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ALK-rearranged renal cell carcinomas in Polish population

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ABSTRACT

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase, the activation of which is considered an important event in the pathogenesis of several neoplasms and a predictive factor for the targeted therapy with ALK inhibitors. Thus far, ALK rearrangements have been identified in 22 renal cell carcinomas in both pediatric and adult patients. We evaluated the incidence of ALK rearrangement-associated RCC in adult Central European population. An immunohistochemical evaluation of 1019 kidney tumors was performed with use of three different clones of anti-ALK antibodies. None of the tested samples showed positive staining, which suggests that the incidence of ALK rearrangement-associated renal cell carcinomas is significantly lower in the Polish population, and indicates a potential association between ethnicity and occurrence of these rare neoplasms.

1. Introduction

ALK is a receptor protein kinase belonging to the superfamily of insulin receptors and encoded by the *ALK* gene located on the 2p23 chromosome. ALK regulates many intracellular pathways, such as PI3K/AKT, MAPK or JAK/STAT. Activation of these pathways leads to the cell proliferation, increased cell survival and motility. ALK hyperactivation may result from various mechanisms, e.g. gene amplification, point mutation and translocation involving the kinase domain of the protein [1].

The role of ALK in carcinogenesis was described for the first time in 1994 by Morris et al. in anaplastic large cell lymphoma [2]. Since then, its aberrations were found in many neoplasms, including diffuse large B cell lymphoma [3], inflammatory myofibroblastic tumor [4], and neuroblastoma [5], however, the most clinically and epidemiologically relevant was identification of ALK rearrangements in about 7% of the cases of lung adenocarcinoma [6,7]. This has led to the development of targeted ALK inhibitors, with crizotinib the first one approved as an effective drug for ALK-positive non-small cell lung carcinoma (NSCLC) in 2011 [8].

Rearrangements of ALK in renal cell carcinomas (RCC) have been described in both adult and pediatric population. Due to their distinctive morphology and their potential response to targeted therapy, they have been included as an emerging/provisional entity in the latest WHO classification [9]. Due to its rarity, ALK-rearranged RCCs (ALK-RCCs) are still poorly understood neoplasms. As of today, no screening study has been published on their incidence in European population.

The following screening study of 1019 patients with renal tumors was aimed at determining the incidence of carcinoma-related ALK alterations among the adult Polish population, as well as conducting a comparative analysis of the previously published results and investigating the immunohistochemical profile of these neoplasms.

2. Material and methods

The study was approved by the Bioethical Committee of the Medical University of Gdansk.

Patient Selection

Tissue samples from 1345 kidney tumors were examined, 610 from the patients treated in the University Clinical Centre (UCC) in Gdansk in years 2008–2016, and 735 from the patients operated in different southern Poland hospitals in years 1992–2005 and retrieved from the

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archives of the Department of Pathomorphology, Jagiellonian University (JU) in Krakow.

2.1. Clinical and pathological features

Clinical features including the patients age at diagnosis and gender as well as pathological features including the histological diagnosis, staging and grading were collected from the medical pathologic reports. All slides were reviewed by pathologist experienced in urologic pathology (WB,KO). The nuclear grading was reassessed according to the ISUP grading system [10].

2.2. Microarray preparation

Tissue microarrays (TMA) from UCC samples consisting of at least 2 representative core sections (2 mm in diameter), with extra sections taken from tumors showing higher morphological heterogeneity, were prepared using the Manual Tissue Arrayer MTA-1 (BeecherInstruments, Inc., Sun Praire, WI, USA) for the purpose of immunohistochemical staining. The TMAs for fluorescent in situ hybridization (FISH) consisted of one core 2,5 mm in diameter, also prepared with MTA-1. TMAs for immunohistochemistry (IHC) from JU consisted of 2 cores 2 mm in diameter and were prepared with a manual device (Histopathology Inc., Hungary).

Non-neoplastic tissue fragments were used as a negative control and location markers in each microarray.

