2010年2月25日(木曜日)
多地点WEB CONFERENCE

Luminals乳癌の治療を考える

浜松オンコロジーセンター
腫瘍内科　渡辺　亨
http://www.oncoloplan.com/

Case for Discussion (1)
31才 閉経前未婚女性

- 右乳癌　T2 N0 M0 stage IIA
- 乳房温存術＋センチネルリンパ節生検
- 浸潤性乳管癌, ly (-), v (-), SLN 陰性
  - t: 12×16　mm
  - grade 1
  - ER: 陽性　(染色陽性割合90%以上)
  - PgR: 陽性 (染色陽性割合90%以上)
  - HER2: 陰性

2

Case for Discussion
抗がん剤の選択は　？

1. 抗がん剤は使用しない
2. CMF 6サイクル
3. UFT　2年間内服
4. AC 4サイクル
5. AC → weekly paclitaxel (80mg/m^2)
6. TC (docetaxel + cyclophosphamide)

3

Case for Discussion
ホルモン剤の選択は？

1. TAM　5年間
2. TAM　5年間＋LH-RH agonist 2年
3. TAM　5年間＋LH-RH agonist 5年
4. AI　5年間＋LH-RH agonist 5年
5. その他

4

微小転移の存在する可能性が高い患者

.II·

再発リスクの高い患者

10th International Conference on Primary Therapy of Breast Cancer (2007)

低リスク	●腋窩リンパ節転移陰性で以下のすべてを充たす症例 病理学的腫瘍径2cm以下 グレード　1 腫瘍周囲の**広域な**脈管浸潤がない HER2タンパク過剰発現/遺伝子増幅がない **ER and/or PgR 発現あり** 年令　35才以上
中間リスク	●腋窩リンパ節転移陰性で以下の一つ以上を充たす症例 病理学的腫瘍径2cmを超える グレード　2,3 腫瘍周囲の**広域な**脈管浸潤がある HER2タンパク過剰発現/遺伝子増幅がある **ER and PgR 発現なし** 年令　35才未満 ●腋窩リンパ節転移1-3個陽性 **ER and/or PgR 発現あり かつ** HER2タンパク過剰発現/遺伝子増幅がない
高リスク	●腋窩リンパ節転移1-3個陽性 **ER and PgR 発現なし、または** HER2タンパク過剰発現/遺伝子増幅がある ●腋窩リンパ節転移４個以上

10th International Conference on Primary Therapy of Breast Cancer (2007)

低リスク

●腋窩リンパ節転移陰性で以下のすべてを充たす症例

- 病理学的腫瘍径2cm以下
- グレード　1
- 腫瘍周囲の広域な脈管浸潤がない
- HER2タンパク過剰発現/遺伝子増幅がない
- ER and/or PgR 発現あり
- 年令　35才以上

中間リスク

●腋窩リンパ節転移陰性で以下の一つ以上を充たす症例

- 病理学的腫瘍径2cmを超える
- グレード　2,3
- 腫瘍周囲の広域な脈管浸潤がある
- HER2タンパク過剰発現/遺伝子増幅がある
- ER and PgR 発現なし
- 年令　35才未満

