Cancer Metastasis

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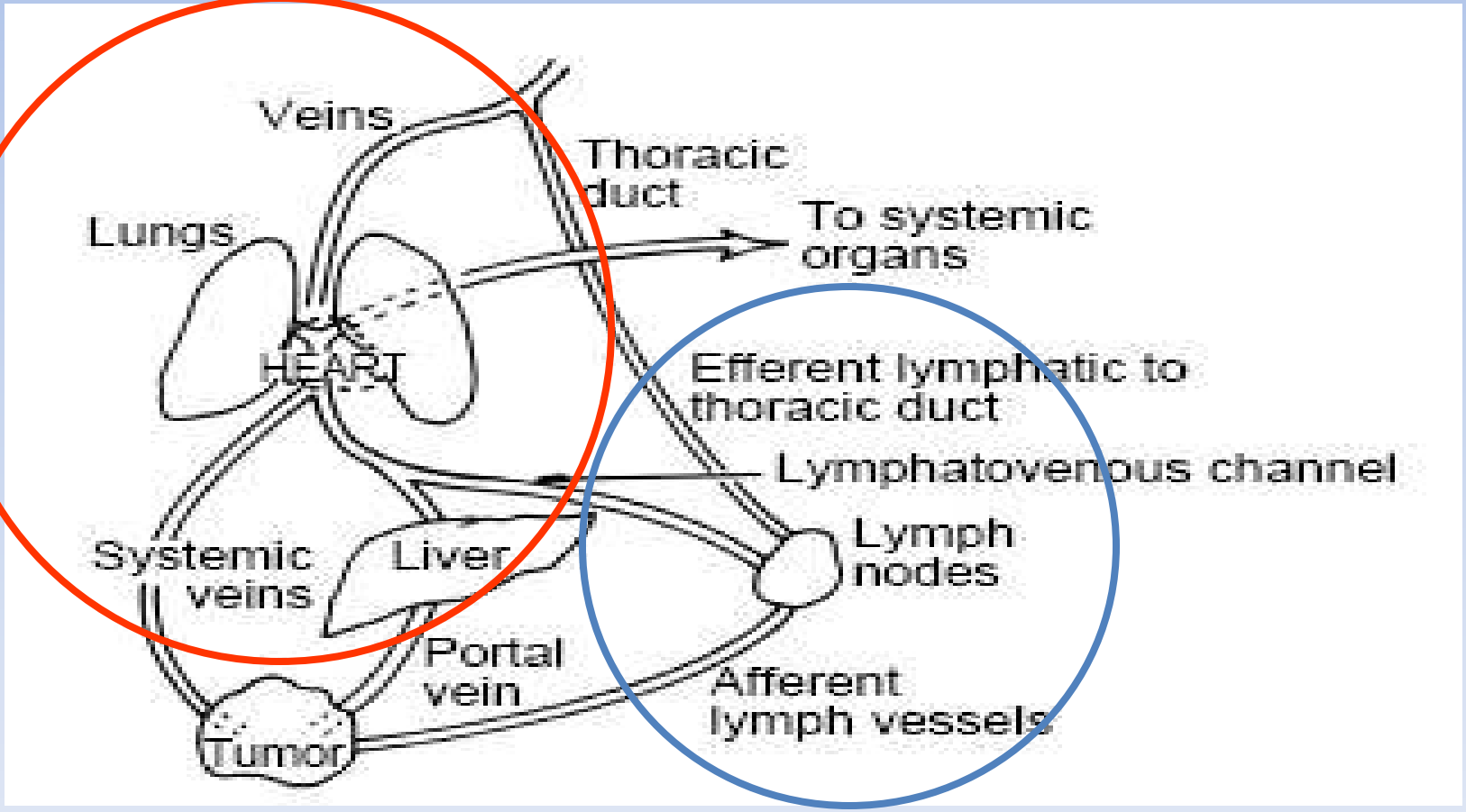
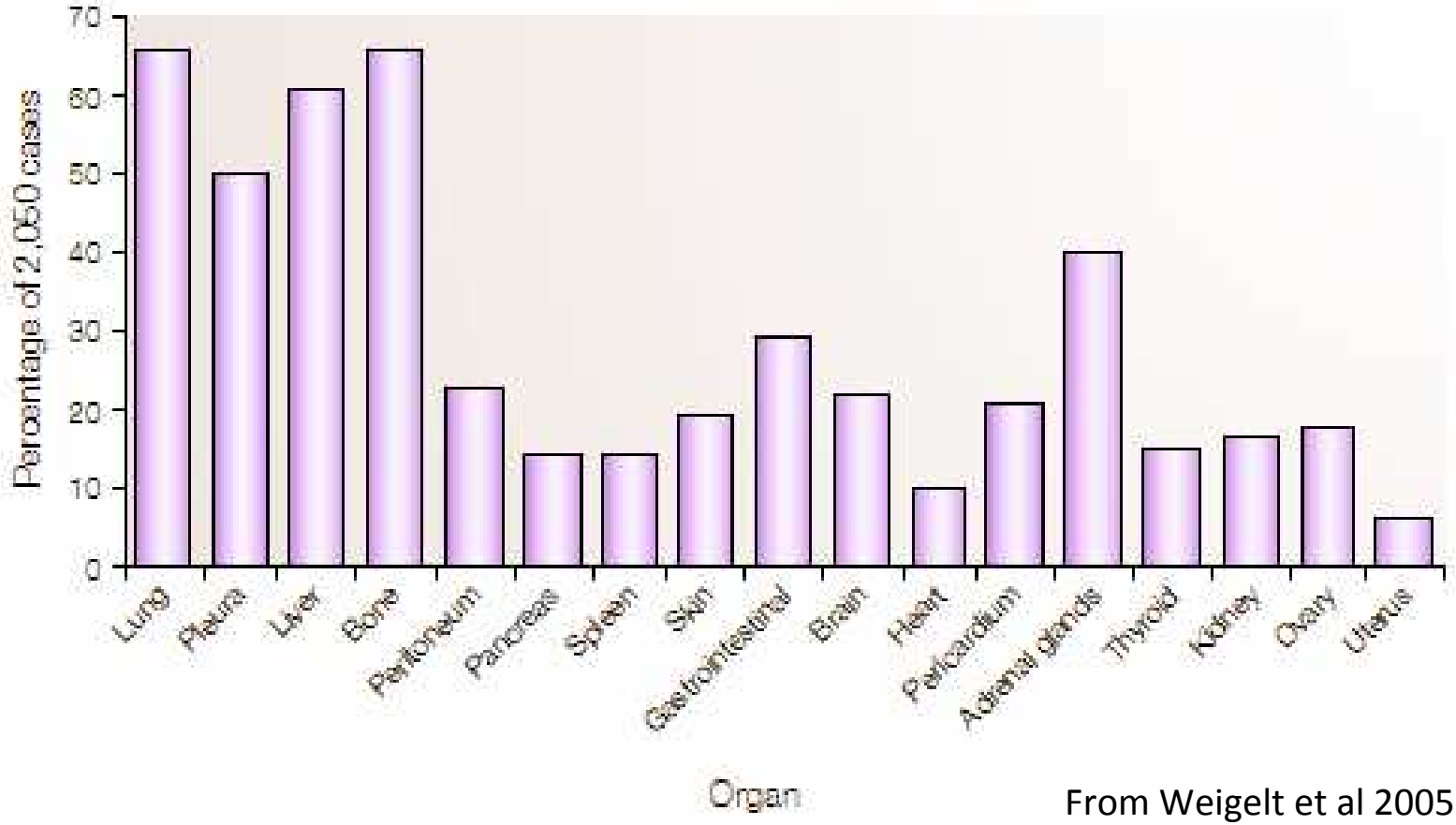
Routes of metastatic spread

Most blood borne cells are arrested in the first pass organ (liver or lung) but circulating tumor cells can be detected.

