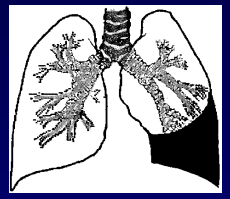

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Indwelling Pleural Catheters in Malignant and Non-Malignant Disease

20th Hellenic Conference November 2011

Najib Rahman
Clinical Lecturer
Oxford Centre for Respiratory Medicine
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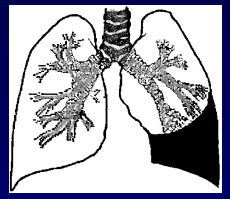

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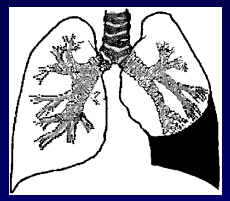
Overview

Malignant Disease:

- Current treatment strategies
- Need for newer treatments:
    - In selected patients
    - As a novel form of primary therapy
- Advantages and disadvantages of indwelling pleural catheters
- Future directions

Benign Disease



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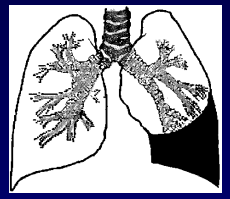
Malignant Pleural Effusion (MPE)



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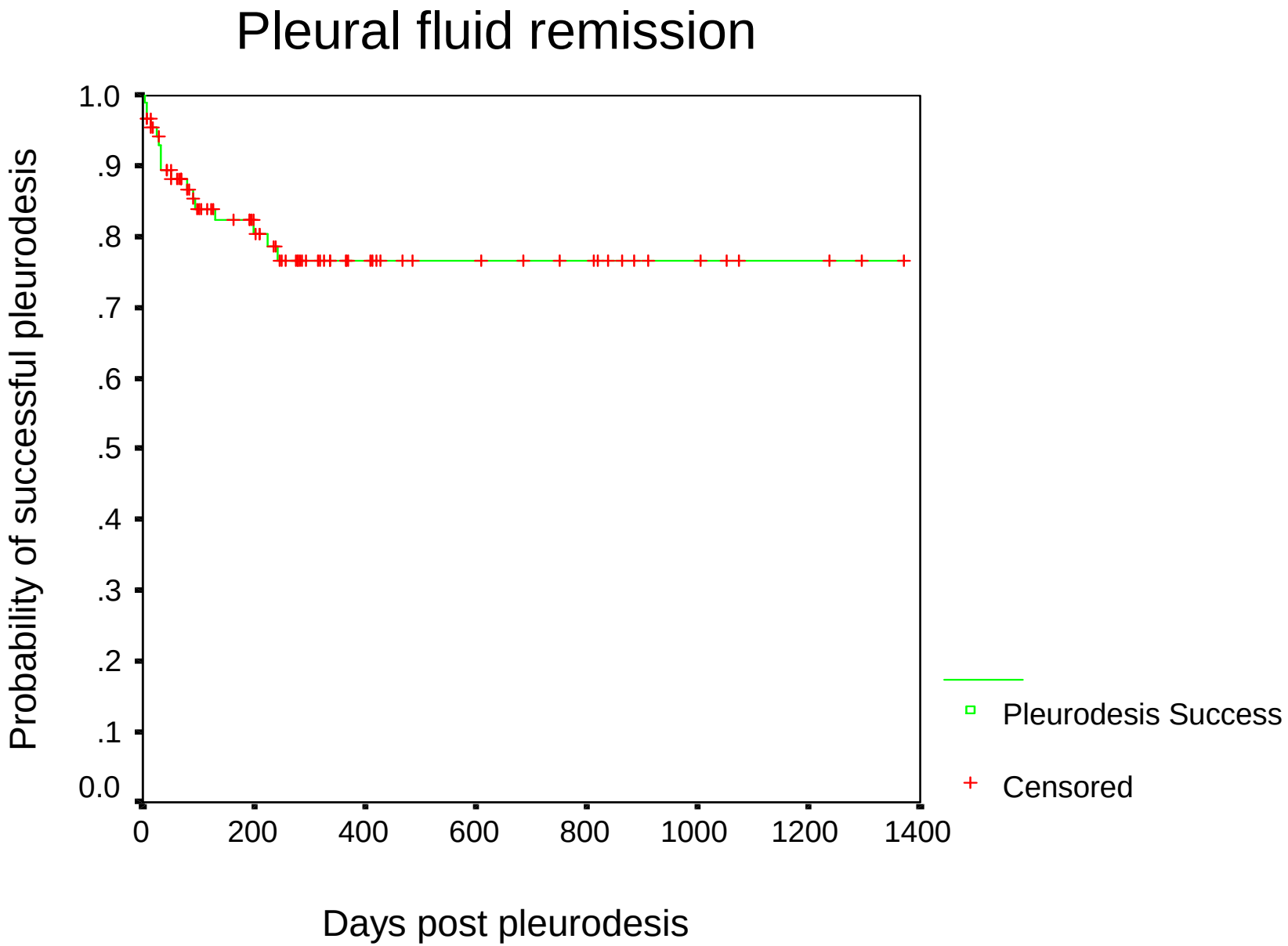
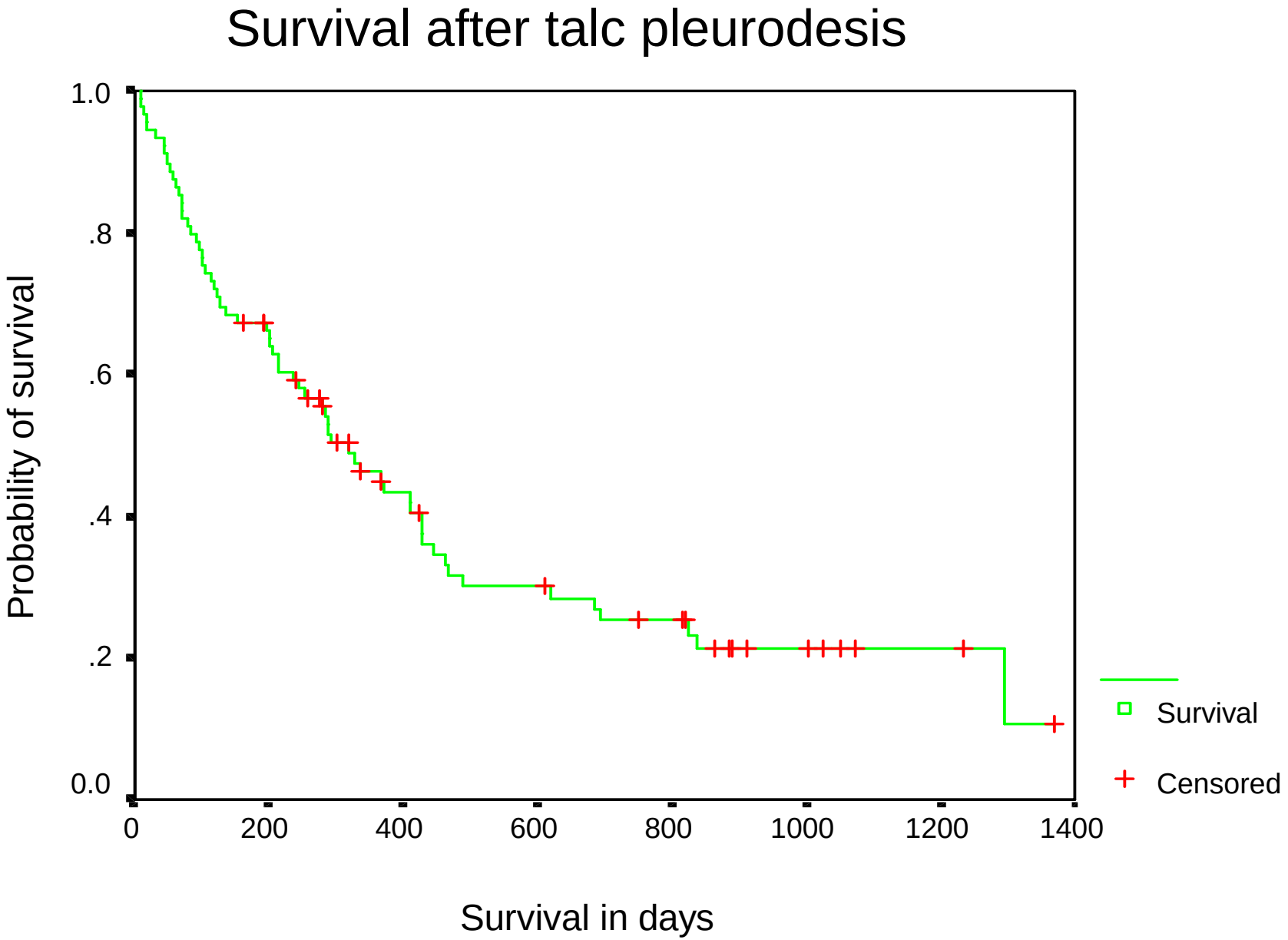
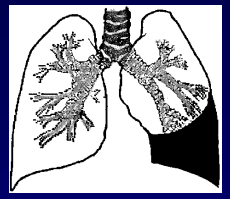
Malignant Pleural Effusion (MPE)

Current treatment Options:

- Recurrent aspiration
  - Patient acceptability
  - Poor ability to predict recurrence
- Pleurodesis
- Indwelling pleural catheters
- Shunts


Pleural fluid remission
Probability of successful pleurodesis
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0.0
0
200
400
600
800
1000
1200
1400
Days post pleurodesis
Pleurodesis Success
Censored


Survival after talc pleurodesis
Probability of survival
1.0
.8
.6
.4
.2
0.0
0
200
400
600
800
1000
1200
1400
Survival in days
Survival
Censored



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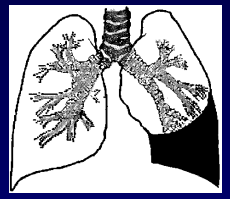
Pleurodesis

Why do we need another strategy?