2.3. Immunohistochemistry

4 μm-thick sections were taken from TMAs and stained with 3 clones of anti-ALK antibodies. Autostainer Link 48 (Agilent Technologies, Santa Clara, CA) was used for staining with ALK1 (Dako, Carpinteria, CA, USA) and 5A4 (NovocastraTM, LeicaBiosystems, Newcastle Upon Tyne, United Kingdom) ready-to-use primary antibodies. The pretreatment was performed using heat-induced antigen retrieval in pH 6,1 buffer with subsequent 20 min incubation with ALK1 antibody, and in pH 9,0 buffer with 45 min incubation for 5A4. Antibody incubation was followed by the standard signal amplification with mouse LINKER at room temperature for 15 min.

IHC for D5F3 (Ventana, Tucson, AZ, USA) was performed on Ventana Benchmark GX automated staining system (Ventana) with ultraView DAB detection kit (Ventana), using the protocol developed by Ventana in all cases from UCC.

Positive control in form of ALK-positive lung cancer and healthy appendix was used for every staining. The H-score was evaluated in every case by multiplying the percentage of tumor that stain positively by the intensity (0 for negative, 1 for weak, 2 for moderate and 3 for strong staining; total H-score equaling 0–300) by two experienced pathologists. In cases showing potentially positive (H-score 10 or above) or ambiguous staining, the staining was repeated on full sections with negative reagent control to rule out the false positive results associated with the limitations of TMA use, as well as to assess the potential heterogeneity of the staining.

2.4. FISH

FISH was performed on TMAs from the 31 RCCs showing positive IHC staining in TMAs as well as from remaining 5 unclassified RCCs. Slides were hybridized using dual-color break-apart *ALK* FISH probe set (Empire Genomics, Williamsville, NY, USA) according to the standard protocol. At least 100 cells were analyzed using the ISIS software (MetaSystems Hard & Software GmbH, Altlussheim, Germany). The cutoff for potential rearrangement of *ALK* was set at 10% of cells showing a split or isolated 3′ pattern, and in these cases the hybridization was to be repeated on the whole sections.

Statistical analysis

Table 1
The clinicopathological characteristics of patients.

			number	%
Diagnosis	CC		798	78,3%
	grading	grade 1	101	9,9%
		grade 2	275	27,0%
		grade 3	193	18,9%
		grade 4	93	9,1%
	CP T1		64	6,3%
	grading	grade 1	26	2,6%
		grade 2	13	1,3%
		grade 3	7	0,7%
		grade 4	0	0,0%
	CP T2		32	3,1%
	grading	grade 1	2	0,2%
		grade 2	7	0,7%
		grade 3	12	1,2%
		grade 4	0	0,0%
	Chr		46	4,5%
	UC		67	6,6%
	Other		12	1,2%
	Total		1019	100%
Stage	T	T1a	241	23,7%
		T1b	229	22,5%
		T2a	28	2,7%
		T2b	82	8,0%
		T3a	276	27,1%
		T3b	95	9,3%
		T4	11	1,1%
	N	N0	112	11,0%
		N1	39	3,8%
	M	M1	7	0,7%
Age	20-92	20-39	19	2,1%
		40-59	311	33,9%
		60-79	517	56,3%
		80-92	71	7,7%
Gender	M		374	36,7%
	F		278	27,3%

CCC - clear cell renal cell carcinoma, CP - papillary renal cell carcinoma, T1 - type 1, T2 - type 2, Chr - chromophobe carcinoma, UC - urothelial carcinoma.

Results of the study were compared to the previously published data using the maximum-likelihood Chi-square test. Statistical analysis was performed using Statistica, version 13 (TIBCO Software Inc., San Francisco, CA, USA), with P-value of < 0.05 considered statistically significant.

