# Πνευμονικές μεταστάσεις: Χειρουργούνται και πότε;

Χαράλαμπος Δ. Ζουμπλιός
Διευθυντής
Ογκολογικό Τμήμα
Νοσ. Ευαγγελισμός

# Δεν υπάρχει σύγκρουση συμφερόντων με τις Χορηγούς Εταιρείες:

**TREATMENT**
**Resectable[h] synchronous liver and/or lung metastases only**

**ADJUVANT TREATMENT[b]**
**(resected metastatic disease)**

Synchronous or staged colectomy[z] with liver or lung resection (preferred) and/or local therapy[aa]
or
Neoadjuvant therapy (for 2–3 months) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFOXIRI (category 2B) followed by synchronous or staged colectomy[z] and resection of metastatic disease
or
Colectomy,[z] followed by chemotherapy (for 2–3 months) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFOXIRI (category 2B) and staged resection of metastatic disease

→ FOLFOX (preferred) or CAPEOX (preferred)
or
Capecitabine or 5-FU/leucovorin
(6 MO TOTAL PERIOPERATIVE TREATMENT PREFERRED)

→ See Surveillance (COL-8)

- Η μεταστασεκτομή αποτελεί κοινή πρακτική από ετών.

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Surgical resection of pulmonary metastases: Benefits, indications, preoper...

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Topic Outline

SUMMARY AND RECOMMENDATIONS

INTRODUCTION

BENEFITS OF RESECTION

While pulmonary metastasectomy is a commonly performed operation, belief in its effectiveness is based upon registry data and surgical follow-up studies; there are no randomized trials. Until trials are completed, uncertainty will remain about the effectiveness of metastasectomy relative to other forms of treatment (eg, chemotherapy, stereotactic radiotherapy) [5]. One such trial is underway in Great Britain for patients with metastatic colorectal cancer (ie, the

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- Πλεονεκτήματα μεταστασεκτομής. Από προκύπτει η γνώση για αυτά τα πλεονεκτήματα;

Despite the lack of randomized trials, multiple case reports and small series suggest that resection prolongs survival and that long-term relapse-free survival (ie, cure) is possible in some patients with isolated lung involvement. The following retrospective reviews illustrate the benefits of a complete pulmonary metastasectomy:

- A review from the International Registry of Lung Metastases identified 5206 patients with a variety of primary metastatic tumors (carcinomas, sarcomas, germ cell tumors, and melanomas) who underwent a pulmonary metastasectomy [3]. This series included 4572 (88 percent) in whom complete resection was carried out [3]. The overall 5-, 10-, and 15-year survival rates were 36, 26, and 22 percent, respectively. Factors associated with a better prognosis included germ cell etiology, disease-free interval of 36 months, and a single metastatic lesion.

GENERAL THORACIC SURGERY

## LONG-TERM RESULTS OF LUNG METASTASECTOMY: PROGNOSTIC ANALYSES BASED ON 5206 CASES

The International Registry of Lung Metastases*
Writing Committee:
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Surgical resection of pulmonary metastases is now considered a standard therapeutic procedure in properly selected cases and is routinely performed in many departments of thoracic surgery. In fact, many tumors may involve the lung as the unique site of distant spread. Complete surgical excision of all pulmonary deposits is often technically feasible with low morbidity and mortality.[1-3]

However, the curative potential of metastasectomy had been recognized slowly. Pulmonary me-

This project has been funded by the Italian National Council for Research (CNR) within the programme "Progetto Finalizzato Applicazioni Cliniche della Ricerca Oncologica" (ACRO

- Πρώτη συστηματική καταγραφή των πνευμονικών μεταστασεκτομών

J Thorac Cardiovasc Surg. 1997

- Η **πενταετής επιβίωση** μετά από πνευμονική μεταστασεκτομή, κυμαίνεται μεταξύ **20% και 40%** όταν συμπεριλάβει κανείς όλους τους ιστολογικούς τύπους των πρωτοπαθών όγκων.
- Η επιβίωση αυτή είναι πολύ **μεγαλύτερη** από την αναμενόμενη από την **χημειοθεραπεία** η την **ακτινοθεραπεία** μόνη.