Lymphatic mets develop along the lymphatic chain draining the tumour site but can also lead to distant mets



Sites of metastasis in breast cancer (from autopsy studies)



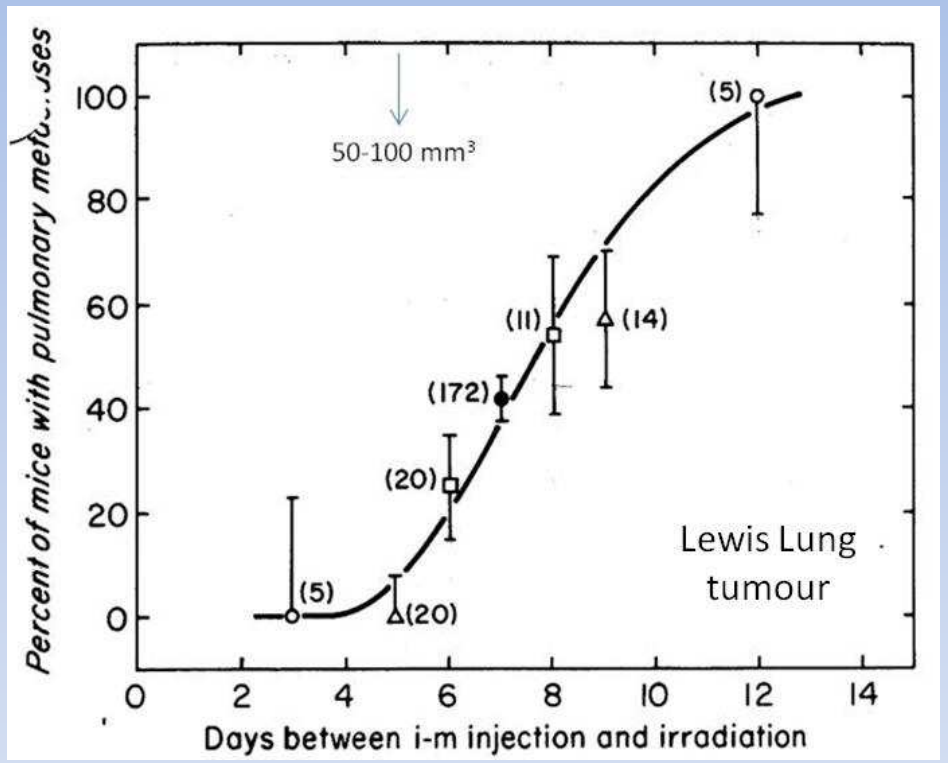
From Weigelt et al 2005

Metastasis in the patient

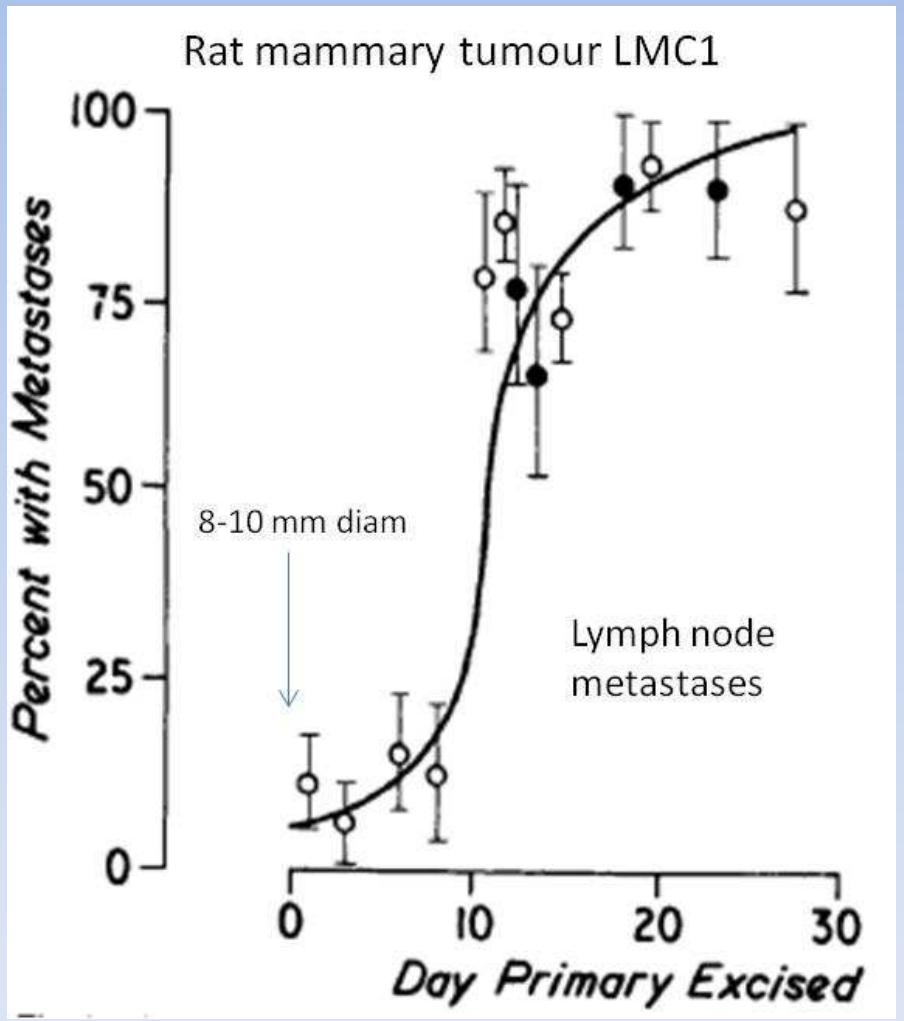
- Most cancer deaths result from the development of blood borne metastasis.
- It is usually assumed that such metastases have seeded prior to diagnosis but remain undectable at diagnosis.

- Can we predict the likelihood of such micrometastases (improved prognostic tests, e.g. gene expression signatures)?
- This decision is important for many patients with early stage disease at diagnosis, e.g which early stage breast cancer patients need adjuvant chemotherapy.
- What level of treatment might be required to treat them effectively?
- Increasingly solitary metastasis can be treated with surgery or radiosurgery. How do identify appropriate patients?

