POMEN HISTOPATOLOŠKIH ZNAČILNOSTI IN STADIJA NA POTEK IN IZID BOLEZNI

Sonja Bebar
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POMEN HISTOPATOLOŠKIH ZNAČILNOSTI IN STADIJA NA POTEK IN IZID BOLEZNI

- Rak jajčnikov ima najslabše preživetje med vsemi ginekološkimi raki
- V zadnjih desetletjih je prišlo do napredka pri zdravljenju (kirurgija, citostatiki, tarčna zdravila)
- Približno polovica bolnic z rakom jajčnikov je živih 5 let po postavljeni diagnozi (47%)
- Če je bolezen odkrita v napredovalih stadijih (FIGO III in IV), je 5 – letno preživetje le okoli 29%
- Več kot tri četrtine bolezni odkrijemo v napredovalih stadijih
- Gre za heterogeno skupino bolezni, ki se med seboj razlikujejo po epidemioloških, molekularnih in kliničnih lastnostih

HISTOPATOLOŠKA KLASIFIKACIJA

EPITELIJSKI RAK JAJČNIKOV (90%)

Serozni karcinom visoke stopnje malignosti (70%)

Endometrioidni karcinom (10%)

Svetlocelični karcinom (10%)

Mucinozni karcinom (3%)

Serozni karcinom nizke stopnje malignosti (5%)

Karcinosarkom

Maligni Brennerjev tumor (zelo redki)

NEEPITELIJSKI RAKI JAJČNIKOV

Stromalni tumorji

Germinalni tumorji

PREŽIVETJE BOLNIC Z RAKOM JAJČNIKOV

Na preživetje bolnic z rakom jajčnikov vpliva več delavnikov:

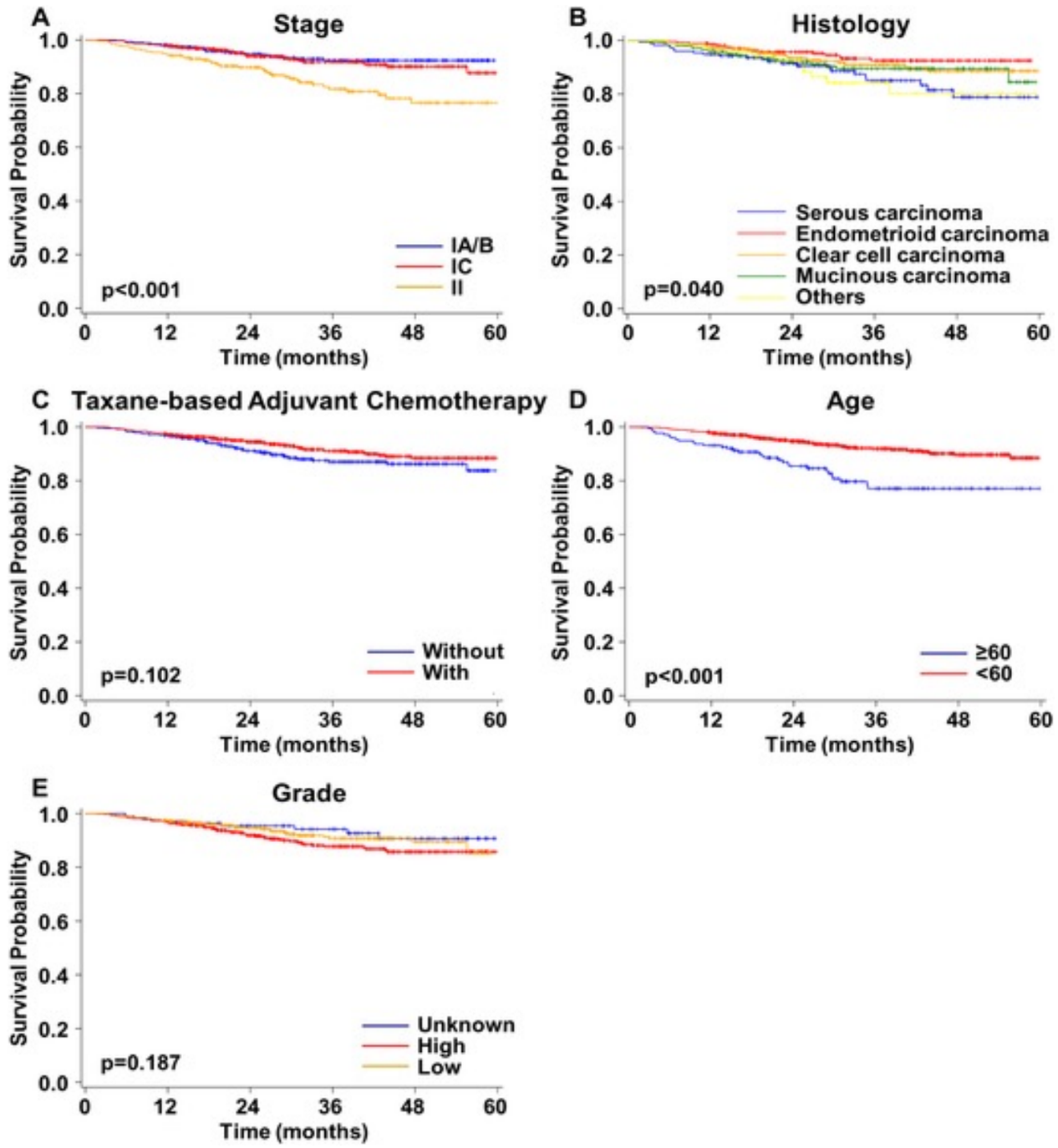
- Stadij bolezni
- Velikost ostanka bolezni po citoreduktivni operaciji
- Histologija
- Starost
- Stanje zmogljivosti
- Spremljajoče bolezni
- Rasna pripadnost

