Polysomy 17 in Breast Cancer

2009年10月15日

たちてん web conference

前回提示した症例

・58歳閉経後女性

右MMK(T4bN1M0 Stage IIIB)に対して H11.8月Bt+Mn+Ax試行

His ; IDC, t= 58mm, n= 9/22, HG3, ER/PR/HER2 = -/+/0

Adj ; ECx6 → TAM 5yrs → ANA(自己中断)

H20年8月(術後8年目) 多発骨転移(腰椎) → **LET + Zometa** 開始

TM一旦低下後、再上昇 → **TAM + Zometa** へ変更

硬膜転移病巣より出血（左半身麻痺） → 開頭止血術、WBRT

転移病巣のHis ; adeno ca., ER/PR/HER2 = -/-/3+

両側肺転移も同時に見つかる

治療方針は？

- TAM継続？（硬膜転移はHR-もTM↓のため他臓器では有効？）
- Chemo?
- **Herceptin?（ Primary;HER2(IHC);0 Meta; HER2(IHC)3+(FISH)- ）**

→ **HER2(IHC)3+(FISH)-はどのような症例？**

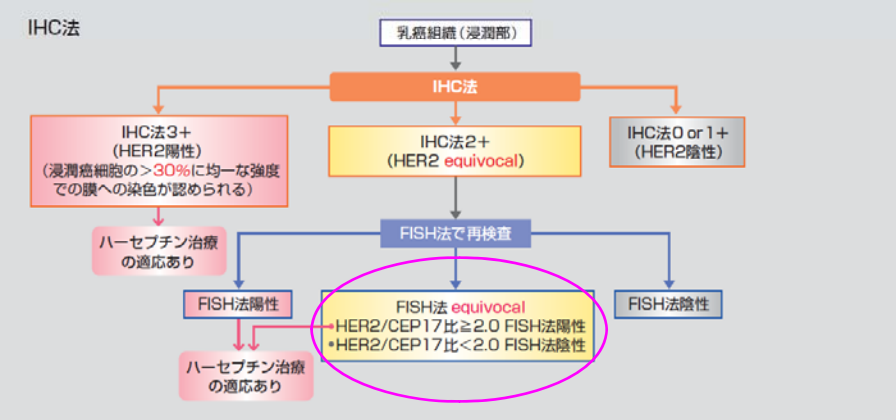
ex) Polysomy17？

→ **Polysomy17であった場合Herceptinは有効？**

用語の定義

- **Disomy ; 核一つあたりの染色体数 正常**
- **Polysomy ; 〃 増加**
- **Monosomy ; 〃 減少**
- **Aneusomy ; 染色体数の異常 を認める (Disomy以外)**
- **HER2遺伝子増幅 ; 特に断りの無い場合はFISH比での増幅を示す**
- **HER2 positive ; IHC3+ or IHC2+FISH+**
- **HER2 negative ; IHC0-1+ or IHC2+FISH-**

HER2検査フローチャート



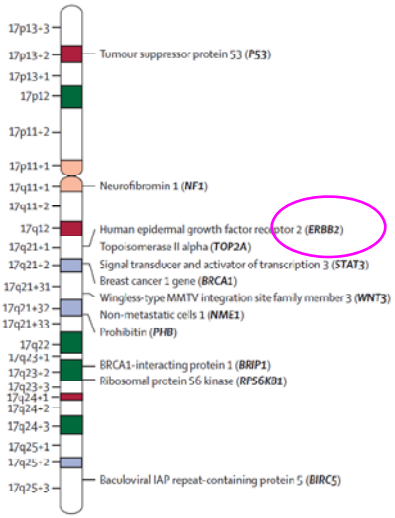
Trastuzumab病理部会作成

Breast cancer and aneusomy 17: implications for carcinogenesis and therapeutic response

Monica M Reinholz, Amy K Bruzek, Daniel W Visscher, Wilma L Lingle, Matthew J Schroeder, Edith A Perez, Robert B Jenkins