●腋窩リンパ節転移1-3個陽性
ER and/or PgR 発現あり かつ HER2タンパク過剰発現/遺伝子増幅がない

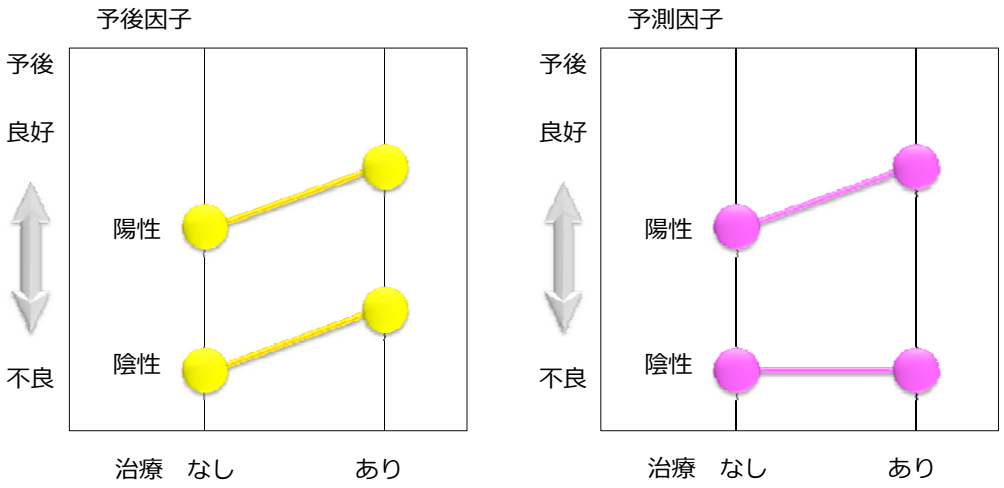
高リスク

●腋窩リンパ節転移1-3個陽性
ER and PgR 発現なし、または HER2タンパク過剰発現/遺伝子増幅がある

●腋窩リンパ節転移４個以上

予後因子
予測因子

予後因子と予測因子

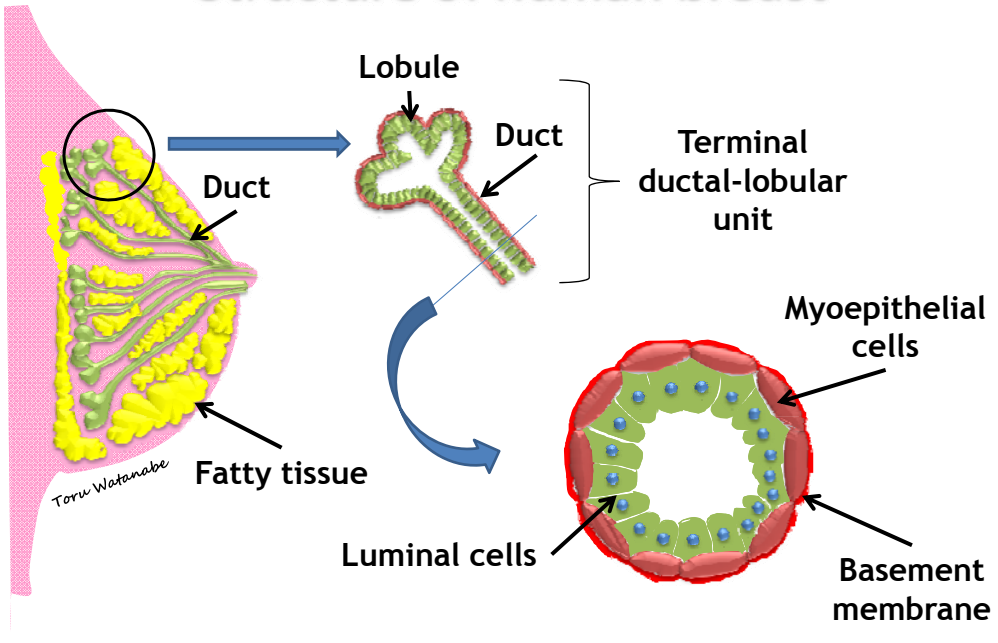


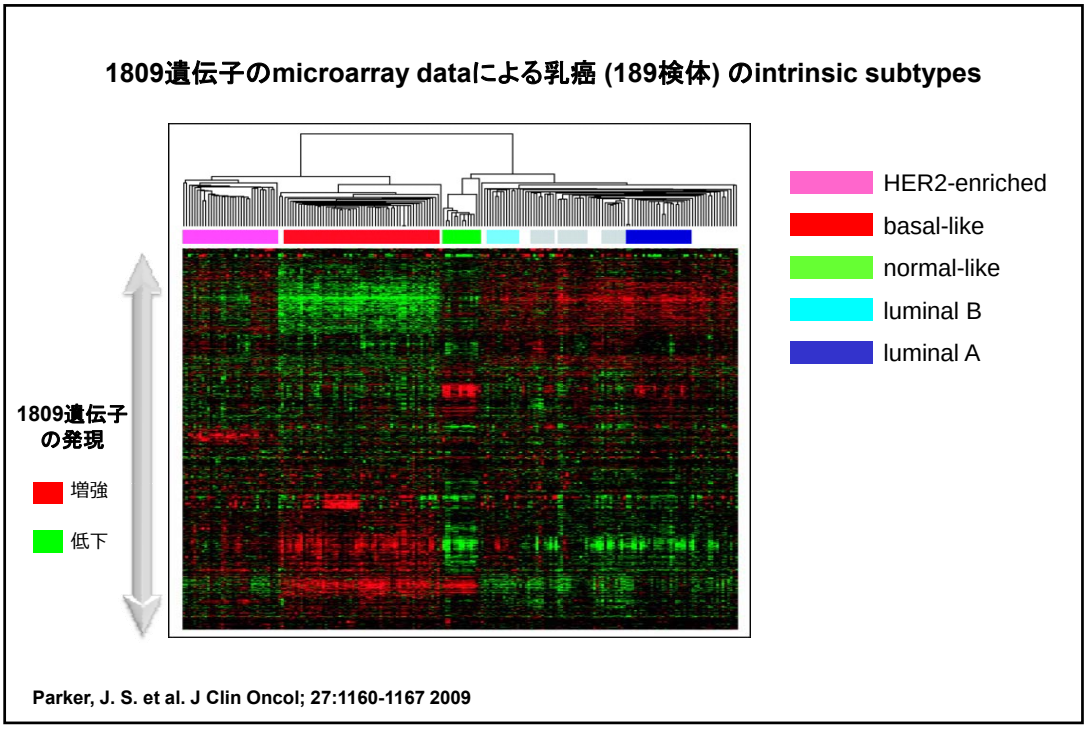
古典的アプローチ
乳腺腫瘍の組織学的分類

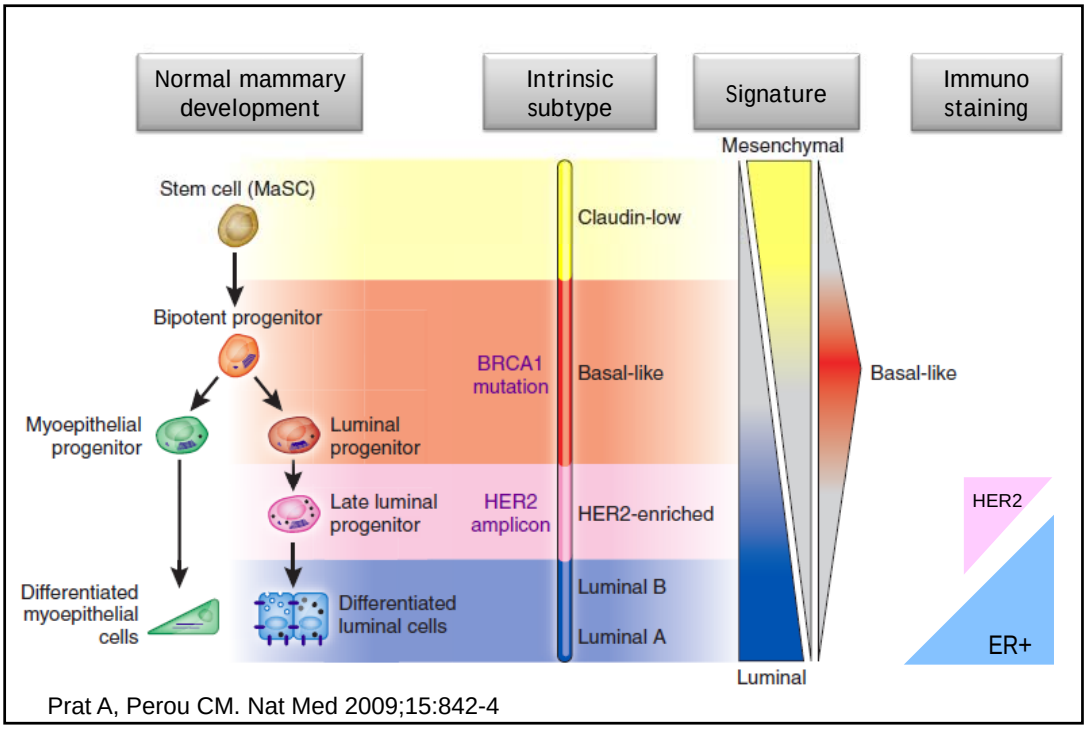
I. 上皮性腫瘍
- A. 良性
  - 1. 乳管内乳頭腫
  - 2. 乳頭部腺腫
- B. 悪性（癌腫）
  - 1. 非浸潤癌
    - a. 非浸潤性乳管癌
    - b. 非浸潤性小葉癌
  - 2. 浸潤癌
    - a. 浸潤性乳管癌
      - a1. **乳頭腺管癌**
      - a2. **充実腺管癌**
      - a3. **硬癌**
    - b. 特殊型
      - b1. 粘液癌
      - b2. 髄様癌
      - b3. 浸潤性小葉癌
      - b4. 腺様嚢胞癌
      - b5. 扁平上皮癌
      - b6. 紡錘細胞癌
      - b7. アポクリン癌
      - b8. 骨・軟骨化生を伴う癌
      - b9. 管状癌
      - b10. 分泌癌（若年性癌）
      - b11. その他