- Talc is perfect:
  - Reasonable efficacy (60-80%)
  - Cheap + cost effective
- Talc has problems:
  - Not 100% successful
  - Up to 15% with trapped lung
  - Is it “safe”?
  - Side effects



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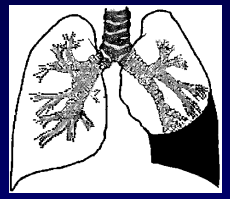
Talc summary

Graded talc:

- Safe
- Moderately effective in outcomes measured
- Side effects (should we just live with them)

Several unanswered questions:

- Tube size
- Analgesic strategy
- Is poudrage truly better
- Predictors of outcome



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Pleurodesis Agents

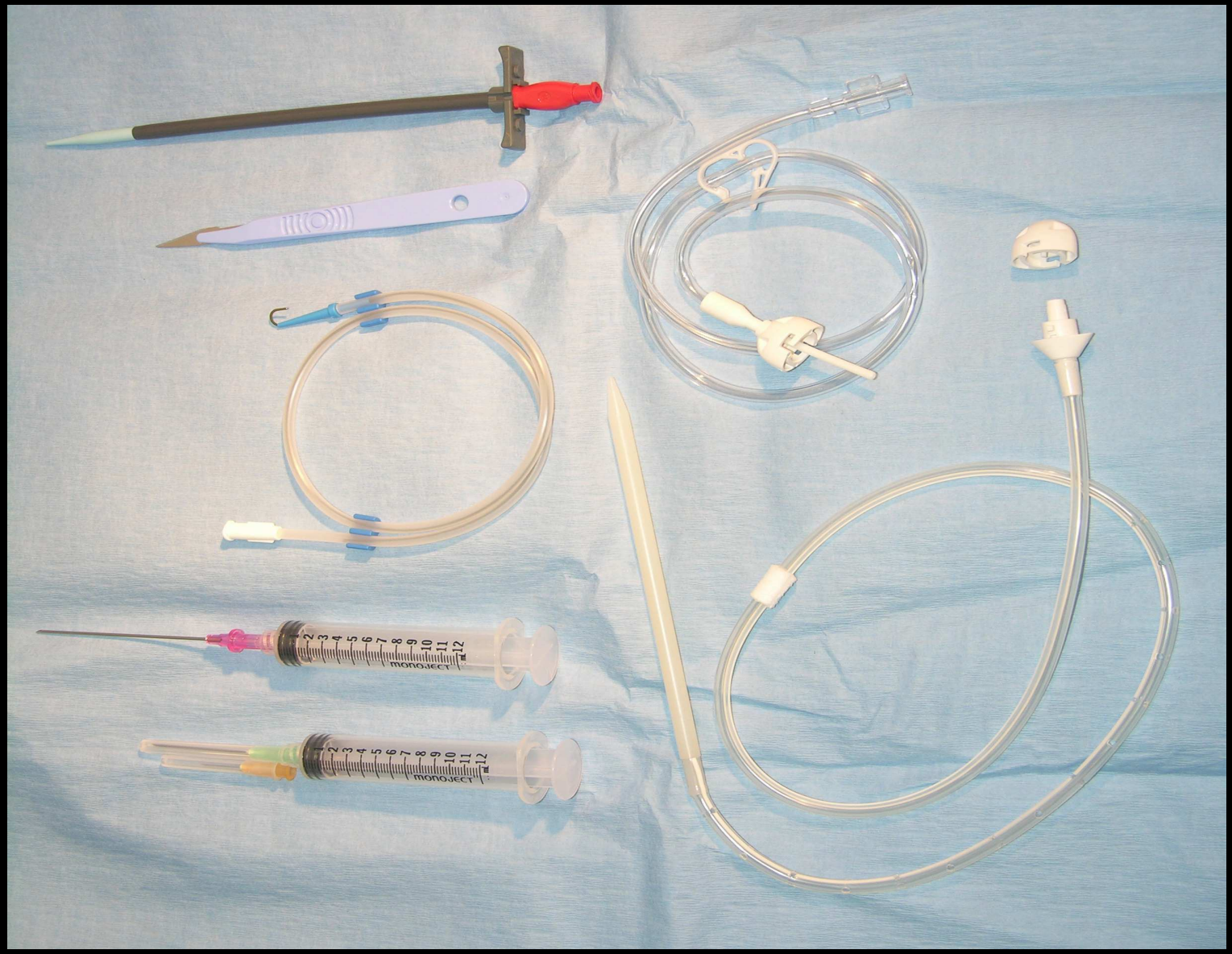
Pleurodesis Agent

Avoid with direct drainage strategy

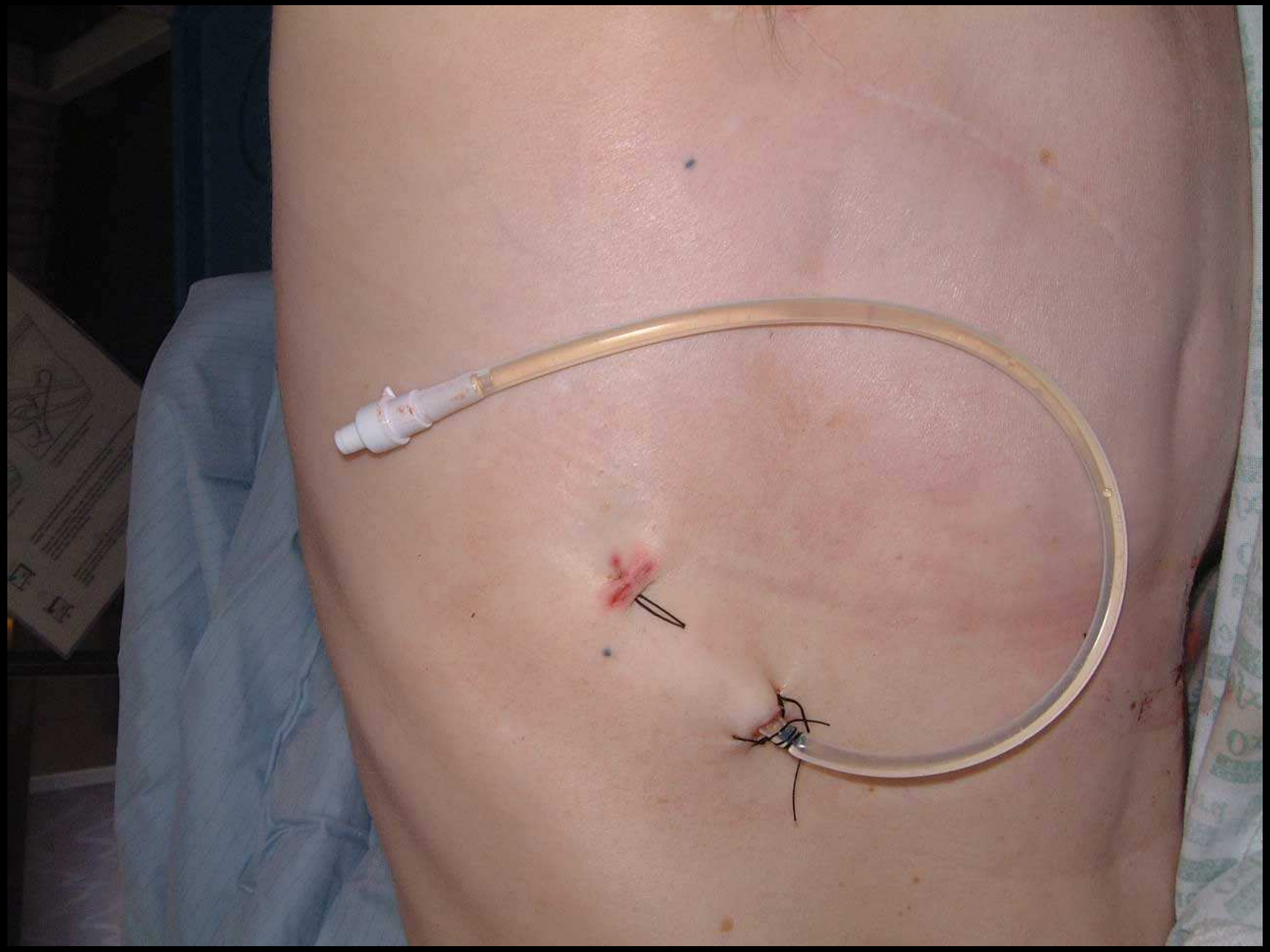
TGF-B driven?

