

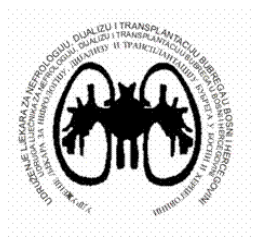
Malignitet i hemodijaliza

Prof. Halima Resić
Klinika za Hemodijalizu
KCU Sarajevo

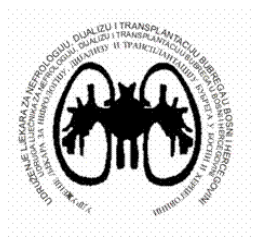
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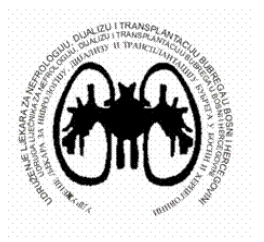
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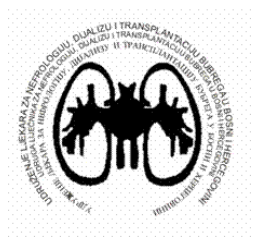
- Uvod
- Epidemiologija
- Riziko faktori
- Prognoza
- Screening



UVOD



- Uremični pacijent imaju veći rizik od razvoja maligniteta i to najčešće bubrega i urinarnog trakta.
- Tumori genito-urinarnog sistema su 4-5 puta češći nego tumori koji se razvijaju na drugim mjestima (pluća, kolon, rektum i dojke).



EPIDEMIOLOGIJA

- Posebna studija unutar ERA-EDTA Registra i uključila je 17.907 pacijenata iz Austrije, Spanije, Italije i UK u periodu od 1994 do 2001.

Table 1. Baseline characteristics of RRT patients by national or regional registry

	All countries	Austria	Catalonia, Spain	Lombardy, Italy	Norway	UK, England/Wales
Number of patients	17907	3859	5932	4292	1204	2620
Incidence of RRT in 2000 (pmp) [§]	–	128.6	145.1	126 [#]	89.1	89
Age at start RRT						
Median (years)	65.4	64.3	67.4	64.8	64.5	63.5
Mean (years)	62.2	62.1	63.7	61.7	61.4	60.3
65+ (%)	51.1	48.4	56.4	49.3	49.1	46.8
75+ (%)	20.4	19.0	23.8	17.6	22.3	18.4
Female (%)	38.8	40.6	38.0	39.6	34.5	38.7
Primary renal disease (%)						
Glomerulonephritis	16.8	13.9	14.8	21.6	20.6	16.6
Interstitial nephritis	11.3	9.8	11.5	11.8	11.1	12.1
Cystic kidney disease	7.5	6.2	8.3	7.8	7.0	7.6
Hypertension/renal vascular disease	17.5	16.5	17.5	17.9	27.1	13.7
Diabetes mellitus	20.4	33.0	19.5	14.3	14.6	16.7
Other multisystem disease	6.2	5.1	4.7	6.2	10.7	8.9
Other congenital and hereditary kidney disease	20.4	15.6	23.8	20.4	9.0	24.6

[§]pmp = per million population; [#]incidence of RRT pmp in 1996 as this year is in the middle of the inclusion period 1994–1997.

