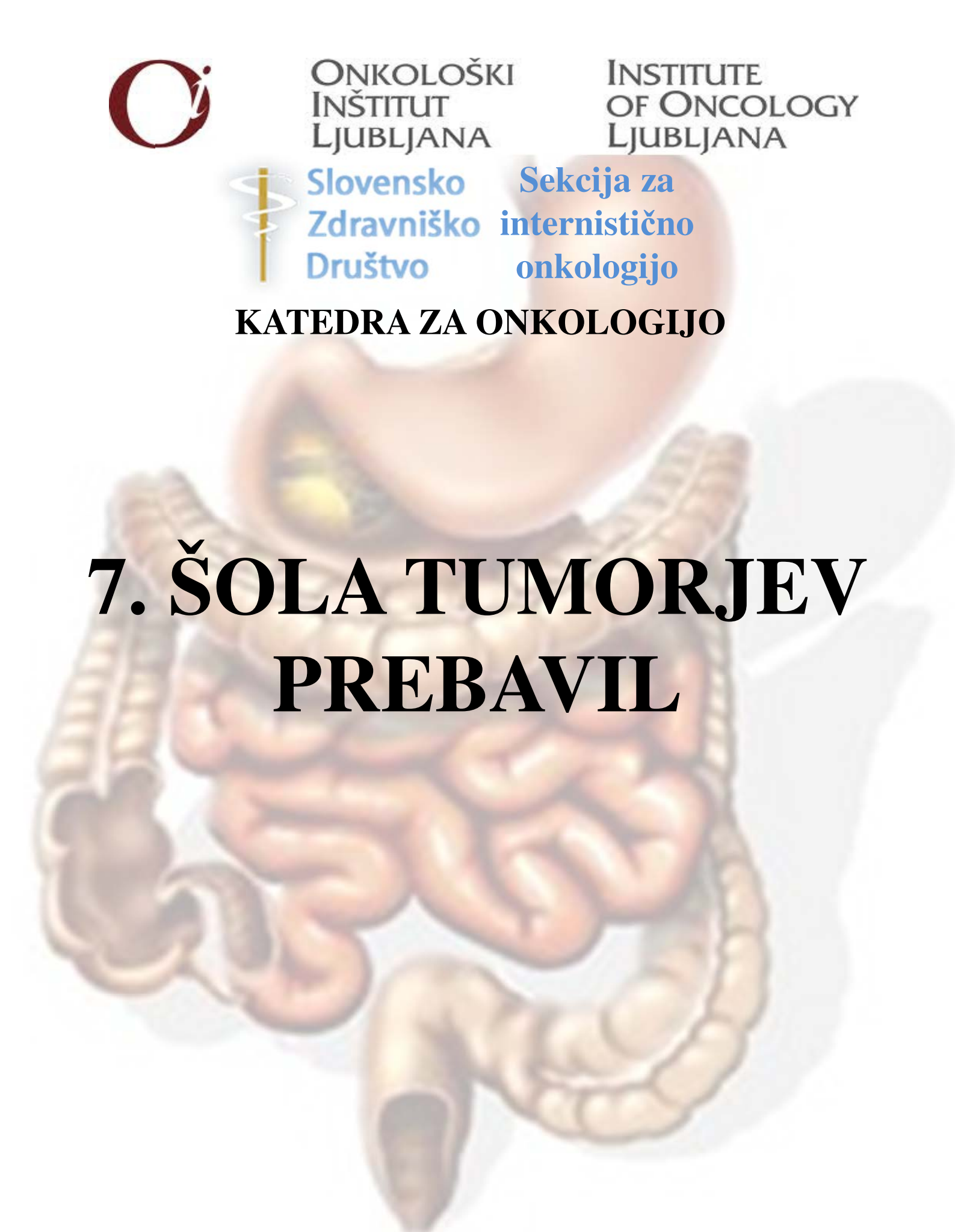
ONKOLOŠKI INŠTITUT LJUBLJANA

INSTITUTE OF ONCOLOGY LJUBLJANA

Slovensko Zdravniško Društvo

Sekcija za internistično onkologijo

KATEDRA ZA ONKOLOGIJO



7. ŠOLA TUMORJEV PREBAVIL

ONKOLOŠKI INŠTITUT LJUBLJANA
20. OKTOBER 2017

Strokovni odbor:
izr. prof. dr. Janja Ocvirk, dr.med.
dr. Martina Reberšek, dr.med.
mag. Zvezdana Hlebanja, dr.med.
Marko Boc, dr.med.