Initiation of lung or lymph node metastasis

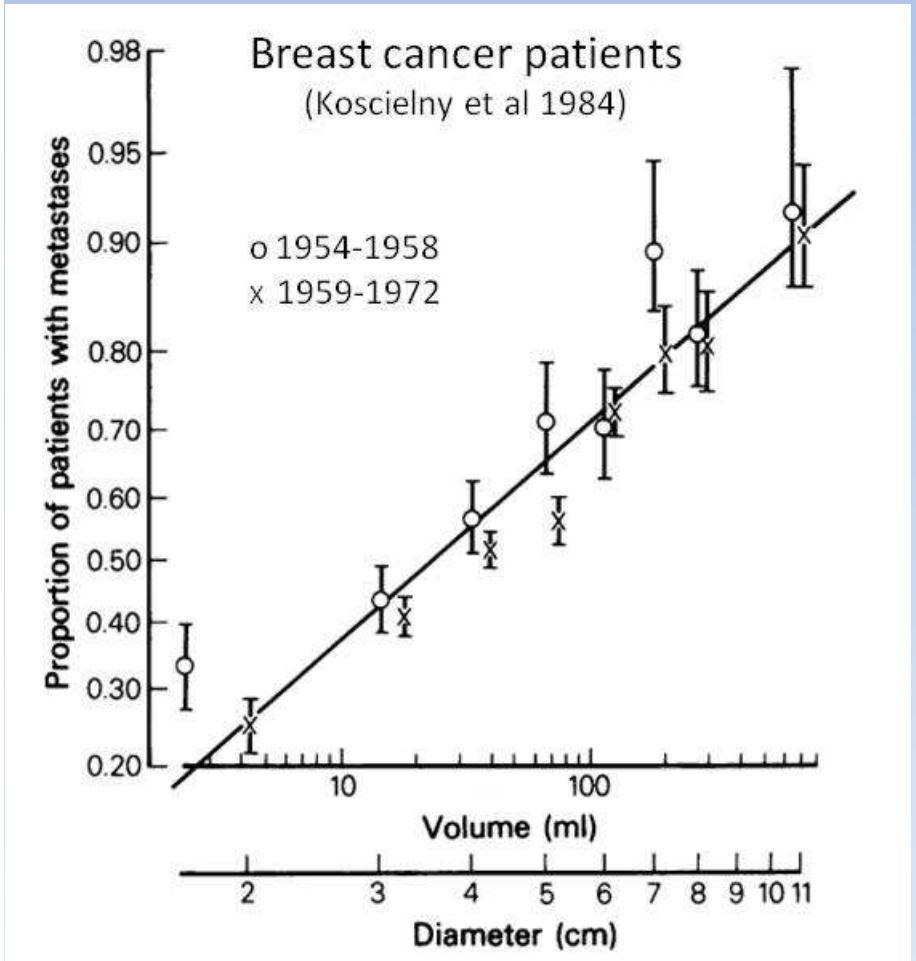


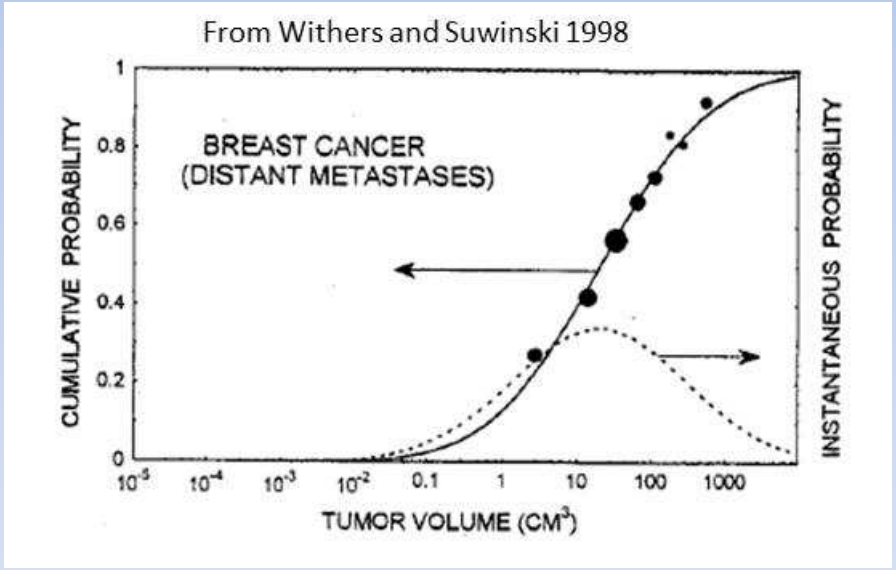
Hill and Stanley 1977



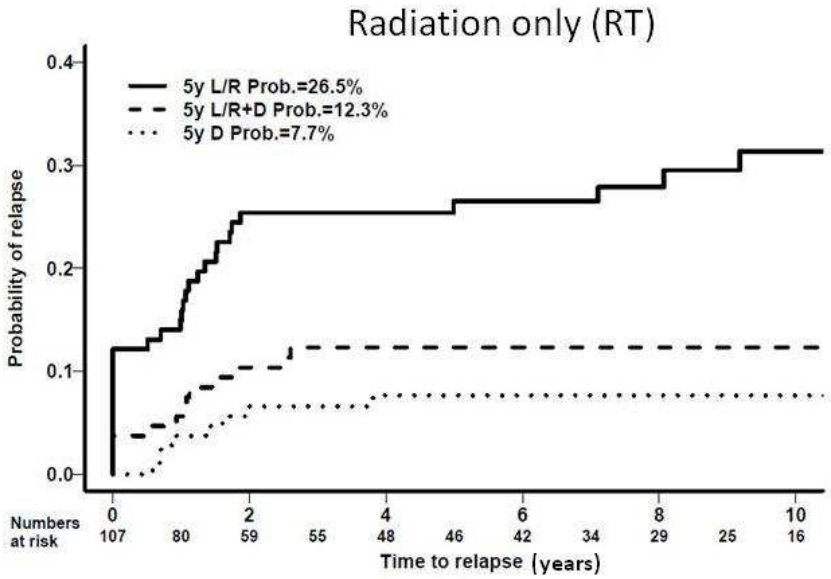
Dixon and Bagnall 1985

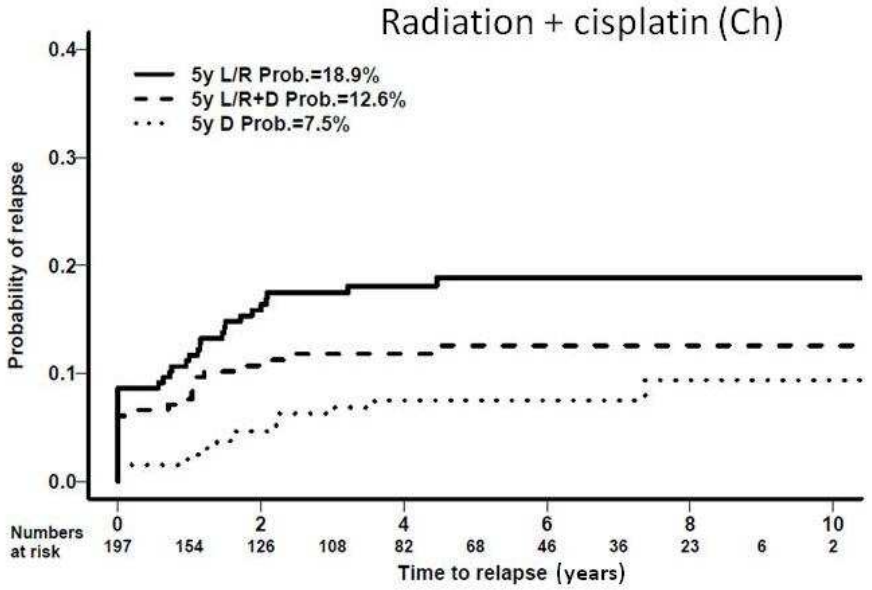
Metastasis in breast Ca vs primary tumour size





Treatment failures in cervix Ca patients (stages 2/3)





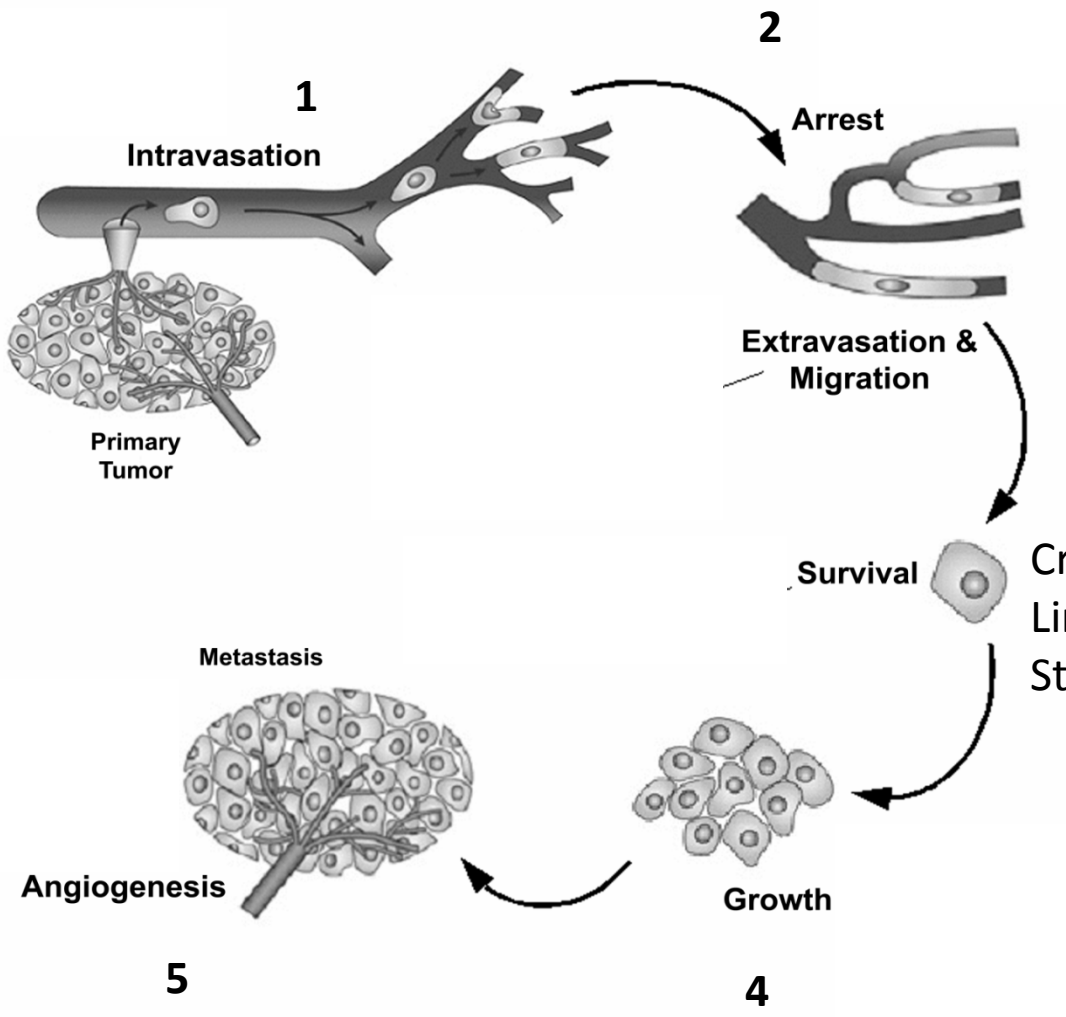
Milosevic, Fyles et al unpublished data 2012

