第16回たちてんウェブカン

Ki67の再現性と有用性に関する検討

相良病院
乳腺科 相良安昭　病理診断科 大井恭代

ER陽性・HER2陰性患者における化学療法の適応を決める臨床病理学的特徴

	化学・内分泌療法の相対的適応	決定に役立たない因子	内分泌療法単独の相対的適応
ER・PgR	低い陽性率		高い陽性率
組織学的グレード	グレード3	グレード2	グレード1
Ki 67	30%以上	20~30%	20%未満
腋窩リンパ節転移	≧4個	1～3個	なし
腫瘍周囲の脈管浸潤	広範である		広範でない
病理学的腫瘍径	＞5cm	2.1～5cm	≦2cm
患者の希望	使用可能な治療を全て希望		化学療法の副作用を避けたい
多遺伝子発現解析	高スコア	中スコア	低スコア

St. Gallen 2009
Goldhirsch, A., et al.：Ann. Oncol., 20, 1319-1329, 2009.

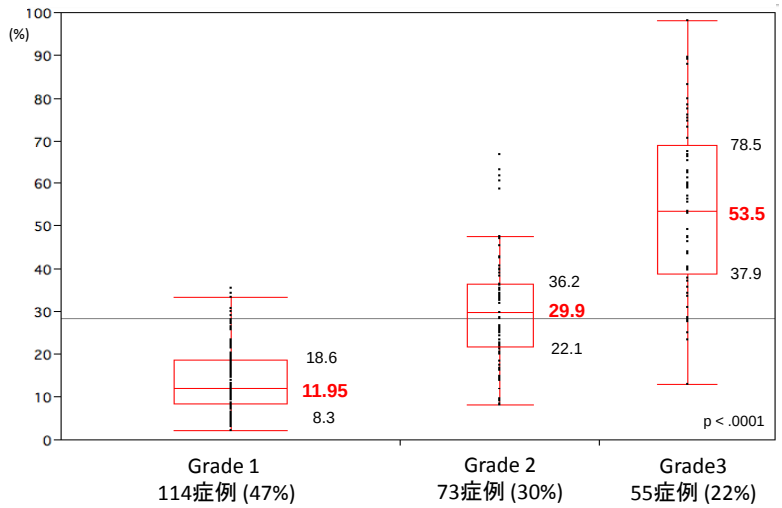
Ki 67の再現性と有用性に関する検討

- 当院データ
  - 化学療法の適応となるKi67 index値は？
- 予後予測となるか？
- 治療の効果予測となるか？
- 症例検討

2009年8月 ～ 2010年2月 242例 (術前薬物療法施行症例を除く)

当院のKI67 DATA

核異型度別のKi 67 Label index



- 核異型度とKi67は相関関係にあるが、Ki67のオーバーラップを認める
- Ki67を用いることで増殖能をより正確に測定出来る
- 当院において、Ki67 30% は核異型度2の中央値に相当する

当院のKi67染色率と 臨床試験との比較

当院

Ki 67 20%以下: 43%の症例

Ki67 13%以下: 30%の症例

	Patients, n	Treatment	Ki67 cut-off point, %	Patients with low Ki67 levels, %	Patients with node-negative tumours, %	Patients with ER+ tumours, %	MFU, months	Outcome	Statistical method
IBCSG Trials VIII (pre-menopausal)[49]	598	Goserelin vs CMF vs CMF+ Goserelin	19	59	100	79	120	DFS	CPHM with treatment by Ki67 interaction term
IBCSG Trials IX (post-menopausal)[49]	923	Tamoxifen vs CMF+ tamoxifen	19	52	100	79	120	DFS	CPHM with treatment by Ki67 interaction term
PACS01[51]	699	FEC vs FEC, followed by docetaxel	20	79	0	40	58·7	DFS	CPHM with biomarker by treatment interaction term
BCIRG 001[50]	1350	TAC vs FAC	<13	22	0	76	55	DFS, OS	CPHM
BR9601 trial[52]	307	CMF vs E-CMF	<13	59	13	54	48	OS, RFS	CPHM with treatment by marker interaction term
Viale G[52]	2685	Tamoxifen vs letrozole	≤11	53	39 (node negative or unknown)	100	51	DFS	CPHM with an interaction term between treatment and Ki67

