

# Circulating tumour cells in peripheral and central venous blood samples of patients with metastatic breast cancer: a comparative study.

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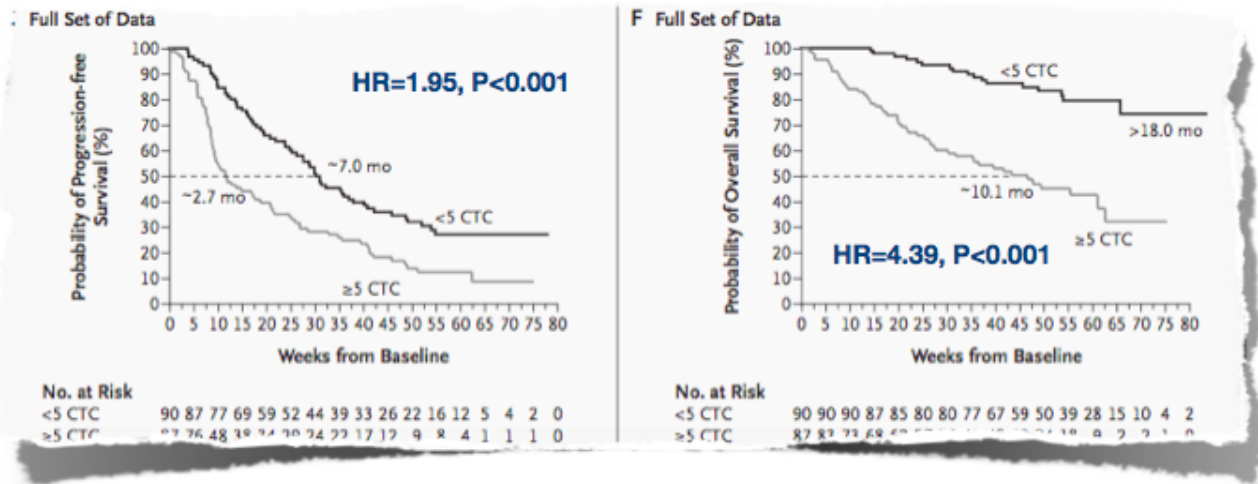
# Introduction

▶ Circulating tumour cells (CTC):

- CellSearch System: immunomagnetic detection of CTC in blood samples of patients with metastatic breast (MBC), colorectal and prostate cancer.

*Riethdorf et al. Clin Cancer Res 2007*

- Prognostic significance in metastatic breast cancer:



*Cristofanilli et al. NEJM 2004*

- Changes in the number of CTC over time: response to treatment.

*Smith et al. J Clin Oncol 2000*  
*Pachmann et al. J Clin Oncol 2008*  
*Molife et al. Brit J Cancer 2010*

## Introduction

▶ Anticipated differences in number of CTC at different sites of the circulatory system:

- Physical mismatch between the size of a normal capillary (3-8  $\mu\text{m}$ ) and a cancer cell (10-30  $\mu\text{m}$ ).
- Solid malignancies: common sites of metastasis predicted based on vascular flow patterns.
- Mouse models: CTC peak transiently in the blood stream after injection in the tail vein or left ventricle.

*Goodale et al Cytom A 2009*

- CTC quickly disappear from the bloodstream after surgical removal of the primary tumour in patients with localized breast cancer.

