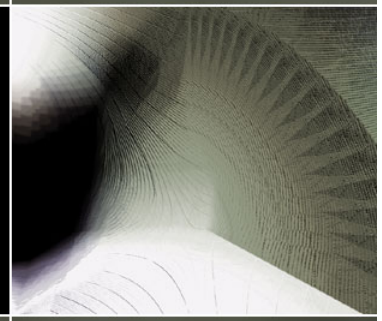
Image
Video
Processing
Laboratory

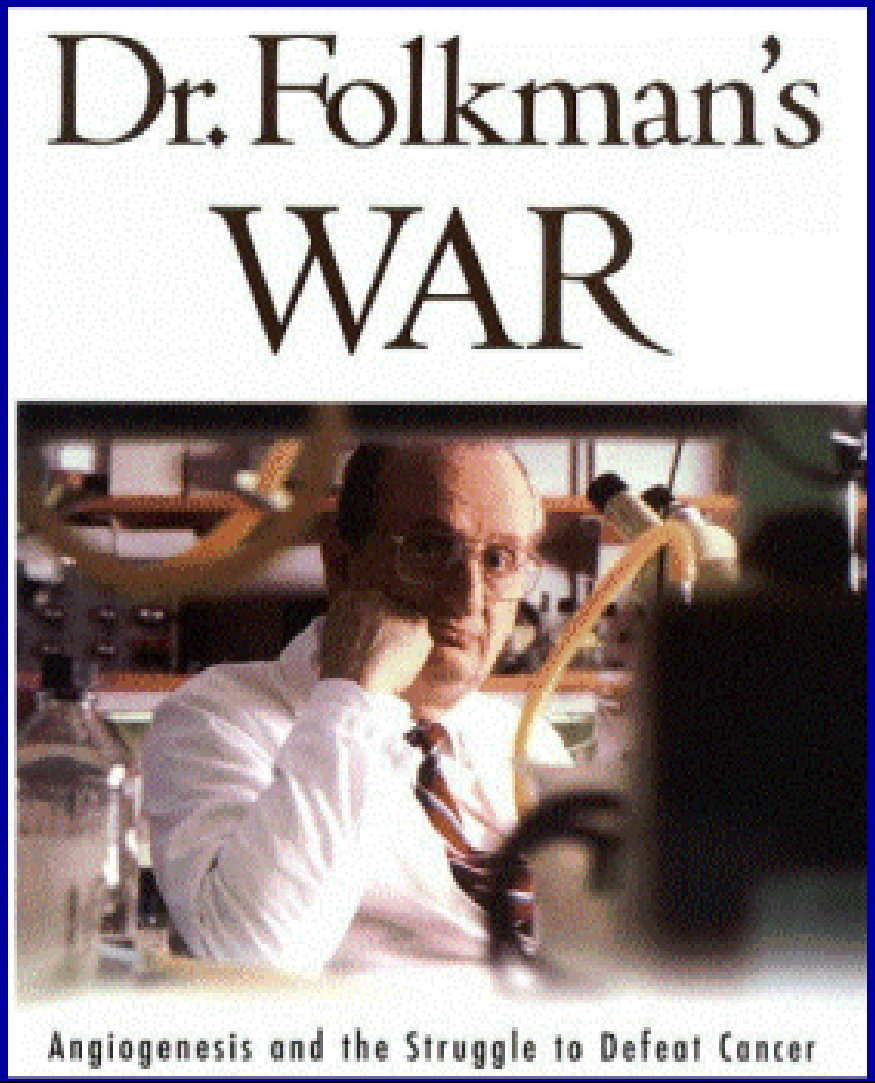
Focus on angiogenesis:
computer-aided diagnosis for breast tumors



黃育仁 教授
東海大學資工系

Outline

- Introduction to Angiogenesis
- Motivation
- Tumor Segmentation
- Vascularity Morphology
- Conclusions

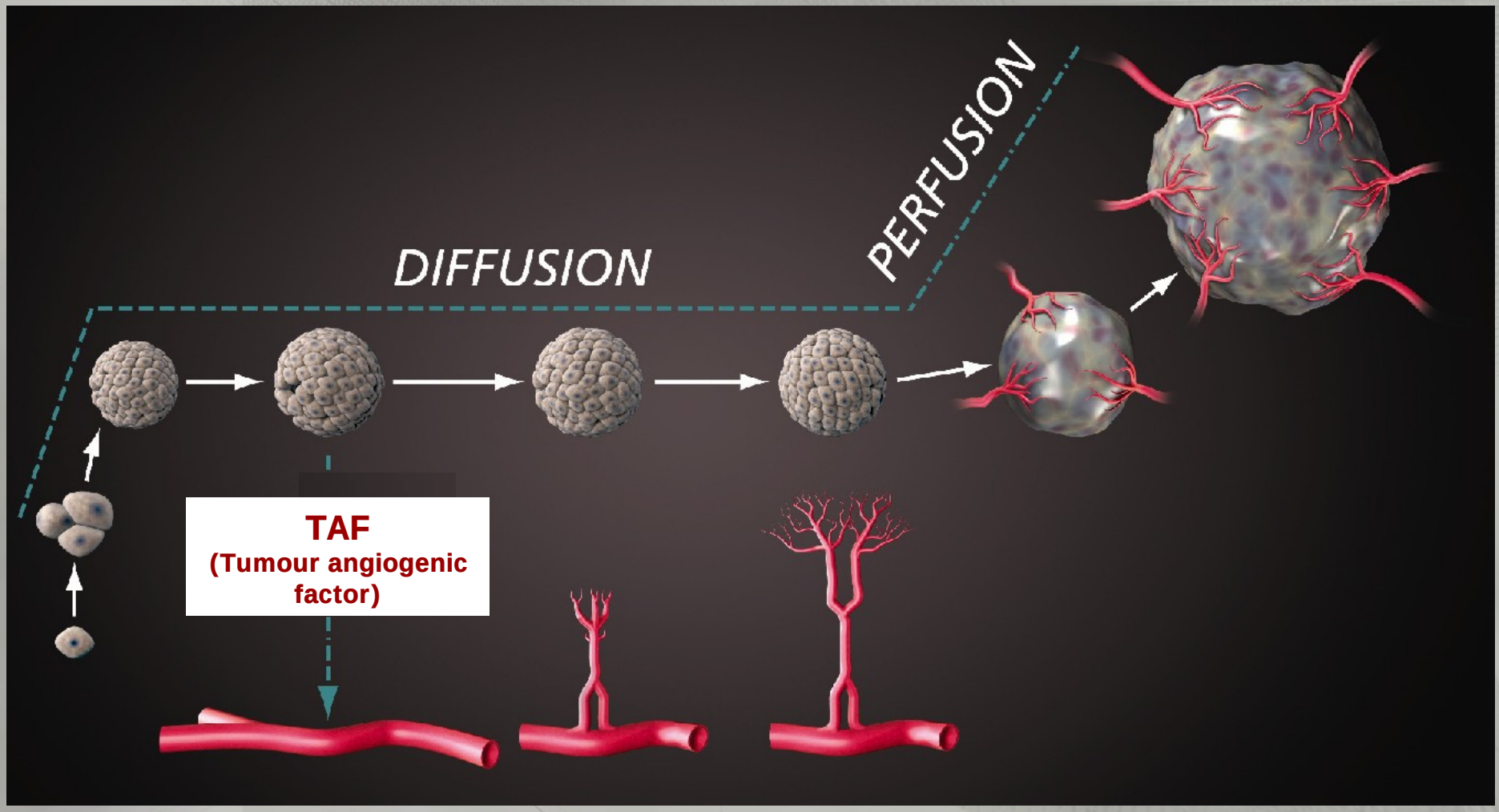


Obituary: M. Judah Folkman (1933-2008): Scientist, surgeon and creator of the field of angiogenesis research

Motivation

- **Angiogenesis**
  - **a fundamental process for the establishment, growth and dissemination of all tumors**
  - **the growth of breast cancer is connected to angiogenesis**

Angiogenesis is essential for sustained tumour growth



Modified from Folkman J. N Engl J Med 1971;285:1182–6

What is VEGF (Vascular endothelial growth factor) ?

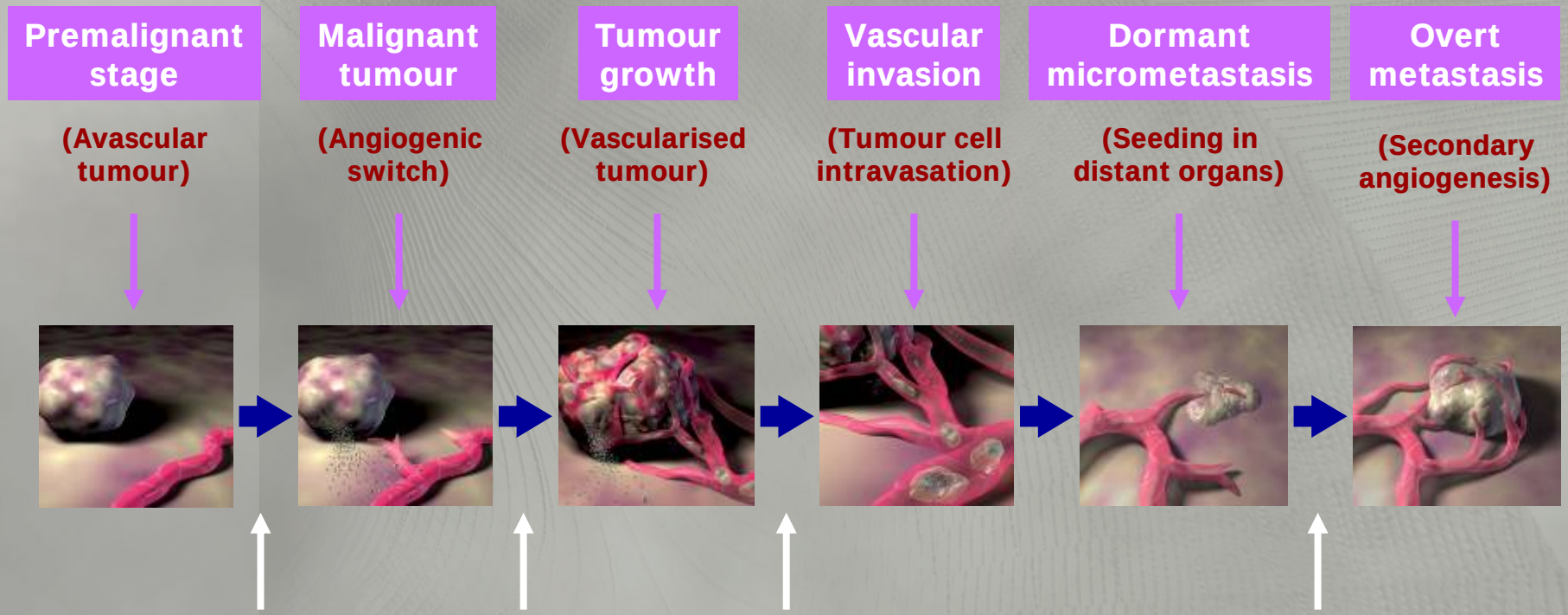
Ferrara N, 1989

1. **Key mediator of angiogenesis**
2. **Stimulates growth of endothelial cells**
3. **Also known as VEGF-A**
4. **Related molecules are VEGF-B, C and D, placental growth factor (PlGF)**
5. **VEGF expression is increased in many tumour types including breast cancer.**
6. **In breast cancer, these increases are associated with poor clinical outcome, including decreased disease-free and overall survival.**

*Predominant molecular species

Ferrara N, et al. Endocr Rev 1997;18:4–25

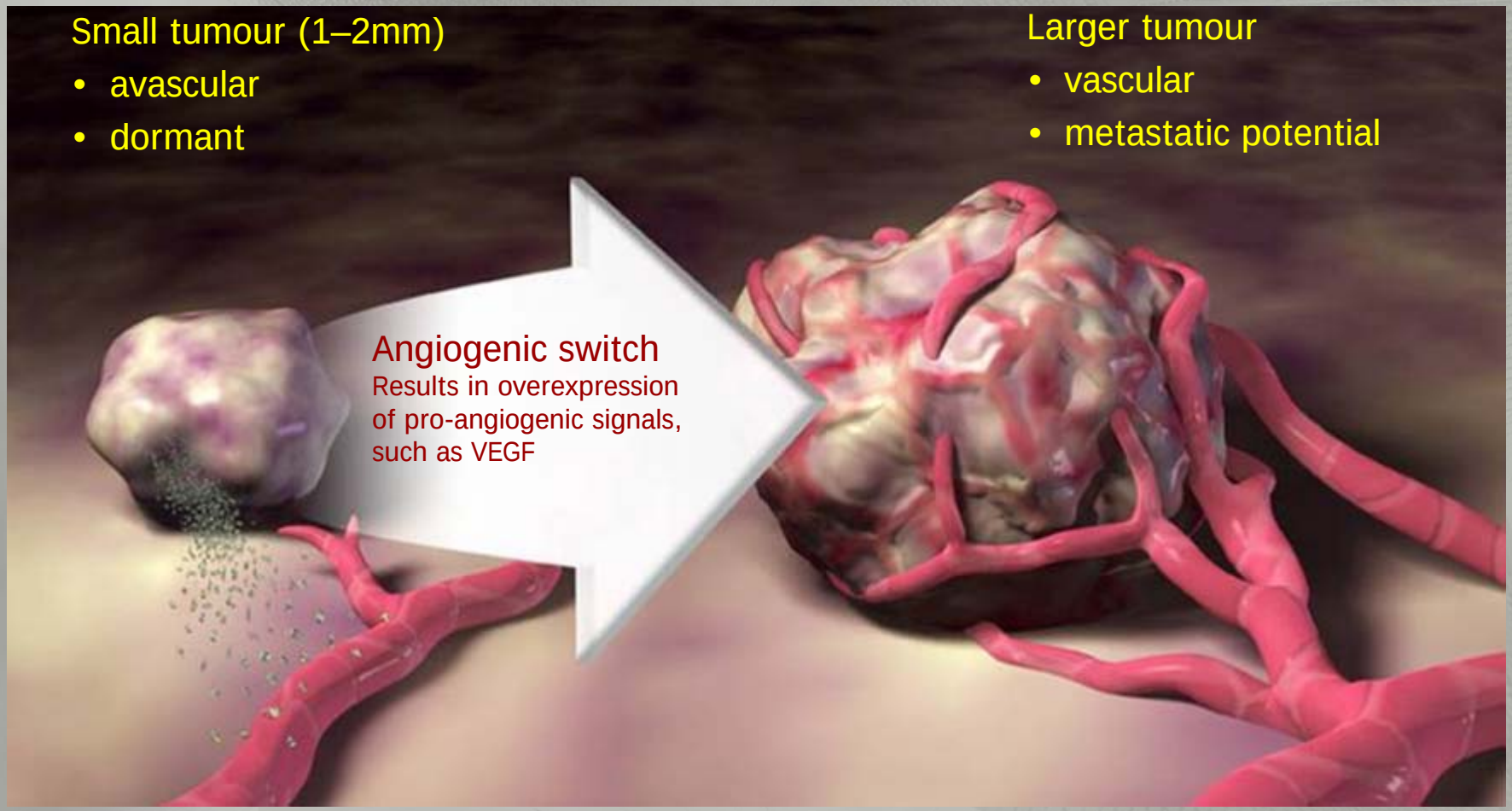
Angiogenesis is involved throughout tumour formation, growth and metastasis