染色割合が低い

当院と同じ程度の染色割合

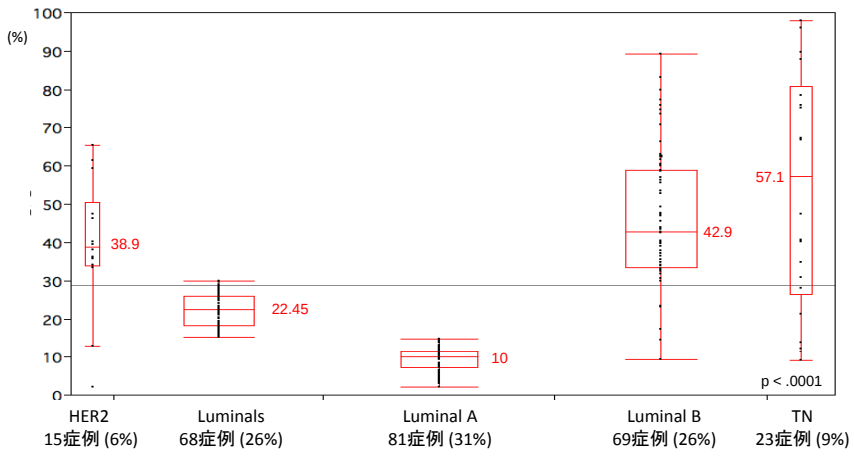
染色割合が低い

MIB-1 was used as an assay in all studies. ER=oestrogen receptor. MFU=median follow-up. IBCSG=International Breast Cancer Study Group. CMF=cy DFS=disease-free survival. CPHM=Cox proportional-hazards model. PgR=progesterone receptor. CT-E=Chemotherapy-endocrine treatment. FEC=fl BCIRG=Breast Cancer International Research Group. TAC=docetaxel, doxorubicin, and cyclophosphamide. FAC=fluorouracil, doxorubicin, and cyclop by CMF. RFS=relapse-free survival. T=tumour size.

Table 1: **Ki67 as a predictive marker in the adjuvant setting**

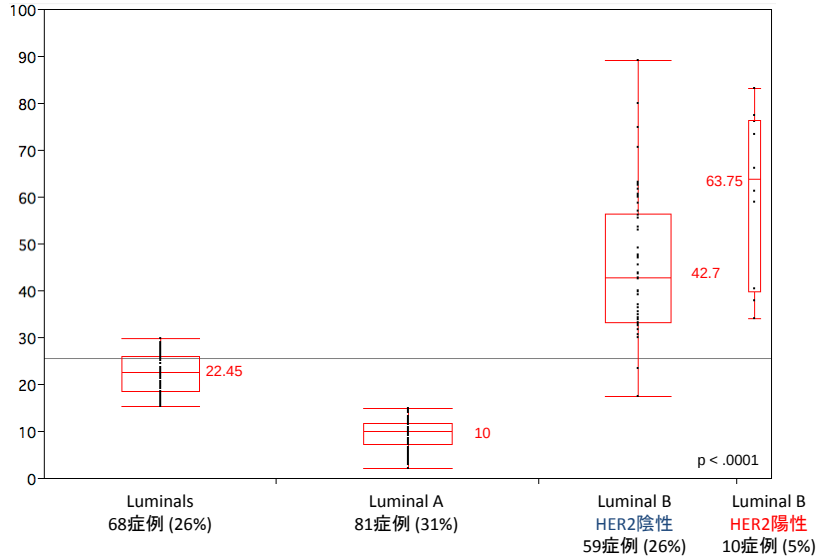
Lancet Oncol 2010; 11: 174–83

Subtype別のKi67 Label index



定義
Luminal A: ER > 1% and Ki67<15%
Luminal B: ER > 1% and (HER2陽性 or grade3 or Ki67>30%)
Luminals: 上記以外

