Supplementary Material

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Supplementary Appendix 1- Full search terms used in the literature search of each database.

1. PubMed

| Search ID | Search Terms |
|-----------|---|
| #1 | ("Cryobiopsy" OR "Cryoprobe biopsy" OR "Forceps biopsy" OR "pleural |
| | cryobiopsy") |
| #2 | ("Pleura*" OR "Pleural effusion "OR "pleural biopsy "OR "pleuroscopy" |
| | OR "thoracoscopy") |
| #3 | #1 AND #2 (Results retrieved n= 68) |

2. Embase

| Search | Searches | | | | | |
|---------|--|--|--|--|--|--|
| History | | | | | | |
| 1 | ((('cryobiopsy'/exp OR cryobiopsy OR 'cryoprobe'/exp OR cryoprobe) AND | | | | | |
| | ('biopsy'/exp OR biopsy) OR 'forceps'/exp OR forceps) AND ('biopsy'/exp OR biopsy) | | | | | |
| | OR pleural) AND ('cryobiopsy'/exp OR cryobiopsy) | | | | | |
| 2 | ((pleura* OR pleural) AND ('effusion'/exp OR effusion) OR pleural) AND | | | | | |
| | ('biopsy'/exp OR biopsy) OR 'pleuroscopy'/exp OR pleuroscopy OR | | | | | |
| | 'thoracoscopy'/exp OR thoracoscopy | | | | | |
| 3 | #1 AND #2 (Results retrieved n= 93) | | | | | |

3. Scopus

TITLE-ABS-KEY (("Cryobiopsy" OR " Cryoprobe biopsy " OR "Forceps biopsy" OR "pleural cryobiopsy") AND (" Pleura*" OR " Pleural effusion " OR " pleural biopsy " OR "pleuroscopy" OR "thoracoscopy")) (Results retrieved n= 106)

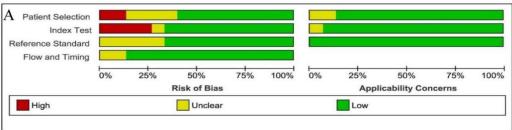
4. Web of Science

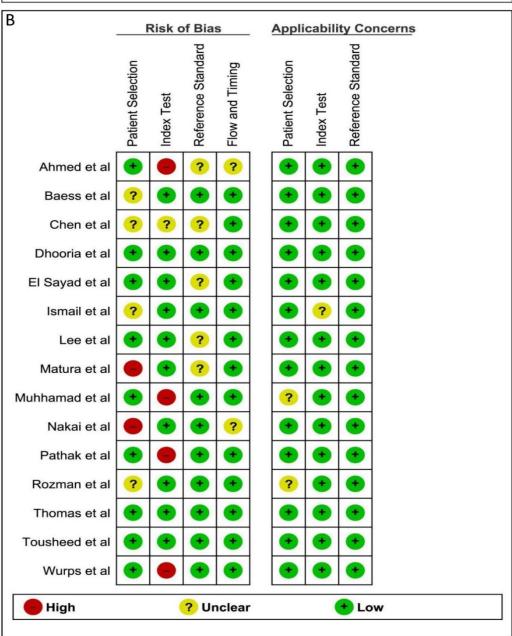
| Search | Searches |
|---------|----------|
| History | |

| #1 | TS=("Cryobiopsy" OR " Cryoprobe biopsy " OR "Forceps biopsy" OR "pleural |
|----|--|
| | cryobiopsy") |
| #2 | TS=("Pleura*" OR "Pleural effusion "OR "pleural biopsy "OR "pleuroscopy" |
| | OR "thoracoscopy") |
| #3 | #1 AND #2 (Results retrieved n= 94) |

