- 4. elt is important to study metastasis because 60-70% of cancer patients have metastases at the time of diagnosis and the presence of metastases have an extremely adverse effect on prognosis.
- 5. It is often the cause of mortality in these patients, and furthermore, there are no drugs clinically available to prevent metastasis.
- 6. There are often multiple metastases in a single organ making surgery difficult.

The Metastatic Cascade:

- 1. Growth at primary site
- 2. Detachment from primary mass
- 3. Local invasion of surrounding tissue matrix degrading and cell migration
- 4. Movement into small blood vessels or lymphatics ("intravasation"). Inside the vessel as single cells, or clumps (emboli).
- 5. Survival in the circulation.
- 6. Arrest at distant site inside the vessel.
- 7. Exit from the vessel and local invasion of tissue ("extravasation").
- 8. Growth at secondary site.
- \rightarrow Metastasis is a very **inefficient** process.

Step 1: Growth at primary site

- Initiated by oncogenic grive On that will confer a grow h autonomy. suppressor gener, which will confer a growth autonomy.
- 2. However, how limited by siffer of Cumours can only grow up to 2mm and after mer surpass this diffusion limit, they require their own blood supply, and this induce angiogenesis.
- 3. This angiogenesis is induced by the tumour cells and the infiltration of the normal cells - symbiotic relationship between the cancer cells and endothelial cells in response to hypoxia, and produce VEGF-A, FGF, IL-8 etc.
- 4. Angiogenesis is important because it permits the increase in tumour mass, and hence increases the risk of metastasis – probability of metastasis increases as the diameter of the tumour increases.
- 5. The extent of vascularization is a *good predictor* of whether that tumour will metastasis.

Step 2: Detachment

- 1. Malignant cells often show reduced adhesion to each other, whereas normal epithelial cells are tightly adhesive and they do **not** generally detach from their neighbours.
- 2. This reduced adhesion is due to the **epithelial to mesenchymal transition (EMT)** is an actual, existing developmental process that occurs in animals.