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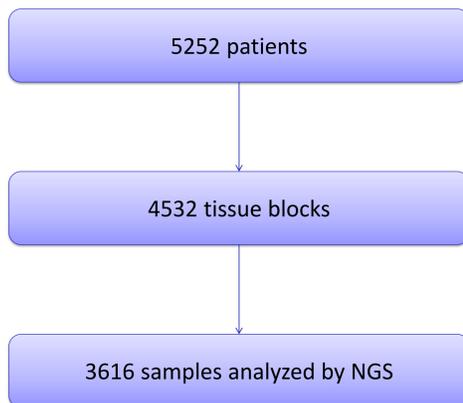
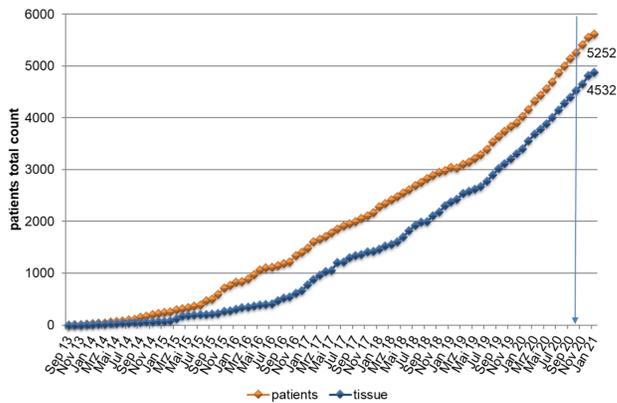
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Background

KRAS and NRAS mutations (allRAS) are frequently found in UICC stage IV colorectal cancer tumors, those patients are excluded from epidermal growth factor receptor (EGFR) directed therapy. Previously distinct KRAS mutations as p.G12C have been shown to be associated with poor prognosis in metastatic Colon cancer. Here we analyzed the prognostic value of distinct mutations in early stages (II-III) in the real life cohort ColoPredict Plus registry.

Methods

5252 patients with UICC stage I to III Colon cancer were registered between Sep 2013 and Oct 2020 in 175 German cancer centers. Mutational status of known oncogenes like KRAS and BRAF was determined by next generation sequencing (NGS) in tumor tissue of 3616 patients so far. Three-year disease free survival (DFS) and five-year overall survival (OS) were estimated using Kaplan-Meier-Statistics.



B

Fig. 1: recruitment statistics

Until October 2020 5252 patients had been recruited into the trial, 4532 tissues were sent into the central pathology, 3616 have been analyzed for mutational status of known oncogenes so far. Ongoing recruitment over time in A, available data Oct. 2020 in B.

Results

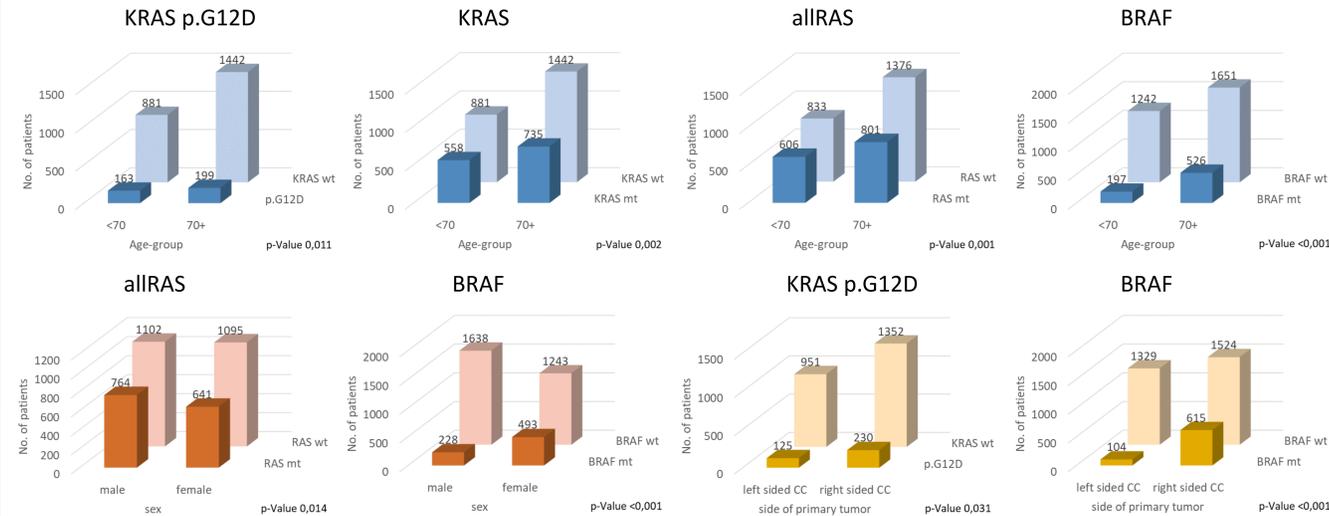


Fig. 2: Differences in mutation frequency

Blue: mutation to age group, orange: mutation to sex, yellow: mutation to side of primary tumor.

