

## **Elevated microsatellite instability at selected tetranucleotide (EMAST) repeats in gastric cancer: a distinct microsatellite instability type with potential clinical impact?.**

Herz, A., Wisser, S., Kohlruss, M, et al. *The Journal of Pathology: Clinical Research*. 2022. IF 3.4 (2023)

### **【要旨】**

**対象:** 胃および胃食道腺癌の術前化学療法 (CTx)において EMAST (Elevated Microsatellite Instability at Selected Tetranucleotide repeats)が与える臨床的な影響を検討した。切除された腫瘍 (583例: CTx未施行272例、CTx後311例)と、CTx前の腫瘍生検 (142例)を対象とした。

**方法:** 5つのテトラヌクレオチド反復マーカのうち2または3マーカに不安定性が見られた場合、EMAST (2+)およびEMAST (3+)と定義した。MSH3を含むミスマッチ修復タンパク質の発現は免疫組織化学を用いて解析した。マイクロサテライト不安定性 (MSI)およびエプスタイン・バーウイルス (EBV)陽性は標準的なアッセイを用いて同定した。

**結果:** EMAST (2+)および(3+)は胃癌の17.8%および胃食道腺癌の11.5%で検出された。MSI-high (MSI-H)腫瘍におけるEMAST (2+)または(3+)の頻度は胃癌で96.2%および胃食道腺癌で92.5%であった。EMASTとMSI-Hは高頻度に重複していた。また、EMASTとMSI状態は関連が見られ ( $p < 0.001$ )、EMAST (2+または3+)はMSI-HおよびEBV陰性腫瘍においてリンパ節陰性と有意に関連した (EMAST (2+)で42.3%、EMAST陰性で28.8%、 $p = 0.045$ )。EMASTは、全生存率 (OS)と有意な関連は認められなかった。EMAST (2+)患者のOS中央値は40.0ヶ月 (95%信頼区間 [CI] 16.4–63.6)であり、EMAST陰性群は38.7ヶ月 (95% CI 26.3–51.1)であった ( $p = 0.880$ )。EMAST (3+)患者のOS中央値は46.7ヶ月 (95% CI 18.2–75.2)であり、陰性群では38.7ヶ月 (95% CI 26.2–51.2)であった ( $p = 0.879$ )。EMASTと術前CTxの反応に有意な関連は認められなかった (EMAST (2+)および(3+)でそれぞれ  $p = 0.992$  および  $p = 0.433$ )。