  - 3. Paget病

9

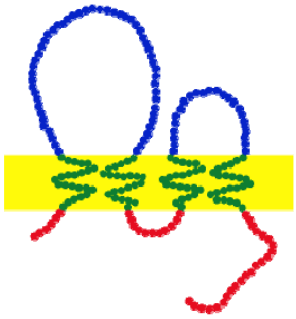
Structure of human breast



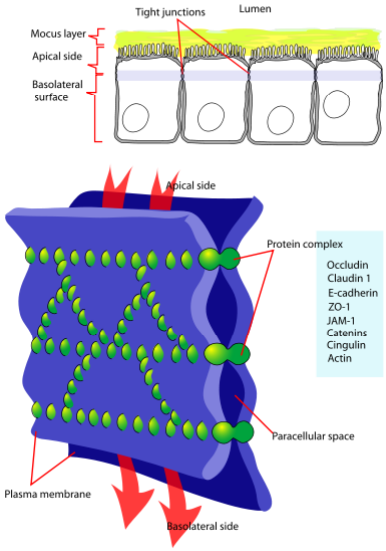

1809遺伝子のmicroarray dataによる乳癌 (189検体) のintrinsic subtypes
1809遺伝子の発現
増強
低下
HER2-enriched
basal-like
normal-like
luminal B
luminal A
Parker, J. S. et al. J Clin Oncol; 27:1160-1167 2009


Normal mammary development
Intrinsic subtype
Signature
Immuno staining
Mesenchymal
Stem cell (MaSC)
Claudin-low
Bipotent progenitor
BRCA1 mutation
Basal-like
Basal-like
Myoepithelial progenitor
Luminal progenitor
Late luminal progenitor
HER2 amplicon
HER2-enriched
HER2
Differentiated myoepithelial cells
Differentiated luminal cells
Luminal B
Luminal A
ER+
Luminal
Prat A, Perou CM. Nat Med 2009;15:842-4

What is Claudin ?