Malignitet i hemodijaliza

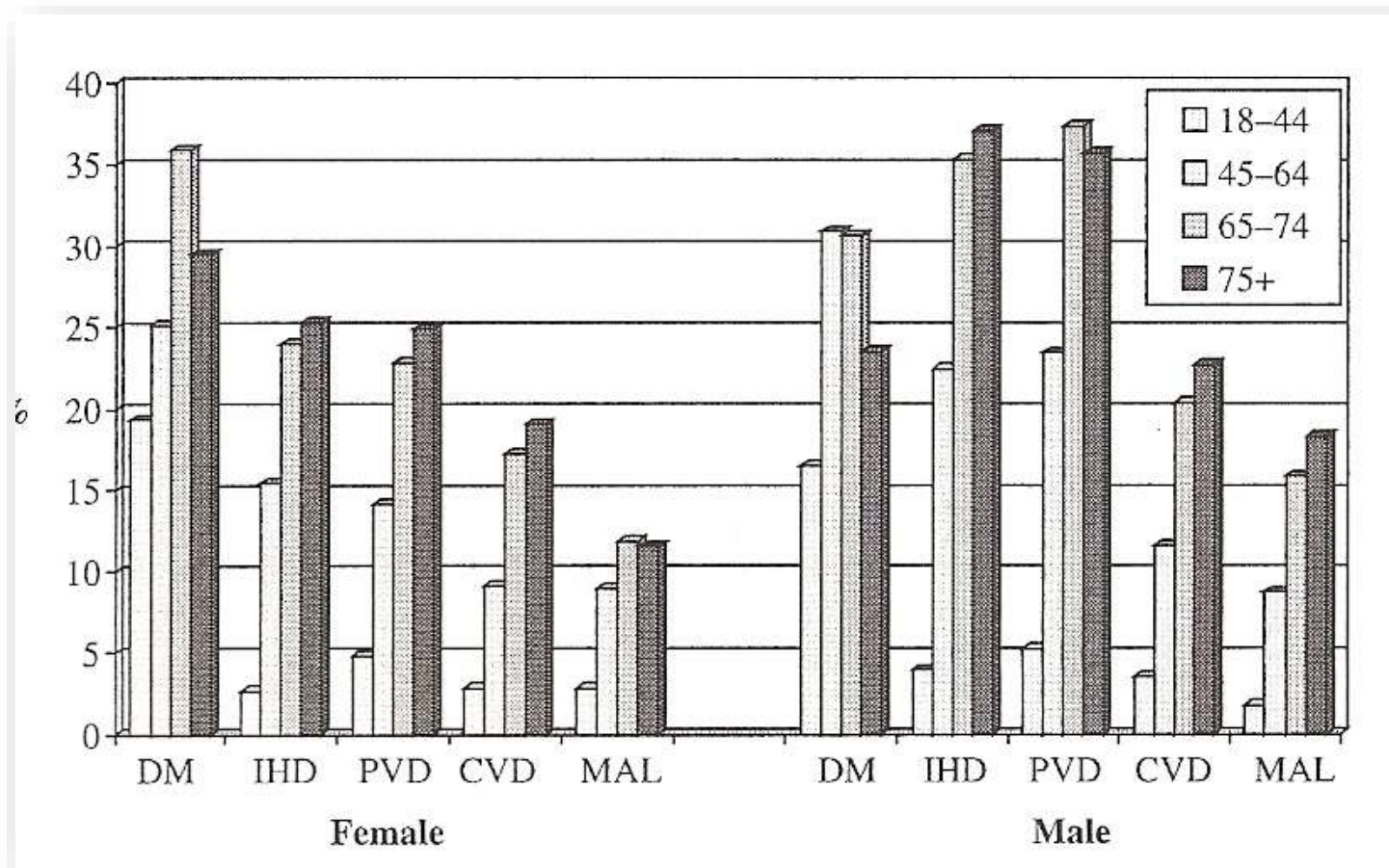


Fig.1. Prevalenca komorbiditeta kod RRT pacijenata naspram spola i dobne skupine

Međunarodna studija renalnih Registra 1980 – 1994 otkrila je pojavu karcinoma u **25,044** od **831,804** pacijenata na **dijalizi** (SAD, Europa, Australija/Novi Zeland), sto je predstavljalo ukupnu standardiziranu incidencu karcinoma (SIR) od **1.18**.

