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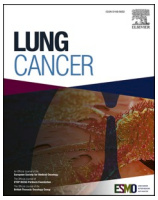

Optimum diagnostic pathway and pathologic confirmation rate of early stage lung cancer: Results from the VIOLET randomised controlled trial

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A B S T R A C T

Background: Pathologic confirmation of lung cancer influences treatment selection for suspected early-stage lung cancer. High pre-treatment tissue confirmation rates are recommended. We sought to define management and outcomes of patients undergoing surgery for primary lung cancer in a UK multi-centre clinical trial.
Methods: VIOLET compared minimally invasive video-assisted thoracic surgery versus open surgery for known or suspected lung cancer. Diagnostic patient pathways were identified and methods of tissue confirmation were documented. The outcome of inappropriate lobectomy for benign disease or inappropriate wedge resection for primary lung cancer was compared with respect to the pathologic diagnosis.
Findings: From July 2015 to February 2019, 502 patients were randomised and underwent surgery; 262 (52%) had a pre-operative pathologic confirmed diagnosis of primary lung cancer, 205 did not have a pre-operative biopsy and 35 had a non-diagnostic pre-operative biopsy.
Of the 240 participants without pre-operative pathologic confirmation of primary lung cancer, intraoperative biopsy and frozen section analysis was undertaken in 144 (60%). The remaining 96 underwent direct surgical resection without tissue confirmation (19% of the entire cohort). Confirmation of histologic diagnosis before surgery was less costly than diagnosis in the operating theatre. The inappropriate surgery rate was 3.6% (18/502 participants, 7 lobectomy for benign disease, 11 wedge resection for lung cancer).
Interpretation: Low levels of inappropriate resection can be achieved at pre-operative tissue confirmation rates of 50% through a combination of intra-operative confirmatory biopsy and correct risk estimation of lung cancer. Practice needs to be monitored to ensure acceptable levels are consistently achieved.

1. Introduction

Pathologic confirmation of lung cancer has important implications for the selection of sequencing and planning for multimodality management where treatment decisions differ according to cell type, genetic mutation, translations, and cell surface markers. Authors of the National Lung Cancer Audit Report 2018 stated a UK target of 90% pathologic confirmation rate for patients with good performance status (PS 0–1) with stage I-II lung cancer [1]. The rationale of tissue confirmation (over "clinical" diagnosis per se) was stated as the need to confirm the diagnosis, origin and sub-type of cancer as well as the molecular profile. In suspected early-stage lung cancer however, the impact of lobectomy

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without tissue confirmation has not been well studied and remains uncertain.

Using data collected prospectively within the context of a national multi-centre randomised trial, we sought to assess practice across participating sites to quantify the proportion of participants who were correctly diagnosed with (or without) primary lung cancer pathologically and were managed appropriately. We also aimed to define the proportion of patients in whom a pre-operative diagnosis was unknown and identify how this was managed.

2. Materials and methods

VIOLET is a randomised trial comparing the outcomes of minimally invasive video-assisted thoracic surgery (VATS) versus open surgery for known or suspected lung cancer with a primary endpoint of physical functioning at 5 weeks. The trial protocol and results have been published [2–4].

Entry of patients was screened by the local (site specific) multidisciplinary team (MDT) and no restrictions were placed on the diagnostic pathway for potential participants with suspected but not pathologically confirmed cancer. Two groups of patients were identified as eligible for VIOLET: a) patients for whom the MDT confirmed the need for lobectomy (i.e. patients with proven primary lung cancer, or without pre-operative tissue diagnosis because a biopsy was deemed not possible or not required) and b) patients for whom the MDT recommended a biopsy with the option to proceed to lobectomy (principally by VATS biopsy and on-site frozen section analysis and real-time reporting) if lung cancer was confirmed.

The outcome of this study was the appropriate extent of surgery with respect to the pathologic diagnosis. This is defined as diagnostic wedge resection only for benign disease (but not for primary lung cancer) and lobectomy for primary lung cancer (but not for benign disease). As a quality standard for the MDT decision (on recommendation of surgery in patients without a pre-operative diagnosis), we stated an a-priori expectation that less than 4% of participants would receive lobectomy for benign disease, a figure proposed and monitored by the trial Data Monitoring and Safety Committee (DMSC). This figure was based on the results of a previous RCT by Bendixen *et al* that reported a benign lobectomy rate of 1.9% (4/206), and the DMSC considered it "unacceptable" to exceed this number by a factor of two [5].

