Surgical Management of Pulmonary Metastases

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Introduction

- Lungs 2nd most common site of metastatic deposition

- 2 main forms recognised:
  - Haematogenous
  - Lymphatic

Introduction

Most common primaries resulting in pulmonary metastases:

- Breast carcinoma
- Colorectal carcinoma
- Renal cell carcinoma
- Uterine leiomyosarcoma
- Head and neck squamous cell carcinoma

Introduction

Less common tumours resulting in pulmonary metastases:

- Choriocarcinoma
- Ewing sarcoma
- Malignant melanoma
- Osteosarcoma
- Testicular tumours
- Thyroid carcinoma

Symptoms

- Present in 15-20% of patients
  - Cough
  - Dyspnoea
  - Haemoptysis
  - Spontaneous pneumothorax

Criteria for resection

- Primary tumour controlled
- Metastases resectable
- Absence of extra pulmonary disease
- Adequate cardiopulmonary reserve

Prognostic Determinants

- No universal criteria which predict long-term survival
- 1990-International registry of lung metastases (IRLM)
  - 5206 cases from 1991-1995
  - Identified 4 major prognostic factors
    - Complete resection
    - Disease-free Interval (DFI)
    - Number of metastases
    - Tumour Doubling Time

Prognostic Determinants

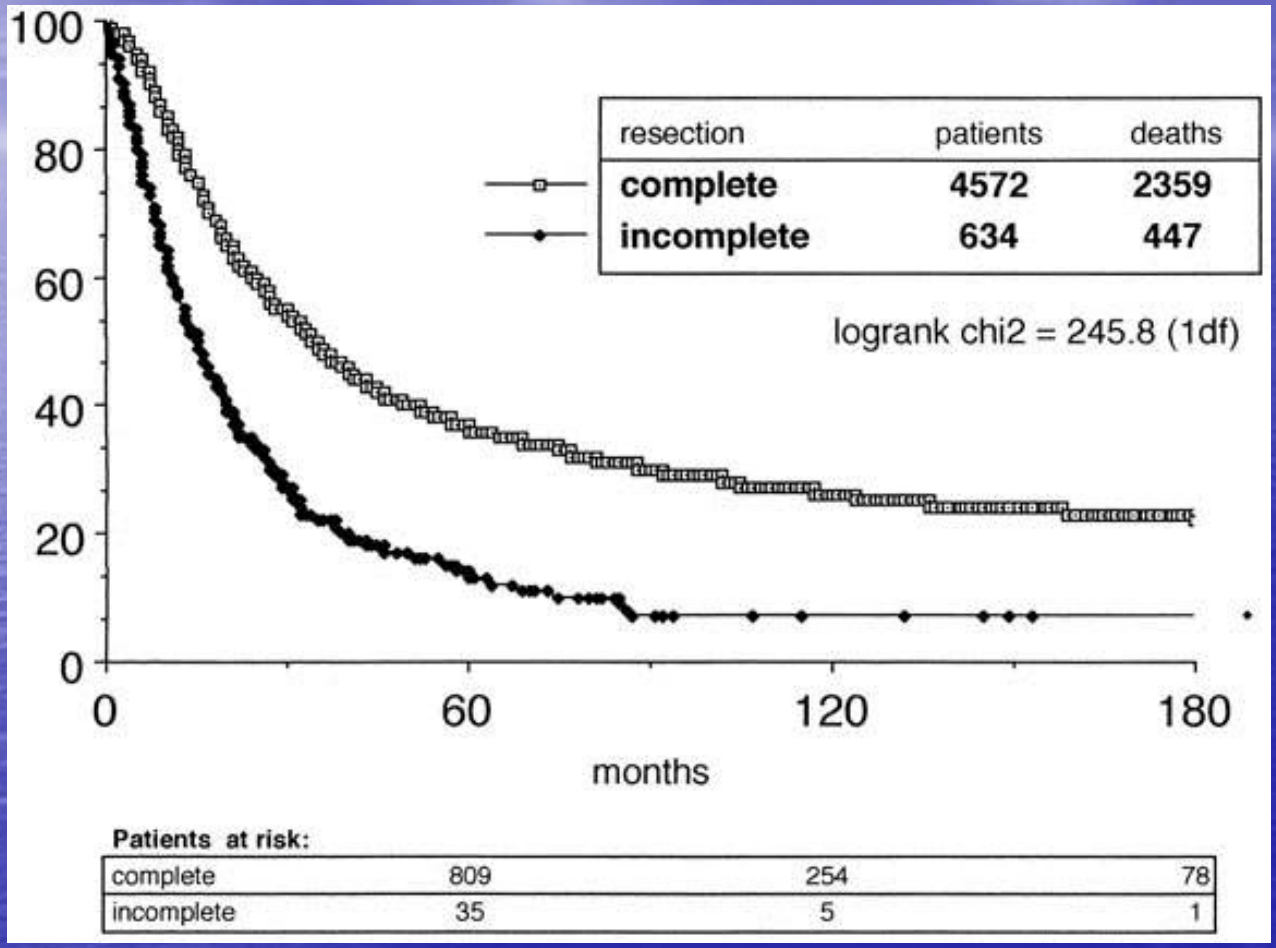
- **Complete Resection**

- Data from International registry:

	Complete Resection	**Incomplete Resection**
Median Survival	35 months	15 months
5 year survival	36%	13%

Prognostic Determinants

COMPLETE RESECTION



Overall actuarial survival after lung metastasectomy: complete resection versus incomplete resection.

Prognostic Determinants

TUMOR DOUBLING TIME

- ***Morton, Joseph et al***
  - Studied patients with variety of tumour types
  - TDT < 40 days – all died within 2-5 years
  - By comparison: TDT > 40days – 63% 5yr survival post resection.

Prognostic Determinants

- ***TUMOR DOUBLING TIME***

Ollila et al (1998) –

- Largest series of melanoma patients.

