Different response rates to chemotherapy between Japanese and German esophageal squamous cell carcinoma: patients may be influenced by *ERCC1* or *ABCB1*

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はじめに

食道扁平上皮癌は人種間によって発生率が違っており
人種による生存率および薬剤の感受性の違いも
指摘されている。

そのため日本とドイツの食道扁平上皮癌治療
ガイドラインも異なっており、日本は術前化学療法
に対しドイツでは術前化学放射線治療をおこなっている。

ドイツ人における術前化学放射線治療効果予測因子

1. ERCC1遺伝子多型が化学放射線治療における効果予測因子となりうる

Bollschweiler E, Holscher AH, Herbold T et al. Molecular markers for the prediction of minor response to neoadjuvant chemoradiation in esophageal cancer: results of the prospective Cologne Esophageal Response Prediction (CERP) study. Ann. Surg. 264(5), 839–846(2016).

2. ABCB1 遺伝子多型はリンパ節転移の効果予測因子となりうる

Narumiya K, Metzger R, Bollschweiler E et al. Impact of ABCB1 C3435T polymorphism on lymph node regression in multimodality treatment of locally advanced esophageal cancer. Pharmacogenomics 12(2), 205–214 (2011).

3. *GNAS 393C* 遺伝子多型は効果予測因子となりうる

Alakus H, Bollschweiler E, Holscher AH et al. Homozygous GNAS 393C-allele carriers with locally advanced esophageal cancer fail to benefit from platinum-based preoperative chemoradiotherapy. Ann. Surg. Oncol. 21(13), 4375–4382 (2014).

Aims:

We analyzed the therapeutic results comparing the data of patients with esophageal squamous cell carcinoma from Japan and Germany according to the frequency of three single-nucleotide polymorphisms.

Materials & Methods:

60 patients from Japan and 127 patients from Germany with ESCC were analyzed according to the SNPs by real-time PCR.

Clinical data of patients with ESCC

	Japanese	German	Significance Japanese - German
Total	n=60	n=127	
Age (median)	61 y	60 y	n.s.
min - max	46 y - 79 y	29 y - 80 y	
Gender			p=0.008
male	52 87%	87 68%	
female	8 13%	40 32%	
T-category		all cT3-4	--
pT1-2	n=10		
pT3	n=10		
ypT0-1	n=7	46 36%	
ypT2	n=5	28 22%	
ypT3-4	n=28	53 42%	
Therapy			--
Surgery	n=20	0	
CTx+ S	n=20	0	
RTx/CTx+S	n=20	n=127	

Frequency of three SNPs of patients with ESCC

	Japanese	German	Significance Japanese - German
Total	n=60	n=127	
ERCC1 rs11615			p <0.0001
CC	28　47%	17　13%	
TT	7　12%	52　41%	
C/T	25　41%	58　46%	
ABCB1 C3435T rs1045642			
CC			p=0.0002
TT	31　52%	28　22%	
C/T	8　13%	32　25%	
	21　35%	67　53%	
GNAS- T393C rs7121			n.s.
CC			
TT	12　20%	39　31%	
C/T	14　23%	24　19%	
	34　57%	64　50%	

Frequency of three SNPs in normal population and patients with ESCC in Japan and Germany ([1] data from Hapmap. [2] data from Abbasi et al. [3] data from Hashiguchi et al.,[5] data from Alakus et al).

| SNP	Japanese normal population	Japanese patients with ESCC	Significance	European normal population	German patients with ESCC	Significance
rs11615	n=122 [1]	n=60		n=647 [2]	n=127	
ERCC1			n.s.			n.s.
CC	50%	47%		13%	13%	
TT	8%	12%		42%	41%	
C/T	42%	41%		45%	46%	
rs1045642	n=299 [3]	n=60		n=226 [3]	n=127	
ABCB1 C3435T			p=0.014			n.s.
CC	31%	52%		15%	22%	
TT	16%	13%		29%	25%	
C/T	52%	35%		56%	53%	
rs7121	n= 90	n=60		n=800 [5]	n=127	
GNAS- T393C			n.s.			n.s.
CC	18%	20%		29%	31%	
TT	33%	23%		22%	19%	
C/T	49%	57%		49%	50%	

Rate of response to preoperative chemotherapy comparing Japanese and German cT3 ESCC patients (VTC=vital tumor cells)