	Australia and New Zealand		Europe		USA	
	n	SIR (95% CI)	n	SIR (95% CI)	n	SIR (95% CI)
All patients	70	9.8 (7.7-12.3)	680	3.3 (3.1-3.6)	1303	3.7 (3.5-3.9)
Age at first dialysis						
0-34 years	4	98.1 (36.8-261)	23	18.7 (11.9-28.1)	68	41.5 (32.2-52.6)
35-64 years	37	9.3 (6.7-12.8)	487	4.1 (3.8-4.5)	742	5.2 (4.8-5.6)
≥65 years	29	9.2 (6.4-18.3)	170	2.0 (1.7-2.3)	493	2.3 (2.1-2.6)
Time after first dialysis						
During year 1	33	15.1 (10.4-21.3)	219	3.7 (3.2-4.2)	380	2.8 (2.5-3.1)
During year 2	8	4.9 (2.1-9.7)	118	2.9 (2.4-3.5)	260	3.2 (2.8-3.6)
During years 3-5	22	9.1 (6.0-13.9)	197	2.9 (2.5-3.4)	411	4.0 (3.7-4.4)
During years 6-10	6	7.0 (3.1-15.5)	126	3.8 (3.1-4.3)	219	6.2 (5.5-7.1)
After year 10	1	9.3 (1.3-65.7)	20	4.5 (2.9-7.0)	33	9.8 (7.0-13.8)
Primary renal disease						
Arteriopathic	5	5.7 (2.4-13.7)	58	2.1 (1.6-2.7)	463	3.7 (3.4-4.1)
Glomerulonephritis	18	7.6 (4.8-12.0)	60	3.5 (2.7-4.5)	194	3.9 (3.4-4.5)
Diabetes	1	1.3 (0.2-9.1)	33	1.5 (1.1-2.1)	244	2.6 (2.3-2.9)
Infective and obstructive nephropathies	6	13.7 (6.1-30.4)	140	3.8 (3.2-4.5)	86	4.0 (3.3-5.0)
Congenital	0	..	3	5.3 (1.7-16.3)	7	30.4 (14.5-63.8)
Familial hereditary	0	..	63	2.9 (2.3-3.7)	45	3.2 (2.4-4.3)
Toxic nephropathies	34	28.4 (20.3-39.8)	122	11.0 (9.5-13.6)	10	4.6 (2.5-8.5)
Miscellaneous	0	..	40	9.1 (6.7-12.5)	16	3.9 (2.4-6.4)
Cause uncertain or missing	6	8.3 (3.7-18.5)	161	2.5 (2.1-2.9)	238	5.1 (4.5-5.8)

n=number of observed cancers.

Table 5: **Kidney cancer risk in ESRD patients**

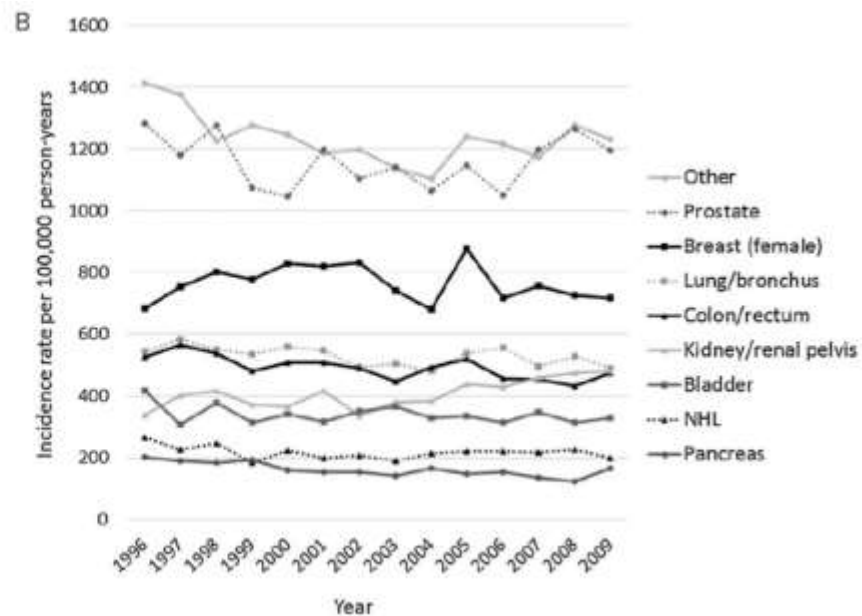
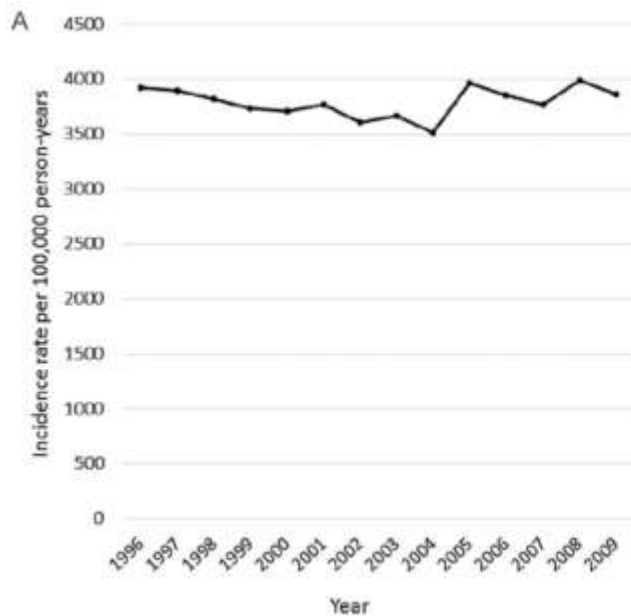
- Najčešće su obolijevali pacijenti ispod 35 godina, a incidenca se smanjivala sa povećanjem godina.
- Tipovi karcinoma koji su bili češći nego kod kontrolnih grupa su:
 - Karcinom bešike (SIR 1,5)
 - Karcinom bubrega (SIR 3,6)
 - Jetre, štitnjače, jezika, cerviksa, Non-Hodgkin limfoma.