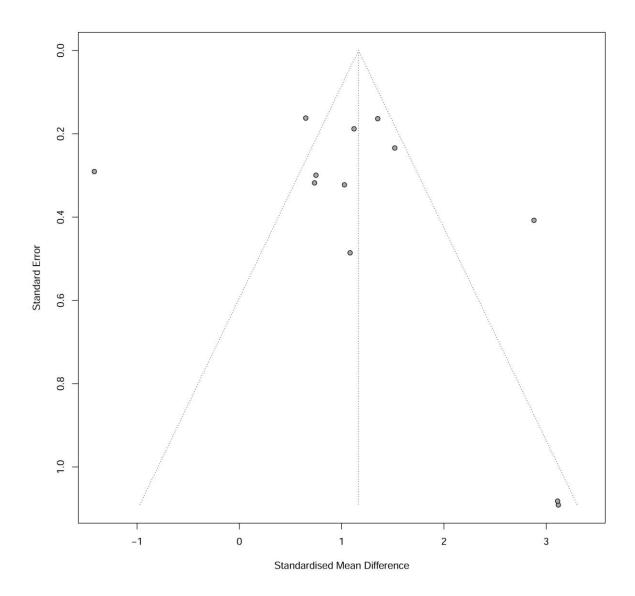
Supplementary Figure 1. Quality assessments of included studies using the QUADAS-2

tool. A) Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included randomized controlled studies. **B)** Risk of bias summary: Review authors' judgments for each risk of bias item for the included studies.





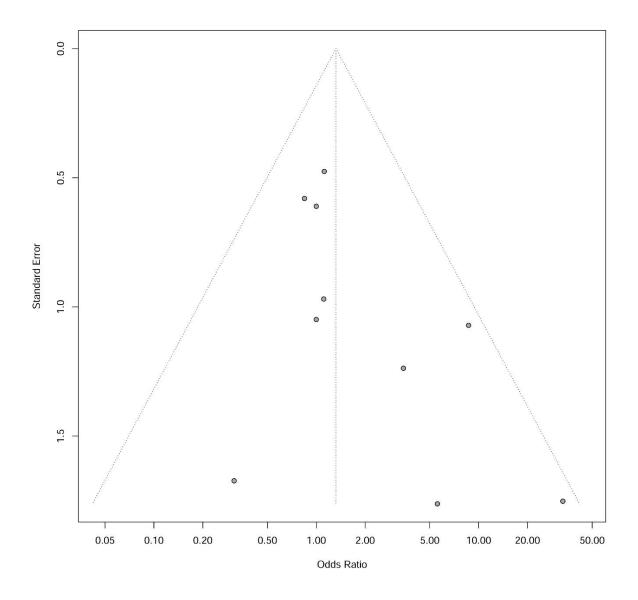
Supplementary Figure 2. Funnel plot to detect publication bias for studies comparing specimen size.



Supplementary Figure 3. Leave-one-out sensitivity analysis of specimen size between cryobiopsy and forceps biopsy

| | Std. Mean Difference | Std. Mean Difference |
|-------------------------|----------------------|----------------------|
| Study | IV, Random, 95% CI | IV, Random, 95% CI |
| Omitting Baess et al | 1.22 [0.50; 1.94] | |
| Omitting Chen et al | 1.16 [0.43; 1.88] | |
| Omitting Dhooria et al | 1.14 [0.42; 1.86] | |
| Omitting El Sayad et al | 0.98 [0.38; 1.58] | |
| Omitting Lee et al | 1.22 [0.50; 1.94] | |
| Omitting Matura et al | 1.06 [0.42; 1.71] | |
| Omitting Muhhamad et al | 1.32 [0.90; 1.73] | |
| Omitting Nakai et al | 1.06 [0.42; 1.71] | |
| Omitting Pathak et al | 1.18 [0.47; 1.90] | - 1 |
| Omitting Thomas et al | 1.19 [0.47; 1.91] | |
| Omitting Tousheed et al | 1.18 [0.46; 1.91] | |
| Omitting Wurps et al | 1.23 [0.51; 1.95] | - |
| Total (95% CI) | 1.16 [0.51; 1.82] | |
| , | | |
| | | -1 0 1 |

Supplementary Figure 4. Funnel plot to detect publication bias for studies comparing diagnostic yield between cryobiopsy and forceps biopsy



