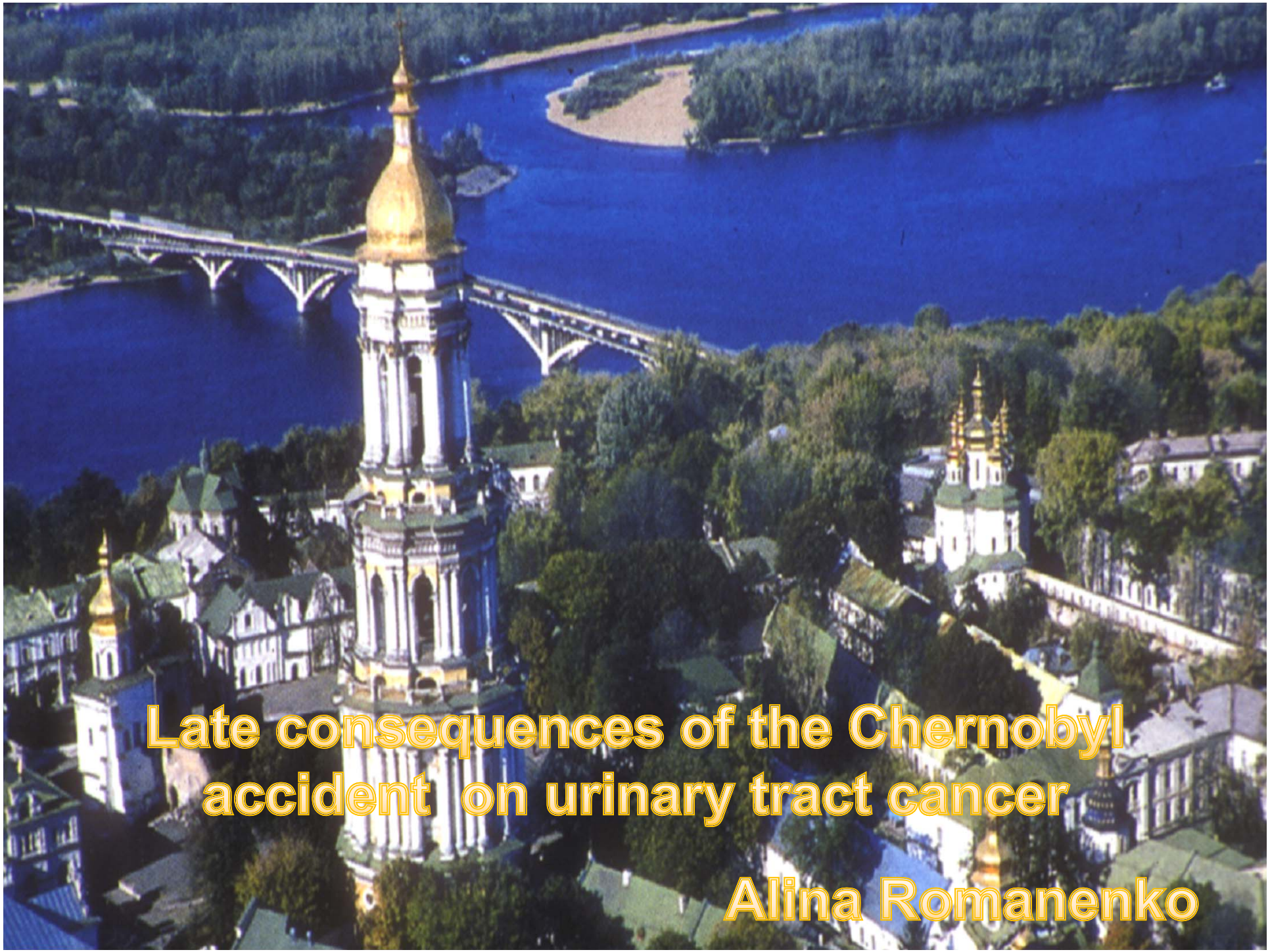
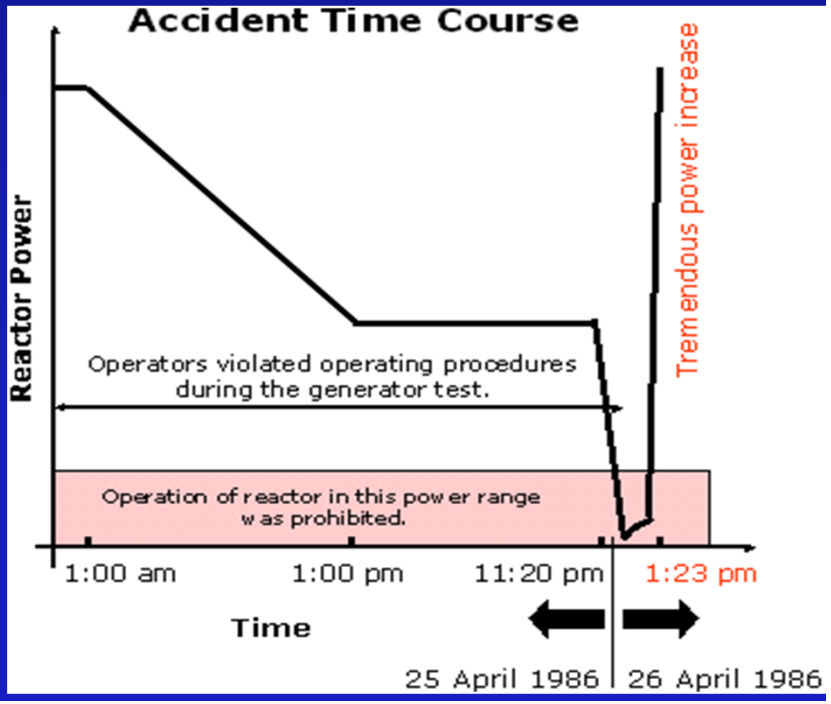


Late consequences of the Chernobyl accident on urinary tract cancer

Alina Romanenko

The consequences of the accident:

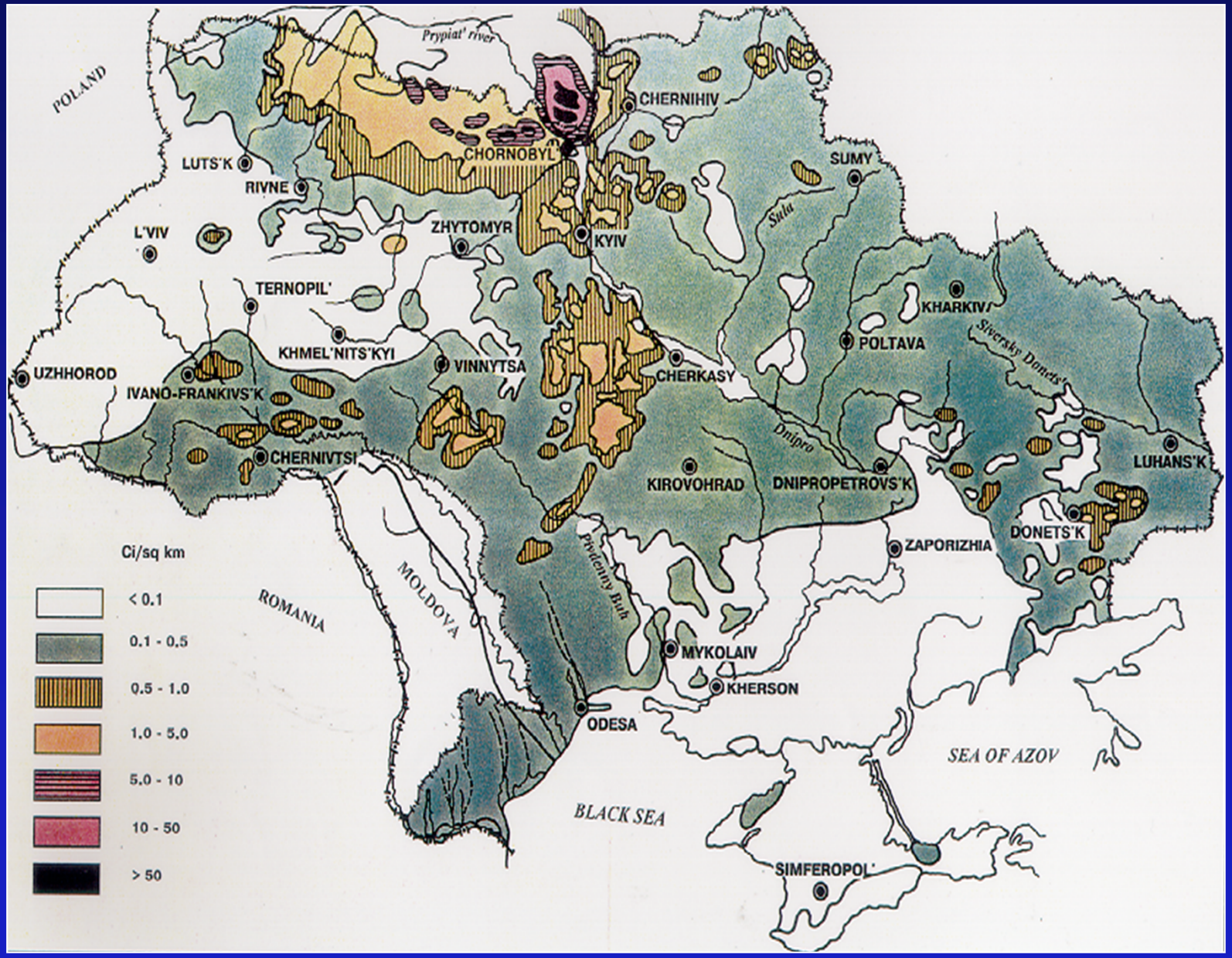
- About **120,000 people were evacuated from the 30 kilometer** distance around the power plant.
- About **600,000 people, called liquidators,** assisted in removing the consequences of the accident.
- The remains of the reactor were covered with a special structure called a **sarcophagus**.



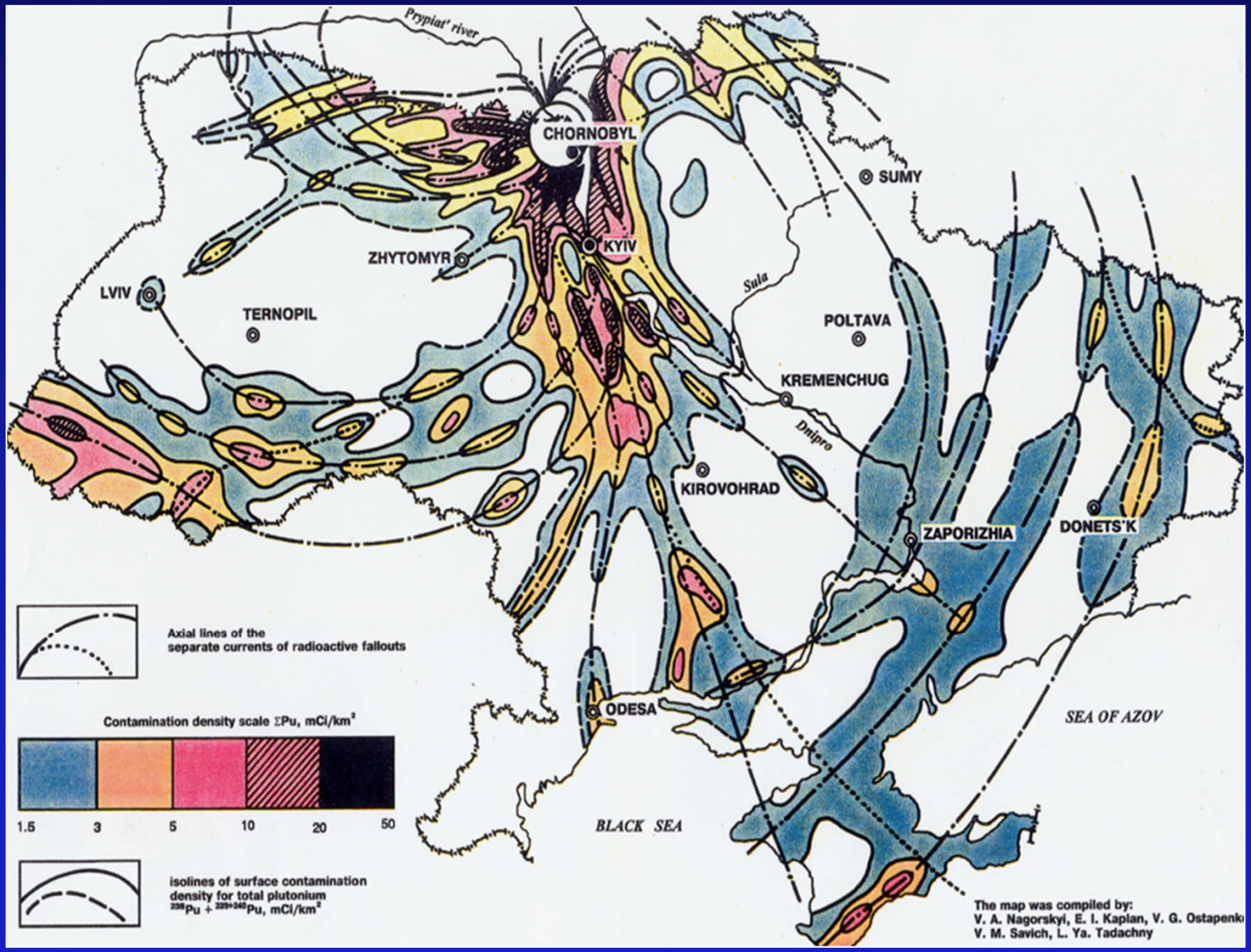
The consequences of the accident:

- **30 kilometer exclusion zone** is still in place.
- After 15 years there has been a dramatic increase in the frequency of cancer.

The map of ^{137}Cs distribution in soils of Ukraine



The structural map for Plutonium contamination of the territory of Ukraine



- **31** firefighters died.

- **134** developed ARS.

- **300 - 400** workers at the plant received whole - body radiation exposure.

- **10 - 20 million** people were exposed to significant levels of fallout.

Cesium-137 (^{137}Cs), which accounts for **90% of the internal radioactivity** in the Ukrainian population exposed to long-term low-dose radiation and **90%** of the more labile pool of ^{137}Cs, is eliminated **by kidneys and excreted via the urine**.

The biological effects of low doses of ionizing radiation (LDIR) and its relationship with carcinogenesis has received a lot of attention in the last few years.

Very low chronic doses of IR can induce a type of genetic instability in cells, which can lead to an enhancement of **mutational events** at the multiple loci responsible for the development of cancer, as has been demonstrated.

Genetic instability appears if the radiation effect becomes saturated by doses in the range **2-4 Gy**, and even with doses as low as **0.18Gy**.

Renal cell carcinomas

Department of Pathology,
Institute of Urology,
Academy of Medical Sciences
of Ukraine

Alina Romanenko,

Alexander Vozianov

Department of Pathology,
University of Valencia

Antonio Llombart-Bosch,

Luisa Morell Quadreny,

Jose Antonio Lopez Guerrero,

Antonio Pellín,

David Ramos

During the 25-year period subsequent to the Chernobyl accident the **morbidity** of malignant renal tumors in Ukraine has increased from 4.7 to **10.7** per 100,000 of total population.

Int. J. Cancer: **87**, 880–883 (2000)

Publication of the International Union Against Cancer

PATHOLOGY AND PROLIFERATIVE ACTIVITY OF RENAL-CELL CARCINOMAS (RCCS) AND RENAL ONCOCYTOMAS IN PATIENTS WITH DIFFERENT RADIATION EXPOSURE AFTER THE CHERNOBYL ACCIDENT IN UKRAINE

A. ROMANENKO[1], L. MORELL-QUADRENY[2], V. NEPOMNYASCHY[1], A. VOZIANOV[1] and A. LLOMBART-BOSCH[2]*

[1]*Departments of Pathology and Urology, Institute of Urology and Nephrology A.M.S. of Ukraine, Kiev, Ukraine*
[2]*Department of Pathology, Medical School of Valencia, Valencia, Spain*

TABLE I – PATIENT CHARACTERISTICS

	Group I		Group II		Group III		Group IV		Group V		Group VI	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Number of patients	30	27	30	25	43	29	11	3	22	16	74	38
Mean age	55 (27–79)		56 (34–75)		55 (18–77)		51 (27–75)		53 (41–75)		57 (26–77)	
Year surgery	1993–1999		1993–1996		1997–1999		1993–1996		1997–1999		1975–1989	
Contamination level in the area (Ci/km^2)[1]	N C[2]		0.5–5		0.5–5		5–30		5–30		N C[2]	

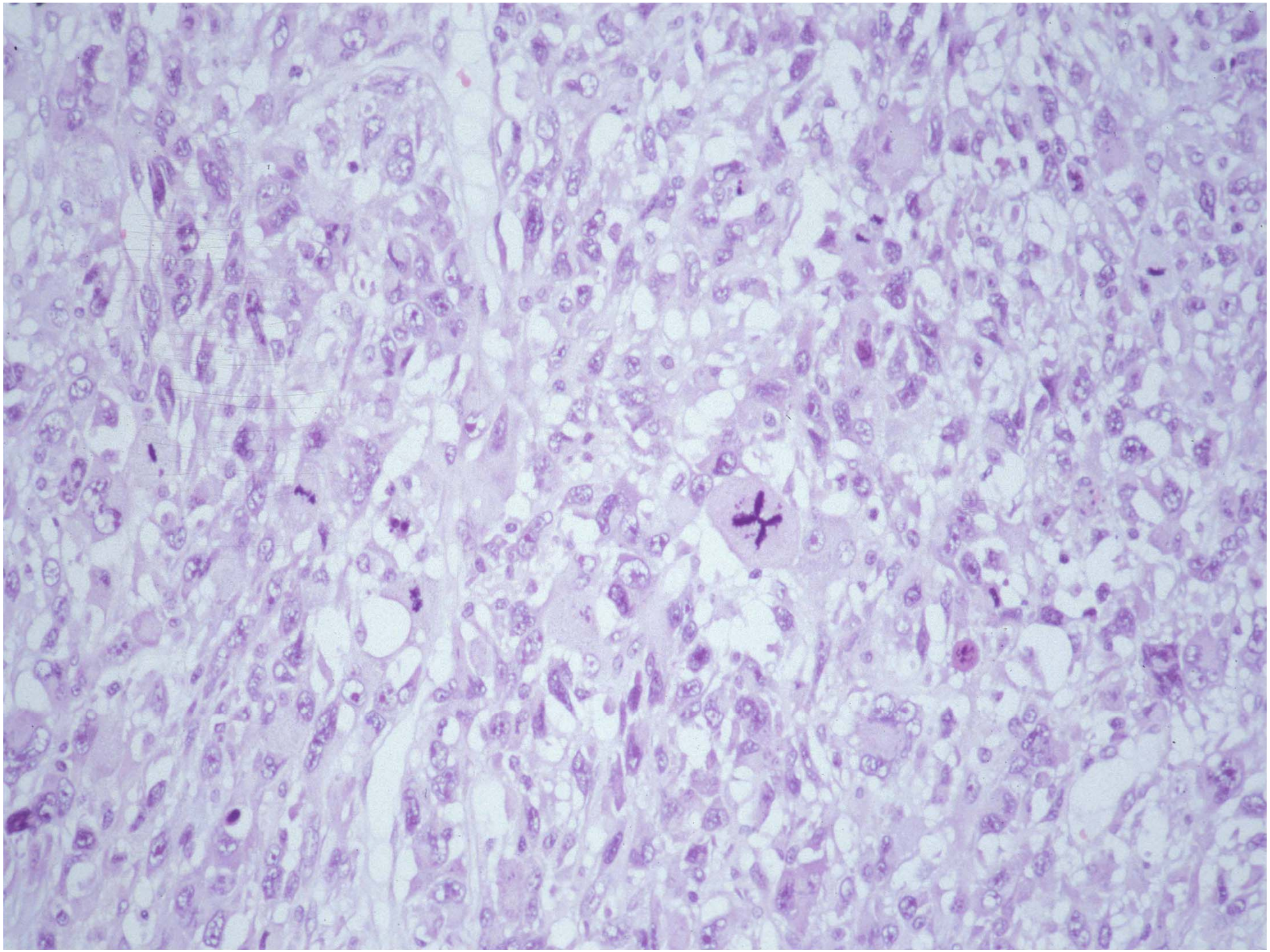
[1]Contamination data are from Raes *et al.* (1991).–[2]NC, non-contaminated area.