We also considered the costs associated with diagnosis. All biopsies undertaken (endobronchial ultrasound (EBUS) biopsy, image guided biopsy and/or biopsy and frozen section analysis and whether the participant went on to receive definitive surgery or not) were identified and costed for each participant regardless of whether the biopsies achieved a diagnostic result or not (see Online Appendix 1 for details of unit costs), and average costs per participant for each pathway were estimated.

3. Results

From July 2015 to February 2019, a total of 2,109 patients were screened across nine centres to obtain 503 patients who were eligible and consented to participate in VIOLET. One participant withdrew from the trial completely prior to surgery so is excluded from the following tables and figures. Of the remaining 502 participants, 486 (97%) had both a pre-operative computerised tomography (CT) and positron emission tomography and CT (PET-CT), eight had a CT alone and eight received a PET-CT alone. Fifty-nine percent of participants (297/502) had a pre-operative biopsy attempted; 242 had an image guided biopsy, and 64 had a bronchoscopy/EBUS (8 participants had both image-guided and EBUS biopsies). Two hundred and sixty-two of these biopsies led to a pre-operative pathologic confirmed diagnosis of primary lung cancer (262/502, 52%), with the remaining 35 being non-diagnostic. The other 205/502 (41%) participants did not have a pre-operative biopsy.

The baseline characteristics and histological types of participants under each biopsy pathway are presented in Table 1.

Of the 240 participants who entered the operating theatre without pathologic confirmation of primary lung cancer, biopsy and frozen section analysis was undertaken in 144 (60%) participants. In the remaining 96 (19% of the entire cohort), surgery was undertaken without tissue confirmation (92 lobectomy, three wedge resection, one segmentectomy). Of the 144 participants in whom a biopsy and frozen section was performed, a diagnostic result was achieved in 139 (97%); cancer was confirmed in 107/139 participants and a benign result was reported in 32/139 participants (of which two were subsequently confirmed as cancer). In the five participants in whom a diagnostic result was not obtained the surgeons proceeded to lobectomy.

Fig. 1 details all possible permutations of the biopsy pathway and outcomes for the 502 participants. The overall lobectomy rate for benign disease in the trial was 1.4% (7 participants). The rate of wedge resection for lung cancer was 2.2% (11 participants), giving an overall rate of inappropriate surgery of 3.6% (18/502 participants). Although the protocol stipulated lobectomy for primary lung cancer, wedge resections could have been performed in situations where the primary lung cancer was not overtly invasive (e.g. adenocarcinoma in situ, minimally invasive adenocarcinoma) or (appropriately) for secondary lung cancer. We are aware of two of these cases of wedge resection being performed for non-primary lung cancer, but we did not have access to the reasons behind the decision making in all cases.

The average cost for each biopsy pathway for all participants is also included in Fig. 1. Average costs of diagnosis were lower for participants who had pre-operative pathologic confirmation of primary lung cancer than for those whose diagnosis was confirmed in the operating theatre.

New secondary cancer was reported in three (0.6%) participants consisting of pancreatic adenocarcinoma, breast, and colorectal cancers. Of these three participants, one had a pre-operative pathologic diagnosis of non-small cell lung cancer adenocarcinoma and then proceeded to lobectomy, and two proceeded straight to lobectomy.

Table 1
Baseline characteristics and histological types.

Characteristic	Cancer confirmed on pre-operative biopsy (n = 262)	Cancer not confirmed on pre-operative biopsy (n = 240)	
		Frozen section attempted (n = 144)	No frozen section attempted (n = 96)
Age (years)	69 (8.8)	68 (9.7)	70 (7.4)
Male	131/262 (50.0%)	75/144 (52.1%)	43/96 (44.8%)
cT stage			
1a	14/262 (5.3%)	24/144 (16.7%)	3/96 (3.1%)
1b	70/262 (26.7%)	56/144 (38.9%)	37/96 (38.5%)
1c	70/262 (26.7%)	40/144 (27.8%)	24/96 (25.0%)
2a	62/262 (23.7%)	20/144 (13.9%)	15/96 (15.6%)
2b	19/262 (7.3%)	1/144 (0.7%)	9/96 (9.4%)
3	27/262 (10.3%)	3/144 (2.1%)	8/96 (8.3%)
cN stage			
0	241/262 (92.0%)	138/144 (95.8%)	91/96 (94.8%)
1	21/262 (8.0%)	6/144 (4.2%)	5/96 (5.2%)
Pre-operative histological type			
Adenocarcinoma	169/262 (64.5%)	1/144 (0.7%)	2/96 (2.1%)
Squamous carcinoma	61/262 (23.3%)	0/144 (0.0%)	1/96 (1.0%)
Other	30/262 (11.5%)	0/144 (0.0%)	0/96 (0.0%)
Baseline histology not confirmed	2/262 (0.8%)	143/144 (99.3%)	93/96 (96.9%)