ある程度分化した上皮細胞で細胞間の接着に関与する膜タンパク
Claudin 1 - 24



13

術後薬物療法の選択

予後因子
予測因子診断

組織診断
グレード
腫瘍浸潤径
脈管浸潤
腋窩リンパ節転移
ER陽性細胞割合
HER2過剰発現
Ki-67

luminal A → Endocrine therapy

luminal B → Endocrine therapy ＋ TC or UFT

HER2-enriched → Trastuzumab ＋ EC±paclitaxel

basal-like → EC⇨paclitaxel

Luminal A/B 症例における化学療法追加の閾値

	化学療法追加		内分泌療法単独
グレード	3	2	1
増殖指標（Ki67)	高い	中程度	低い
ER,PgR陽性割合	低い		高い
腋窩リンパ節転移	4 個以上	1-3 個	陰性
腫瘍周囲脈管浸潤	広汎		なし
病理学的浸潤径	> 5cm	2.1 - 5.0 cm	≤ 2cm
患者の意向	利用可能な治療希望		化療の副作用は避けたい
遺伝子発現解析	高スコア		低スコア

Case for Discussion (2)
57才 閉経後女性

- 乳房腫瘤を自己発見
- 左D領域乳癌 T2 (2.2 cm) N0 M0 stage IIA
- 乳房全摘術＋SLNB (1/4)→ 腋窩郭清 (1/15)
- 浸潤性乳管癌（充実腺管癌）
  - t: 30 x 20 x 15 mm
  - grade 3
  - ER: 陽性細胞割合 40 %
  - PgR: 陽性細胞割合 5 %
  - HER2: IHC 2+ FISH 1.1X (陰性）
- 有効な治療なら副作用はいとわない

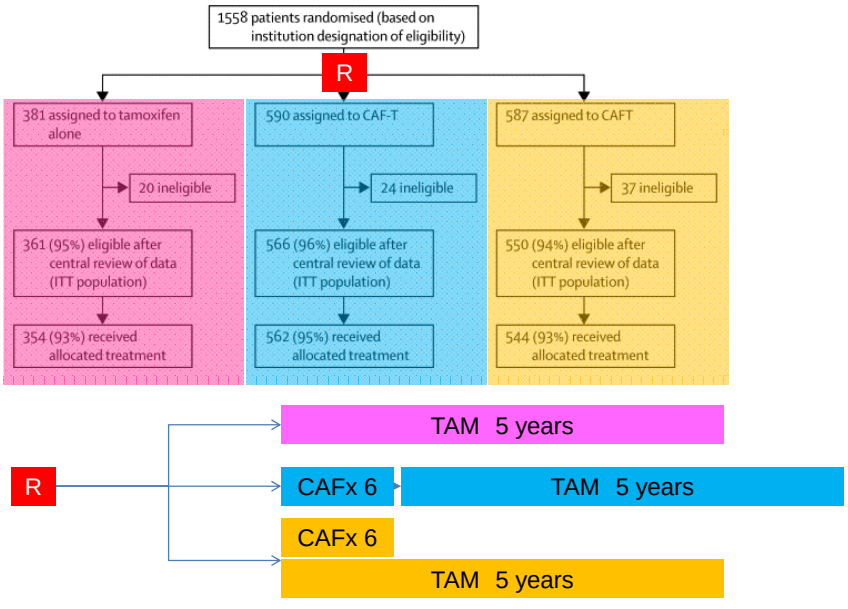
Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial

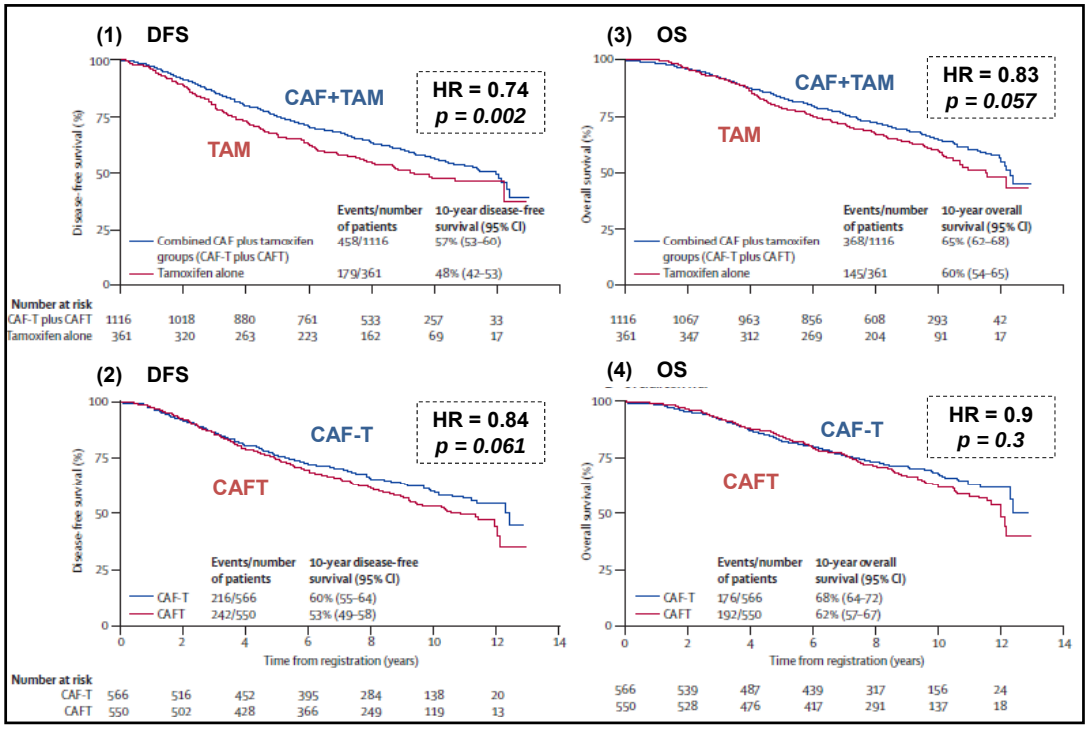
1558 patients
June, 1989 ~ July, 1995.