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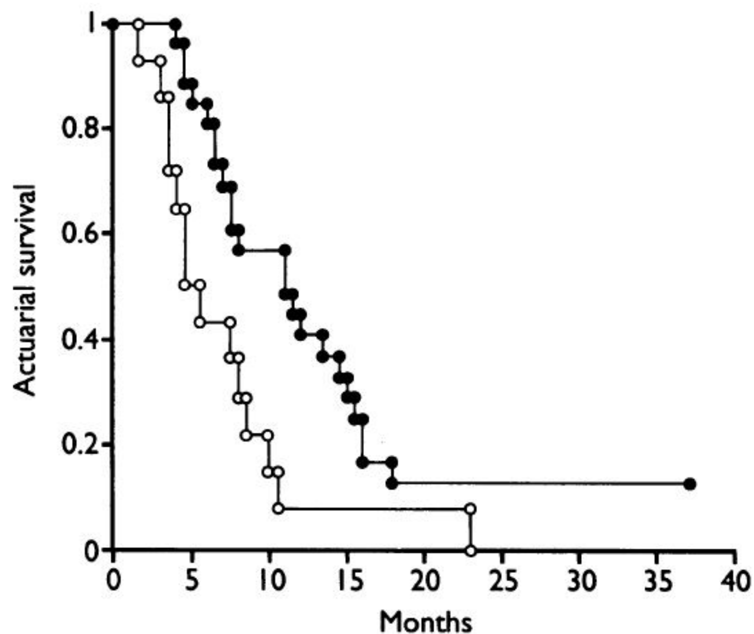
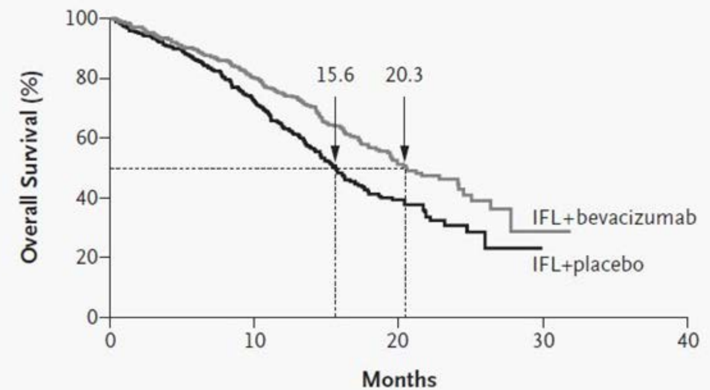
The data so far available suggest that lung metastasectomy is able to improve significantly the overall and disease-free survival with a limited morbidity and mortality. The overall 5-year survival ranges between 20% and 40% when all the primary sites are combined,[1, 2] much higher than expected after chemotherapy or radiotherapy alone.[10-12]

J Thorac Cardiovasc Surg. 1997




1—*Survival of patients with metastatic colorectal cancer randomised to chemotherapy plus supportive care (●—●) and to supportive care alone (○—○)*




**No. at Risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| IFL+bevacizumab | 402 | 362 | 320 | 178 | 73 | 20 | 1 | 0 |
| IFL+placebo | 411 | 363 | 292 | 139 | 51 | 12 | 0 | 0 |

**Figure 1. Kaplan–Meier Estimates of Survival.**
The median duration of survival (indicated by the dotted lines) was 20.3 months in the group given irinotecan, fluorouracil, and leucovorin (IFL) plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 (P<0.001).

Επιβίωση ασθενών με καρκίνωμα παχέος εντέρου σταδίου IV το **1993** με κύριο φάρμακο την 5-φθοριοουρακίλη.

Επιβίωση ασθενών με καρκίνωμα παχέος εντέρου σταδίου IV το **2004** με συνδυασμό 5-φθοριοουρακίλης, ιρινοτεκάνης και μπεβασιζουμάμπης.

# Είναι σωστός ο υπολογισμός της επιβίωσης από τις μελέτες της πνευμονικής μεταστασεκτομής;

- Πως κρίνεται η αναφερόμενη επιβίωση από τις υπάρχουσες μελέτες πνευμονικής μεταστασεκτομής.
- Η επιβίωση αυτή, προκύπτει από μελέτες οι οποίες είναι:
- **αναδρομικές**,
- αποτελούμενες στην πλειοψηφία από ασθενείς με **μονήρεις** η **λίγες** μεταστατικές εστίες και με
- **χρονική απόσταση** μεταξύ της εκδήλωσης του πρωταρχικού όγκου και της δευτεροπαθούς μετάστασης **μεγαλύτερη από 2-3 έτη**.