3. Results

From 1345 tissue samples immunohistochemical analysis was successful in 1019 cases, including 798 clear cell carcinomas, 96 papillary carcinomas, 46 chromophobe carcinomas, 67 urothelial carcinomas, 6 unclassified carcinomas, 3 squamous cell carcinomas, 2 collecting duct carcinomas, 1 multilocular cystic renal neoplasm of low malignant potential. The detailed clinicopathologic characteristics of successfully stained cases are shown in Table 1. The staining was unsuccessful in 326 samples, mainly due to the insufficient tumor tissue in the TMAs.

After TMAs staining, 31 cases were considered either potentially positive or indeterminable based on staining with at least one clone of anti-ALK antibody. 15 cases showed nuclear staining with ALK1 clone with H-score ranging from 10 up to 50 (average 20) without any nuclear or cytoplasmic staining (Fig. 1C), and no positive reaction with the remaining clones. Another 16 cases showed weak cytoplasmic staining with all 3 clones of antibodies, with highest H-score of 56 (average 25) (Fig. 2A,C), however the staining pattern of the cores was highly suggestive for non-specific reaction, e.g. due to the peripheral location on TMAs or large amount of necrotic tissue. None of those 31 cases showed a specific positive reaction in the repeated staining of the whole sections while compared to the negative reagent control (Figs. 1D, 2B,2D).

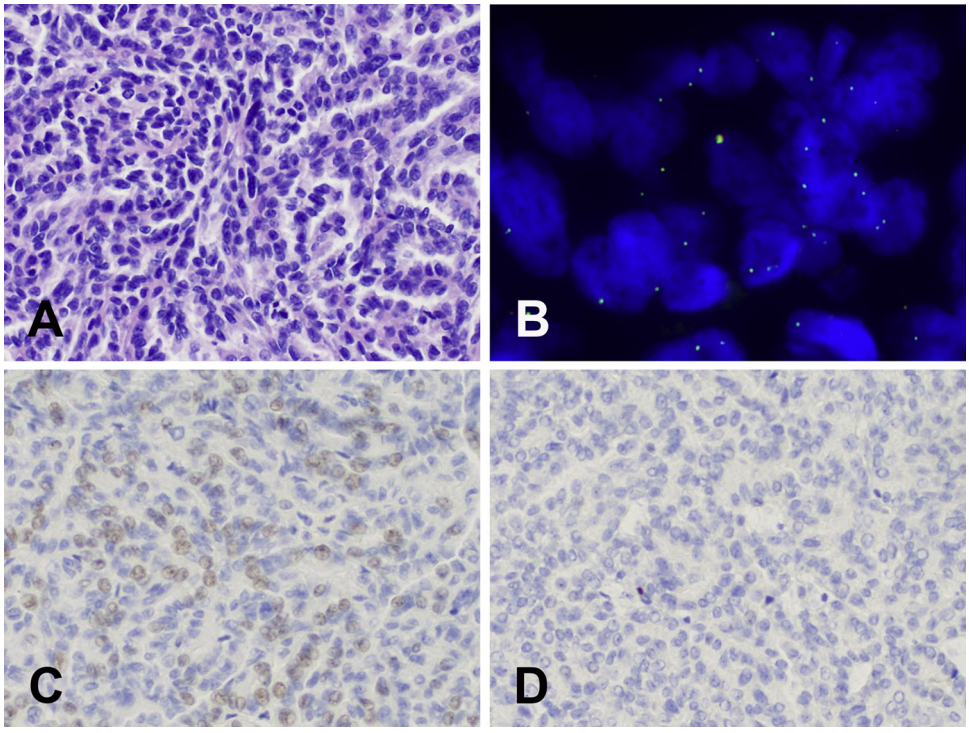

Fig. 1. Papillary RCC showing strong nuclear staining with ALK1 antibody (A,C). FISH was negative for *ALK* rearrangements (B). The staining repeated on the whole section was negative in all 3 clones of anti-ALK antibodies (D).

The FISH analysis did not show *ALK* rearrangements in any of the evaluated tumors. It was also negative in the remaining 5 unclassified carcinomas (Fig. 1B).