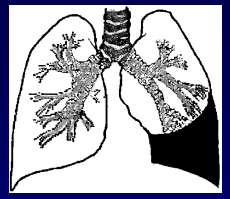
Pleural / systemic inflammation

Fibrosis and pleurodesis



Indwelling pleural catheter (Rocket UK version)





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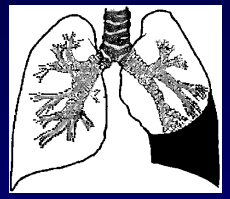
Indwelling Pleural Catheters (IPCs)

Potential advantages:

- Single procedure
- Day-case placement
- Patient “in control”

Unanswered questions:

- Many



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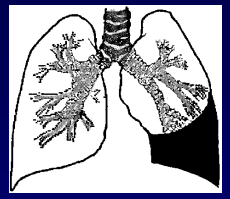
Indwelling Pleural Catheters (IPCs)

Important clinical questions:

1. Are there subgroups in which IPCs are the preferred treatment?
    - Trapped lung
    - Failed talc pleurodesis

2. Should IPCs be used as primary therapy?



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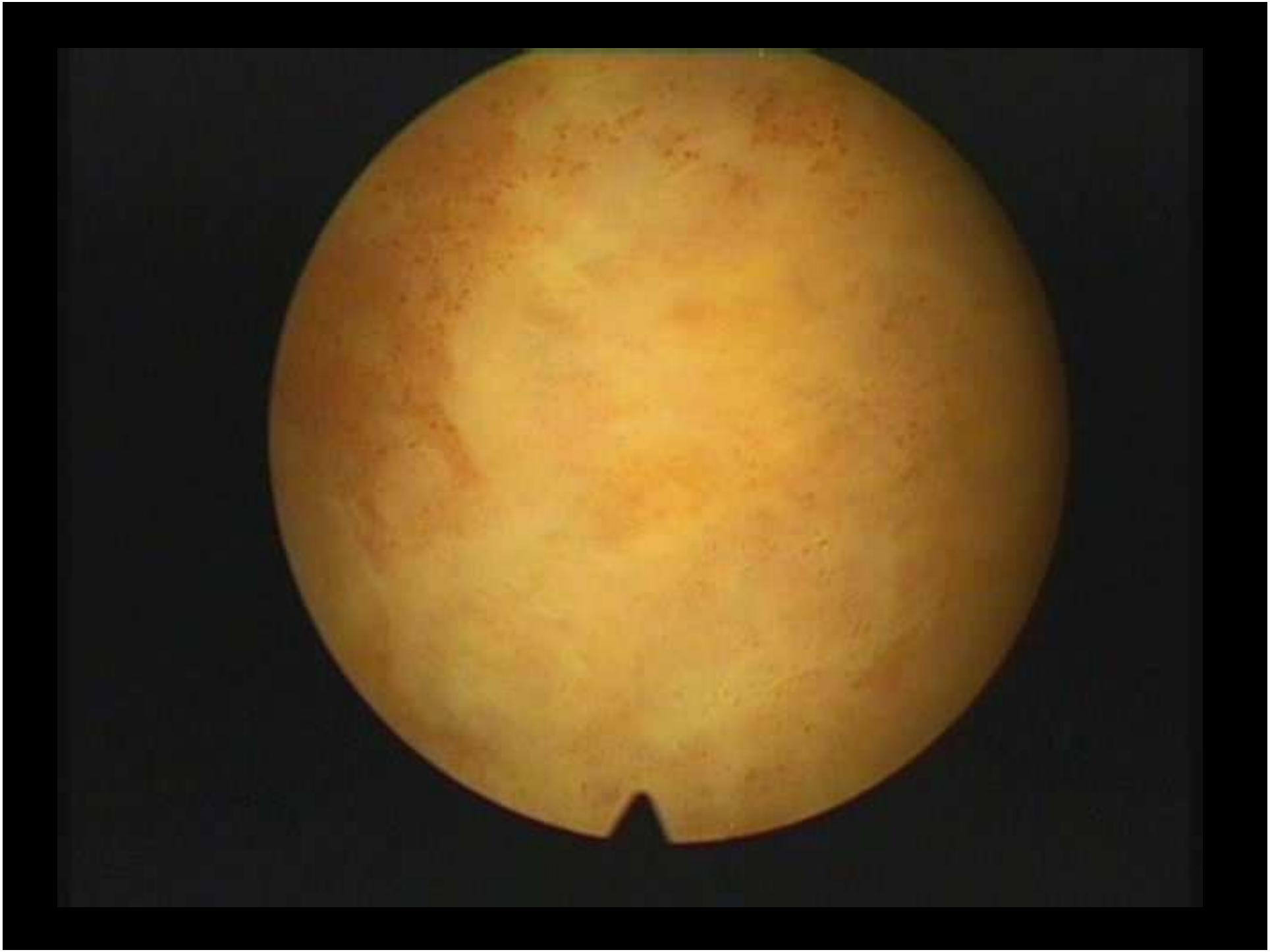
1. Trapped Lung

The problem:

- 70/482 (15%) “trapped” lung in RCT
- Often very symptomatic
- Often poor prognosis
- May be diagnosed after drainage / talc poudrage



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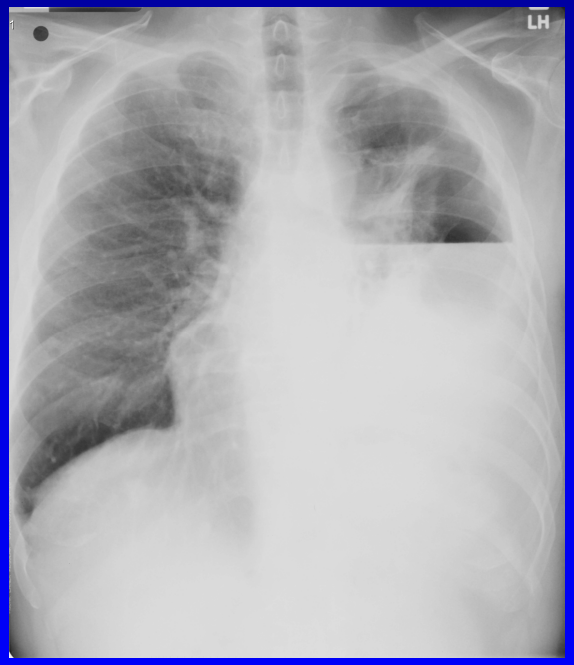
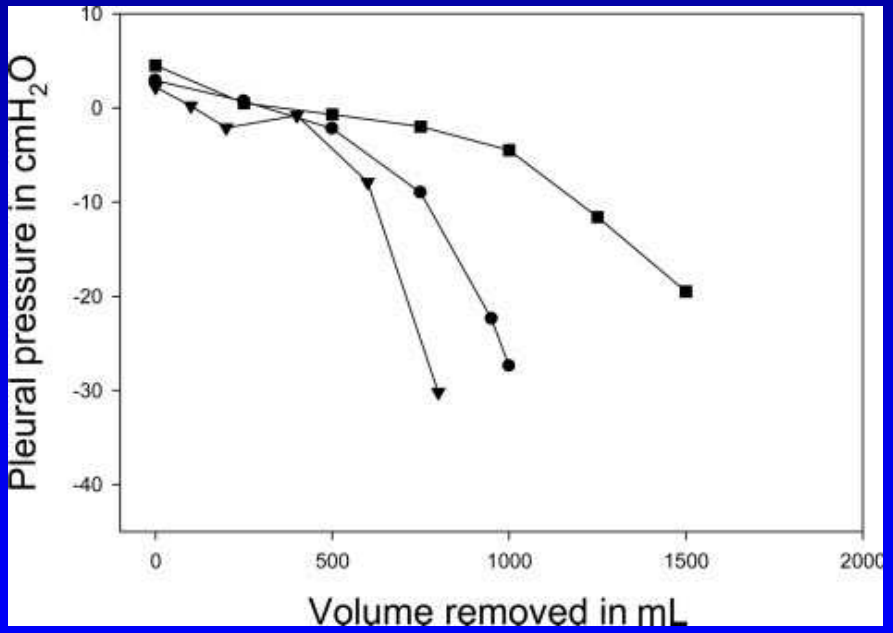
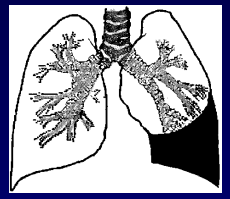
Trapped Lung