	Median Survival	5yr survival
TDT < 60 days	16 mo	0
TDT > 60 days	29.2	20.7

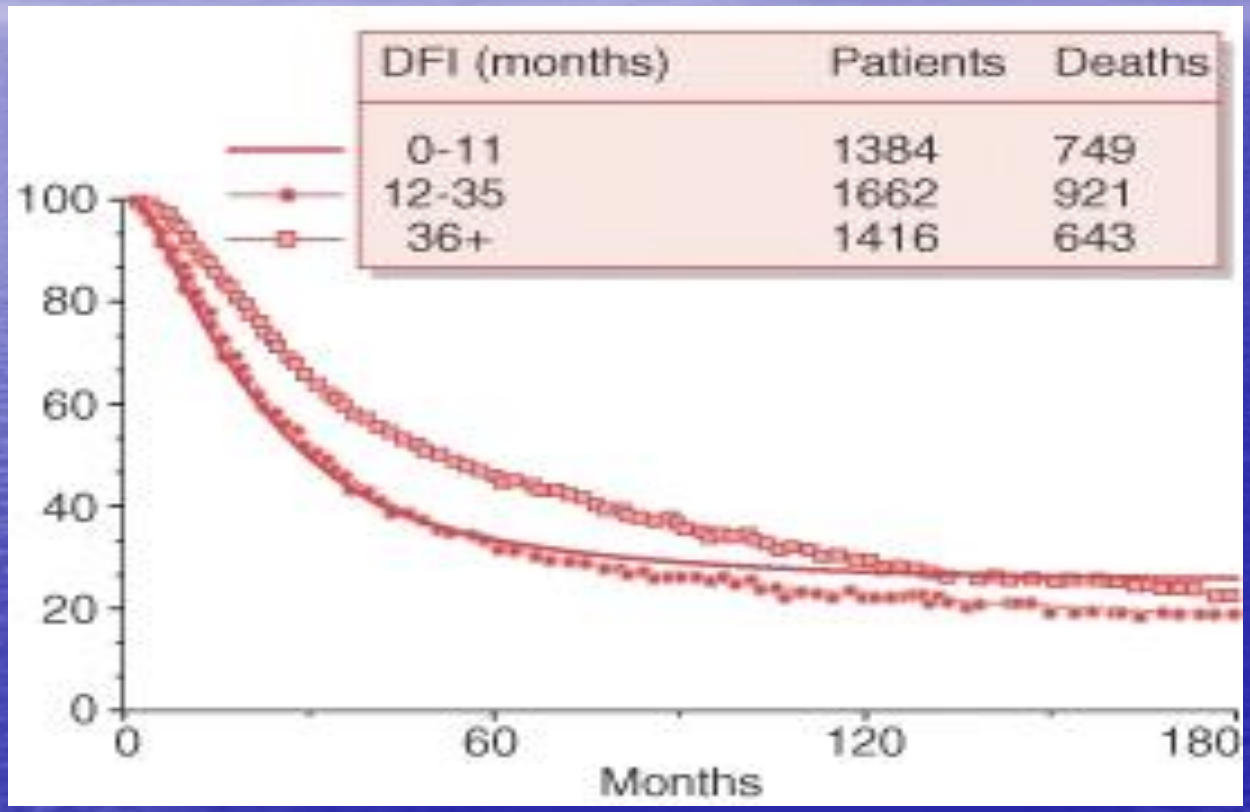
Prognostic Determinants

Disease-free interval (DFI)

- Important prognostic factor:
  - Pastorino U, et al 1997
  - Todd TR, et al 1997
  - Kandiolar, et al 1998