Pulmonary metastasectomy: what is the practice and where is the evidence for effectiveness?

Tom Treasure,[1] Mišel Milošević,[2] Francesca Fiorentino,[3] Fergus Macbeth[4]

ABSTRACT
Pulmonary metastasectomy is a commonly performed

but most referrals for metastasectomy come from oncologists.

follow-up studies. These retrospective series are comprised predominately of solitary or few metastases with primary resection to metastasectomy intervals longer than 2–3 years. Five-year survival rates of 30–50% are

metastasectomy and survival cannot be interpreted as causation. Cancers for which lung metastasectomy is used are considered in four pathological groups. In non-

is the 1997 report from the International Registry of Lung Metastasectomy (IRLM) of 5206 patients from Europe and North America.[1 2]

Thorax. 2014

- Οι περισσότερες μελέτες στην βιβλιογραφία είναι με μικρό αριθμό ασθενών και περιορισμένης παρακολούθησης.
- Ακόμα και στις μεγαλύτερες σειρές είναι δύσκολο να κάνει κανείς προσαρμογή λόγω της ετερογένειας των ασθενών όσον αφορά:
- ηλικία
- φύλο
- Τύπου πρωτοπαθούς όγκου
- έκταση της μεταστατικής διασποράς
- χειρουργικών τεχνικών
- ταυτόχρονων ιατρικών θεραπειών

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Unfortunately, the majority of the experiences reported in the literature are affected by small numbers and limited follow-up. Even in the largest series it is difficult to adjust properly for the heterogeneity of patients in terms of age, sex, primary tumor type, extent of metastatic spread, surgical techniques, and concurrent medical treatments.[13-16]

J Thorac Cardiovasc Surg. 1997

- Περιοχές αντιπαράθεσης παραμένουν:
- Η επιλογή των ασθενών
- Ο μέγιστος αριθμός των χειρουργήσιμων μεταστάσεων
- Η αμφοτερόπλευρη χειρουργική σταδιοποίηση
- Η επικουρική χημειοθεραπεία
- Οι προγνωστικοί παράγοντες

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Major areas of controversy remain with respect to the following aspects: selection of patients (i.e., maximum number of resectable metastases), bilateral surgical staging, adjuvant chemotherapy, and prognostic factors for each primary tumor site.[8, 14, 17]

J Thorac Cardiovasc Surg. 1997

- Για όλους αυτούς τους λόγους προσπαθήσαμε να ξεπεράσουμε τους περιορισμούς της παρούσης γνώσης με μια πολυκεντρική κλινική μελέτη.
- Δημιουργήθηκε μια **κοινή βάση δεδομένων**, από τα μεγαλύτερα κέντρα θωρακικής χειρουργικής της Ευρώπης και των ΗΠΑ.

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For all these reasons it appeared reasonable to try to overcome the limits of present knowledge by a cooperative multicentric clinical study. The International Registry of Lung Metastases was launched in 1990 with a few clear objectives: set up a common database through the major centers of thoracic surgery in Europe and the United States to facilitate the exchange of information; perform a more homogeneous evaluation of the results for the various primary tumors; define prognostic factors by multivariate analysis; propose a novel system of stage grouping; and define areas of uncertainty concerning surgery and other therapeutic modalities to be explored by prospective randomized trials.

J Thorac Cardiovasc Surg. 1997

- Συμπεράσματα:
- Οι ασθενείς που υποβλήθηκαν σε **πλήρη εκτομή** σε σύγκριση με αυτούς στους οποίους η εκτομή **δεν ήταν πλήρης**, είχαν καλύτερα ποσοστά επιβίωσης στα 5, 10 και 15 έτη.
- Δεν υπάρχει όμως το σκέλος των ασθενών που υποβλήθηκαν σε άλλη θεραπεία.