- ? Manometry to identify







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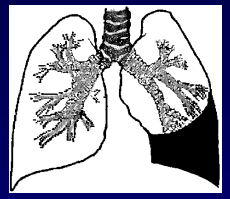
Trapped Lung

IPCs:

- Likely the “best” treatment option
- Freedom for the patient
- Poor prognosis – therefore realistic costs
- Spontaneous pleurodesis rate

Other treatment options available:

- Recurrent thoracocentesis
- Surgical options



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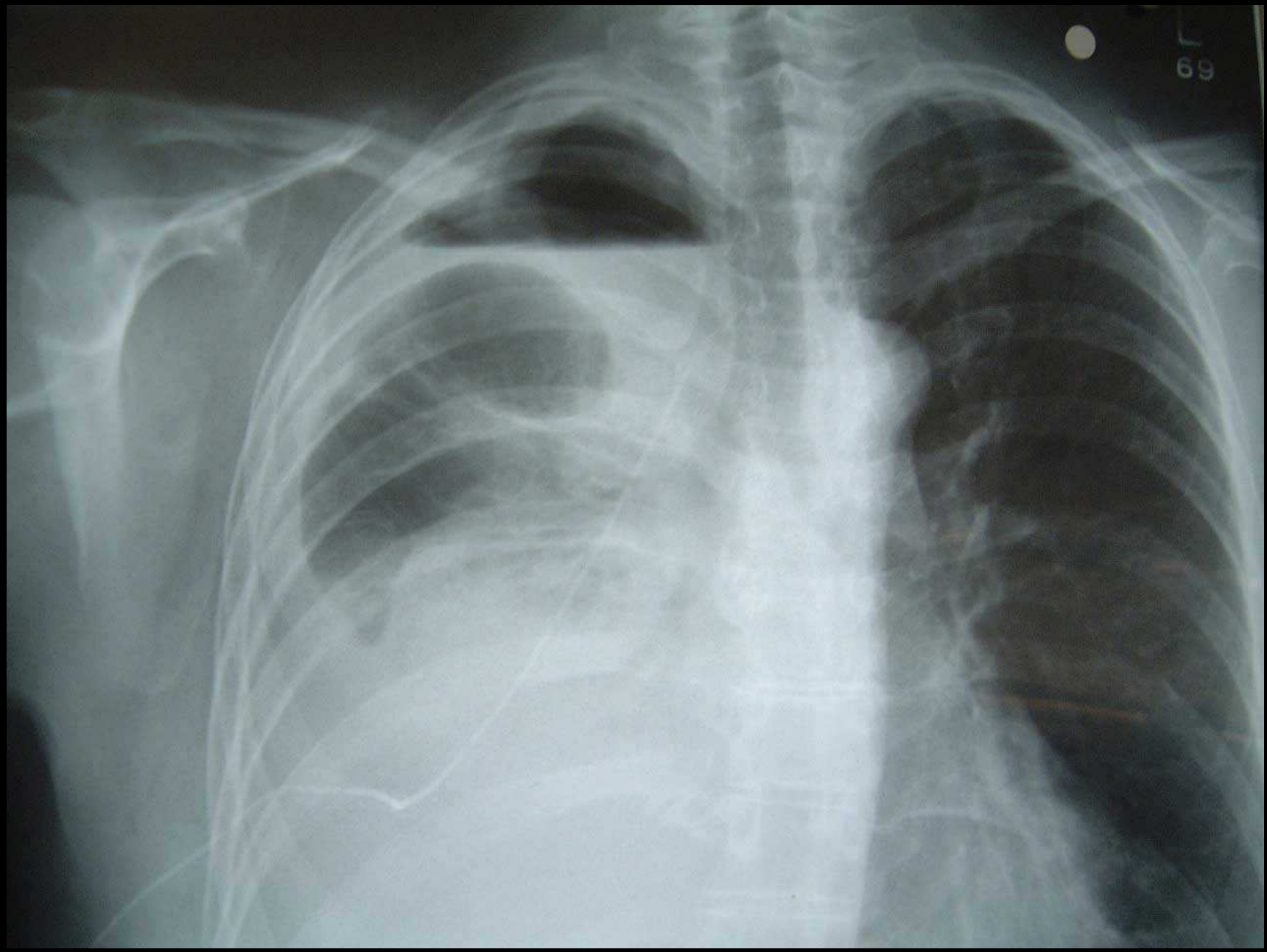
IPC in trapped lung

11 symptomatic effusions with trapped lung:

- Retrospective case review
- Later talc pleurodesis via IPC in 2 patients
- ‘No major complications’
  - 1 catheter occlusion
  - 4 infections
- Well tolerated with good symptom relief

Pien *et al.* Chest 2001; 119: 1641-6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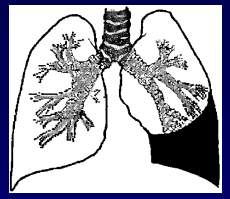

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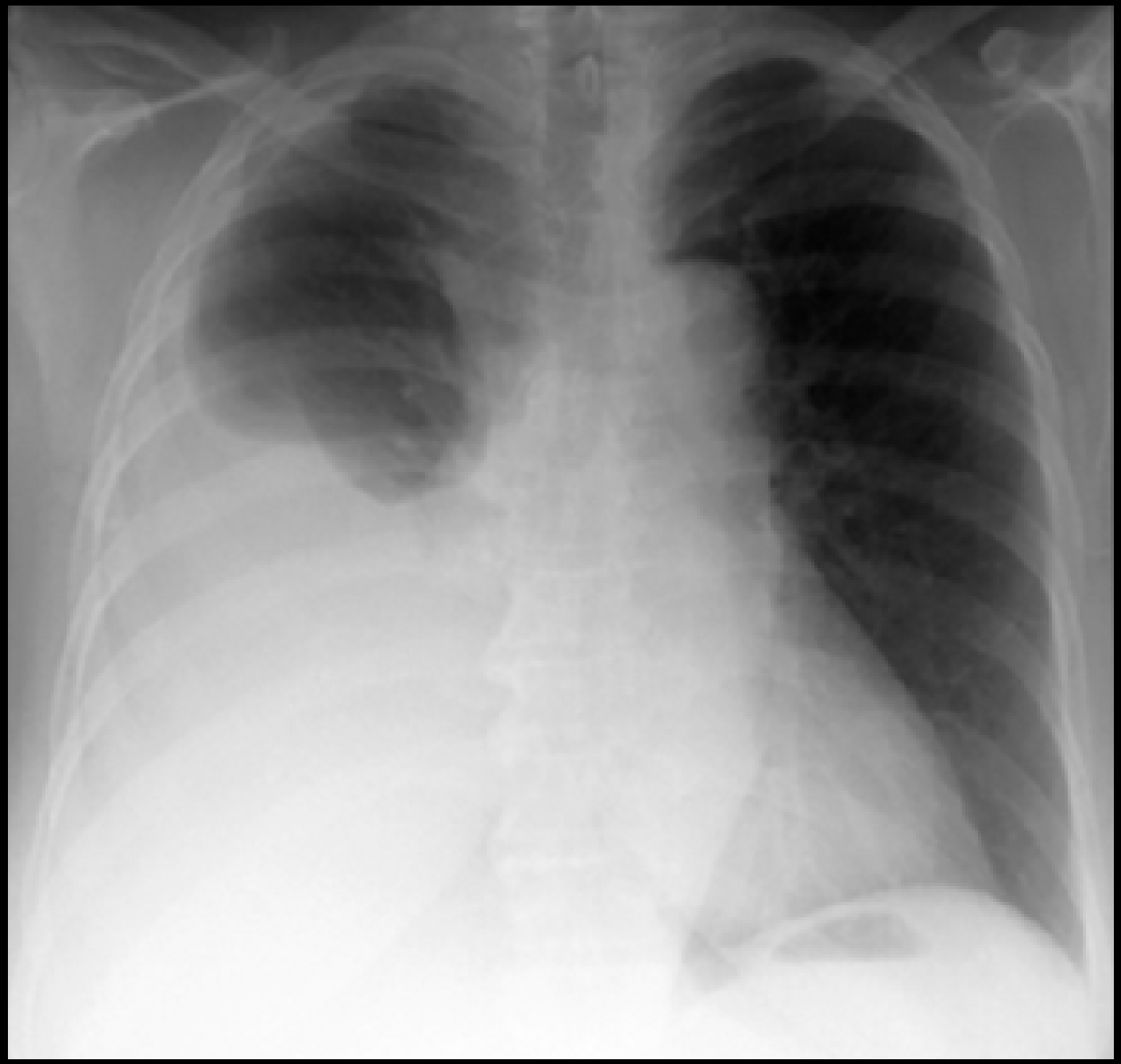
2. Failed talc pleurodesis