Organizacijski odbor:
izr. prof. dr. Janja Ocvirk, dr.med.
dr. Martina Reberšek, dr.med.
mag. Zvezdana Hlebanja, dr.med.
Marko Boc, dr.med.
ga. Lidija Kristan

Uredniki zbornika:
Marko Boc, dr.med.
dr. Martina Reberšek, dr.med.
izr. prof. dr. Janja Ocvirk, dr.med.

Organizator in izdajatelj (založnik):
Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo
Katedra za onkologijo

Ljubljana, oktober 2017

VSEBINA:

PROGRAM SREČANJA: **PETEK, 20.10.2017**

07.00-08.30 **REGISTRACIJA UDELEŽENCEV**

Moderator: dr. Neva Volk, dr.med., doc. dr. Blaž Trotovšek, dr.med.

08.30-08.50 *Volk N.:* Epidemiologija raka prebavil
08.50-09.10 *Trotovšek B.:* Elektrokemoterapija pri HCC
09.10-09.40 *Ocvirk J.:* Novosti v sistemskem zdravljenju HCC
09.40-10.05 *Reberšek M.:* Novosti v sistemskem zdravljenju karcinoma žolčnika in žolčevodov
10.05-10.20 **Razprava**

10.20-10.35 **ODMOR**

10.35-11.05 *Boc N.:* Diagnostika karcinoze peritoneja
11.05-11.35 *Ocvirk J.:* Nevroendokrini tumorji – smernice
11.35-12.05 *Ocvirk J.:* Rak debelega črevesa in danke – lega tumorja, sekvence zdravljenja
12.05-12.15 **Razprava**
12.15-13.00 **SATELITNO PREDAVANJE 1 (SERVIER)**

13.00-14.00 **KOSILO**

Moderator: asist. dr. Martina Reberšek, dr.med., izr. prof. dr. Vaneja Velenik, dr.med.

14.00-14.45 **SATELITNO PREDAVANJE 2 (ELI LILLY)**
14.45-15.00 *Hlebanja Z.:* Novosti v adjuvantnem zdravljenju raka trebušne slinavke
15.00-15.30 *Brecelj E.:* Elektrokemoterapija pri zdravljenju metastaz raka debelega črevesja in danke
15.30-16.00 *Boc M.:* Sodobno sistemsko zdravljenje raka požiralnika

16.00-16.10 **ODMOR**

Moderator: mag. Zvezdana Hlebanja, dr.med., dr. Erik Brecelj, dr.med.

16.10-16.35 *Velenik V.:* Stranski učinki RT pri zdravljenju tumorjev prebavil in njihovo obvladovanje
16.35-17.05 *Pilko G.:* Pomen paliativne kirurgije v zdravljenju tumorjev prebavil
17.05-17.45 *Oblak I.:* Pomen stereotaksije pri zdravljenju tumorjev prebavil