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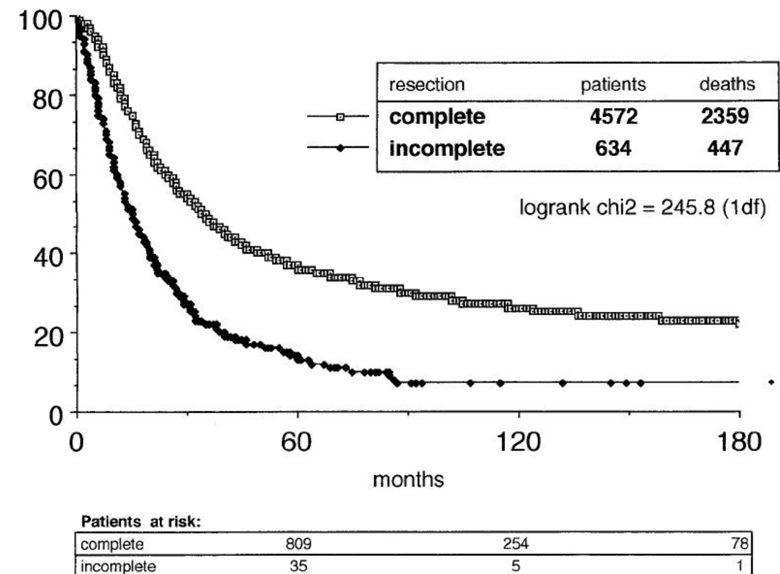



**Patients at risk:**

| | | | |
|---|---|---|---|
| complete | 809 | 254 | 78 |
| incomplete | 35 | 5 | 1 |

**Fig. 1.** Overall actuarial survival after lung metastasectomy: complete resection versus incomplete resection. The number of patients at risk at 5, 10, and 15 years is reported at the bottom of the curve.

J Thorac Cardiovasc Surg. 1997

# Κριτήρια πνευμονικής μεταστασεκτομής

**Criteria for considering a resection** — There are few published guidelines from expert groups that deal with patient selection for pulmonary metastasectomy. Available guidelines include the consensus-based guidelines for resectability of colorectal cancer lung metastases from the National Comprehensive Cancer Network (NCCN) [11] and a consensus document on pulmonary metastasectomy from the Society of Thoracic Surgeons (STS) [10].

- **Κριτήρια μεταστασεκτομής**:
- Ο κολοορθικός καρκίνος (NCCN)
- Εταιρεία θωρακοχειρουργών (Ann Thorac Surg. 2019)

# Expert Consensus Document on Pulmonary Metastasectomy

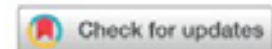
John R. Handy, MD, Ross M. Bremner, MD, Todd S. Crocenzi, MD, Frank C. Detterbeck, MD, Hiran C. Fernando, MD, Panos M. Fidias, MD, Scott Firestone, MS, Candice A. Johnstone, MD, Michael Lanuti, MD, Virginia R. Litle, MD, Kenneth A. Kesler, MD, John D. Mitchell, MD, Harvey I. Pass, MD, Helen J. Ross, MD, and Thomas K. Varghese, MD

Thoracic Surgery, Providence Health & Services, Portland, Oregon; Norton Thoracic Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona; Medical Oncology, Providence Cancer Center, Providence Health & Services, Portland, Oregon; Section of Thoracic Surgery, Yale University School of Medicine, New Haven, Connecticut; Inova Cardiac and Thoracic Surgery, Department of Surgery, Inova Fairfax Medical Campus, Falls Church, Virginia; Medical Oncology, Center for Cancer Care, Exeter Hospital, Exeter, New Hampshire; The Society of Thoracic Surgeons, Chicago, Illinois; Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin; Division of Thoracic Surgery, Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts; Department of Surgery, Boston University Medical Center, Boston, Massachusetts; Section of Thoracic Surgery, Indiana University School of Medicine, Indianapolis, Indiana; Department of Surgery, University of Colorado School of Medicine, Aurora, Colorado; Department of Cardiothoracic Surgery, Langone Medical Center, New York University School of Medicine, New York, New York; Division of Hematology/Medical Oncology, Mayo Clinic, Phoenix, Arizona; and Division of Cardiothoracic Surgery, University of Utah, Salt Lake City, Utah

**Ann Thorac Surg. 2019**

- Από το 1980 έχουν δημοσιευθεί περισσότερες από 1.000 μελέτες για την πνευμονική μεταστασεκτομή, από τις οποίες **ούτε μία** δεν είναι ελεγχόμενη τυχαιοποιημένη μελέτη.
- Οι περισσότερες είναι χειρουργικές σειρές από ένα ίδρυμα και περιλαμβάνουν ένα η πολλούς τύπους κακοήθειας.
- Δεν αναφέρεται η δεξαμενή των από την οποία προήλθαν οι ασθενείς, αποκλείοντας έτσι την συγκριτική ανάλυση της επιβίωσης.