Metastatic Inefficiency (Blood borne)

- Many tumor cells are shed into the circulation from primary tumors, but metastasis do not develop consistently.
  - 10^6 cells/hr or 10^7 – 10^9 per day (patient data)
  - 10^7 – 10^8 shed from transplanted tumors (animal data) with less than 100 mets.
- Tumour cells can be detected in the circulation of many patients Such cells may be predictive for treatment outcome but still some controversy about techniques used.

- Why?
  - Random (survival)process with low probability of seeding
  - Stem cell proportion
  - Metastatic niche

Events during metastasis process



Primary tumor growth,
Angiogenesis,
Diversification
Metastatic subclone,

Critical Limiting Steps?

1. Intravasation
Adhesion/invasion of BM
Passage through ECM,

2. Arrest, Extravasation, Migration.
Adhesion to BM, Apoptosis

3. Survival /interaction;
Lymphoid cells, Apoptosis

4. Growth and Angiogenesis
Metastatic deposit

5. Angiogenesis

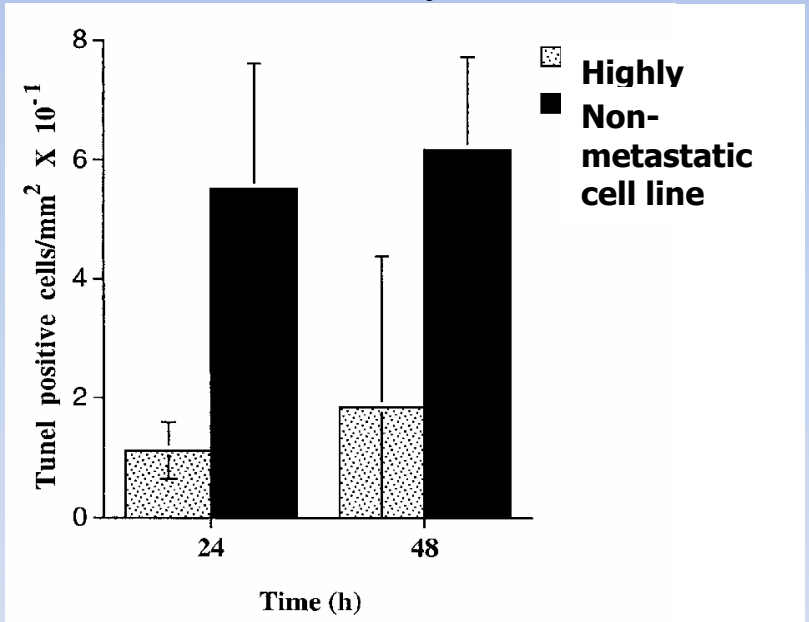
Sequence of metastasis formation in Liver by D2A1 mammary tumor cells

- 70% of injected cells had extravasated into liver parenchyma by Day 3.
- 64% of injected cells still remained as individual cells at Day 10 (reduced to 19% by Day 14).
- 0.62% of injected cells had formed micro-metastasis at Day 10
- 0.006% of injected cells formed macro-metastasis at Day 19.