Data are presented as mean (SD) or n/N (%).

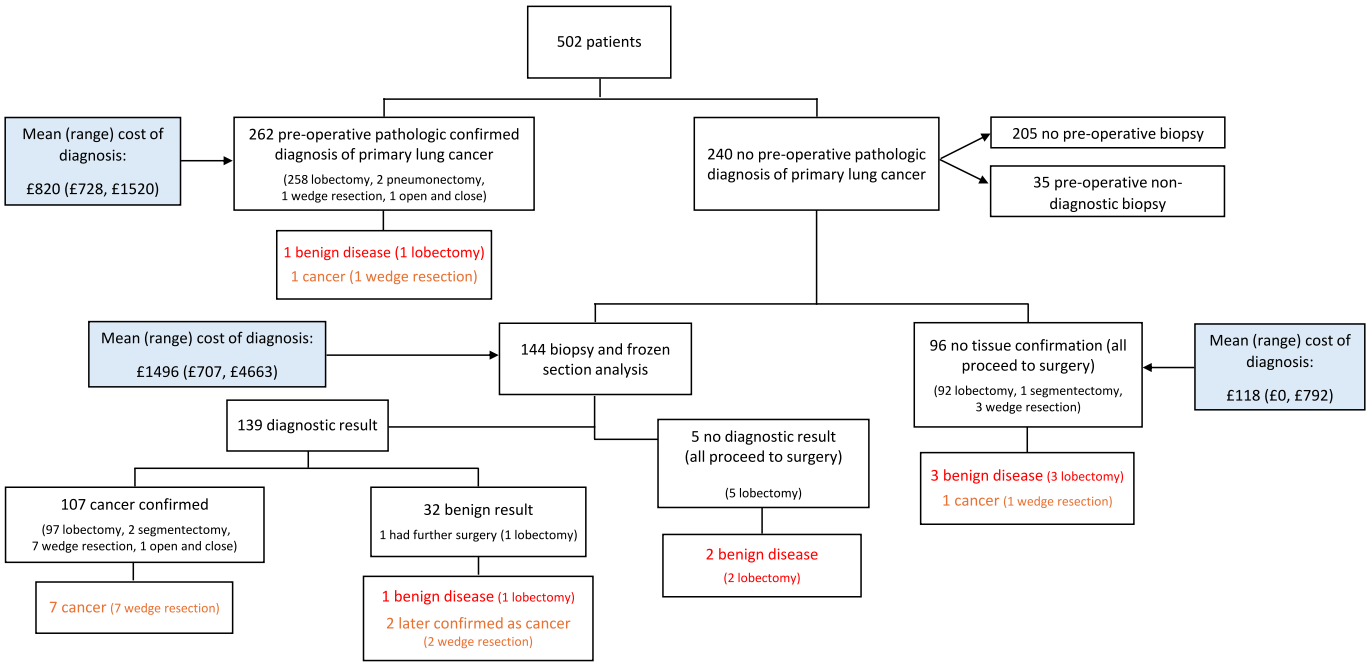

Fig. 1. Biopsy pathways and outcomes for VIOLET participants who underwent surgery*. *Surgeries for outcomes in red/orange text are inappropriate (red for a participant with benign disease undergoing lobectomy, orange for a participant with cancer undergoing wedge resection). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

The results of our work suggest low levels of inappropriate resections can be achieved with pre-operative tissue confirmation rates of 52%. We found an inappropriate surgery rate of 3.6% and a benign resection rate of 1.4%, below the 4% threshold stipulated at the start of the trial. From a cost perspective, average costs were lower for participants who had pre-operative pathological confirmation of their lung cancer.