- **Others:** DFI not an important factor - no influence on outcome:
  - Robert JH, et al 1997

Prognostic Determinants

Disease-free interval

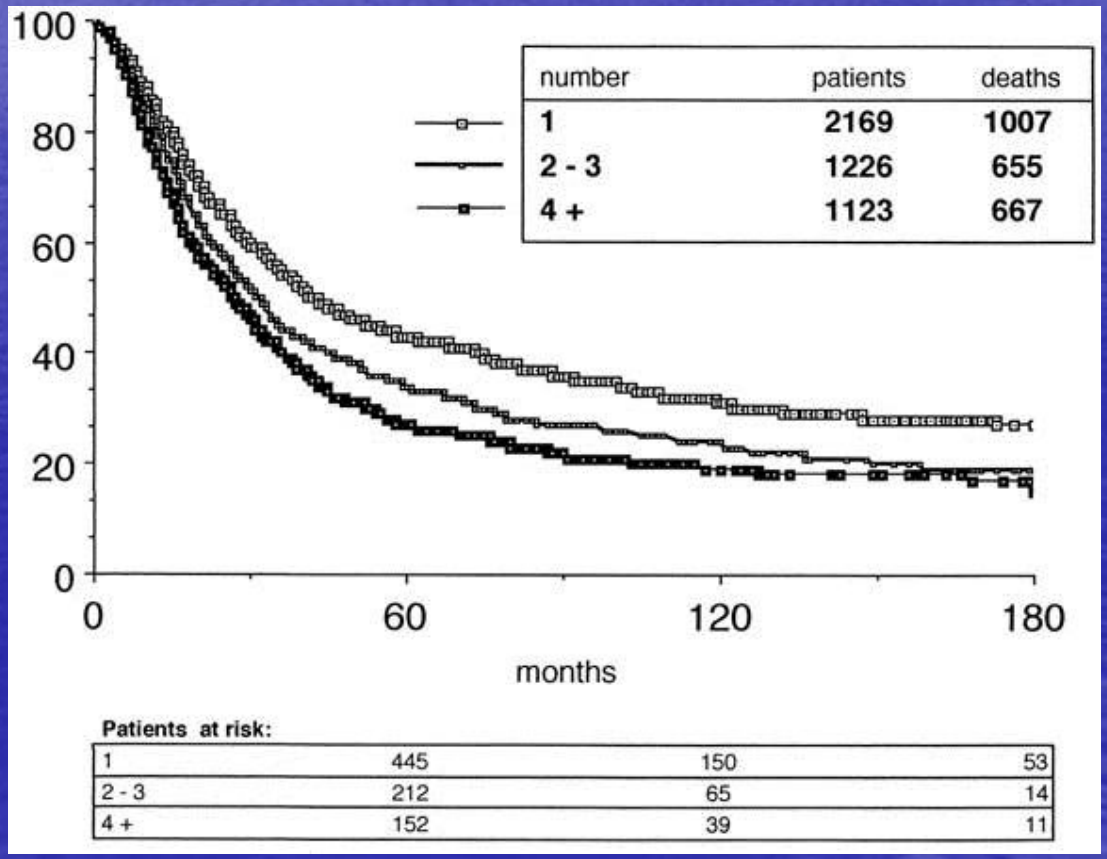


IRLM: Survival of the complete resection according to DFI

Prognostic Determinants

Number and distribution of pulmonary metastases

- IRLM Series:



Recurrent Pulmonary Metastases

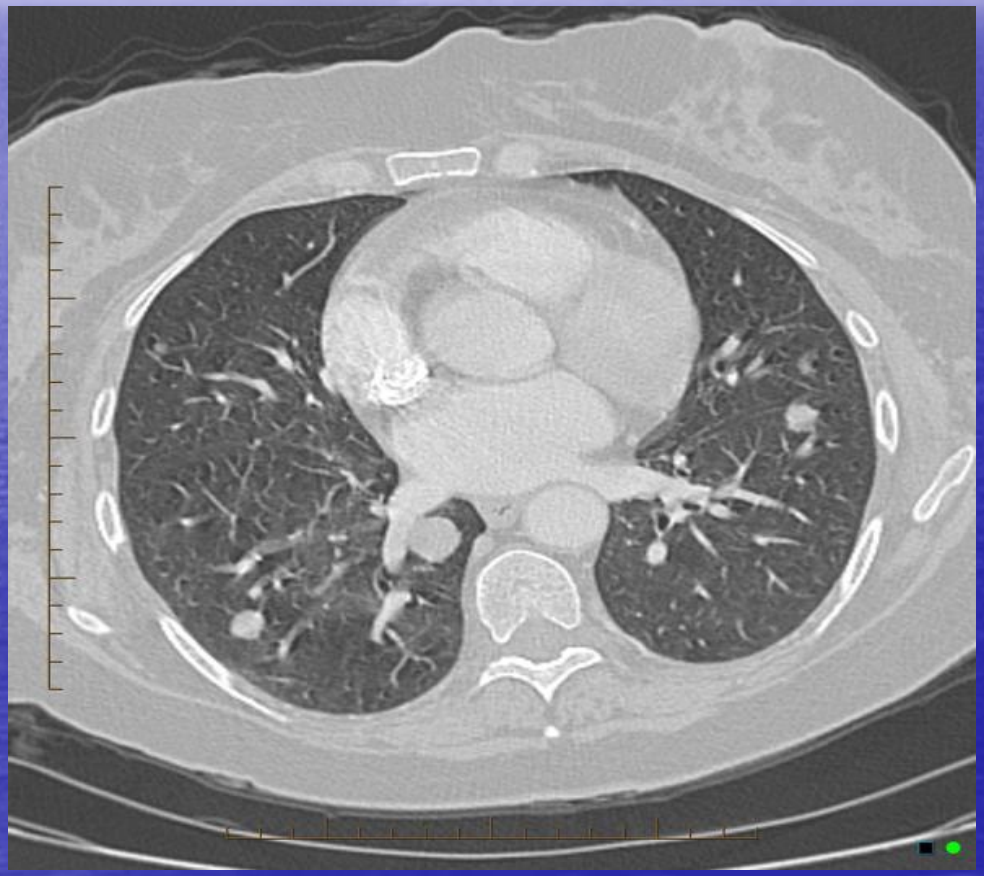
- Controversy regarding efficacy of metastasectomy.
- Studies examining survival of patient with recurrent pulmonary mets:
  - **Series from University of Vienna**
    - 5 year survival – 48%
    - 35 patients
- Landmark IRLM report
  - 5 year survival – 44%
  - 10 year survival – 29%
  - DFI strongly associated with improved survival

PRE-OP EVALUATION OF PATIENTS

CHEST X-RAY

CHEST X-RAY

CT-SCAN



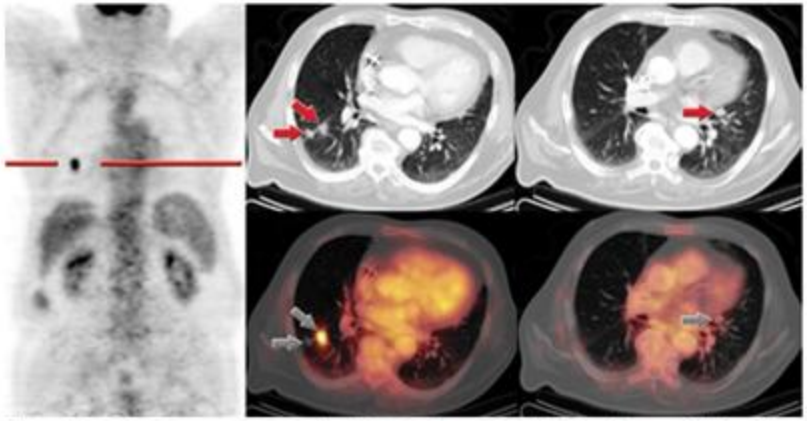
PET SCAN

Lung Cancer - SPN Lung Cancer Case 6

Clinical History

A 67 year old man, underwent a CT scan, which revealed three pulmonary nodules, one in the left lung and two in the right lung. He was referred for PET•CT scan for further evaluation.