ルミナルズのKi67 Label index



治療効果予測因子となるか？

大規模無作為化試験におけるKI67

PACS 01: Study Design

Stratification:
- Center
- Age: < or ≥ 50
- N: 1-3; ≥ 4

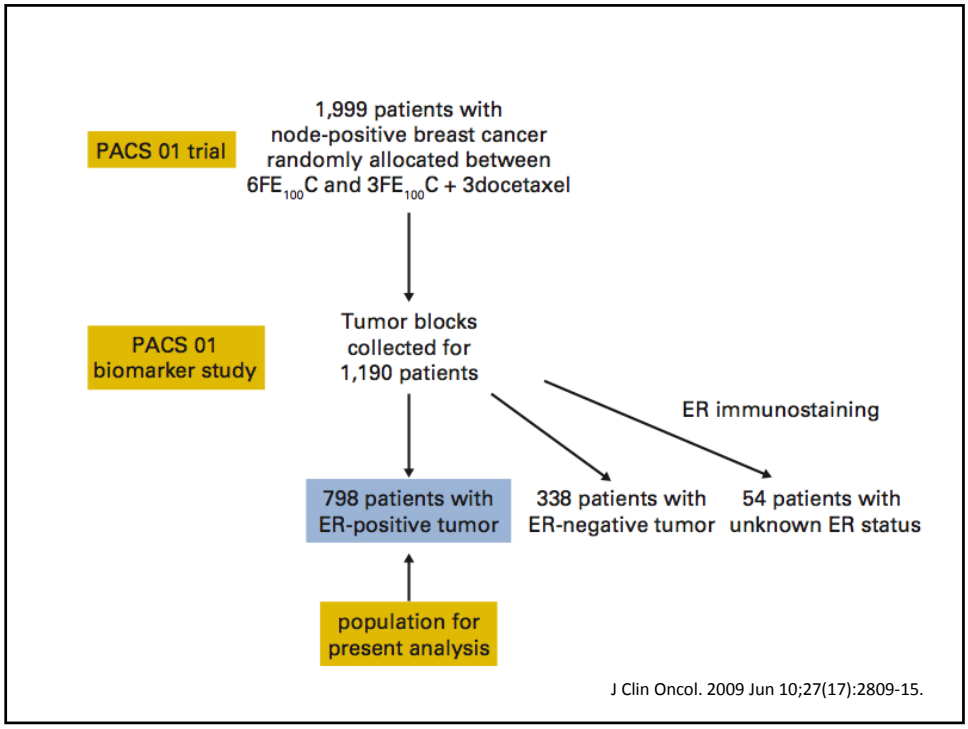
R

6 FEC100
Fluorouracil 500 mg/m² d1
Epirubicin 100 mg/m² d1
Cyclophosphamide 500 mg/m² d1
6 cycles q 21 d

3 FEC100 - 3 Taxotere
3 cycles of FEC 100 q 21 d followed by
3 cycles of Taxotere 100 mg/m² d1 q 21 d

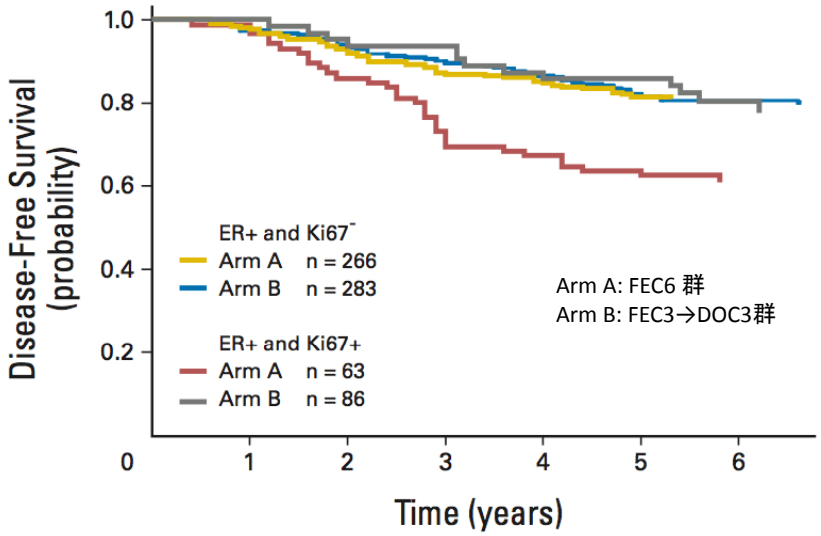
- Radiotherapy delivered within 4 wk after last chemotherapy cycle
- Tamoxifen 20 mg/d x 5 y for HR+ postmenopausal women after chemo

Roché et al. *Breast Cancer Res Treat.* 2004;88(suppl 1):S16. Abstract 27.