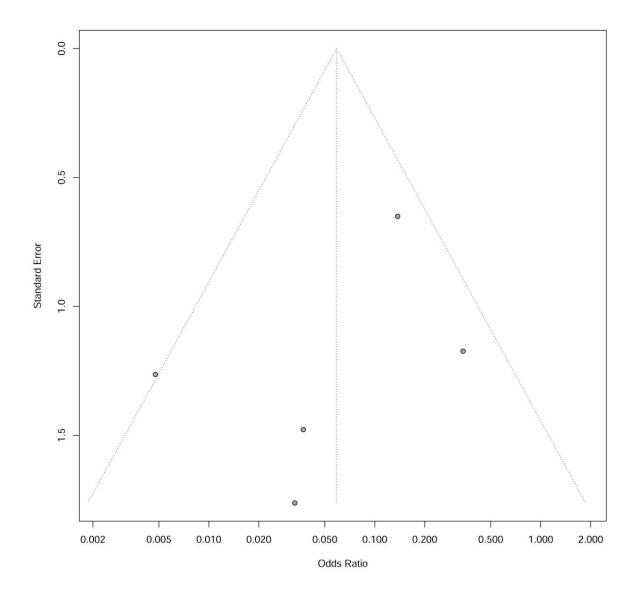
Supplementary Figure 5. Forest plot of leave-one-out meta-analysis of the diagnostic yield

| | Odds Ratio | Odds Ratio |
|-------------------------|--------------------|--------------------|
| Study | MH, Random, 95% CI | MH, Random, 95% CI |
| Omitting Ahmed et al | 1.41 [0.80; 2.49] | - - |
| Omitting Baess et al | 1.32 [0.79; 2.21] | |
| Omitting Chen et al | 1.17 [0.69; 1.99] | - • |
| Omitting Dhooria et al | 1.42 [0.77; 2.63] | - |
| Omitting El Sayad et al | 1.32 [0.79; 2.21] | - • |
| Omitting Ismail et al | 1.32 [0.79; 2.21] | - • |
| Omitting Lee et al | 1.34 [0.79; 2.29] | - • |
| Omitting Matura et al | 1.28 [0.76; 2.15] | - • |
| Omitting Muhhamad et al | 1.32 [0.79; 2.21] | - • |
| Omitting Nakai et al | 1.23 [0.73; 2.07] | - • |
| Omitting Pathak et al | 1.32 [0.79; 2.21] | - • |
| Omitting Rozman et al | 1.37 [0.82; 2.31] | - • |
| Omitting Thomas et al | 1.35 [0.79; 2.29] | - • |
| Omitting Tousheed et al | 1.26 [0.75; 2.14] | - 1 |
| Omitting Wurps et al | 1.48 [0.83; 2.64] | |
| T-4-1 (050/ CI) | 4 22 [0 70, 2 24] | |
| Total (95% CI) | 1.32 [0.79; 2.21] | |
| | | 0.5 1 2 |

Supplementary Figure 6. Forest plot of the leave-one-out meta-analysis of crush artifacts

| | Odds Ratio | | Od | ds R | atio | |
|-------------------------|--------------------|----------------|---------|------|----------|-----|
| Study | MH, Random, 95% CI | ľ | ИH, Rai | ndon | ո, 95% C | I |
| Omitting Baess et al | 0.04 [0.01; 0.28] | - | | | | |
| Omitting Dhooria et al | 0.04 [0.01; 0.20] | _ | - | | | |
| Omitting Matura et al | 0.06 [0.01; 0.36] | 55 | + | 8 | | |
| Omitting Muhhamad et al | 0.06 [0.01; 0.38] | | | | | |
| Omitting Thomas et al | 0.12 [0.05; 0.34] | | - | | | |
| | | | | | | |
| Total (95% CI) | 0.06 [0.01; 0.26] | _ | | | | |
| | | I | 2. | J | | l, |
| | | 0.01 | 0.1 | 1 | 10 | 100 |

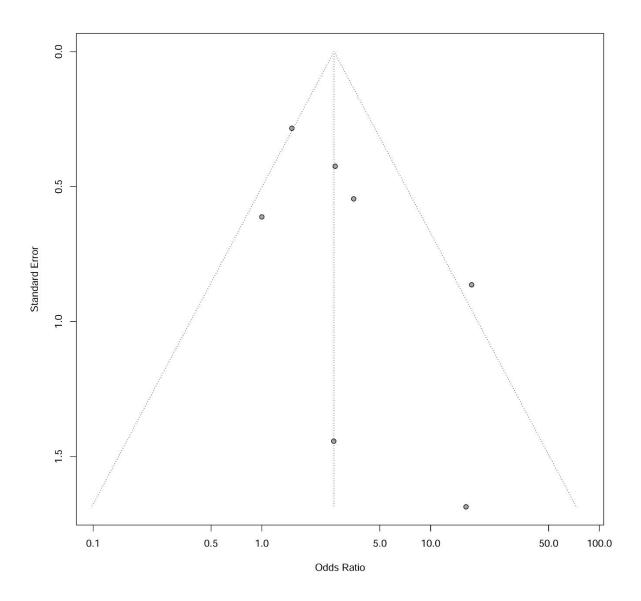
Supplementary Figure 7. Funnel plot to detect publication bias for studies comparing crush artifacts between cryobiopsy and forceps biopsy