Imaging Findings



The PET•CT scan revealed that the medial lesion within the right lung demonstrated marked FDG uptake. The remaining nodule in the right lung and the left lung nodule showed no significant FDG uptake.

MALIGNANT MELANOMA

- Aggressive and unpredictable tumour.
- Pulmonary nodule first sign of metastatic disease in 40% patients with melanoma.
- 7 months survival post diagnosis of pulmonary mets.

MALIGNANT MELANOMA

A number of studies have reported their results of surgical resection:

- ***Mathis et al (1979):***
  - Mean survival 10.5 months in unresectable patients
  - Mean survival 12 months – in patients rendered disease – free in the lungs.
- ***Morrow et al (1980):***
  - 12% - 5 year survival.
- ***Pogrebniak et al (no. 77):***
  - 13 months mean survival.
  - 7%, 5 year survival.

MALIGNANT MELANOMA

- ***Initial report by JWCI***:

  - 1971 – 1986, 5 year survival – 25%.
    - mean survival 19 months
    - 5 year survival – 31.6%
  - Results reflect strict selection criteria:
    - TDT > 40 days
    - Limited number of pulmonary mets
    - Long DFI

MALIGNANT MELANOMA

More recently:

- **JWCI investigators**:

  - 106 patients undergoing resection
  - Control group – 878 patients
    - were matched
    - managed non-operatively

  - Results:
    - Surgical patients: 27%, 5 year survival.
    - Non-surgical patients 3%, 5 year survival.
    - Highest survival (39%) occurred in patients with single mets

MALIGNANT MELANOMA

- **Kolodziejski et al (1999) :**
  - reported on 93 patients undergoing pulmonary metastasectomy from various primaries.
  - 28%, 5 year survival in patients with cutaneous melanoma.

PULMONARY METASTASECTOMY FOR BREAST CANCER

- Metastatic Breast Cancer (BC) known to be a systemic disease even in early stages.
- Frequently spreads to multiple organ sites.
- Very infrequently spreads only to the lungs.
- Mayo Clinic (96) reported only 0.4% incidence of metastatic disease to the lungs.

Question: Is there a significant role for pulmonary resection in breast cancer?

PULMONARY METASTASECTOMY FOR BREAST CANCER

Studies:	***5 year survival:***
- Mountain et al	14%
- McCormack + Martini	30%
- Lanza et al (more recently)	50%
- Mayo Clinic Group (1994)	37.8%

PULMONARY METASTASECTOMY FOR BREAST CANCER

- ***Prognostic factors***:
  - Complete resection
  - Long DFI
  - Number of metastasis
  - Positive hormone receptor

➢ ***Complete resection:***

- Most studies – no survival difference concerning complete and incomplete resection.
- McDonald et al (1994) - better 5 year survival for patients having incomplete resection (42.1%) vs. 35.6% after complete resection.

PULMONARY METASTASECTOMY FOR BREAST CANCER

- ***Disease free interval (DFI)***

- Long DFI seems to be of prognostic relevance.

- Interval reaching significance – 1 year or longer.

- Seems to represent:
  - Slowly growing tumour
  - Long effective antihormone therapy
  - Minor tumour burden

PULMONARY METASTASECTOMY FOR BREAST CANCER

Number of metastases:

- An important prognostic factor in other tumours

IR:
included various histological types:
- single mets – 43% survival at 5 years
- > 4 mets – 27% survival at 5 years

- This difference does however not reach significance in most publications concerning MBC.

  - Tanaka, F (2005)
  - Rena O (2007)
  - Planchard D (2004)

PULMONARY METASTASES OF BREAST CANCER

Oestrogen Receptor Status (ERS)

- Only a small number of studies examined ERS for it's prognostic relevance.
- Welter 3 (2008) in E.J.C – T Surgery
  - Demonstrated a survival benefit for patients with ER positive metastasis on a significant level.
  - 5 year survival 70% in receptive positive status and 12.1% in receptor negative ones.
  - A similar survival difference was found for the status of the Her 2 – neu receptor.
- Rahman et al (1999)
  - 1581 MBC cases
  - Median survival difference of 28.6 mo for positive – versus 18.1 mo for receptor negative patients.