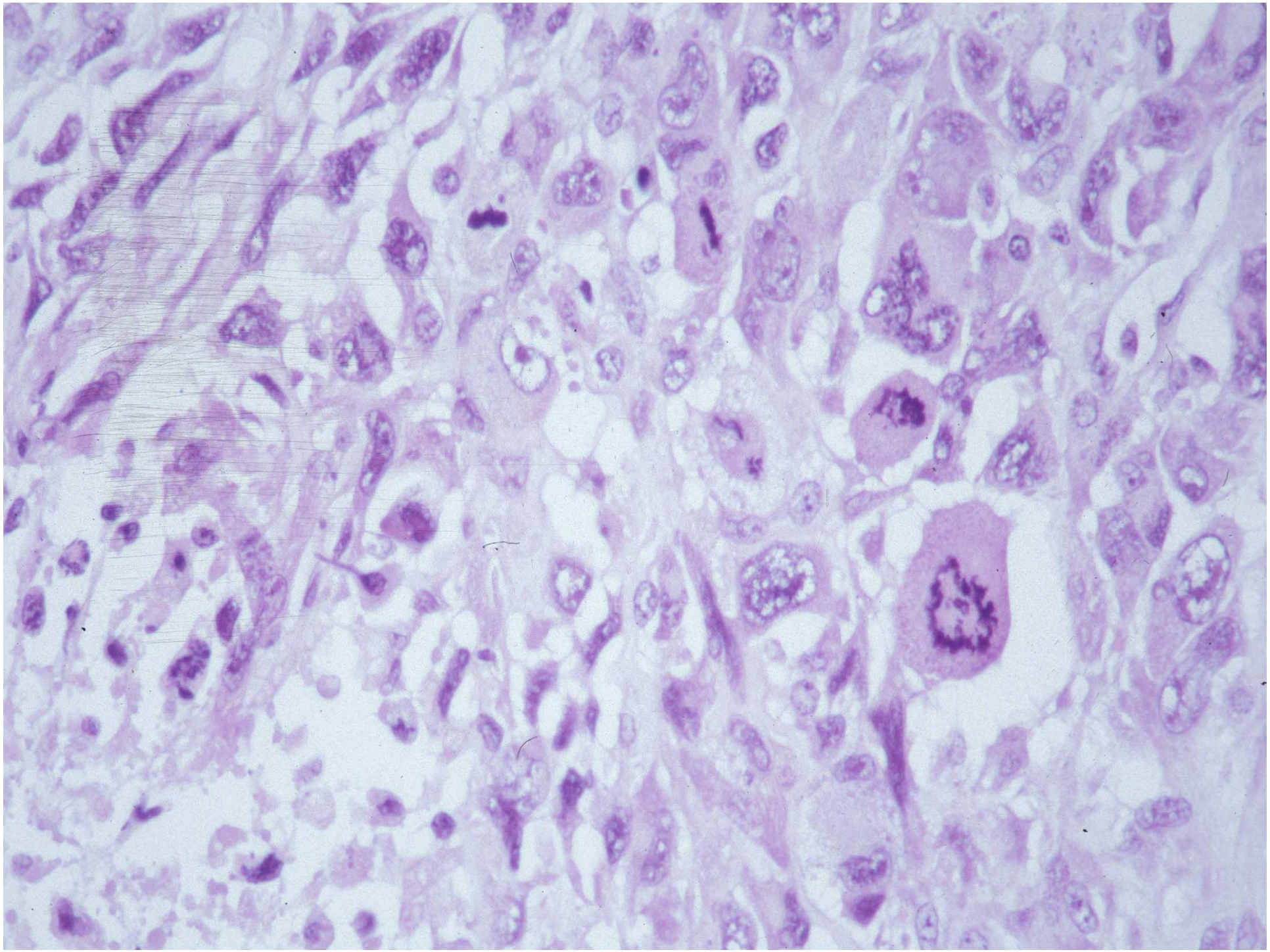
The strong significant differences between the Ukrainian and Spanish groups were found in **tumoral nuclear grade**, in the percentage of **sarcomatoid changes**, the level of the **peritumoral inflammatory response** as well as in the **peritumoral lesions**.

TABLE II – INCIDENCES OF CLINICAL AND PATHOLOGICAL FEATURES OF RCCS AND PERITUMORAL KIDNEY TISSUES IN DIFFERENT GROUPS OF PATIENTS[1]

Groups	Number of cases[1]	TNM stage				Histological type[2]						Grade			Sarcomatoid changes	Peritumoral changes[3]			
		I	II	III	IV	1	2	3	4	5	6	1	2	3		1	2	3	4
I	57	28	17	7	5	39	13	—	—	4	1	8	37	12	12	32	3	33	27
II	55	31	16	6	2	37	7	3	3	2	3	8	20	27	11	33	4	45	35
III	72	36	27	6	3	40	11	5	2	9	5	12	23	37	25	55	9	49	63
IV	14	7	5	1	1	10	1	1	—	—	2	3	8	3	4	10	1	9	10
V	38	21	11	6	—	18	6	1	1	8	4	10	16	12	10	30	6	22	37
VI	112	43	38	14	17	67	16	3	3	12	11	21	59	32	11	8	1	97	—
Statistical significance		$\chi^2 = 7.22$, pns				$\chi^2 = 27.2$, pns						$\chi^2 = 29.6$, $p < 0.005$			$\chi^2 = 12.4$, $p < 0.001$	$\chi^2 = 133.66$, $p < 10^{-6}$			

[1]Number of cases noted.–[2]1, conventional; 2, papillary; 3, chromophobe; 4, collecting ducts; 5, oncocytoma; 6, others.–[3]1, Nuclear atypia; 2-CIS; 3, Inflammation; 4, Radiation Nephropathy.



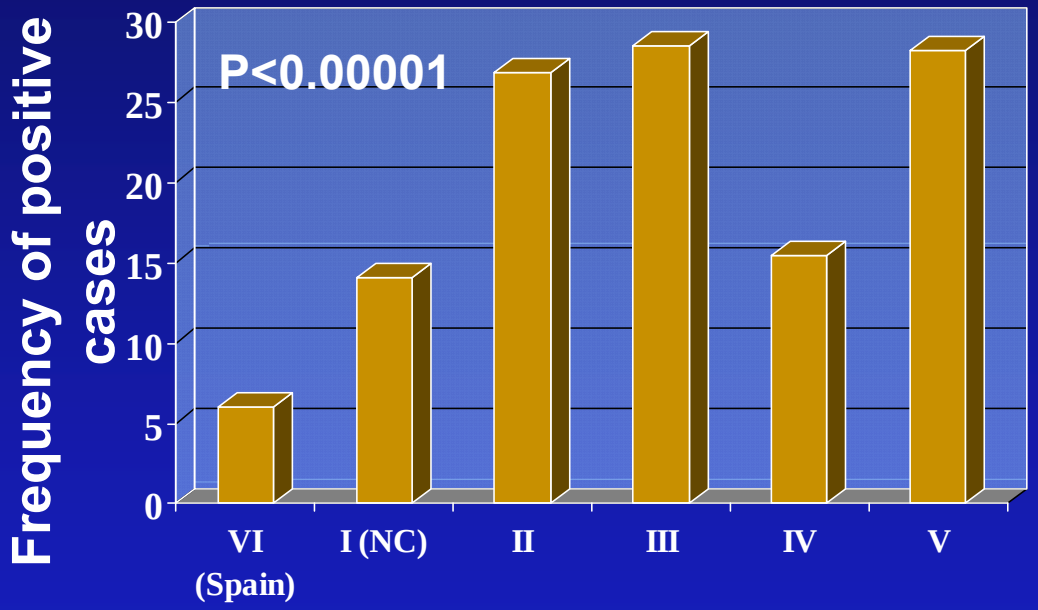


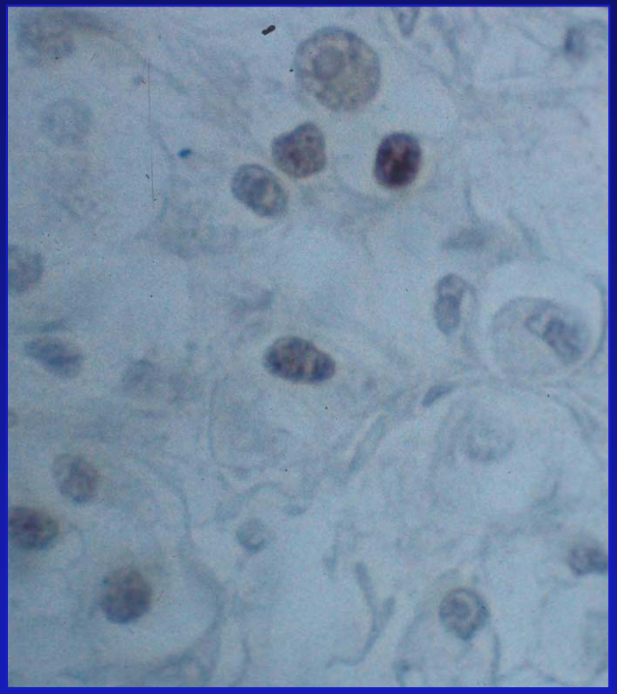
The dramatic increase of aggressivity and proliferative activity supported by **strong PCNA and K-ras expression** of RCCs from Ukrainian groups, associated with chronic radiation nephropathy of peritumoral kidney tissue, show good correlation with the duration of radiation exposure and confirms the influence of chronic but regular and sustained low dose of ionizing radiation on renal carcinogenesis of the Ukrainian population.

TABLE III – INCIDENCES OF PCNA AND K-RAS TUMORAL EXPRESSION IN DIFFERENT GROUPS OF PATIENTS

	Groups						Statistical analysis
	I	II	III	IV	V	VI	
PCNA (+)	16	43	60	12	20	78	$F = 14.66$
Mean	14.1	26.8	28.5	15.4	28.2	6	$p < 10^{-6}$
Standard deviation	18.9	23.2	26.3	15.3	21	14.6	
K-ras (+)	10	22	49	7	13	43	$\chi^2 = 28.1$
>50% stained	6	12	45	7	13	17	$p < 0.001$
Total cases	26	55	65	14	20	112	

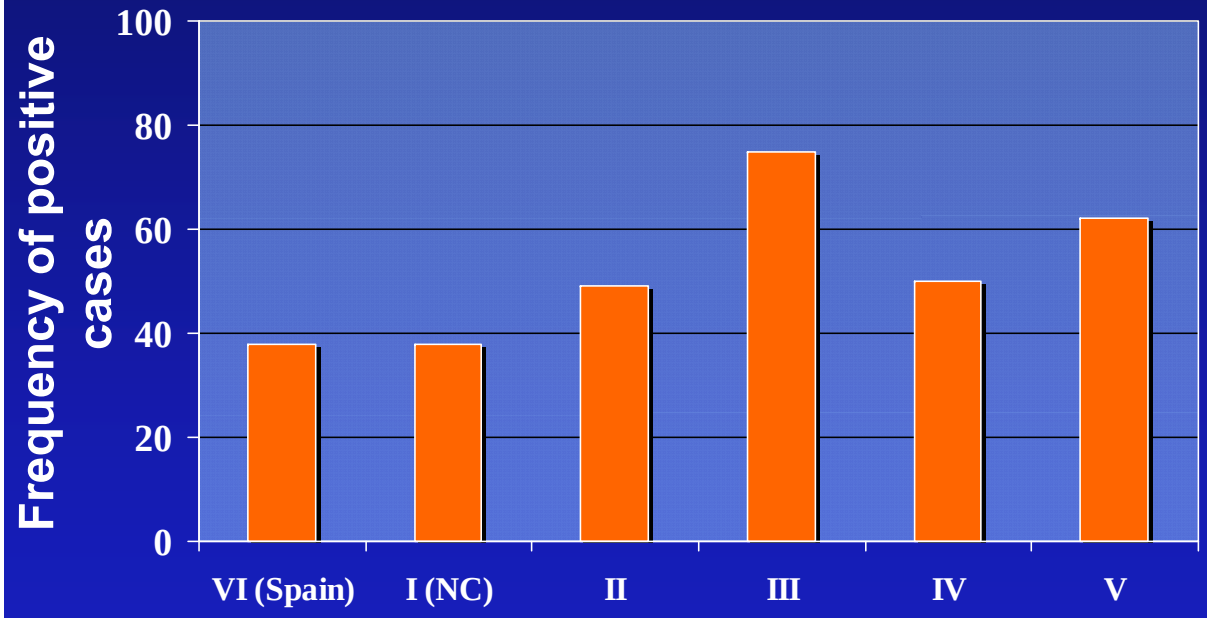
PCNA

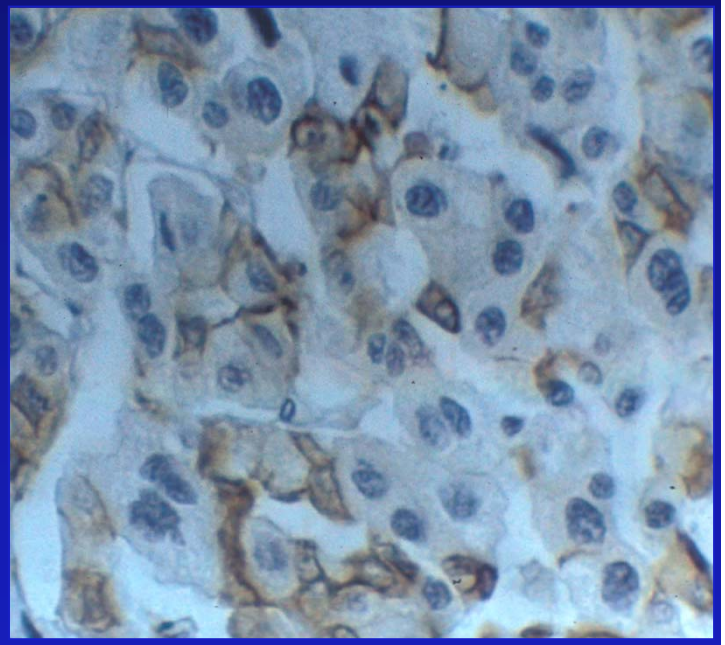

Frequency of positive cases
30
25
20
15
10
5
0
P<0.00001
VI (Spain)
I (NC)
II
III
IV
V