Supplementary Figure 8. Forest plot of specimen depth of pleural cryobiopsy versus forceps biopsy

| | Cryob | iopsy | Fo | rceps | | Odds R | atio | Odds Ratio |
|-----------------------|---------------|--------------|-----------------|--------|------------|-----------------|----------|----------------------------------|
| Study | Events | Total | Events | Total | Weight | MH, Random | , 95% CI | MH, Random, 95% CI |
| Baess et al | 8 | 24 | 8 | 24 | 15.7% | 1.00 [0.30; | 3.32] | - |
| Dhooria et al | 30 | 46 | 20 | 49 | 21.6% | 2.72 [1.18; | 6.25] | - |
| Matura et al | 4 | 6 | 0 | 4 | 3.5% | 16.20 [0.59; | 441.68] | - |
| Muhhamad et al | 21 | 30 | 12 | 30 | 17.6% | 3.50 [1.20; | 10.20] | - |
| Nakai et al | 2 | 5 | 1 | 5 | 4.6% | 2.67 [0.16; | 45.14] | - + |
| Thomas et al | 14 | 22 | 2 | 22 | 10.3% | 17.50 [3.22; | 95.16] | |
| Wurps et al | 49 | 99 | 41 | 104 | 26.7% | 1.51 [0.86; | 2.63] | - |
| | | | | | | | | |
| Total (95% CI) | | 232 | | | 100.0% | | 5.16] | • |
| Heterogeneity: Tai | $u^2 = 0.340$ | 07; Chi | 2 = 11.58, | df = 6 | (P = 0.07) |); $I^2 = 48\%$ | | |
| Test for overall effe | ect: Z = 2. | .94 (P < | < 0.01) | | | | | 0.01 0.1 1 10 100 |
| | | | | | | | | Favors forceps Favors cryobiopsy |

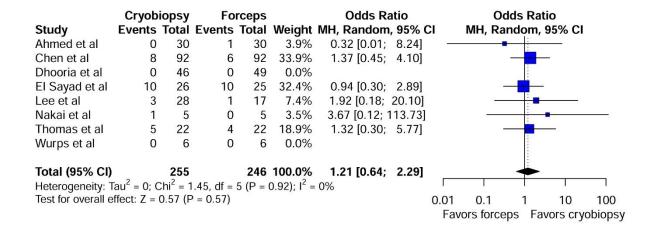
Supplementary Figure 9. Funnel plot to detect publication bias for studies comparing specimen depth between cryobiopsy and forceps biopsy



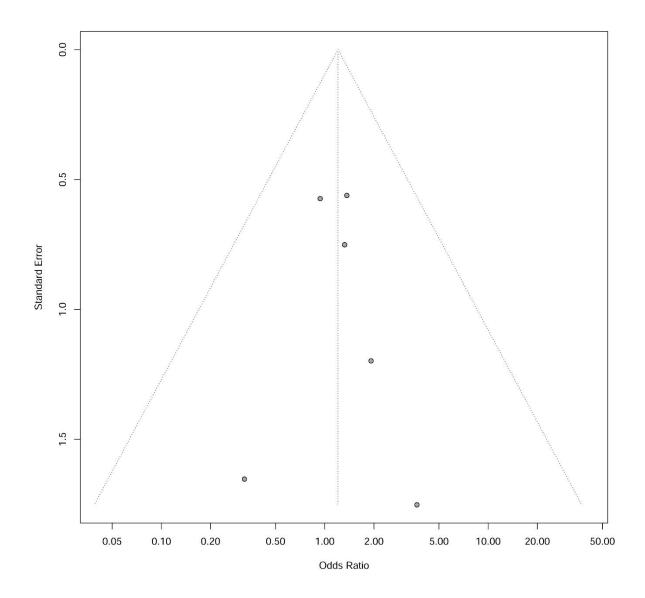
Supplementary Figure 10. Forest plot of the leave-one-out meta-analysis of specimen depth