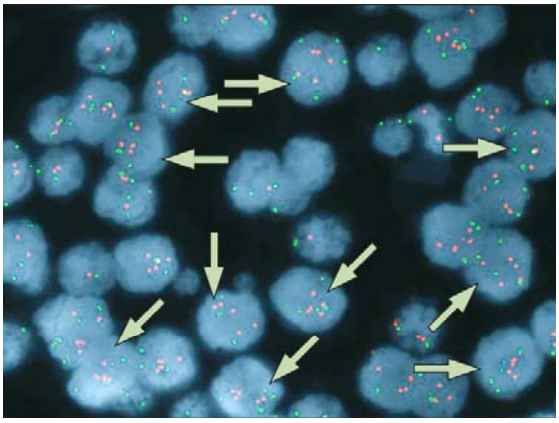
Lancet Oncol 2009; 10: 267–77

Ideogram of chromosome 17



Lancet Oncol 2009; 10: 267-77

FISH detection of ERBB2 non-amplification and chromosome 17 polysomy in invasive breast cancer



Red signals ; ERBB2 gene

Green signals ; Centromere Enumerator Probe (CEP)

Lancet Oncol 2009; 10: 267-77

Prevalence of chromosome 17 aneusomy in invasive breast cancer estimated FISH analysis

	Breast material	Number of specimens	Number of nuclei counted	Disomy		Monosomy		Polysomy		
				Cutoff	%	Cutoff	%	Cutoff	%	Association with ERBB2 protein expression*
Herrington et al (1995)[9]	FNA	49	≥100	MS=2	40	MS<2	5·0	MS>2	55	NR
Ichikawa et al (1996)[10]	FNA	80	>200	>80†	48	>15†	14	>20§	34	NR
McManus et al (1999)[11]	FNA	69	≥100	2¶	26	≥20†	0·0	≥10§	68	NR
Merola et al (2006)[18]	FFPE	343	200	2¶	30	1¶	24	>3·76**	7	3+
								>3¶	46	2+
								2·4‖	40	NR
								>4**	5·8	NR
Takehisa et al (2007)[19]	FNA	40	>100	NR	48	>15†	10	>20§	43	NR
Hofmann et al (2007)[13]	FFPE	95	60	NR	NR	NR	NR	≥3¶	27	3+
Hyun et al (2008)[6]	FFPE	369	≥60	1·95–3·35¶	NR	<1·95¶	1·3	≥3·76¶	33	3+
								2·26–3·75‖	26	NR
								>3·76**	5·8	NR

FNA=fine needle aspirate. FFPE=formalin-fixed paraffin-embedded. NR=not explicitly reported in reference. MS=mode chromosome 17 signal per nucleus. *=no association found. †The association between polysomy 17 and ERBB2 expression (scored as 0–3+ staining intensity) in ERBB2 non-amplified tumours. ‡Percent of cells displaying 2 signals per nucleus. §Percent of nuclei with loss of centromeric region or entire chromosome (typically with 0 or 1 chromosome 17 signal per nucleus). ¶Percent of nuclei with gain of centromeric region or entire chromosome (typically >2 or ≥3 chromosome 17 signals per nucleus). ‖Average number of chromosome 17 signals per nucleus. **Low-level polysomy. ††High-level polysomy. ‡‡Association was found between high polysomy (>3·76) and 10 tumours with ERBB2 immunohistochemical scores of 3+.