PREŽIVETJE BOLNIC Z RAKOM JAJČNIKOV

Boljše preživetje

- Mlajše bolnice
- Neserozna histologija
- Zgodnji stadiji bolezni
- Brez rezidualne bolezni po citoreduktivni kirurgiji
- Odsotnost ascitesa
- Nizke vrednosti CA 125

Fig 2. Overall survival curves for patients with early-stage epithelial ovarian cancer.



Chang LC, Huang CF, Lai MS, Shen LJ, Wu FLL, et al. (2018) Prognostic factors in epithelial ovarian cancer: A population-based study. PLOS ONE 13(3): e0194993. https://doi.org/10.1371/journal.pone.0194993

INVASIVE EPITHELIAL OVARIAN CANCER SURVIVAL BY HISTOTYPE AND DISEASE STAGE

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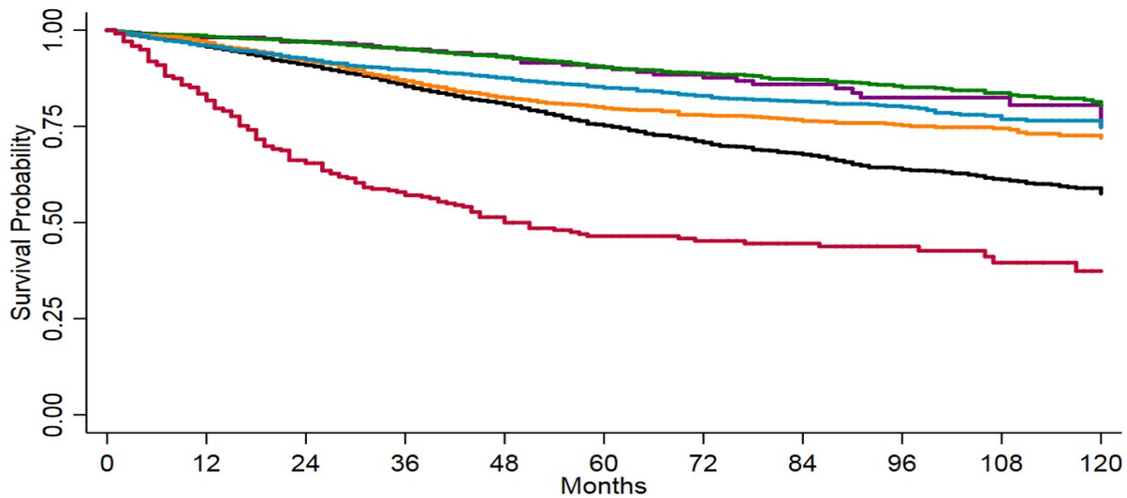
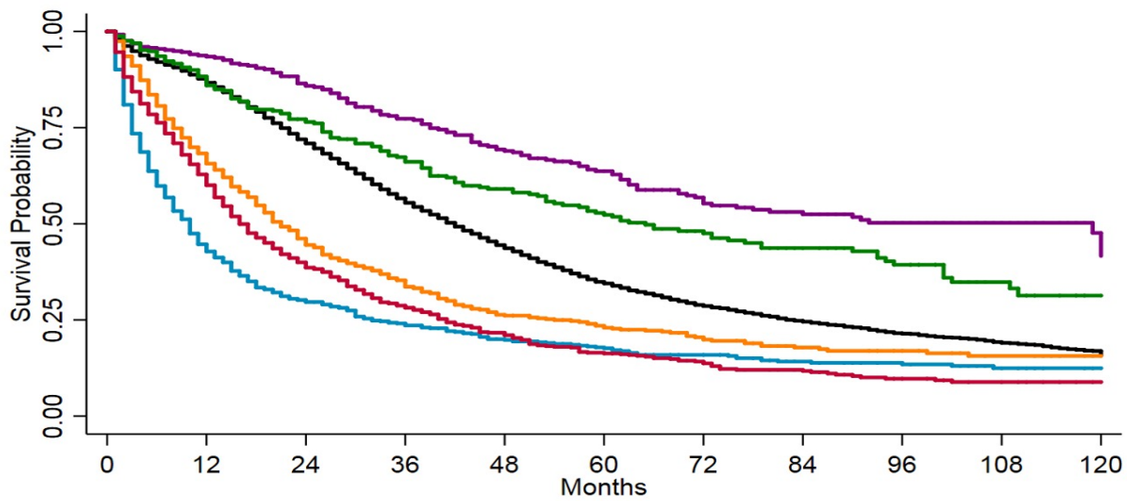
A



Number at risk

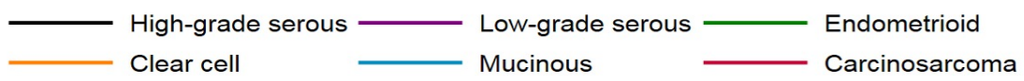
High-grade serous	3939	3378	2892	2395	1942	1525	1177	901	661	418	206
Low-grade serous	330	291	262	226	182	150	110	82	59	42	14
Endometrioid	2452	2151	1867	1615	1378	1122	910	702	520	337	163
Clear cell	1950	1674	1419	1161	932	768	614	469	350	237	113
Mucinous	1935	1618	1391	1176	1000	835	661	536	403	253	134
Carcinosarcoma	342	244	173	140	109	87	71	59	43	25	9