	Japanese		German		Significance
	n	%	n	%	p
Total	40	100 %	127	100%	
ypT-category					p=0.027
ypT0-1	7	18%	46	36%	
ypT2-4	33	82%	81	64%	
Histopathologic response					p<0.0001
<=50% VTCs	19	48%	107	84%	
Progression or >50% VTCS	21	52%	20	26%	
ypN-category					p=0.006
ypN0	11	28%	46	54%	
ypN1-3	29	72%	81	46%	

Frequency of genotypes of three SNPs and response to preoperative therapy comparing Japanese and German cT3 ESCC patients

	Japanese	Response ypT0-1			German	Response ypT0-1		ypN0	
		ypT0-1		ypN0		ypT0-1		ypN0	
		n	%	n	%		n	%	n	%
Total	n=40	7	18%	11	28%	n=127	46	36%	68	54%
ERCC1 rs11615										
CC										
TT	17	2	12%	5	29%	17	6	35%	6	29%
C/T	6	2	33%	2	33%	52	14	25%	24	48%
	17	3	18%	4	23%	58	26	45%	39	67%
ABCB1 C3435T rs1045642										
CC										
	25	5	20%	5	20%	28	12	42%	12	43%
TT										
	3	1	33%	3	100%	32	11	34%	21	66%
C/T										
	12	1	8%	3	25%	67	23	34%	36	54%
GNAS- T393C rs7121										
CC	9	2	22%	5	56%	39	10	26%	19	49%
TT	11	2	18%	2	18%	24	9	38%	12	50%
C/T	20	3	15%	4	20%	64	26	41%	37	58%

The multivariate regression analysis showed that the influence of these SNPs on response varies between Japanese and German patients
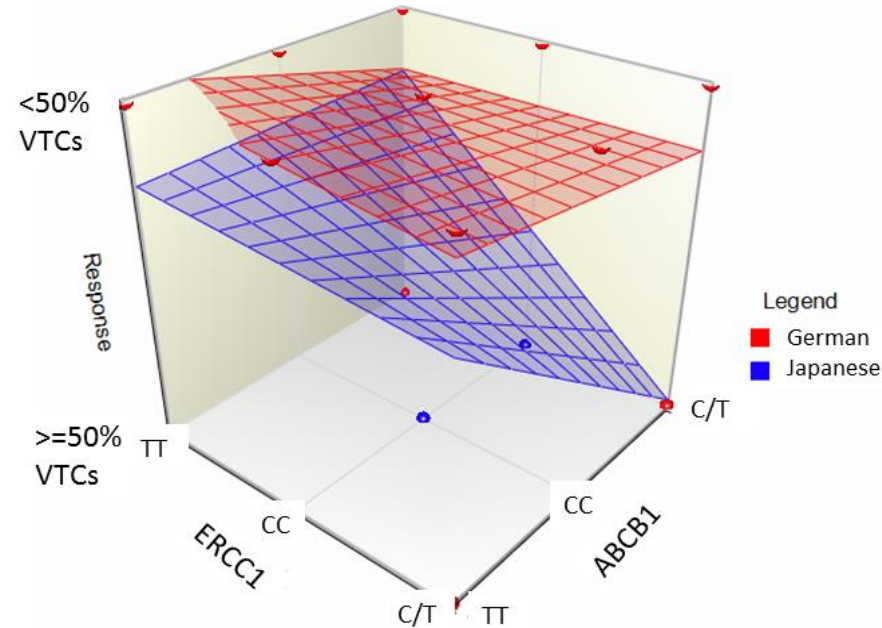
Influence of *ERCC1* rs16115 and *ABCB1* C3435T rs1045642 to the response rate after neoadjuvant chemotherapy differ between Japanese and German patients with squamous cell carcinoma of the esophagus. Japan: response yes = 0.62 + 0.14*ERCC1* + 0.19**ABCB1** -0.18ERCC1*ABCB1*. Germany: Response yes = 1.25 - 0.99**ERCC1* - 0.15**ABCB1** + 0.03ERCC1*ABCB1* with *ERCC1*rs16115 TT = 1, CC = 2 and C/T = 3 and *ABCB1* C3435T rs1045642 TT = 1, CC = 2 and C/T = 3.VTC: Vital tumor cell.

