>
<td>Song et al. (2013), Oncol Lett, China [5]</td>
<td>30 consecutive patients undergoing lobectomy for NSCLC: - ligation of the PA first and the PV last (PA group), n = 15 - ligation of the PV first and the PA last (PV group), n = 15</td>
<td>Number of circulating tumour cells in the PV per 2.5 ml of blood</td>
<td>After thoracotomy - PA group: 3.9 - PV group: 5.0 P = 0.4</td>
<td>Although patients were not randomly assigned into PV-first lobectomy or PA-first lobectomy groups, the results suggest that PV first provides no advantage over PA first in prevention of spillage of tumour cells by surgical manipulation</td>
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</table>

The authors suggest avoiding excessive manipulation of the tumour-bearing lobe especially before ligation of the draining PV if venous invasion is suspected.

Results suggest that ligation of the PV should be performed first during lobectomy. Surgical manipulation itself may stimulate the occurrence of blood micrometastases. Ligation of the PV first during surgery may help prevent blood micrometastases.

Continued
### Table 1: (Continued)

<table>
<thead>
<tr>
<th>Author, date, journal and country</th>
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<tr>
<td>Kurusu et al. (1998), J Thorac Cardiovasc Surg, Japan [6]</td>
<td>Prospective randomized cohort study (level 1b)</td>
<td>30 patients undergoing lobectomy for NSCLC and 6 patients undergoing lobectomy after induction chemotherapy for SCLC randomized to have either PV (n = 15) or PA (n = 15) ligation first. Four time points of peripheral blood sampling: I: before operation, II: 5 min after first vessel ligation (PV or PA), III: 5 min after second vessel ligation (PA or PV) and IV: after the completion of surgery. - 10 patients undergoing open lung biopsy for interstitial lung disease (control) - 41 healthy volunteers</td>
<td>CK19 (strongly associated with the presence of lung cancer metastases or recurrence, particularly after surgery) levels during the early and late periods</td>
<td>PA group Early period: 11.21 ± 3.14 Late period: 8.60 ± 4.02 <em>P</em> = 0.050 PV group Early period: 10.60 ± 3.15 Late period: 10.30 ± 2.98 <em>P</em> = 0.532</td>
<td>Of 16 patients with positive CEA mRNA before operation, PV ligation led to neutralization of CEA mRNA in peripheral blood (four in PV-ligation first and four in PA-ligation first groups), suggesting that PV ligation may partly prevent shedding of cancer cells in the bloodstream. Of 14 patients with negative CEA mRNA before operation, PV ligation first led to positive peripheral blood CEA mRNA in 3 of 7 patients in this group, while PA ligation first led to positive peripheral CEA mRNA in 6 of 7 patients in this group. These results might suggest that delay in ligation of the PV leads to shedding of cancer cells in the bloodstream. Patients with even limited-stage SCLC are likely to have systemic disease and surgical treatment might have little impact on their prognosis.</td>
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<td>Ge et al. (2006), J Cancer Res Clin Oncol, China [7]</td>
<td>Prospective randomized study (level 1b)</td>
<td>23 consecutive patients undergoing anatomical lung resection (lobectomy) for primary lung cancer: - ligation of the PA first and the PV last (PA group), n = 11 - ligation of the PV first and the PA last (PV group), n = 12</td>
<td>Pattern of peripheral blood CEA mRNA in patients with SCLC undergoing lobectomy</td>
<td>NSCLC Perioperative CK19 mRNA levels PA-ligation first group: n = 3 PV-ligation first group: n = 6</td>
<td>In patients undergoing lobectomy for primary lung cancer the PV should be ligated first, before the ligation of the pulmonary arterial branches. However, this strategy cannot prevent the tumour cells from spreading to an ectopic site through a lymphatic channel.</td>
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<tr>
<td>Ai et al. (2008), Zhong Nan Da Xue Xue Bao Yi Xue Ban, China [8]</td>
<td>Prospective randomized study (level 1b)</td>
<td>26 patients undergoing lung resection for NSCLC were randomized into two groups: - ligation of the PA first and the PV last (PA group), n = 12 - ligation of the PV first and the PA last (PV group), n = 12</td>
<td>pin1 mRNA expression between patients with and without NSCLC</td>
<td>PA group: 5.085 PV group: 4.503 <em>P</em> = 0.086 PA group: 4.817 PV group: 4.397 <em>P</em> = 0.075</td>
<td>Ligation of the PV before the PA in patients with NSCLC undergoing curative resection may decrease the expression of pin1 mRNA in the peripheral</td>
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</table>
RESULTS

Refaei et al. [2] reviewed 279 patients undergoing anatomical lung resection for NSCLC and classified them into two groups: \( n = 133 \), PV ligated first (PV group), vs \( n = 149 \) PA first group (PA). The mean follow-up period was 22.6 months (range: 0.16–106 months); disease recurrence did not differ among the two groups (PV: \( n = 68 \) (51%), PA: \( n = 78 \) (53%), \( P = 0.7 \)). Multivariate analysis did not demonstrate the sequence of vessel interruption affecting disease recurrence (odds ratio = 1.29, 95% confidence interval 0.73–2.29, \( P = 0.4 \)).