| Study | Odds Ratio MH, Random, 95% CI | Odds Ratio MH, Random, 95% CI |
|-------------------------|----------------------------------|----------------------------------|
| | | Will, Kalldolli, 95% Cl |
| Omitting Baess et al | 3.26 [1.56; 6.80] | : |
| Omitting Dhooria et al | 2.91 [1.18; 7.19] | |
| Omitting Matura et al | 2.48 [1.30; 4.74] | - - |
| Omitting Muhhamad et al | 2.70 [1.16; 6.26] | |
| Omitting Nakai et al | 2.74 [1.34; 5.60] | |
| Omitting Thomas et al | 1.99 [1.27; 3.11] | |
| Omitting Wurps et al | 3.36 [1.49; 7.58] | - |
| | | |
| Total (95% CI) | 2.68 [1.39; 5.16] | |
| | | |
| | | 0.2 0.5 1 2 5 |

Supplementary Figure 11. Forest plot of mild to moderate bleeding events occurred during pleural cryobiopsy versus forceps biopsy



Supplementary Figure 12. Funnel plot of studies comparing cryobiopsy versus forceps biopsy for mild to moderate bleeding events



Supplementary Figure 13. Forest plot of the leave-one-out meta-analysis of mild to moderate bleeding events

| | Odds Ratio | Odds Ratio |
|-------------------------|--------------------|--------------------|
| Study | MH, Random, 95% CI | MH, Random, 95% CI |
| Omitting Ahmed et al | 1.27 [0.66; 2.44] | |
| Omitting Chen et al | 1.13 [0.51; 2.49] | |
| Omitting Dhooria et al | 1.21 [0.64; 2.29] | - • |
| Omitting El Sayad et al | 1.36 [0.62; 2.96] | |
| Omitting Lee et al | 1.16 [0.60; 2.26] | - • |
| Omitting Nakai et al | 1.16 [0.60; 2.22] | - • |
| Omitting Thomas et al | 1.18 [0.58; 2.40] | - • |
| Omitting Wurps et al | 1.21 [0.64; 2.29] | - • |
| | | |
| Total (95% CI) | 1.21 [0.64; 2.29] | |
| | | |
| | | 0.5 1 2 |

Supplementary Table 1. Average specimen size obtained by pleural cryobiopsy and forceps biopsy

| Study (year) | Average biopsy size cryobiopsy | Average biopsy size forceps biopsy | | |
|------------------------------|--|--|--|--|
| Ahmed et al | NR | NR | | |
| Baess et al | $4.1 \pm 2.4 \text{ cm}^2$ (Surface area \pm SD | $2.7 \pm 1 \text{ cm}^2 \text{(Surface area} \pm \text{SD)}$ | | |
| Chen et al ¹² | 9.4 mm ± 4.9 mm (mean size \pm SD) | 4.2 mm ± 2.3 mm (mean size \pm SD) | | |
| Dhooria et al ²³ | 7 mm(6–10) (median size, range) | 4 (3–5) (median size, range) | | |
| El Sayad et al | 14.07 ± 4.29 (mean size \pm SD) | 5.04 ± 0.53 (mean size \pm SD) | | |
| Ismail et al | NR | NR | | |
| Lee et al ¹³ | 9.1 ± 5.7 mm (mean size \pm SD) | 5.3 ± 3.8 (mean size \pm SD) | | |
| | $56.0 \pm 61.3 \text{ mm}^2 \text{ (mean area} \pm \text{SD)}$ | $10.2 \pm 14.3 \text{ mm}^2 \text{ (mean area} \pm \text{SD)}$ | | |
| | $232.1 \pm 411.4 \text{ mm}^3 \text{ (volume } \pm \text{SD)}$ | $13.4 \pm 22.6 \text{ mm}^3 \text{ (volume } \pm \text{SD)}$ | | |
| Matura et al ¹⁴ | 9.17 ± 1.84 mm (mean size \pm SD) | 3.75 ± 0.96 mm (mean size \pm SD) | | |
| Muhhamad et al ¹⁵ | 0.338 ± 0.247 cm ² (Surface area \pm SD) | 0.819 ± 0.404 cm ² (Surface area \pm SD) | | |
| Nakai et al ¹⁶ | 18.9 (15.2–19.8) mm ² (cross-sectional | 6.7 (5.9–6.8) mm ² (cross-sectional area; | | |
| | area; median, range) | median, range) | | |
| Pathak et al ¹⁷ | 320 mm ³ mean tissue volume | 80 mm ³ mean tissue volume | | |
| Rozman et al ²¹ | NR | NR | | |
| Thomas et al ¹⁸ | 10 (7-15.8) mm (median size, range) | 4 (3-8) mm (median size, range) | | |
| Tousheed et al ¹⁹ | 13.2 ± 6.7 mm (mean size \pm SD) | 6.8 ± 3.3 mm (mean size \pm SD) | | |
| Wurps et al ²⁰ | $14.4 \pm 12.8 \text{ mm}^2 \text{ (mean area} \pm \text{SD)}$ | $7.1 \pm 9.3 \text{ mm}^2 \text{ (mean area} \pm \text{SD)}$ | | |