	Australia and New Zealand		Europe		USA	
	n	SIR (95% CI)	n	SIR (95% CI)	n	SIR (95% CI)
All patients	53	4.8 (3.6-6.2)	660	1.5 (1.4-1.7)	933	1.4 (1.3-1.5)
Age at first dialysis						
0-34 years	3	79.6 (25.7-247)	10	8.0 (3.8-14.7)	12	9.2 (4.8-16.1)
35-64 years	36	7.1 (5.1-9.8)	396	1.9 (1.8-2.1)	287	1.5 (1.4-1.7)
≥65 years	14	2.3 (1.4-3.9)	254	1.1 (1.0-1.3)	634	1.4 (1.3-1.5)
Time after first dialysis						
During year 1	20	6.1 (3.7-9.4)	223	1.9 (1.6-2.1)	380	1.4 (1.3-1.6)
During year 2	6	2.4 (0.9-5.2)	126	1.5 (1.3-1.8)	225	1.5 (1.3-1.7)
During years 3-5	17	4.5 (2.8-7.2)	229	1.6 (1.4-1.9)	243	1.3 (1.2-1.5)
During years 6-10	9	6.7 (3.5-12.8)	74	1.0 (0.8-1.3)	79	1.4 (1.1-1.7)
After year 10	1	5.9 (0.8-42.0)	8	0.8 (0.4-1.6)	6	1.2 (0.6-2.7)
Primary renal disease						
Arteriopathic	9	5.8 (3.0-11.2)	69	1.0 (0.8-1.3)	321	1.4 (1.2-1.5)
Glomerulonephritis	11	2.8 (1.5-5.0)	28	0.8 (0.6-1.2)	145	1.5 (1.2-1.7)
Diabetes	2	1.9 (0.5-7.5)	31	0.8 (0.5-1.1)	138	0.9 (0.8-1.1)
Infective and obstructive nephropathies	4	6.3 (2.4-16.9)	160	2.1 (1.8-2.4)	149	3.2 (2.8-3.8)
Congenital	0	..	3	3.2 (1.0-9.9)	3	7.1 (2.3-21.9)
Familial hereditary	1	1.0 (0.1-7.1)	33	0.8 (0.6-1.2)	19	0.7 (0.5-1.2)
Toxic nephropathies	24	16.2 (10.9-24.2)	131	7.8 (6.6-9.3)	12	2.5 (1.4-4.4)
Miscellaneous	1	6.5 (0.9-45.8)	32	3.2 (2.3-4.6)	21	2.5 (1.6-3.8)
Cause uncertain or missing	1	0.8 (0.1-5.6)	173	1.3 (1.1-1.5)	125	1.4 (1.2-1.7)

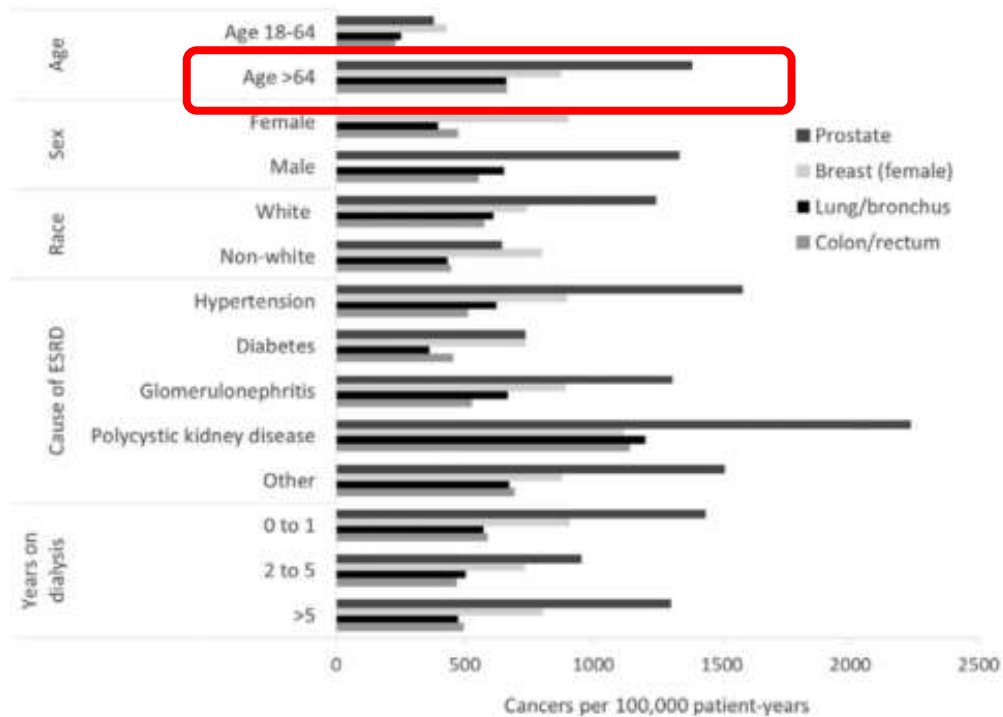
n=number of observed cancers.