Lancet Oncol 2009; 10: 267-77

Polysomy 17は

- 基準値は確立していない
- 乳癌全体の27-55%に存在する

Prevalence of chromosome 17 aneusomy in invasive ERBB2 amplified and non-amplified breast cancer estimated by FISH analysis

	Number of specimens			Disomy			Monosomy				Polysomy				Association with ERBB2 expression in ERBB2 non amplified tumours
	Total	Amp*	Non-amp	Cutoff	Total N (%)	Amp N (%)	Non-amp N (%)	Cutoff	Total N (%)	Amp N (%)	Non-amp N (%)	Cutoff	Total N (%)	Amp N (%)	Non-amp N (%)	
Meszaros et al (1998)[17]	58	24	28	2†	20 (35)	15 (63)	5 (18)	1†	2 (3·4)	1 (4·1)	1 (3·6)	>2†	5 (8·6)	4 (17)	1 (3·6)	NR
Farabegoli et al (2006)[20]	79	19	60	2‡	NR	NR	15 (25)	1‡	NR	NR	12 (20)	≥3‡	NR	NR	33 (55)	NA
Beser et al (2007)[21]	50	11	39	1·35–1·85†	35 (70)	9 (82)	26 (67)	<1·35†	6 (12)	0 (0)	6 (15)	>1·85†	9 (18)	2 (18)	7 (18)	NR
Torres et al (2007)[22]	457	54	403	NR	NR	NR	NR	NR	NR	NR	NR	≥3‡	77 (17)	9 (17)	68 (17)	NR
Merola et al (2006)[18]	343	101	242	2‡	102 (30)	NR	NR	1‡	83 (24)	49 (49)	34 (14)	≥3‡	158 (46)	24 (24)	NR	2+
Reinholz et al (2007)[23]	1888	1488	156	Loss ≥60‖ Gain ≤30**	625 (33)	544 (37)	81 (52)	>60‖	89 (4·7)	79 (5·3)	5 (3·2)	>30**	935 (50)	865 (58)	70 (36)	NR
Vanden Bempt et al (2008)[24]	226	975	126	NR	NR	NR	NR	NR	NR	NR	NR	≥3‡	104 (46)	42 (43)	62 (49)	NA

Amp=ERBB2 amplification. Non-amp=ERBB2 non-amplification. N=number of specimens. NR=not explicitly reported in reference. NA=ERBB2 expression was not associated with polysomy 17. *ERBB2 amplification defined as ERBB2/CEP17 ratio >2·0 unless otherwise indicated. †Disomy defined as 2 ERBB2 gene signals related to 2 chromosome 17 signals was found in all cells; monosomy defined as ERBB2 signals =chromosome 17 signals; polysomy defined as equal numbers of both signals and ratio >2. ‡Average number of chromosome 17 signals per nucleus. §ERBB2 amplification defined as >10% with >5 ERBB2 signals per nucleus. ERBB2 non-amplification >10% with ≤2 signals per nucleus. Percent of nuclei with 2 chromosome 17 signals per cell. ‖Percent of nuclei with loss of centromeric region or entire chromosome (typically with 0 or 1 chromosome 17 signal per cell). **Percent of nuclei with gain of centromeric region or entire chromosome (typically >2 or ≥ 3 chromosome 17 signals per cell). ††Inferred from literature to be disomic. ‡‡ERBB2 amplification defined by mode ERBB2 signal or mode chromosome 17 signal ≥2. §§ERBB2 amplification defined as ERBB2/CEP17 ratio >2·2.

Lancet Oncol 2009; 10: 267-77

Polysomy 17は

- HER2遺伝子の増幅と相関する傾向にある
- 単独ではHER2蛋白の発現との相関はcontroversialである

Prevalence of aneusomy 17 in breast cancer progression estimated by FISH analysis

	Breast tissue	Number of specimens	Number of nuclei counted	Disomy			Monosomy			Polysomy		
				Cut-off	%	N	Cut-off	%	N	Cut-off	%	N
Micale et al (2000)[6]	Proliferative lesion	8	200–400	Loss ≤45*	50	4	>45*	50	4	>10†	0	0

	Specimens (N)*	Disomy			Monosomy			Polysomy		
		N_{NR}	N	%†	N_{NR}	N	%†	N_{NR}	N	%†
Proliferative lesion	23	6	13	76	0	5	22	0	0	0
Ductal carcinoma in situ	32	24	2	25	3	10	34	0	16	50
Lobular carcinoma in situ	10	9	0	0	0	3	30	0	0	0
Invasive carcinoma	21	19	0	0	3	7	39	3	9	50

N=number of specimens. NR=not explicitly reported in reference. *Percent hybridisations from table 3 and associated tumours are not included. †Does not include NR specimens.