Stages at which angiogenesis plays a role in tumour progression

Adapted from Poon RT-P, et al. J Clin Oncol 2001;19:1207–25

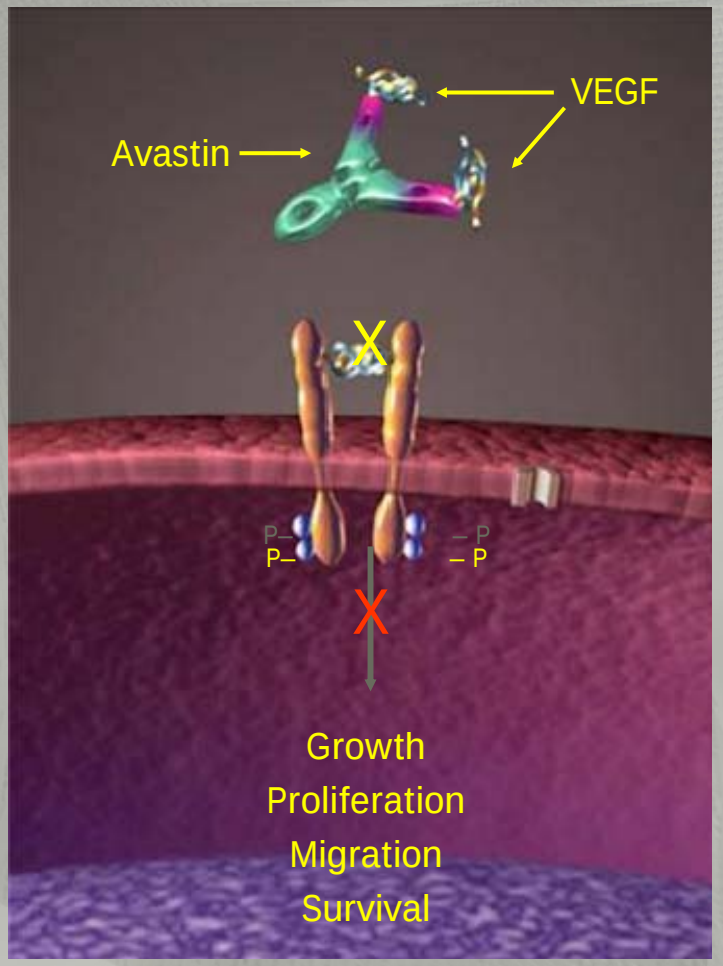
The angiogenic switch in tumor development



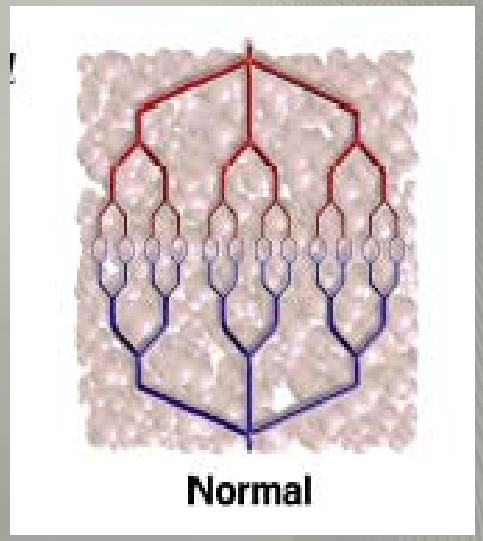
Adapted from Bergers G, et al. Nat Rev Cancer 2002;3:401–10

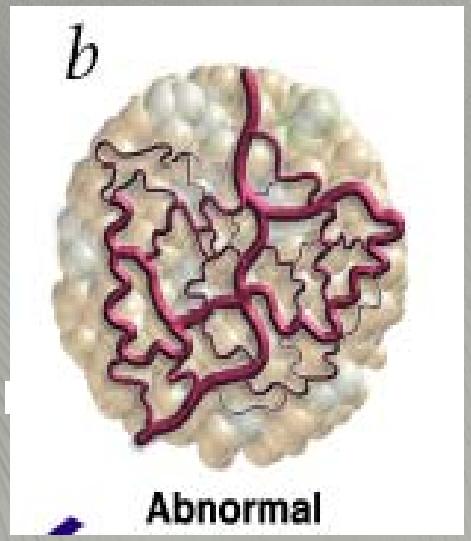
Avastin® (bevacizumab), the first anti-angiogenic agent to show clinical benefit in cancer

- **Recombinant humanised monoclonal anti-VEGF antibody**
  - **humanised murine antibody (93% human, 7% murine)**
    - **prevents possible immune reactions**
  - **recognises and binds to all major isoforms of human VEGF-A**
    - **prevents VEGF from interacting with its receptors**
    - **results in the inhibition of activation of downstream signalling pathways**
  - **terminal half-life = 17–21 days**
    - **enables convenient combination with concomitant therapy schedules**

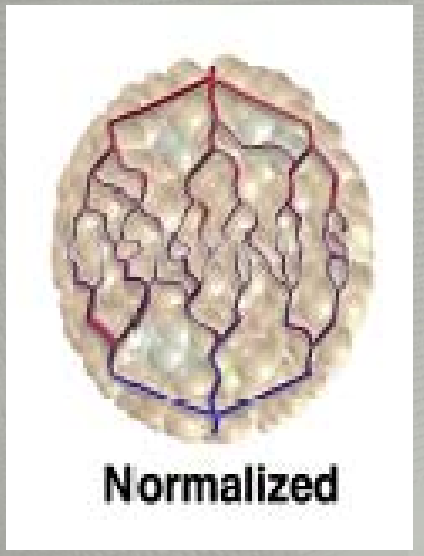


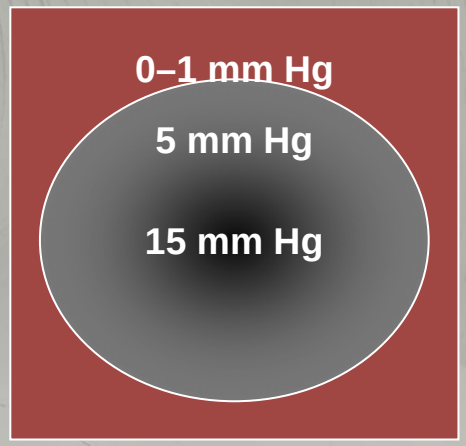
Anti-VEGF antibody 'normalises' the tumour vasculature





Anti-VEGF





Reduces
IFP & MVD
&
Increases
drug delivery

Jain 1988, 1990

Jain R. Nature Med 2001;7:987–9; Willett CG, et al. Nat Med 2004;10:145–7;
Wildiers H, et al. Br J Cancer 2003;88:1979–86

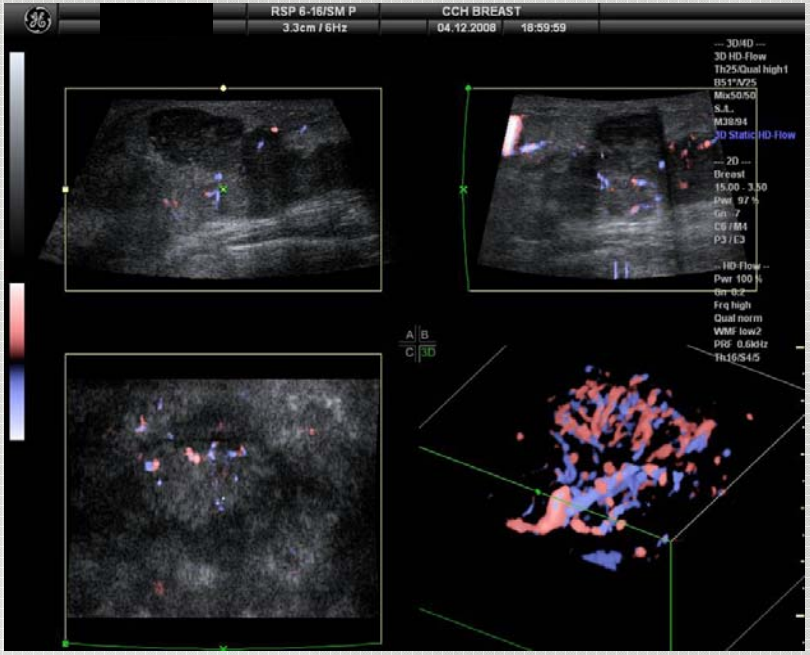
Motivation

- **Tumor vascularity**
  - **an important indicator in the assessment of tumor growth and metastasis**
  - **would be used as a factor to evaluate the effect of the neo-adjuvant chemotherapy prior to surgery**

3D power Doppler ultrasound

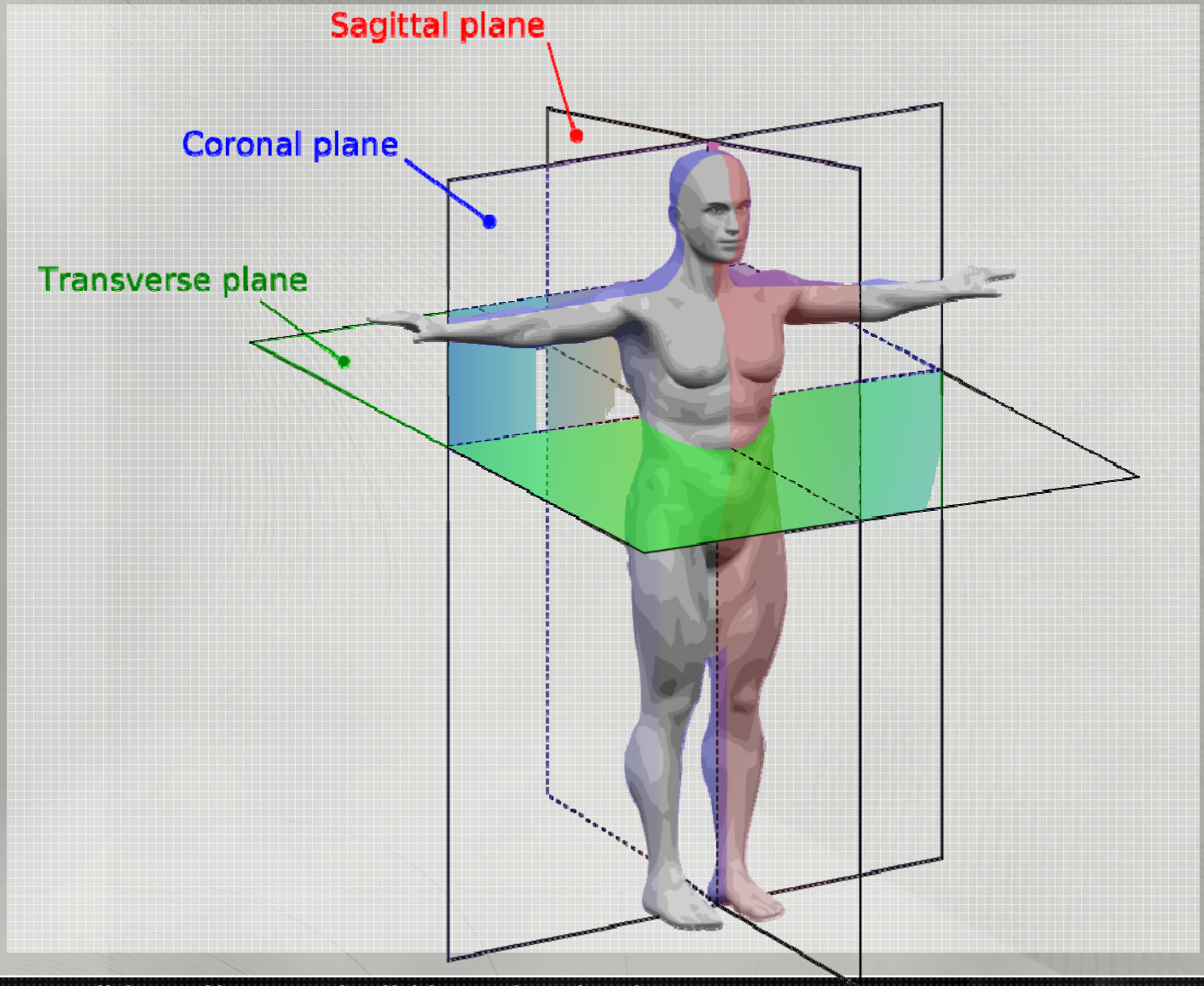
- can quantify the power Doppler signal and detect the total vascularity within the entire volume of breast tumor
- **High-definition flow** (HDF) PDU was performed to investigate blood flow and solid directional flow information in breast tumors.