B

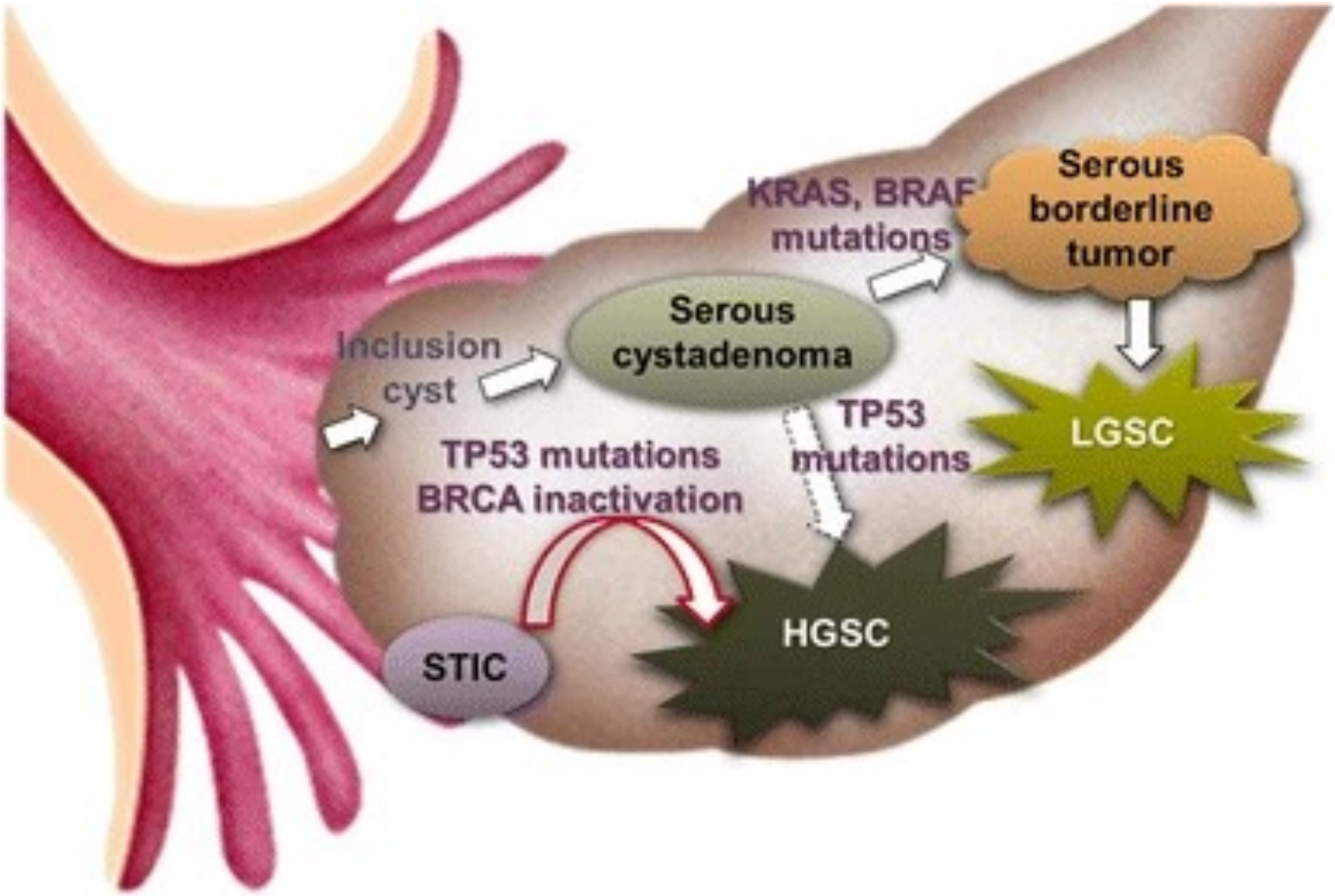


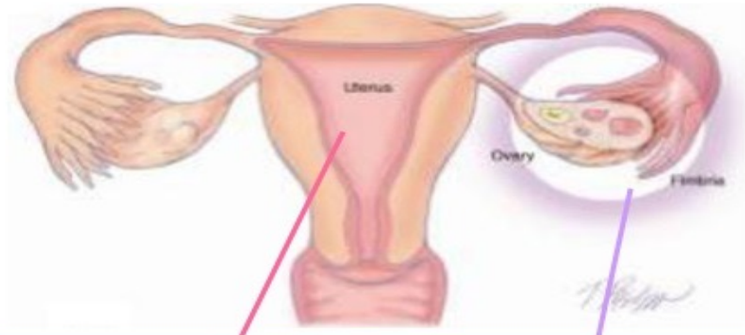
Number at risk

High-grade serous	13898	11098	8173	5622	3824	2526	1710	1150	726	424	179
Low-grade serous	378	320	277	222	181	147	109	87	62	34	16
Endometrioid	330	262	211	166	131	105	80	57	42	21	9
Clear cell	745	464	279	189	117	93	68	45	31	19	10
Mucinous	706	285	181	134	102	76	60	42	34	22	12
Carcinosarcoma	1039	560	319	201	130	84	60	42	26	17	6



