Oligometastatic NSCLC
The changing role of surgery

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Eric Vallières MD FRCSC
Thoracic Surgery
Swedish Cancer Institute

Outline

- **Background**
- Synchronous or metachronous disease
- Brain
- Adrenal
- Others
- Personal opinions/ conclusions

Principles

- There is no randomized data addressing this topic
- The data is almost exclusively retrospective and most series span over very long periods of time

- Most data is highly selective and the true denominators are unknown

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Timing of M1b disease

- In most series, metachronous presentation of the M1 focus carries a better survival than synchronous presentation (*makes sense*…)

- That does not mean that we should not consider synchronous presenters for "bifocal therapy"

Zabel et al, Lung Cancer 2002; 37:87-94

Timing of M1b disease: metachronous

- In metachronous presentation, the algorithm is simpler as the lung primary has been taken care of in the past (hopefully with a long DFI)…
- If true solitary deposit and R0 resectable/ treatable M1 @low morbidity … go for it

Timing of M1b disease: synchronous

- When do we incorporate chemotherapy in chemo naïve patients?

The timing of chemotherapy is dataless…

Timing of M1b disease: synchronous

Arguments for surgery first:

- get tissue for analysis/ genomics
- efficacy of chemotherapy potentially better with the least amount of cancer cells around
- better PS at time of surgery
- would encourage MIS resection if possible to hopefully allow quicker access to chemo…

Timing of M1b disease: synchronous

Arguments for chemotherapy first:

- “in vivo” testing
- no delay in systemic treatment
- potentially easier delivery before surgery
- buys you time to let more occult M1 disease declare itself

Timing of M1b disease: synchronous

MSKCC Prospective phase II

- **1992-1999**
- 22 pts with synchronous M1 disease
- 12 pts completed the **preop MVP*3** chemo
- **5/11 "progressed" while on chemo**
- 6/11 complications of chemo

