

KRAS mutational status in Japanese patients with colorectal cancer: Results from a multicenter, cross-sectional, large observational study conducted by the Japan Study Group of KRAS Mutation in Colorectal Cancer

ESMO 210
Abstract 595P

K. Yamazaki¹, T. Watanabe², T. Yoshino³, H. Uetake⁴, M. Ishiguro⁴, K. Sugihara⁴, Y. Ohashi⁵

¹ Shizuoka Cancer Center, Shizuoka, Japan; ² Teikyo University School of Medicine, Tokyo, Japan; ³ National Cancer Center Hospital East, Chiba, Japan; ⁴ Tokyo Medical and Dental University, Graduate School, Tokyo, Japan; ⁵ Public Health Research Foundation, Tokyo, Japan

Background

- The KRAS mutation mainly located in the codon 12 and 13 in colorectal tumors.
- The KRAS mutation indicates unresponsiveness of patients with metastatic colorectal cancer (CRC) to anti-epidermal growth factor receptor (EGFR) antibodies.
- Various studies have reported that 30–40% of CRC patients have KRAS mutations¹⁻³.
- However, the data on the frequency of KRAS mutation in Japanese CRC patients is limited to small sample size case-series.

Objectives

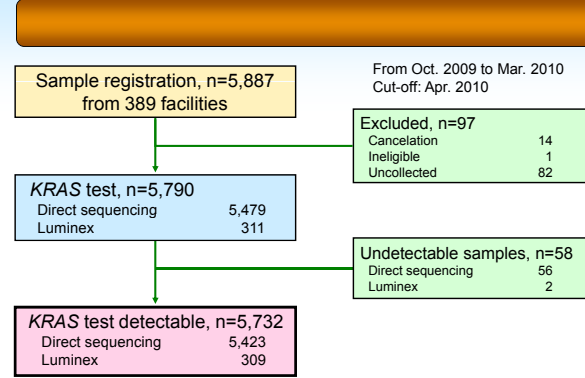
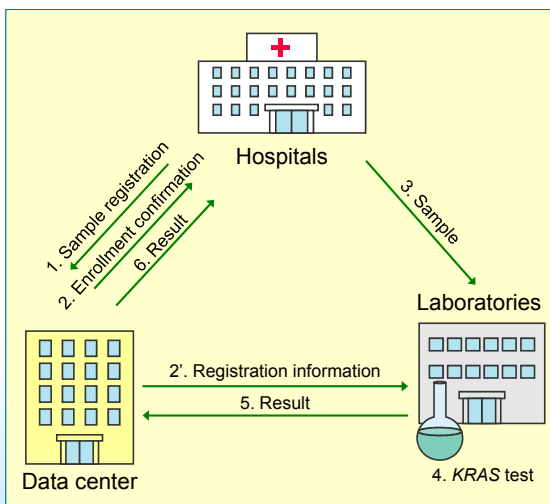
To elucidate KRAS mutational status in Japanese CRC patients in this multicenter, cross-sectional, observational study.

Methods

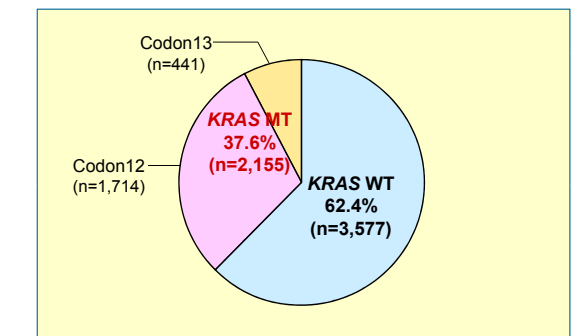
Key eligibility criteria

- Histologically confirmed colorectal adenocarcinoma
- Adequate tumor samples for this study

- Send formalin-fixed paraffin-embedded tumor blocks or thinly sliced tumor sections to commercial laboratories
- Investigate KRAS point mutations in the codon 12 and 13 by following laboratories' SOP