(Voluson 730, GE Medical Systems)



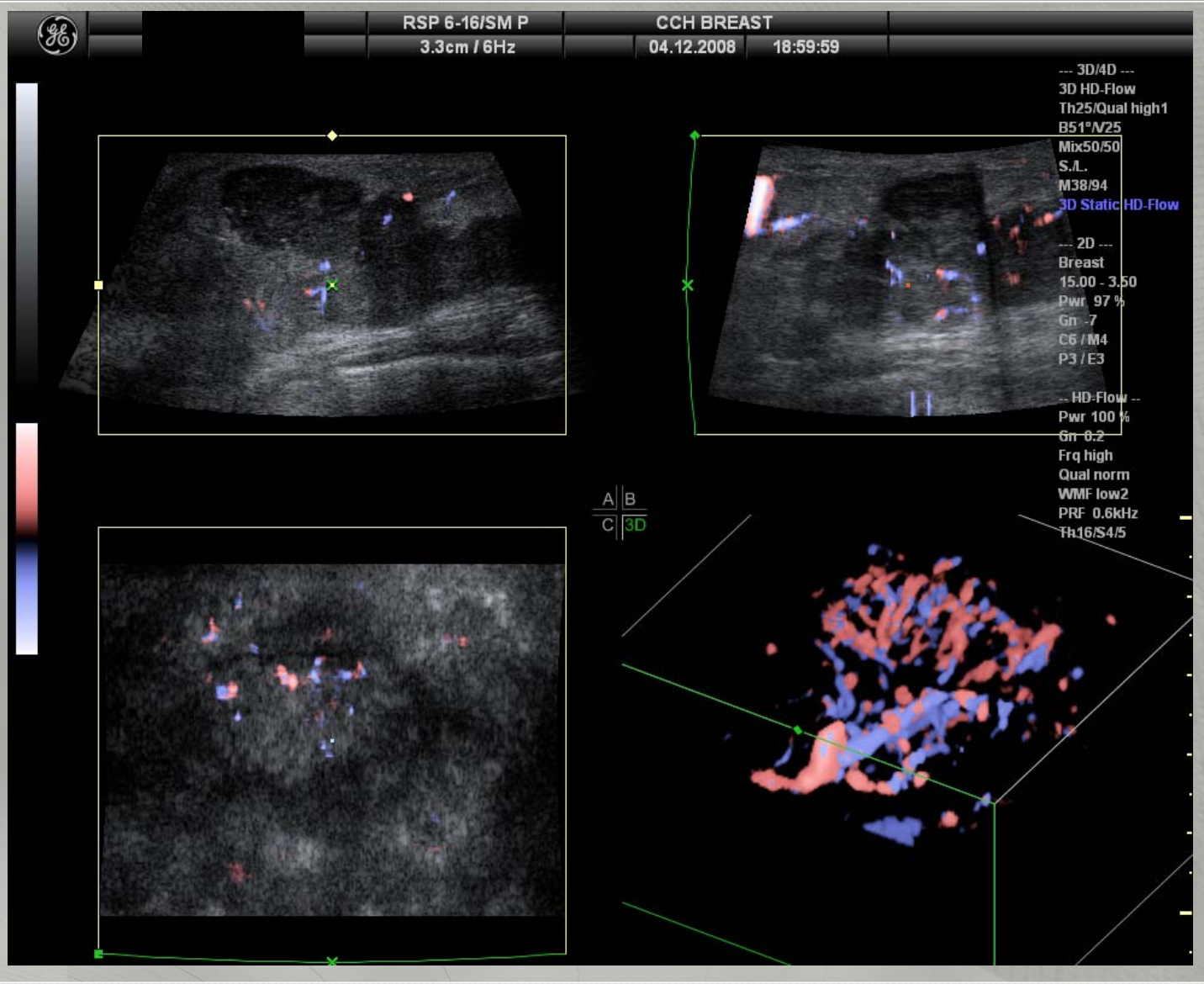
3D B-mode ultrasound image of a malignant tumor and the corresponding HDF PDU image

Human anatomy planes

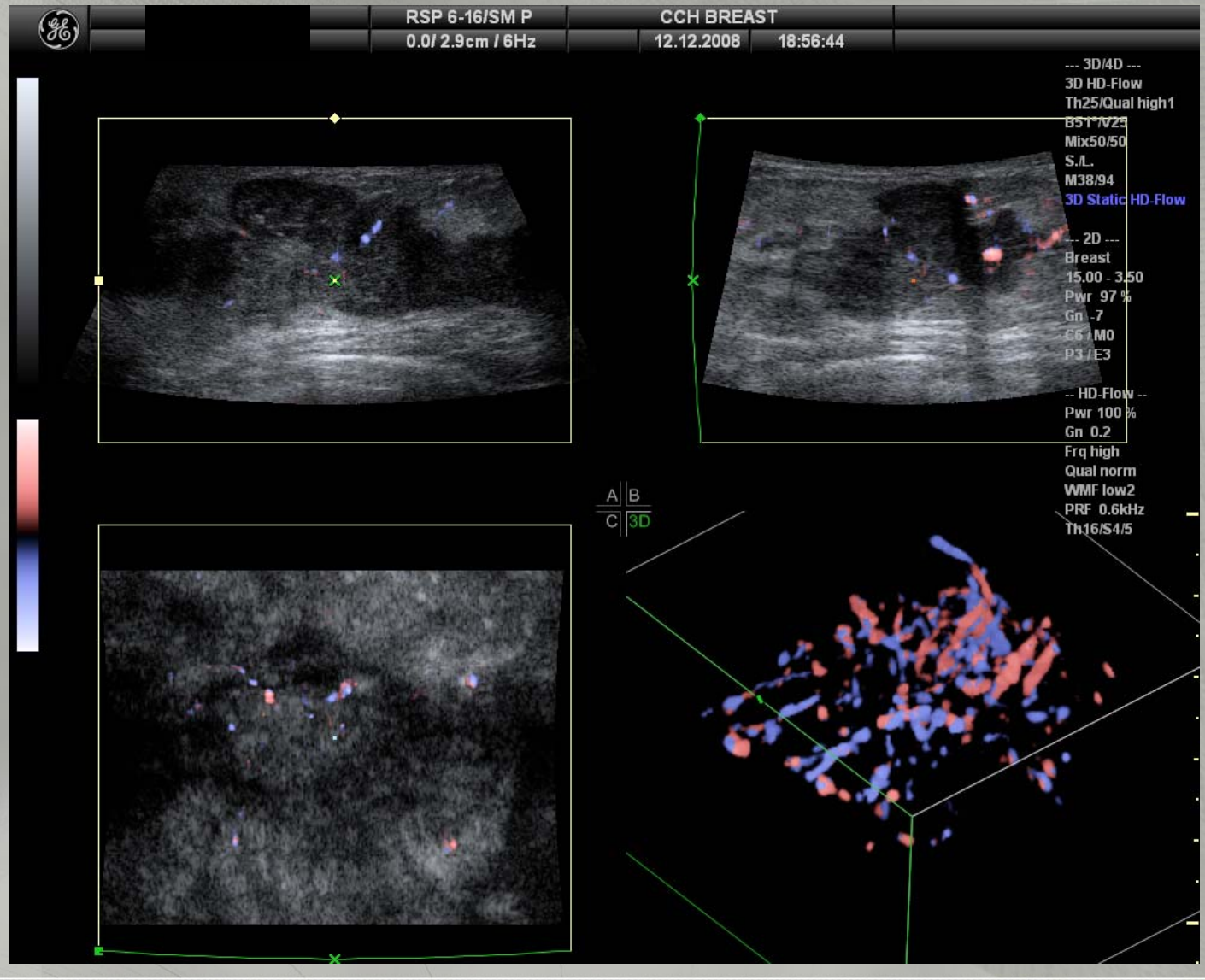


http://en.wikipedia.org/wiki/Sagittal_plane

N0


RSP 6-16/SM P
3.3cm / 6Hz
CCH BREAST
04.12.2008
18:59:59
--- 3D/4D ---
3D HD-Flow
Th25/Qual high1
B51°/V25
Mix50/50
S./L.
M38/94
3D Static HD-Flow
--- 2D ---
Breast
15.00 - 3.50
Pwr 97 %
Gn -7
C6 / M4
P3 / E3
-- HD-Flow --
Pwr 100 %
Gn 8.2
Frq high
Qual norm
WMF low2
PRF 0.6kHz
Th16/S4/5
A B
C 3D

1-1TA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0.0/ 2.9cm / 6Hz
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12.12.2008
18:56:44
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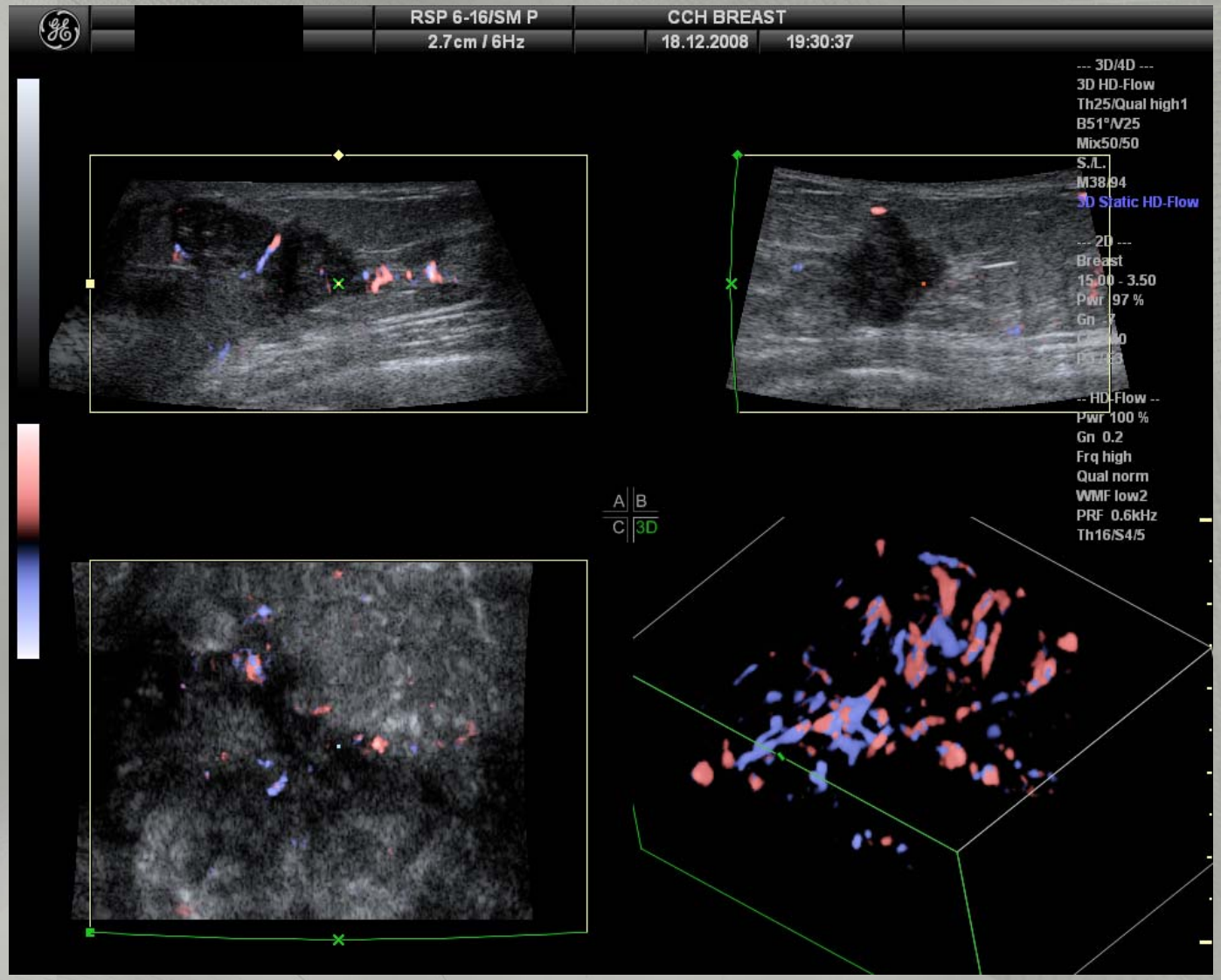
3D HD-Flow
Th25/Qual high1
Mix50/50
S./L.
M38/94
3D Static HD-Flow
--- 2D ---
Breast
15.00 - 3.50
Pwr 97 %
Gn -7
C6 / M0
P3 / E3
-- HD-Flow --
Pwr 100 %
Gn 0.2
Frq high
Qual norm
WMF low2
PRF 0.6kHz
Th16/S4/5
A B
C 3D