J Clin Oncol. 2009 Jun 10;27(17):2809-15.

Ki67別にみた各治療群のDFS



J Clin Oncol. 2009 Jun 10;27(17):2809-15.

Biomarker別にみたDocetaxelの効果

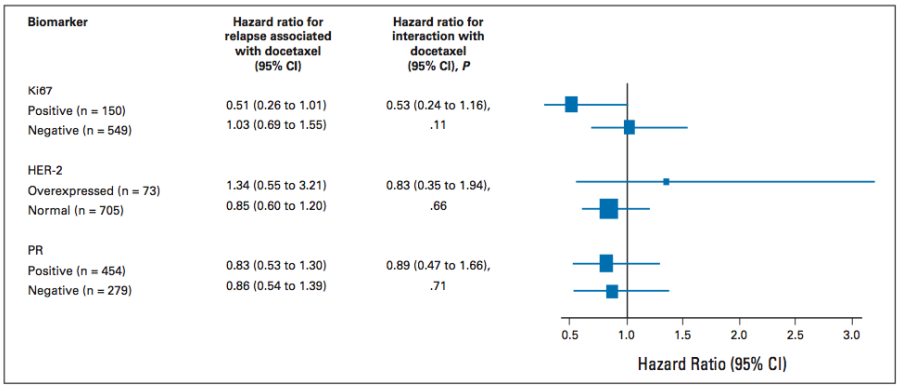
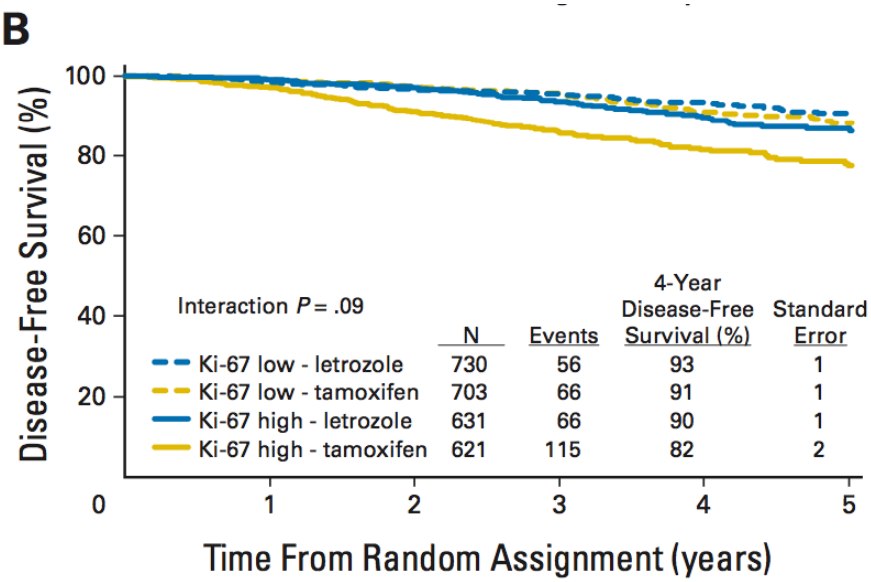
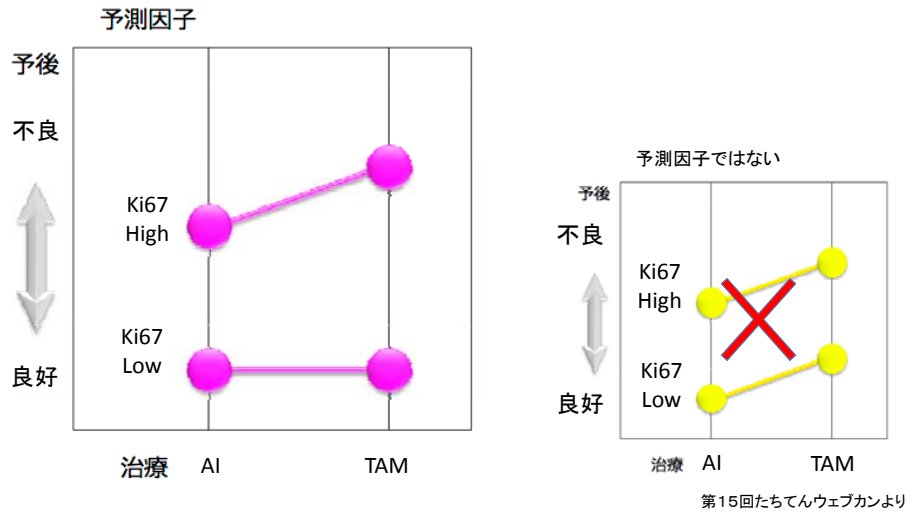