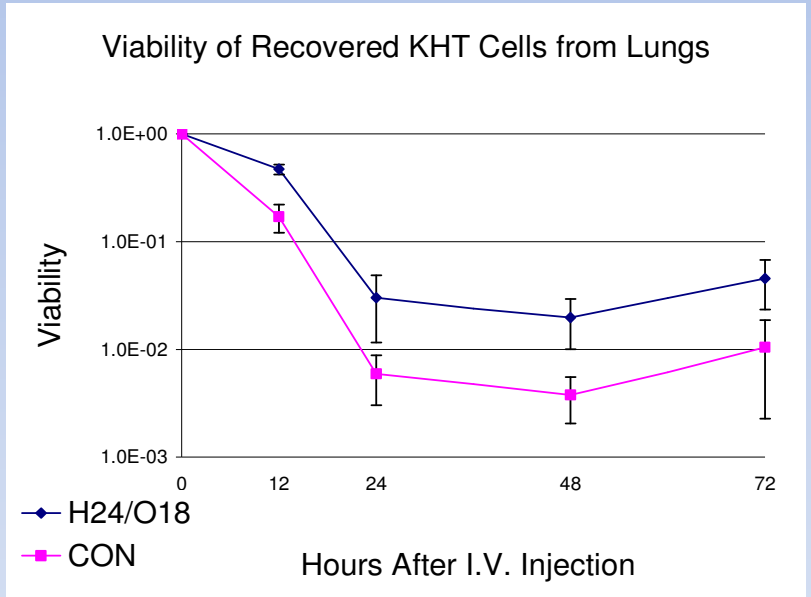
From Cameron et al Can Res 2000

Apoptosis: An Important Event in Metastatic Inefficiency

Apoptotic cells in lung at times after IV injection

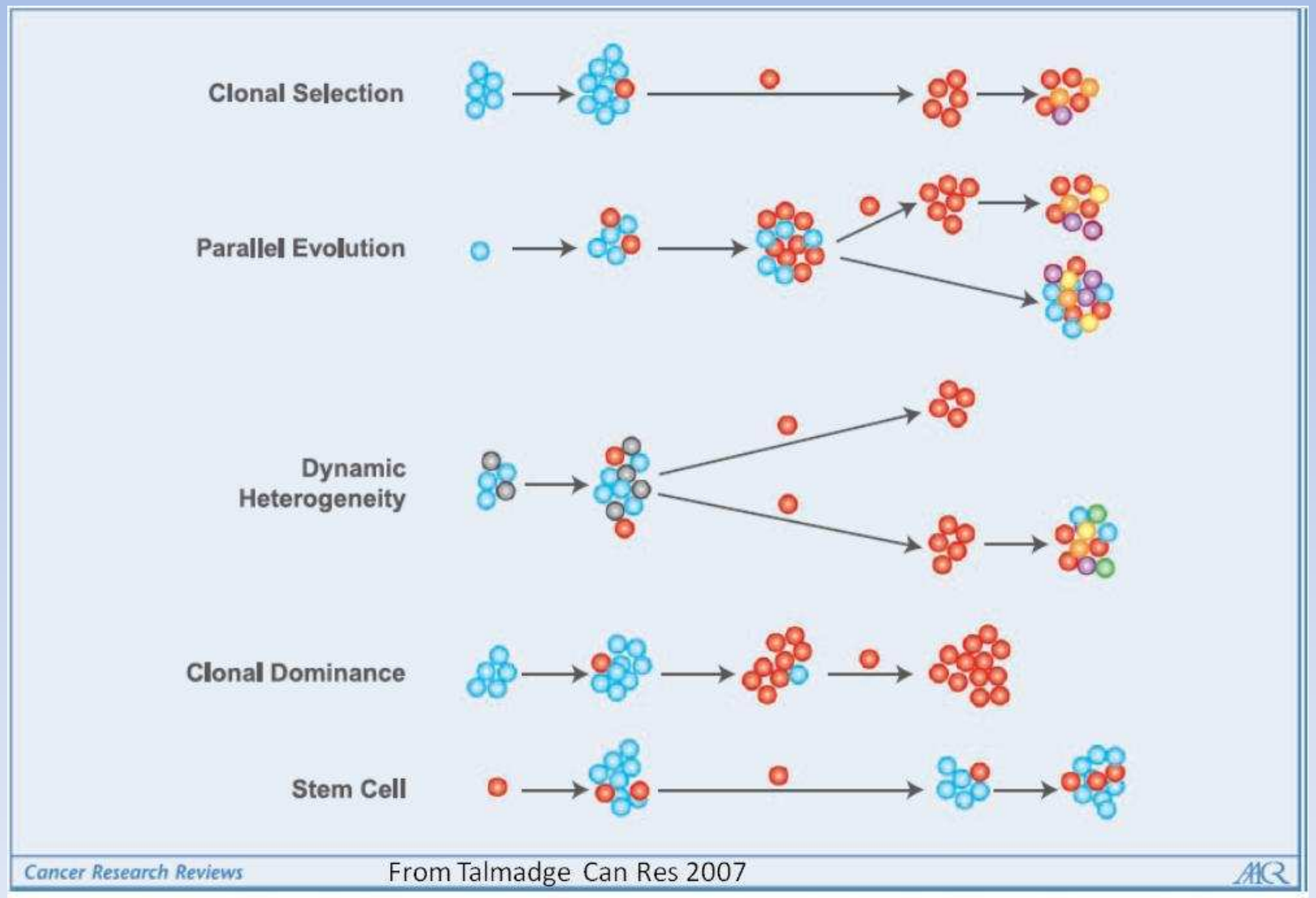


Wong et al, Cancer Research, 2001



Zhang et al Cancer Research 2004.

Models of Metastasis

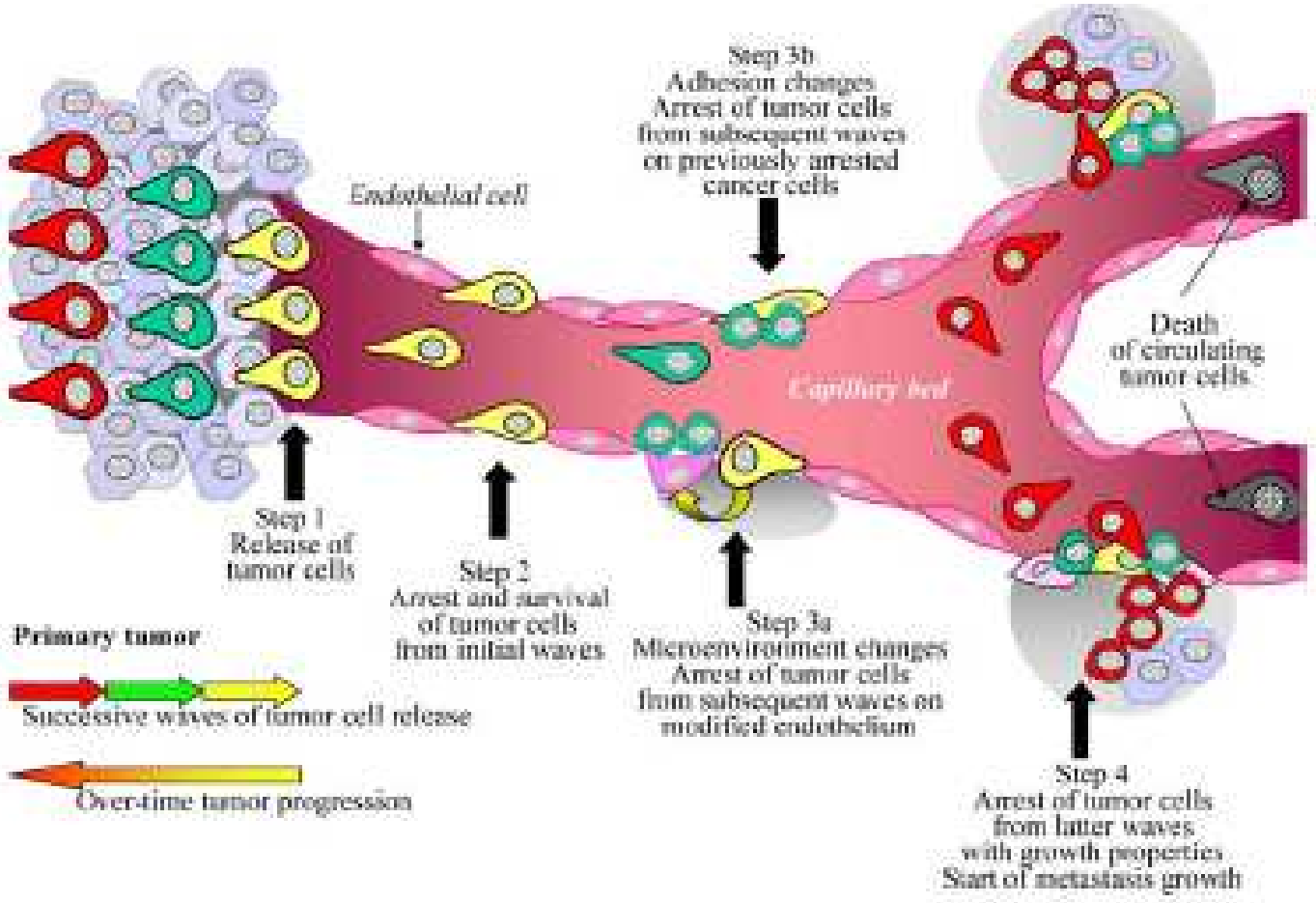


Circulating tumour (stem) cells

- Have been widely detected in cancer patients (although some concern remains about specificity of markers).
- Number of circulating tumour cells (3-300 CTC/7.5 ml of blood in breast Ca) detected has been reported to be predictive for treatment outcome. (Wang et al 2012)
- Only a few studies have examined ‘stem cell’ markers in circulating tumour cells (or in blood using RT-PCR).
- Wang et al reported 2-5% of CTC in breast cancers expressed CSC markers.

Premetastatic niche

Fig. 1 Premetastatic niche conditioning. Possible cooperations between successive waves of homogeneous or heterogeneous circulating cancer cells



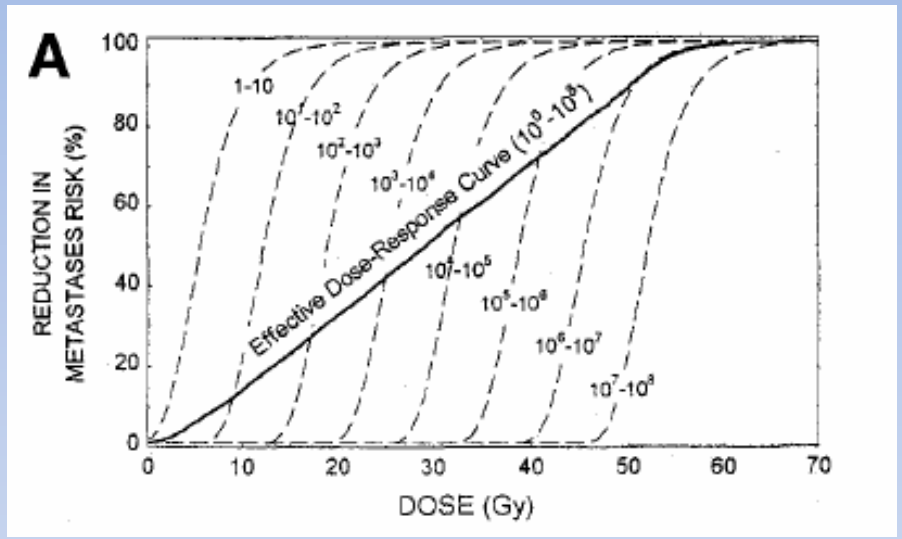
from Bidard et al 2008

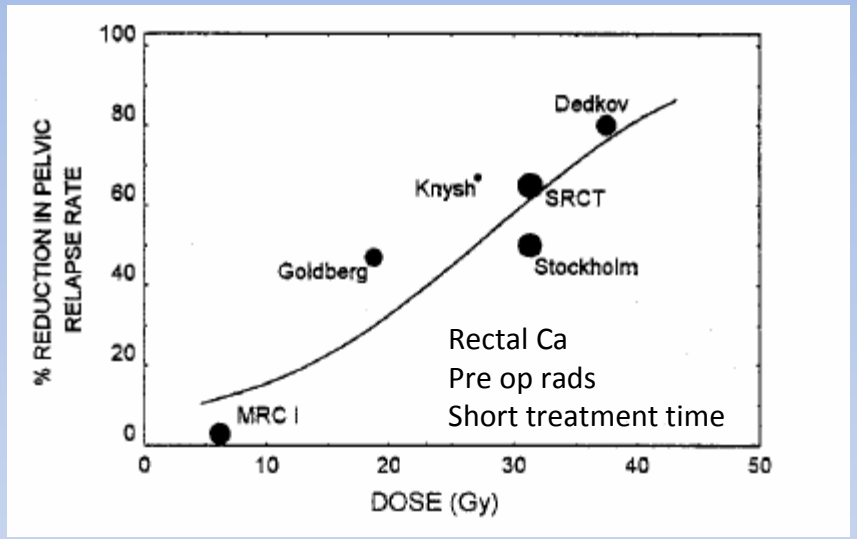
Treating metastasis (1)