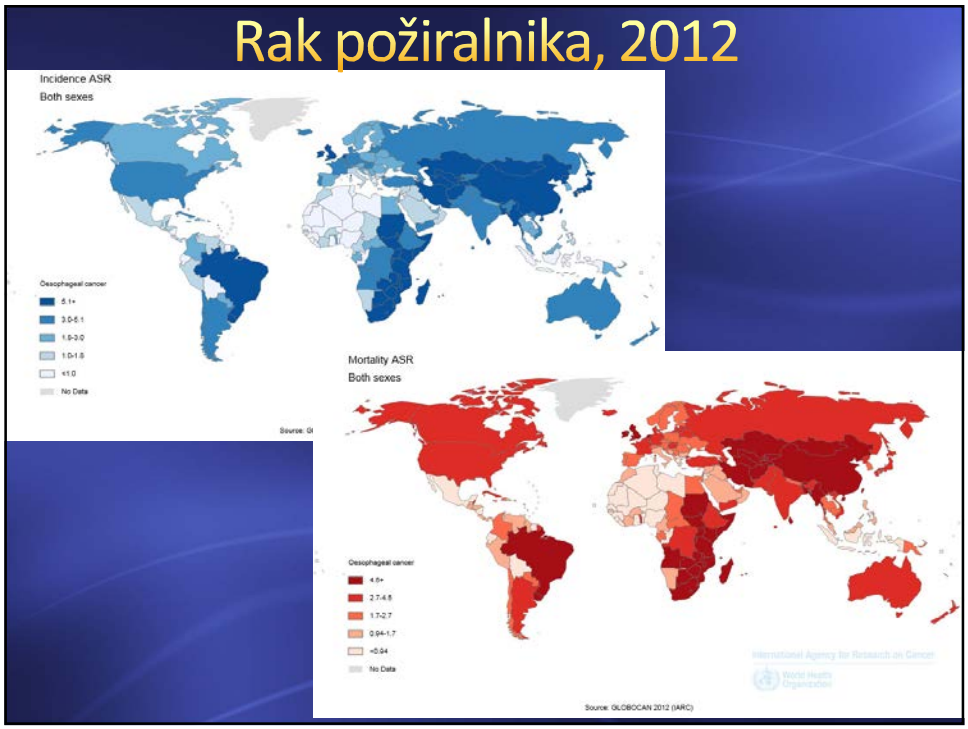
17.45-18.15 **RAZPRAVA IN ZAKLJUČEK SREČANJA**

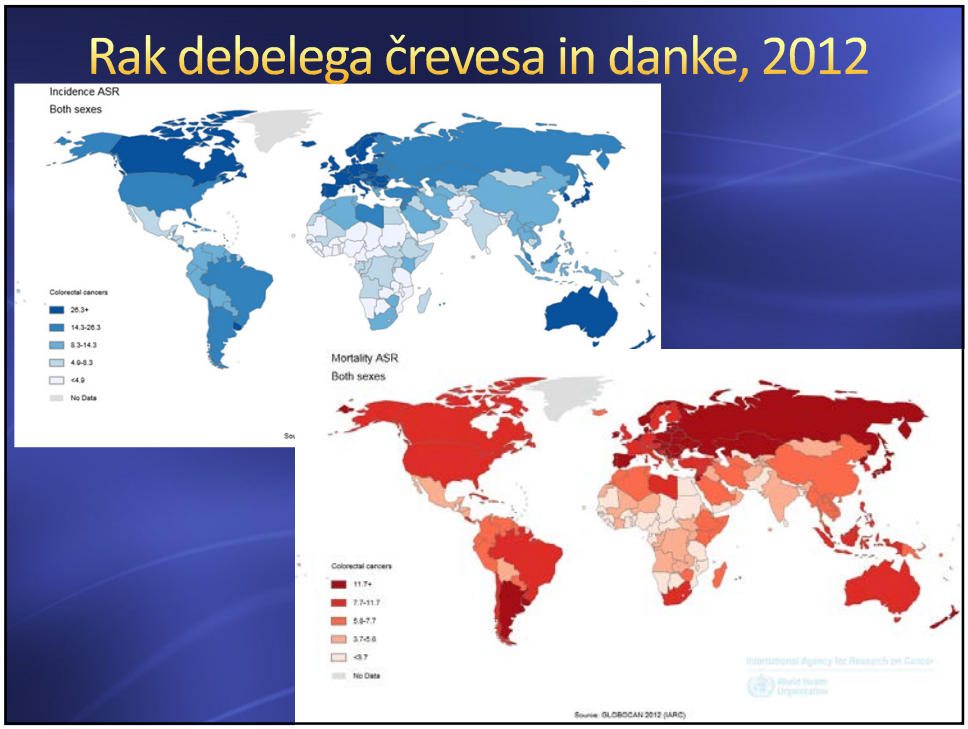
Epidemiologija raka prebavil

Dr. Neva Volk, dr. med.
Sektor za internistično onkologijo
Onkološki inštitut, Ljubljana