Fig 2. Forest plots showing hazard ratios associated with docetaxel according to biomarker expression. PR, progesterone receptor.

J Clin Oncol. 2009 Jun 10;27(17):2809-15.

Ki67別にみた各治療群のDFS
BIG 1-98: LET 5yr vs. TAM 5yr





第１５回たちてんウェブカンより

Ki67: AIやタキサンの治療効果予測因子
(かつ予後予測因子)

Review

Ki67 in breast cancer: prognostic and predictive potential

Rinat Yerushalmi, Ryan Woods, Peter M Ravdin, Malcolm M Hayes, Karen A Gelmon

Lancet Oncol 2010; 11: 174–83

Division of Medical Oncology (R Yerushalmi MD, R Woods MSc, K A Gelmon MD) and Department of Pathology (M M Hayes MD), British Columbia Cancer Agency, Vancouver, BC, Canada; and University of Texas, Health Sciences Center, San Antonio, TX, USA (P M Ravdin MD)

The leading parameters that define treatment recommendations in early breast cancer are oestrogen-receptor, progesterone-receptor, and human epidermal growth-factor status. Although some pathologists report Ki67 in addition to other biological markers, the existing guidelines of the American Society of Clinical Oncology do not include Ki67 in the list of required routine biological markers. The advent of new genetic tests has emphasised the role of proliferative genes, including Ki67, as prognostic and predictive markers. Additionally, randomised studies have retrospectively reviewed data and reported on the role of Ki67 in breast cancer. In light of new data, we have re-assessed evidence that could change guidelines to include Ki67 in the standard pathological assessment of early breast cancers. This review provides an update on the current knowledge on Ki67 and of the evidence in the published work about the prognostic and predictive role of this marker, and provides information on the laboratory techniques used to determine Ki67.