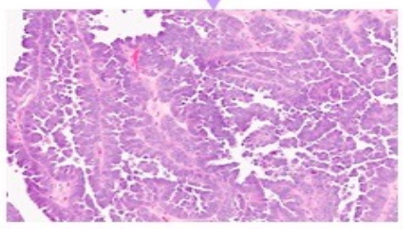
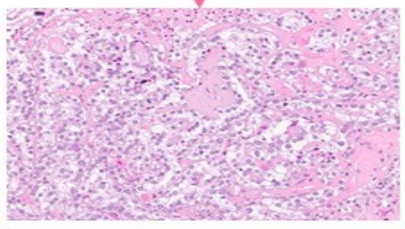
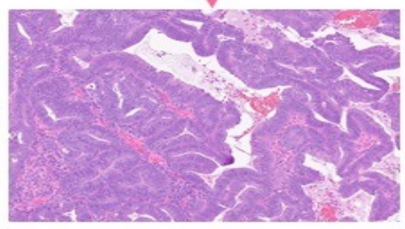
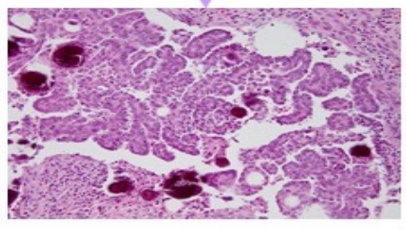
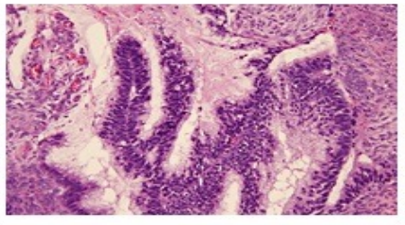
NIZKO MALIGNI (LOW GRADE) IN VISOKO MALIGNI (HIGH GRADE) TUMORJI JAJČNIKOV





?Retrograde Menstruation

Origin

	Fallopian Tube Epithelium	Endometriosis	Endometriosis	Fallopian Tube Epithelium	?Unknown
					

	High-Grade Serous Carcinoma	**Clear Cell Carcinoma**	**Endometrioid Carcinoma**	**Low-Grade Serous Carcinoma**	**Mucinous Carcinoma**
% of all Ovarian Carcinomas	~70%	~10%	~10%	<5%	<5%
Precursor Lesions	Serous tubal intraepithelial carcinoma (STIC)	Clear Cell Borderline Tumor	Endometrioid Borderline Tumor	Serous Borderline Tumor	Mucinous Borderline Tumor
Inherited Syndromes	BRCA1/2, Hereditary Breast and Ovarian Cancer (HBOC)	Lynch Syndrome	Lynch Syndrome	?	?
Common Mutations and Molecular Aberrations	TP53 BRCA1/2 and HRD Chromosomal instability Aneuploidy (100%)	ARID1A PIK3CA CTNNB1 PPP2R1A MSI	PTEN CTNNB1 ARID1A PPPR2R1A MSI	KRAS BRAF	KRAS HER2 amplification
Potential Molecular Targeted Therapies	PARP inhibitors, immune checkpoint inhibitors	Tyrosine kinase inhibitors	mTOR inhibitors	MEK1/2 inhibitors	Trastuzumab

VPLIV RASE NA PREŽIVETJE

- Rasna pripadnost vpliva na preživetje
- Serozni karcinom je v svetovnem merilu najpogostejši s 70% deležem, na Tajskem je ta delež le 20 do 30%, je pa toliko večji delež svetloceličnih, endometrioidnih in mucinoznih karcinomov
- Azijke, ki živijo v ZDA imajo boljše 5-letno preživetje, zbolevajo mlajše, z zgodnejšimi stadiji bolezni, ki so neseroznega tipa
- Svetlocelični karcinom je redek na zahodu, a veliko pogostejši med Japonkami in Tajkami, kjer dosega delež 19% do 25%
- Delež endometrioidnega karcinoma je na zahodu 19%, med azijsko žensko populacijo pa preko 27%