K-ras

P<0.001


Frequency of positive cases
100
80
60
40
20
0
VI (Spain)
I (NC)
II
III
IV
V



Virchows Arch (2001) 438:146–153
DOI 10.1007/s004280000334

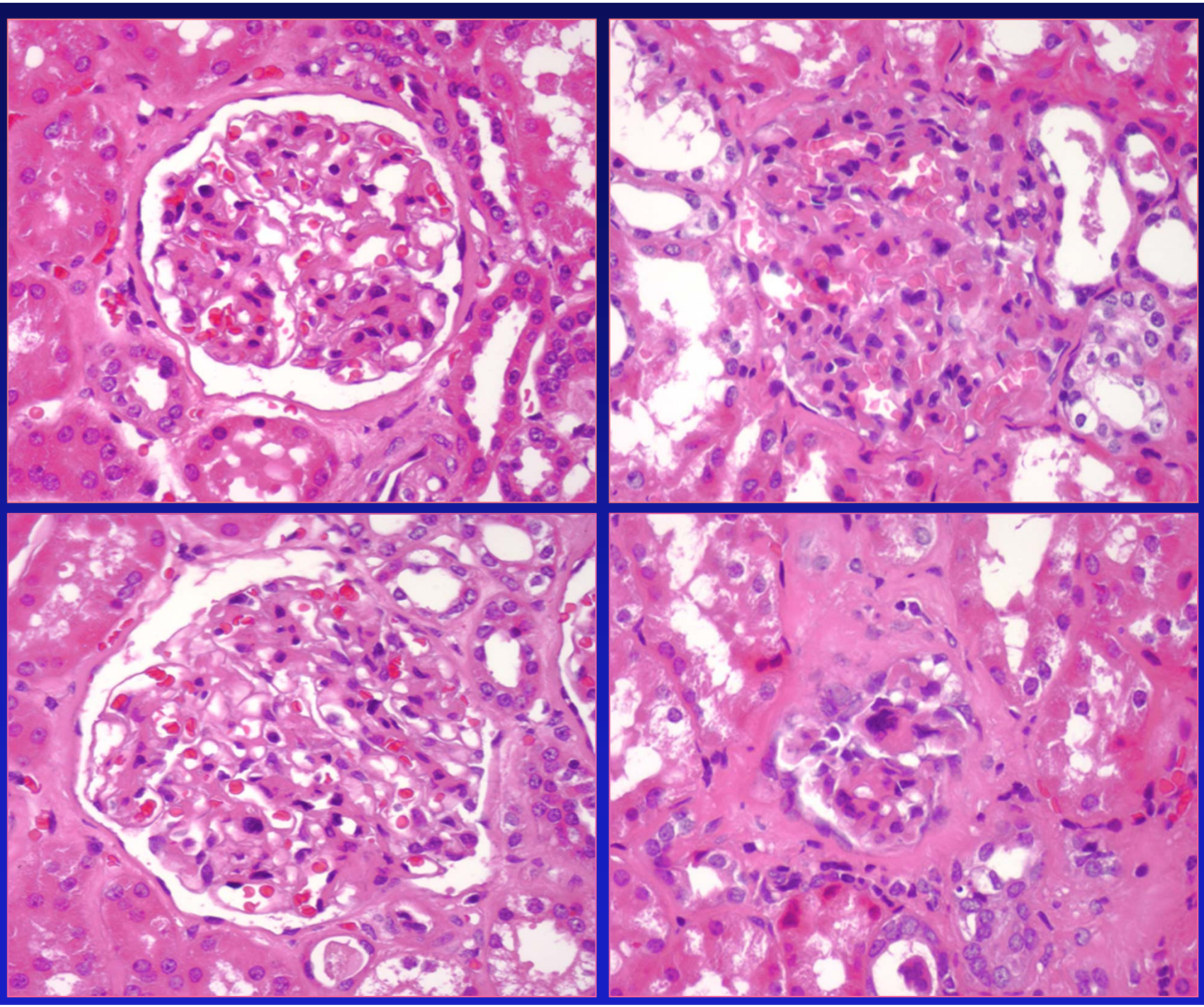
ORIGINAL ARTICLE

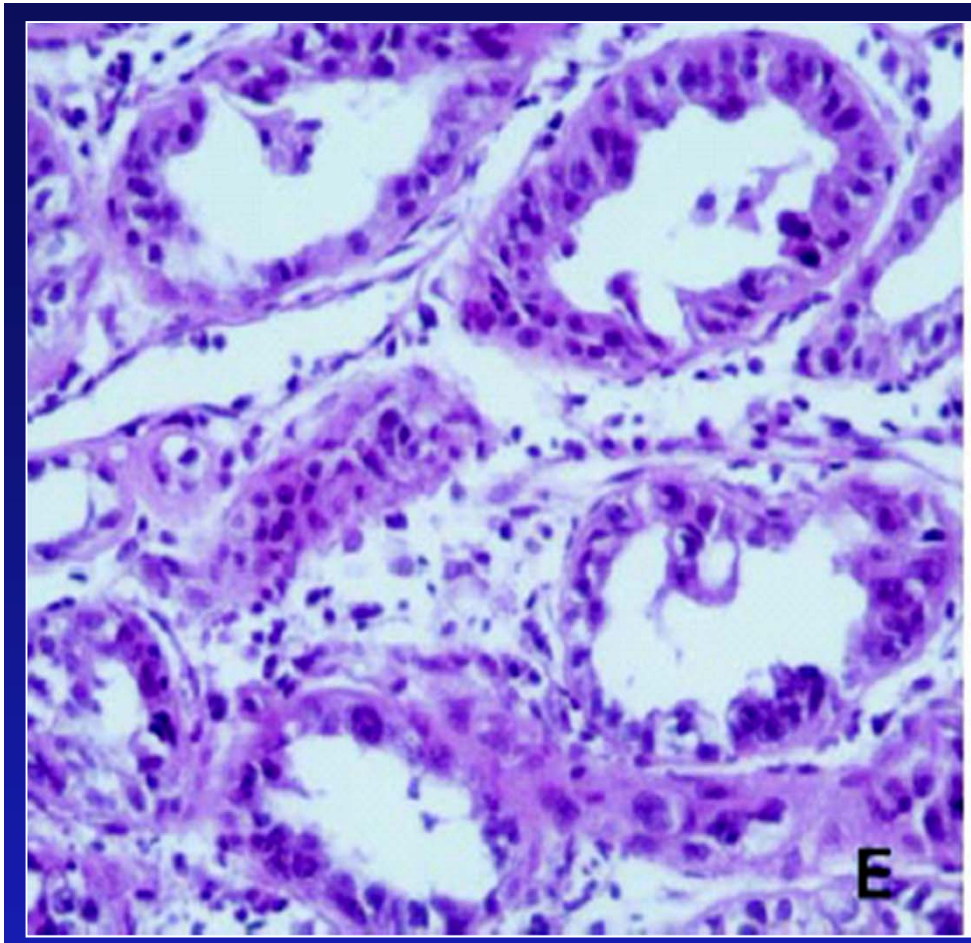
A. Romanenko · L. Morell-Quadreny
V. Nepomnyaschy · A. Vozianov · A. Llombart-Bosch

Radiation sclerosing proliferative atypical nephropathy of peritumoral tissue of renal-cell carcinomas after the Chernobyl accident in Ukraine

Received: 11 January 2000 / Accepted: 22 September 2000 / Published online: 7 December 2000

	Group I	Group II	Group III	Group IV
No. of patients	42	69	56	85
Mean age (years; range)	55 (27–79)	57 (34–75)	55 (29–77)	58 (26–77)
Contamination level	NC	0.5–5	5–30	NC





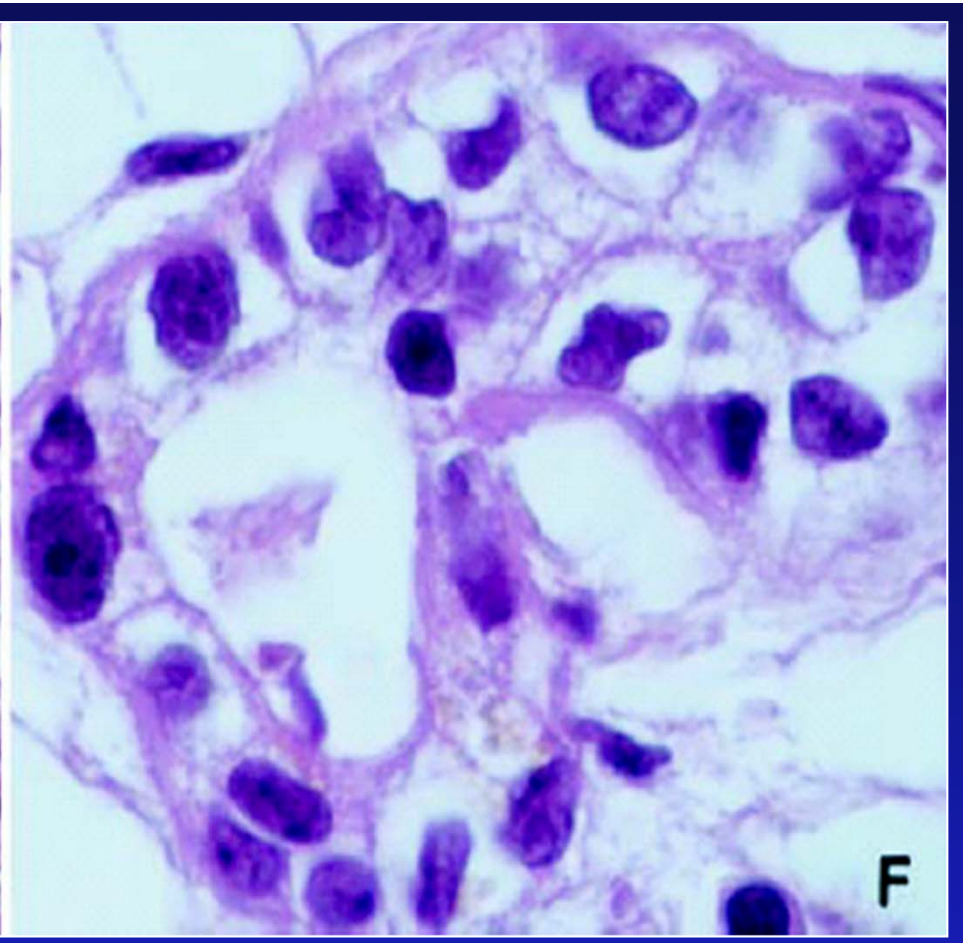
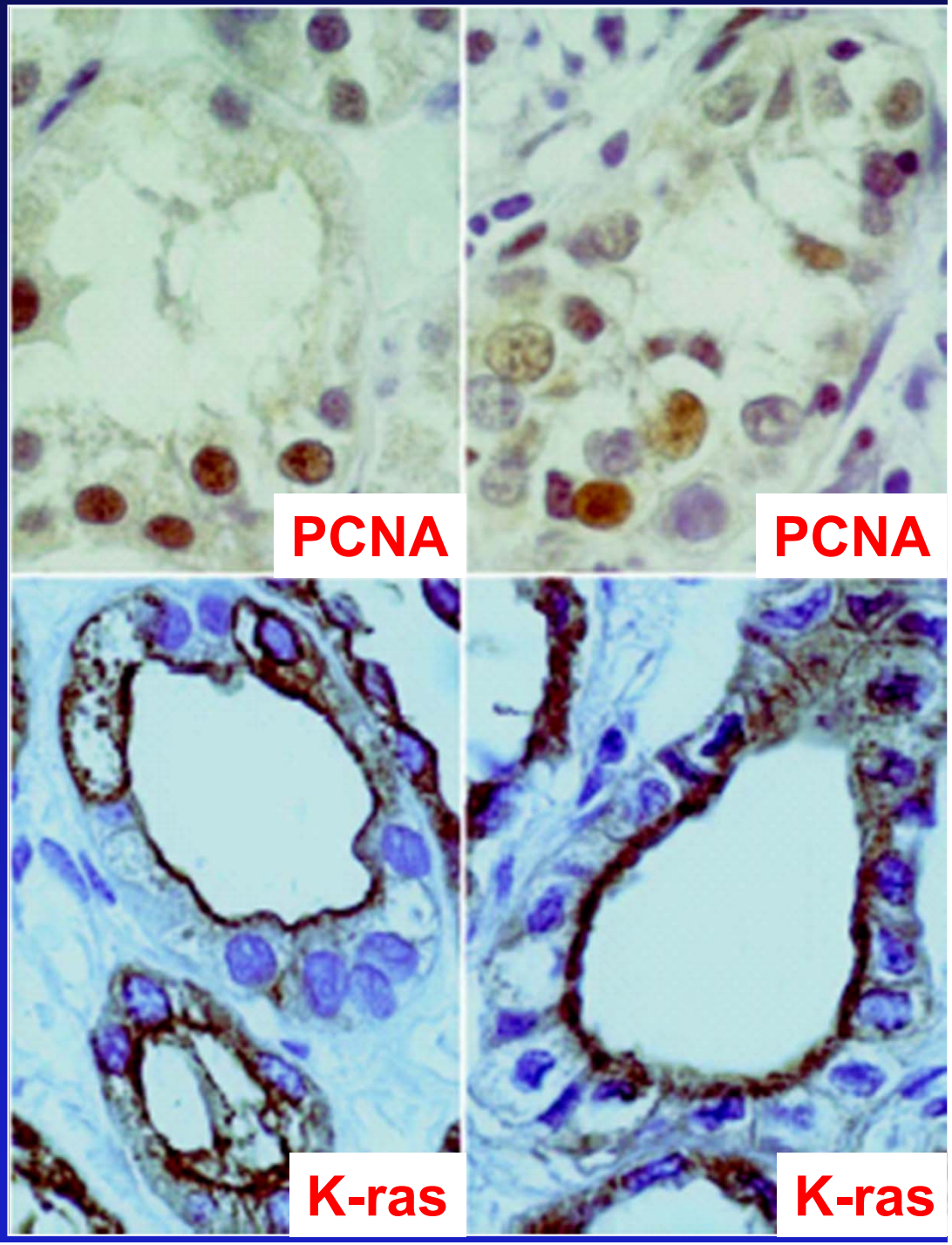


Table 3 Incidences of peritumoral kidney epithelial nuclear atypia and carcinoma in situ (CIS) in the different groups. χ^2=80.8, P<0.001

Groups	No. of cases	Nuclear atypia (%)	CIS (%)
I	42	17 (40%)	8 (19%)
II	69	52 (75%)	20 (29%)
III	56	40 (71%)	20 (36%)
IV	85	8 (7%)	1 (0.8%)

Immunohistochemical findings for peritumoral kidney tissues of Ukrainian patients exposed to long-term, low-dose IR.



Virchows Arch
DOI 10.1007/s00428-006-0160-2

JrnlID 428_ArtID 160_Proof# 1 - 31/01/2006

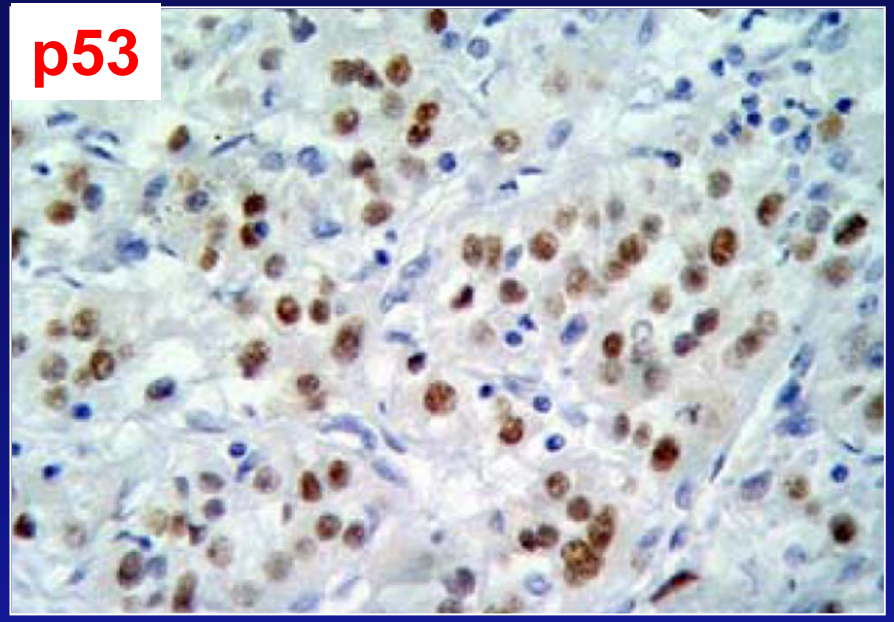
ORIGINAL ARTICLE

Alina Romanenko · Luisa Morell-Quadreny · David Ramos ·
Valentin Nepomnyaschiy · Alexander Vozianov · Antonio Llombart-Bosch

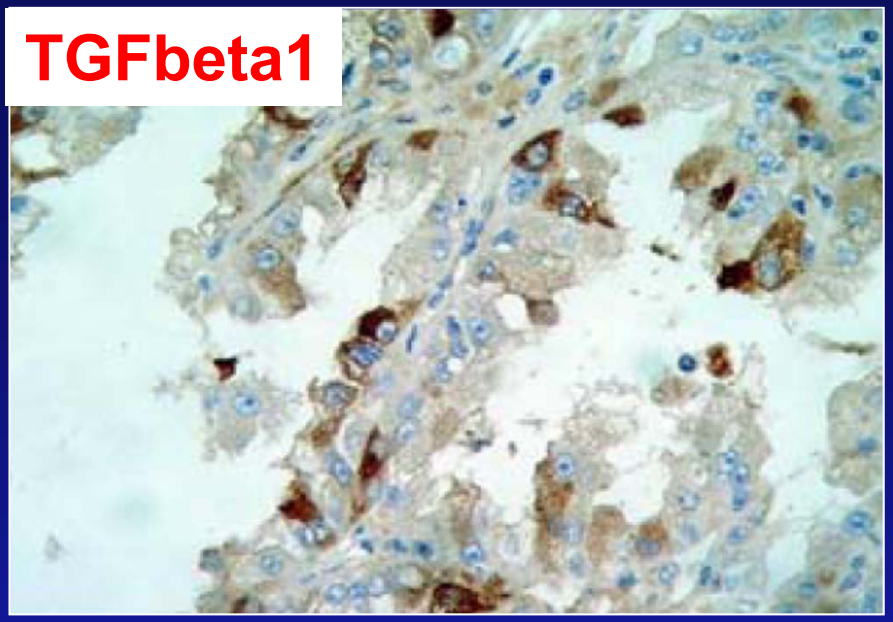
Extracellular matrix alterations in conventional renal cell carcinomas by tissue microarray profiling influenced by the persistent, long-term, low-dose ionizing radiation exposure in humans