Statistical analysis showed that obtained results differed significantly from data gathered from four previously published large institutional studies based on TMAs screening on adult population (0/1019 vs 7/2195; Maximum-Likelihood Chi-square test, $\chi 2 = 5.35$, $p = 0.02$; Fig. 3) [11–14].

4. Discussion

Since the first description in 2010, 22 cases of ALK-RCCs have been reported [11–25], for 21 of which there is pathoclinical data available (Table 2). Although initial reports suggested association between ALK-RCCs and black children harboring sickle cell traits, it is now known that these tumors may occur in various age and ethnic populations with slight male predilection (male/female ratio 1.5:1), and the sickle cell

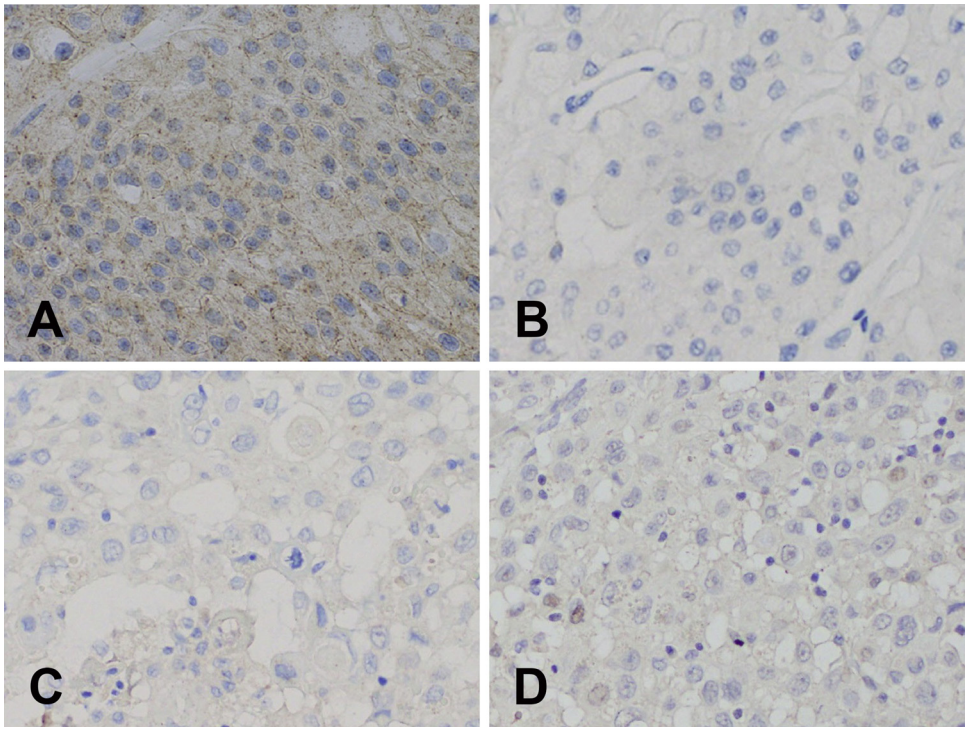

Fig. 2. Examples of false positive cytoplasmic reactions. Chromophobe RCC showing moderate cytoplasmic staining in all 3 clones of anti-ALK antibodies (A) The staining was negative in the repeated whole-section slides (B); Clear cell RCC showing weak cytoplasmic staining in all 3 clones (C), however, the reaction was proven to be unspecific by using the negative reagent control (D).

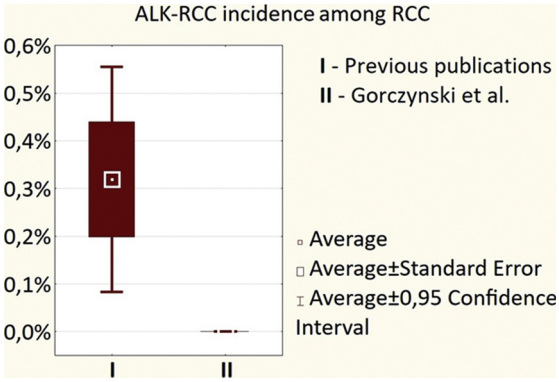

Fig. 3. The statistical difference between previous publications and the results of the current study.

traits were found in the minority of patients (3/21). In the previous institutional retrospective screening studies ALK rearrangement was found in 0.12-0.56% of the renal tumors [11,12,14,23].