Kathy Albain

Albain KS et al. The Lancet 374:2055,2009

INT-0100

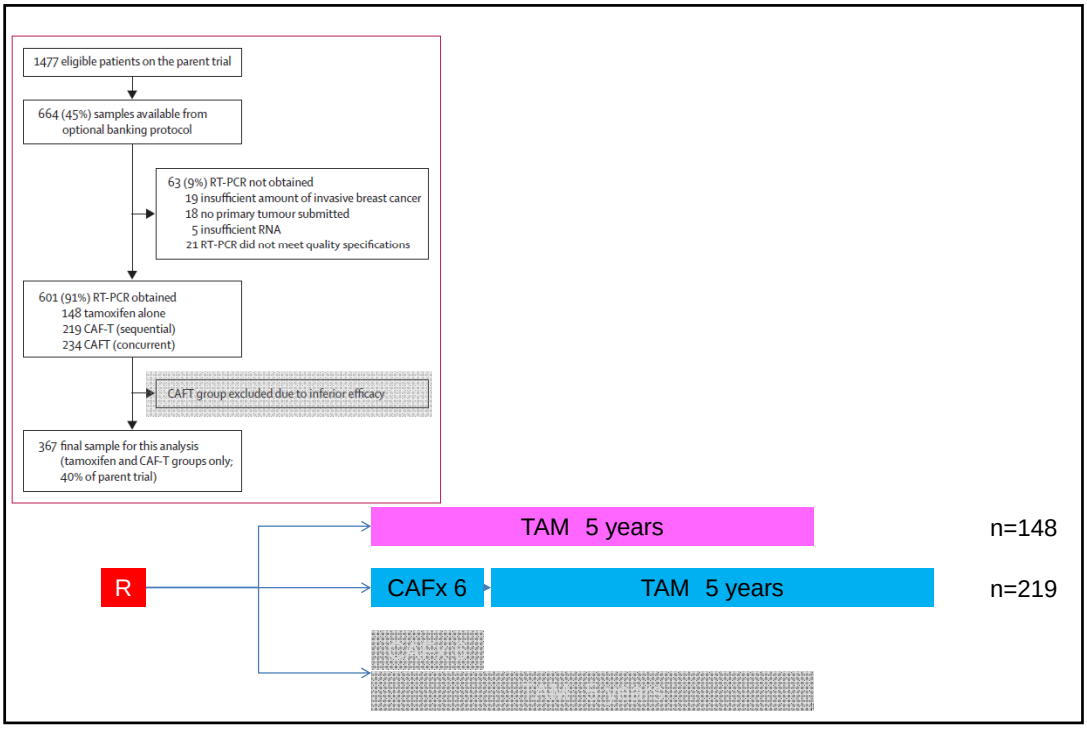


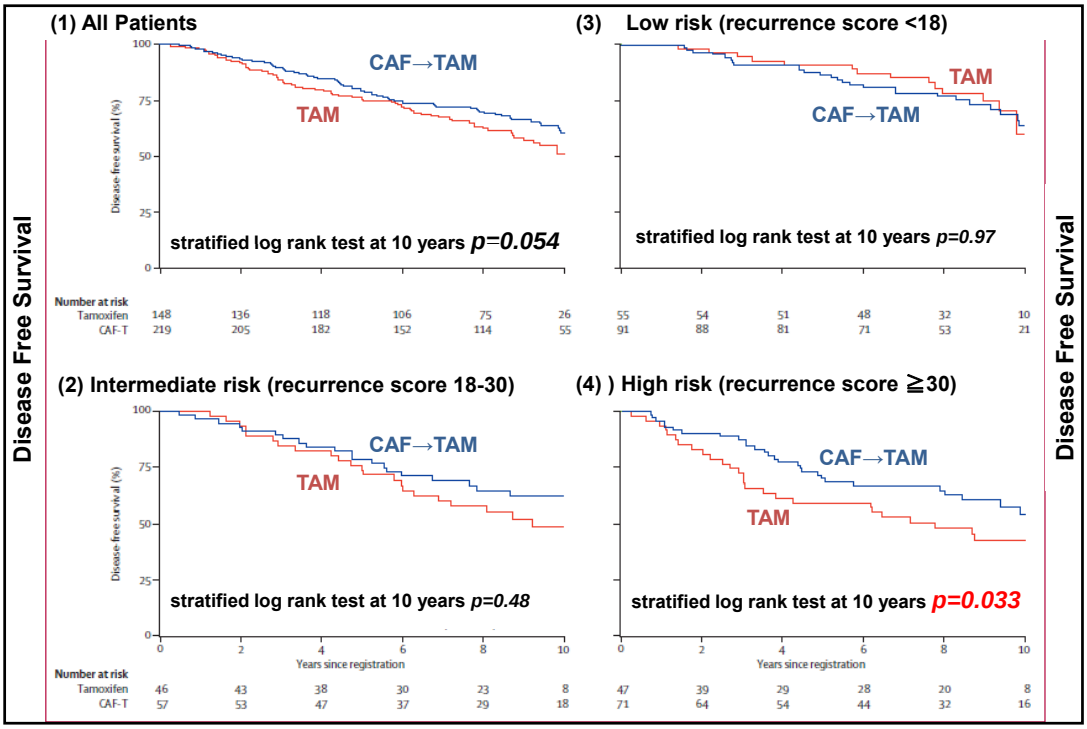


Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial

Albain KS et al. Lancet Oncology, 11:55, 2010

Kathy Albain


1477 eligible patients on the parent trial
664 (45%) samples available from optional banking protocol
63 (9%) RT-PCR not obtained
19 insufficient amount of invasive breast cancer
18 no primary tumour submitted
5 insufficient RNA
21 RT-PCR did not meet quality specifications
601 (91%) RT-PCR obtained
148 tamoxifen alone
219 CAF-T (sequential)
234 CAFT (concurrent)
CAFT group excluded due to inferior efficacy
367 final sample for this analysis (tamoxifen and CAF-T groups only; 40% of parent trial)
R
TAM 5 years
n=148
CAFx 6
TAM 5 years
n=219


(1) All Patients
CAF→TAM
TAM