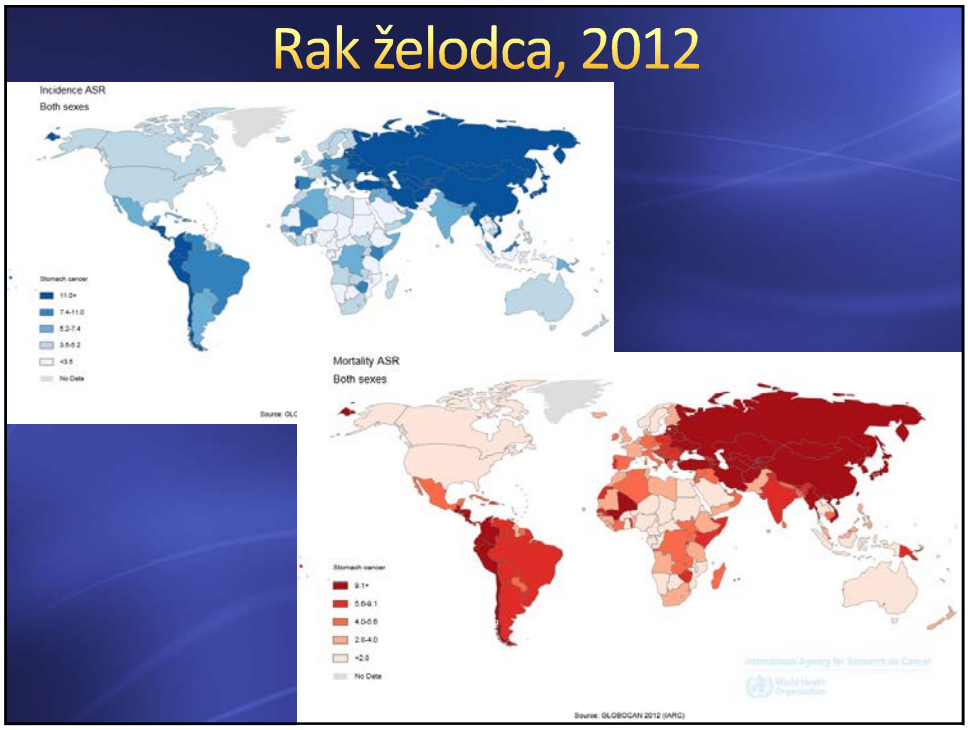
Raki prebavil

- Najpogostejše vrste rakov
- Velike razlike v pojavnosti, med razvitim in ne-razvitim svetom