Downey et al, Lung Cancer 2002; 38:193-7

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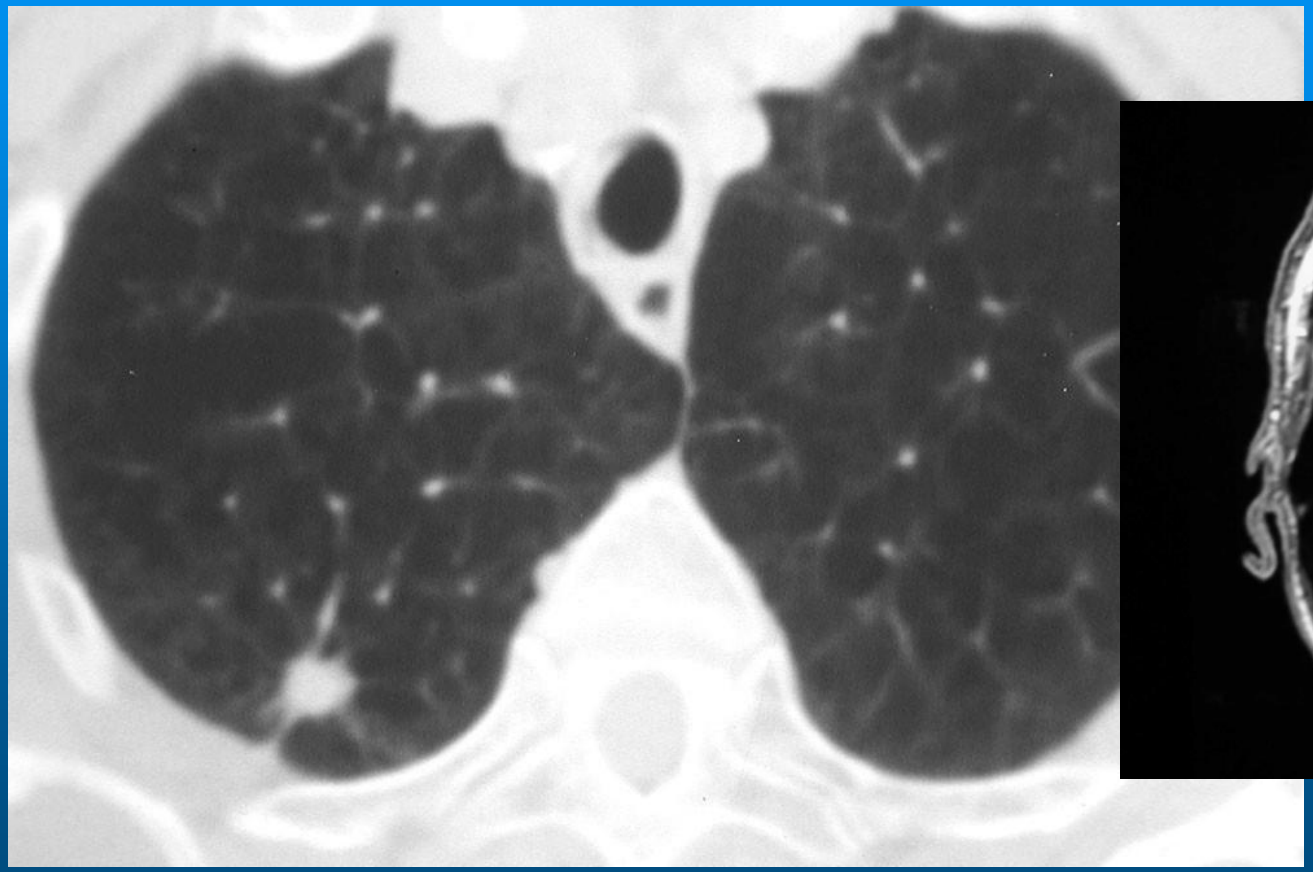
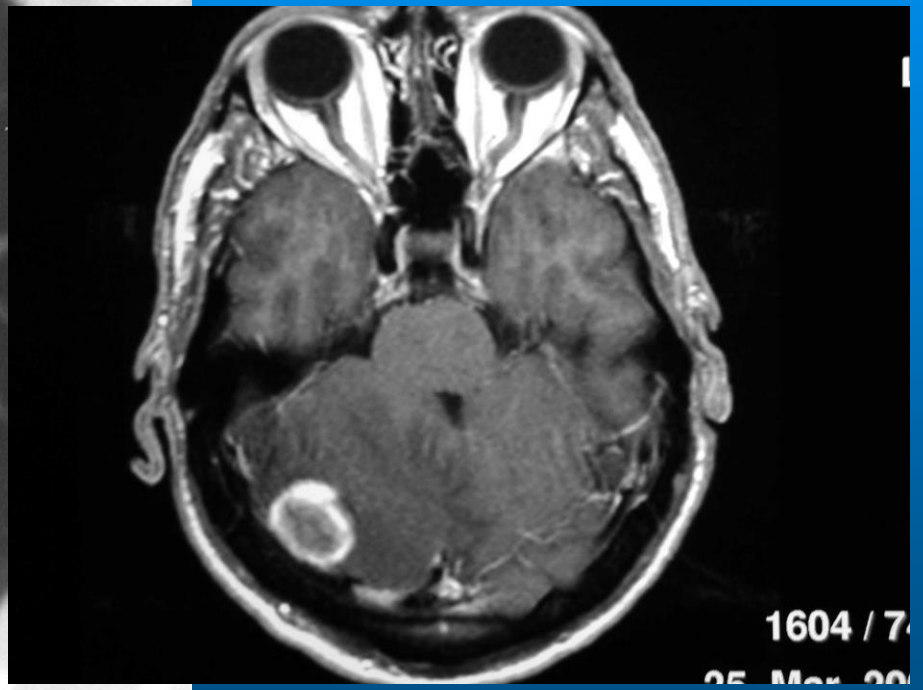
cT1aN0M1b(brain)





M1b brain

The most common in the “bifocal local therapy” literature

Randomized trials have addressed the role of surgery for solitary brain mets…

Patchell et al, NEJM 1990; 322:494-500
Noordijk et al, Int J Rad Onc Bio Phys 1994; 29:711

M1b brain: synchronous

Common scenario:

patient presents with CNS symptoms

> brain imaging > “resection”

… a few days later, the pathologist calls:

“ Did you get a CXR?”