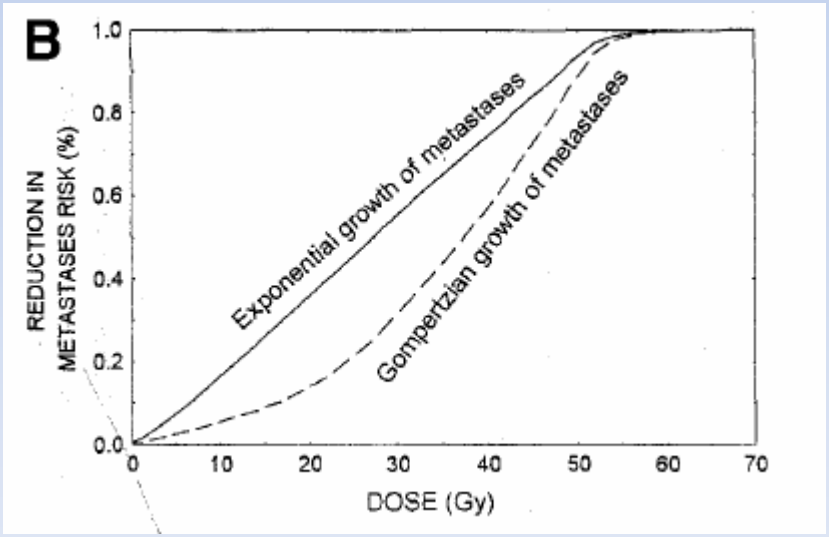
- There is a wide range of heterogeneity in metastatic propensity. BUT
- If we assume that metastatic seeding increases with the size of the primary there will be a range of sizes of metastases in patients once the process has started.
- If we further assume that the individual metastases grow at a similar rate (although not necessarily the same as the primary)

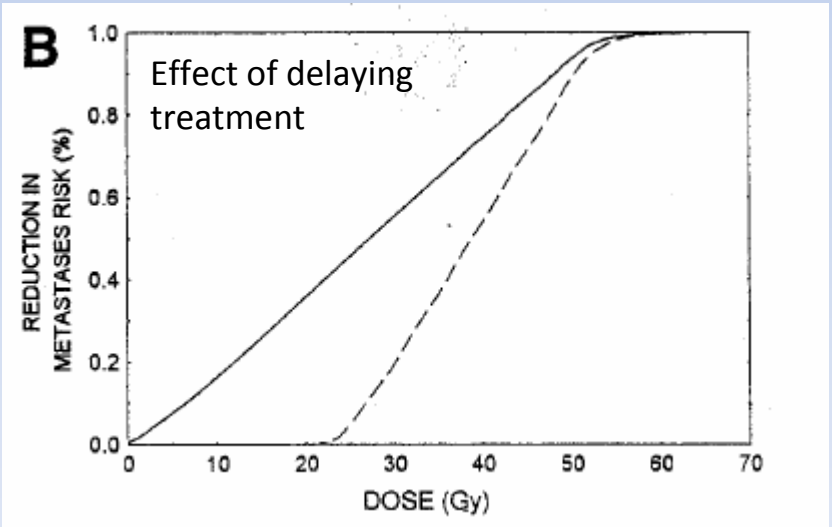
  THEN
- Treatment which is started after the initiation of metastasis will have to be effective against metastases of different sizes.
- If a patient is not given adjuvant treatment for metastasis, then the earlier the first metastasis is detected the more likely that there are other smaller metastasis present.

Modelling metastasis growth and response









From Withers and Suwinski 1998

Treating metastasis (2)

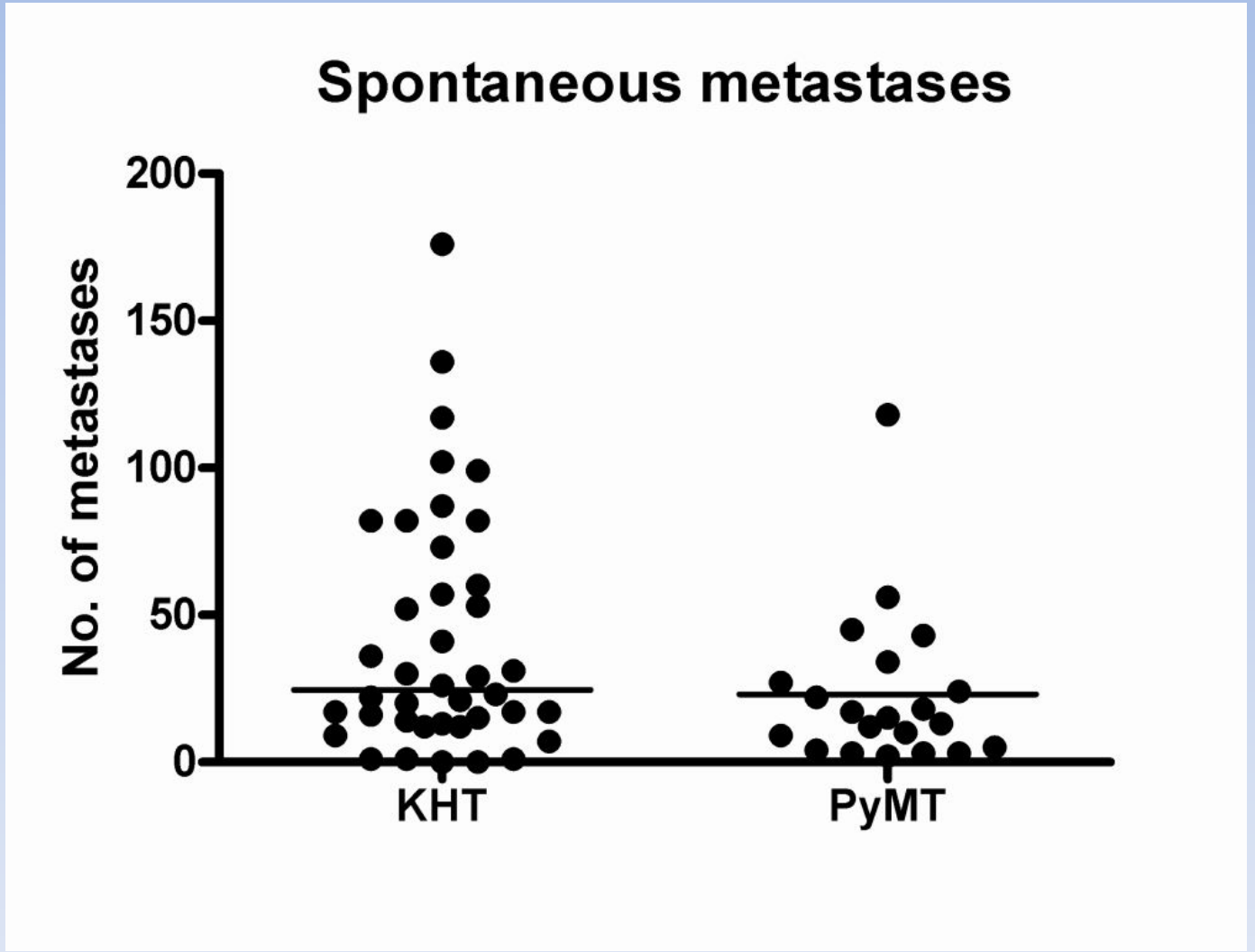
- Increasingly solitary metastasis can be treated with surgery or radiosurgery.
- Thus when a metastasis is detected an important question for treatment is whether it is a solitary metastasis or the “first of many”
  - This depends on time of seeding relative to treatment
  - Time of detection relative to treatment
  - Growth rate of the metastasis
  - Whether adjuvant chemotherapy could eliminate the smaller “follower” metastases.