Kaplan-Meier survival curves comparing Japanese and German patients with cT3NxM0 squamous cell carcinoma of the esophagus treated with neoadjuvant therapy based on cisplatin/5-FU followed by transthoracic esophagectomy.
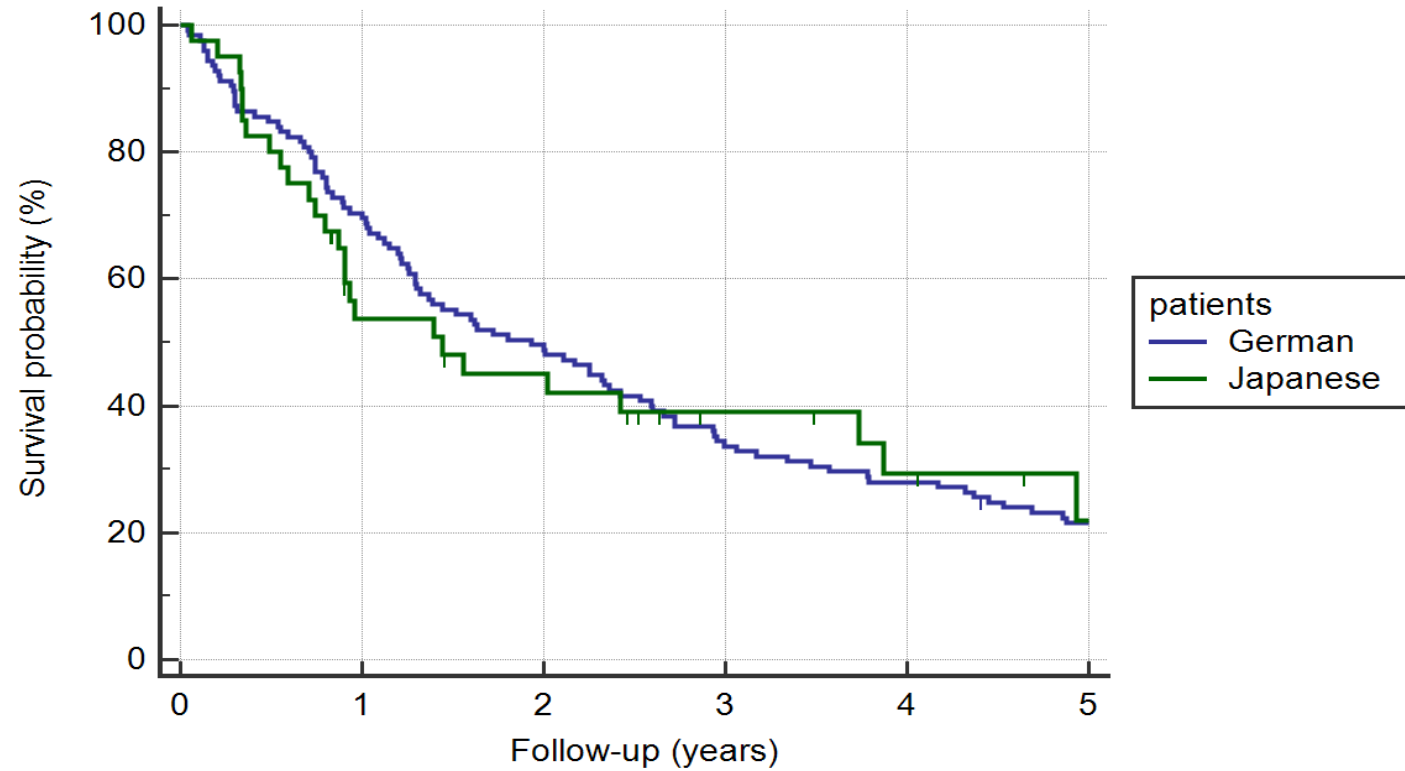
Number at risk
Group: German

125	87	61	42	35	26

Group: Japanese

40	19	15	9	6	3

Results:

- The distribution of the genotypes of ERCC1 rs16115 and of ABCB1 C3435T rs1045642 was significantly different. This response was significantly lower in Japanese patients than in German patients. The influence of the three SNPs on response varied between patients from Japan and Germany.

Conclusion:

- This result can be partly explained by different expressions of ERCC1 and ABCB1 SNPs in the Japanese compared with the German patients.

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