stratified log rank test at 10 years p=0.054
(3) Low risk (recurrence score <18)
TAM
CAF→TAM
stratified log rank test at 10 years p=0.97
(2) Intermediate risk (recurrence score 18-30)
CAF→TAM
TAM
stratified log rank test at 10 years p=0.48
(4)) High risk (recurrence score ≧30)
CAF→TAM
TAM
stratified log rank test at 10 years p=0.033
Disease Free Survival
Disease-free survival (%)
Years since registration
Number at risk
Tamoxifen 148 136 118 106 75 26 | 55 54 51 48 32 10
CAF-T 219 205 182 152 114 55 | 91 88 81 71 53 21
Tamoxifen 46 43 38 30 23 8 | 47 39 29 28 20 8
CAF-T 57 53 47 37 29 18 | 71 64 54 44 32 16

ホルモン低感受性閉経後乳がん

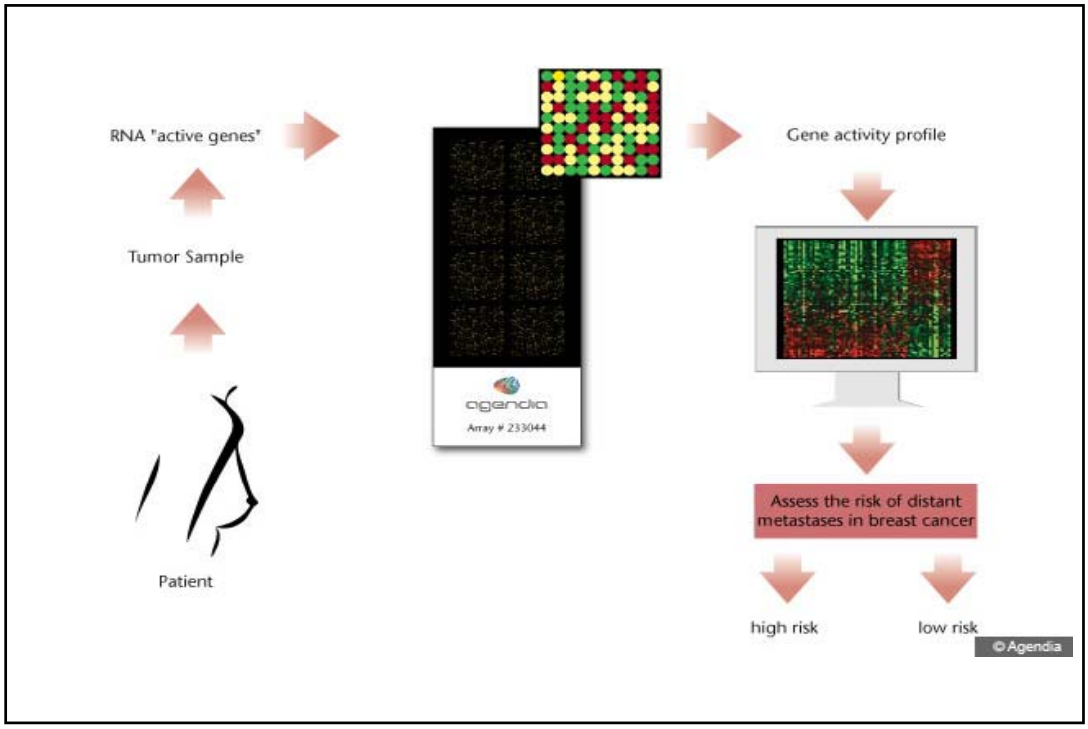
AC
or
CAF
or
EC
or
TC

→ AI 5年

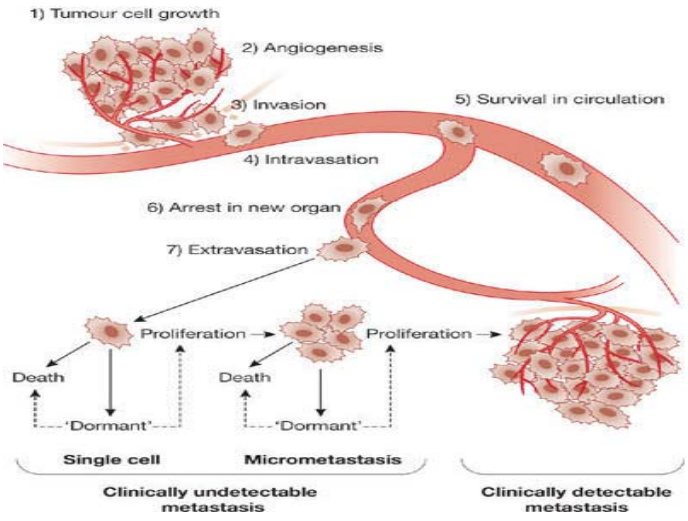
Table 1. Commercially Available Genomic Assays for the Prediction of Clinical Outcome in Patients with Breast Cancer.*