Received: 7 June 2005 / Accepted: 27 December 2005

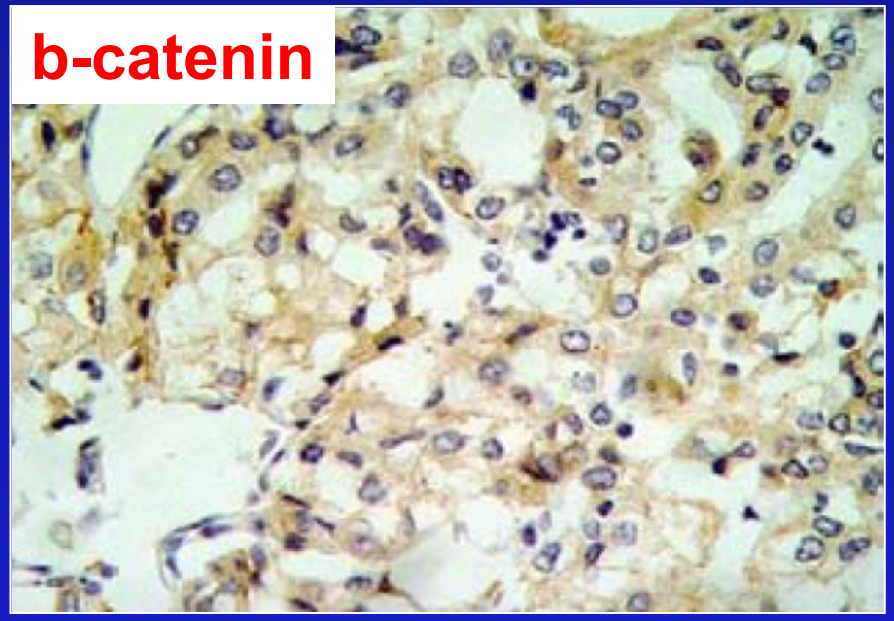
p53



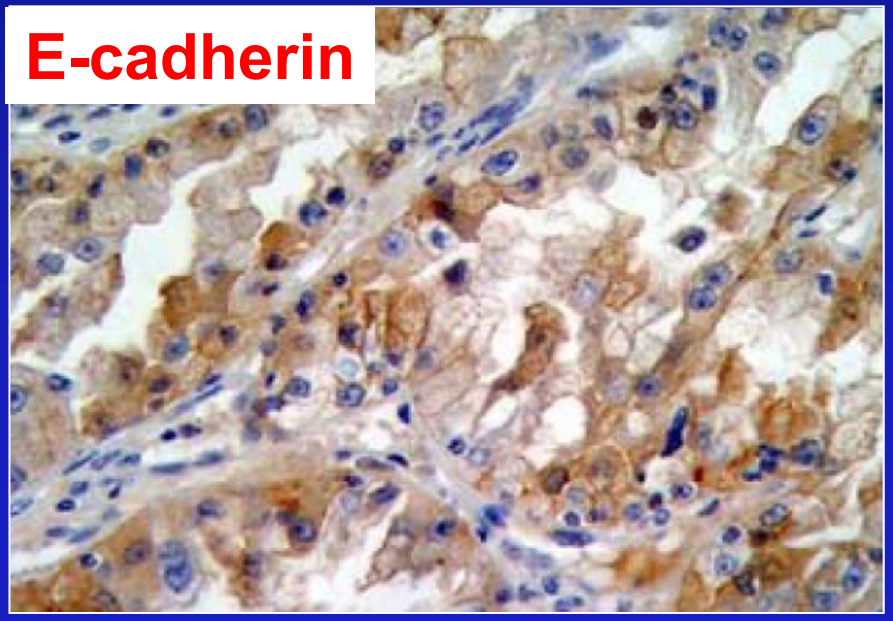
TGFbeta1



b-catenin



E-cadherin



Results:

Decrease, loss or abnormal distribution of **fibronectin**, **laminin**, **E-cadherin / beta-catenin** complexes accompanied by elevated levels of **p53** and **TGF-beta1** are detected in the Ukrainian cRCCs from ^{137}Cs-contaminated areas with statistically significant differences.

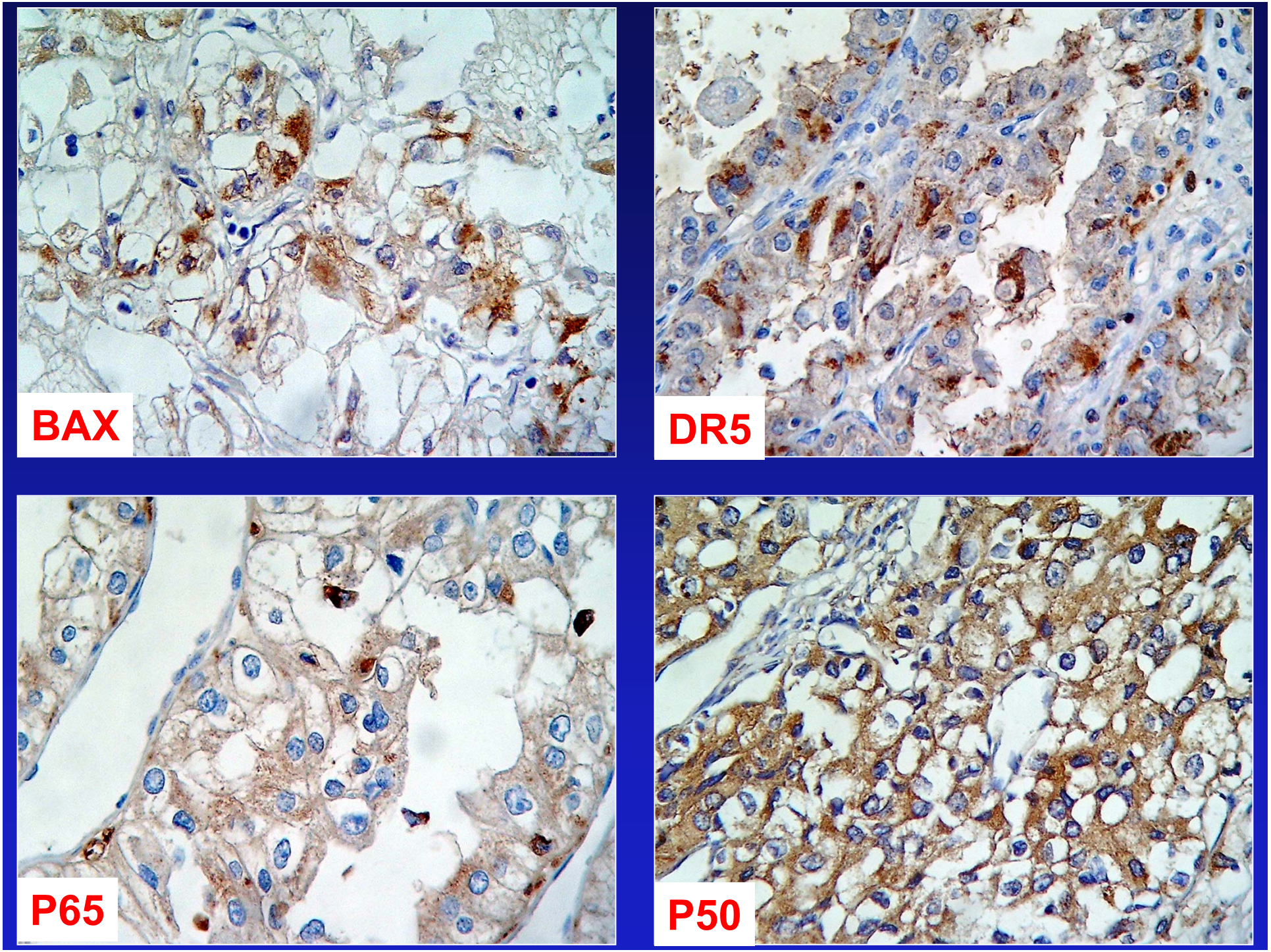
This study shows that chronic long-term, low-dose IR exposure results in global remodeling of ECM components of the RCCs with disruption in peri-epithelial stroma and epithelial basement membranes.

CANCER GENOMICS & PROTEOMICS 3: 107-112 (2006)

Alteration of Apoptotic Regulatory Molecules in Conventional Renal Cell Carcinoma Influenced by Chronic Long-term Low-dose Ionizing Radiation Exposure in Humans Revealed by Tissue Microarray

ALINA ROMANENKO[1*], LUISA MORELL-QUADRENY[2], DAVID RAMOS[2], ALEXANDER VOZIANOV[3] and ANTONIO LLOMBART-BOSCH[2]

Departments of [1]Pathology and [3]Urology, Institute of Urology, Academy of Medical Sciences of Ukraine, 9a, Yu. Kotzubinsky Street, 04053, Kiev, Ukraine;
[2]Department of Pathology, Medical School of Valencia University, Avda Blasco Ibañez 17, 46010 Valencia, Spain
**Visiting Professor, Department of Pathology, Medical School of Valencia University, Spain*


BAX
DR5
P65
P50

Results:

BAX and DR5-positive cRCCs tend to **increase among the Ukrainian patients living in the radio-contaminated areas** along with the suppression of anti-apoptotic molecules (**Bcl-2** and **Bcl-x**) and with **p65** and **p50** overexpression in these same tumors.

This study suggests that chronic long-term, low-dose radiation exposure might result in the **alteration of apoptotic regulatory mechanisms**, which in turn, could lead to enhanced tumor progression and resistance to apoptosis.

Diagnostic Molecular Pathology 11(3): 163–169, 2002

$p16^{INK4A}$ and $p15^{INK4B}$ Gene Alteration Associated with Oxidative Stress in Renal Cell Carcinomas After the Chernobyl Accident (Pilot Study)

Alina Romanenko, M.D., Luisa Morell-Quadreny, M.D., Jose Antonio Lopez-Guerrero, Ph.D., Antonio Pellin, Ph.D., Valentin Nepomnyaschy, M.D., Alexander Vozianov, M.D., and Antonio Llombart-Bosch, M.D.

Virchows Arch (2004) 445:298–304
DOI 10.1007/s00428-004-1056-7

ORIGINAL ARTICLE

Alina Romanenko · Luisa Morell-Quadreny · Jose Antonio Lopez-Guerrero · Antonio Pellin · Valentin Nepomnyaschy · Alexander Vozianov · Antonio Llombart-Bosch

The INK4a/*ARF* locus: role in cell cycle control for renal cell epithelial tumor growth after the Chernobyl accident

Human $p16^{INK4A}$, $p14^{ARF}$ and $p15^{INK4B}$ genes (at 9p21) are implicated in the G1 to S-phase cell cycle transition, and constitute the unique tumor- suppressor genes responsible for low-level DNA damage control as a "rheostat" that guards the cumulative effects of minor changes.

CELL CYCLE IN RENAL TUMORS

Patients : 78 conventional renal cell carcinomas (cRCCs) from Ukrainian patients with different degrees of radiation exposure, in comparison with Spanish tumors.

Immunohistochemistry, using a tissue microarray **p53, mdm2, p21WAF1/ CIP1, p16INK4a, p14ARF and Ki-67** proteins.

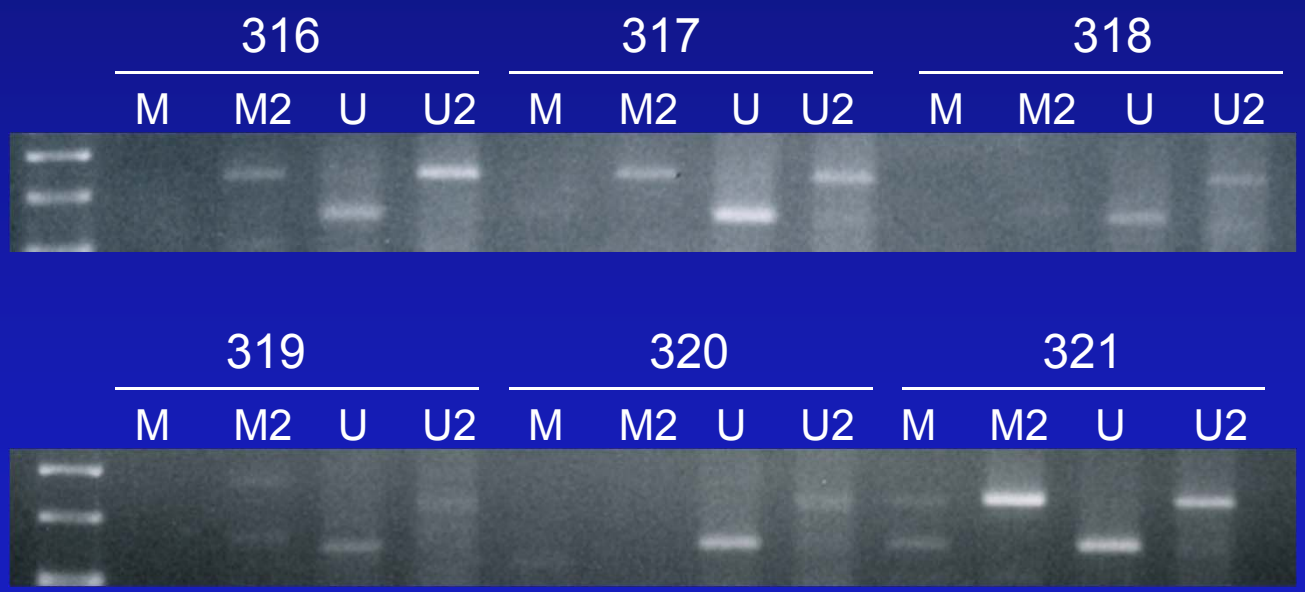
Molecular analysis of the 9p21 locus and MDM2 and CDK4 gene amplification.

CELL CYCLE IN RENAL TUMORS

Chronic long-term, low-dose IR exposure leads to activation and alteration of both **p53/mdm2** and **p21WAF1/CIP1** protein expression as well as **p16INK4a/p14ARF** locus proteins which causes disruptions and loss of cell cycle checkpoints and, enhance tumor progression and aggressiveness.

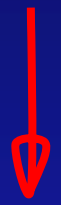
CELL CYCLE IN RENAL TUMORS

$p16^{INK4A}$ methylation



CELL CYCLE IN RENAL TUMORS

$p14^{ARF}$ and $p16^{INK4A}$ promoter methylation



		DELETION			*METHYLATION*			*AMPLIFICATION*	
		p15	*p16a*	*p16b*	*p14*	*p15*	*p16*	*cdk4*	*mdm2*
TUMOR	positive	1	0	0	6	1	12	0	0
(n=35)	negative	28	32	32	17	30	11	33	33
	nv	6	3	3	12	4	12	2	2
NORMAL	positive	0	0	0	14	1	12	0	0
(n=35)	negative	28	25	28	16	27	15	32	32
	nv	7	10	7	5	7	8	3	3

This study represents the first finding of a specific lesion in *INK4a/ARF* locus in human RCC from patients chronically exposed to low doses of IR.

RCC from Ukrainian patients living in the radio-contaminated areas **show aberrant hypermethylation of *p14^{ARF}*and *p16^{INK4A}* genes** associated with **increased mdm2 and cyclin D1 protein levels**.

These data suggest the existence of multiple levels of "cross-talk" between the ***p16^{INK4A}/pRb*** and ***p14^{ARF}/p53*** pathways in RCCs.

Oxidative stress, **induced by LDIR**, involves ROS production by activated mitochondria, causing activation of MAP kinases. Long-term low-dose exposure to IR of people living in radio-contaminated areas chronically induces the **persistent activation of transcription factors via a p38MAPK cascade**.

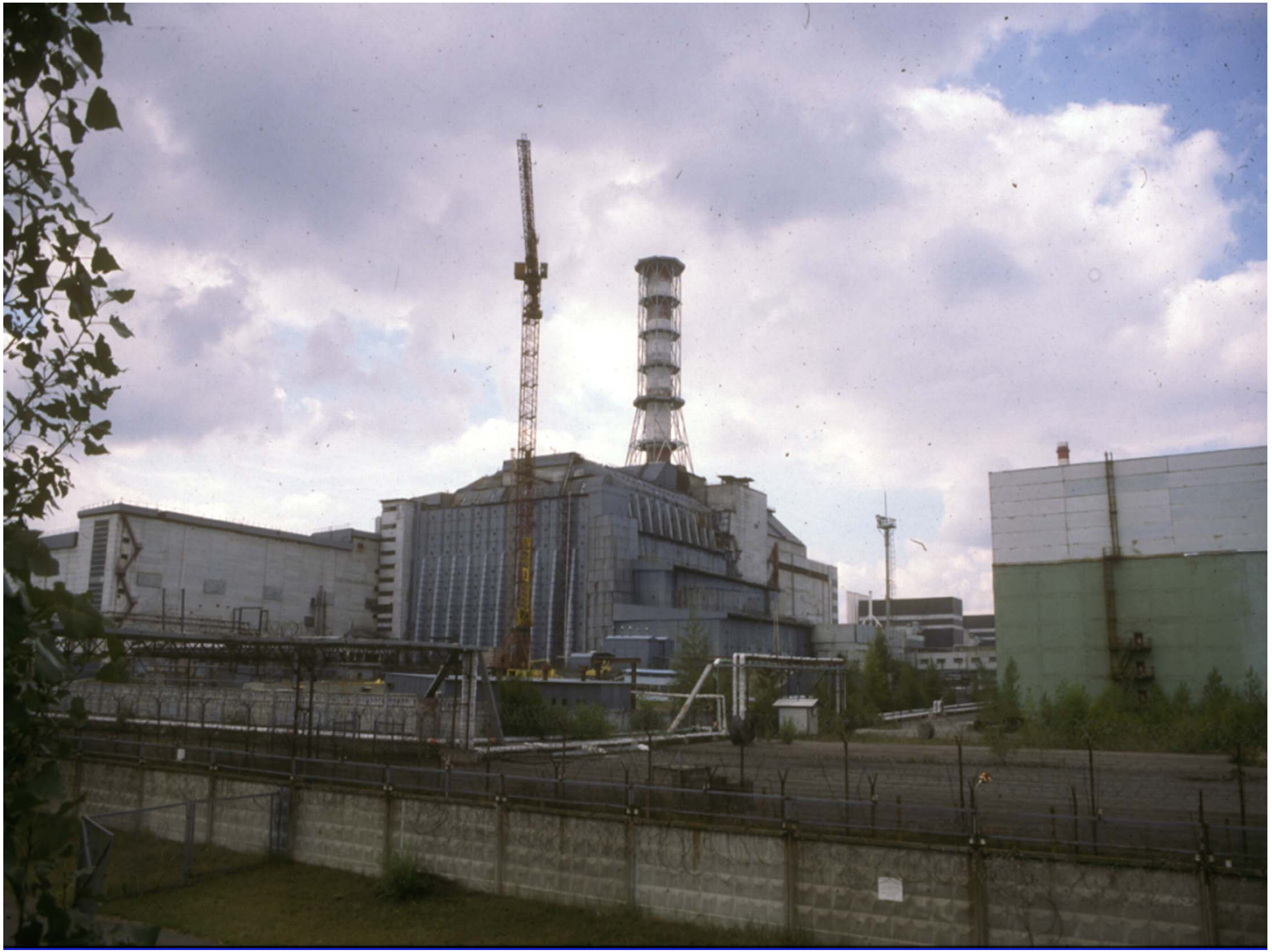
Urinary Bladder Carcinogenesis

Department of Pathology,
Institute of Urology,
Academy of Medical Sciences
of Ukraine