**結論:** MSI-HとEMASTはほぼ完全な交差を示し、EMASTは胃癌患者の顕著な臨床病理学的特性と関連する不安定性タイプではないことが示唆された。

### **Take home message :**

1. 胃癌および胃食道腺癌においてMSI-HとEMASTはほぼ完全な交差を示す。
2. 胃癌および胃食道腺癌において、EMASTはOSと関連しない。

Table 1. Patient's characteristics

Category	Value	Resected tumours without and after neoadjuvant CTx		Biopsies before neoadjuvant CTx	
		n	%	n	%
Cases	Total	583	100	142	100
Age (years)	Median	64.6		61.4	
	Range	29.2–90.9		23.3–79.1	
Follow-up period (months)	Median	57.8		69.6	
	95% CI	53.3–62.4		61.1–78.2	
Overall survival (months)	Median	44.4		48.1	
	95% CI	29.5–59.3		26.3–69.9	
Number of events		276	47.3	77	54.2
Sex	Male	433	74.3	108	76.1
	Female	150	25.7	34	23.9
Tumour localisation	Proximal	285	48.9	100	70.4
	Middle	144	24.7	23	16.2
	Distal	123	21.1	13	9.2
	Total/linitis	27	4.6	6	4.2
	N/A	4	<1	–	–
Laurén classification	Intestinal	326	55.9	72	50.7
	Non-intestinal	257	44.1	70	49.3
Tumour grade	G1/2	118	20.2	33	23.2
	G3/4	384	65.9	109	76.8
	N/A	81	13.9	–	–
Clinical tumour stage	cT2	132	22.6	7	4.9
	cT3/cT4	449	77.0	129	90.8
	N/A	2	<1	6	4.2
(y)pT*	(y)pT0	–	–	9	6.3
	(y)pT1	53	9.1	12	8.5
	(y)pT2	73	12.5	19	13.4
	(y)pT3	308	52.8	81	57.0
	(y)pT4	149	25.6	19	13.4
	N/A	–	–	2	1.4
(y)pN*	Negative	180	30.9	61	43.0
	Positive	403	69.1	79	55.6
	N/A	–	–	2	1.4
Metastasis status	No	503	86.3	96	67.6
	Yes	80	13.7	44	31.0
	N/A	–	–	2	1.4
Resection category	R0	443	76.0	116	81.7
	R1	140	24.0	24	16.9
	N/A	–	–	2	1.4
Neoadjuvant CTx	No	272	46.7	–	–
	Yes	311	53.3	142	100
Tumour regression grade <sup>†</sup>	TRG1	–	–	45	31.7
	TRG2	147	25.2	34	23.9
	TRG3	164	28.1	63	44.4
	Total <sup>†</sup>	311	53.3	142	100
Response	TRG1	–	–	45	31.7
	TRG2/3	311	100	97	68.3
MSI status	MSS	502	86.1	120	84.5
	MSI-L	28	4.8	7	4.9
	MSI-H	53	9.1	15	10.6
EBV status	EBV negative	563	96.6	137	96.5
	EBV positive	20	3.4	5	3.5
EMAST status	Negative	479	82.2	111	78.2
	Positive 2+	104	17.8	31	21.8
EMAST status	Negative	516	88.5	120	84.5
	Positive 3+	67	11.5	22	15.5

\*TNM classification of malignant tumours according to the Seventh Edition of the UICC

†TRG corresponded only to patients with tumours treated with neoadjuvant CTx.

Fig 1

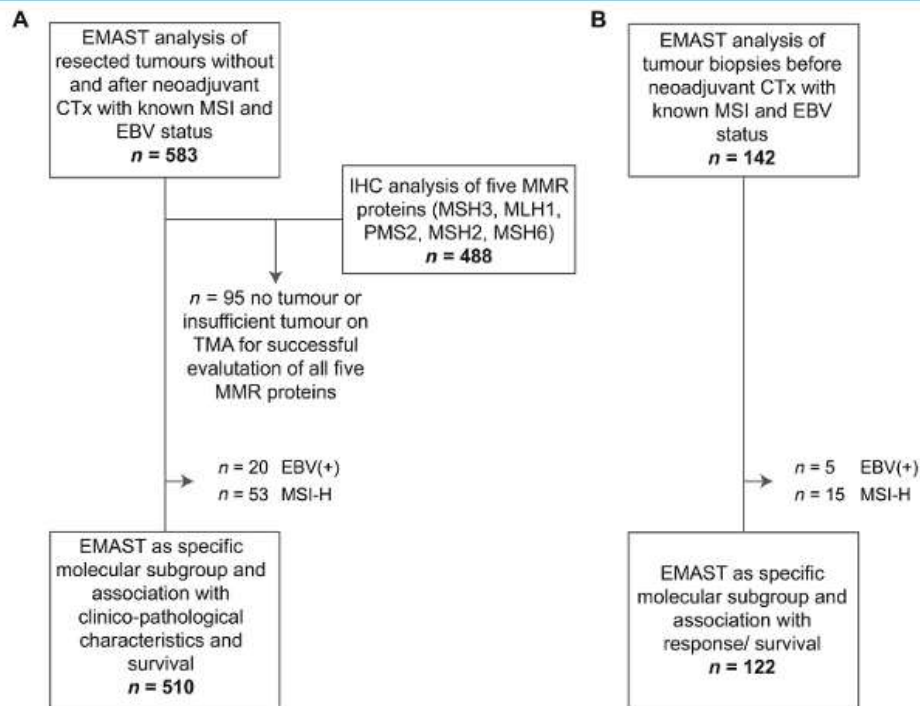
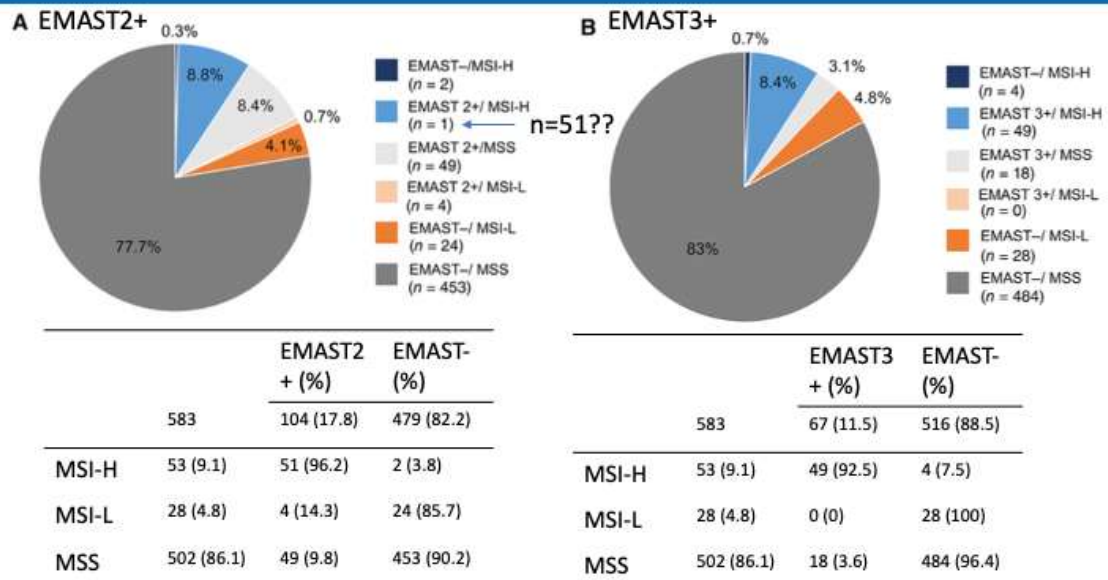