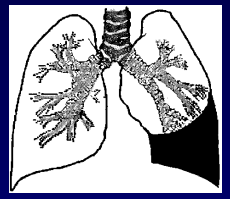
Optimal treatment strategy:

- (In absence of trapped lung)
- Unknown
- No convincing data

- Patient preference likely to be influential

- Clinical / biological predictors of success would be valuable
  - ? pH
  - ? Fibrinolytic indices





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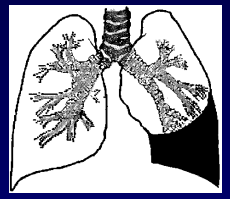
3. Primary therapy

Must compete:

- With talc pleurodesis / poudrage
  - Cheap
  - Effective
  - Widely available
- Consider talc as possible “one stop” treatment versus IPC which may be ongoing
- Consider relative side effect profiles



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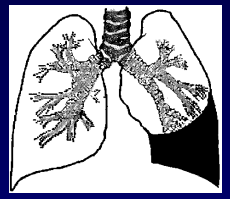
IPC in malignant effusion

250 IPC insertions in 223 patients:

- Retrospective analysis (prospective series)
  - 97 (39%) complete symptom control
  - 125 (50%) partial symptom control
  - 9 (3.6%) no benefit and 10 (4%) failed insertion
- 103/240 (43%) spontaneous pleurodesis
- 90% of patients no further drainage

Tremblay and Michaud *et al.* Chest 2006; 129: 362-8



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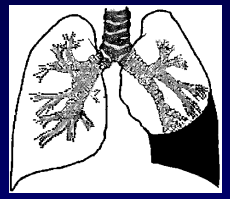
IPC in malignant effusion

• Failed/displaced insertion	4.0%	
• Symptomatic loculation	8.4%	
• Asymptomatic loculation	4.0%	
• Empyema	3.2%	
• Air in pleural space	2.4%	
• Infection	1.6%	
• Dislodged	1.2%	
• Bleeding	0.8%	
• Tumour seeding	~~0.4%~~	**6.7%**
• Pain requiring removal	0.4%	

Tremblay and Michaud *et al.* Chest 2006; 129: 362-8

Janes, Rahman, Davies, Lee. Chest 2007; 129: 362-8



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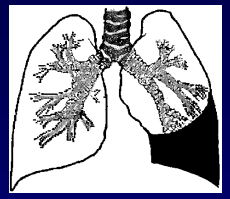
IPC in malignant effusion

Subset of 109 suitable for standard pleurodesis

- Criteria for analysis
  - Good lung expansion
  - Survival >90 days
  - Effusion <20% at 14 days
- Spontaneous pleurodesis rate in 70% of patients

Tremblay, Mason and Michaud *et al.* ERJ 2007; 30: 759-62



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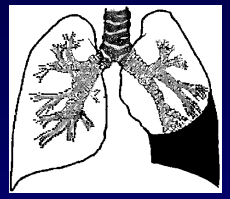
First line therapy

19 recurrent malignant effusions (21 catheters)

- Retrospective case review
- Later talc pleurodesis via IPC in 2 patients
- 11/19 (58%) spontaneous pleurodesis
- ‘No major complications’
  - 5 patients with cellulitis/empyema
  - 1 catheter track invasion
- Well tolerated with good outcome

Musani *et al.* Respiration 2004; 71: 559-66



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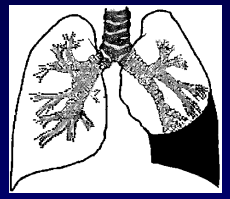
First line therapy

17 recurrent malignant effusions

- Retrospective case review
- '70-80% symptom relief with few complications'
- 'No major complications'
    - 2 patients with infection
    - 1 catheter dislocation

Van den Toorn *et al.* Lung Cancer 2005; 50: 123-127



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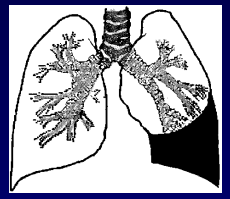
First line therapy

28 symptomatic effusions

- Retrospective case review
- 29/31 (94%) symptomatically improved dyspnoea
- 20/22 (91%) improved dyspnoea at 30 days
- ‘No major complications’
  - 1 displaced catheter
  - 1 infection
- Well tolerated with good symptom relief

Pollak *et al.* J.Vasc.Interven.Radiol 2001; 12: 201-8



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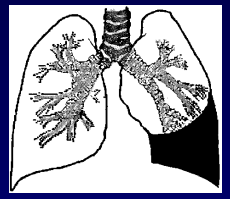
Comparative Studies

168 consecutive malignant effusions:

- Retrospective review
- IPC n=100, standard care = 68
- Good symptom control
- Median hospital stay
  - Standard care 7 days, IPC 0 days
- Cheaper – hospital costs only
  - Standard care $11,188
  - IPC $3,391
- 19 (19%) complications

Putman *et al.* Ann.Thorac.Surg.; 2000; 69: 369-75



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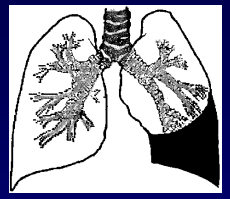
RCT of IPC v doxycycline

144 patients: randomised 2:1 (99/45) IPC v Doxy

- Inclusion criteria
  - Malignancy, moderate effusion, dyspnoea relief on aspiration
- Outcomes
  - Hospital inpatient time
  - IPC median 1 day, Doxy 6.5 p<0.001
  - No difference in simply assessed SOB / HRQL / pain / mortality
  - 12/91 (13%) adverse events with IPC
  - Recurrences 12/91 (13%) IPC v 6/28 (21%) Doxy

Putman *et al.* Cancer; 1999; 86: 1992-9



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Where does all this leave us?

Conclusions on the current evidence:

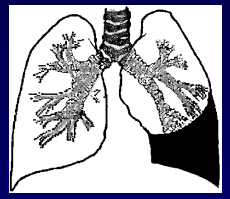
- IPC is effective for trapped lung

- As first line treatment for malignant effusion

Purpose of pleurodesis?

NOT a clean CXR
NOT volume of pleural fluid avoided / produced
Symptomatic relief

- But:
  - Adverse event profile
  - Nuisance
  - Cost



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Calculating the costs

£5000

£200

£50 / 250mls

Median survival post talc = 300 days

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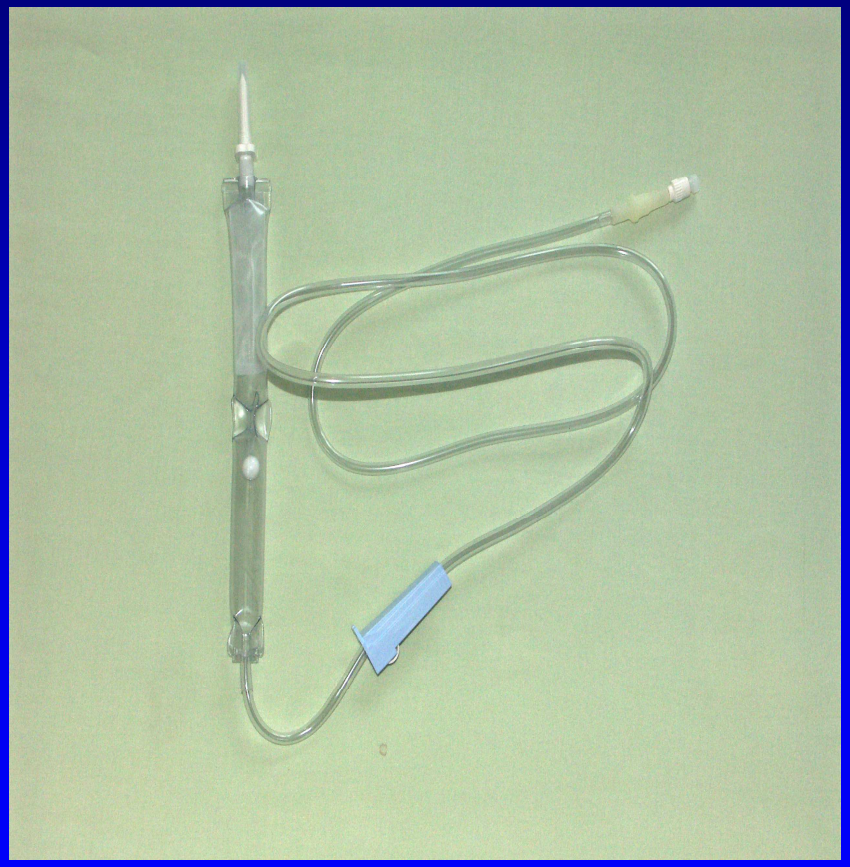
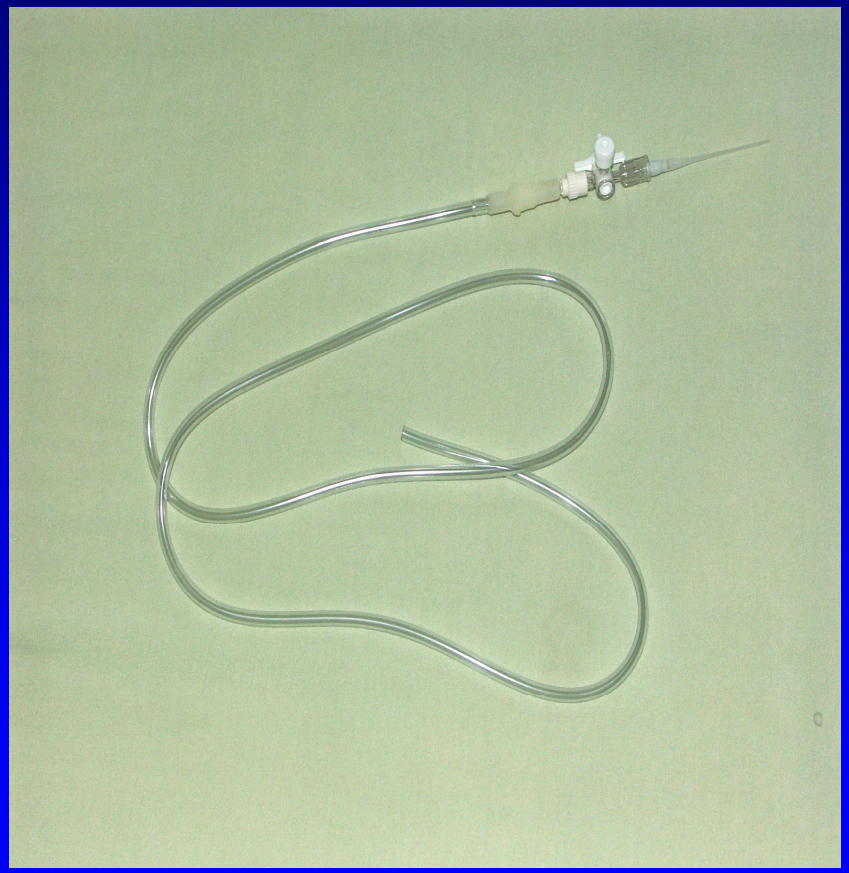
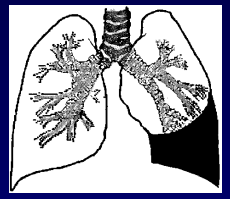
Cheaper solutions