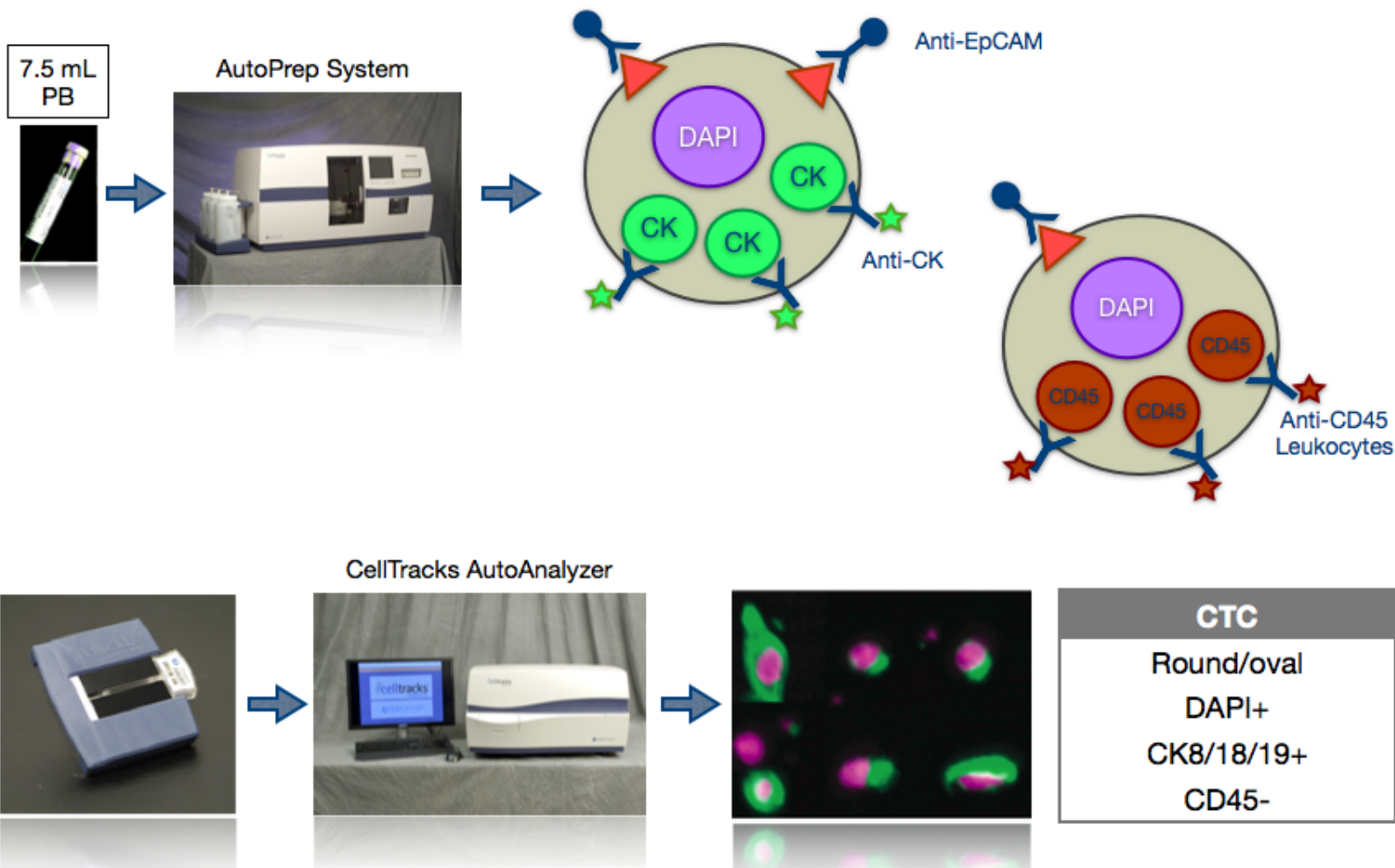
*Krag et al. Breast J 1999*

*Biggers et al. Ann Surg Oncol 2009*

▶ Aim: to compare the number of CTC in different vascular compartments of patients with MBC.