Lancet Oncol 2010; 11: 174–83

臨床試験におけるKi67と治療効果との関係

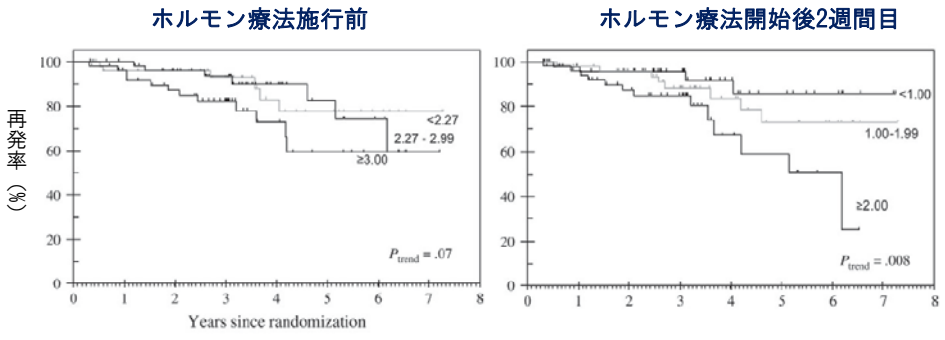
	Patients, n	Treatment	Ki67 cut-off point, %	Patients with low Ki67 levels, %	Patients with node-negative tumours, %	Patients with ER+ tumours, %	MFU, months	Outcome	Statistical method	Results
IBCSG Trials VIII (pre-menopausal)[49]	598	Goserelin vs CMF vs CMF+ Goserelin	19	59	100	79	120	DFS	CPHM with treatment by Ki67 interaction term	p value for Ki67-treatment interaction=0·90 (initial model) and 0·69 (in multivariate model adjusting for PgR, T, grade, and HER2)
IBCSG Trials IX (post-menopausal)[49]	923	Tamoxifen vs CMF+ tamoxifen	19	52	100	79	120	DFS	CPHM with treatment by Ki67 interaction term	High Ki67 subgroup: HR (CT-E vs tamoxifen)=1·03 (95% CI 0·73–1·45); low Ki67 subgroup: HR (CT-E vs tamoxifen)=0·86 (0·61–1·20); p value for Ki67-treatment interaction=0·45 (initial model), 0·41 (in multivariate model adjusting for PgR, T, grade, and HER2)
PACS01[51]	699	FEC vs FEC, followed by docetaxel	20	79	0	40	58·7	DFS	CPHM with biomarker by treatment interaction term	p value for Ki67-treatment interaction term=0·11 in multivariate model; trend towards patients with high Ki67 having a better response to treatment (high Ki67 subgroup HR=0·51 [95% CI 0·26–1·01]; low Ki67 subgroup 1·03 [0·69–1·55]).
BCIRG 001[50]	1350	TAC vs FAC	<13	22	0	76	55	DFS, OS	CPHM	Patients in the luminal B group showed a significant improvement in 3-year DFS favouring the taxane group (85·2% vs 79% for TAC vs FAC, respectively). HR 0·66 (95% CI 0·46–0·95; p=0·025); this apparent benefit of the taxane was not noted in the luminal A group (p=0·472).
BR9601 trial[52]	307	CMF vs E-CMF	<13	59	13	54	48	OS, RFS	CPHM with treatment by marker interaction term	p values (interaction): RFS=0·736, OS=0·249.
Viale G[53]	2685	Tamoxifen vs letrozole	≤11	53	39 (node negative or unknown)	100	51	DFS	CPHM with an interaction term between treatment and Ki67	High Ki67 subgroup—HR (letrozole vs tamoxifen)=0·53 (95% CI 0·39–0·72); low Ki67 subgroup—HR (letrozole vs tamoxifen)=0·81 (0·57–1·15); p value for Ki67-treatment interaction=0·09.

MIB-1 was used as an assay in all studies. ER=oestrogen receptor. MFU=median follow-up. IBCSG=International Breast Cancer Study Group. CMF=cyclophosphamide, methotrexate, and fluorouracil. DFS=disease-free survival. CPHM=Cox proportional-hazards model. PgR=progesterone receptor. CT-E=Chemotherapy-endocrine treatment. FEC=fluorouracil, epirubicin, and cyclophosphamide. HR=hazard ratio. BCIRG=Breast Cancer International Research Group. TAC=docetaxel, doxorubicin, and cyclophosphamide. FAC=fluorouracil, doxorubicin, and cyclophosphamide. OS=overall survival. E-CMF=epirubicin followed by CMF. RFS=relapse-free survival. T=tumour size.