The fusion partners of the *ALK* were identified in 16 cases and included *VCL*, *HOOK1*, *TPM3*, *EML4*, and *STRN*, with *VCL* and *HOOK1* rearrangements described only in pediatric population, and VCL limited to the cases with sickle cell trait. In the 2016 WHO classification the pediatric ALK-RCC were recognized to show distinct morphology similar to that of renal medullary carcinoma (RMC), with large polygonal cells, eosinophilic cytoplasm and intracytoplasmic lumina [9]. Contrary to the classic RMC, these tumors retain INI-1 expression and harbor much more favorable prognosis. ALK-RCC found in adults are much more heterogenic, although papillary features, as well as abundant intra- and extracellular mucin, rhabdoid and signet-ring cells are commonly present. The ISUP grading is usually high [13,14,17].

Diagnosis of the ALK-RCCs is clinically relevant not only on account of their uncertain prognosis despite high grade morphology, but also because the patients can potentially benefit from anti-ALK therapy. Thus far successful use of such targeted therapy in ALK-RCC was reported only once, in a 12 year old female with recurrent inoperable tumor. The patient remained alive after more than a year of continuous treatment [18].

The immunohistochemical (IHC) analysis of ALK production has been proven a valuable tool in diagnosis of ALK-positive NSCLC, and is routinely used for screening purposes to identify the patients eligible for treatment with ALK inhibitor. In the United States (US) the standardized IHC CDx Assay using D5F3 clone of anti-ALK antibody was approved by the US Food and Drug Administration (FDA) and does not require confirmation by fluorescent in situ hybridization (FISH) [26]. In kidneys 18 out of 19 tested ALK-RCCs showed cytoplasmic and/or membranous staining pattern with various clones of anti-ALK antibodies. The negative staining in one case was contributed to the use of old FFPE slide and poor antigen retrieval [25].

Because of their rarity and heterogeneous morphology ALK-RCCs create a potential diagnostic pitfall and might be easily misdiagnosed as RMC, unclassified carcinomas (URCC), PRCC or MiT family translocation renal cell carcinomas (MiT-RCC). Their lack of recognizable IHC markers other than ALK combined with uniform expression of TFE3 in pediatric cases makes the initial diagnosis of MiT-RCC even more justifiable. It is worth noticing, however, that MiT-RCC are negative in ALK staining, and ALK-RCC will not show TFE3 translocations in FISH. The immunohistochemical profile of reported cases can be found in Table 3.

In the present study, the most extensive screening for ALK-RCC thus far, 1019 renal tumors collected from two large national centers were tested, without any positive cases identified. Potential causes for which these results diverge from those previously published [11–14] include difference in laboratory method, laboratory error or variance in the selected population. The chosen methodology was similar to that used by other authors, with small variance in the number of cores taken and their diameter. As previous publications suggested that different clones may show wide-ranging sensitivity and specificity in ALK-positive cancers [27], three different clones of anti-ALK antibody, namely 5A4, D5F3 and ALK1, were used in the study. For all stains a negative internal control, a positive control, as well as negative reagent control was used, leaving no doubts as to the correctness of the method.

31 cases were considered potentially positive or showed ambiguous

Table 2
. Summary of the available pathoclinical data of ALK-RCC patients and of a tumor showing ALK-RCC morphology with ALK copy gain (case 22).