	p.G12C	p.G12D	KRAS	NRAS	allRAS	BRAF	all (NGS)	KRAS wt	NRAS wt	RAS wt	BRAF wt
N	81 (2,2%)	368 (10,2%)	1293 (35,8%)	122 (3,4%)	1407 (38,9%)	723 (20%)	3616 (100%)	2323 (64,2%)	3494 (96,6%)	2209 (61,1%)	2893 (80%)
min	42	29	27	38	27	29	25	25	25	25	25
max	87	92	96	92	96	100	100	100	100	100	96
median age	73	71	72	72	72	76	73	73	73	73	72
age <70	28 (0,8%)	163 (4,5%)	558 (15,4%)	50 (1,4%)	606 (16,8%)	197 (5,4%)	1439 (39,8%)	881 (24,4%)	1389 (38,4%)	833 (23%)	1242 (34,3%)
age 70+	52 (1,4%)	199 (5,5%)	735 (20,3%)	72 (2%)	801 (22,2%)	526 (14,5%)	2177 (60,2%)	1442 (39,9%)	2105 (58,2%)	1376 (38,1%)	1651 (45,7%)
male	37 (1%)	189 (5,2%)	694 (19,2%)	75 (2,1%)	764 (21,1%)	228 (6,3%)	1866 (51,6%)	1172 (32,4%)	1791 (49,5%)	1102 (30,5%)	1638 (45,3%)
female	42 (1,2%)	173 (4,8%)	597 (16,5%)	47 (1,3%)	641 (17,7%)	493 (13,6%)	1736 (48%)	1139 (31,5%)	1689 (46,7%)	1095 (30,3%)	1243 (34,4%)
left sided CC	26 (0,7%)	125 (3,5%)	482 (13,3%)	58 (1,6%)	538 (14,9%)	104 (2,9%)	1433 (39,6%)	951 (26,3%)	1375 (38%)	895 (24,8%)	1329 (36,8%)
right sided CC	51 (1,4%)	230 (6,4%)	787 (21,8%)	63 (1,7%)	844 (23,3%)	615 (17%)	2139 (59,2%)	1352 (37,4%)	2076 (57,4%)	1295 (35,8%)	1524 (42,1%)
UICC stage II	35 (1%)	178 (4,9%)	636 (17,6%)	59 (1,6%)	693 (19,2%)	336 (9,3%)	1758 (48,6%)	1122 (31%)	1699 (47%)	1065 (29,5%)	1422 (39,3%)
UICC stage III	36 (1%)	165 (4,6%)	575 (15,9%)	53 (1,5%)	625 (17,3%)	332 (9,2%)	1591 (44%)	1016 (28,1%)	1538 (42,5%)	966 (26,7%)	1259 (34,8%)
Chemotherapy	26 (0,7%)	139 (3,8%)	483 (13,4%)	43 (1,2%)	524 (14,5%)	215 (5,9%)	1276 (35,3%)	793 (21,9%)	1233 (34,1%)	752 (20,8%)	1061 (29,3%)
no ACT	43 (1,2%)	177 (4,9%)	628 (17,4%)	61 (1,7%)	683 (18,9%)	415 (11,5%)	1848 (51,1%)	1220 (33,7%)	1787 (49,4%)	1165 (32,2%)	1433 (39,6%)

Table 1: Baseline characteristics

Given are the baseline characteristics for the whole cohort analyzed for mutational status so far (all NGS). Highlighted in blue, green, purple and orange are pairs with a significant difference (p-Value < 0,05), see also Fig. 2. CC: colon cancer, ACT: adjuvant chemotherapy, wt: wild type

Survival all UICC-stages

	p.G12C	p.G12D	KRAS	NRAS	allRAS	BRAF	all (NGS)	KRAS wt	NRAS wt	RAS wt	BRAF wt
5-year OAS	79,70%	65,40%	68,60%	57,20%	68,20%	66,10%	67,60%	67,00%	68,30%	67,30%	68,00%
p-Val. OAS	0,815	0,671	0,415	0,978	0,386	0,119	x	x	x	x	x
3-year DFS	75,60%	67,00%	68,10%	68,30%	68,20%	70,90%	69,20%	69,80%	69,50%	69,90%	68,80%
p-Val. DFS	0,788	0,851	0,451	0,87	0,442	0,891	x	x	x	x	x