NOVA IN STARA FIGO KLASIFIKACIJA

FIGO (2013)		FIGO (ovary, 1988)	
I	Tumor confined to ovaries or **fallopian tube(s)**	I	Tumor limited to ovaries
IA	Tumor limited to 1 ovary (capsule intact) or **fallopian tube**	IA	Tumor limited to 1 ovary
IB	Tumor limited to both ovaries or **fallopian tubes**	IB	Tumor limited to both ovaries
IC	Tumor limited to 1 or both ovaries or **fallopian tubes**, with any of the following	IC	Tumor limited to 1 or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface; malignant cells in ascites
IC1	**Surgical spill**	IC(1/2)	Malignant cells in peritoneal washings/ascites
IC2	**Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface**	IC(a/b)	Capsule ruptured before surgery/surgical spill
IC3	**Malignant cells in the ascites**		
II	Tumor involves 1 or both ovaries or **fallopian tubes** with pelvic extension or **primary peritoneal cancer**	II	Tumor involves 1 or both ovaries with pelvic extension
IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries	IIA	Extension and/or implants on uterus and/or tube(s)
IIB	Extension to other pelvic intraperitoneal tissues	IIB	Extension to other pelvic tissues
		IIC	Pelvic extension with malignant cells in ascites
III	Tumor with spread to peritoneum outside the pelvis and/or metastasis to retroperitoneal lymph nodes	III	Tumor with peritoneal metastases outside pelvis and/or regional lymph node metastasis
IIIA1	**Positive retroperitoneal lymph nodes only**	IIIA	Microscopic peritoneal metastasis beyond pelvis
IIIA1(i)	**Metastasis ≤ 10 mm**		
IIIA1(ii)	**Metastasis > 10 mm**		
IIIA2	Microscopic extrapelvic peritoneal involvement		
IIIB	Macroscopic peritoneal metastasis beyond pelvis ≤2 cm	IIIB	Macroscopic peritoneal metastasis beyond pelvis ≤2 cm
IIIC	Macroscopic peritoneal metastasis beyond pelvis >2 cm	IIIC	Peritoneal metastasis beyond pelvis >2 cm and/or regional lymph node metastasis
IV	Distant metastasis excluding peritoneal metastases	IV	Distant metastasis (excludes peritoneal metastasis)
IVA	**Pleural effusion with positive cytology**		
IVB	Parenchymal metastases and metastases to extraabdominal organs		

OVARIAN CANCER

survival rates

	Invasive epithelial ovarian cancer	Ovarian stromal tumors	Ovarian germ cell tumors	Fallopian tube carcinoma
Stage 1	90%	95%	98%	87%
Stage 2	70%	78%	94%	86%
Stage 3	39%	65%	87%	52%
Stage 4	17%	35%	69%	40%

Source: https://www.cancer.org/cancer/ovarian-cancer/detection-diagnosis-staging/survival-rates.html healthline