#	Sex	Age	Race	Sickle cell trait	Observation (months)	Death	Size (mm)	TNM	Initial Diagnosis	WHO grade	ALK IHC	clone	location	% FISH positive cells	Fusion partner	References
1	M	6	B	1	21	0	46	T1aN0	RMC	3	+	ALK1	C	80	VCL	20
2	M	16	B	1	9	0	65	T3aN1	URCC	3	+	5A4	C	> 50	VCL	21
3	F	36	A	0	24	0	40	T1aN0	URCC	3	+	5A4	C	> 15	TPM3	14
4	F	53	A	0	84	0	25	T1aN0	PRCC	2	+	5A4	C	> 15	EML4	14
5	M	61	n/d	0	48	1	50	T1bNx	PRCC	2	+/-	ALK1	C	100	n/d	11
6	M	59	n/d	0	16	1	55	T1bNx	PRCC	3	+	ALK1	C	100	n/d	11
7	M	44	A	0	144	0	30	T1aN0	PRCC	3	+	ALK1	C	tests not conducted		12
8	M	6	B	1	19	0	30	T1aN0	URCC	4	+/-	ALK01	M	95	VCL	22
9	M	40	B	n/d	48	0	62	T1bN0	PRCC	n/d	n/d	n/d	n/d	n/d	STRN	23
10	M	16	n/d	0	n/d	n/d	45	T3aNx	URCC	4	–	n/d	–	n/d	TPM3	25
11	F	16	n/d	0	n/d	n/d	70	T3aN1	URCC	4	+	n/d	C/M	n/d	TPM3	25
12	M	14	n/d	0	n/d	n/d	37	T1aN1	URCC	4	+	n/d	C/M	30	TPM3	25
13	M	16	W	0	n/d	n/d	55	n/d	MiT RCC	4	n/d	n/d	n/d	n/d	HOOK1	15
14	F	40	n/d	0	15	0	45	T1bN0	ALK-RCC	3	+	D5F3	C	90	n/d	16
15	F	33	A	0	324	0	n/d	T2aN1	PRCC	3	+	D5F3	C	88	STRN	17
16	M	38	A	0	3	0	45	T1aN2M1	n/d	4	+	D5F3	C	62	STRN	17
17	F	12	n/d	0	25	0	60	T3aNx	MiT RCC	4	+	ALK1	C/M	85	TPM3	18
18	M	49	A	0	24	0	60	T1bN1	URCC	4	+	D5F3	C	> 50	TPM3	13
19	M	52	A	0	8	0	36	T1aN0	PRCC	2	+	D5F3	C	> 50	EML4	13
20	F	55	n/d	0	8	0	31	T1aNx	n/d	4	+	5A4	C	54	TPM3	19
21	F	19	A	0	16	0	70	n/d	ALK-RCC	4	+	D5F3	C/M	92	not found	32
22	M	36	B	0	12	0	65	T1bN0	URCC	4	+/-	ALK1	C	0	copy gain	33

Population: B - black, African or African-American; A – Asian; W – white or Caucasian; CRMC - renal medullary carcinoma; URCC - unclassified renal carcinoma; PRCC - papillary renal cell carcinoma; MiT RCC - MiT family translocation renal cell carcinomas; ALK-RCC - *ALK* rearrangement-associated renal cell carcinoma C – cytoplasmic; M – membranous; n/d – not described.

Table 3
Immunohistochemical profiles of 21 published cases of ALK-RCC and of a tumor showing morphology similar to ALK-RCC with ALK copy gain (Case No 22).