Table 4: Bladder cancer risk in ESRD patients

- Nešto novija studija „US Medicare“ HD pacijenata između 1996 i 2009 pronašla je SIR od 1.42.
- Najveći rizik bio je od **karcinoma bubrega (SIR 4.03)** i **bešike (SIR 1.57)**.



- Nasuprot proslj studiji, ovdje je nađen veći rizik za razvijanje karcinoma kod osoba **starijih od 65 godina** u vrijeme počinjanja HD.



- Studija kod Tajvanskih pacijenata na dijalizi pronašla je povećan rizik od razvoja karcinoma beške i jetre.
- Međutim kod ovih pacijenata najveći rizik bio je kod mlađih pacijenata, te u prvoj godini od započinjanja dijalize.

Table 3. Risk factors for all-cause mortality in end-stage renal disease dialysis patients with cancer.

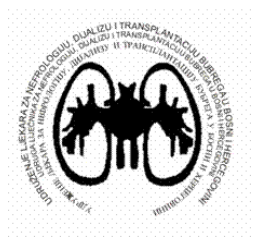
Variables	Univariate Analysis	Multivariate Analysis
	*HR (95% CI)	*HR (95% CI)
Age at cancer diagnosis (years)		
< 35	1 (reference)	1 (reference)
35-64	2.60 (1.34-5.02)*	2.25 (1.16-4.38)*
≥ 65	5.00 (2.59-9.66)*	3.66 (1.88-7.12) **
Gender (Male vs. Female)	1.53 (1.36-1.72)*	1.16 (1.02-1.32)*
Diabetes mellitus (yes vs. no)	1.69 (1.50-1.90)*	1.27 (1.12-1.45) **
Hypertension (yes vs. no)	1.30 (1.14-1.48)*	0.89 (0.77-1.02)
Cardiovascular disease (yes vs. no)	1.54 (1.37-1.74)*	1.15 (1.01-1.31)*
Chronic lung disease (yes vs. no)	1.47 (1.23-1.76)*	1.17 (0.97-1.40)
Chronic liver disease (yes vs. no)	1.34 (1.14-1.58)*	1.02 (0.85-1.22)
Cancer site		
Kidney	1 (reference)	1 (reference)
Bladder	1.45 (1.11-1.90)*	1.38 (1.06-1.81)*
Liver	4.37 (3.39-5.62)*	3.92 (3.02-5.09) **
Colon / Rectum	2.68 (2.02-3.55)*	2.15 (1.61-2.86) **
Lung	8.81 (6.62-11.72)*	6.31 (4.70-8.48) **
Stomach	4.85 (3.49-6.75)*	3.86 (2.76-5.41) **
Mouth	3.57 (2.32-5.48)*	2.99 (1.96-4.63) **
Tongue	3.57 (2.03-6.30)*	3.49 (1.97-6.19) **
Nasopharynx	5.64 (3.34-9.52)*	5.81 (3.42-9.85) **
Thyroid	0.51 (0.19-1.40)	0.60 (0.22-1.64)
Prostate	2.38 (1.48-3.85)*	1.61 (0.98-2.63)
Breast	1.30 (0.90-1.88)	1.35 (0.93-1.96)
Cervix	3.24 (2.21-4.74)*	2.88 (1.96-4.25) **

HR, hazard ratio; CI, confidence interval.