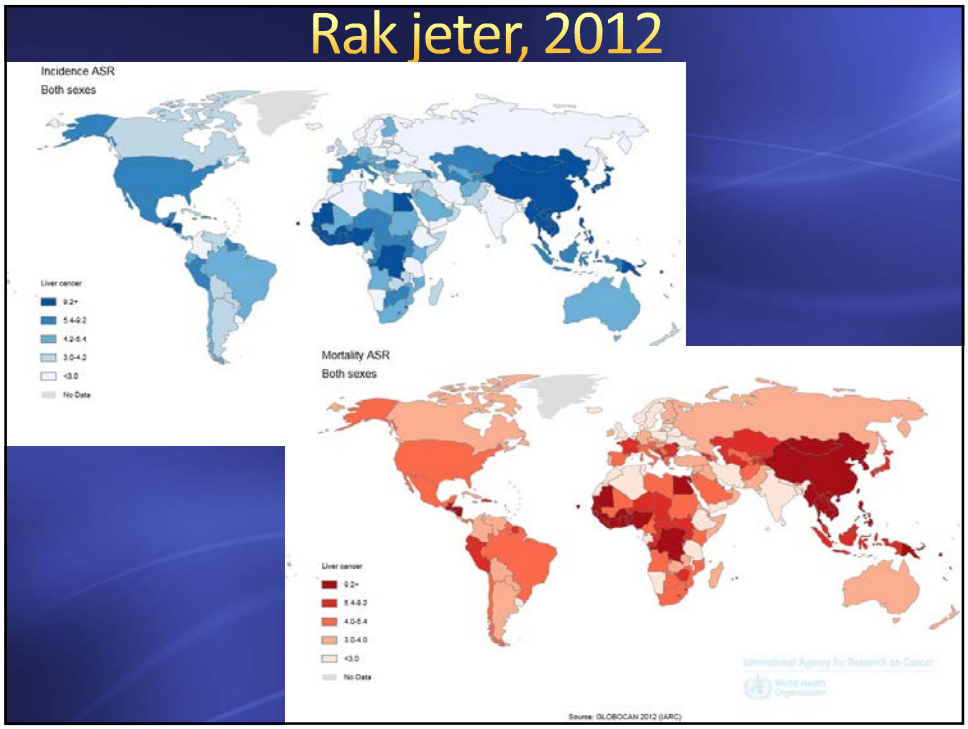

Rak požiralnika, 2012
Incidence ASR
Both sexes
Oesophageal cancer
Mortality ASR
Both sexes
Oesophageal cancer
Source: GLOBOCAN 2012 (IARC)


Rak debelega črevesa in danke, 2012
Incidence ASR
Both sexes
Colorectal cancers
Mortality ASR
Both sexes
Colorectal cancers
Source: GLOBOCAN 2012 (IARC)