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	%	22
ALK	+	+	+	+	+/-	+	+	+/-	n/d	–	+	+	n/d	+	+	+	+	+	+	+	+	94,7%	+/-
CK AE1/AE3	+	+	+	+	+	+	+	+/-		+	+	+		+			+/-	+	+	+	+	100,0%	+/-
CK7	–	+/-	+	+	+	+	+			+/-			+/-	+/-	+	+		–	+	–	+	81,3%	+/-
CAM5.2	+	+	+	+	+	+	+/-				+											100,0%	+
34βE12				+														–	–		+	50,0%	
EMA	+	+	+	+			+	+		+	+	+	+				+	+	+		+	100,0%	–
CA IX														–				–	–			**0,0%**	
AMACR			+/-	+	+	+	–							–	–	+		–	+	+	+/-	66,7%	
INI-1	+	+						+		+	+	+	+	+			+				+	100,0%	
TFE3	+	+					–	+		+	+	+	+	–	–	–		+	–	+/-	+	66,7%	
cathepsin-K								–						–	+	+				–		40,0%	
vimentin	+	+	+		+	+	+			+		+	+	+				+	+	+	+	100,0%	+
p53	–	+/-						–		+/-	–	–	–								–	25,0%	
TTF1			–	–											-/+	+					–	25,0%	
CD10	+	–	+/-	–			+/-			–	+/-	+/-		–	+	+	–	–	–	–	–	43,8%	+/-
RCC		–	–	–				–		–	–	+/-						–	–			11,1%	+
CD117							–							–				–	–		–	**0,0%**	–
CD68																	–	–	–			**0,0%**	
melan A								–			–				–	–	–	–	–	–		**0,0%**	–
HMB45	–	–					–	–		–	–	–					–	–	–			**0,0%**	–
PAX2			+/-	+/-			+								+	+		+	+			100,0%	
PAX8			+/-	+/-										+	+	+		+	+			100,0%	
Ki67		5%	1%					5%													1,7%	**3,2%**	
References	20	21	14	14	11	11	12	22	23	25	25	25	15	16	17	17	18	13	13	19	32		33

The cases' numbers correspond to those listed in Table 2.
% - percentage of cases with at least focal positivity.

staining pattern based on the initial results of the IHC using TMAs. The nuclear staining pattern observed in 15 cases has never been reported in any ALK-RCC, however, it was described in other neoplasms harboring ALK translocation [1]. All 31 cases were proven to be negative for ALK overproduction using the whole sections IHC with negative reagent control, and in most of them the initial false positive results in microarrays were regarded to result from the non-specific border reaction, as the IHC-positive cores were localized almost exclusively on the margins of the TMAs. The absence of *ALK* rearrangement was further confirmed in all these cases using FISH method. All URCCs were also selected for FISH analysis, as these tumors were proved to present with the highest incidence of underlying ALK-rearrangement [24]. Normal *ALK* status was confirmed in all of these cases.

The summary of clinical data of all screening studies for ALK-RCC is presented in Table 4. The structure of diagnosed tumors in the analyzed population corresponds in vast extent to that conducted by Sugawara et al. [14], in which the authors were able to demonstrate ALK translocations in 2 among the 355 examined tumors. Because of the typical morphology of ALK-RCC, the number of cases diagnosed as PRCC or URCC might be relevant. In presented study the highest total number of such tumors was examined as compared to the three other screening studies that were not focused on specific tumor subtypes [12–14]. The age of patients was similar to that shown in the other publications. Gender of patients has been rarely mentioned previously, but observed male to female ratio is noticeably lower than in population examined by Sukov et al and the Cancer Genome Atlas (TCGA) Research Network sequencing study of 161 papillary carcinomas (1.35:1 vs 3:1 and 2.63:1 respectively) [11,23]. It is worth noticing, however, that among ALK-RCC cases reported in adult population this ratio was even lower (1.17:1, 7:6) and this factor should not have influenced the final results.

This study is the first one to be performed on group of adult patients belonging to an almost homogeneous Caucasian population [28], and our results might suggest that the incidence of ALK-RCC is significantly lower in this ethnic group. Such racial disparity is well known to occur in other cancers [29,30]. Ethnic background can also affect the incidence of specific renal cancer subtypes, with established association between black ethnicity and papillary histologic features [31].