-HR adjusted for gender, age, diabetes mellitus, hypertension, cardiovascular disease, chronic lung disease, and chronic liver disease.

*P<0.05.

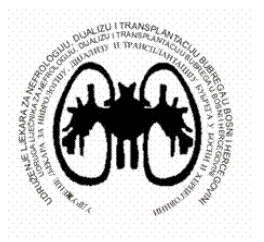
**P < 0.001.



RIZIKO FAKTORI

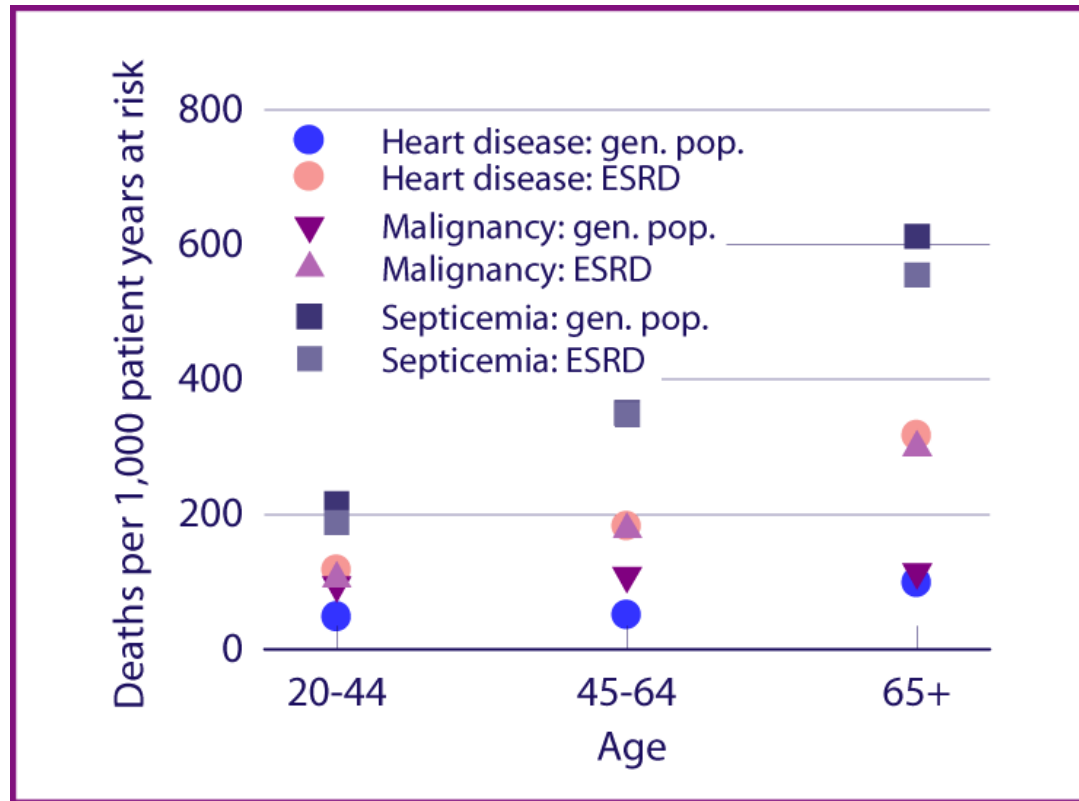
Faktori koji mogu doprinijeti povećanoj prevalenci maligniteta kod ljudi sa bubrežnim oboljenjem:

- Stečena policistična bolest bubrega – karcinom bubrega
- Infekcija hepatitisom B ili C – karcinom jetre
- Infekcija sa HPV – karcinom cerviksa
- Produžena upotreba oralnog ciklofosfamida – karcinom bešike
- Produženo korištenje analgetika – tranzicioni karcinom bešike i uretera
- Pogoršana funkcija imunog sistema
- Nedostatak selena i drugih supstanci



PROGNOZA

- U United States Renal Data Survey (USRDS) 2007 pronađeno je da su karcinomi bili odgovorni za otprilike sedam smrtnih slučajeva na 1000 prevalent pacijenata - godine od 2003 – 2005.
- To je dosta niže u odnosu npr. na srčani zastoj (38 slučajeva na 1000 prevalent pacijenata).



ESRD & general Medicare patients with diagnosis in 2005; adjusted for gender & race. Medicare patients, 2005, used as reference cohort.