PULMONARY METASTASES OF BREAST CANCER

- In conclusion thoracotomy for MBC should not be routinely done except for solitary pulmonary lesions.
- Other indications for surgery include:

(1) To find and resect primary lung cancer and rule out benign lesions.

(2) To prove the histology and investigate grading, hormone receptor status in order to adapt medical treatment.

SOFT TISSUE SARCOMA

- Preferentially spreads to the lungs.
- Resection – yields 20-30% rate of prolonged survival:

➢ Mc Cormack & Martini (51) (Memorial Sloane Kettering)	25%, 5 year survival
➢ Creagan et al (83)	29%, 5 year survival
➢ Roth et al (84)	30%, 3 year survival
➢ European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group	- 255 patients - 38%, 5 year survival

SOFT TISSUE SARCOMA

- Memorial Sloane Kettering
  - 779 patients
  - Complete mestastasectomy associated with:
    - Median survival 33 mo
    - 5 yr actuarial survival rate of 37%

SOFT TISSUE SARCOMA

Recurrence:

- Rate high – 80% will recur in lung
- ***Weiser et al (2000)***
  - Re-explore 86 patients
  - Median disease specific survival 42.8mo.
  - Identified 3 independent prognostic factors which were associated with poor outcomes:
    - >3 nodules
    - Largest metastases > 2cm
    - High-grade primary tumour histology

OSTEOGENIC SARCOMA

- Primary tumour spreads directly to lungs – where it may be initially restricted before metastasizing to other visceral organs.
- Prognosis particularly good
  - McCormack and Martini (1979) — 5yr survival of 25%
  - Huth et al (1980) — 4yr survival of 40% (soft tissue + osteogenic sarcoma)
  - NCI study — 43 patients Actuarial 5yr survival rate of 40%

- Mountain & colleagues (1984)

  50.7%, 5yr survival in review of patients presenting with metastatic osteogenic sarcoma.

- Antunes and colleagues (1999)

  3yr overall survival rate of 61%

  - patients who had chemotherapy post resection.

COLORECTAL CANCER

- Metastatic lesions rarely limited to the lungs.
- Patients thus infrequent candidates for pulmonary metastasectomy.
- However if extra pulmonary disease excluded, results of resection similar to those of pulmonary metastases from other sites.

- ***Outcome of patients undergoing surgical resection of Pulmonary Metastases from CRC***

Author, yr	No. patients	5yr survival, %
Mansel et al, 1986	66	38
Goya et al 1989	62	42
McAfee et al 1992	139	35
McCormack et al 1992	144	40

- Five year survival ranges from 20-40%

COLORECTAL CANCER

- At least 3 larger series address the issue of long-term outcome after pulmonary metastases from CRC

  (1) ***Japanese series (1989):***

  * 62 patients
  * 5yr survival – 42%
    10yr survival – 22%
  * Highest survival rate – solitary metastasis < 3.0cm
  * Survival not influenced by:
    - Gender
    - Age
    - DFI
    - Extent of resection

COLORECTAL CANCER

(2) ***Mayo Clinic (1986, 1992):***

* 139 patients undergoing pulmonary resection for metastatic CRC between 1960-1988
* 30.5% alive at 5 years
  16.2% at 20 years
* 5 year survival rate:
  - solitary met - 36.9%
  - 2 mets - 19.3%
  - >2 mets - 7.7%