UICC stage III only

	p.G12C	p.G12D	KRAS	NRAS	allRAS	BRAF	all (NGS)	KRAS wt	NRAS wt	RAS wt	BRAF wt
5-year OAS	84,5	59,20%	67,90%	30,90%	66%	57,35%	x	59,80%	64,30%	61,90%	65,60%
p-Val. OAS	0,326	0,476	0,028*	0,202	0,074	0,009*	x	x	x	x	x
3-year DFS	82,20%	61,80%	64,30%	47,40%	63%	61,30%	x	61,40%	62,90%	62,10%	62,80%
p-Val. DFS	0,361	0,438	0,257	0,158	0,528	0,184	x	x	x	x	x

UICC stage II only

	p.G12C	p.G12D	KRAS	NRAS	allRAS	BRAF	all (NGS)	KRAS wt	NRAS wt	RAS wt	BRAF wt
5-year OAS	75,70%	71,40%	69,80%	80,70%	70,40%	75%	x	73,80%	72,00%	73,50%	71,50%
p-Val. OAS	0,557	0,952	0,505	0,232	0,804	0,893	x	x	x	x	x

Table 2: Survival data

For OAS the 5-year survival probability has been calculated using the Kaplan-Meier method. For DFS the 3-year survival probability is given. A significant (below 0,05) p-Value is highlighted with *. OAS: overall survival, DFS: disease free survival, allRAS: KRAS or NRAS mutation

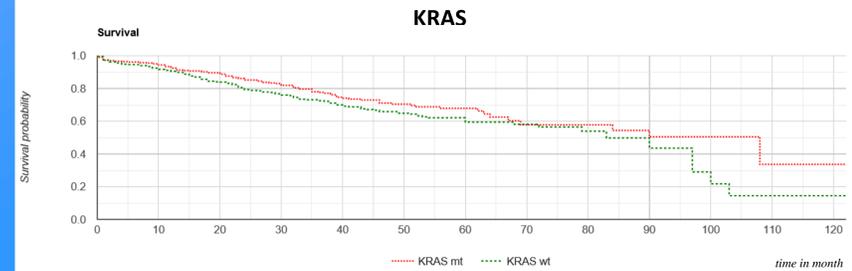


Fig. 3: OAS in UICC stage III KRAS

OAS for UICC stage III colon cancers with a KRAS mutation versus no KRAS mutation. Number of death: KRAS: 106; KRAS wt: 204; p-Value 0,028.

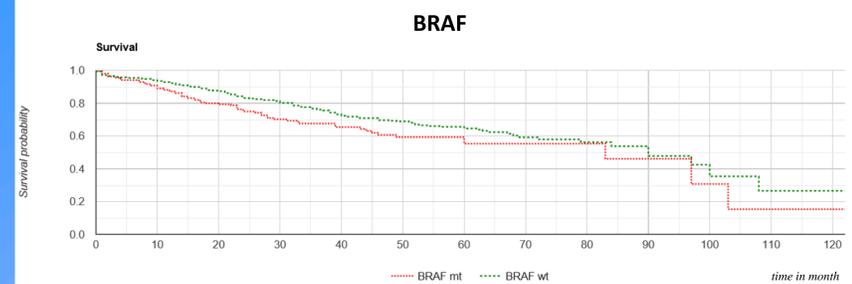


Fig. 4: OAS in UICC stage III BRAF

OAS for UICC stage III colon cancers with a BRAF mutation versus no BRAF mutation. Number of death: BRAF: 76; BRAF wt: 234; p-Value 0,009.

Resume

Mutation frequency was significantly higher in men for NRAS and allRAS (p-Value 0.034 / 0.014) and in women for BRAF (p-Value <0.001). Younger patients below 70 years carried more KRAS and allRAS mutations (p-Value 0.003 / 0.002), 70 years and older patients had more BRAF mutations (p-Value <0.001). There was no significant difference in UICC stage for all 4 markers. BRAF was more frequent in right sided tumors (p-Value <0.001). Within UICC stage III KRAS mutated tumors had a better OS (p-Value 0.028) than KRAS wild type tumors and BRAF mutated tumors had a worse outcome (p-Value 0.009) than BRAF wild type tumors possibly due to age. Most affected codon in KRAS was codon 12 (64.3%), NRAS codon 61 (41.9%) and BRAF codon 600 (94.3%). There was no significant difference between the subgroup of KRAS p.G12C mutations and the KRAS wild type cohort in age group, sex, localization, UICC stage and ACT nor for DFS or OS. The KRAS p.G12D variant was significantly more frequent in younger patients below 70 years (p-Value 0.011) and in right side tumors (p-Value 0.031) compared to the KRAS wild type group.

In our real life cohort we did not find a prognostic value for the KRAS p.G12C mutation in early Colon cancer stages, nor did the alteration show association with distinct clinical features.

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