All-cause mortality: patients with major diseases, 2005



- Incidenca smrti od karcinoma je veća sa povećanjem trajanja dijalize (9 naspram 6,5 smrtnih slučajeva kod pacijenata koji su na dijalizi tri ili jednu godinu).
- Malignitet je češći kod HD pacijenata nasuprot CAPD pacijentima, te češći kod starijih pacijenata iznad 65 godina (osim u Tajvanskim studijama).



Incidenca tumora kod pacijenata sa ESRD

Cancer	SIR	Risk factors in ESRD	References
Renal cell	3.6–24.1	Acquired cystic disease	2–8
Bladder and ureter	1.5–16.4	Analgesic abuse, Balkan nephropathy, oral cyclophosphamide	2,3,5,6,8
Tongue	1.2–1.9	Human papilloma virus	2,3,6
Cervical and uterine	0.9 2.7–4.3+	Human papilloma virus	6 2,3
Liver	1.4–4.5	Hepatitis B and C	2,3,5,6
Thyroid and other	2.2–2.3		2,3,6
Endocrine organs			
Breast (women)	0.8–1.42		3,6,8
Lung/bronchus	0.5–1.28		3,6,8
Colon/rectum	1.0–1.27		3,6,8
Pancreas	1.08		8
Prostate	0.5–1.08		3,6,8



- Hipotetski model studije screeninga maligniteta iz 1996 predložio je da bi u prosjeku screening maligniteta kod ESRD pacijenata donio neto benefit u prezivljavanju od 5 (pet) dana u poredjenju sa opcom populacijom.
- Screening se bazirao na mammografiji, Papanicolaou testu, fleksibilnoj sigmoidoskopiji, serum PSA antigenu.
- Zaključak studije je da rutinski screening maligniteta kod ESRD pacijenata ne predstavlja adekvatno trošenje sredstava.
- Druga studija iz 2008, fokusirala se na screening tumora dojke kod dijaliznih pacijenata, nasla je apsolutnu redukciju mortaliteta tumora dojke od 0.1%, sa neto dobiti u prezivljavanju od 1,3 dana.



Table 3. Suggested cancer screening in ESRD patients: Individualized, considering expected survival, risk factors, and transplant status

Cancer	Recommended screening
Breast	-Yearly mammogram beginning age 40 and on transplant list Clinical breast examination every 3 years for ages 20–39 and yearly for age >40
Colorectal	Beginning age 50: Yearly FIT or FOBT for those on transplant lists and flexible sigmoidoscopy, colonoscopy, double contrast barium enema, or virtual colonoscopy per transplant evaluation protocols Positive FIT or FOBT will require additional evaluation
Cervical	Begin screening at age 21: 21–65, yearly Pap for those on transplant list; consider HPV DNA and HPV vaccine in transplant candidates
Prostate	Age 50, annual PSA and digital rectal examination for men on transplant list Age 45 if African American or father or brother had prostate cancer before the age of 65
Renal cell	Yearly CT or MRI in patients on dialysis >3 years and on transplant list

For all the above cancers, consider screening in high-risk patients with long expected survival. FIT, fecal immunochemical test; FOBT, fecal occult blood test. Adapted from references 22–29.



- Na Klinici za hemodijalizu je 2008 godine rađena studija, u kojoj smo evaluirali ishode za 31 pacijenta sa karcinomom od ukupno 200 pacijenata u periodu 2002-2007.
- Od 31 pacijenta ukupno je umrlo 15 u follow-up periodu.
- Tri pacijenta od 15 imalo je karcinom prostate, a četiri su imali papilarni karcinom.

	Male	Female	Total	p
No.	18	13	31	
Mean age	65.8 ± 11.61	62.5 ± 10.64	64.4±11.16	ns

Table 1. Pathological and prognostic data and co-existent kidney disease (deceased patients)