Marinho et al (2000)[8]	Proliferative lesion	9	≥200	NR	100	9	>37·5*	0	0	>10†	0	0
	Ductal carcinoma in situ	11			NR	NR		46	5		46	5
	Invasive ductal carcinoma	16						38	6		50	8

N=number of specimens. NR=Not explicitly reported in reference. *Percent of nuclei with loss of centromeric region or entire chromosome (typically with 0 or 1 chromosome 17 signals per cell). †Percent of nuclei with gain of centromeric region or entire chromosome (typically >2 or ≥3 chromosome 17 signals per cell). ‡Percent of cells displaying 2 signals per nucleus. §Average number of chromosome 17 signals per nucleus. ¶Prevalence based on hybridisations. ||Heterogeneous chromosome 17 copy number (tumour cells contained variable number of chromosome 17 copies per nucleus). **Invading cells were compared to residual in-situ population in the 12 breast carcinomas studied.

Lancet Oncol 2009; 10: 267-77

Polysomy 17 in Breast Cancer: Clinicopathologic Significance and Impact on HER-2 Testing

Isabelle Vanden Bempt, Peter Van Loo, Maria Drijkoningen, Patrick Neven, Ann Smeets, Marie-Rose Christiaens, Robert Paridaens, and Christiane De Wolf-Peeters

J Clin Oncol 26:4869-4874.

Polysomy in relation to HER2 testing results

Variable	PS 17 + *HER2* GA (n = 42) No.	%	PS 17 − *HER2* GA (n = 62) No.	%
HER-2 status by IHC				
Positive, score 3+	33	78.6	0	0
Equivocal, score 2+	9	21.4	46	74.2
Negative, score 0/1+	0	0	16	25.8
HER-2 status by FISH, *HER2*				
Positive, *HER2* > 6	42	100	5	8.1
Equivocal, 4 ≤ *HER2* ≤ 6	0	0	44	71.0
Negative, *HER2* < 4	0	0	13	20.9
HER-2 status by FISH, R				
Positive, R > 2.2	42	100	0	0
Equivocal, 1.8 ≤ R ≤ 2.2	0	0	3	4.8
Negative, R < 1.8	0	0	59	95.2

JCO 2009; 26: 4869-4874

Distribution of clinicopathologic features in polysomy 17 tumors in the absence of HER2 gene amplification compared with HER2 negative and HER2 positive tumors

Characteristic	HER-2 Negative (n = 67) No.	%	P*	Polysomy 17 (n = 62) No.	%	P†	HER-2 Positive (n = 97) No.	%	P‡
Age, years			.99			.18			.99
≤ 50	21	31.3		14	22.6		42	43.3	
> 50	46	68.7		48	77.4		55	56.7	
Tumor grade			.00			3.1×10^{-3}			7.5×10^{-9}
1	6	8.9		5	8.1		1	1.0	
2	38	56.7		23	37.1		14	14.5	
3	23	34.4		34	54.8		82	84.5	
Tumor size, cm			.99			.99			.99
≤ 2	29	43.3		24	38.7		41	42.3	
> 2	38	56.7		38	61.3		56	57.7	
Nottingham Prognostic Index			.99			.71			.030
I	20	29.8		15	24.2		9	9.3	
II	30	44.8		27	43.5		45	46.4	
III	17	25.4		20	32.3		43	44.3	
Lymph node status			.99			.99			.99
Negative	41	61.2		35	56.5		44	45.4	
Positive	26	38.8		27	43.5		53	54.6	
Lymphovascular invasion			.99			.99			.99
Negative	55	82.1		53	85.5		72	74.2	
Positive	12	17.9		9	14.5		25	25.8	
Estrogen receptor status			.99			1.2×10^{-4}			1.4×10^{-4}
Negative	5	7.5		4	6.5		38	39.2	
Positive	62	92.5		58	93.5		59	60.8	
Progesterone receptor status			.99			.024			6.2×10^{-3}
Negative	18	26.9		18	29.0		54	55.7	
Positive	49	73.1		44	71.0		43	44.3	
Follow-up			NA			NA			NA
Mean, months	47.7			48.6			33.3		
Metastasis	3	4.5		9	14.5		21	21.6	