Fig 2 / Table2



## Table3 EMAST (2+,3+)とMSH3 IHCの比較

Table 3. Association of EMAST/MSI status and MSH3 expression.

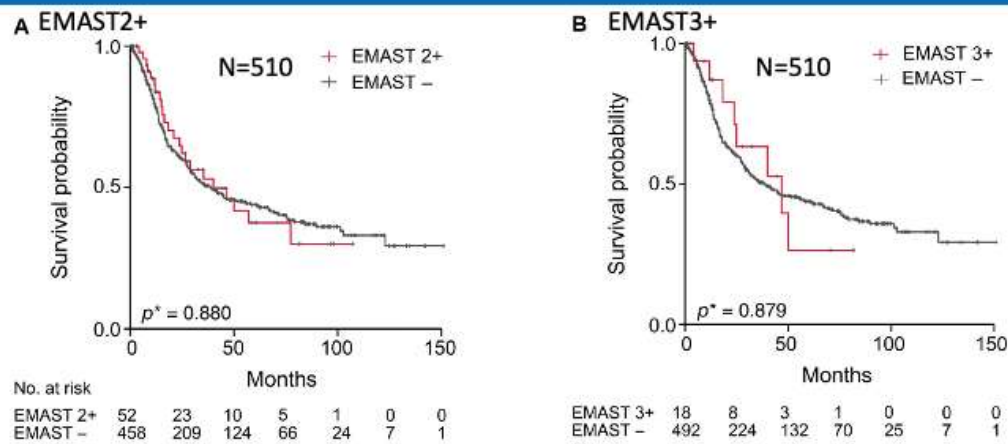
Status	MSH3 expression			P value*	MSH3 expression		P value*
	Reduced (<10%), n = 7	Moderate (10–50%), n = 79	Strong (>50%), n = 402		Reduced/moderate (≤50%), n = 86	Strong (>50%), n = 402	
EMAST –	6 (85.7)	57 (72.2)	332 (82.6)	0.092	63 (73.3)	332 (82.6)	0.046
EMAST 2+	1 (14.3)	22 (27.8)	70 (17.4)		23 (26.7)	70 (17.4)	
EMAST 3+	6 (85.7)	63 (79.7)	358 (89.1)	0.072	69 (80.2)	358 (89.1)	0.025
EMAST –	1 (14.3)	16 (20.3)	44 (10.9)		17 (19.8)	44 (10.9)	
MSI MSS	5 (71.4)	65 (82.3)	346 (86.1)	0.358	70 (81.4)	346 (86.1)	0.506
MSI-L	1 (14.3)	4 (5.1)	20 (5.0)		5 (5.8)	20 (5.0)	
MSI-H	1 (14.3)	10 (12.6)	36 (8.9)		11 (12.8)	36 (8.9)	