**Expert Consensus Document on Pulmonary Metastasectomy**

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Since 1980, greater than 1,000 publications addressed PM, without a single randomized controlled trial. Most of the studies are surgical series, usually from a single institution, and include single or multiple pathologies. The pool of patients from which metastasectomy patients derive is not reported, allowing no comparative survival analysis. Historical controls are used or met-

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-Υπάρχουν λίγα (**8 όλα και όλα**) άρθρα από βάσεις δεδομένων, και αυτό με την μεγαλύτερη επίδραση, **δεν** είχε ένα κοινό παρονομαστή από τον οποίον προήλθαν οι ασθενείς που υποβλήθηκαν σε μεταστασεκτομή.

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A few registry articles (eight in total) have largely defined practice. The most influential reported 5,206 patients with multiple pathologies from the International Registry of Lung Metastases (IRLM) [6], without a denominator of cancer patient population from which the metastasectomy patients derived (Table 1).

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- Χαρακτηριστικά της βιβιογραφίας για την πνευμονική μεταστασεκτομή:
- Απουσία τυχαιοποιημένων μελετών
- Διάχυτη μεροληψία επιλογής των ασθενών
- Απουσία συγκριτικής ανάλυσης της επιβίωσης
- Ατελής περιγραφή των συνυπαρχουσών θεραπειών
- Διάστημα παρακολούθησης που ποικίλει
- Αποτυχία να διακριθούν οι προγνωστικοί και οι προδηλωτικοί παράγοντες
- Δεν αποσαφηνίζεται ο ρόλος της πνευμονικής μεταστασεκτομής στην επιμήκυνση της επιβίωσης η την θεραπεία

*Table 1. General Characteristics of the Pulmonary Metastasectomy Literature*

| |
|---|
| No randomized controlled trials |
| Pervasive selection bias |
| No comparative survival analysis |
| Inconsistent description of accompanying local or systemic therapies |
| Variable follow-up length |
| Fails to distinguish between prognostic or predictive characteristics |
| Does not clarify the role of pulmonary metastasectomy in prolongation of survival or cure |

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Consensus statements were developed using a modified Delphi method. The proposed statements were subject to a vote using a 5-point Likert scale. An 80% response rate among the authors was required, and statements in which 75% of respondents selected “agree” or “strongly agree” were considered to have reached consensus. Three statements did not achieve 75% agreement after the first round of voting, and after minor revisions, were included after a second round of voting. The American College of Cardiology Foundation/American Heart Association classification system used in clinical practice guidelines to rate the strength, and level of evidence was not used for this report because the expert consensus process adopted by STS results in opinion statements rather than formal recommendations.

## Pulmonary Metastasectomy Expert Consensus Statements

1. When caring for patients with cancer and pulmonary oligometasta… should be … team (MDT)…
2. In oncologic… small cell l… from PM sh… analysis, incl… guide future…
3. In oncologica… PM can be … mally invasi… postoperative… of life.
4. If goals of R… are not accor… to open app… clam shell), …
5. Pneumonect… except in c… MDT manag…
6. Although th… tastases is … candidate selection for PM is best suited to patients harboring 3 or fewer pulmonary metastases.
7. Lymph node (LN) sampling/dissection concomitant with PM should be considered, because pulmonary metastasis accompanied by mediastinal LN metastasis predicts poor survival.
8. Thermal ablation or stereotactic ablative body … herapy for pa-… s, particularly … section or who … ung perfusion … of pulmonary … be considered … temic therapy … can be consid-… PM can be … ered within an … nd neck cancer … a disease-free … hs, ability to … LN metastases. … germ cell tu-… l residual lung abnormalities ≥ 10 mm after platin-based chemotherapy with normalized serum tumor markers (STMs) suspected of containing teratoma.