1-2T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2.7cm / 6Hz
CCH BREAST
18.12.2008
19:30:37
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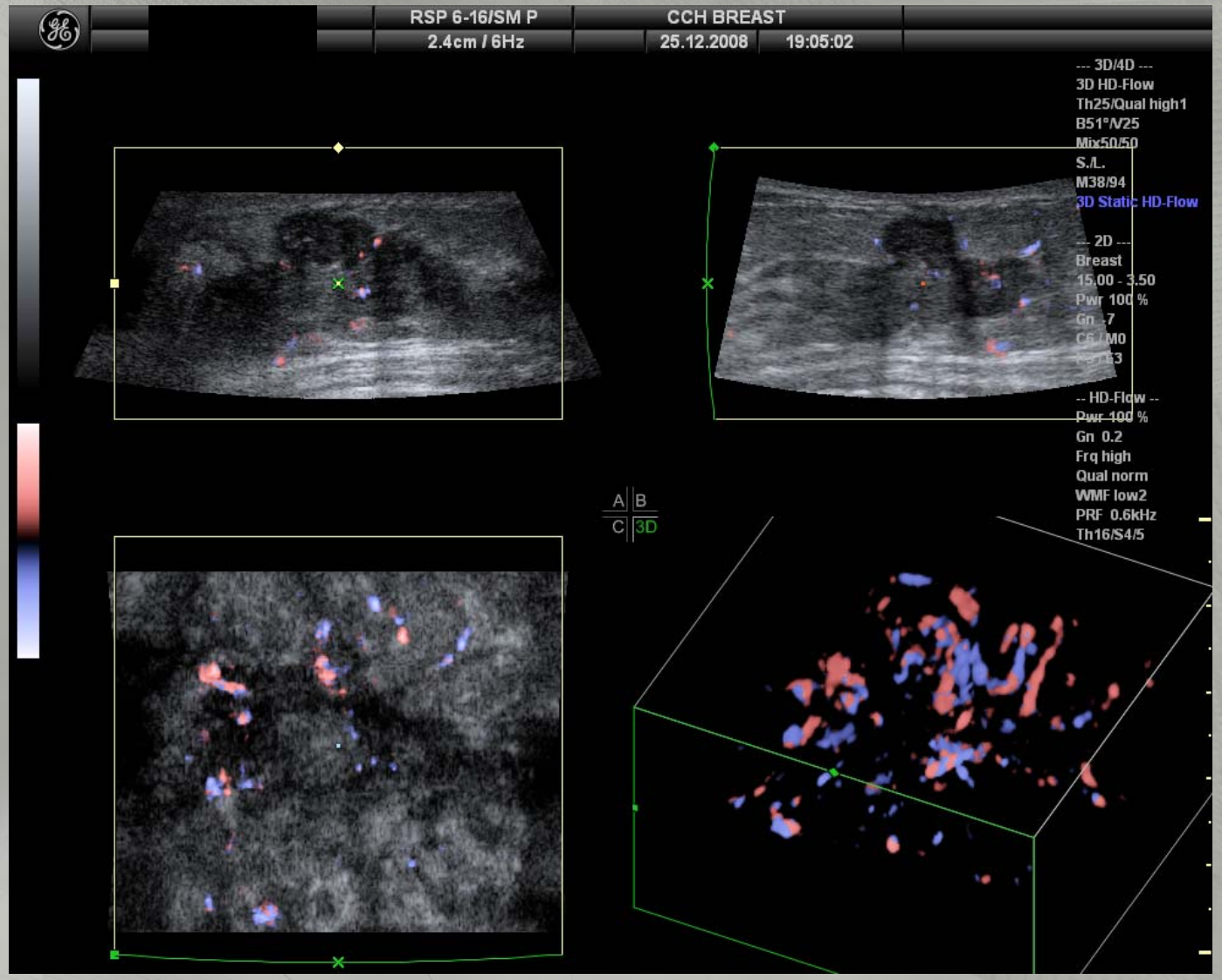
3D HD-Flow
Th25/Qual high1
B51°/V25
Mix50/50
S.L.
M38.94
3D Static HD-Flow
--- 2D ---
Breast
15.00 - 3.50
Pwr 97 %
-- HD-Flow --
Pwr 100 %
Gn 0.2
Frq high
Qual norm
WMF low2
PRF 0.6kHz
Th16/S4/5
A B
C 3D

1-3TA


RSP 6-16/SM P
2.4cm / 6Hz
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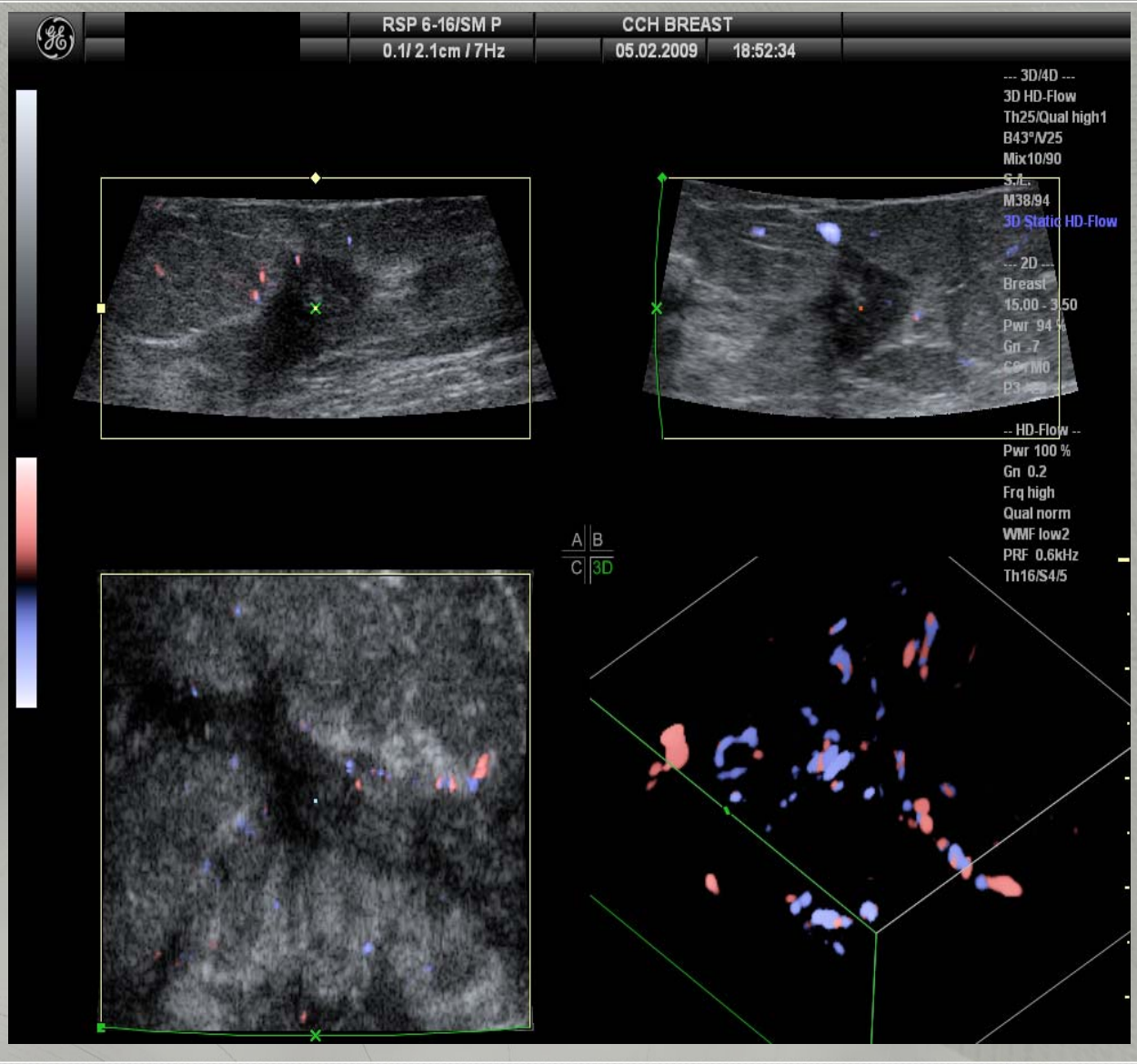
3D HD-Flow
Th25/Qual high1
B51°/V25
Mix50/50
S./L.
M38/94
3D Static HD-Flow
--- 2D ---
Breast
Pwr 100 %
-- HD-Flow --
Pwr 100 %
Gn 0.2
Frq high
Qual norm
WMF low2
PRF 0.6kHz
Th16/S4/5
A
B
C
3D

3-1TA


RSP 6-16/SM P
0.1/ 2.1cm / 7Hz
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18:52:34
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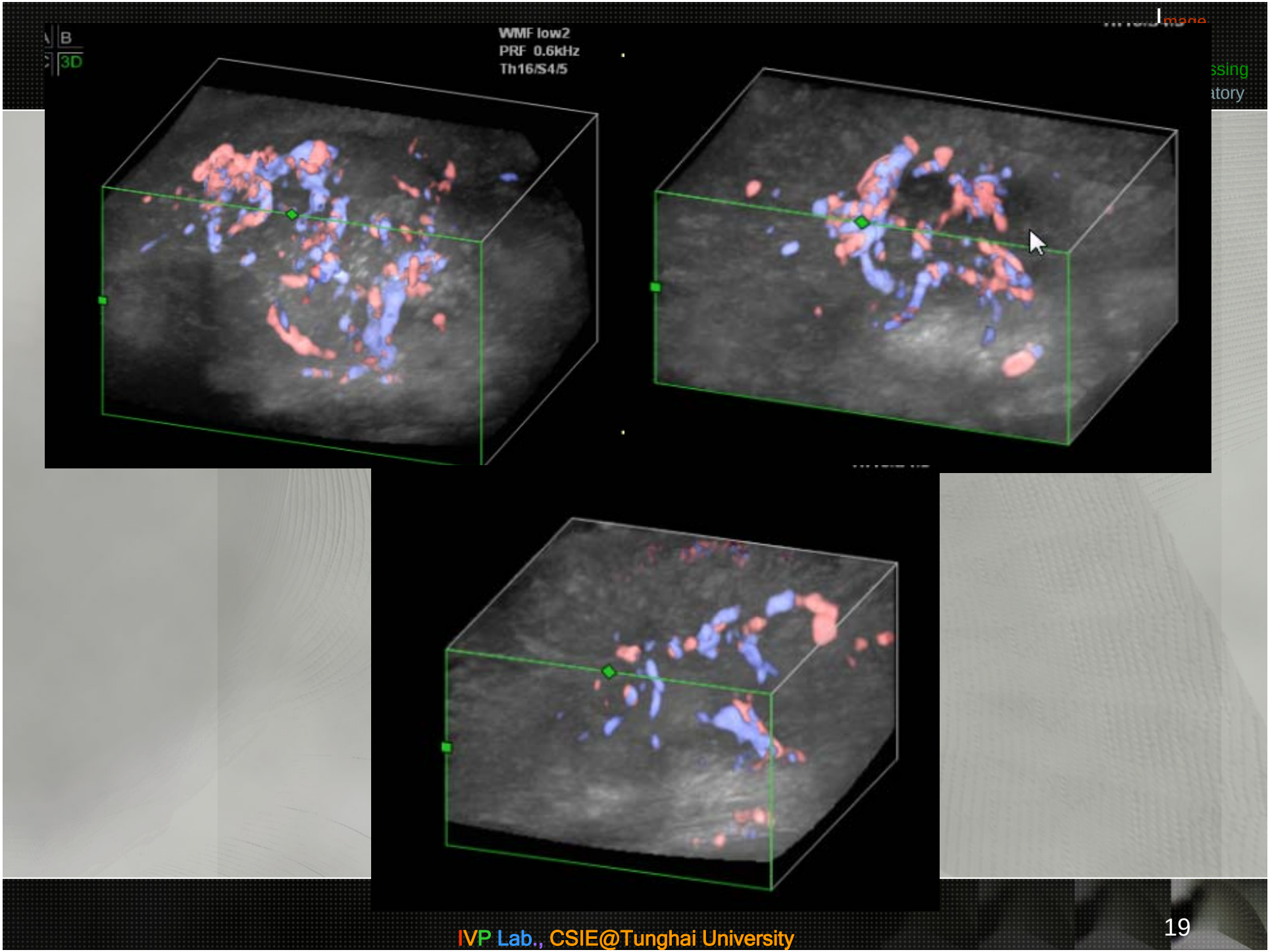
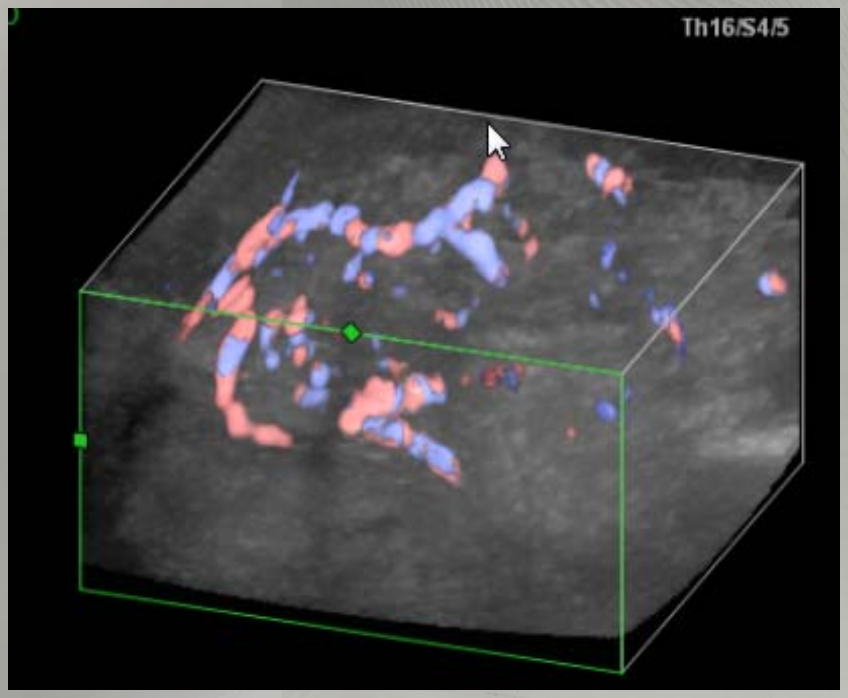
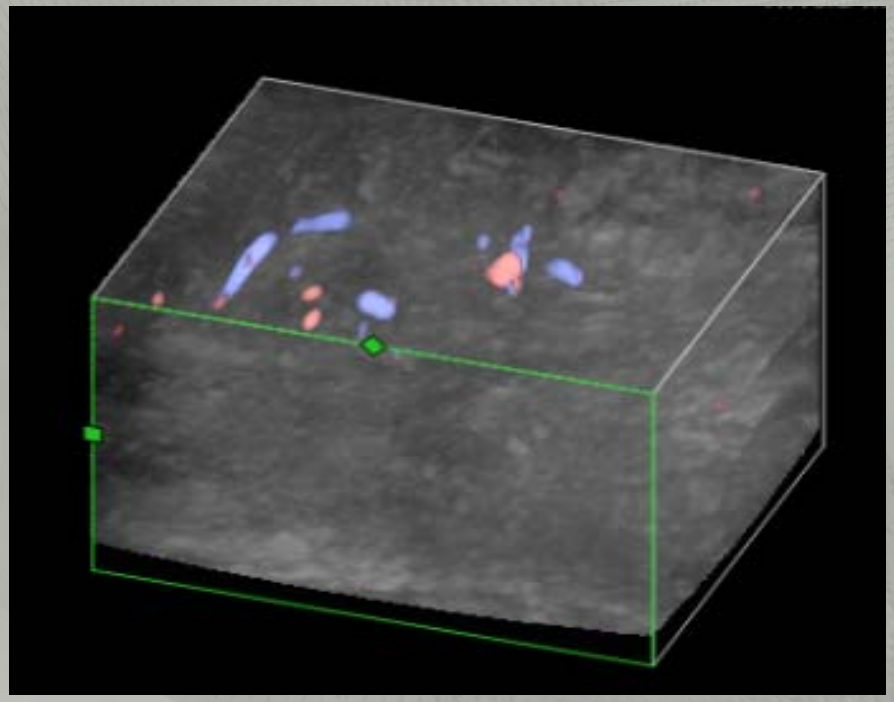
3D HD-Flow
Th25/Qual high1
B43°/V25
Mix10/90
S/L
M38/94
3D Static HD-Flow
--- 2D ---
Breast
15.00 - 3.50
Pwr 94 %
Gn 7
C0/M0
P3
-- HD-Flow --
Pwr 100 %
Gn 0.2
Frq high
Qual norm
WMF low2
PRF 0.6kHz
Th16/S4/5
A B
C 3D