PREŽIVETJE PO STADIJIH BOLEZNI

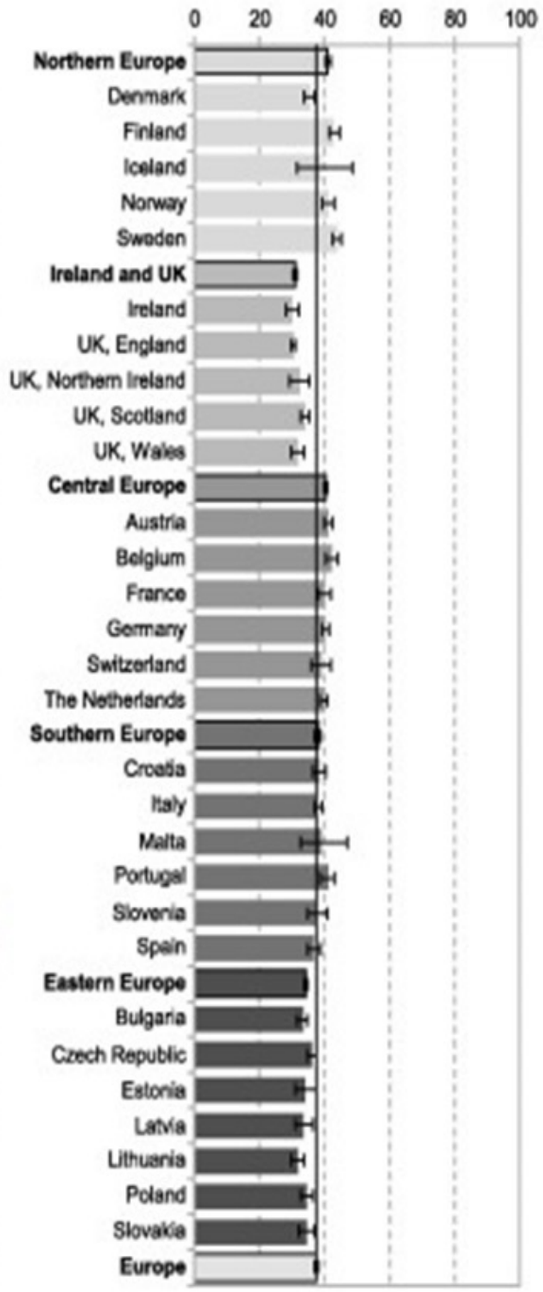
- Stage IA - 87%
- Stage IB - 71%
- Stage IC - 79%
- Stage IIA - 67%
- Stage IIB - 55%
- Stage IIC – 57
- Stage IIIA – 41%
- Stage IIIB - 25%
- Stage IIIC - 23%
- Stage IV - 11%
- Overall survival rate – 46%

EUROCARE – 5 (2015)

Age-standardised 1-year, 5-year relative survival, and 5-year relative survival conditional to surviving 1 year, with 95% confidence intervals in parentheses