JCO 2009; 26: 4869-4874

Clinical Significance of Polysomy 17 in the HER2+ NCCTG N9831 Intergroup Adjuvant Trastuzumab Trial

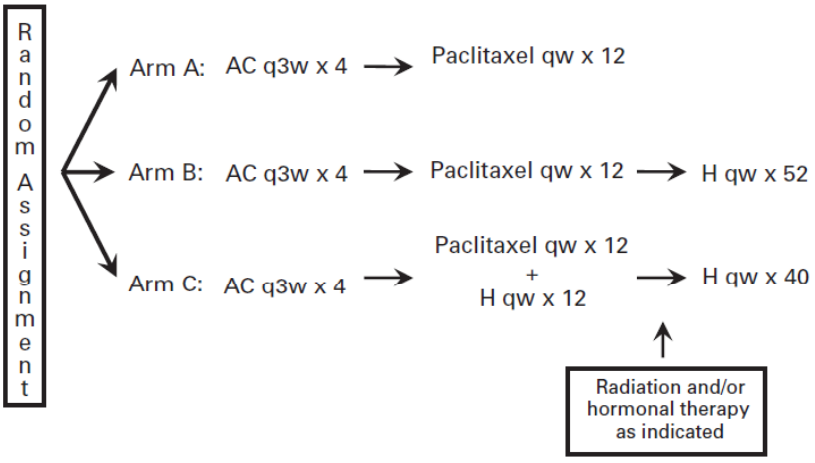
Reinholz MM, Jenkins RB, Hillman D, Lingle WL, Davidson N, Martino P, Kaufman P, Kutteh L, and Perez EA.
NCCTG, ECOG, SWOG, CALGB

Reinholz et al: SABCS 2007 (abstract #36)

CP1270832-15

N9831 random assignment schema

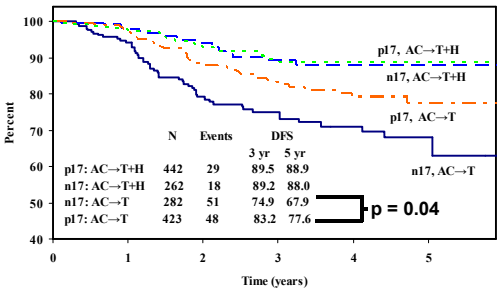
2766Pts,HER2(+),n(+) or Hign risk n(-)



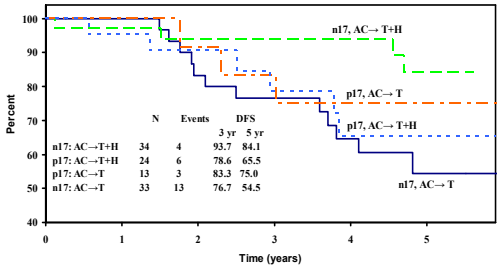
JCO 2009; 27: 2638-2644

DFS Based on Chromosome 17 Status and Treatment Arm

All had HER2 amplification



HER2 Normal
(by IHC and FISH)



Reinholz et al: SABCS 2007 (abstract #36)