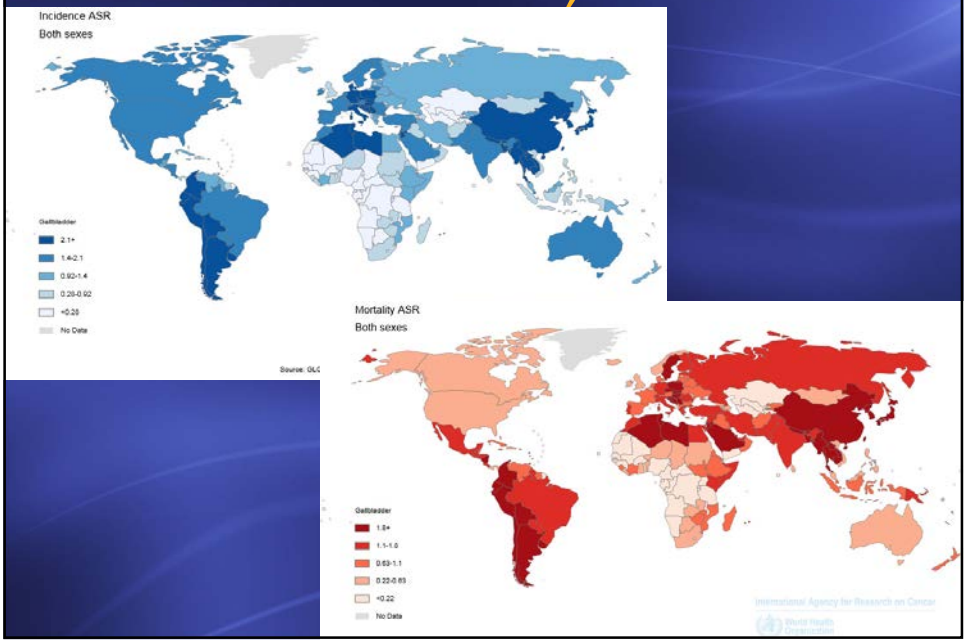
Rak želodca, 2012



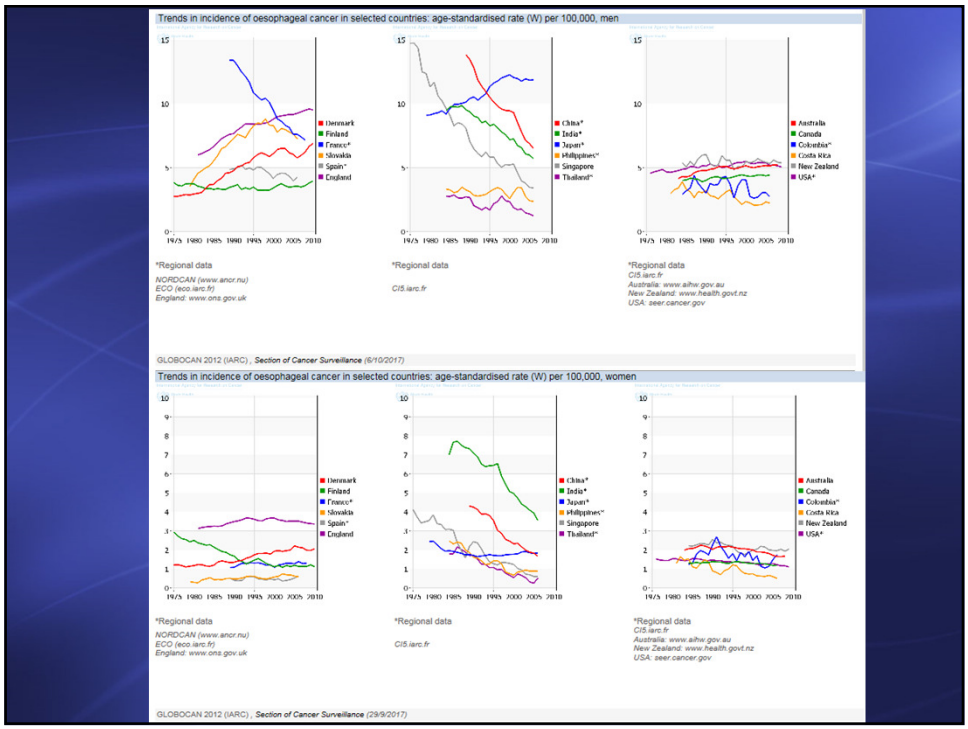
Rak jeter, 2012



Rak žolčnika, 2012



Rak trebušne slinavke, 2012