Case	Tumor type	Cause of ESRD	Outcome	Follow up period (months)
1	Prostatic Adenocarcinoma	Nephroangiosclerosis	HD, without metastasis	36
2	Ovarian Cancer	GN	HD, metastasis, ascites	24
3	Transitional cell carcinoma	Nephritis interstitialis	HD, tumor free	36
4	Endometrial Cancer	GN	HD, tumor free	12
5	Laryngeal Cancer	PKD	HD, tumor free	48
6	Papillary Cancer	GN	HD, tumor free	54
7	Breast Cancer BC	PN	HD, tumor free	50
8	Prostatic Cancer	Pyelonephritis Calculosa	HD, tumor free	48
9	Prostatic Cancer	Nephrolithiasis	HD, tumor free	60
10	Labial Planocellular Cancer	NI	HD, tumor free	56
11	Papillary Carncer (PC)	Renal polycystosis	HD, tumor free	70
12	Bronchial Tumor	Nephroangiosclerosis	HD, tumor free	12
13	Non Hodgkin malignant lymphoma	Nephroangiosclerosis	HD,Chemoth.	16
14	Papillary Cancer	NI	HD, tumor free	18
15	Papillary Cancer	ACKD	HD, tumor free	48

GN-Glomerulo nephritis; PKD-Polycystic Kidney Disease; ACKD-Acquired Cystic Kidney Disease; NI-Nephritis interstitialis

- Ponovljena studijska analiza podataka na Klinici za Hemodijalizu KCUS za period 2008 – 2018 evaluirala je 28 pacijenta sa karcinomom od ukupno 300 pacijenata.
- Od 28 pacijenata ukupno je umrlo 13 u follow-up periodu.
- Ukupno je bilo 7 žena i 21 muškarac.
- Srednja životna dob testiranih pacijenata je bila 68.7 ± 11.00 (SE \bar{x} : 2.12) godina.
- Najviše karcinoma je pripadalo digestivnom traktu i plućima, urinarnom traktu i koži.

	Male	Female	Total	p
No.	21	7	28	
Mean age	69.1±12.45	67.57±5.79	68.32 ± 11.00	ns

Case	Tumor type	Cause of ESRD	Outcome
1	Ca colonis	GN	Egzitus letalis
2	Ca thyreoidae	Ca renis bill	HD
3	Melanoma	Nephroangiosclerosis	HD
4	Ca prostatae	GN	HD
5	Ca auriculae	GN	HD
6	Ca renis	Polycistosis	HD
7	Non Hodgkin lymphoma	St.post Tx; GN chr.	HD
8	Ca papillary thyreoideae.	Glomerulonephritis membranoproliferativa	HD
9	Ca pulmonis	Diabetic nephritis	Egzitus letalis
10	Myeloma multiplex	GN	Egzitus letalis
11	Ca mammae	Diabetic nephritis	HD
12	Ca vesicae fellae	GN unknown	Egzitus letalis
13	Ca vesicae urinariae	Diabetic nephritis	Egzitus letalis
14	Ca laryngis	Sy nephroticum sec	Egzitus letalis
15	Ca testis	GN	HD
16	Ca pulmonis	Nephritis tubulointerstitiais chr	Egzitus letalis
17	Ca nasopharyngeal	Unknown	Egzitus letalis
18	Ca colonis	Glomerulonephritis membranosa	Egzitus letalis
19	Ca colonis	unknown	Egzitus letalis
20	Ca pulmonis	unknown	Egzitus letalis
21	Ca pulmonis	GN	HD
22	Epithelioma BCC	GN	HD
23	Ca sqvamocellulare in situ	GN	HD
24	Ca pulmonis	unknown	Egzitus letalis
25	Ca vesicae urinariae	GN	Egzitus letalis
26	Ca ventriculi	GN	Egzitus letalis
27	Epitelioma baseocellulare	Polycistosis	HD
28	Tu Brown	GN	HD

Take home messages



- Iako tumor mokraćne besike i virusno-posredovani tumori (tumor grlica materice posredovan HPV virusom ili tumor jetre posredovan hepatitis B i C virusima), su cesci kod pacijenata sa ESRD, nije preporučljiva opsta rutina screeninga kod ovakvih pacijenata.
- ESRD pacijenti kod kojih je preporučljiv screening su:
 - Pacijenti sa dobrim izgledima za prezivljavanje
 - Kandidati za transplantaciju bubrega
 - Pacijenti sa vecim rizikom za razvoj tumora, ali dobrim izgledima za prezivljavanje.
- Nije preporučljiv screening za pacijente sa policisticnom bolesti bubrega iako postoji povecan rizik od razvoja Ca bubrega.
- Ukupne raspoložive informacije pokazuju da rutinski screening kod ESRD pacijenata ipak nije preporučljiv, ali da se protokol screeninga može obavljati kod individualiziranih pacijenata na osnovu personalnih riziko faktora.



HVALA NA PAŽNJI