Table 1: **Ki67 as a predictive marker in the adjuvant setting**

Lancet Oncol 2010; 11: 174–83

術前ホルモン治療におけるKi67
IMPACT trial



術前治療開始前よりも開始後2週間目の
Ki67値の方が予後と有意に相関

J Natl Cancer Inst 2007;99:167–70

症例 1

39歳　閉経前

手術: Bp + SLNB

病理結果：Invasive ductal carcinoma,

浸潤径25×23mm, 3mm, 5mm,　広がり：40mm

センチネルリンパ節転移陽性, n=1/8

ER: 50-90%, PgR: 50-90%, HER2:陰性

核異型度 2, Ki67: 34.3%, ly++, v-

術後治療は？

症例 2

53歳　閉経前

手術: Bp + Ax

病理結果：Invasive ductal carcinoma,

浸潤径18×15mm, 広がり20×15mm

n=1/20

ER: 0%, PgR: 0%, HER2:陰性

核異型度 2, Ki67: 20%, ly±, v-

術後治療は？

症例 3

65歳　閉経後

手術: Bp + SLNB

病理結果：Invasive ductal carcinoma,

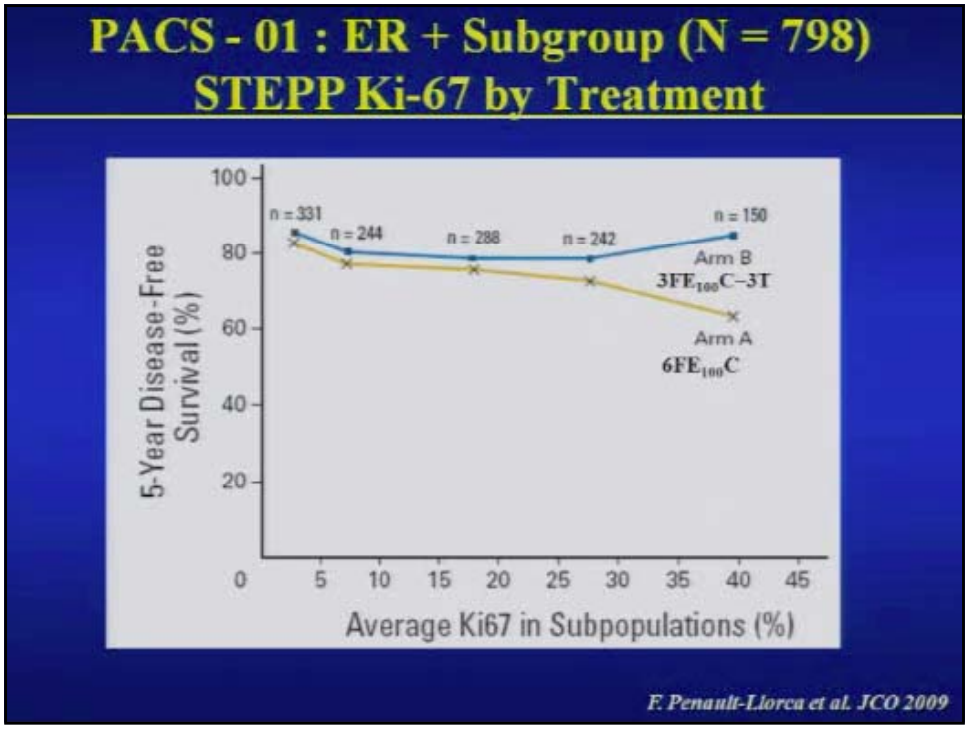
浸潤径12×10, 10×8mm, 乳管内進展なし

センチネルリンパ節転移陰性

ER: 1-10%, PgR: 0%, HER2:陰性

核異型度 3, Ki67: 67%, ly-, v-

術後治療は？



症例 4

42歳　閉経前

手術: Bp + SLNB

病理結果：Invasive ductal carcinoma,

浸潤径30×25mm, 乳管内進展なし

センチネルリンパ節転移陰性

ER: 90%以上, PgR: 90%以上, HER2:陰性

核異型度 3, Ki67: 53%, ly±, v-

術後治療は？

転移性乳癌におけるKi67と治療効果との関係

	Patients, n	Treatment	Cut-off point	Patients with low Ki67 levels, %	Patients with ER+ tumours, %	Site of metastases, %	Median follow-up, months	Outcome	Statistical method	Results
Nishimura[73]	74	Trastuzumab with or without chemotherapy	Three subgroups: ≤19%, 20–49%, ≥50%	NA	34	Liver, 51	44	TTP	Univariate and multivariate Cox proportional-hazards models	Univariate analysis—no evidence of an association with TTP; HR (Ki67 20–49% *vs* ≤19%)=2·05 (p=0·10); HR (Ki67 ≥50% *vs* ≤19%)=1·31 (p=0·65). Multivariate analysis—no associations reported
Yamashita[72]	73	Endocrine	Scoring 0–4	64	100	NA	74	Clinical response	χ^2 test examining association between response and Ki67	Response rates for patients who did or did not express Ki67 were 27% and 57%, respectively (p=0·024)
Kai[72]	53	Endocrine	Score 1–3; tumours with scores 2 and 3 were considered positive	33	91	Visceral metastases, 42	25	Time to endocrine therapy failure	Univariate and multivariate Cox proportional-hazards model	Univariate analysis—Ki67 status was associated with more rapid treatment failure (HR 2·3; p=0·047). Multivariate analysis—Ki67 not significant (p=0·16). Variables considered: P53, HER2, DFS, and RFET