B
3D
WMF low2
PRF 0.6kHz
Th16/S4/5

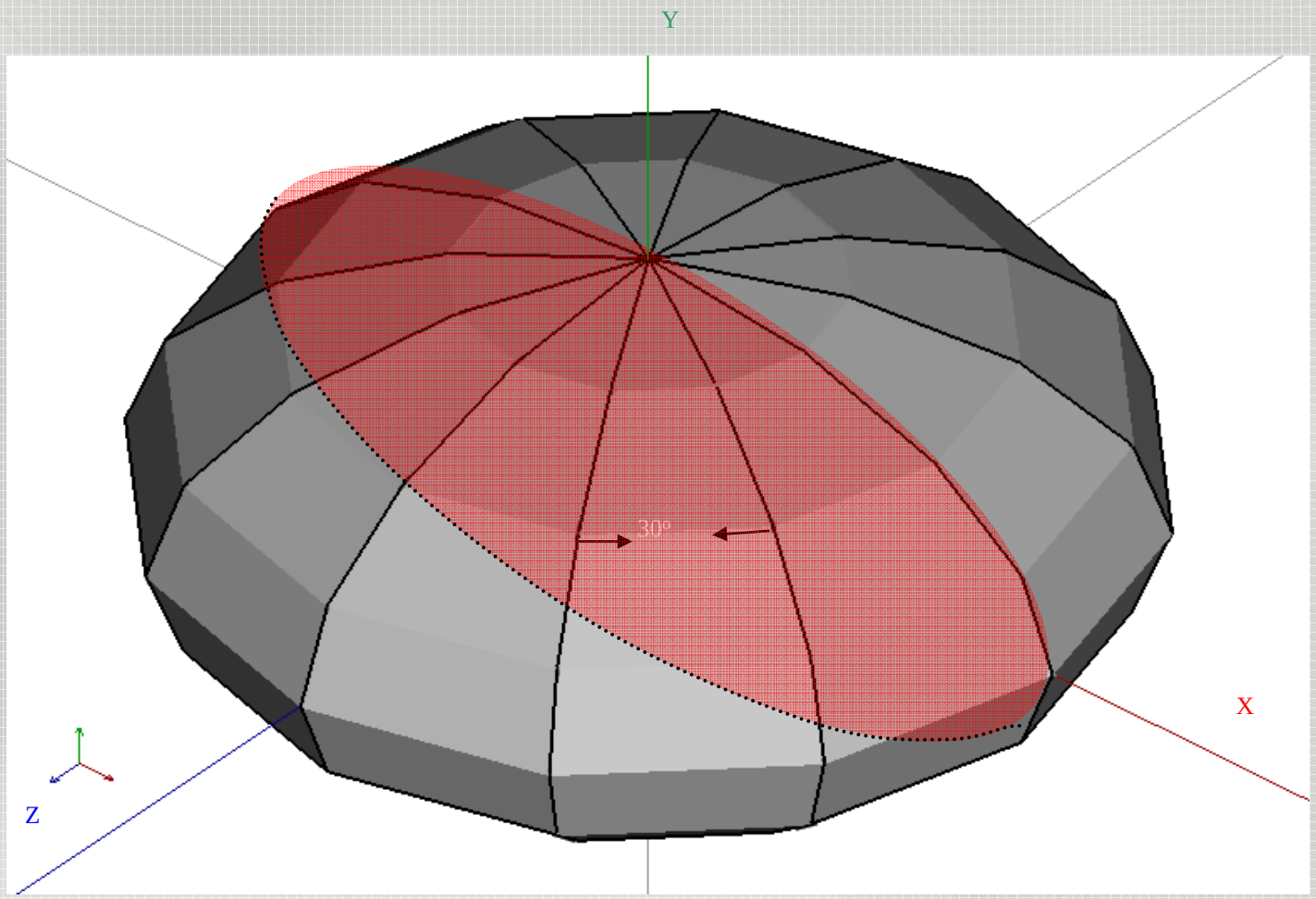

Th16/S4/5



Three-dimensional segmentation

- **Interpretation manually determined 3D contour of the tumor by using three distinct modes**
  - **The entire manual sketching (EMS) mode**
  - **The partial manual sketching (PMS) mode**
    - The virtual organ computer-aided analysis (VOCAL) scheme within 4D view software
  - **The partial automatic sketching (PAS) mode**
    - Six preliminary tumor contours extract by using 2D region growing

PMS & PAS Mode



The proposed automatic method

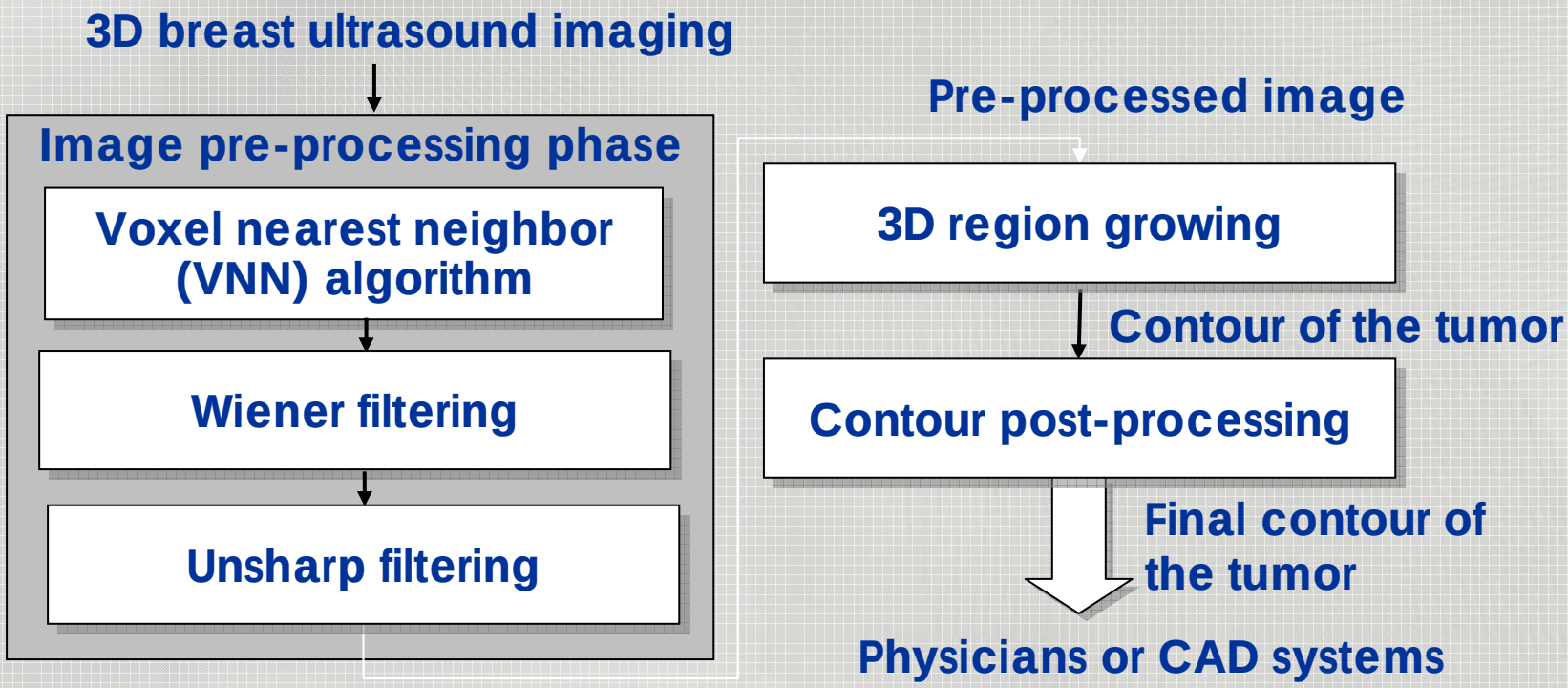
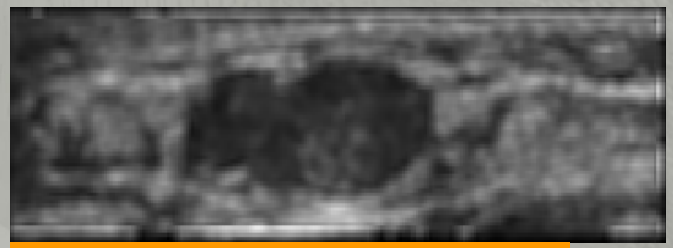


Image pre-processing

- Combine the voxel nearest neighbor (VNN) algorithm, Wiener filtering and unsharp filtering to reduce noise and enhance image contrast

Original image

VNN processed image

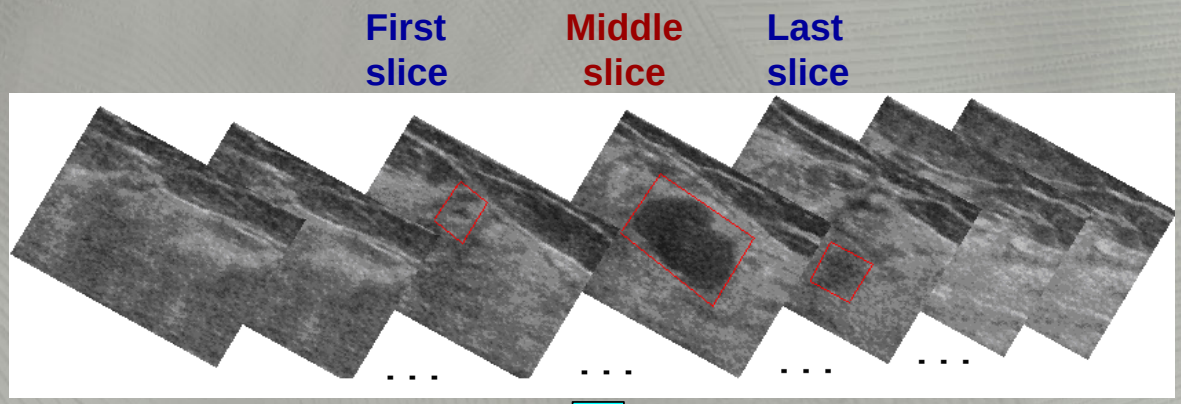


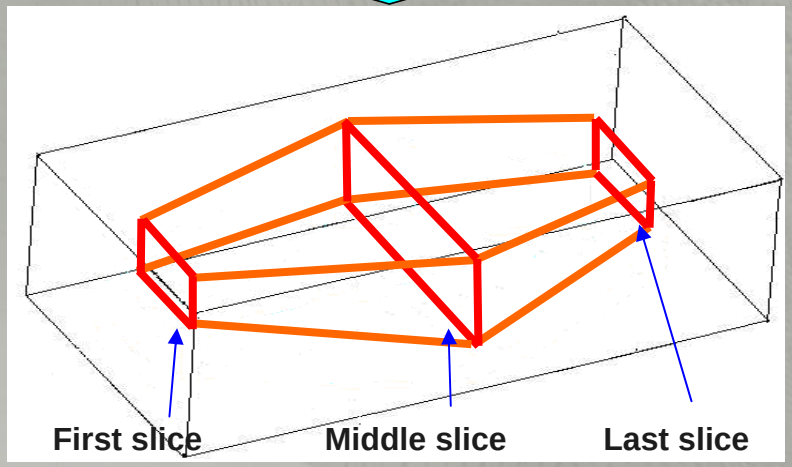
Pre-processed image

Image pre-processing

VOI extraction

- VOI area would be extracted from the 3D volume by using the three manual sketched ROI regions