Alina Romanenko,
Vladimir Vinnichenko,
Wadim Zaparin,
Alexander Vozianov

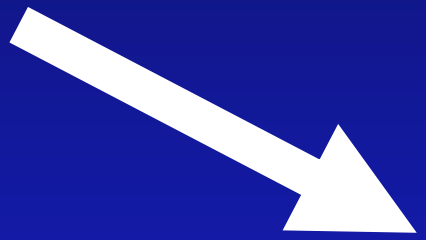
Department of Pathology,
Osaka City University
Medical School (Japan)

Anna Kakehashi,
Keiichirou Morimura,
S.Yamamoto,
Min Wei,
Hideki Wanibuchi,
Shoji Fukushima



The incidence of urinary bladder cancer in Ukraine

1986 — 26.2 person



2010 — 54.2 person

per 100,000 of population

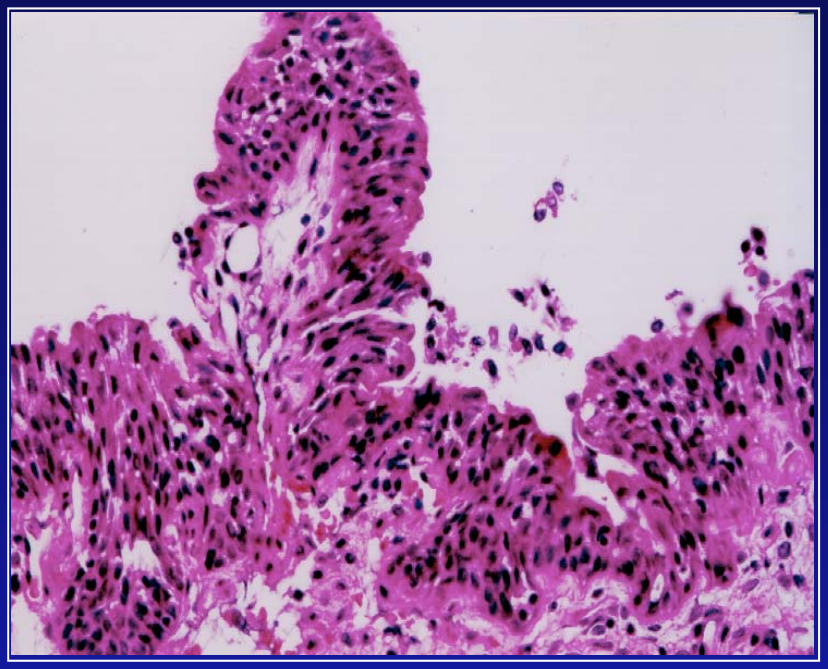
Chronic long-term low dose ionizing radiation (IR) leads to the development of a previously unknown disease – **radiation induced proliferative atypical cystitis ("Chernobyl cystitis")**

(*A. Romanenko et al. 2002, 2003*)

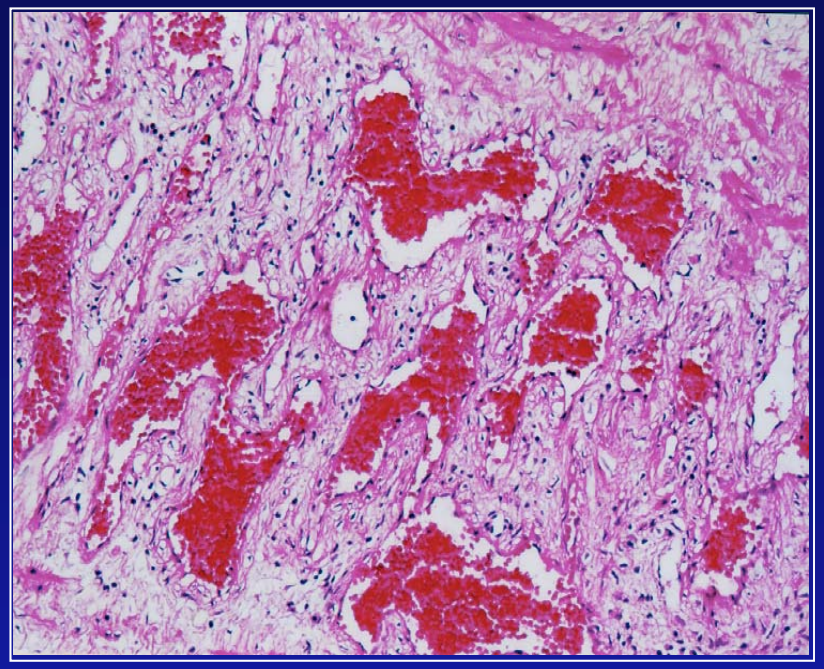
“Chernobyl cystitis”

radiation chronic proliferative atypical cystitis in humans

- multiple areas of dysplasia, CIS;
- sclerosis and gyalinosis of connective tissue;
- strongly increased angiogenesis;
- lack of inflammatory reaction.



Transitional
cell carcinoma



Irradiation
chronic cystitis

Pathological findings

Urinary bladder lesions induced by persistent chronic low-dose ionizing radiation

Alina Romanenko,[1] Keiichirou Morimura,[2] Hideki Wanibuchi,[2] Min Wei,[2] Wadim Zaparin,[3] Wladimir Vinnichenko,[3] Anna Kinoshita,[2] Alexander Vozianov[3] and Shoji Fukushima[2, 4]

Departments of [1]Pathology and [3]Urology, Institute of Urology, Academy of Medical Sciences of Ukraine, 9a, Yu. Kotzuinsky Street, 04053, Kiev, Ukraine and [2]Department of Pathology, Osaka City University Medical School, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585

Table 3. Incidence of urinary bladder dysplasias and carcinomas

Groups	No. of cases	Dysplasia (%)	Carcinomas		
			Total (%)	CIS[1)]	Papillary UC[2)]
I	73	71 (97)[3)]	53 (73)[3)]	47[3)]	6
II	58	48 (83)[3)]	37 (64)[3)]	34[3)]	3
III	33	9 (27)[4)]	0 (0)	0	0

1) Carcinoma *in situ*.
2) Urothelial carcinoma.
3) Significantly different vs. group III at $P<0.0001$ (χ^2 or Fisher's exact probability test).
4) Mild dysplasia.

^{137}Cs levels in urine

	Group I	Group II	Group III
No. of Patients examined	55	53	12
Contamination levels in soil (Ci/km^2)[a]	5-30	0.5-5	NC[b]
^{137}Cs levels in urine (Bq/L)	6.47 ± 14.30[c, d]	1.23 ± 1.01[d]	0.29 ± 0.03

[a]; data from Raes et al. (1991), [b]; non-contaminated

[c]; mean ± SD, [d]; Significantly different v.s. Group III at $P<0.001$ (Steel type separate ranking test)

Examined molecules and methods

1. **Cancer related genes:**

   p53, cyclin D1, PCNA

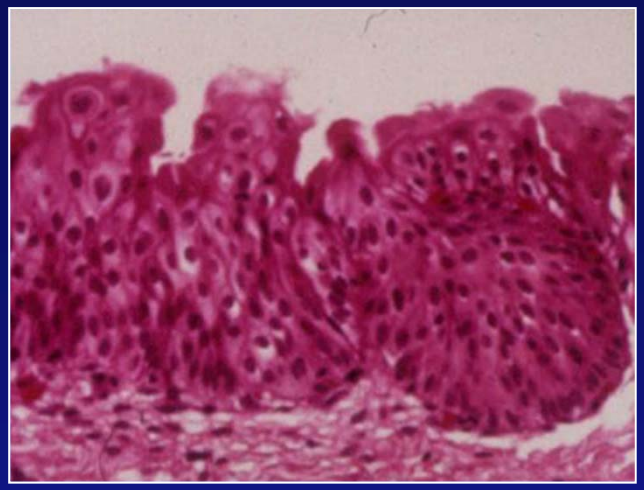
   - **PCR-SSCP & direct sequence**
   - **Immunohistochemistry (IHC score)**

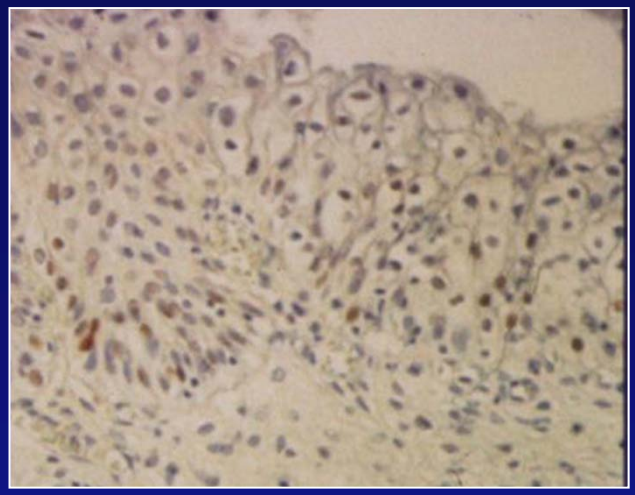
2. **Oxidative stress markers:**

   iNOS, 8-OHdG, COX-2,

   - **Immunohistochemistry (IHC score)**

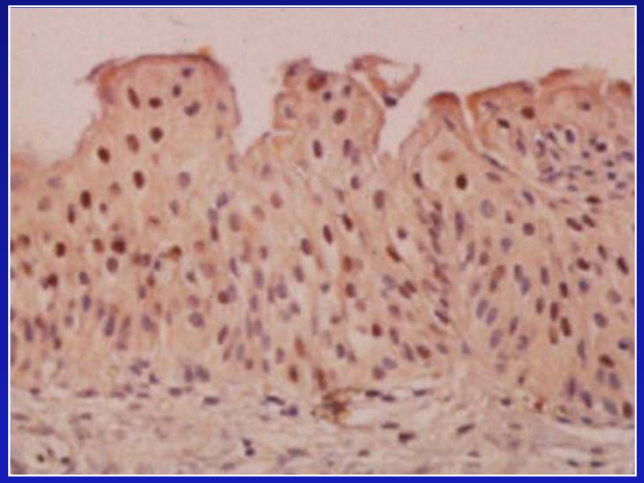
H & E

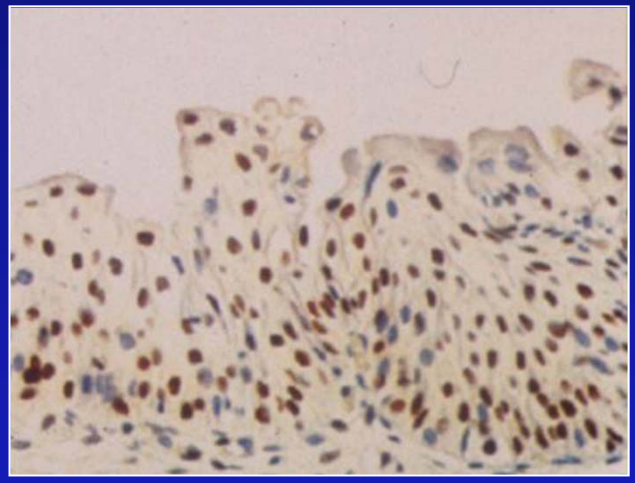




p 53

cyclin D1





PCNA

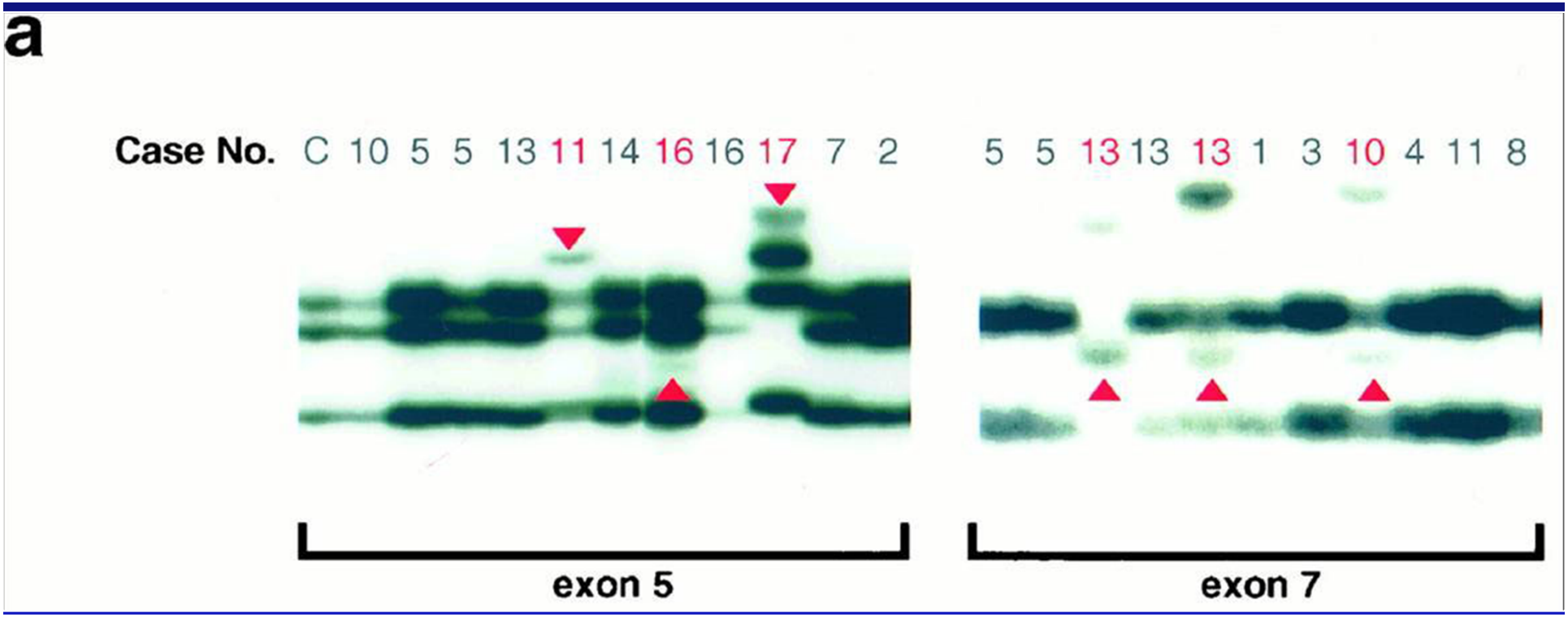
Immunohistochemistry of cancer related genes

[CANCER RESEARCH 59, 3606–3609, August 1, 1999]

Specific *p53* Gene Mutations in Urinary Bladder Epithelium after the Chernobyl Accident[1]

Shinji Yamamoto, Alina Romanenko, Min Wei, Chikayoshi Masuda, Wadim Zaparin, Wladimir Vinnichenko, Alexander Vozianov, Chyi Chia R. Lee, Keiichirou Morimura, Hideki Wanibuchi, Mitsuhiro Tada, and Shoji Fukushima[2]

Department of Pathology, Osaka City University Medical School, Osaka 545-8585, Japan [S. Y., M. W., C. M., C. C. R. L., K. M., H. W., S. F.]; Departments of Pathology [A. R.] and Urology [W. Z., W. V., A. V.], Institute of Urology and Nephrology, Academy of Medical Sciences of Ukraine, Kiev 252053, Ukraine; and Laboratory for Molecular Brain Research, Hokkaido University School of Medicine, Sapporo 060-8638, Japan [M. T.]



Results of mutational analyses of the p53 gene for lesions in patients living in radiocontaminated areas of Ukraine. a, PCR-SSCP analysis of p53 gene exons 5 (left panel) and 7 (right panel) using DNAs prepared from altered urothelium. Case numbers with mutations are shown in red. Case C is human genomic DNA (Promega) used as a control.

Relative hot spot at codon **245** was found in **56% cases with mutations** and **73%** determined mutations were **G:C to A:T transitions at CpG dinucleotides**.

Therefore the frequent and specific mutations found in these male patients may alert to a future **elevated occurrence of urinary bladder cancers in the radiocontaminated areas**.