\*Fisher's exact or chi-squared test.

EMAST (2+,3+) でMSH3reduced/moderateの割合が増加するが、EMASTの判定には適さない

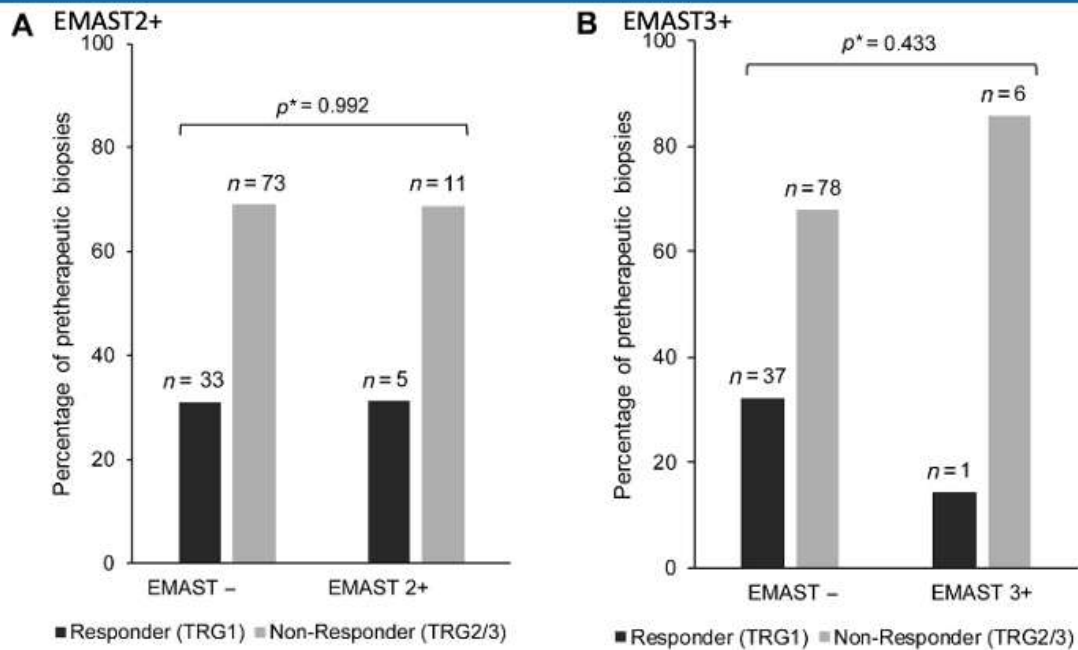
使用抗体：Abcam, EPR4334(2)

## Fig 3：予後の比較



EMAST (2+,3+)はOSに影響しない

Fig 4



EMAST (2+,3+)はCTxに影響しない

MSI-H, EBV+を除外

Table 4

Table 4. EMAST as specific molecular group and association with clinical-pathological characteristics