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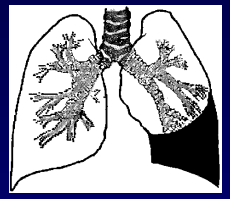
Future Directions

1. Define role of IPC in primary therapy:

- Clear evidence of cost / symptom benefit is needed
- Purpose of pleurodesis is:
  - NOT a clean CXR
  - NOT volume of pleural fluid avoided / produced
  - Symptomatic relief
- Therefore trials needed which assess:
  - Cost
  - Quality of life (positive and negative effects of IPC)
  - Direct comparison to a cheap and available solution (talc)



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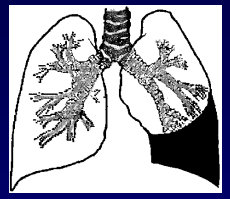
Future Directions

2. Improve the already available treatment:

- Predictors of pleurodesis success
- Intrapleural adjunctive therapy:
    - Thrombolytics in septated effusion
- Radiological stratification

3. Forget drainage:

- Manipulate the biology of pleural fluid production
- Better chemotherapy agents



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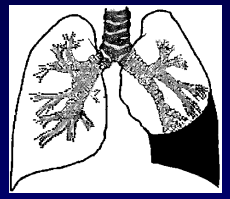
What is needed

Study which:

- Defines role of IPC in primary therapy
  - Provides evidence of cost benefit
  - Provides evidence of symptom benefit

- Therefore trial needed which assesses:
  - Cost
  - Quality of life (positive and negative)
  - Direct comparison to a cheap and available solution (talc)



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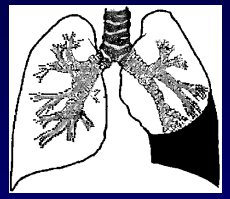
BRITISH LUNG FOUNDATION

A randomised controlled trial to assess the efficacy and safety of patient controlled malignant pleural effusion drainage by indwelling ambulatory pleural catheter, compared to standard care.

The TIME 2 trial



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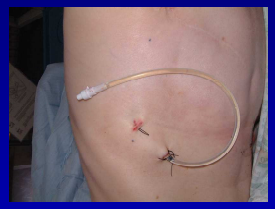
T.I.M.E. 2

BRITISH LUNG FOUNDATION

UNIVERSITY OF OXFORD

MPE requiring pleurodesis



Randomisation

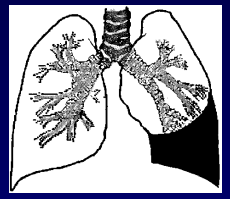
Indwelling pleural catheter

12F drain and pleurodesis

Daily visual analogue score (dyspnoea)

Days 1 to 42

Follow up weeks 2 / 4 / 6 / 10 / 18 / 22 / 26
Health questionnaires
Hospital costs



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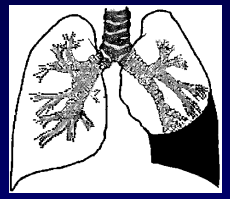
Power Calculation

Sample size:

- Assess outcome at 6 weeks (? Persists)
- Requires 90 patients (randomised 1:1) to show benefit with IPC (alpha 0.05, power 90%)
- Expected mortality = 20% @ 6 weeks
- Loss to follow up assumed to be 25%
- Total requirement = <u>104 patients</u>



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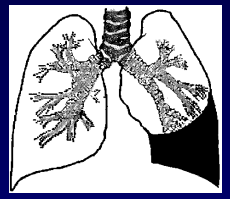
Patient Population

Inclusion:

- Clinically confident diagnosis of malignant pleural effusion requiring pleurodesis. The diagnosis may be established by:
  - Histocytologically proven pleural malignancy **or**
  - Recurrent large pleural effusion in the context of histologically proven cancer outside the thorax

- Written informed consent



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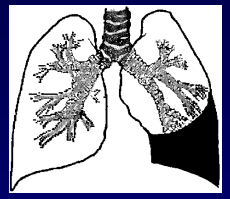
Trial Protocol

IPC group:

- Daycase insertion
- Initial large volume drainage
- Out-patient education in catheter use
- To drain when breathless

Pleurodesis:

- 12F Seldinger drain
- Pleurodesis once good radiological result (not in trapped lung)
- Drain out once <150mls / 24 hours drainage or day 5



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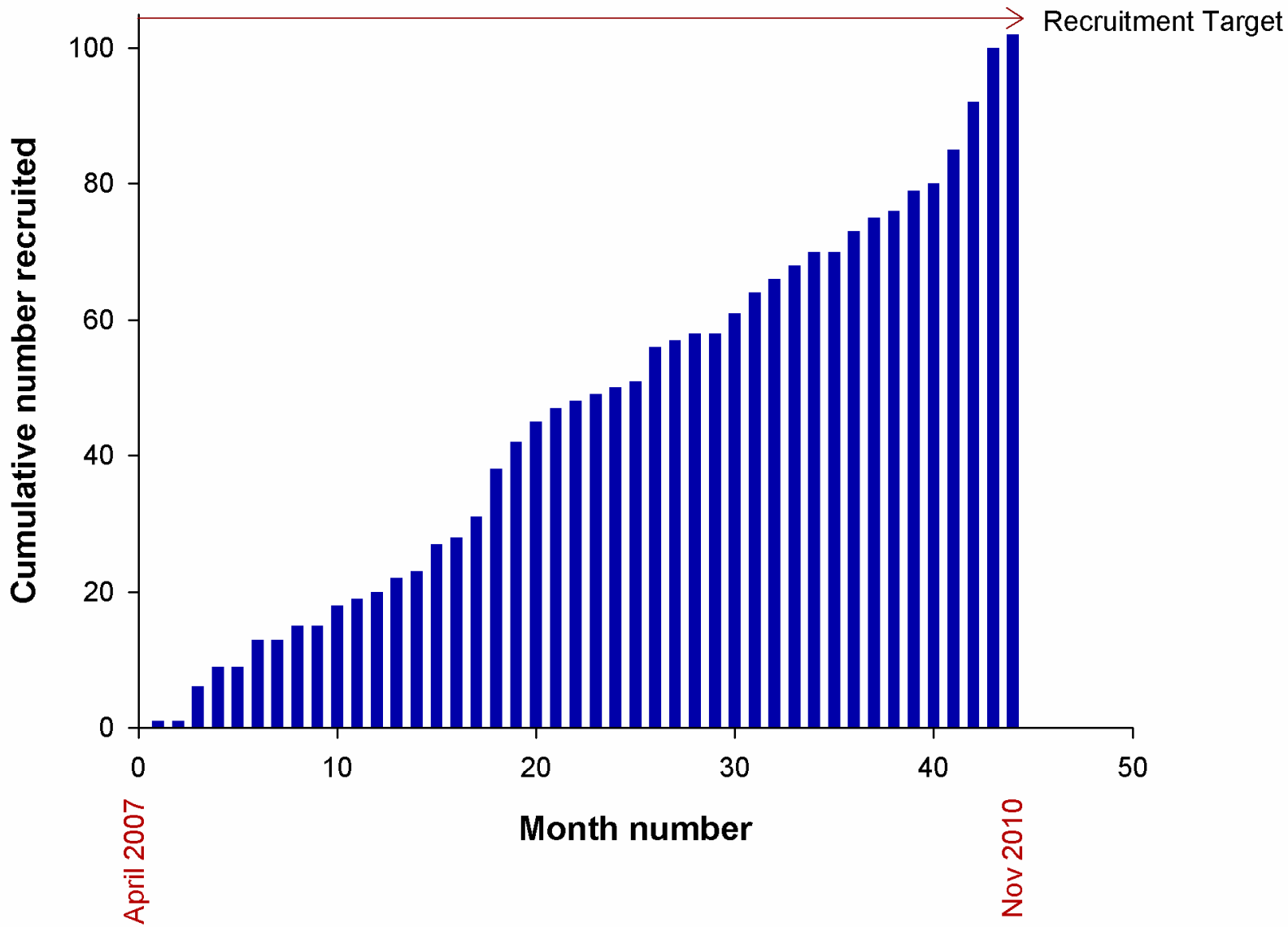
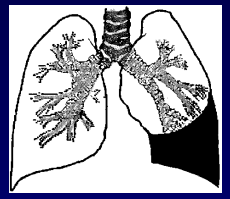
Trial Protocol