Int. J. Cancer: **86,** 790–798 (2000)

Publication of the International Union Against Cancer

INCREASED OXIDATIVE STRESS WITH GENE ALTERATION IN URINARY BLADDER UROTHELIUM AFTER THE CHERNOBYL ACCIDENT

Alina ROMANENKO[1], Keiichirou MORIMURA[3], Hideki WANIBUCHI[3], Elsayed I. SALIM[3], Anna KINOSHITA[3], Masahiro KANEKO[3], Alexander VOZIANOV[2] and Shoji FUKUSHIMA[3]*

[1]*Department of Pathology, Institute of Urology and Nephrology, Academy of Medical Science of Ukraine, Kiev, Ukraine*
[2]*Department of Urology, Institute of Urology and Nephrology, Academy of Medical Science of Ukraine, Kiev, Ukraine*
[3]*First Department of Pathology, Osaka City University Medical School, Osaka, Japan*

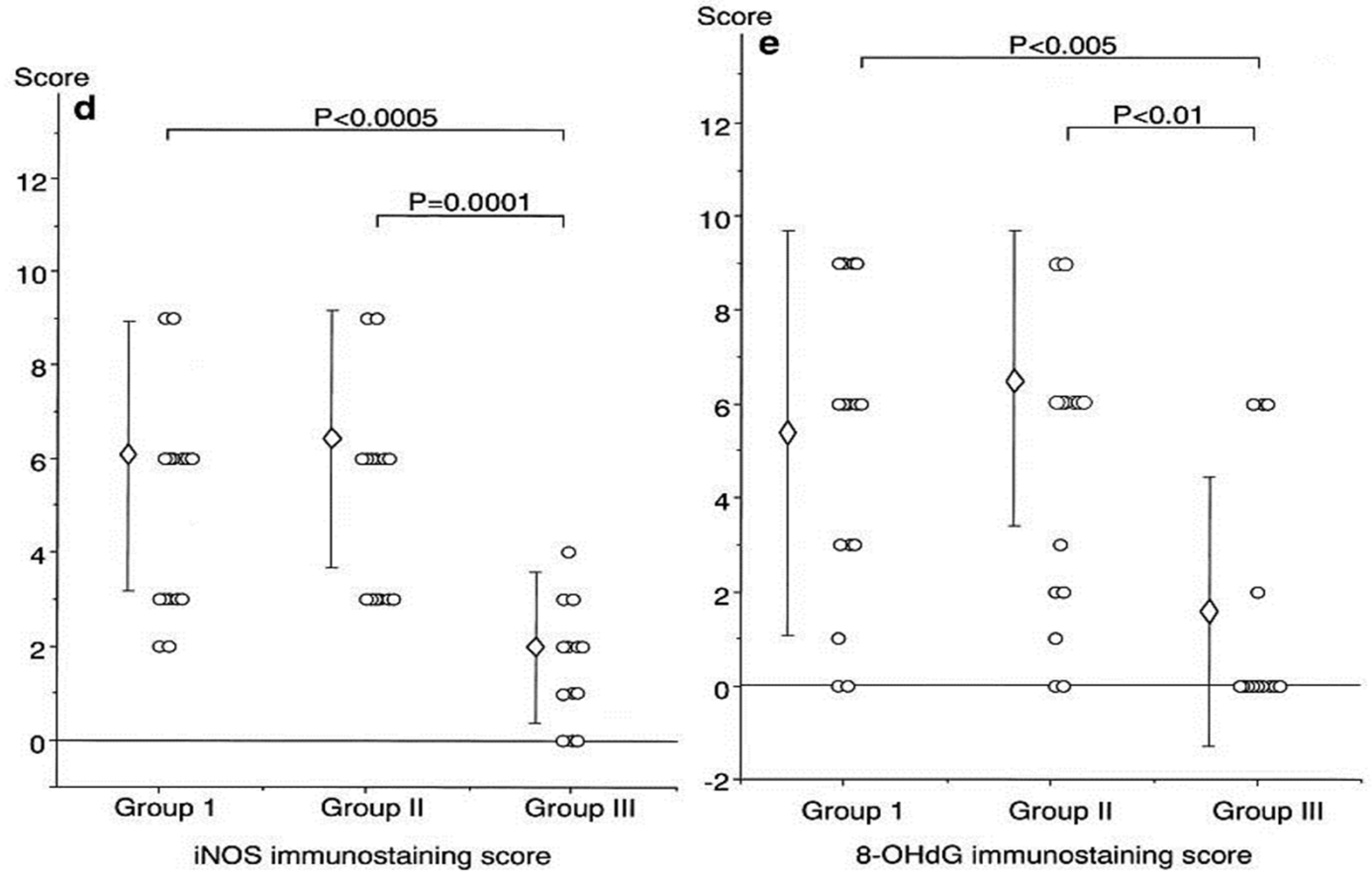
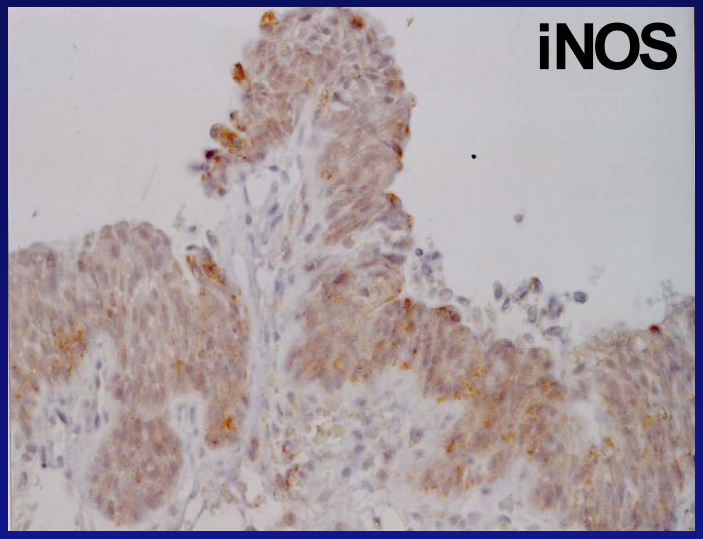
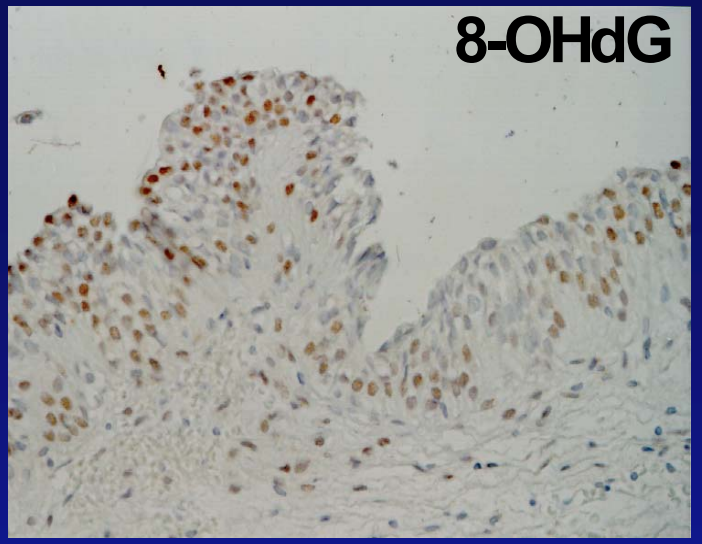
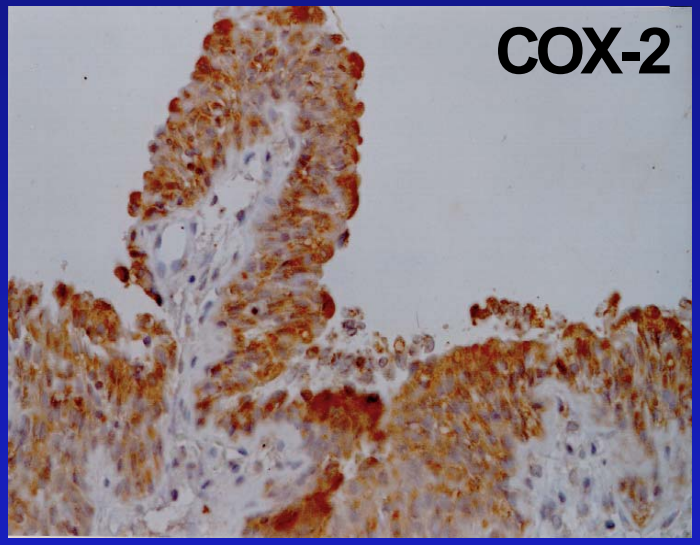
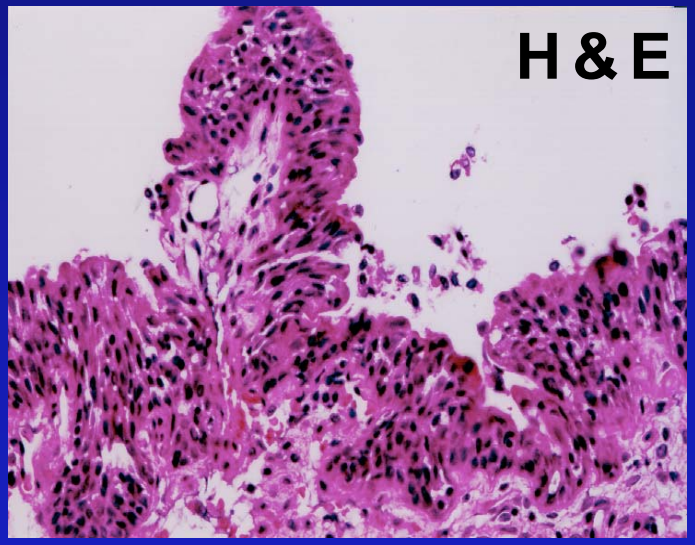


Figure 5. IHC scores for bladder urothelium in groups I through III for (a) p53, (b) H-ras, (c) COX-2, (d) iNOS and (e) 8-OHdG. Vertical bars, mean ± SD. Mann-Whitney U-test was used for statistical analysis.









Immunohistochemistry of oxidative stress markers

These findings support the hypothesis that **iNOS**, **COX-2** and **8-OHdG** in bladder urothelium are induced by long-term exposure to low-dose IR with a close relationship to **p53 overexpression** that could predispose to **bladder carcinogenesis**.

Exposure of cells to a variety of stresses including IR, induces compensatory activation of multiple **intracellular signaling pathways**.

Upregulation of fibroblast growth factor receptor 3 and epidermal growth factor receptors, in association with Raf-1, in urothelial dysplasia and carcinoma *in situ* after the Chernobyl accident

Alina M. Romanenko,[1] Keiichirou Morimura,[3] Anna Kinoshita,[3] Hideki Wanibuchi,[3] Satoru Takahashi,[4] Wadim K. Zaparin,[2] Wladimir I. Vinnichenko,[2] Alexander F. Vozianov[2] and Shoji Fukushima[3,5]

Departments of [1]Pathology and [2]Urology, Institute of Urology, Academy of Medical Sciences of Ukraine, Yu. Kotzubinsky Street 9a, 04053, Kiev, Ukraine; [3]Department of Pathology, Osaka City University Medical School, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585; [4]Department of Experimental Pathology and Tumor Biology, Nagoya City University Graduate School of Medical Science, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

Table 4. Immunohistochemical scores

Protein/factor	Group 1	Group 2	UC group 2
FGFR3	$8.1 \pm 2.0^{*\dagger}$	5.5 ± 1.7	$3.8 \pm 2.4^{\#\#}$
EGFR1	$5.1 \pm 1.6^{**\dagger}$	2.9 ± 2.0	2.7 ± 2.4
EGFR2/*neu*	$4.6 \pm 3.0^{\dagger}$	3.3 ± 3.0	2.0 ± 2.0
Raf-1	$4.6 \pm 2.5^{\#\dagger}$	0.9 ± 1.7	2.1 ± 2.3
p53	$5.7 \pm 2.4^{\ddagger}$	$4.4 \pm 2.0^{\ddagger}$	$5.6 \pm 2.7^{\ddagger}$

Significantly different versus group 2: $^{*}P < 0.0001$, $^{**}P < 0.001$, $^{\#}P < 0.005$, $^{\#\#}P < 0.05$. †Significantly different versus urothelial carcinoma (UC) group 2 ($P < 0.005$). ‡Fisher double-sided exact test ($P < 0.0001$). The relationship between fibroblast growth factor receptor 3 (FGFR3) and p53 protein expression was compared. EGFR, epidermal growth factor receptor.

doi: 10.1111/j.1349-7006.2006.00309.x

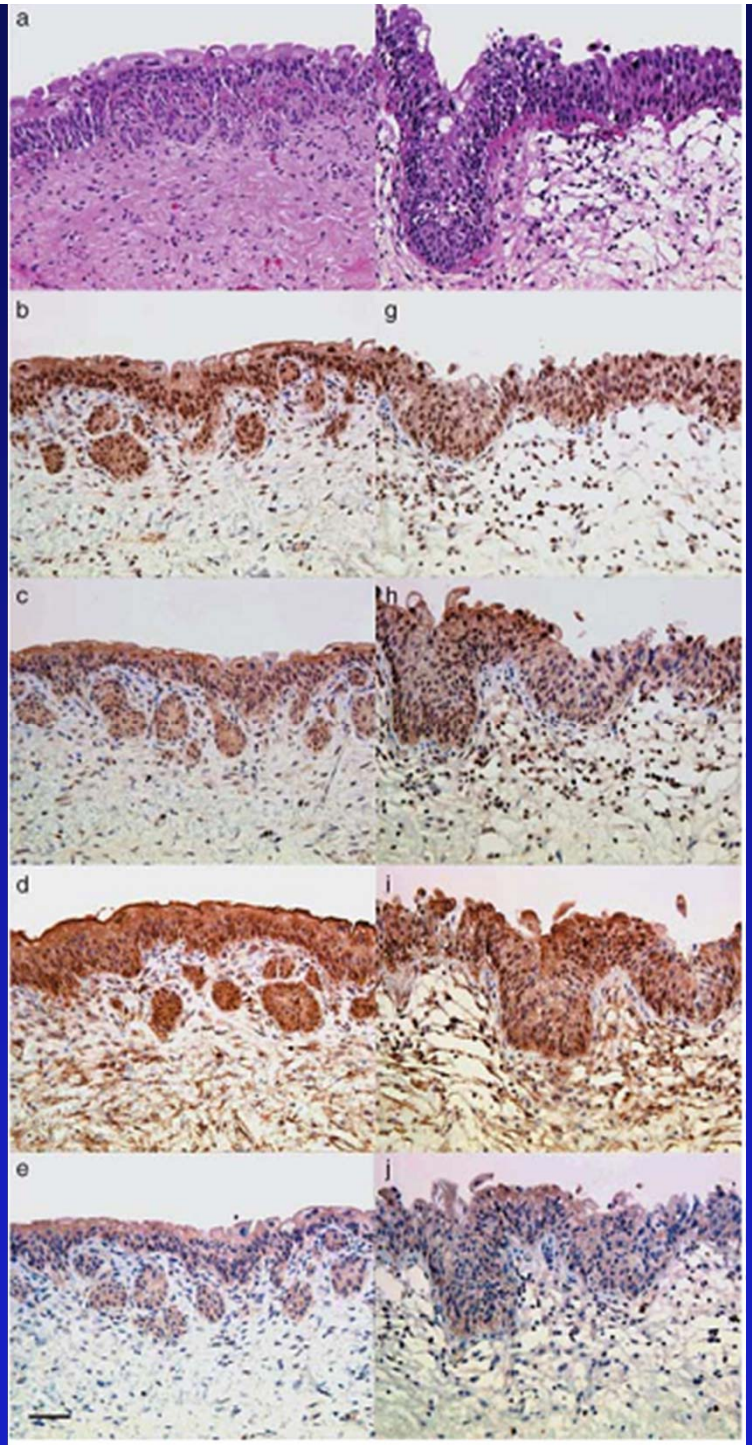
H & E

FGFR-3

EGFR1

EGFR2/neu

Raf-1



H & E

FGFR-3

EGFR-1

EGFR2/neu

Raf-1

Our findings suggest that **FGFR** and **EGFR signaling pathways**, associated with **p53** and **Raf-1 activation**, may contribute to multistage urothelial carcinogenesis caused by IR through **autocrine or paracrine growth stimulation**.

Our results suggest that increased oxidative stress in the bladder urothelium of the Ukrainian population in radio-contaminated areas is accompanied by **marked DNA damage and repair (base and nucleotide excision repair)**.

0022-5347/02/1683-0973/0
THE JOURNAL OF UROLOGY®

Vol. 168, 973–977, September 2002
Printed in U.S.A.
DOI: 10.1097/01.ju.0000026808.26025.3b

DNA DAMAGE REPAIR IN BLADDER UROTHELIUM AFTER THE CHERNOBYL ACCIDENT IN UKRAINE

ALINA ROMANENKO, KEIICHIROU MORIMURA, MIN WEI, WADIM ZAPARIN, ALEXANDER VOZIANOV AND SHOJI FUKUSHIMA*

From the Departments of Pathology and Urology, Institute of Urology and Nephrology, Academy of Medical Sciences of Ukraine, Kiev, Ukraine, and Department of Pathology, Osaka City University Medical School, Osaka, Japan

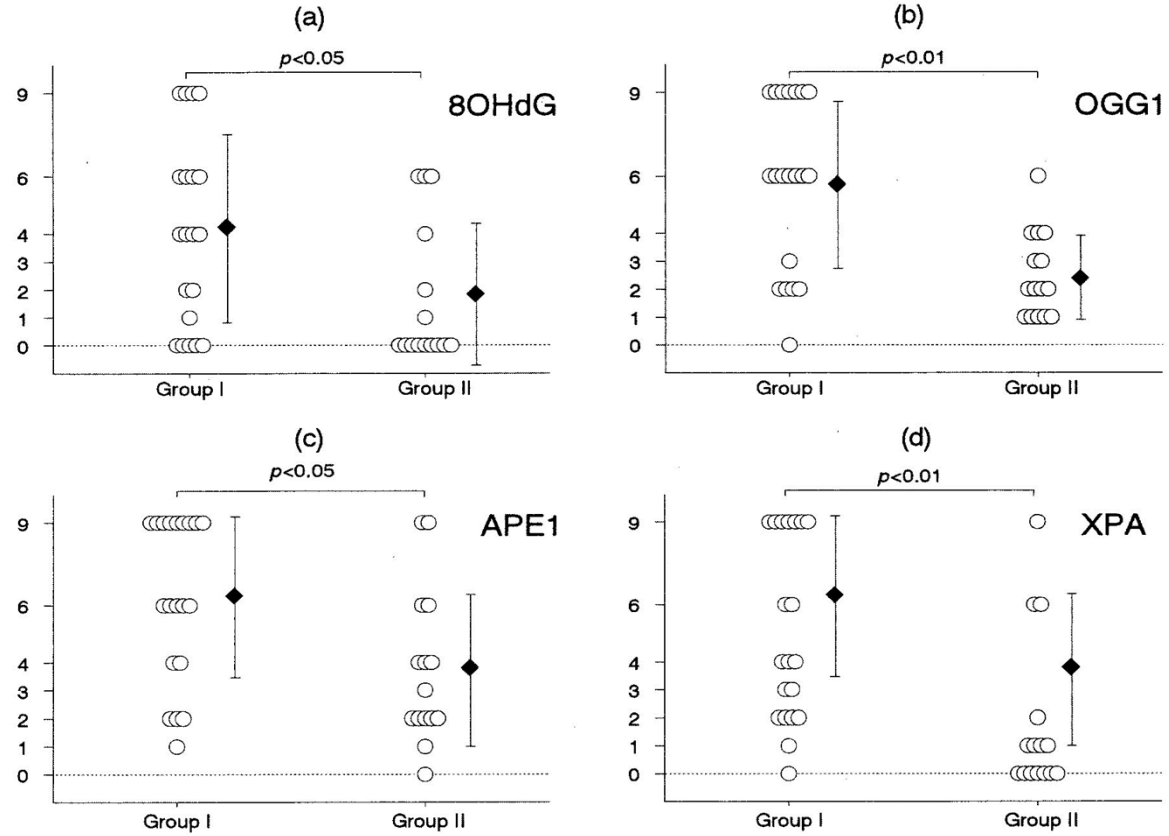


FIG. 1. Immunohistochemical scores for bladder urothelium in groups 1 (*I*) and 2 (*II*). *a*, 8OHdG. *b*, OGG1. *c*, apurinic/apyrimidinic endonuclease 1 (*APE1*). *d*, xeroderma pigmentosum A (*XPA*). Bars represent mean plus or minus standard deviation. Mann-Whitney U test p values.