Whilst pathologic confirmation was achieved in 89% of patients across the UK in the audit period of 2017, in line with the National Lung Cancer Audit Report authors UK target of 90% [1], the pre-operative tissue confirmation rate in VIOLET (52%) is well below the national 89% achievement, suggesting that the audit findings might be more reflective of end of treatment pathologic confirmation rather than pre-treatment tissue diagnosis (at a time point that influences patient selection for treatments).

Many patients with surgically resectable stage I or II disease (more than 52%) [6] do not present with lymph node involvement and therefore do not have the option of bronchoscopy and needle aspiration (to confirm primary lung cancer and obtain tissue for staging). Confirmatory tissue diagnosis prior to surgery therefore is commonly achieved for peripherally sited lesions by percutaneous CT biopsy.

If the lesion is deep seated (inaccessible) or percutaneous biopsy cannot be performed for any other cause, two common management options are employed. If the pre-treatment risk of malignancy is low, a surgical biopsy (with on-site frozen section analysis) is often considered prior to formal lung resection to confirm primary lung cancer, and if the pre-treatment risk of primary lung cancer is very high, or surgical biopsy cannot be performed for technical or patient factors, then a lobectomy is undertaken without tissue confirmation of primary lung cancer.

National benchmarks for the optimum pre-treatment diagnostic tissue confirmation rate should be considered against what is to be achieved. If it is to minimise inappropriate resections, results from VIOLET suggest the standard of care across UK MDTs and participating thoracic surgeons are sufficiently high (benign resection rate of 1.4%) despite pre-treatment tissue confirmation rate of 52%. This was achieved through biopsy prior to formal lung resection and correctly estimating (high) risk where lobectomy was performed without tissue confirmation (19% of our cohort). To frame the figure to a point of reference, in the Danish VATS lobectomy RCT, the benign resection rate was 1.9% (4/206) [5]. Real-world data from the United States also showed a low level of inappropriate resection with a pre-treatment tissue confirmation rate of 52% [7]. Lobectomy was performed without tissue confirmation in 26% (698/2651) of their cohort and the benign resection rate was 2.6% (70/2651). It becomes harder to define what an acceptable benign or inappropriate resection rate might be, but it is not possible nor reasonable to assume that it should be 0%. Even with pre-operative tissue "confirmed" diagnosis, the benign resection rate was 0.4% (1/262) when the final pathology was reported.

To delve further into discussions, we need to consider the definition of "benign". In the 2011 International Association for the Study of Lung Cancer (IASLC)/ American Thoracic Society (ATS)/ European Respiratory Society (ERS) reclassification of adenocarcinoma, new sub-sets of non-invasive disease (atypical adenomatous hyperplasia, adenocarcinoma in situ and minimally invasive adenocarcinoma) were identified [8]. Currently uncertainty exists with regards to the need for a lobectomy, a question currently being investigated in other clinical trials [9,10]. In our series, 298 participants were diagnosed with adenocarcinoma and of these eight (3%) did not proceed to lobectomy. However, a limitation of this study is we cannot determine how many of these participants had non-invasive adenocarcinoma to report the lobectomy rate in this sub-set as we were unable to access pathology reports.

Average costs of diagnosis for participants who had pre-operative pathologic confirmation of primary lung cancer were 30% lower compared to those whose diagnosis was confirmed in the operating theatre (£820 compared to £1,496). While diagnosis in theatre without subsequent surgery occurred in only 6% (31/502 participants), it is very much more expensive (£3,871 per participant). From a cost perspective, diagnosis should be confirmed pre-operatively, whenever possible.

The work for this study was undertaken in the era prior to licensing and widespread use of neo-adjuvant and *peri*-operative chemo-immunotherapies that mandate tissue confirmation and molecular analyses prior to surgery which limits the generalisability to the cohort of patients who would not currently qualify (tumours less than 4cm

without lymph node involvement). Other limitations are we did not collect reasons why pre-operative biopsies were not attempted so are unable to explain why a high percentage of participants did not undergo pre-operative histological confirmation of their lung cancer, we did not have access to reasons behind surgical decision making in all cases, and we did not mandate the pre-operative staging with CT and PET-CT was required.

5. Conclusions

In early-stage lung cancer, standards for pre-operative tissue confirmation rates should be set to achieve low levels of inappropriate lung resection. The results from VIOLET suggest low levels of inappropriate resection can be achieved at pre-surgical tissue confirmation rates of 50% through a combination of intra-operative confirmatory biopsy and correct risk estimation of lung cancer. If biopsy is required, it is less costly to undertake it before surgery. Our recommendations would need to be monitored by formal audit to ensure acceptable levels are consistently achieved across multi-disciplinary teams caring for patients with suspected primary lung cancer.