Kozak et al. [3] prospectively randomized 385 patients undergoing lobectomy for NSCLC into PV first (\( n = 170 \)) or PA first (\( n = 215 \)) groups. The mean follow-up duration was 61.5 ± 39.5 months. There were no differences in either the 5-year overall survival (PV 54 vs PA 50%, \( P = 0.82 \)), or in the incidence of haematogenous metastases during the follow-up period (PV 14.7% vs PA 20.5%, \( P = 0.18 \)).

Hashimoto et al. [4] studied the effect of surgical manipulation of the tumour-bearing lobe on the spillage of tumour cells. The authors performed a non-randomized study where 30 patients undergoing lobectomy for NSCLC had PA ligation first (PA group, \( n = 21 \)) or PV ligation first (PV group, \( n = 9 \)). There was no difference in tumour cell spillage in the blood after thoracotomy and before the resection (PA group: 3.9 vs PV group 5.0, \( P = 0.4 \)) and after the completion of the lobectomy (PA group: 70.0 vs PV group 38.0, \( P = 0.23 \)).

Song et al. [5] randomized 30 patients undergoing lobectomy for NSCLC in either PA ligation first (\( n = 15 \)), or PV ligation first (\( n = 15 \)). The authors studied the expression of CD44v6 and CK19 from blood samples retrieved from the proximal part of the PV immediately after thoracotomy and before its dissection. Patients undergoing PA ligation first had significantly increased levels of CD44v6 (\( P = 0.008 \)) and CK19 (\( P = 0.05 \)) at the conclusion of the lobectomy (when the draining vein was cut-off), while those undergoing PV ligation first did not have any difference (\( P = 0.558 \) and \( P = 0.532 \), respectively).

Kurusu et al. [6] randomized 30 patients who had lobectomy for NSCLC into two groups depending on whether the PV (\( n = 15 \)) or artery (\( n = 15 \)) was ligated first. Carcinoembryonic antigen messenger RNA (CEA mRNA) in the peripheral blood before surgery,
5 min after first vessel ligation, 5 min after second vessel ligation and after the completion of surgery was measured. CEA mRNA was taken as a marker of neoplastic cells. Of 30 preoperative samples, 16 were CEA mRNA positive; of these 16, 8 remained positive after lobectomy. The remaining 8 (n = 4 in each group) were negative. Of the 14 initially negative samples (n = 7 in each ligation group), 9 became positive during the operation. The conversion during the operation was more common with PA ligation first (n = 6, 85.7%) vs PV ligation (n = 3, 42.9%).

Ge et al. [7] randomized 23 patients undergoing anatomical lung resection for primary lung cancer in either the PA ligation first (PA group, n = 11) or PV ligation first group (PV group, n = 12). The expression of either CK19 mRNA (PA group 5.058 vs PV group 4.503, P = 0.086) or CEA mRNA (PA group 4.817 vs PV group 4.397, P = 0.075) did not differ significantly between these two groups.

Finally, Ai et al. [8] prospectively randomized 26 patients undergoing lobectomy for NSCLC into two groups, namely PV first (n = 14) vs PA first (n = 12). Levels of pin1 mRNA were measured as a surrogate marker of tumour cell dispersion (an isomerase overexpressed in several human cancers in peripheral blood samples. Pin1 mRNA is overexpressed in patients with NSCLC when compared with healthy volunteers and patients with benign lung disease (P < 0.05), and it is increased in patients with stage III disease when compared with patients with Stage I and II disease (18.48 ± 1.64 vs 10.57 ± 1.05, respectively, P < 0.05), as well as in patients with lymph node positive disease when compared with those with lymph node negative disease (18.93 ± 2.10 vs 10.02 ± 1.23, respectively, P < 0.05). Furthermore, pin1 mRNA levels were elevated in the distal PV when compared with the proximal PV (30.56 ± 1.37 vs 20.31 ± 1.48, respectively, P < 0.05). However, there were no significant differences in peripheral blood pin1 mRNA after surgery between patients undergoing either pulmonary vein or artery ligation first (9.95 ± 0.91 vs 14.71 ± 1.64, respectively, P > 0.05).

**CLINICAL BOTTOM LINE**

Based on the two studies assessing the long-term outcome of patients with primary lung cancer undergoing anatomical curative resection, the sequence of ligation of pulmonary vessels does not seem to influence oncological outcomes or survival. However, the other studies focusing on the influence of these techniques on circulating tumour cells or their molecular products report conflicting results, the clinical consequences of which cannot be predicted.

**Conflict of interest:** none declared.

**REFERENCES**