Our data show that DNA repair (**base and nucleotide excision repair pathways**) is related to the increased oxidative stress and associated with urothelial dysplasia and CIS, was **inefficient** and thus, it may be related to the carcinogenic potential of the urothelial lesions.

Carcinogenesis vol.30 no.11 pp.1821–1831, 2009
doi:10.1093/carcin/bgp193
Advance Access publication July 30, 2009

REVIEW

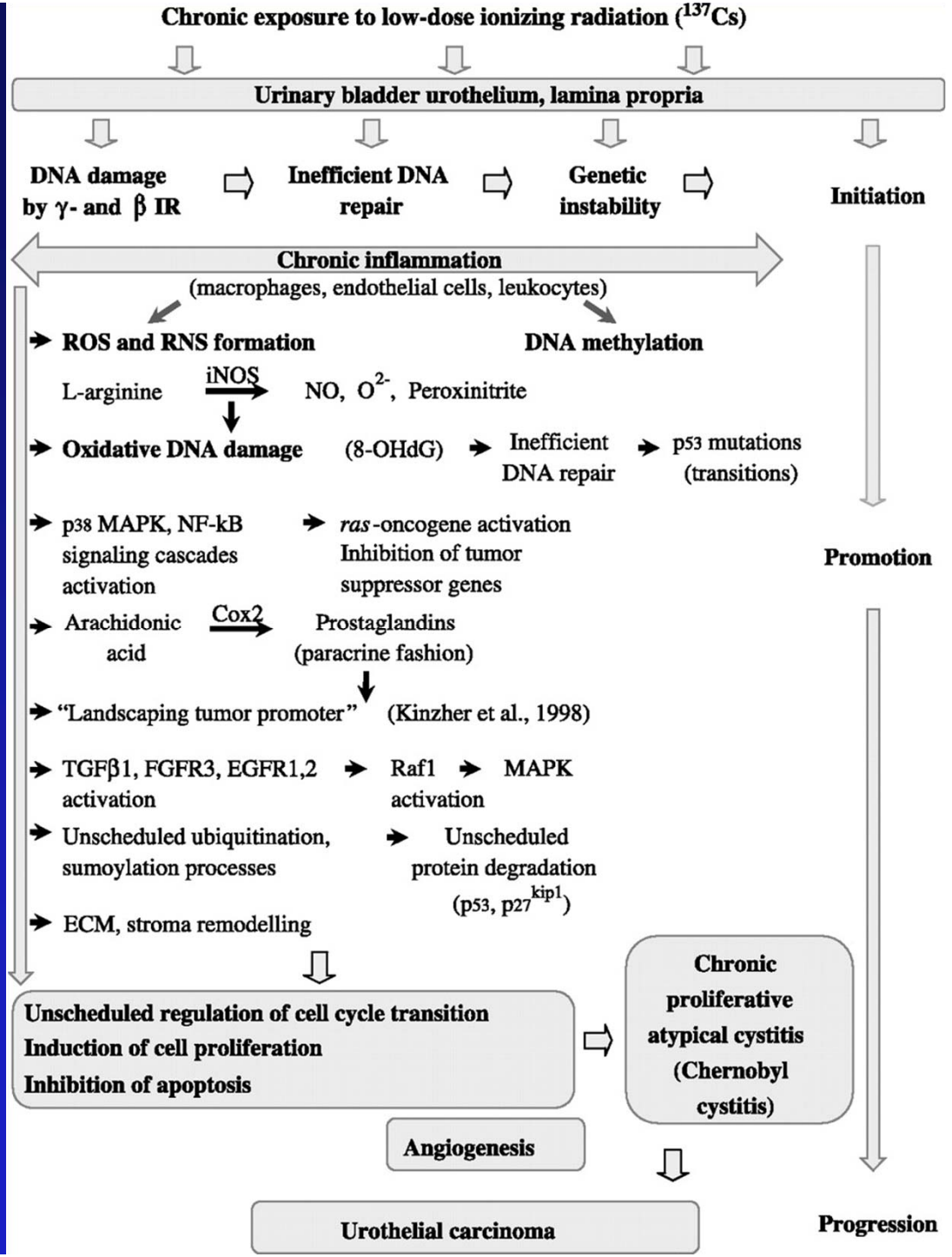
Urinary bladder carcinogenesis induced by chronic exposure to persistent low-dose ionizing radiation after Chernobyl accident

Alina Romanenko, Anna Kakehashi[1], Keiichirou Morimura[1], Hideki Wanibuchi[1,*], Min Wei[1], Alexander Vozianov[2] and Shoji Fukushima[1,3]

Department of Pathology, Institute of Urology, Academy of Medical Sciences of Ukraine, 9a, Yu. Kotzubinsky Street, 04053 Kiev, Ukraine, [1]Department of Pathology, Osaka City University Medical School, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan and [2]Department of Urology, Institute of Urology, Academy of Medical Sciences of Ukraine, 9a, Yu. Kotzubinsky Street, 04053 Kiev, Ukraine

Our data support the hypothesis of **distinct molecular carcinogenesis pathways for bladder cancer** in Ukraine before and after the Chernobyl disaster.

Schematic representation of cellular and molecular responses induced by exposure to chronic long-term, low-dose IR in the bladder urothelium of people living in ^{137}Cs-contaminated areas of Ukraine after the Chernobyl accident.



Romanenko A et al. Carcinogenesis 2009;30:1821-1831

Prostate Carcinogenesis

induced by chronic exposure to persistent low-dose IR (Pilot study)

Department of Pathology, Institute of Urology, Academy of Medical Sciences of Ukraine

Alina Romanenko,
Anna Chekalova,
Alexander Vozianov

Tumor Biology Wallenberg Laboratory Lund University Hospital in Malmo (Sweden)

Pirkko Harkonen

Incidence and Morbidity of Prostate Cancer in Ukraine

Prostate cancer	1989	2010
Morbidity	12.0	**29.4**
Incidence	17.2	**149.7**

Per 100,000 of male population

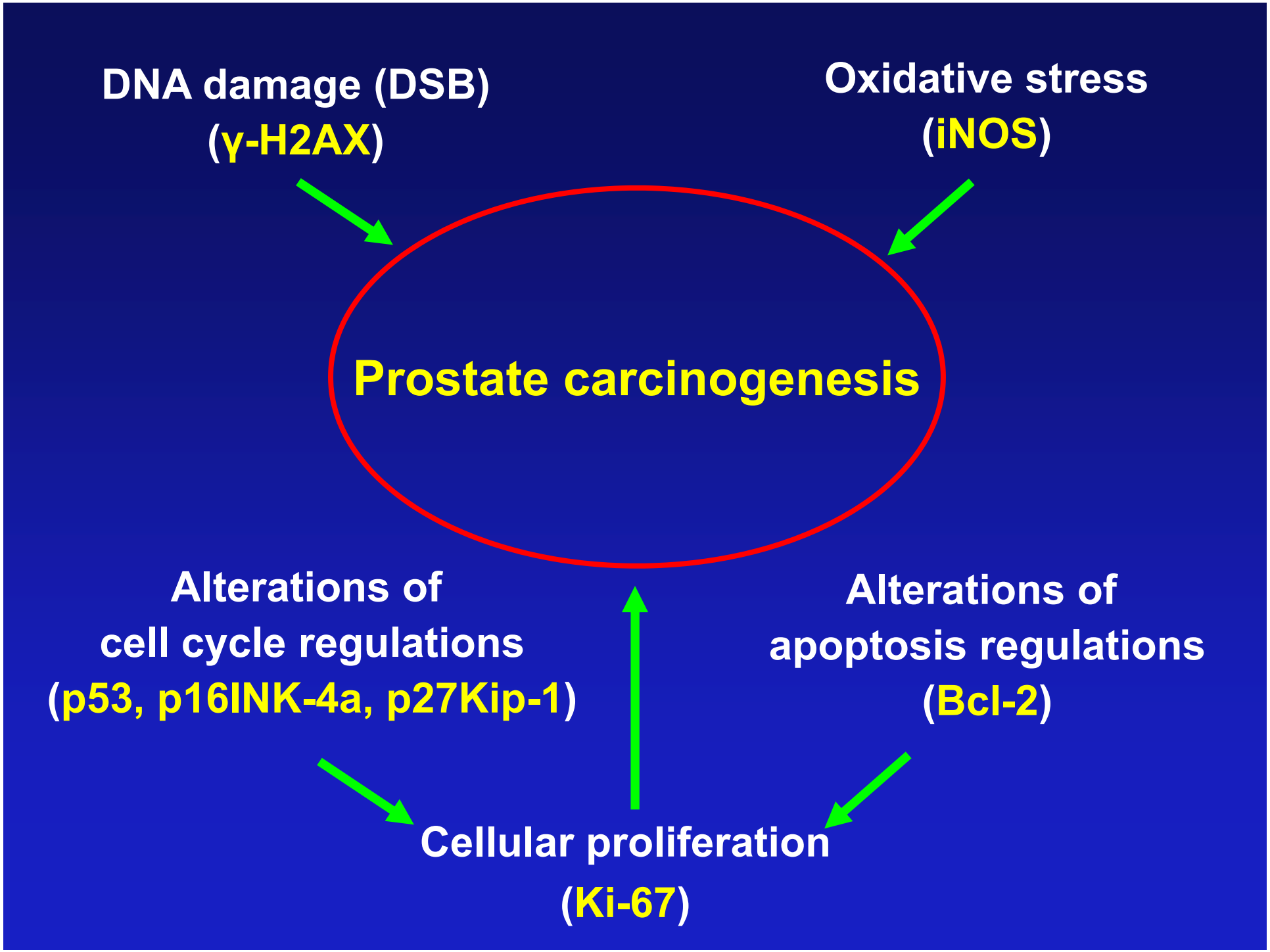
Characteristics of patients that were included in this study

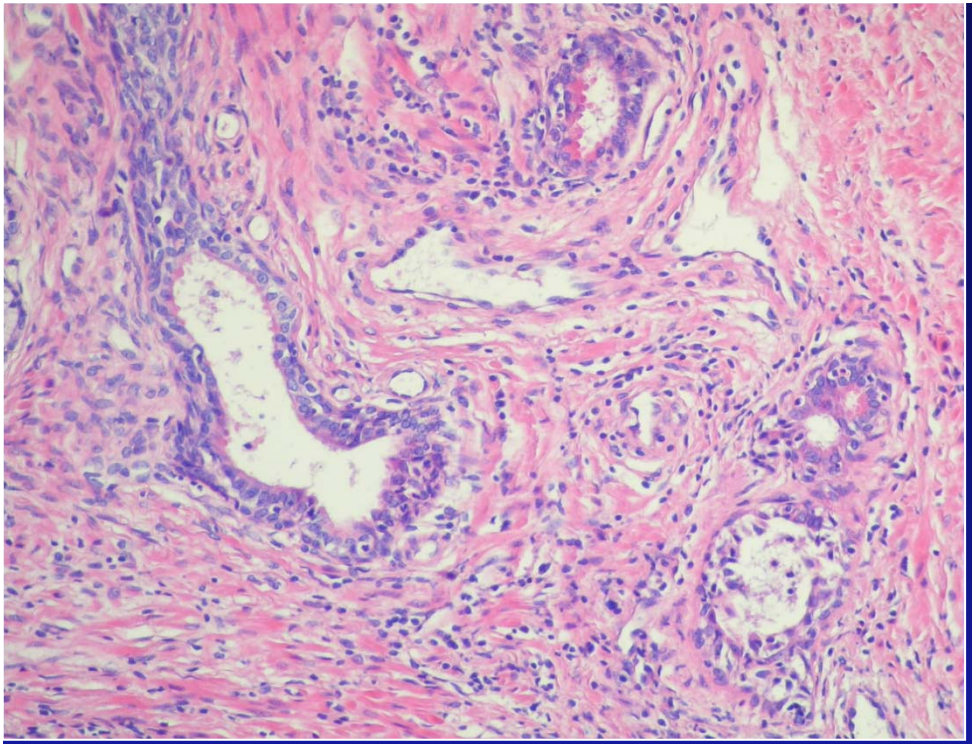
Patients	Group 1	Group 2
No. of men	30	90
Median age (range)	52-91 (65±2.01)	51-88 (64±1.08)
Cigarette smokers (%)	11 (33.3)	22 (30.1)
Year of surgery	2007-2010	2007-2010
Contamination levels in soils [Ci/km^2] [a]	NC [b]	0.5-30

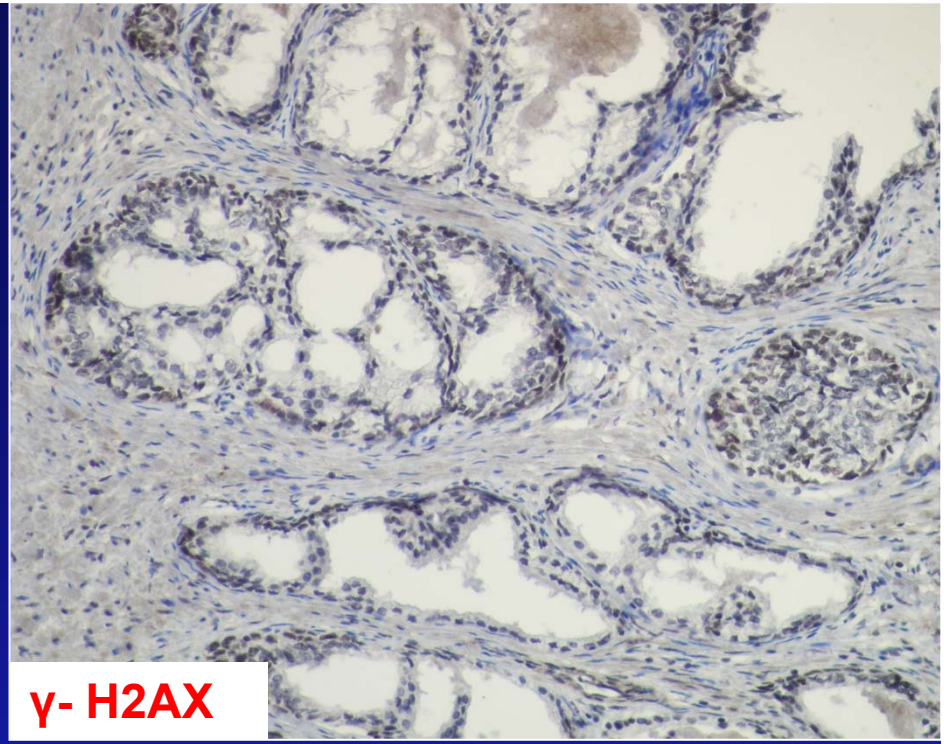
a – data from Raes et al. (1991);
b – not contaminated

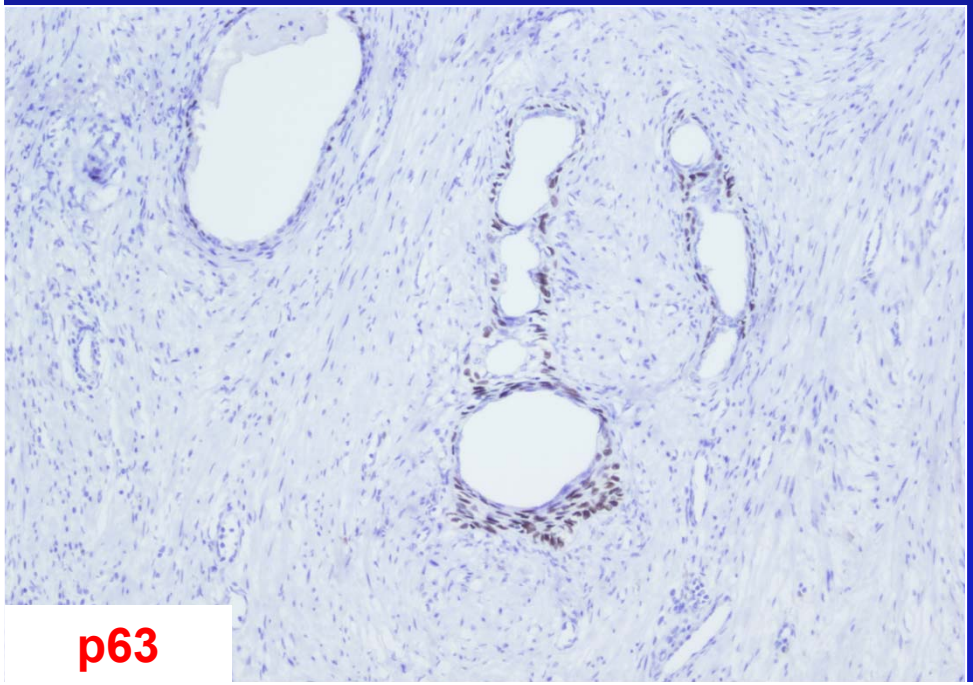
Incidence of dysplasias and carcinomas in patients with BPH