NR= Not reported

Supplementary Table 2. Artefacts reported in included studies comparing pleural cryobiopsy versus forceps biopsy

| Author | Occurrence of artefacts | Number of patients in | Number of patients in |
|----------------|--------------------------|-----------------------|-----------------------|
| | | CB, n (%) | FB, n (%) |
| Baess et al | Crushed cells negative | 17/24 (70.8) | 6/24 (25) |
| | Crushed cells <5% | 6/24 (25) | 14/24 (58.3) |
| | Crushed cells 5-10% | 1/24 (4.2) | 0/24 (0) |
| | Crushed cells 10-25% | 0/24 (0) | 4/24 (16.7) |
| Dooria et al | None | 45/46 (97.8) | 46/49 (93.9) |
| | Crush | 1/46 (2.2) | 3/49 (6.1) |
| | Freeze | 0/46 (0) | 0/49 (0) |
| Matura et al | Crush artefacts | 0/6 (0) | 3/4 (75) |
| Muhhamad et al | Crushed cells | 0/30 (0) | 9/30 (30) |
| | No crushed cells | 30/30 (100) | 21/30 (70) |
| Thomas et al | Crush artefacts nil | 20/22 (91) | 1/22 (4.5) |
| | Crush artefacts mild | 1/22 (4.5) | 19/22 (86.4) |
| | Crush artefacts moderate | 1/22 (4.5) | 2/22 (9.1) |
| | Crush artefacts severe | 0/22 (0) | 0/22 (0) |

Supplementary Table 3. Qualitative analysis of depth of biopsy between pleural cryobiopsy and forceps biopsy

| Author | Depth of tissue | Number of | Number of |
|----------------|----------------------------------|-------------------|-------------------|
| | | patients in CB, n | patients in FB, n |
| | | (%) | (%) |
| Baess et al | Fat cells negative | 12/24 (50) | 8/24 (33.3) |
| | Fat cells <5% | 4/24 (16.7) | 8/24 (33.3) |
| | Fat cells (5-10%) | 5/24 (20.8) | 2/24 (8.3) |
| | Fat cells (10-25%) | 3/24 (12.5) | 6/24 (25) |
| Dooria et al | Up to mesothelial connective | 16/46 (34.8) | 29/49 (59.2) |
| | tissue | | |
| | Up to extrapleural fat or deeper | 30/46 (65.2) | 20/49 (40.8) |
| Matura et al | Subpleural adipose tissue | 4/6 (66.7) | 0/4 (0) |
| Muhhamad et al | Biopsies containing fatty tissue | 21/30 (70) | 12/30 (40) |
| | Biopsies containing no fat | 9/30 (30) | 18/30 (60) |
| | tissue | | |
| Nakia et al | Pleural surface | 1/5(20) | 4/5 (80) |
| | Adipose tissue | 2/5 (40) | 1/5(20) |
| | Skeletal muscle | 2/5 (40) | 0/5 (0) |
| Thomas et al | Fibrotic pleura | 22/22 (100) | 21/22 (95.5) |
| | Adipose tissue | 14/22 (63.6) | 5/22 (22.7) |
| | Skeletal muscle | 10/22 (45.5) | 2/22 (9.1) |
| | Lung | 1/22 (4.5) | 1/22 (4.5) |
| | Fragments | 0/22 (0) | 1/22 (4.5) |
| Wurps et al | Biopsies including fatty tissue | 49/99 (49.5) | 41/104 (39.4) |
| | Biopsies Negative for fatty | 50/99 (50.5) | 63/104 (60.6) |
| | tissue | | |

CB, cryobiopsy; FB, Forceps biopsy