	Number of cases	1-year			5-year			Conditional		
Northern Europe	**18,724**	**76.4**	**(75.7 -**	**77.0)**	**41.1**	**(40.3 -**	**42.0)**	**53.9**	**(52.8 -**	**54.9)**
Denmark	4,637	70.5	(69.1 -	71.8)	35.5	(33.9 -	37.2)	50.4	(48.2 -	52.6)
Finland	3,937	76.4	(75.0 -	77.7)	43.1	(41.3 -	45.0)	56.5	(54.3 -	58.7)
Iceland	150	71.8	(65.1 -	79.1)	39.1	(31.5 -	48.5)	54.5	(44.9 -	66.1)
Norway	3,719	76.3	(74.9 -	77.7)	41.4	(39.5 -	43.4)	54.3	(52.0 -	56.7)
Sweden	6,281	81.1	(80.1 -	82.1)	44.1	(42.6 -	45.6)	54.3	(52.6 -	56.1)
Ireland and UK	**51,024**	**62.7**	**(62.2 -**	**63.1)**	**31.0**	**(30.6 -**	**31.5)**	**49.5**	**(48.9 -**	**50.2)**
Ireland	2,599	61.4	(59.6 -	63.3)	30.3	(28.4 -	32.5)	49.4	(46.5 -	52.5)
UK, England	39,620	62.6	(62.2 -	63.1)	30.6	(30.0 -	31.1)	48.8	(48.1 -	49.6)
UK, Northern Ireland	1,293	62.7	(60.2 -	65.3)	32.3	(29.4 -	35.5)	51.5	(47.3 -	56.0)
UK, Scotland	4,752	65.1	(63.8 -	66.4)	34.0	(32.5 -	35.6)	52.3	(50.2 -	54.5)
UK, Wales	2,760	59.8	(58.1 -	61.6)	31.7	(29.7 -	33.7)	52.9	(50.0 -	56.0)
Central Europe	**37,796**	**73.7**	**(73.3 -**	**74.2)**	**40.5**	**(39.9 -**	**41.1)**	**55.0**	**(54.3 -**	**55.7)**
Austria	5,932	71.9	(70.8 -	73.1)	41.4	(40.0 -	42.9)	57.6	(55.8 -	59.5)
Belgium	4,583	77.1	(75.9 -	78.3)	42.4	(40.7 -	44.1)	55.0	(53.0 -	57.1)
France	2,945	77.3	(75.7 -	78.8)	40.1	(38.2 -	42.1)	51.9	(49.7 -	54.3)
Germany	13,307	73.7	(72.9 -	74.4)	40.3	(39.3 -	41.3)	54.7	(53.5 -	56.0)
Switzerland	1,538	76.9	(74.9 -	79.0)	38.9	(36.1 -	42.0)	50.6	(47.2 -	54.3)
The Netherlands	9,491	71.6	(70.7 -	72.5)	39.9	(38.7 -	41.1)	55.7	(54.2 -	57.2)
Southern Europe	**21,971**	**69.1**	**(68.5 -**	**69.7)**	**38.0**	**(37.3 -**	**38.7)**	**55.0**	**(54.1 -**	**55.9)**
Croatia	3,872	61.7	(60.1 -	63.3)	38.6	(36.6 -	40.7)	62.5	(59.8 -	65.4)
Italy	11,759	70.9	(70.2 -	71.7)	38.1	(37.2 -	39.1)	53.7	(52.5 -	55.0)