The association between the ethnicity of the patients and ALK-RCC incidence has not been yet analyzed. Eight of the published cases described Asian patients – five Japanese, two Chinese and one Korean, all of which belonged to the adult population (age 19–53) [12–14,17,32]. There was also one black patient with *STRN-ALK* rearrangement documented in the TCGA study on papillary carcinomas [23]. Additionally, a renal cancer showing morphology suggestive for ALK-RCC was described in a 36-year-old African male, in which *ALK* copy gain with no gene rearrangement was found [33]. Whether this copy gain contributed to the morphology of the tumor is debatable, as previous studies showed that more than 10% of all renal cell carcinomas show *ALK* copy gain, with no impact on their morphology other than a larger tumor size and higher nuclear grading [11]. Immunophenotype of this tumor also differed from other ALK-RCCs, with negative staining for EMA and positive staining for RCC (case 22 in Table 3). There were no adult patients of disclosed Caucasian ethnicity with ALK-RCC in the literature.

To conclude, the results of this study indicate that the incidence of ALK-RCC shows various geographic distribution, and is particularly low in the Polish population. This suggests that ALK-RCC incidence might be ethnically-related, therefore, for further analyses, ethnicity of ALK-RCC patients should be disclosed in the following reports of ALK-rearranged carcinomas.

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Table 4
Summary of clinical data and methods used for screening in published ALK-RCCs.

Source	Sugawara et al. [14]	Sukov et al. [11]	Lee et al. [12]	Yu et al. [13]	Cajaiba et al. [25]	TCGA [23]	Chen et al. [24]	Current study
Total no of patients successfuly tested	355	534	829	477	168	161	62	1019
CC RCC	255 (71.8%)	250 (46.8%)	689 (83.1%)	318 (66.7%)	39 (23.2%) (CC RCC + PRCC + ChrC)	0	0	798 (78,3%)
PRCC	32 (9.0%)	284 (53.2%)	53 (6.4%)	75 (15.7%)		161 (100%)	0	96 (9,4%)
ChrC	34 (9.6%)	0	73 (8.8%)	67 (14.0%)		0	0	46 (4,5%)
URCC	10 (2.8%)	0	n/d	6 (1.3%)	33 (19.6%)	0	62 (100%)	6 (0,6%)
Other	24 (6.8%) [6 CDC (1.7%), 6 S-RCC (1.7%), 12 other (3.4%)]	0	14 (1.7%)	11 (2.3%)	96 (57.1%) [78 MiT RCC (46.4%) 18 RMC (10.7%)]	0	0	73 (7,2%)
Number of ALK-RCC	2 (0.56%)	2 (0.37%)	1 (0.12%)	2 (0.42%)	6 (3.57%)	1 (0.62%)	1 (1.61%)	0
Clone of antibody	5A4	ALK1	ALK1	D5F3	n/d	IHC not performed	IHC not performed	ALK1, 5A4, D5F3
Number/size of TMA cores from each patient	n/d	4 x 0.6 mm	1 x 2 mm	1 x 3 mm	TMA not used			2 x 2 mm
Age of patients (median)	n/d	30-89 (64-66)*	n/d	n/d	< 18 (n/d)	28-85 (60)	12-86 (60)	20-92 (63)
Gender (M/F)	n/d	3:1	n/d	n/d	n/d	2.63:1	1.22:1	1.35:1
Population	Japanese	American	Korean	Chinese	n/d	American	American	Polish
pT1	n/d	328 (62.5%)	n/d	n/d	n/d	102 (63.4%)	22 (35.5%)	470 (49.9%)
pT2		89 (17.0%)				16 (10.0%)	4 (6.5%)	110 (11.4%)
pT3		105 (20.0%)				42 (26.1%)	36 (58.1%)	371 (38.6%)
pT4		3 (0.5%)				1 (0.6%)	(T3 + T4)	11 (1.1%)

CC RCC - clear cell renal cell carcinoma (RCC). PRCC - papillary RCC. ChrC - chromophobe RCC. URCC - unclassified RCC. CDC - collecting duct RCC. S-RCC - sarcomatoid RCC. IHC - immunohistochemistry. * - median disclosed for various risk groups only.

Declaration of Competing Interest

Dr. Wojciech Biernat has obtained a compensatory consultant fee from MSD.

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