M1b brain: synchronous

… path calls: " Did you get a CXR?"

- Patient will need: full metastatic evaluation, WBRT (?), systemic chemo and a negative mediastinoscopy before resection…

… timing/sequence of it all???

M1b brain: synchronous

- Patient will need: full metastatic evaluation, WBRT, systemic chemo and a negative mediastinoscopy before resection…

Brain imaging should be

MRI with/ without contrast

Reports of 50% of apparently solitary brain mets by CT have multiple lesions on MRI…

Schellinger et al, J Neurooncol 1999; 44:275-81

M1b brain: synchronous

If the “complete picture” is identified before any resection, which one do you treat first?

- If symptoms: go there first (usually the brain)
- If no symptoms: usually brain first as likely to become symptomatic first
  - One exception is the equivocal brain imaging where one could consider the lung first and reevaluate later…

M1b brain: data

Magilligan (first in 1976), updated 1986

- 41pts/ 25 yrs
- “Dual surgery” +/- WBRT+/- Chemo:
- 21%/ 5y

Magilligan DJ et al. Ann Thorac Surg 1986; 42:360-4

M1b brain: data

Mayo 2001

Synchronous 28 pts/ 22 yrs

OS	21%/ 5y
N1-2	**0/ 3y**
N0	35%/ 5y

Conclude: negative med is mandatory…

Billings PS et al J Thorac CV Surg 2001; 122:548-53

M1b brain: data

France 2001

Synchronous 103 pts/ 13 yrs, multi-institutional

OS median	12 months
OS	13%/ 3y

>Multivariate analysis: adenos did better

Bonnette P et al, Chest 2001; 119:1469-75

M1b brain: data

Rome (Gemelli) 2001

Synch 20 pts-Metach 10/ solitary single brain met/ 10 yrs

OS median	23 months
OS	17%/ 3y

>adenos did better, as did N0

Granone P et al, Eur J Cardiothor Surg 2001; 20:361-6

M1b brain: data

Southhampton, UK 2009: Best evidence topic review
(11/153 papers)

Median survival: 19-27 months
I y survival : 56-69% (vs. 33-40% if palliative)
5 y survival: 11-24%

Concludes that: if neg mediastinoscopy, bi-focal resection improved prognosis
Adenocarcinomas, low CEA, response to induction C and a good PS may be prognostic

Modi A, Vohra HA and Weeden DF Interact CV and Thor Surg 2009; 8:467-73

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M1b adrenal

The second most common in the “dual surgery” literature

Same “principles” as with brain…

M1b adrenal: data

USA (MSKCC) 2000

Retrospective, 35 pts

analyzed 17 clinical parameters

Only N status was prognostic

N0 58%/ 5y, N+ 0%/5y

Proc. ASCO 2000; 19: abstract 2010

M1b adrenal: data

France 2001

Retrospective, 11 yrs, 8 centers

22 synchronous: mean S 14.7 m

21 metachronous: mean S 15.3 m

No preop factor helped identifying better candidates

Porte H et al Ann Thorac Surg 2001; 71: 981-5

M1b adrenal: data

France 2006

Retrospective, 5 years, single institution

Synchronous 6, metachronous 17

OS	23.3 %/5y
DFI < 6 months:	no survival at 2 yrs
DFI ≥ 6 months:	38%/ 5y

Mercier J Thorac CV Surg 2005; 130: 136-40

M1b adrenal: data

Moffitt 2008

Review of 10 papers/ 114 pts

Synchronous (DFI≤6 months) 42%, metachronous 58%

DFI < 6 months: median OS 12 months, 5y 26%

DFI ≥ 6 months: median OS 31 months, 5y 25%

Tanvetyanon T et al J Clin Oncol 2008; 26: 1142-7

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M1b Bone

- Even weaker data… same principles

“M1b” others

- Skin
- Axillary lymph node
- Renal…
  - Case reports only

Ambrogi et al Ann Surg Oncol 2001; 8: 663-6

M1a Pleura

- Very weak data…

- Few single institution experiences (Japan, the Brigham)… very hard to recommend surgery outside of a trial setting…
- Should we consider for a subset of adenocarcinomas in this era of targeted therapies and PET imaging???