Malta	288	59.6	(54.2 -	65.5)	39.3	(32.8 -	47.0)	65.9	(56.5 -	76.7)
Portugal	2,395	71.6	(69.6 -	73.6)	41.0	(38.7 -	43.4)	57.2	(54.4 -	60.1)
Slovenia	1,446	72.7	(70.3 -	75.2)	37.9	(35.0 -	41.1)	52.2	(48.6 -	56.0)
Spain	2,211	69.6	(67.7 -	71.6)	36.8	(34.7 -	39.0)	52.8	(50.2 -	55.6)
Eastern Europe	**27,879**	**62.2**	**(61.6 -**	**62.8)**	**34.4**	**(33.7 -**	**35.1)**	**55.3**	**(54.3 -**	**56.3)**
Bulgaria	6,208	57.1	(55.7 -	58.6)	33.4	(31.7 -	35.2)	58.5	(55.9 -	61.1)
Czech Republic	8,825	65.5	(64.5 -	66.6)	36.3	(35.1 -	37.6)	55.4	(53.7 -	57.2)
Estonia	1,217	63.2	(60.4 -	66.0)	34.1	(31.0 -	37.6)	54.0	(49.5 -	59.0)
Latvia	2,205	63.6	(61.5 -	65.9)	33.7	(31.3 -	36.3)	52.9	(49.6 -	56.5)
Lithuania	2,789	59.2	(57.4 -	61.1)	31.7	(29.8 -	33.8)	53.6	(50.7 -	56.6)
Poland	3,704	63.3	(61.6 -	65.1)	34.5	(32.5 -	36.5)	54.4	(51.7 -	57.3)
Slovakia	2,931	63.0	(61.0 -	65.0)	34.5	(32.2 -	36.8)	54.7	(51.6 -	58.0)
Europe	**157,394**	**70.3**	**(69.9 -**	**70.7)**	**37.6**	**(37.2 -**	**38.0)**	**53.5**	**(52.9 -**	**54.1)**

Age-standardised 5-year relative survival (%)



Ovary and uterine adnexa

European age-specific and age-standardised observed (obs, %) and relative (rel, %) survival

Age group	Number of cases		1-year	3-year	5-year
15-44	14,549	obs	90.9	78.2	70.5
		rel	91.0	78.4	70.9
45-54	25,887	obs	88.2	67.7	55.3
		rel	88.5	68.3	56.1
55-64	37,744	obs	82.4	56.3	43.1
		rel	82.8	57.3	44.5
65-74	40,137	obs	70.7	43.5	31.3
		rel	71.6	45.5	33.9
75+	39,076	obs	43.6	21.9	14.5
		rel	46.4	26.2	20.1
All cases	157,393	obs	69.0	45.5	34.8
		rel	70.3	47.7	37.6

MUTACIJE BRCA1/2

- Mlajše bolnice, BRCA1
- Serozni karcinomi
- Ni mejno malignih tumorjev
- Boljši odgovor na terapijo s preparati platine
- Boljši odgovor na zdravljenje s PARP inhibitorji
- Daljši interval brez ponovitve bolezni
- Nosilke BRCA2 mutacije imajo boljše preživetje kot nosilke BRCA 1 mutacije ali spontano obolele