	No. of sample	KRAS WT	KRAS MT	P value
All	5,732	3,577 (62.4%)	2,155 (37.6%)	
Site of Mutation				
Codon 12		1,714 (79.5%)		
Codon 13		441 (20.5%)		



	No. of sample	KRAS WT	KRAS MT	P value
Gender				<0.0001
Male	3,475 (60.6%)	2,243 (64.5%)	1,232 (35.5%)	
Female	2,257 (39.4%)	1,334 (59.1%)	923 (40.9%)	
Age				0.0007
< 50	560 (9.8%)	389 (69.5%)	171 (30.5%)	
50-59	1,258 (21.9%)	798 (63.4%)	460 (36.6%)	
60-69	2,081 (36.3%)	1,289 (61.9%)	792 (38.1%)	
70 =<	1,833 (32.0%)	1,101 (60.1%)	732 (39.9%)	
Type of sample				0.4133
Surgically resected	5,364 (93.6%)	3,340 (62.3%)	2,024 (37.7%)	
Biopsy	368 (6.4%)	237 (64.4%)	131 (35.6%)	
Year the sample obtained 1				0.0549
< 2006	748 (13.0%)	497 (66.4%)	251 (33.6%)	
2006	445 (7.8%)	282 (63.4%)	163 (36.6%)	
2007	761 (13.3%)	463 (60.8%)	298 (39.2%)	
2008	1,255 (21.9%)	752 (59.9%)	503 (40.1%)	
2009	1,843 (32.2%)	1,150 (62.4%)	693 (37.6%)	
2010	312 (5.4%)	196 (62.8%)	116 (37.2%)	
Biopsy				
< 2009	110 (1.9%)	79 (71.8%)	31 (28.2%)	
2009 =<	258 (4.5%)	158 (61.2%)	100 (38.8%)	
Year the sample obtained 2				0.0285
Surgically resected				
< 2006	748 (13.0%)	497 (66.4%)	251 (33.6%)	
2006	445 (7.8%)	282 (63.4%)	163 (36.6%)	
2007 =<	4,171 (72.8%)	2,561 (61.4%)	1,610 (38.6%)	
Biopsy				
< 2009	110 (1.9%)	79 (71.8%)	31 (28.2%)	
2009 =<	258 (4.5%)	158 (61.2%)	100 (38.8%)	0.0524

Result

Site of the sample obtained	Primary tumor	Metastasis	No. of sample	KRAS WT	KRAS MT	P value
liver	216 (45.6%)	146 (67.6%)	70 (32.4%)			0.9838
lung	74 (15.6%)	48 (64.9%)	26 (35.1%)			0.1347
lymph node	37 (7.8%)	22 (59.5%)	15 (40.5%)			
local	45 (9.5%)	29 (64.4%)	16 (35.6%)			
dissemination	70 (14.8%)	34 (48.6%)	36 (51.4%)			
others	32 (6.8%)	17 (53.1%)	15 (46.9%)			