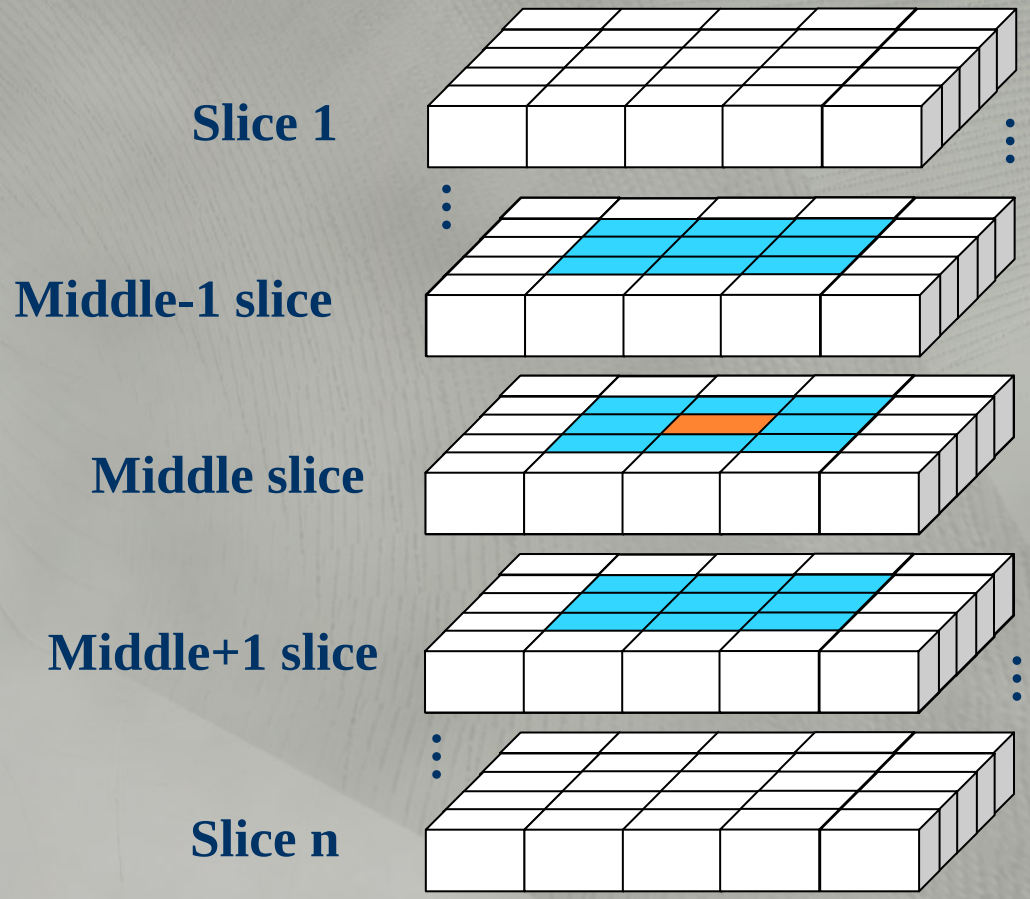


Volume of interest (VOI) area

Region growing segmentation

- Chose the centroid of ROI area in middle slice as the initial seed point and perform the automatic 3D region growing method to separate the tumor region from background

26-adjacency around a 3D voxel

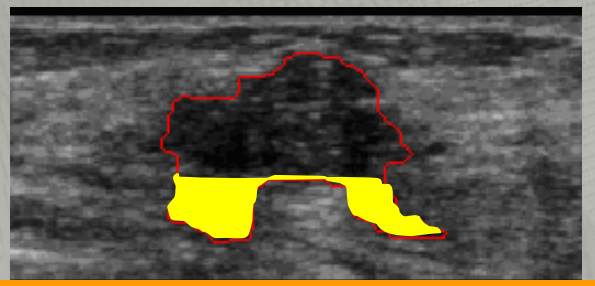


D. CohenOr and A. Kaufman, "3D line voxelization and connectivity control," *IEEE Computer Graphics and Applications*, vol. 17, no. 6, pp. 80-87, Nov.1997.

Contour post-processing

- Eliminate the shadow area and retain the true tumor region

Original contour



Shadow area elimination

Post-processed contour

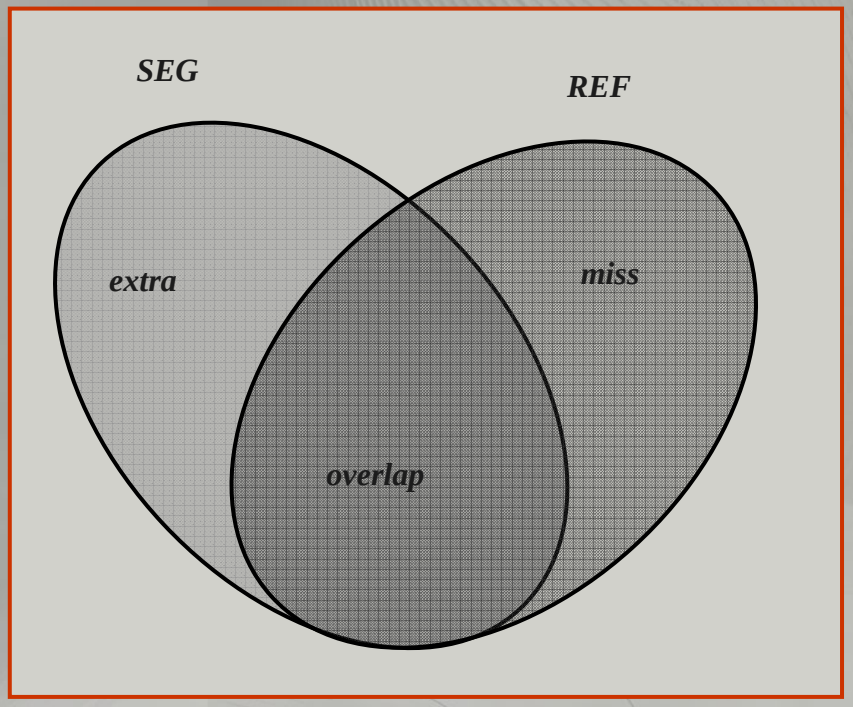
Contour post-processing

Segmentation Materials

- **Data Acquisition**
  - **The image database utilized in this study was collected during the period of July 2007 to August 2009**
  - **20 3-D volumes**
    - **10 benign breast tumor**
    - **10 malign breast tumor**
  - **Each 3-D volume**
    - **Contained approximately 200 2D slices**
    - **The spatial resolution of each slice was approximately 250 ×200 pixels**
  - **Patient's age ranged from 17 to 80 years**

Segmentation Results (1/2)

- **Four similarity measures**, the similarity index (*SI*), overlap fraction (*OF*), overlap value (*OV*), and extraction fraction(*EF*) between the manually sketched contours and the automatically determined contours were calculated for quantitative analysis of the contouring result.



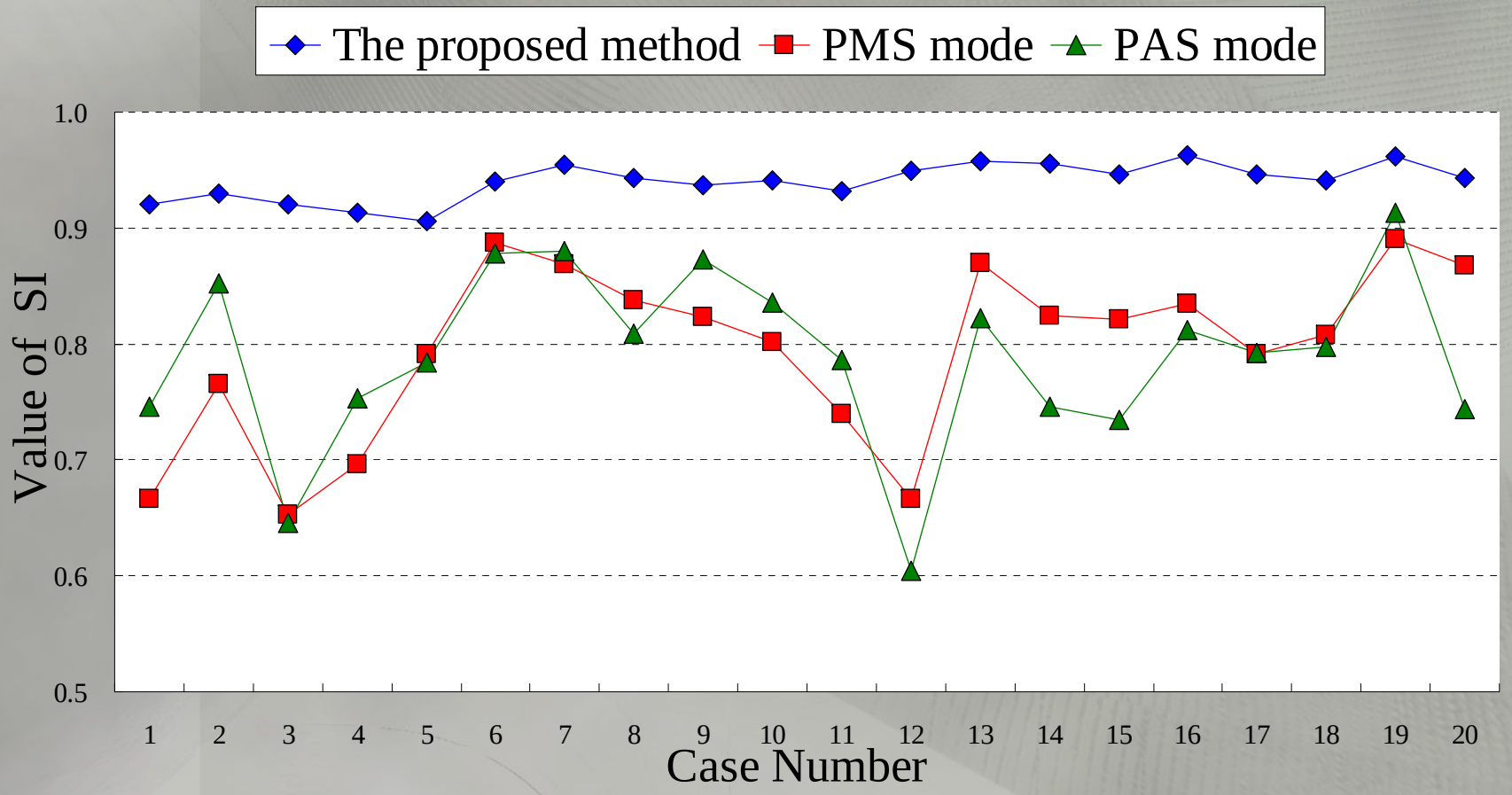
$$SI = \frac{2*(REF \cap SEG)}{REF + SEG}$$

$$OF = \frac{REF \cap SEG}{REF}$$

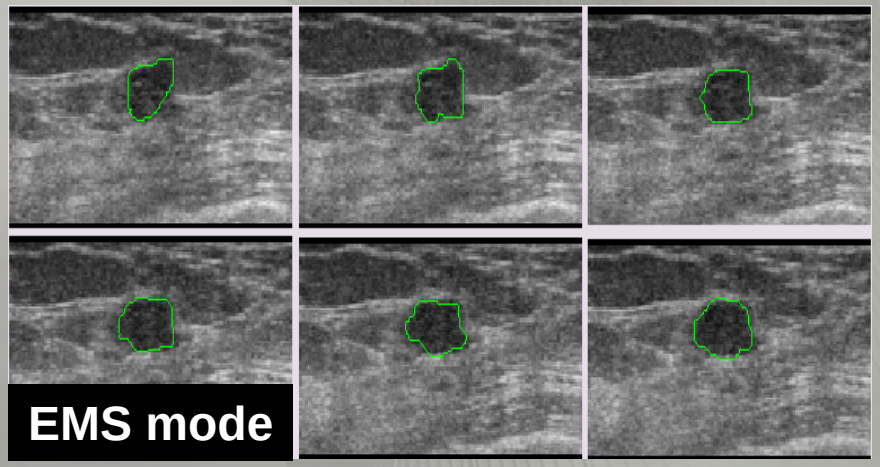
$$OV = \frac{REF \cap SEG}{REF \cup SEG}$$

$$EF = \frac{\overline{REF} \cap SEG}{REF}$$

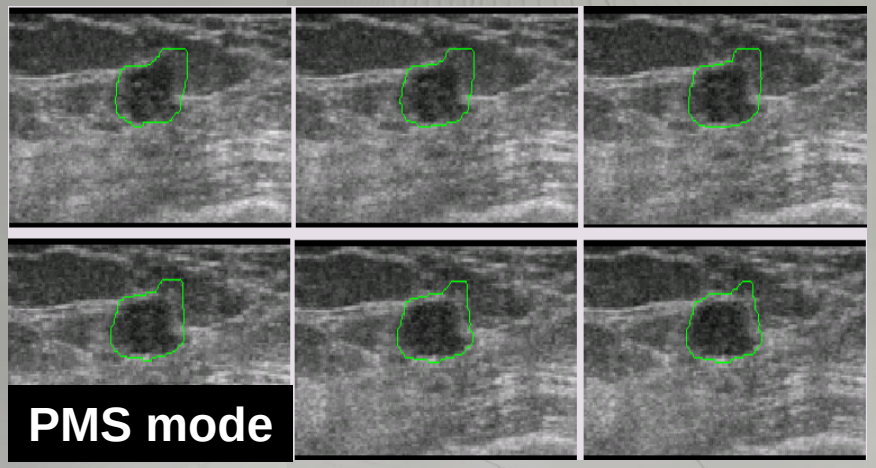
Segmentation Results (2/3)