- **NCCTG N9831**

  原発性乳癌患者を対象とした臨床試験において、

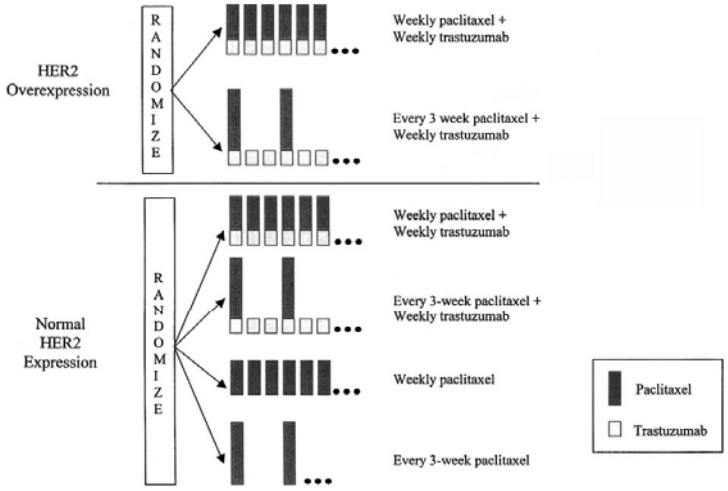
  HER2遺伝子の増幅の有無に関わらず、Polysomy 17と

  Trastuzumabの治療効果に相関は認めなかった

  → NSABP B-31, HERA trialでも同様の結果であった

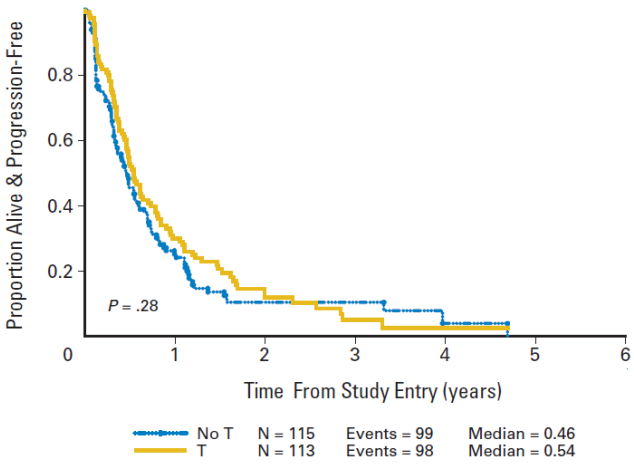
CALGB 9840 Random assignment schema

585Pts, MBC, Up to one line of Cx for MBC was allowed



JCO 2001; 19: 2587-2595

Time to progression by trastuzumab use in HER2 nonoverexpressors



JCO 2008; 26: 1642-1649

CALGB 9840: Central Testing

HER2-negative subjects in C9840	585
Tissue blocks available for C150002	303
HER2:CEP17 FISH ratio <2	192
CEP17 copy number > 2.2 (polysomy)	38
IHC 0-2+ / IHC 3+	34 / 3

RESPONSE in FISH Ratio <2	PAC	PAC + Trastuzumab	*P* Value
No polysomy	18/50 (36%)	19/53 (36%)	NS
Polysomy	5/19 (26%)	12/19 (63%)	*P*=0.048

Kaufman. *ASCO*. 2007 (abstr 1009).

- **CALGB9840**

  HER2蛋白0-2+が大部分を占めるHER2遺伝子非増幅の再発乳癌患者群に対して、Polysomy 17の有無はTrastuzumab投与の治療効果と相関する可能性が示唆された

まとめ

Polysomy 17とは・・・

- Polysomyを示す基準値は確立していない
- 乳癌全体の27-55%に存在する
- HER2遺伝子の増幅と相関する傾向を認める
- 単独ではHER2蛋白発現との相関はControversialである
- 細胞の増殖が強い細胞(IDC,DCIS > LCIS,Proliferative lesion)に多く認める
- 単独ではTrastuzumabの治療効果との相関は無いとの報告が多い

考察

- Polysomy 17を伴うHER2(IHC)2+かつFISH(-)乳癌群の中に、HER2遺伝子単独での増幅を認めTrastuzumab投与が奏功する症例が存在する可能性がある

- しかし、現時点ではPolysomy 17の有無をTrastuzumab投与の判断材料とするだけの十分な根拠が無い