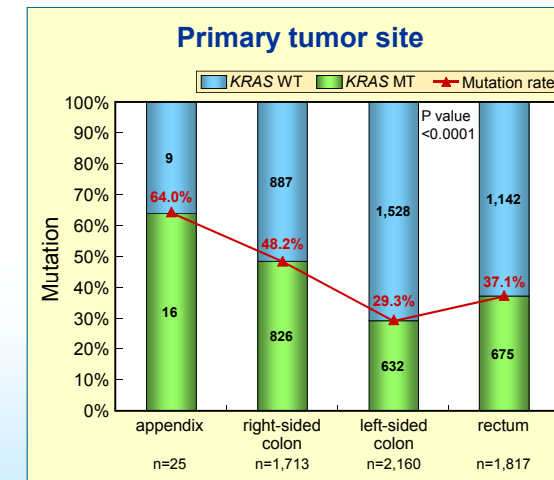
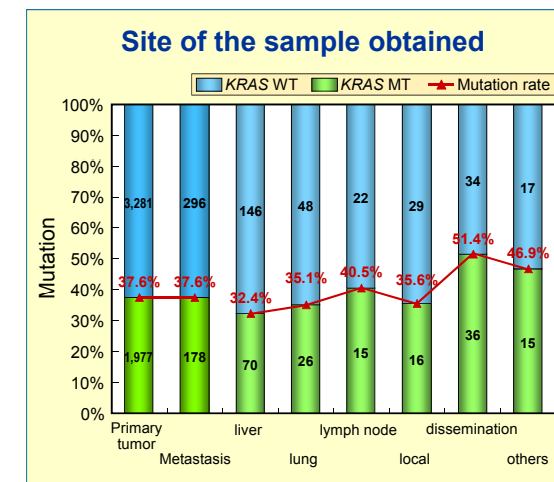
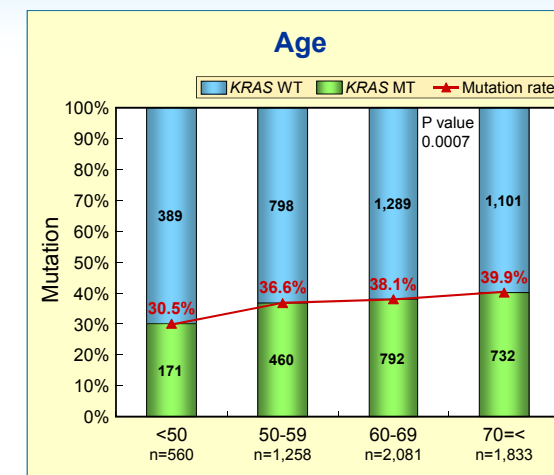
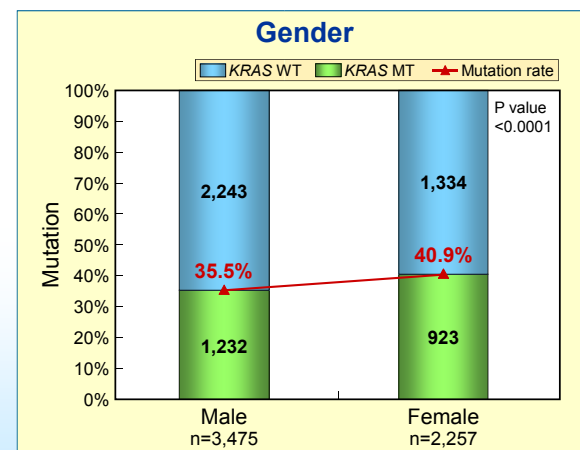
Primary tumor site 1	appendix	cecum	ascending colon	transverse colon	descending colon	sigmoid colon	rectosigmoid	rectum	anus, anal canal*	others/unknown*	No. of sample	KRAS WT	KRAS MT	P value
appendix	25 (0.4%)	9 (36.0%)	16 (64.0%)								25	9	16	64.0%
cecum	420 (7.3%)	168 (40.0%)	252 (60.0%)								420	168	252	60.0%
ascending colon	877 (15.3%)	423 (48.2%)	454 (51.8%)								877	423	454	51.8%
transverse colon	416 (7.3%)	296 (71.2%)	120 (28.8%)								416	296	120	28.8%
descending colon	270 (4.7%)	180 (66.7%)	90 (33.3%)								270	180	90	33.3%
sigmoid colon	1,433 (25.0%)	1,039 (72.5%)	394 (27.5%)								1,433	1,039	394	27.5%
rectosigmoid	457 (8.0%)	309 (67.6%)	148 (32.4%)								457	309	148	32.4%
rectum	1,817 (31.7%)	1,142 (62.9%)	675 (37.1%)								1,817	1,142	675	37.1%
anus, anal canal*	5 (0.1%)	4 (80.0%)	1 (20.0%)								5	4	1	20.0%
others/unknown*	12 (0.2%)	7 (58.3%)	5 (41.7%)								12	7	5	41.7%