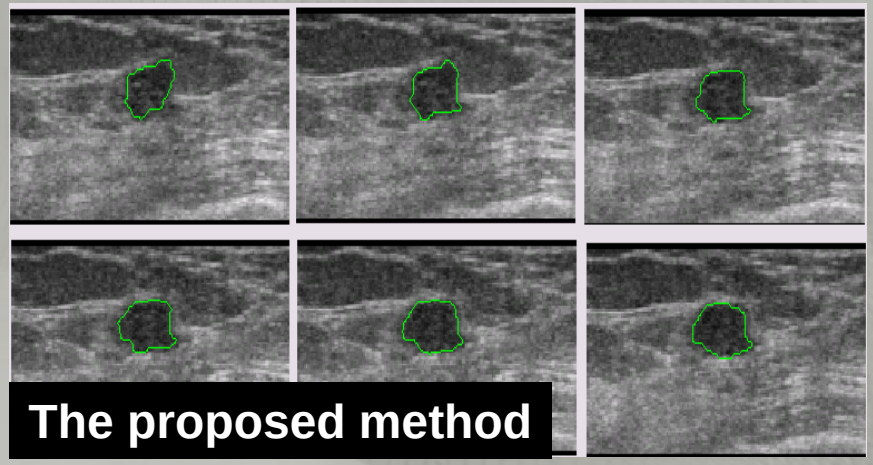


Segmentation Results (3/3)



- **The average indices of measure (*SI*, *OF*, *OV*, *EF*)** on tumor contours from the proposed segmentation method, PMS, PAS modes are (0.94, 0.94, 0.89, 0.06), (0.80, 0.84, 0.67, 0.29) and (0.79, 0.75, 0.65, 0.15), respectively.





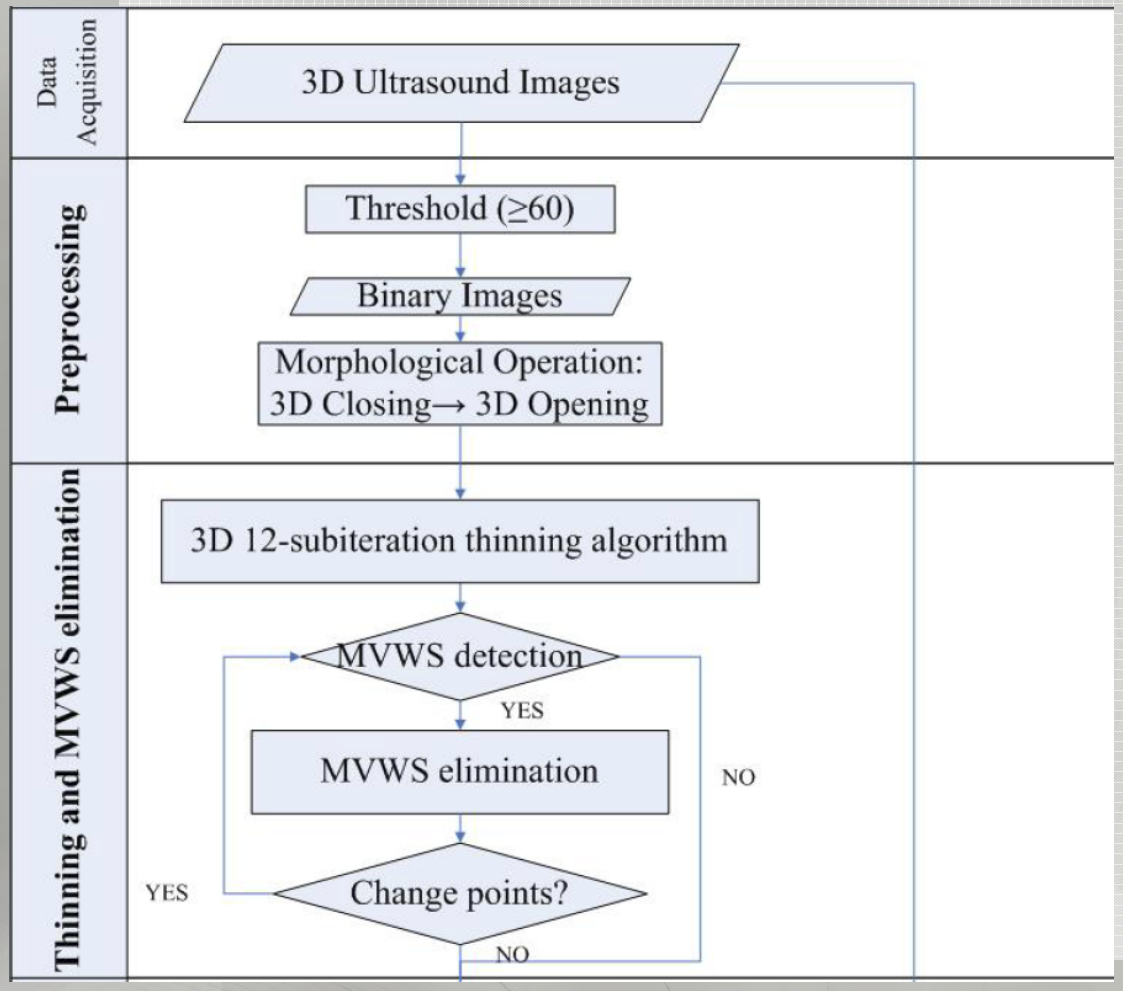
Vascularity Morphology

- **The study**
  - **aim at evaluating vascular morphology from the HDF Doppler sonography to find out potential early predictors for good responses to neo-adjuvant chemotherapy.**
  - **16 characteristics were considered as features**
    - **3 fundamental vascularization indices**
    - **13 vascular morphological features**

Materials and Methods (1/6)

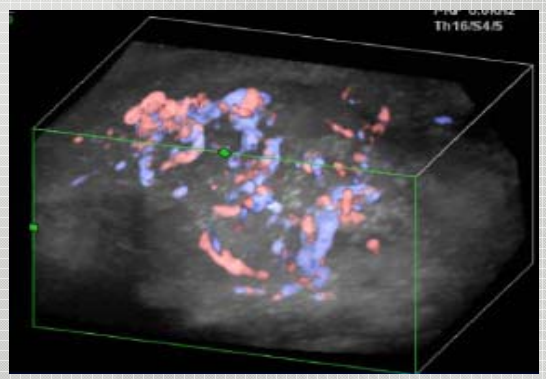
- ***Patients and chemotherapy***
  - **16 consecutive T2 breast cancer (Tumor size > 2cm and ≤ 5cm) patients, who received neo-adjuvant chemotherapy were recruited for this study**
  - **Pre-operative intravenous chemotherapy was given for six courses in each patient and three weeks per cycle**
  - **Sonography evaluations were done before each cycle of neo-adjuvant chemotherapy**
    - **obtained using GE Healthcare Voluson730 system**

o *Vascular centre-line extraction*

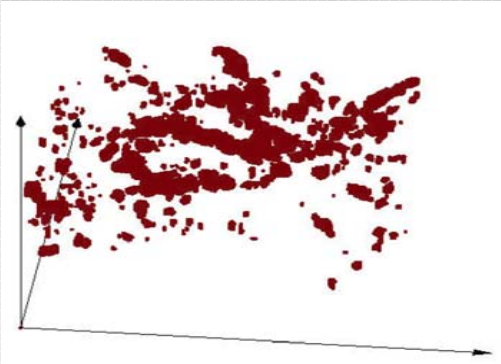


WVWS: multiple voxels wide skeleton

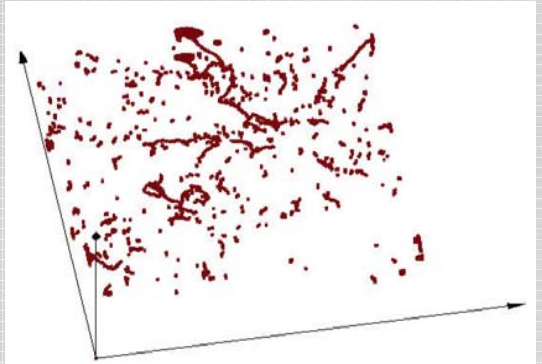
Materials and Methods (3/6)



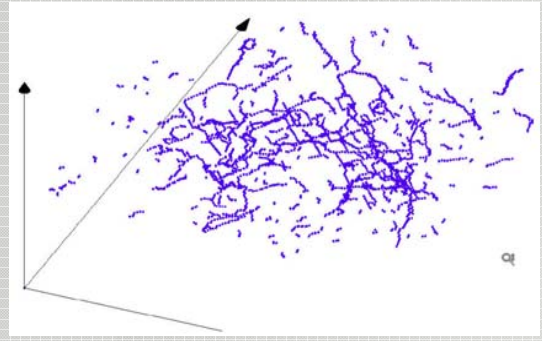
(a)



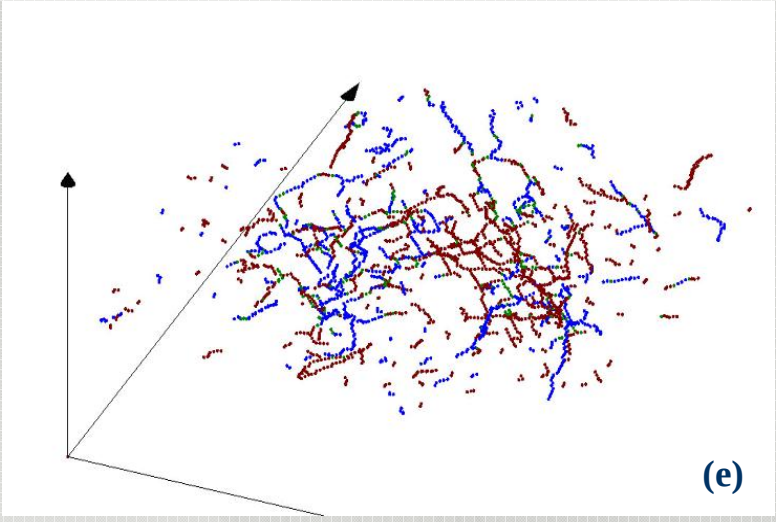
(b)



(c)



(d)



(e)

Vascular centre-line extraction

Materials and Methods (4/6)

- **Feature Extraction**
  - **three indices were evaluated from 3D HDF power Doppler ultrasound**
    - **vascularization index (VI)**
    - **flow index (FI)**
    - **vascularization flow index (VFI)**
  - **13 vascular morphological features were also estimated**
    - **number of vascular centre-lines (NT)**
    - **sum of the length of vascular centre-lines (LV)**
    - **number of branching point of vascular centre-lines (NB)**
    - **average number of neighbors for all points of vascular centre-lines (NN)**
    - **average number of neighbors in branches (BN)**
    - **average distance metric of all vascular centre-lines (ADM)**

Materials and Methods (5/6)

- weighted distance metric of all vascular centre-lines (PDM)
- number of cycles of vascular centre-lines (NC)
- average radius of vascular centre-lines (MR)
- average intensity of the voxels on the vascular centre-lines (TFI)
- ratio of points with opposite directions (OPR)
- frequency of direction changes in vascular centre-lines (FDC)
- average FDC (AFDC)

- **A total of 16 features from three regions surrounding the breast lesion were calculated**
  - **the volume of interest (VOI) area of tumor**
  - **the boundary area (+/- 3mm) on the VOI border**
  - **the entire volume area.**

Materials and Methods (6/6)

- ***Evaluation of chemotherapy response***
  - **The chemotherapy treatment effect of the 16 patients was evaluated by the clinical tumor response**
  - **The patients were classified into two groups:**
    - **the responder- complete response (CR) or partial response (PR)**
    - **the non-responder- stable disease (SD) or progressive disease (PD)**
  - **Among 16 patients**
    - **11 were responders to chemotherapy**
    - **4 remained stable in their disease**
    - **1 developed progressive disease.**

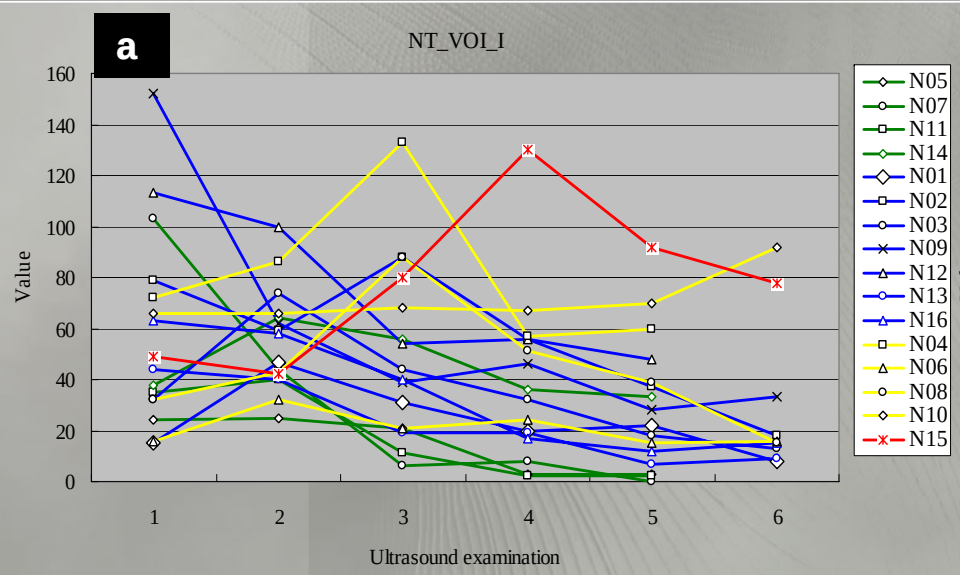
Results (1/5)