MIB-1 was used as an assay in all studies except in the first study, where assay information was not available. ER+=oestrogen-receptor positive. NA=not available. TTP=Time to progression. HR=hazard ratio. DFS=disease-free survival. RFET=response to first-line endocrine therapy.

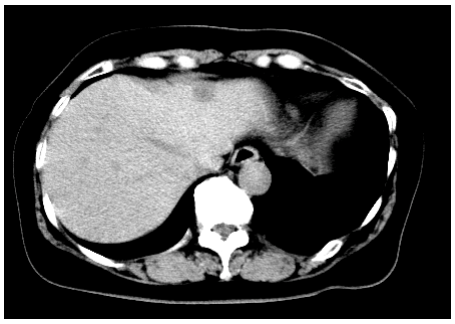
Table 3: Ki67 as a predictive marker in the metastatic setting

Lancet Oncol 2010; 11: 174–83

59歳 女性

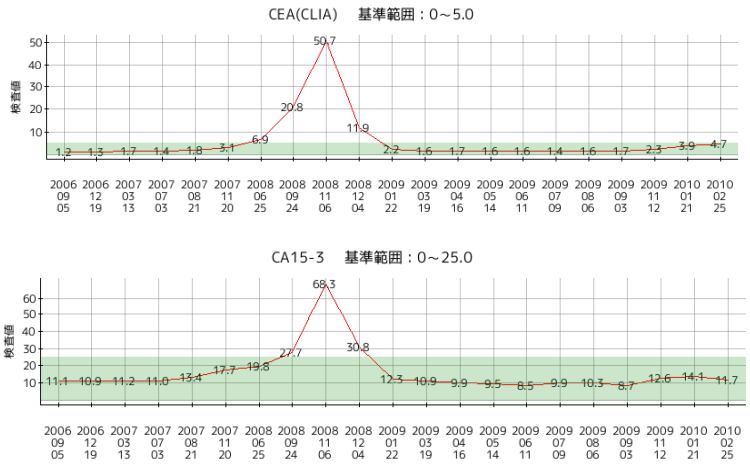
2003年10月　右乳癌（t2n1M0 stageⅡb）
ER:強陽性, PgR:陰性, HER2:陰性, grade3
EC(60,600)4 サイクル施行後、AI5年間内服

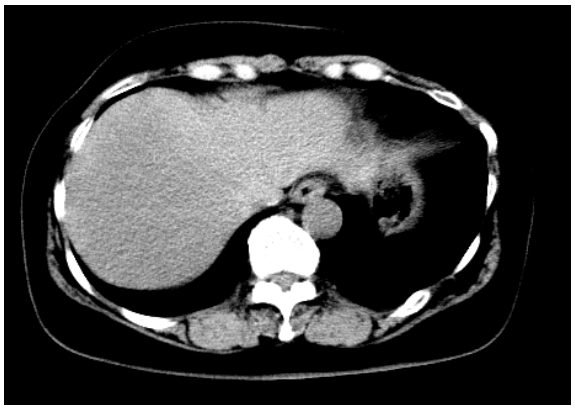
2008年 10月　肝転移(15mm単発), 多発骨転移(頸椎・胸椎),
(DFI 5y)　右上下鎖骨LN meta.



CEA: 20.8
CA15-3: 27.7

2008年10月 TAM + Zometa 開始





現在 TAM継続にてClinical CR継続中

原発巣
Ki 67 :15.2%

ある程度の臓器転移を有していても、
Ki67LI低値であればnon-life threadingである