Category	Value	Resected tumours without or after neoadjuvant CTx*		Pvalue <sup>†</sup>	EMAST 3+		Pvalue <sup>†</sup>
		EMAST-	EMAST 2+		EMAST-	EMAST 3+	
		n (%)	n (%)		n (%)	n (%)	
Cases	Total	458 (100)	52 (100)		492 (100)	18 (100)	
Age (years)	Median	64.4	64.0		64.4	65.1	
	Range	30.2-90.9	35.4-88.3		30.2-90.9	35.4-78.7	
Follow-up period (months)	Median	57.9	48.8		57.9	44.4	
	95% CI	52.5-63.3	24.7-72.9		53.1-62.8	20.1-68.7	
Overall survival (months)	Median	38.7	40.0		38.7	46.7	
	95% CI	26.3-51.1	16.4-63.6		26.2-51.2	18.2-75.2	
Number of events		228 (49.8)	23 (44.2)		243 (49.4)	8 (44.4)	
Gender	Male	340 (74.2)	40 (78.9)	0.873	368 (76)	11 (61.1)	0.184
	Female	118 (25.8)	12 (23.1)		123 (25)	7 (38.9)	
Tumour localisation	Proximal	226 (49.4)	34 (65.4)	0.153	248 (50.4)	12 (66.6)	0.356
	Middle	110 (24.0)	9 (17.3)		115 (23.4)	4 (22.2)	
	Distal	95 (20.7)	6 (11.5)		100 (20.3)	1 (5.6)	
	Total/In situ	23 (5.0)	3 (5.8)		25 (5.1)	1 (5.6)	
	N/A	4 (<1)	-		4 (<1)	-	
Laurén classification	Intestinal	248 (54.1)	32 (61.5)	0.310	269 (54.7)	11 (61.1)	0.580
	Non-intestinal	210 (45.9)	20 (38.5)		223 (45.3)	7 (38.9)	
Tumour grade	G1/2	92 (20.1)	15 (28.8)	0.267	100 (20.3)	7 (38.8)	0.096
	G3/4	301 (65.7)	34 (65.4)		325 (66.1)	10 (55.6)	
	N/A	65 (14.2)	3 (5.8)		67 (13.6)	1 (5.6)	
Clinical tumour stage	cT2	105 (22.9)	14 (26.9)	0.474	116 (23.6)	3 (16.7)	0.567
	cT3/cT4	352 (76.9)	37 (71.2)		375 (76.2)	14 (77.7)	
	N/A	1 (<1)	1 (1.9)		1 (<1)	1 (5.6)	
(y)pp <sup>‡</sup>	ypT1	41 (8.9)	7 (13.5)	0.725	48 (9.8)	-	0.570
	ypT2	56 (12.3)	7 (13.5)		61 (12.4)	2 (11.1)	
	ypT3	240 (52.4)	26 (50.0)		254 (51.6)	12 (66.7)	
	ypT4	121 (26.4)	12 (23.0)		129 (26.2)	4 (22.2)	
	Negative	132 (28.8)	22 (42.3)	0.045	149 (30.3)	5 (27.8)	0.820
	Positive	326 (71.2)	30 (57.7)		343 (69.7)	13 (72.2)	
Metastasis status	No	386 (84.3)	47 (90.4)	0.244	416 (84.5)	17 (94.4)	0.250
	Yes	72 (15.7)	5 (9.6)		76 (15.5)	1 (5.6)	
Resection category	R0	341 (74.5)	41 (78.8)	0.489	368 (74.8)	14 (77.8)	0.774
	R1	117 (25.5)	11 (21.2)		124 (25.2)	4 (22.2)	
Tumour regression grade <sup>§</sup>	TRG2	128 (48.8)	11 (52.4)	0.825	135 (50)	2 (40)	1.000
	TRG3	128 (50.4)	10 (47.6)		135 (50)	3 (60)	
	Total <sup>¶</sup>	254 (100)	21 (100)		270 (100)	5 (100)	
Neoadjuvant CTx	No	204 (44.5)	31 (59.6)	0.039	222 (45.1)	13 (75.0)	0.023
	Yes	254 (55.5)	21 (34.4)		270 (54.9)	5 (28.0)	

<sup>†</sup>Only patients with EBV and MSI-H-negative tumours are included in the analysis.<sup>‡</sup>Fisher's exact or chi-squared test.<sup>§</sup>TNM classification of malignant tumours according to the Seventh Edition of the UICC.<sup>¶</sup>TR0 corresponded only to patients with tumours treated with neoadjuvant CTx.EMAST2+  
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