Variable	MammaPrint	Oncotype DX	Theros	MapQuant Dx
Provider	Agendia	Genomic Health	Biotheranostics	Ipsogen
Type of assay	70-Gene assay	21-Gene recurrence score	2-Gene ratio of HOXB13 to IL17R (H/I) and molecular-grade index	Genomic grade
Type of tissue sample	Fresh or frozen	Formalin-fixed, paraffin-embedded	Formalin-fixed, paraffin-embedded	Fresh or frozen
Technique	DNA microarrays	Q-RT-PCR	Q-RT-PCR	DNA microarrays
Centrally certified laboratory†	Yes	Yes	Yes	Yes
Indication	To aid in prognostic prediction in patients <61 yr of age with stage I or II, node-negative disease with a tumor size of ≤5 cm	To predict the risk of recurrence in patients with ER-positive, node-negative disease treated with tamoxifen; to identify patients with a low risk of recurrence who may not need adjuvant chemotherapy	To stratify ER-positive patients into groups with a predicted low risk or high risk of recurrence and a predicted good or poor response to endocrine therapy	To restratify grade 2 tumors into low-risk grade 1 or high-risk grade 3 tumors, specifically for invasive, primary, ER-positive grade 2 tumors
Level of evidence (I–V)‡	III	II	III	III
FDA clearance	Yes	No	No	No
Availability	Europe and United States	Europe and United States	United States	Europe

* ER denotes estrogen receptor, FDA Food and Drug Administration, and Q-RT-PCR quantitative reverse-transcriptase–polymerase chain reaction.
† Laboratories were certified according to the criteria of the Clinical Laboratory Improvement Amendments or by the International Organization for Standardization.
‡ Levels of evidence are measured on a scale ranging from I (strongest) to V (weakest).[54]



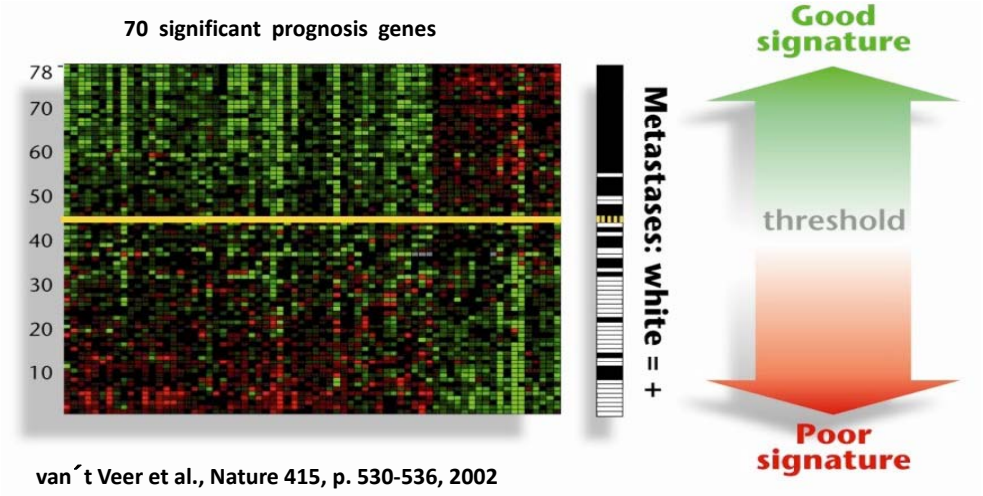
MammaPrint 70 genes are involved in all aspects of tumor cell biology



MammaPrint prognosis Profile

"the 70 gene profile"

70 significant prognosis genes



van´t Veer et al., Nature 415, p. 530-536, 2002

threshold set at 10% false negatives
91 % sensitivity, 73% specificity

The New England Journal of Medicine

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VOLUME 347 DECEMBER 19, 2002 NUMBER 25

A GENE-EXPRESSION SIGNATURE AS A PREDICTOR OF SURVIVAL IN BREAST CANCER

MARC J. VAN DE VIJVER, M.D., PH.D., YUDONG D. HE, PH.D., LAURA J. VAN 'T VEER, PH.D., HONGYUE DAI, PH.D., AUGUSTINUS A.M. HART, M.SC., DOREN W. VOSKUIL, PH.D., GEORGE J. SCHREIBER, M.SC., JOHANNES L. PETERSE, M.D., CHRIS ROBERTS, PH.D., MATTHEW J. MARTON, PH.D., MARK PARRISH, DOUWE ATSMA, ANKE WITTEVEEN, ANNUSKA GLAS, PH.D., LEONIE DELAHAYE, TONY VAN DER VELDE, HARRY BARTELINK, M.D., PH.D., SJOERD RODENHUIS, M.D., PH.D., EMIEL T. RUTGERS, M.D., PH.D., STEPHEN H. FRIEND, M.D., PH.D., AND RENÉ BERNARDS, PH.D.