All patients:

- Daily breathlessness VAS 100mm days 0 to 42
- Daily temperature days o to 7
- Health status questionnaires + spirometry at follow up points (weeks 1 / 2 / 4 / 6 / 10 / 18 / 22 / 26 then 6 months and 9 months)

TIME2 Recruitment November 2010





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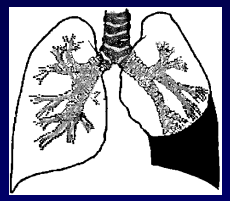
Trial Outcomes

- Primary outcome: data available in 93% of patients
- Similar quality on other outcomes

Primary data available in next 3 months



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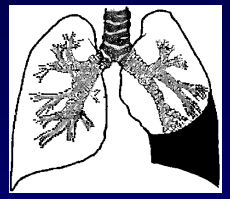
IPCs in benign disease



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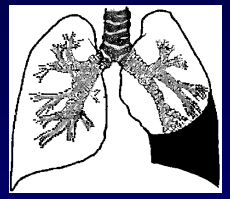
IPCs in benign disease

Which disease states?

- Resistant heart failure effusions
- Pleural infection:
  - Associated with pleural thickening
  - Not suitable for surgical intervention
- Rheumatoid visceral pleural thickening

Currently:

- Generally avoided in benign disease
- Concerns about
  - Long term presence
  - Infection
  - Erosion



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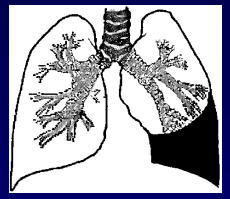
Untested



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IPCs in benign disease

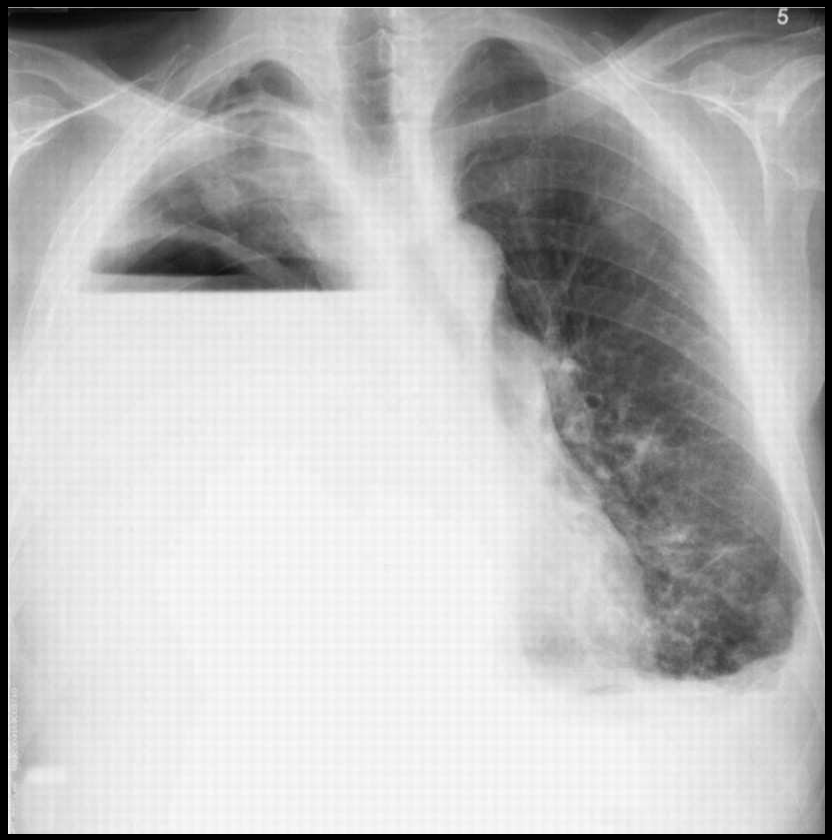
Pleural infection

- Around 20% mortality, 15% surgical rate
- Surgery denied to high risk patients:
    - Elderly
    - Comorbidity
- Associated high surgical morbidity

Failed medical treatment and not fit for surgery:

- Rib resection and open drainage
- Eloesser flap
- Long term antibiotic therapy
- Recurrent aspiration in presence of trapped lung

? Role for IPCs here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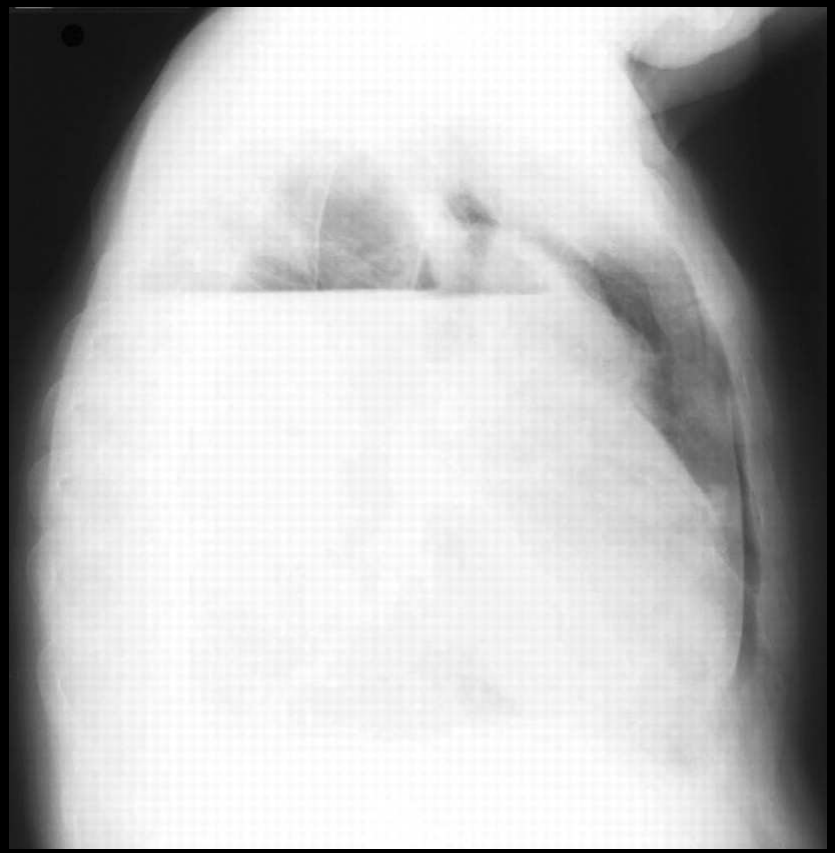