…. toda – razlike so v podrobnostih

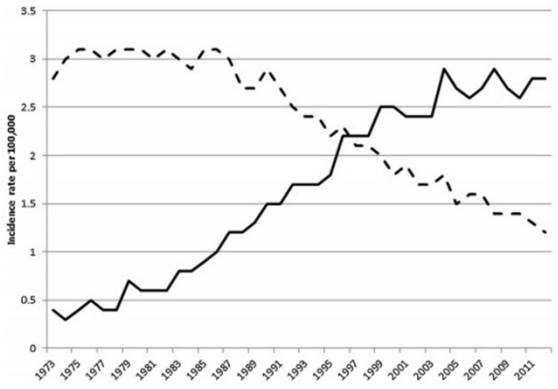
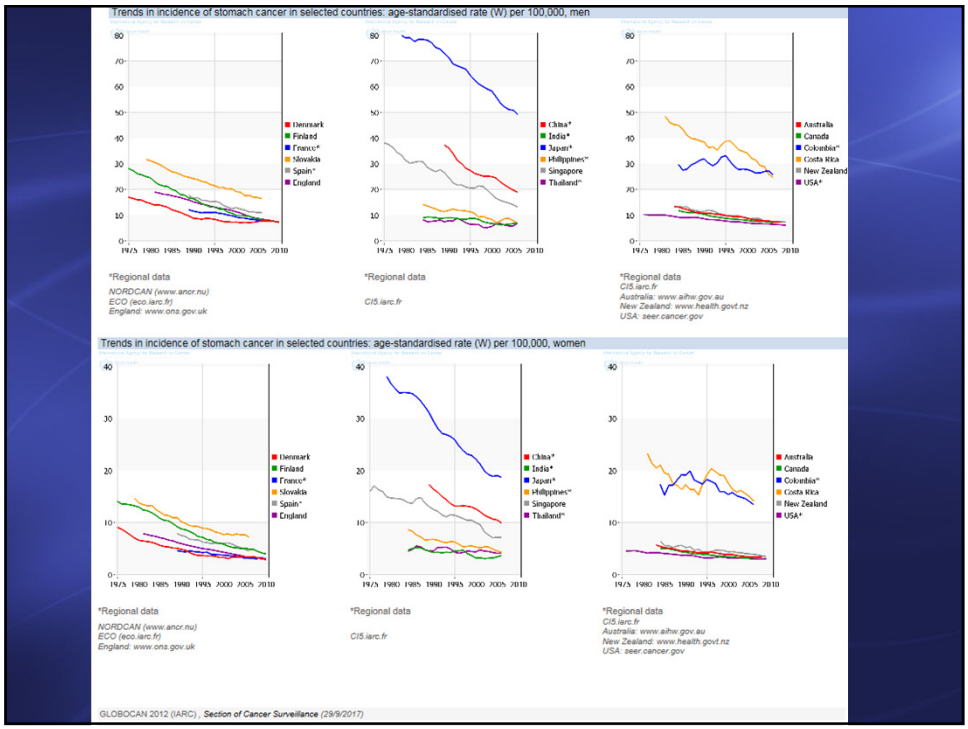
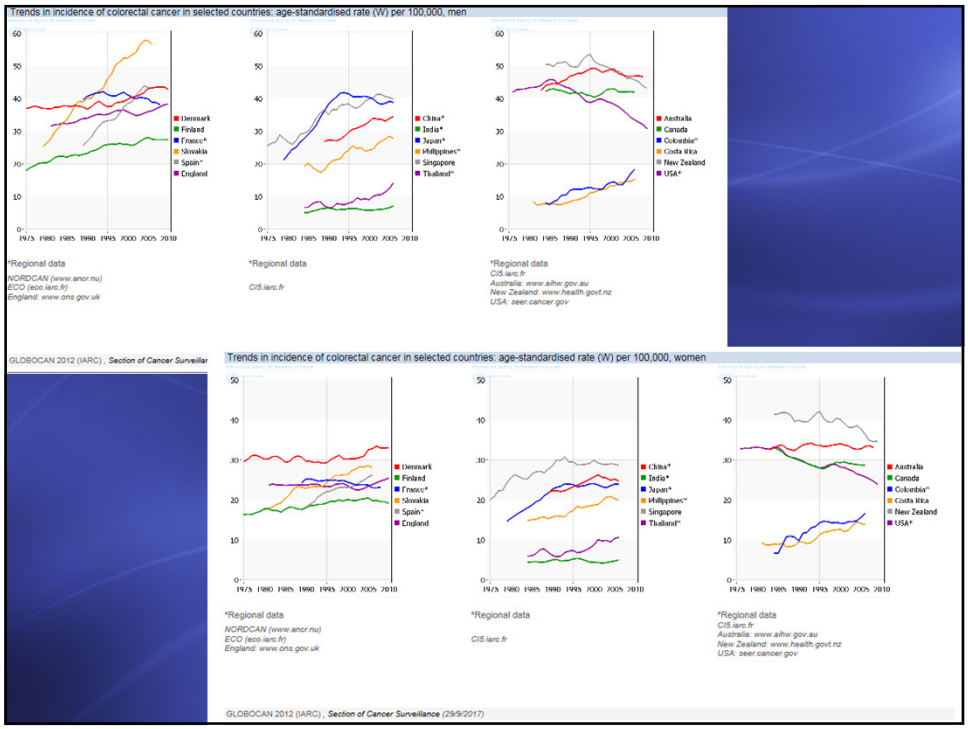
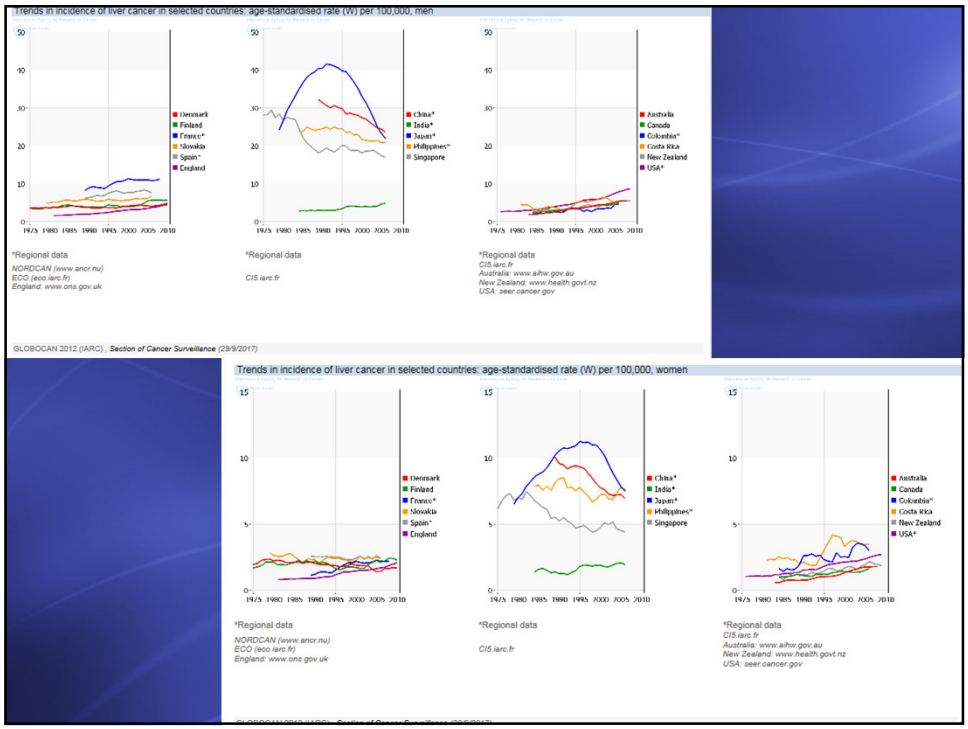