ABSTRACT

Background A more accurate means of prognostication in breast cancer will improve the selection of patients for adjuvant systemic therapy.

Methods Using microarray analysis to evaluate our previously established 70-gene prognosis profile, we classified a series of 295 consecutive patients with primary breast carcinomas as having a gene-expression signature associated with either a poor prognosis or a good prognosis. All patients had stage I or II breast cancer and were younger than 53 years old; 151 had lymph-node–negative disease, and 144 had lymph-node–positive disease. We evaluated the predictive power of the prognosis profile using univariable and multivariable statistical analyses.

Results Among the 295 patients, 180 had a poor-prognosis signature and 115 had a good-prognosis signature, and the mean (±SE) overall 10-year survival rates were 54.6±4.4 percent and 94.5±2.6 percent, respectively. At 10 years, the probability of remaining free of distant metastases was 50.6±4.5 percent in the group with a poor-prognosis signature and 85.2±4.3 percent in the group with a good-prognosis signature. The estimated hazard ratio for distant metastases in the group with a poor-prognosis signature, as compared with the group with the good-prognosis signature, was 5.1 (95 percent confidence interval, 2.9 to 9.0; P<0.001). This ratio remained significant when the groups were analyzed according to lymph-node status. Multivariable Cox regression analysis showed that the prognosis profile was a strong independent factor in predicting disease outcome.

Conclusions The gene-expression profile we studied is a more powerful predictor of the outcome of disease in young patients with breast cancer than standard systems based on clinical and histologic criteria. (N Engl J Med 2002;347:1999-2009.)

Copyright © 2002 Massachusetts Medical Society.

ADJUVANT systemic therapy substantially improves disease-free and overall survival in both premenopausal and postmenopausal women up to the age of 70 years with lymph-node–negative or lymph-node–positive breast cancer.[1,2] It is generally agreed that patients with poor prognostic features benefit the most from adjuvant therapy.[3,4] The main prognostic factors in breast cancer are age, tumor size, status of axillary lymph nodes, histologic type of the tumor, pathological grade, and hormone-receptor status. A large number of other factors have been investigated for their potential to predict the outcome of disease, but in general, they have only limited predictive power.[5]

Using complementary DNA (cDNA) microarrays to analyze breast-cancer tissue, Perou et al. identified tumors with distinct patterns of gene expression that they termed "basal type" and "luminal type."[6] These subgroups differ with respect to the outcome of disease in patients with locally advanced breast cancer.[7] In addition, microarray analysis has been used to distinguish cancers associated with *BRCA1* or *BRCA2* mutations[8,9] and to determine estrogen-receptor status[9,10] and lymph-node status.[11,12]

Using inkjet-synthesized oligonucleotide microarrays, we recently identified a gene-expression profile

From the Division of Diagnostic Oncology (M.J.V., L.J.V., D.W.V., H.L.P., D.A., A.W., A.G., L.D.), Radiotherapy (A.A.M.H., H.B.), Medical Oncology (S.R.), Biometrics (T.V.), Surgical Oncology (E.T.R.), and Molecular Carcinogenesis (R.B.), Netherlands Cancer Institute, Amsterdam; the Center for Biomedical Genetics, Amsterdam (R.B.); and Rosetta Inpharmatics, Kirkland, Wash. (Y.D.H., H.D., G.J.S., C.R., M.J.M., M.P., S.H.F.). Address reprint requests to Dr. Bernards at the Division of Molecular Carcinogenesis, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands, or at r.bernards@nki.nl.

Drs. van de Vijver, He, and van 't Veer contributed equally to this article.

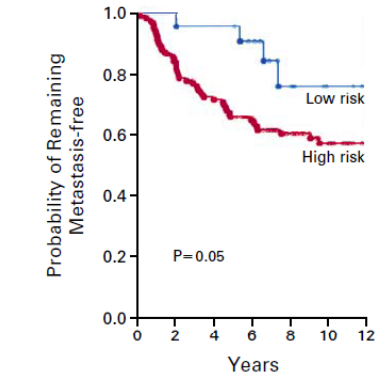
N Engl J Med, Vol. 347, No. 25 · December 19, 2002 · www.nejm.org · 1999

Van de Vijver et al. (2002)

New England J. Med. 347, 1999-2009

MammaPrint による予後予測性の改善
n=151

St Gallen Criteria

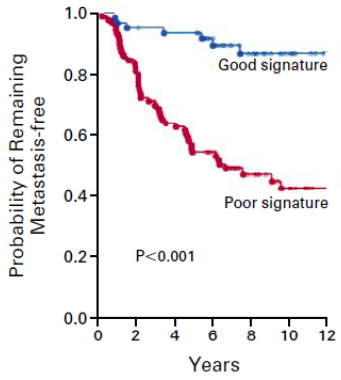


No. at Risk

Low risk	22	22	21	17	9	5	2
High risk	129	107	88	69	48	34	19

15% low risk
85% high risk

MammaPrint



No. at Risk

Good signature	60	57	54	45	31	22	12
Poor signature	91	72	55	41	26	17	9

40% good signature
60% poor signature

がん治療パラダイムの二段階シフト

古典的病理診断 → 非選択的薬剤選択

1

病型分類 （予後因子、予測因子）の明確化 → 薬剤選択の集団的個別化

2

個別特性 （遺伝子発現）の明確化 → 薬剤選択の個別的個別化

渡辺 亨 twatanab@oncoloplan.com