Many Uncertainties

- Heterogeneity in the growth rate of metastases.
- Heterogeneity in seeding of metastases in different organ environments.
- Effect of primary tumour microenvironment on seeding of metastasis.
- Role of metastatic niche.

Metastases are heterogeneous

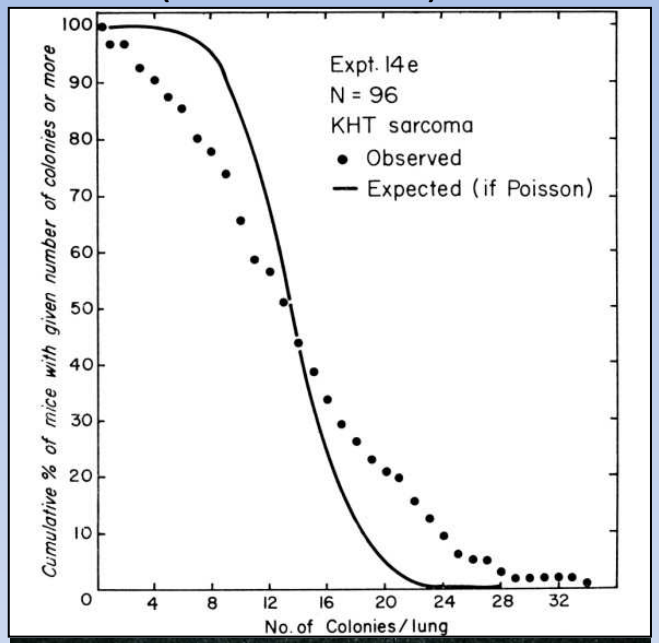
(mets in two syngeneic rodent models)



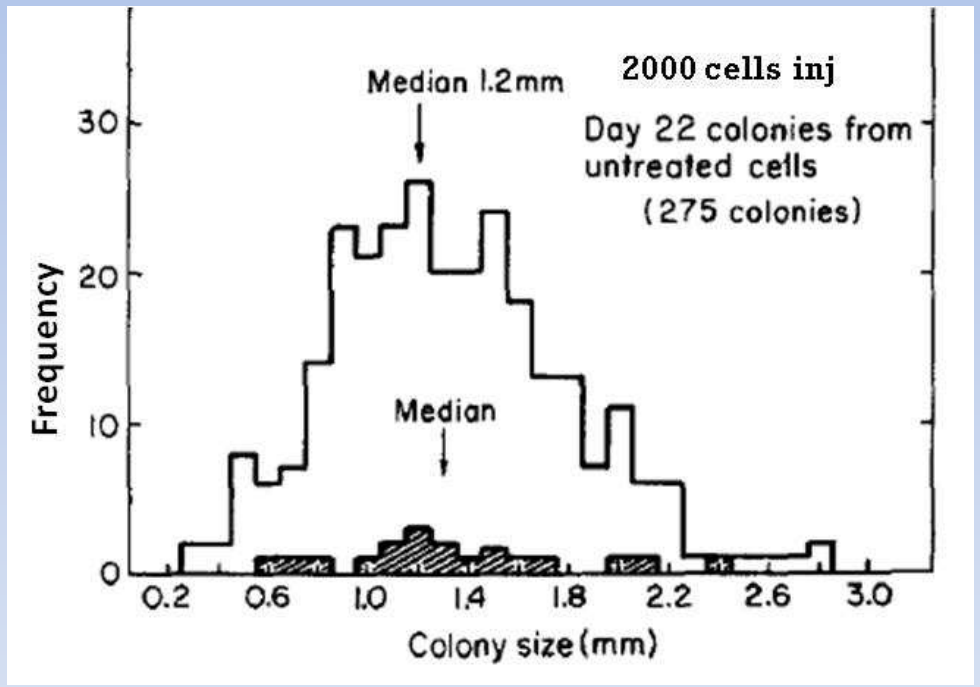
From Hill , Models of metastasis, 2007

Growth of lung metastases

(KHT sarcoma)

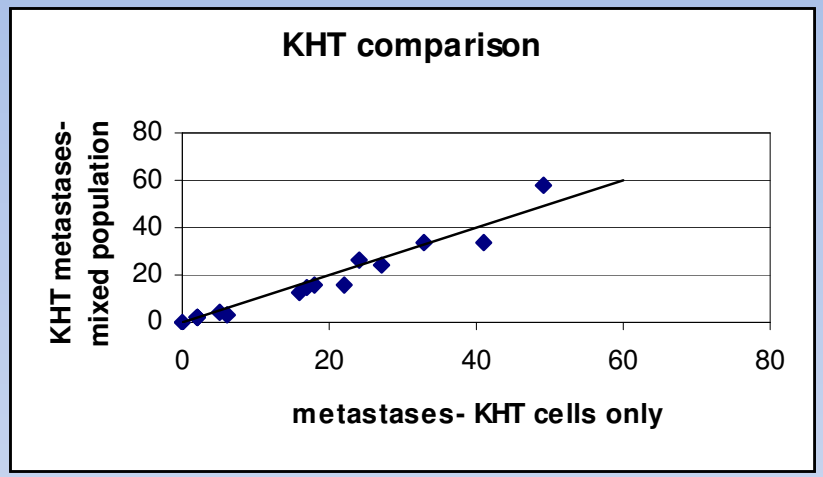


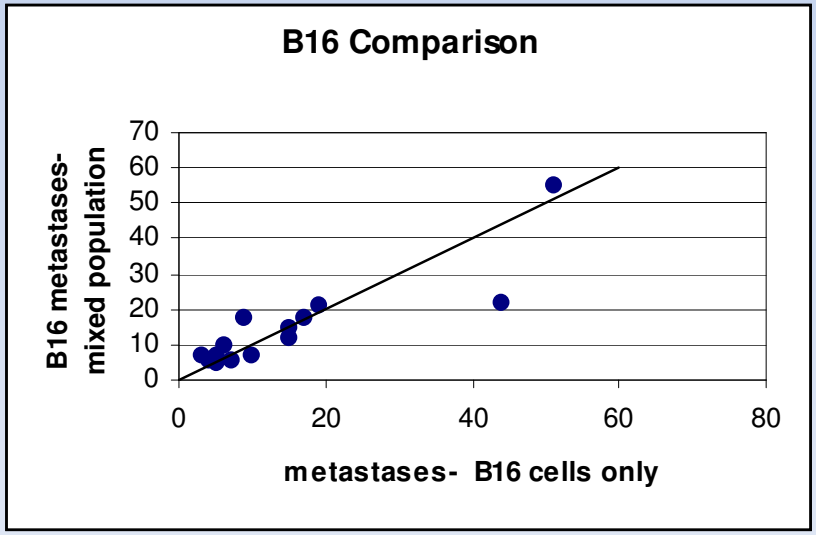
(B16 Melanoma)