## Methods

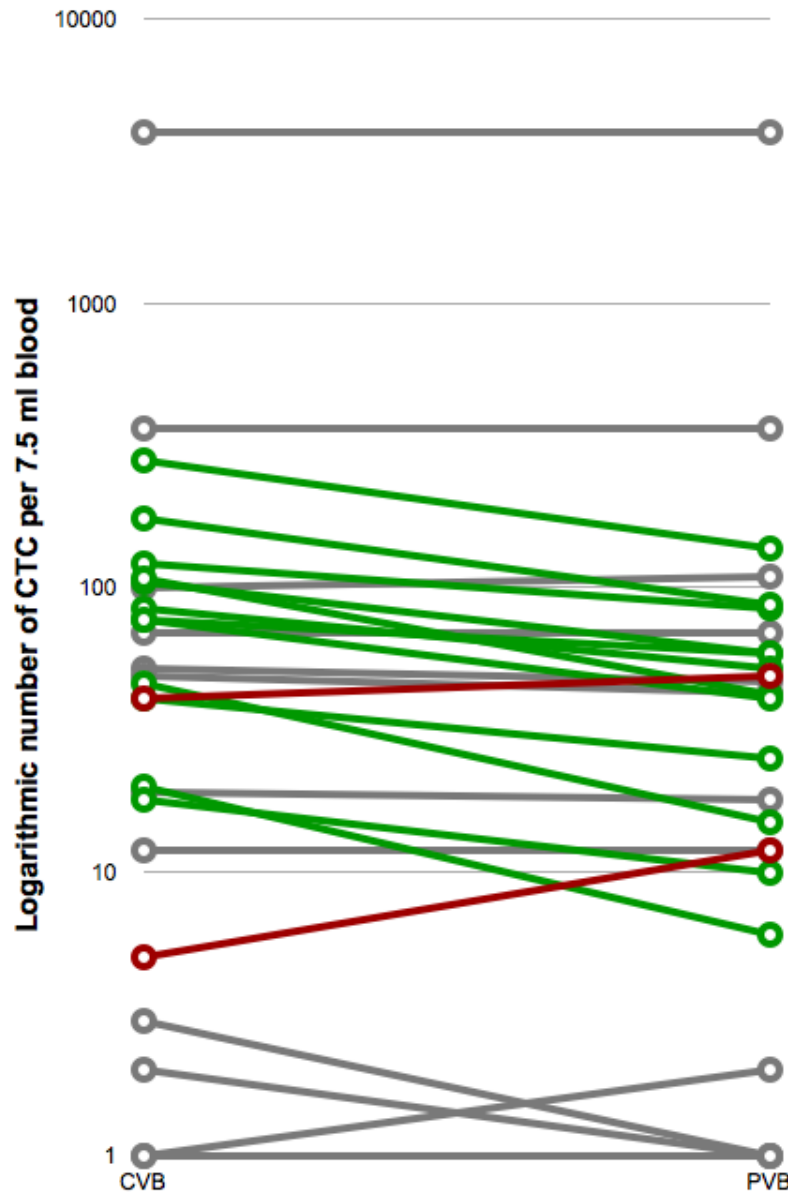
- ▶ 30 consecutive patients with metastatic breast cancer
  - Central venous blood (CVB): central venous access system
  - Peripheral venous blood (PVB): antecubital vein



## Patient characteristics

Variable	N=30
<i>Age (median; range)</i>	62y (40y-85y)
<b>Primary or recurrent MBC</b>	
<b>Primary MBC</b>	<b>4 (13%)</b>
<b>Recurrent MBC</b>	<b>26 (87%)</b>
<i>Histology</i>	
Invasive ductular carcinoma	27 (90%)
Invasive lobular carcinoma	3 (10%)
<i>Histological grade</i>	
I, good	4 (13%)
II, moderate	10 (33%)
III, poor	16 (54%)
<i>Hormonal status</i>	
ER and/or PR positive	25 (83%)
Negative for both	5 (17%)
<i>HER2/neu status</i>	
Positive	4 (13%)
Negative	24 (80%)
<i>Triple negative</i>	
<b>Number of organs involved</b>	
<b>One</b>	<b>4 (13%)</b>
<b>Two-five</b>	<b>26 (87%)</b>
<b>Metastatic sites</b>	
Bone	26 (87%)
Lung	10 (33%)
Liver	20 (67%)
Central nervous system	5 (17%)
Other (locoregional, pleural, skin, peritoneal, lymph nodes, adrenal glands, or ovaries)	16 (54%)

## Results



	CVB	PVB
Median	<b>43,5</b>	<b>33</b>
Range	0-4036	0-4013
	p<0,001	
CTC > 0	<b>26/30 (87%)</b>	<b>26/30 (87%)</b>
	100% concordance	
CTC ≥ 5	<b>22/30 (73%)</b>	<b>22/30 (73%)</b>
	100% concordance	

► In 26 patients with detectable CTC:

- Cut-off: 15% difference between both counts and ≥5 CTC/7.5 ml in both compartments

#CTC <sub>CVB</sub> > #CTC <sub>PVB</sub>	<b>12/26 (46%)</b>
Mean fold difference	<b>2</b>
Range	1,3-3,3
#CTC <sub>CVB</sub> = #CTC <sub>PVB</sub>	<b>12/26 (46%)</b>
#CTC <sub>CVB</sub> < #CTC <sub>PVB</sub>	<b>2/26 (8%)</b>
Mean fold difference	<b>1,8</b>
Range	1,2-2,4

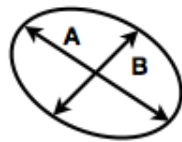
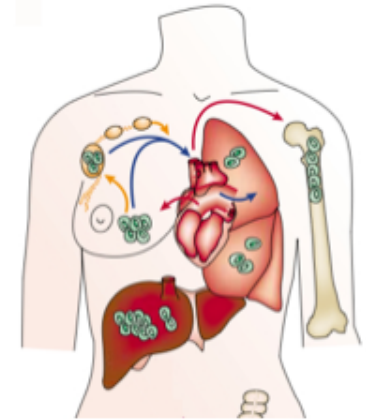
► No association CTC distribution and sites of metastasis.

## Results

- Average number of CTC retained by the lung microvascular system per day in 12 patients with  $CTC_{CVB} > CTC_{PVB}$ :

$$\frac{(\#CTC_{CVB} - \#CTC_{PVB})}{7.5 \text{ ml}} \times 5000 \text{ ml/min} \times 1440 \text{ min/day}$$

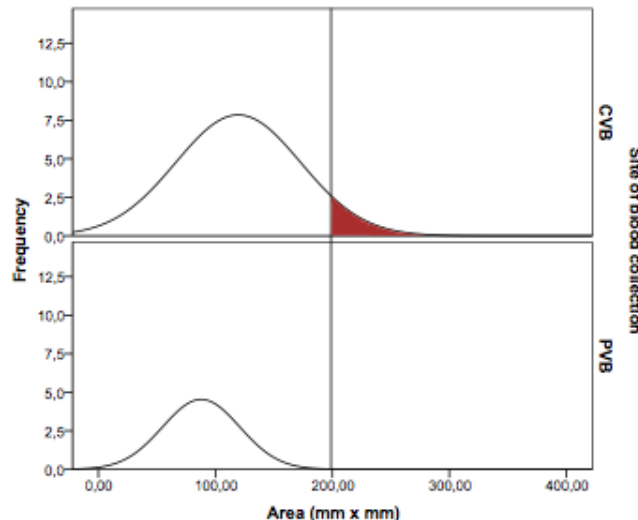
- 32.6 million CTC /day (range 7.7 million - 138.2 million)



Contribution score of size

$$\text{Area} = \pi \times \frac{A}{2} \times \frac{B}{2}$$

$$= \frac{\# \text{ of CTC in red area}}{\#CTC_{CVB} - \#CTC_{PVB}}$$



- CTC in CVB were significantly larger than CTC in PVB ( $p < 0.001$ ):
  - Mean CTC area in CVB:  $77.59 \pm 4.68 \text{ mm}^2$
  - Mean CTC area in PVB:  $62.28 \pm 5.02 \text{ mm}^2$
- On average **19% (range: 0-48%) of the numerical difference in CTC counts** between CVB and PVB could be attributed to differences in CTC size.

## Discussion

- ▶ Significantly higher numbers of CTC were measured in CVB compared to PVB in patients with MBC.
- ▶ Registration of the site of blood collection is warranted in clinical practice and studies evaluating the role of CTC assessment in the management of cancer patients.
- ▶ The observed differences suggest an important filtering function for the lung microvascular system.
- ▶ Potential explanation for some radiologically unexplained respiratory distress syndromes frequently observed in end-stage cancer patients.
- ▶ Limitations:
  - Heterogeneous lines and types of treatment
  - Diffuse metastatic involvement ↔ metastasis confined to either systemic or pulmonary circulatory system
  - Size ↔ organ specific homing, apoptosis



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