16. When managing NSCGTs, contralateral lung abnormalities can be observed if histology of unilateral PM demonstrates complete tumor necrosis.

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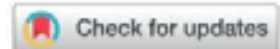
- Εισαγωγή του άρθρου:
- Τα ακόλουθα είναι η **συμφωνία των ειδικών** και **ΔΕΝ** φθάνουν στο επίπεδο των **οδηγιών**, λόγω της **ελλαττωματικής** βιβλιογραφίας που μας υποστηρίζει.

## Expert Consensus Document on Pulmonary Metastasectomy

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### Introduction

PM has long been practiced, albeit in the face of a large literature with low level of evidence. Recognizing a need for some standardization, The Society of Thoracic Surgeons (STS) Work Force of Evidence Based Surgery formed a task force and subjected "pulmonary metastasectomy" to STS expert consensus development process. The task force membership included thoracic surgery, medical, and radiation oncology. The following is the resulting expert consensus, not rising to the level of guidelines due to the flawed supporting literature.

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# Είναι δυνατόν να αποκτήσουμε αποδείξεις;

- Στην Βρετανία. διεξάγεται μία τυχαιοποιημένη μελέτη (PulMiCC trial, NCT01106261),
- Οι ασθενείςμε καρκίνωμα παχέος εντέρου οι οποίοι κατανέμονται σε δύο σκέλη:
- 1) Μεταστασεκτομή,
- 2) ενεργός παρακολούθηση.

**A Randomised Trial of Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC)**

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

**Sponsor:**
University College, London

**Collaborators:**
Royal Brompton & Harefield NHS Foundation Trust
University of Cambridge
University of Sussex

**Information provided by (Responsible Party):**
University College, London

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

**Study Description**

Brief Summary:

Patients who have been treated successfully for bowel cancer (colorectal cancer) sometimes go on to develop nodules of disease in another part of the body. If this disease is f
liver.

There is a growing trend to remove lung metastases with an operation, in the belief that this will help patients live longer, however there have not been any scientific studies to p
feasibility study to determine whether it will be possible to conduct a large randomised controlled trial investigating the value of pulmonary metastasectomy (surgery to remove l
Firstly, patients will be invited to consent to having a full range of investigations to assess their suitability for surgery. If found to be suitable, they will then be invited to consent t
regularly for 5 years to assess their disease status and to measure their quality of life and lung function.

| Condition or disease | Intervention/treatment |
|---|---|
| Colorectal Cancer | Procedure: Metastasectomy |
| Pulmonary Metastases | Procedure: Active monitoring |

- NCT01106261

# Συμπέρασμα

- Η οδηγίες για την πνευμονική μεταστασεκτομή μέχρι σήμερα **δεν** στηρίζονται σε αποδείξεις.

# Πότε ΔΕΝ κάνουμε πνευμονική μεταστασεκτομή.

- Όταν η νόσος **δεν** είναι πλήρως αφαιρέσιμη.
- Όταν ο ασθενής **δεν** έχει κατάλληλες καρδιοπνευμονικές εφεδρείες.
- Όταν η μεταστασεκτομή **δεν** είναι τεχνικώς δυνατή.
- Όταν ο πρωτοπαθής όγκος **δεν** είναι ελεγχόμενος.
- Όταν υπάρχει ταυτόχρονα εξωπνευμονική νόσος η αν υπάρχει, δεν είναι ελεγχόμενη.

**Criteria for resection**

•The pulmonary metastases appear to be **completely** resectable based upon preoperative imaging.

•The patient has adequate cardiopulmonary **reserve** to tolerate resection.

•Metastasectomy is technically **feasible**.

•The **primary** tumor is **controlled** or controllable.

•**Extrapulmonary** metastatic disease is **absent**, and if present, the disease must be controllable with surgery or another treatment modality.

•Uncommonly, resection of **one or more** lung lesions may be indicated in a patient with a **known** malignancy who does not meet these criteria. As examples:

•A **new primary** lung cancer cannot be excluded.

•**Symptomatic** metastases (e.g., bronchial **obstruction** with distal suppuration) **cannot** be managed in any other way.

•**Tissue needs** to be obtained for a novel therapeutic strategy (e.g., an autologous vaccine), preferably within the confines of a clinical trial.

# Ευχαριστώ για την προσοχή σας