6. Funding statement

This study is funded by the NIHR Health Technology Assessment programme (reference number 13/04/03). This trial was designed and delivered in collaboration with the Bristol Trials Centre, a UK Clinical Research Collaboration–registered clinical trials unit (CTU), which is in receipt of NIHR CTU support funding, and the Bristol Royal College of Surgeons Trials Centre. The research team acknowledges the support of the NIHR Clinical Research Network and the UK Thoracic Surgery Research Collaborative. The views and opinions expressed are those of the authors and do not necessarily reflect those of the NIHR Health Technology Assessment programme, the NHS, or the Department of Health and Social Care.

7. Trial registration

This trial is registered as ISRCTN13472721.

Ethical approval

The trial was approved by the Research Ethics Committee London–Dulwich (reference 14/LO/2129) on 7 January 2015.

Informed consent

All study participants gave written informed consent before joining the trial.

Contributor statement

All authors have made a) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and b) contributed to the drafting the work or reviewing it critically for important intellectual content; and c) have approved the version to be published; and d) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EL, ES, RAH and CAR have directly accessed and verified the underlying data reported in the manuscript. EL had final responsibility for the decision to submit for publication.

Data sharing statement

Anonymised individual participant data used in these analyses are available from https://data.bris.ac.uk/data/dataset/2v1717k5zgzff2dvfqxsy8zc71. Researchers must complete a University of Bristol Research Data Request and have ethical approval for the proposed use of the data. Only data from participants who have consented for their data to be shared with other researchers are available.

CRediT authorship contribution statement

Rosie A. Harris: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Elizabeth A. Stokes:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Tim J.P. Batchelor:** Writing – review & editing, Investigation. **Eveline Internullo:** Writing – review & editing, Investigation. **Doug West:** Writing – review & editing, Investigation. **Simon Jordan:** Writing – review & editing, Investigation. **Andrew G. Nicholson:** Writing – review & editing, Investigation. **Ian Paul:** Writing – review & editing, Investigation. **Charlotte Jacobs:** Writing – review & editing, Investigation. **Mike Shackcloth:** Writing – review & editing, Investigation. **Sarah Feeney:** Writing – review & editing, Investigation. **Vladimir Anikin:** Writing – review & editing, Investigation. **Niall McGonigle:** Writing – review & editing, Investigation. **Richard Steyn:** Writing – review & editing, Investigation. **Maninder Kalkat:** Writing – review & editing, Investigation. **Dionisios Stavroulias:** Writing – review & editing, Investigation. **May Havinden Williams:** Writing – review & editing, Investigation. **Syed Qadri:** Writing – review & editing, Investigation. **Karen Dobbs:** Writing – review & editing, Investigation. **Vipin Zamvar:** Writing – review & editing, Investigation. **Lucy Macdonald:** Writing – review & editing, Investigation. **Surinder Kaur:** Writing – review & editing. **Chris A Rogers:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Eric Lim:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Eric Lim reports personal fees from Abbott Molecular (Abbott Park, IL, USA), GlaxoSmithKline plc (Brentford, UK), Pfizer Inc. (New York, NY, USA), Novartis Pharmaceuticals UK Ltd (London, UK), Medtronic plc/Covidien (Dublin, Ireland), Roche Diagnostics (Hertford, UK), Lilly Oncology (Indianapolis, IN, USA), Boehringer Ingelheim (Bracknell, UK), Medela (Baar, Switzerland), Johnson & Johnson/Ethicon (New Brunswick, NJ, USA), AstraZeneca (Cambridge, UK) and Bristol-Myers Squibb (New York, NY, USA); grants from Clearbridge BioMedics (Singapore Science Park, Singapore), Illumina (San Diego, CA, USA) and Guardant Health (Redwood City, CA, USA); and grants and personal fees from ScreenCell (Sarcelles, France) outside the submitted work. In addition, Eric Lim has patents P52435GB and P57988GB issued to Imperial Innovations (London, UK). Timothy Batchelor reports personal fees from Johnson & Johnson, Medtronic plc, Medela and AstraZeneca outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2024.108070.

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