Primary tumor site 2	appendix	right-sided colon	left-sided colon	rectum	others*	No. of sample	KRAS WT	KRAS MT	P value
appendix	25 (0.4%)	9 (36.0%)	16 (64.0%)			25	9	16	64.0%
right-sided colon	1,713 (29.9%)	887 (51.8%)	826 (48.2%)			1,713	887	826	48.2%
left-sided colon	2,160 (37.7%)	1,528 (70.7%)	632 (29.3%)			2,160	1,528	632	29.3%
rectum	1,817 (31.7%)	1,142 (62.9%)	675 (37.1%)			1,817	1,142	675	37.1%
others*	17 (0.3%)	11 (64.7%)	6 (35.3%)			17	11	6	35.3%

Stage at the time of sample collection	I	II	III	IV	recurrence	unknown*	No. of sample	KRAS WT	KRAS MT	P value
I	166 (2.9%)	111 (66.9%)	55 (33.1%)				166	111	55	33.1%
II	814 (14.2%)	510 (62.7%)	304 (37.3%)				814	510	304	37.3%
III	1,765 (30.8%)	1,092 (61.9%)	673 (38.1%)				1,765	1,092	673	38.1%
IV	2,805 (48.9%)	1,752 (62.5%)	1,053 (37.5%)				2,805	1,752	1,053	37.5%
recurrence	152 (2.7%)	93 (61.2%)	59 (38.8%)				152	93	59	38.8%
unknown*	30 (0.5%)	19 (63.3%)	11 (36.7%)				30	19	11	36.7%

Duration of Formalin fixation	< 24h	24 - 48h	48 h<	unknown*	No. of sample	KRAS WT	KRAS MT	P value
< 24h	1,042 (18.2%)	642 (61.6%)	400 (38.4%)		1,042	642	400	38.4%
24 - 48h	2,554 (44.6%)	1,590 (62.3%)	964 (37.7%)		2,554	1,590	964	37.7%
48 h<	1,495 (26.1%)	933 (62.4%)	562 (37.6%)		1,495	933	562	37.6%
unknown*	641 (11.2%)	412 (64.3%)	229 (35.7%)		641	412	229	35.7%

*not included in the denominator of the logistic regression



Logistic regression

				odds-ratio	95% confidence interval
Gender	Female	VS	Male	1.211	1.082 - 1.355
Age	50 - 59	VS	< 50	1.308	1.053 - 1.624
	60 - 69	VS	< 50	1.382	1.126 - 1.695
	70 =<	VS	< 50	1.408	1.145 - 1.733
Year the sample obtained	Surgically resected (2006)	VS	Surgically resected (<2006)	1.147	0.894 - 1.472
	Surgically resected (2007=<)	VS	Surgically resected (<2006)	1.193	1.009 - 1.410
	Biopsy	VS	Surgically resected (<2006)	0.820	0.524 - 1.283
	Biopsy (2009 =<)	VS	Biopsy (<2009)	1.494	0.914 - 2.443
Primary tumor site	left-sided colon	VS	right-sided colon	0.462	0.404 - 0.528
	appendix	VS	right-sided colon	1.926	0.844 - 4.396
	rectum	VS	right-sided colon	0.674	0.587 - 0.773

(Odds ratios of biopsy (2009=<) and biopsy (<2009) against surgery specimen (<2006) are estimated as (0.820 × 1.494)^{1/2}=1.107 (0.820/1.494)^{1/2}=0.741, respectively.)

Conclusion

- This is the largest observational study of KRAS mutational status in CRC in Japan.
- The frequency of KRAS mutation (37.6%) in Japanese CRC patients is similar to those reported in previous studies from western countries.
- There are the significant difference of the frequency of KRAS mutation between
 - male (35.5%) and female (40.9%)
 - left-sided colon (29.3%) and right-sided colon (48.2%).
 - As the age is higher there is more frequent KRAS mutation.

Reference

- Karapetis CS, et al. N Engl J Med. 2008
- Amado RG, et al. J Clin Oncol. 2008
- Van Cutsem E, et al. N Engl J Med. 2009

Acknowledgement

This study was funded by Comprehensive Support Project for Oncology Research (CSPOR) of Public Health Research Foundation. The research institutes are Tokyo Medical and Dental University, Teikyo University School, and National Cancer Center Hospital East. We would like to thank 389 sample provided hospitals.