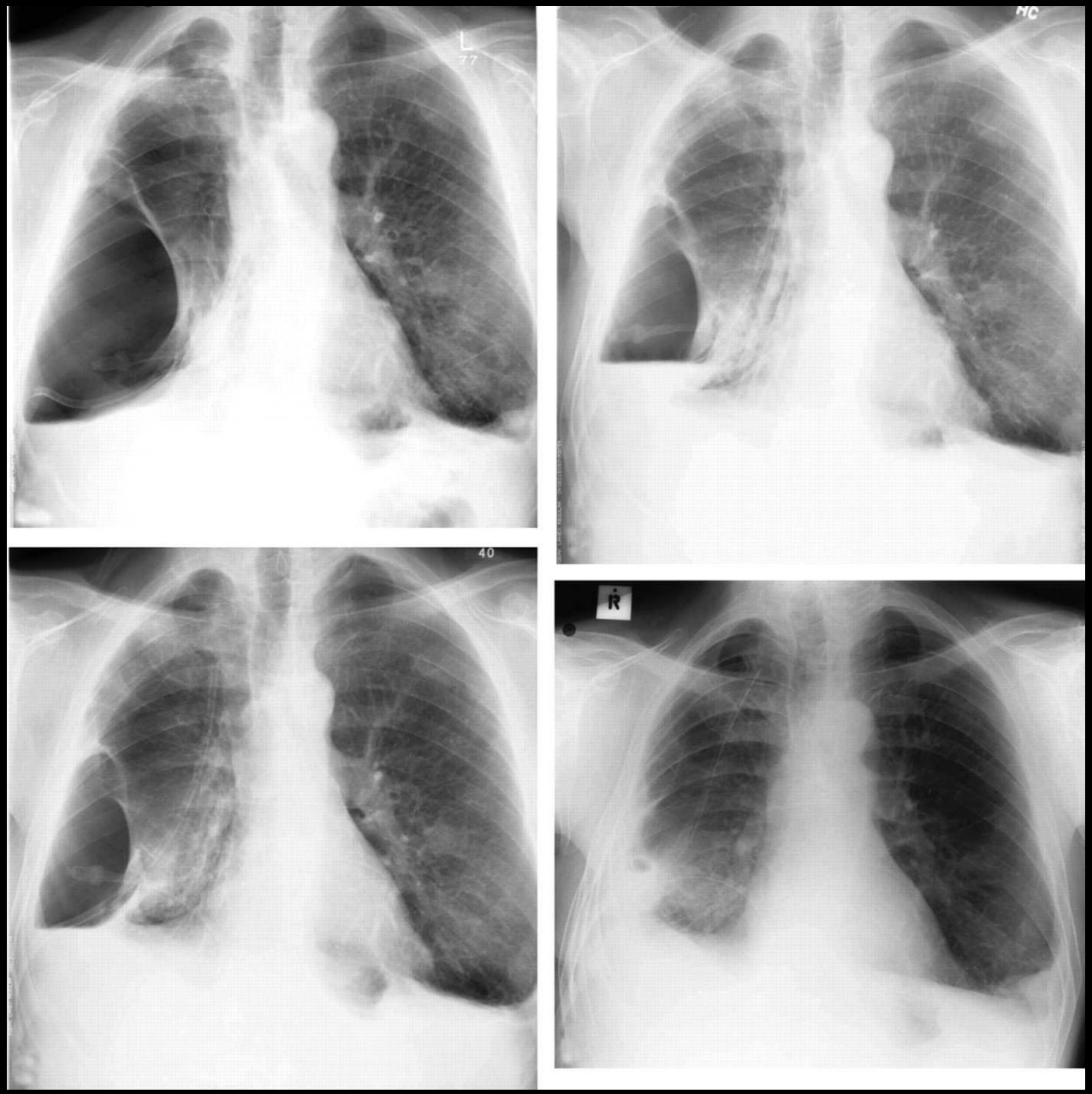
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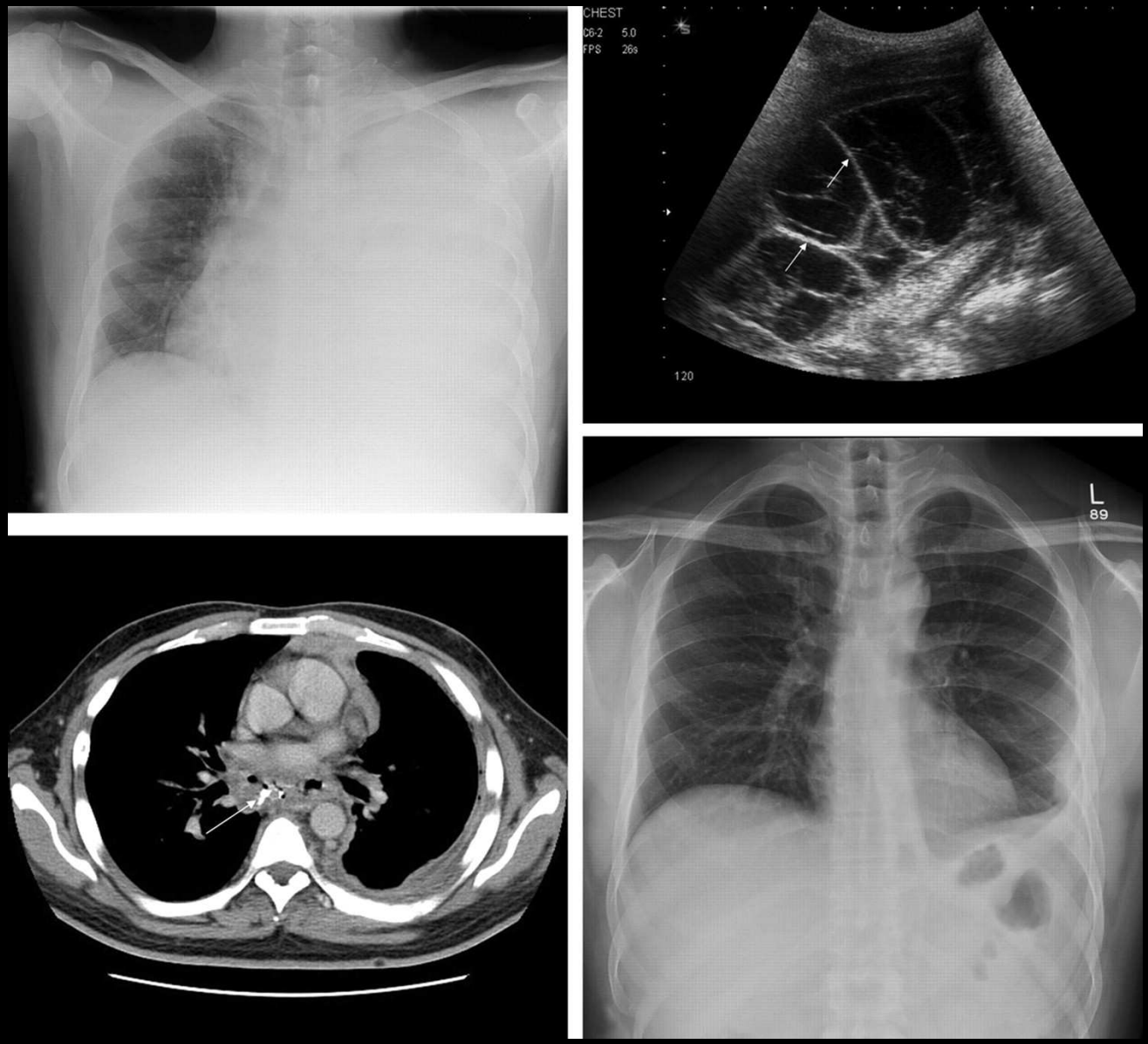
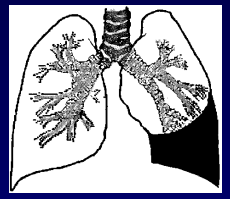


Davies HE, Rahman NM, Parker RJ, Davies RJO. Chest 2008;133:546-549



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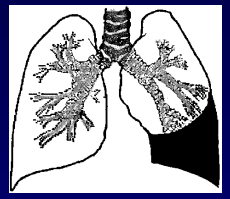
IPCs in benign disease

Heart failure:

- Single case series (Herlihy et al, Tex Heart Inst J. 2009)
- 2 year recruitment:
    - 5 patients included
    - 1 to 15 months drainage period
- No complications in 2/5
- Loculation in 1/5 – removed
- Empyema in 2/5

Hepatic hydrothorax:

- Single case report (Mercky et al, Respiration 2010)
- “Treatment success”
- Required removal for skin cellulitis after 6/12



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Summary - MPE

Indications for IPC use:

- IPCs probably treatment of choice for patients with trapped lung
- IPCs a reasonable option on patients who have failed talc pleurodesis

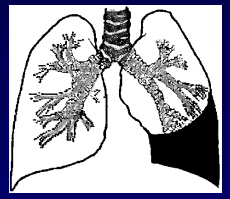
Primary therapy:

- Not sufficient data to support IPCs as primary therapy for MPE
- Specific randomised trials addressing this will report soon

Implications of IPC use:

- Cost of kit / to service
- Complications and “bothersome” factor

Treatment of MPE is palliative



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Summary – benign disease

Poor experience and evidence base

Pleural infection:

- Important potential addition
- Highly selected patients
- More studies required

Heart failure / other transudates:

- More studies required