* Elevated CEA had significant effect on survival

COLORECTAL CANCER

(3) ***MSKCC group:***

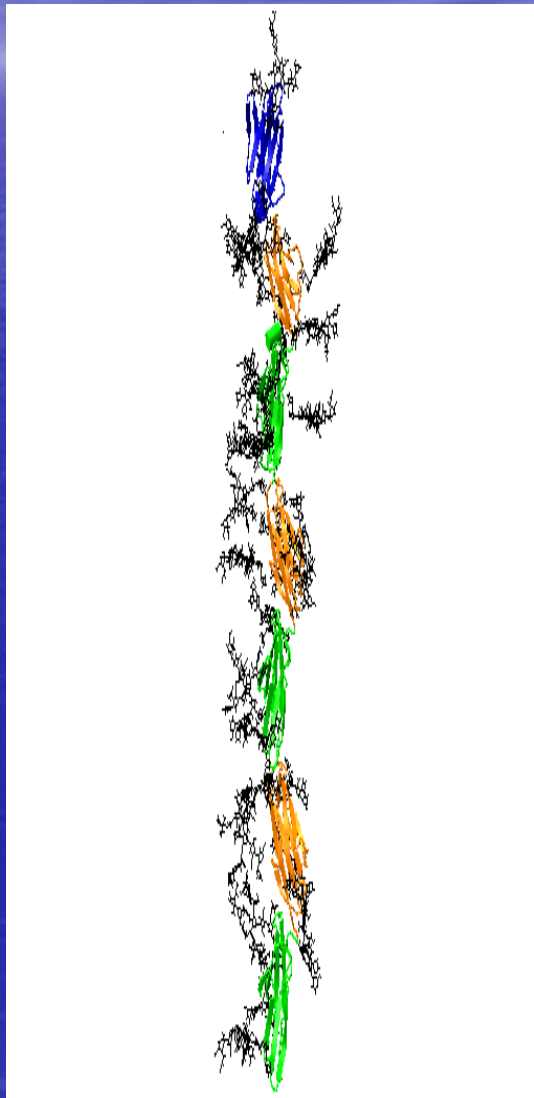
* Results similar to Mayo Clinic
* 144 patients undergoing resection for pulmonary mets between 1960 & 1988
* 5 year survival – 40%
  10 year survival – 30%
* Majority of patients (80 of 144) presented with solitary Pulmonary nodule.
  - Had a slightly but not statistically significant, better survival than patients who had > 1 nodule.

Both Mayo Clinic & MSKCC series:

- Found that patients could experience long-term survival after multiple sequential resections for pulmonary metastases.

Carcinoembryonic antigen (CEA)

- A 70kDa protein with 3 conserved repeat domains
- Member of adhesion molecule family
- Expressed on the apical surface of colon epithelial cells
- CEA expression is associated with progression of colorectal cancers
- Maintained in more than 95% of colorectal cancers and their metastases.



CARCINO-EMBRYONIC ANTIGEN (CEA)

Two recent retrospective studies

(1) Phillip Girard (Paris):

- Found pre-op CEA a statistically significant factor in 86 colorectal patients undergoing pulmonary metastasectomy.
- Overall 5 year probability of survival 24%.
- Estimated 5 year survival rate reached 60% for those with a normal prethoracotomy CEA level
- Conclusion

except for resectability not a single prognostic factor (including no. of mets) has been found so far to be as effective as CEA for predicting survival after pulmonary metastasectomy.

CARCINO-EMBRYONIC ANTIGEN (CEA)

(2) ***Mark Allen***

Normal CEA pre-op	- 28 patients - 46.8% 5 year survival
Raised CEA pre-op	- in 24 patients - 16%, 5year survival

(Found a very similar predictive value with CEA – in their patients with resectable colon mets to the lung)

Conclusion

- CEA an important marker
- Does show statistical significance as far as survivability
- However one should not refuse pulmonary resection based only on an increased CEA level

COLORECTAL CARCINOMA

- Liver 33% and lung 22% most common sites of metastases from CRC.
- Surgical resection or isolated:
  - Liver mets – 5yr survival range from 25-42%
  - Lung mets – 5yr survival range from 21-43%

James Headrick of Mayo Clinic (2001):

- Retrospective review – all patients who underwent both hepatic and pulmonary resection for metastatic CRC between 1980 – 1988.
  - 264 - Pulmonary metastasectomy
  - 804 - Liver resection
  - 58 - Resection of both lung and liver mets
- Concluded that resection of hepatic & pulmonary secondary to colon cancer safe and results in long term survival.

Robinson et al (1999)

- 48 patients
- Found longer survival after resection at both locations

SUMMARY

- Pulmonary metastasectomy can improve survival of cancer patients.
- Mandatory criteria for resection are complete logoregional control of the tumor and complete resection of the metastases.
- Long disease-free interval, few metastases and small size of the dominant nodule are favourable prognostic factors.
- Contra indication to surgery include incomplete resection, no logoregional control of the primary tumor, widespread metastatic cancer, inadequate pulmonary reserve and a medical condition not allowin lung surgery.