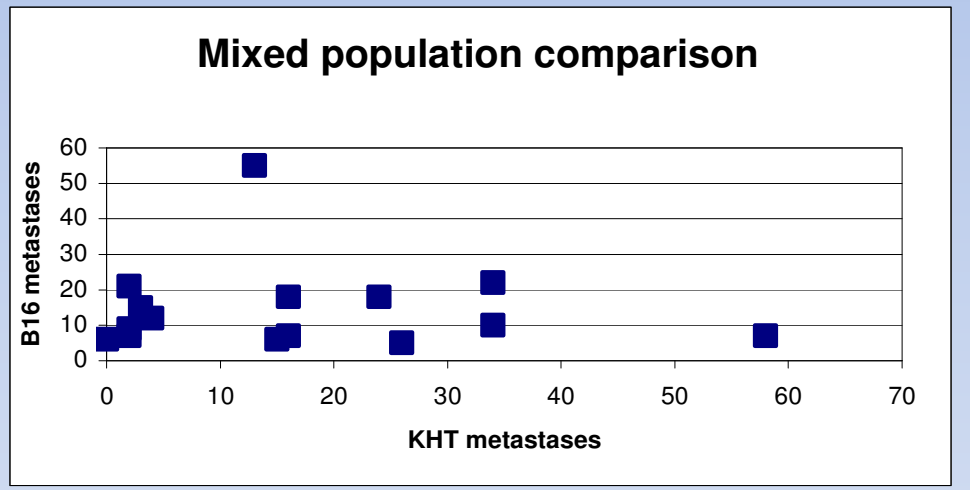


From Hill and Stanley 1975

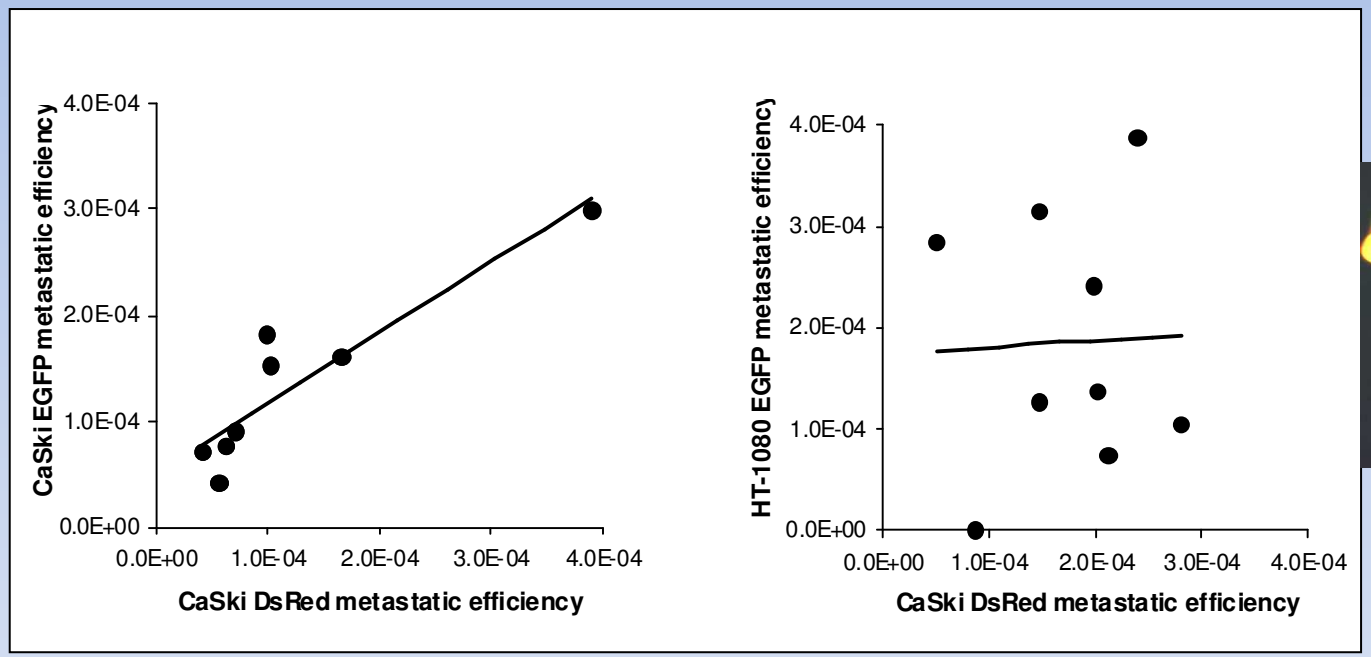
Metastases from mixed cell injection

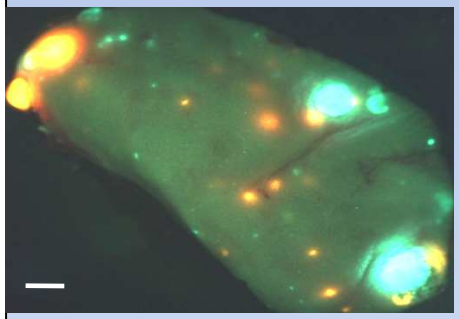




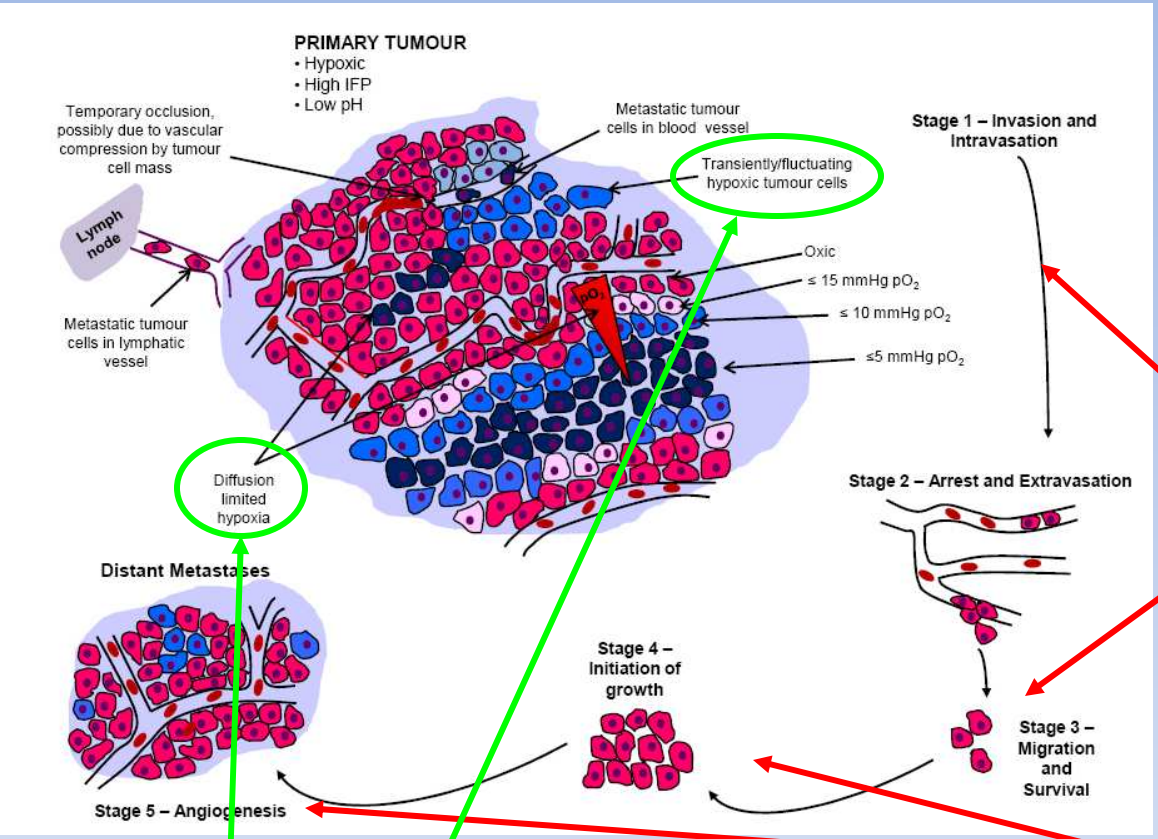


Metastases from different cell populations in the same mouse.





Tumour hypoxia and metastasis



Exposure to hypoxia causes upregulation of expression of metastasis-related genes promoting :

1) Increased invasive capacity (eg. uPAR)

2) Increased resistance to apoptosis (eg Mdm-2)

3) Increased ability to establish growth at a new site (eg VEGFs, CXCR4, LOX).

These effects can occur both in cells exposed to transient (fluctuating) hypoxia and chronic (diffusion-limited) hypoxia. But cells in a chronic hypoxic environment likely have more difficulty accessing the vasculature than cells which are exposed to transient hypoxia.

Conclusions

- Metastases causes many cancer deaths
- Adjuvant (prophylatic) treatment may reduce/prevent metastasis but toxicity is involved in such treatments.
- Can we develop realistic models that may help to predict whether a single metastasis detected some time after primary treatment is “solitary” or the leading edge of a wave of metastasis?

Thank you