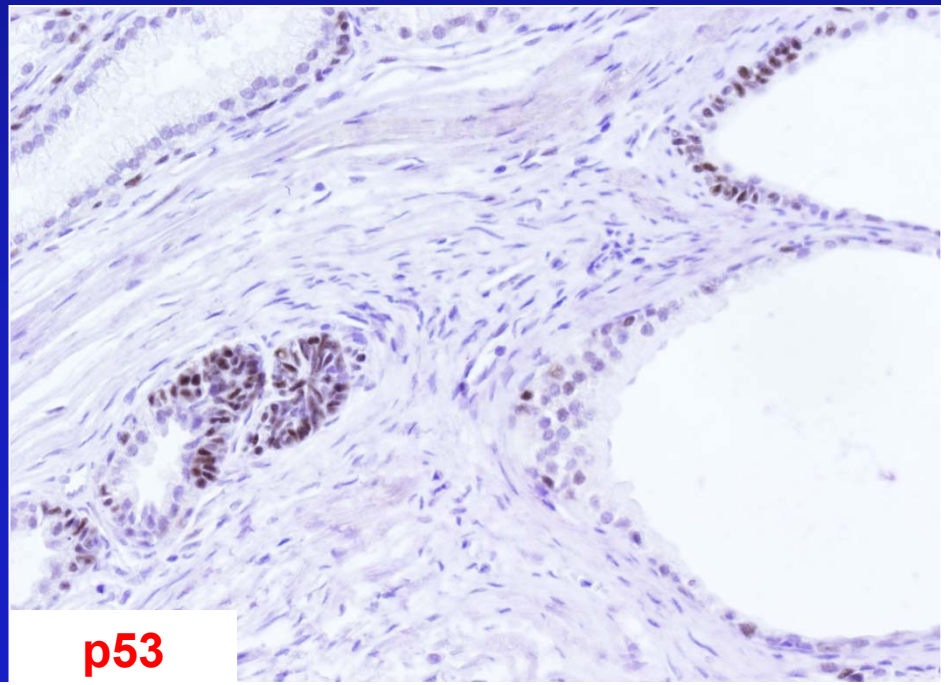
Histological findings	Groups		Significance	
	I	II	χ^2	p
Chronic prostatitis	16 (53,3)	58 (64,4)	1,2	0,3
LG PIN	8 (26,7)	23 (25,6)	0,01	0,9
HG PIN	0	**10 (11,1)**	3,6	0,06
PIA	6 (20)	17 (18,9)	0,02	0,9
PIA with cellular atypia	2 (6,7)	**22 (24,4)**	4,4	0,035
BCH	7 (23,3)	32 (35,6)	1,5	0,2
BCH with cellular atypia	0	**15 (16,7)**	5,7	0,017
Latent carcinoma	5 (16,7)	11 (12,2)	0,4	0,5
Total no. of cases (%)	30 (100)	90 (100)	-	-

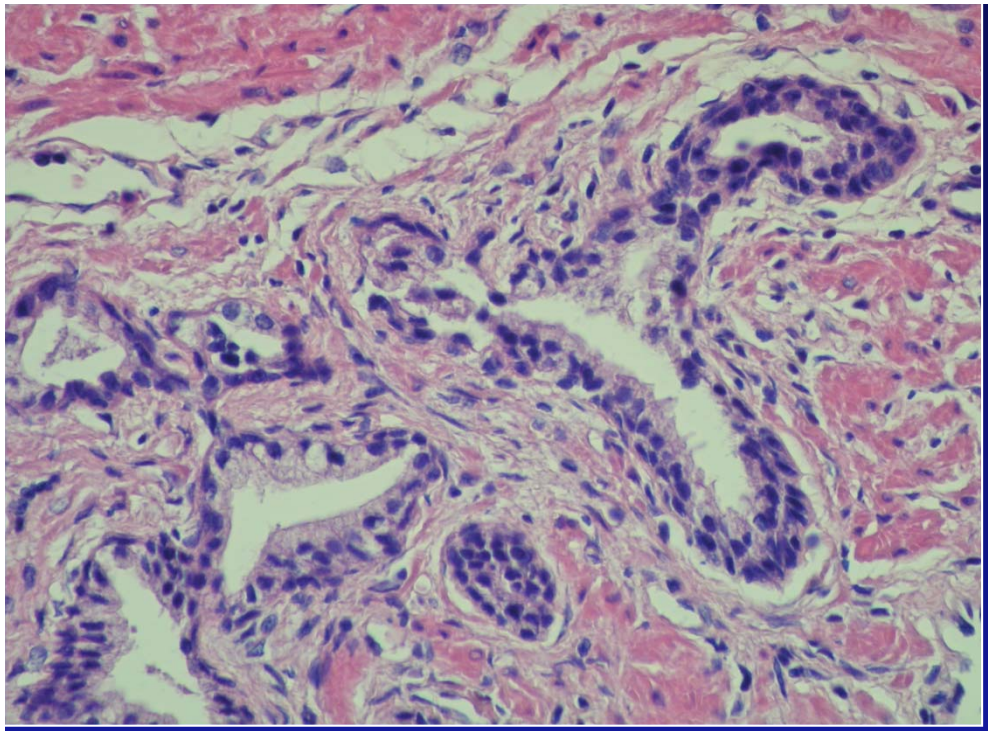

DNA damage (DSB)
(γ-H2AX)
Oxidative stress
(iNOS)
Prostate carcinogenesis
Alterations of
cell cycle regulations
(p53, p16INK-4a, p27Kip-1)
Alterations of
apoptosis regulations
(Bcl-2)
Cellular proliferation
(Ki-67)

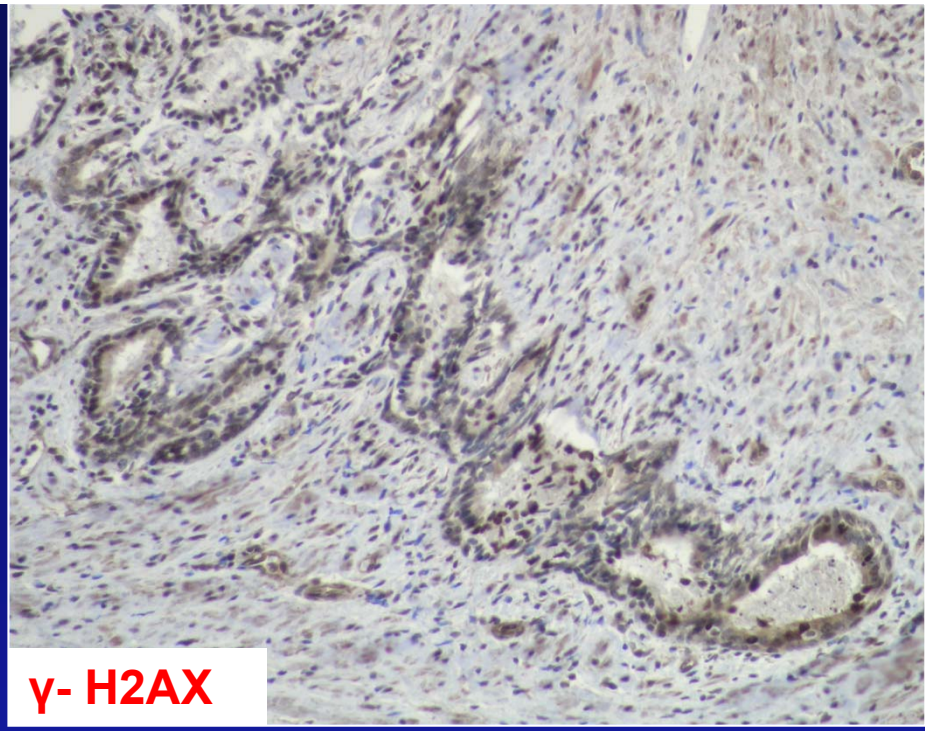


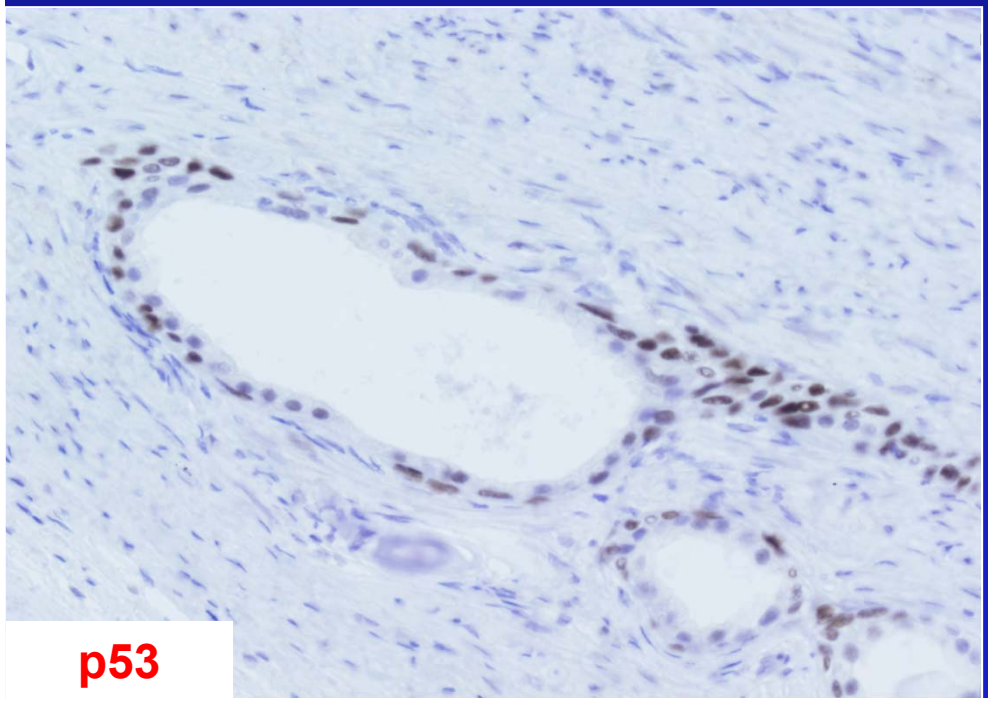

γ- H2AX

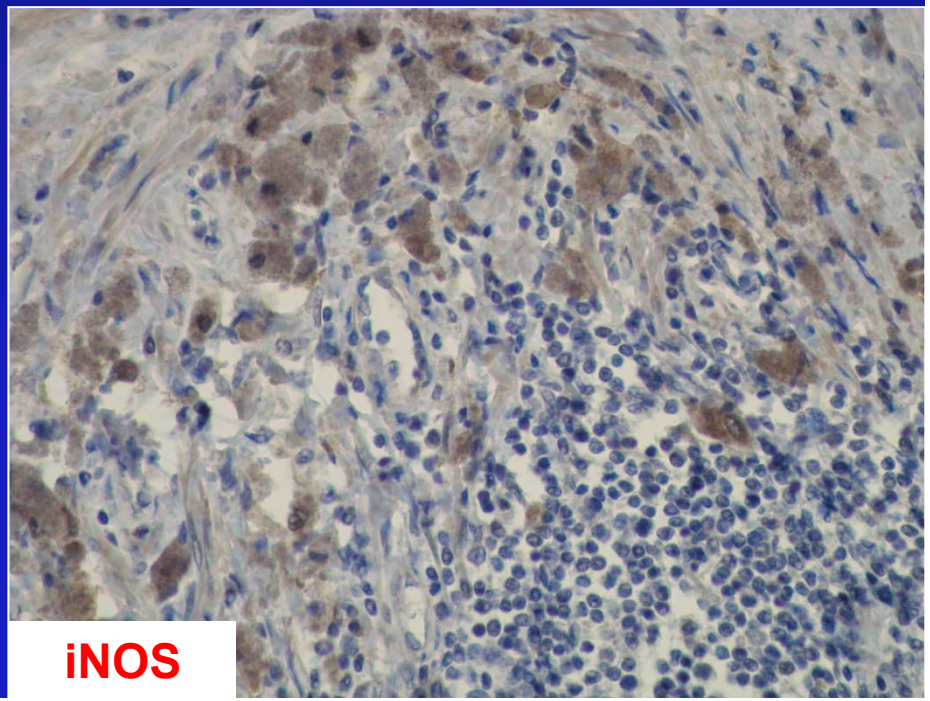

p63


p53




γ- H2AX


p53


iNOS

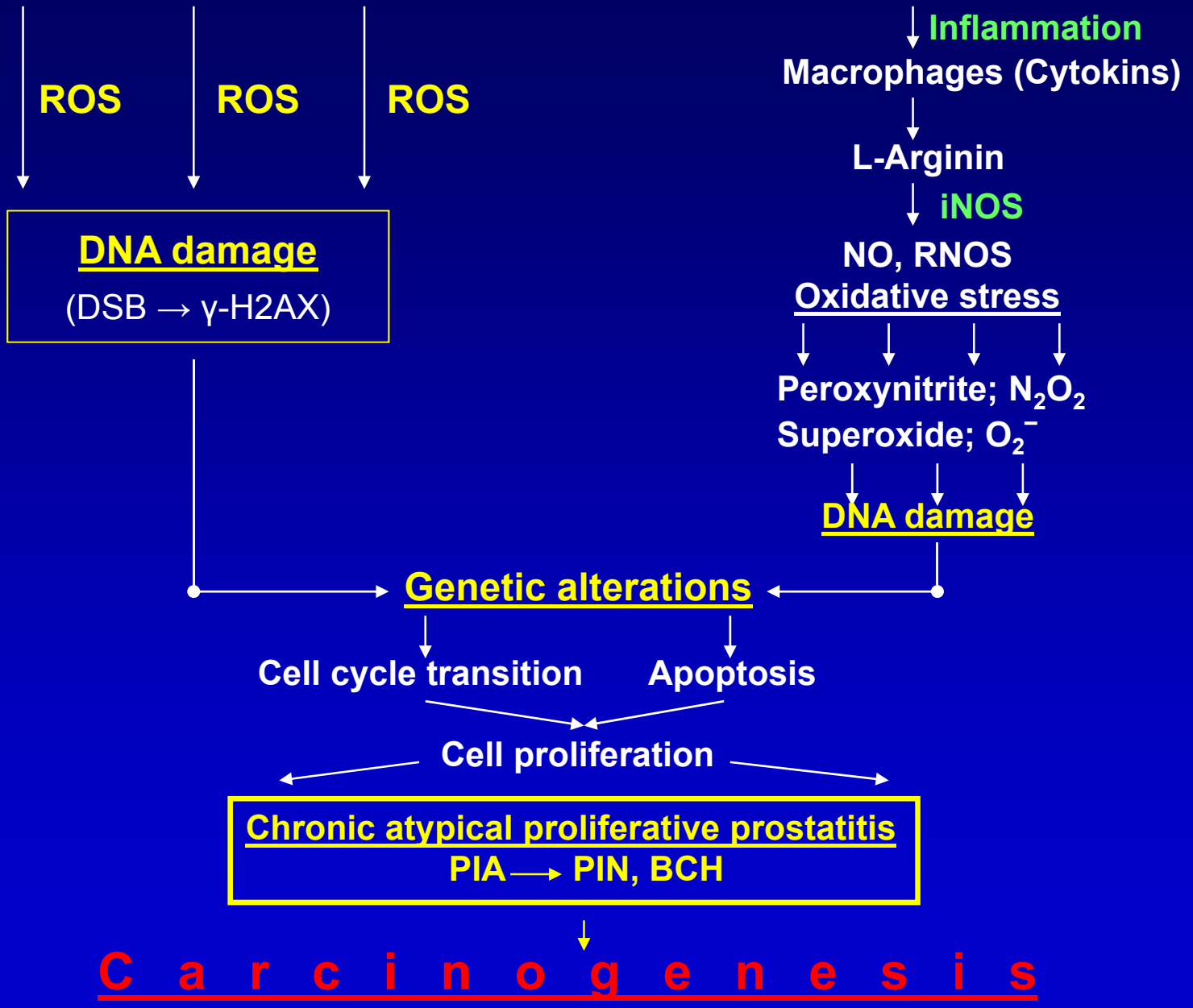
Chronic atypical proliferative prostatitis

- multiple areas of PIA, PIN, BCH (with cellular atypia);
- focal acinar atrophia;
- stromal sclerosis; blood vessels dilatation and sclerotic changes;
- poor inflammatory reaction

Comparative analysis of IHC results in different types of dysplasia that were found in BPH group 2 patients

Protein expression	Type of dysplasia			Significance, P
	PIA	PIA with cellular atypia	PIN	
γ-H2AX	6.9 ± 2.2	8.1 ± 1.4	3.5 ± 1.3	<0.001
iNOS	4.4 ± 2.2	6.3 ± 1.8	2.8 ± 1.2	0.002
p53	6.2 ± 1.8	8.5 ± 1.2	3.2 ± 0.9	0.001
Ki-67	4.9 ± 1.4	8.3 ± 1.3	6.5 ± 1.9	0.04
p27Kip1	4.0 ± 1.1	3.9 ± 1.2	4.2 ± 1.3	0.02
p63	3.9 ± 0.9	2.4 ± 0.8	4.0 ± 1.0	<0.001
Bcl-2	3.5 ± 0.9	6.7 ± 1.8	3.2 ± 1.3	0.002

Persistent chronic low-dose IR



Final conclusions

1. **Kidney** (RCCs), **urinary bladder urothelium** and **prostate** (BPH) as well as cells in the microenvironment (endothelial elements, fibroblasts and lymphocytes, leyomiocytes, macrophages) demonstrate a number of similar responses to chronic persistent long-term, low-dose IR.

2.Increase of oxidative stress.

3.DNA damage and inefficient DNA repair indicating the apparent disruption of the base and nucleotide repair machinery in cells.

4.Alterations of the apoptotic regulatory mechanisms.

5. Disruption of the periepithelial stroma and basement membranes with global remodeling of the extracellular matrix.

6. Disregulation of the cell cycle transition processes.

7. Radiation sclerosing atypical nephropathy, Chernobyl cystitis and chronic atypical proliferative prostatitis development (precancer lesions) were firstly described.