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M1a lung cancer

- The main issue here is diagnostic: is this a true M1a or is it multifocality of disease?
- Martini-Melamed criteria (1975) still useful
- Additional modern day profiling of tissue may help but is not full proof
- Additional clues on imaging: Xfocal GGOs

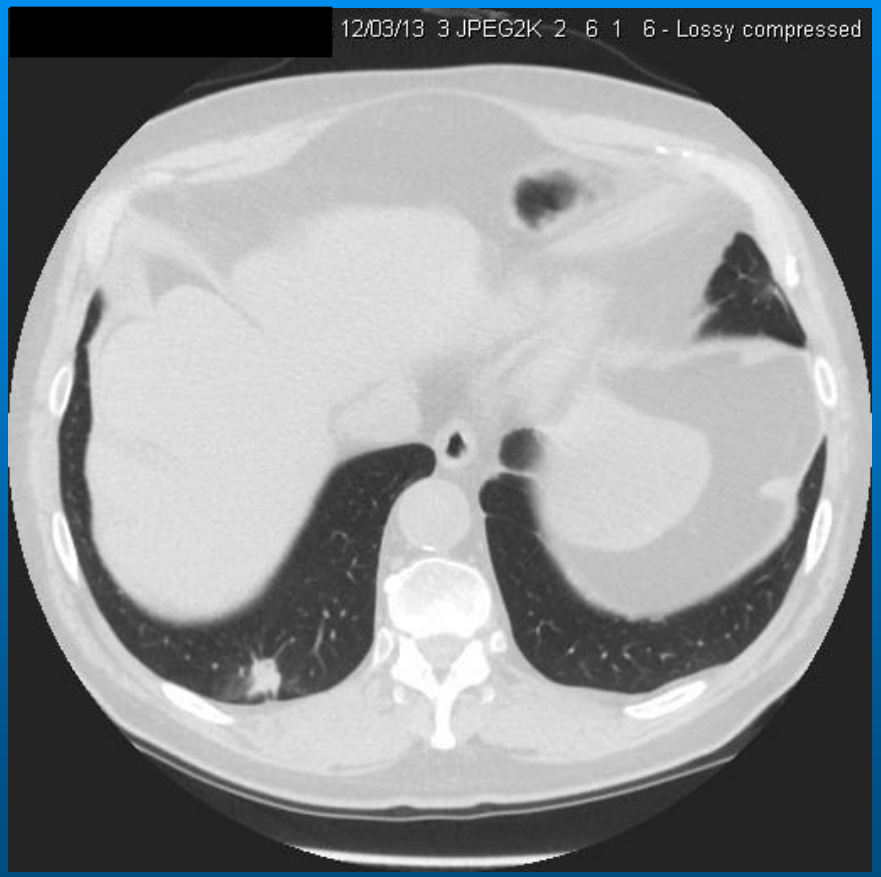
M1a lung cancer

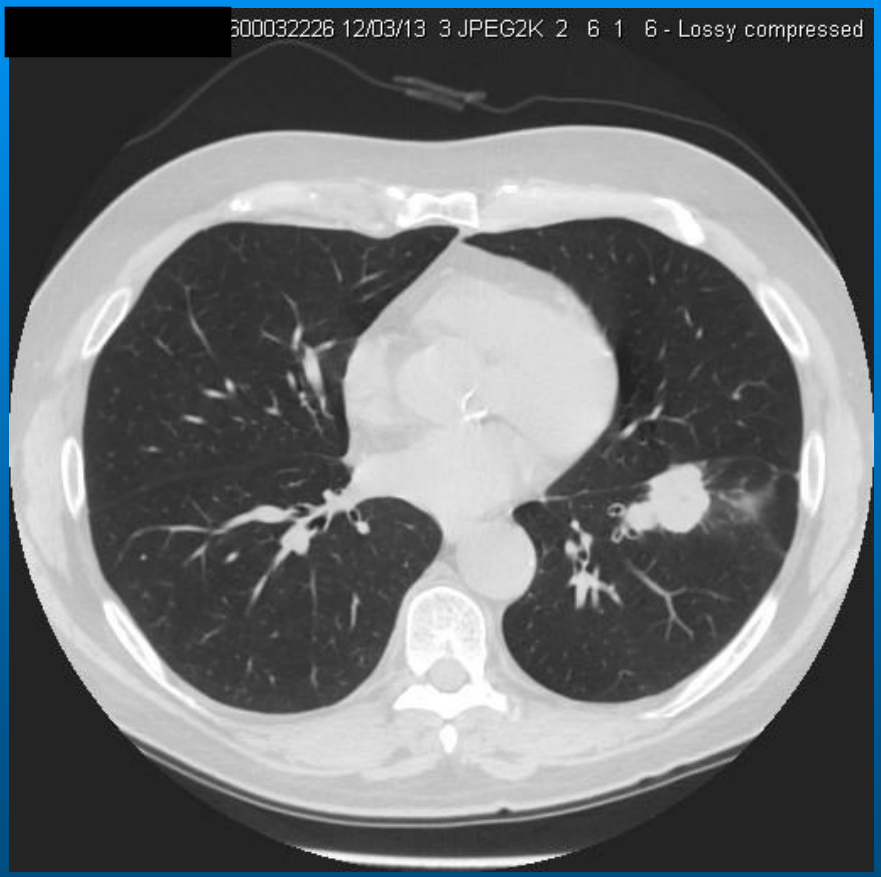
- When in doubt > give the runner a chance

when NED elsewhere, including a negative mediastinoscopy

- Resect dominant lesion but favoring parenchyma sparing anatomical resections, N+ disease may change your approach to the other side..
- Combined surgery for larger lesion and SART for other(s), though bilateral resections gives more information (adjacent CiS, etc…)

Surgery or SART:
Peripheral vs. mid vs. central





Location and size matters > 100% reviewed at MDTB

Additional excellent reviews:

- **Van Shil PE et al.: Expert Rev Anticancer Ther 2008; 8(12): 1931-38**

- **Pfannschmidt J, Dienemann H: Lung Cancer 2010; 69: 251-8**

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PET CT staging

Allows for better selection of potential candidates…

European Inst Oncology, Milan

5 yrs, 1509 pts = 10 pts (0.7%) synchronous

(brain 6, adrenal 2, bone 2)

Median OS 26 months

De Pas, Ann Thorac Surg 2007; 83: 231-5

Synchronous presentation
Timing of chemotherapy

I personally usually favor chemo before the resection

Helps tease out the crowd…

M1b brain: concurrent C with WBRT?

Conclusions

- With both synchronous and metachronous presentations, there is a role for a “local therapy” approach to both the primary and the secondary sites in a very well selected group of patients…

Conclusions

- … with R0 resected or resectable primary lung cancer

- … with N0-1 resected or resectable primary lung cancer (negative mediastinoscopy mandatory)

Conclusions

- … in the presence of single organ M1b disease
- … in the presence of a clinically “resectable” solitary metastatic deposit (oligometastases)*

*(maybe 2 in the brain?)

Conclusions

- … in good PS patients
- … who have undergone a full metastatic work up, including CT-PET, brain MRI +/- gadolinium and negative mediastinoscopy

Very individualized decision making

Conclusions

In reality, when working up the majority of potential patients for “dual local therapy”, you will find something else that will rule them out for it…

Conclusions

The favorable biology of these unusual malignancies is what drives their prognosis and the impact that our “local” interventions have on this prognosis remains unclear…

Conclusions

But a lack of “clarity” should not translate into a lack of intervention as long as the morbidity of this intervention is reasonable.

Thank you