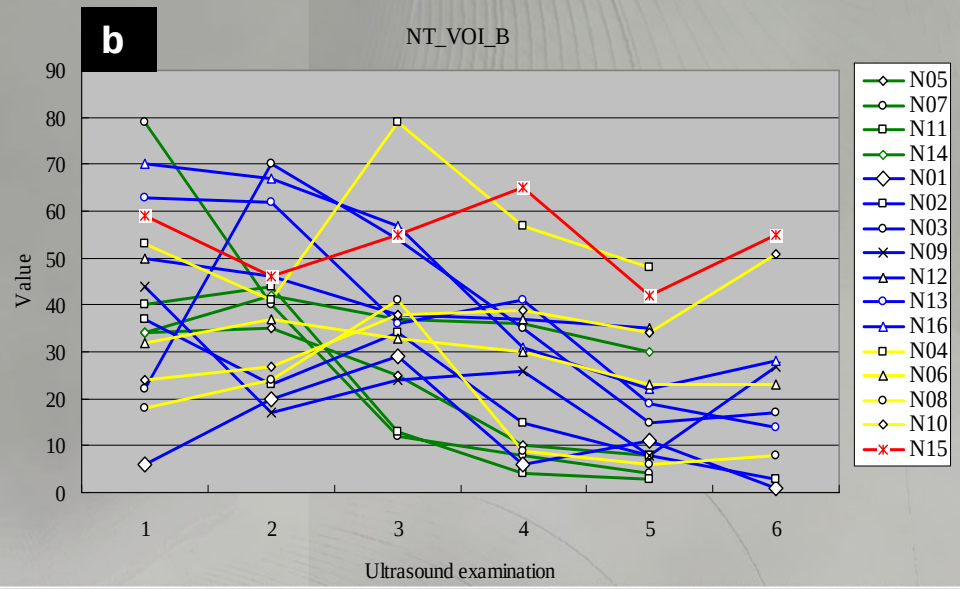
- **The simulations**
  - **evaluated the vascularization indices from both the responder and non-responder groups to identify practical features for tumor angiogenesis**

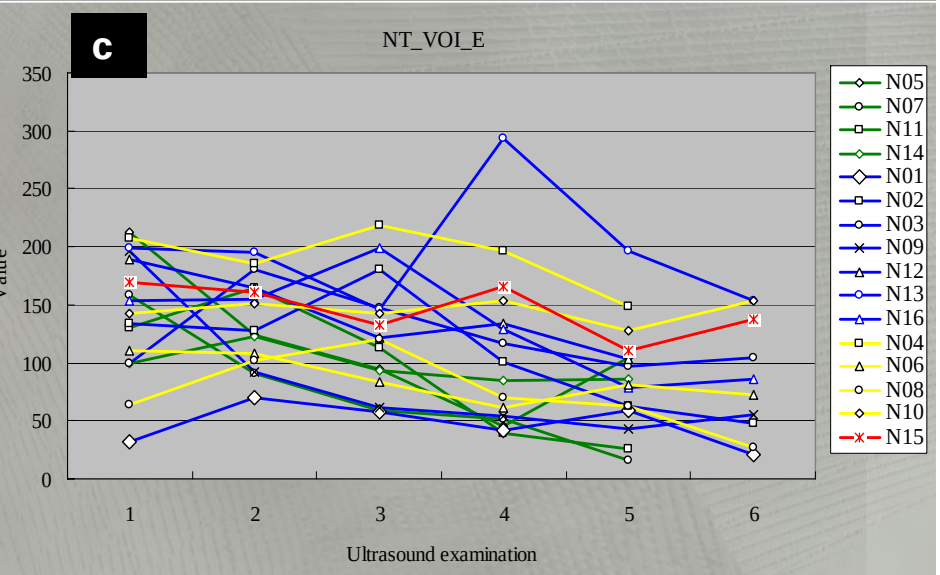
—&— the responder
—&— the non-responder

Results (2/5)

Image Video Processing Laboratory



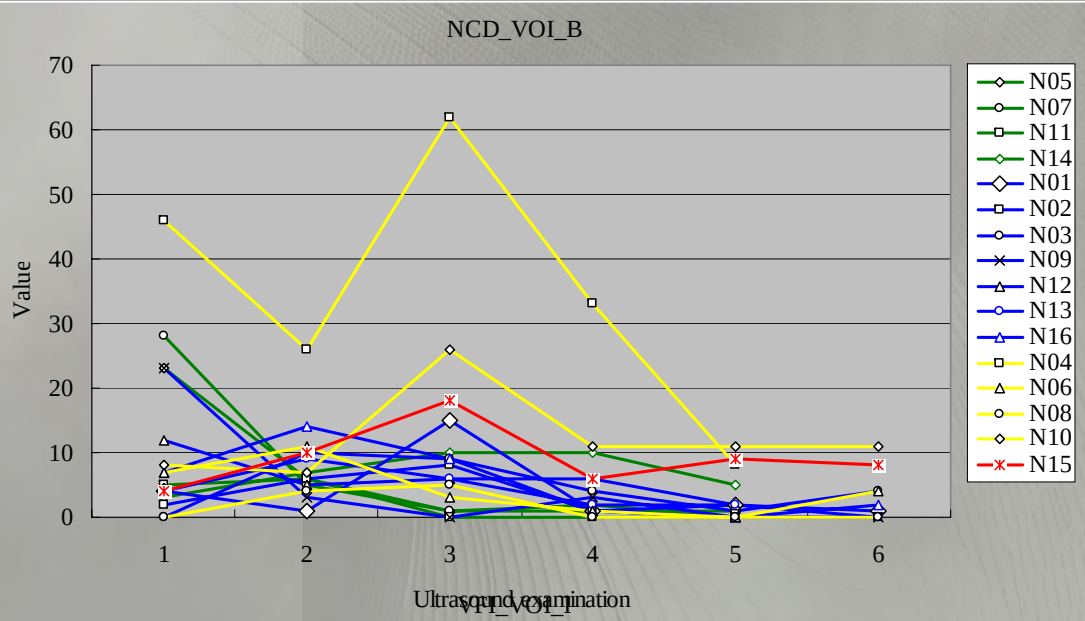




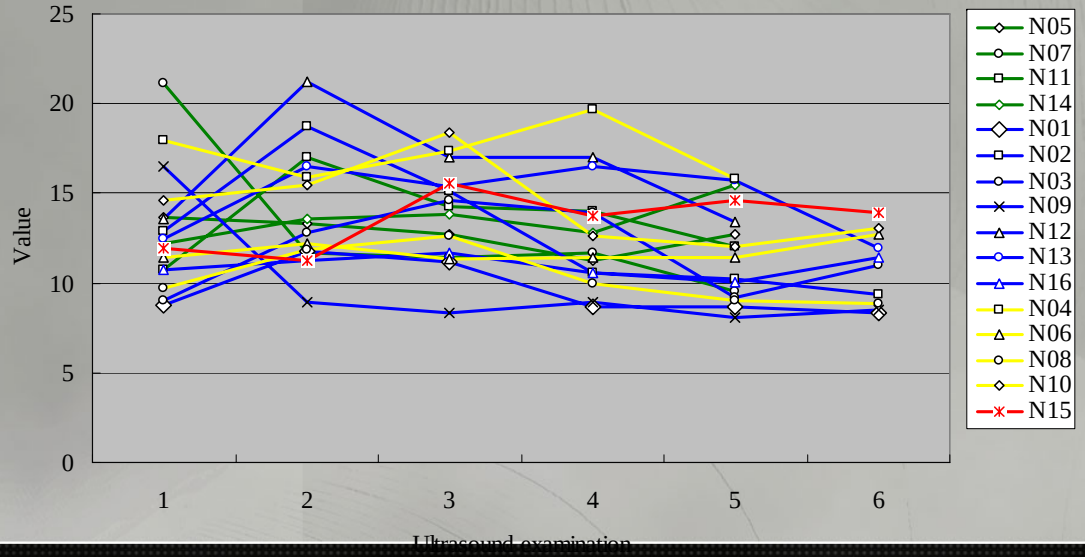
The value of NT (number of vascular centre-lines) of 3D HDF Doppler ultrasound imaging during the six ultrasound examinations: (a) inside VOI, (b) VOI boundary, (c) entire VOI.

—&— the responder
—&— the non-responder

Results (3/5)



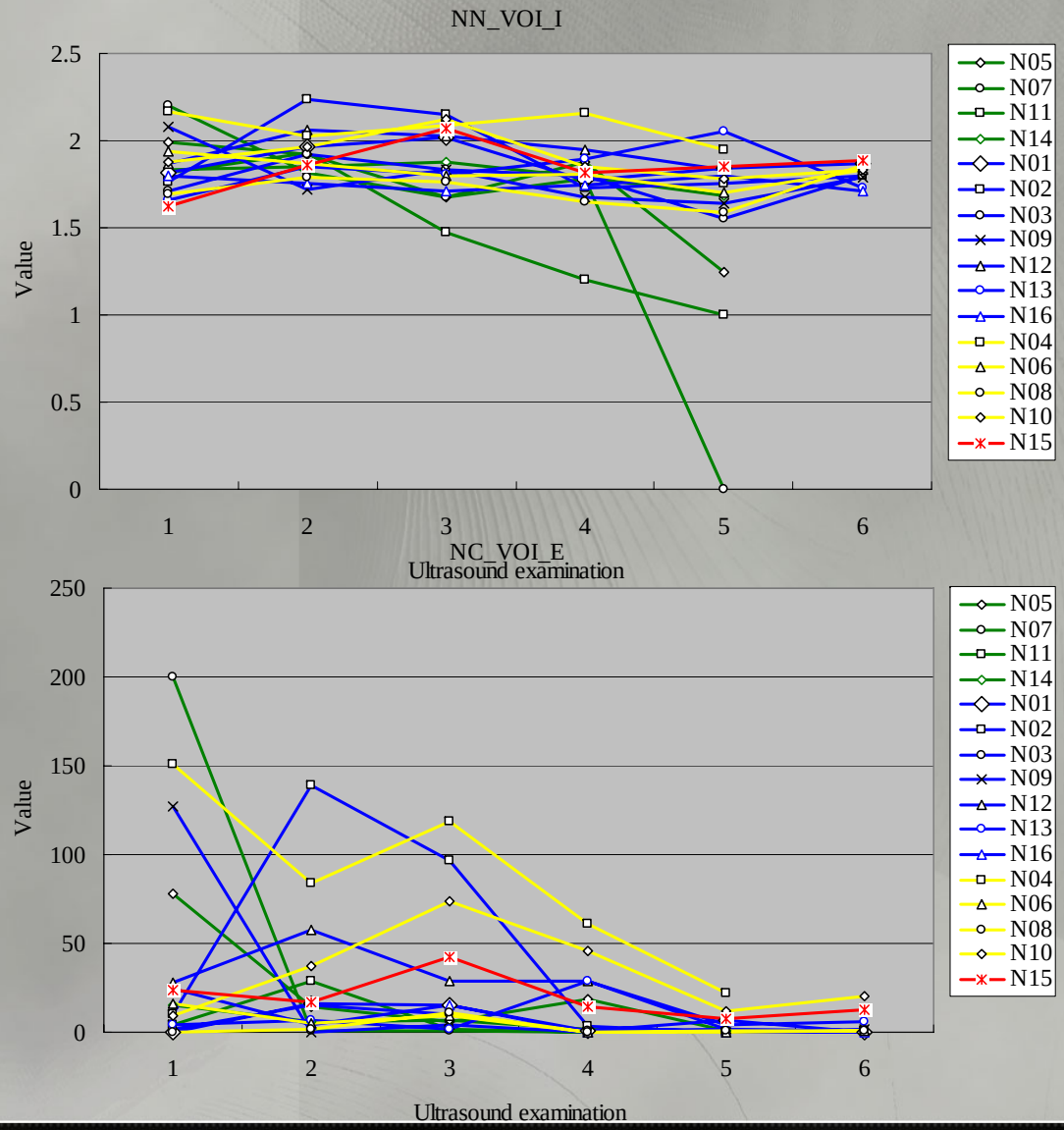
The value of FDC (frequency of direction changes in vascular centre-lines) of 3D HDF Doppler ultrasound imaging examinations: VOI boundary



The value of VFI (vascularization flow index) of 3D HDF Doppler ultrasound imaging examinations: VOI boundary

—&— the responder
—&— the non-responder

Results (4/5)



The value of NN (average number of neighbors for all points of vascular centre-lines) of 3D HDF Doppler ultrasound imaging during the six ultrasound examinations: inside VOI

The value of NC (number of cycles of vascular centre-lines) in the entire VOI of 3D HDF Doppler ultrasound imaging : entire VOI

Results (5/5)

- The results indicated
  - VI, NT, LV, NB, FI, FDC and PDM that extracted from all the three regions would be potential early predictors for good responses to neo-adjuvant chemotherapy
  - NN and AFDC within the VOI area, VFI on the boundary area and NC from the entire volume area were beneficial as well

Conclusions

- This study evaluated vascularity morphology from the cases of the neo-adjuvant chemotherapy using 3D HDF Doppler ultrasound imaging.
- The tendencies and peaks of the vascularization indices might be useful information for physicians to prognose the effect of chemotherapy treatments.
- Early prediction of the effect of neo-adjuvant chemotherapy could decrease the unnecessary treatments for patients.

Thank you for your attention !