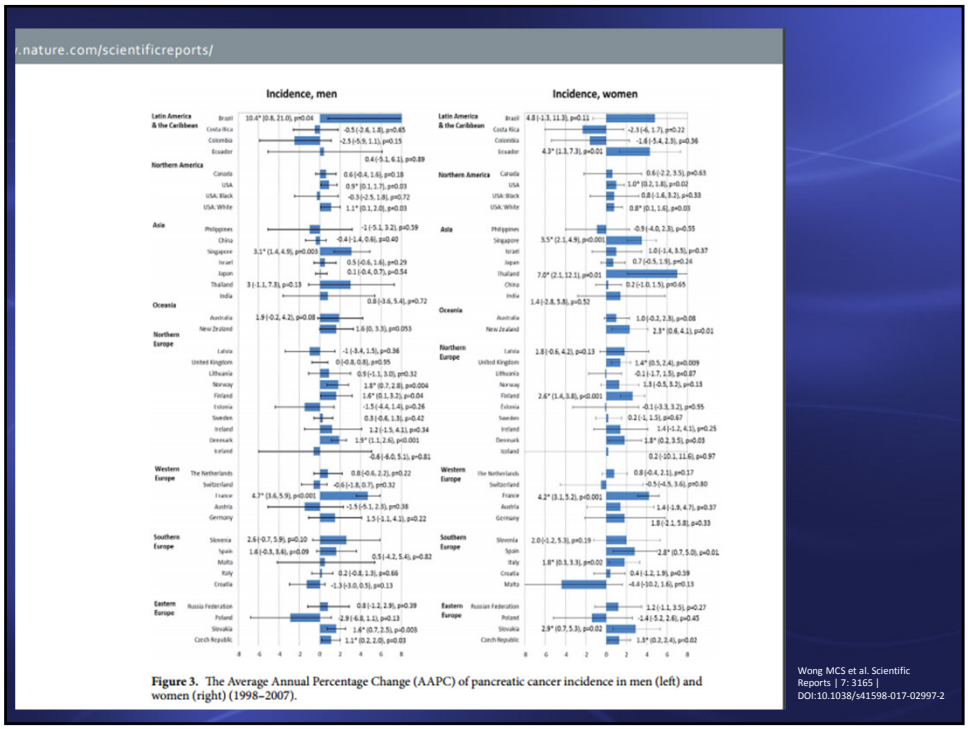
Fig. 2. Incidence rates per 100,000 for oesophageal adenocarcinoma (solid line) and oesophageal squamous-cell carcinoma (dashed line) in US SEER 9 registries, 1973–2012.

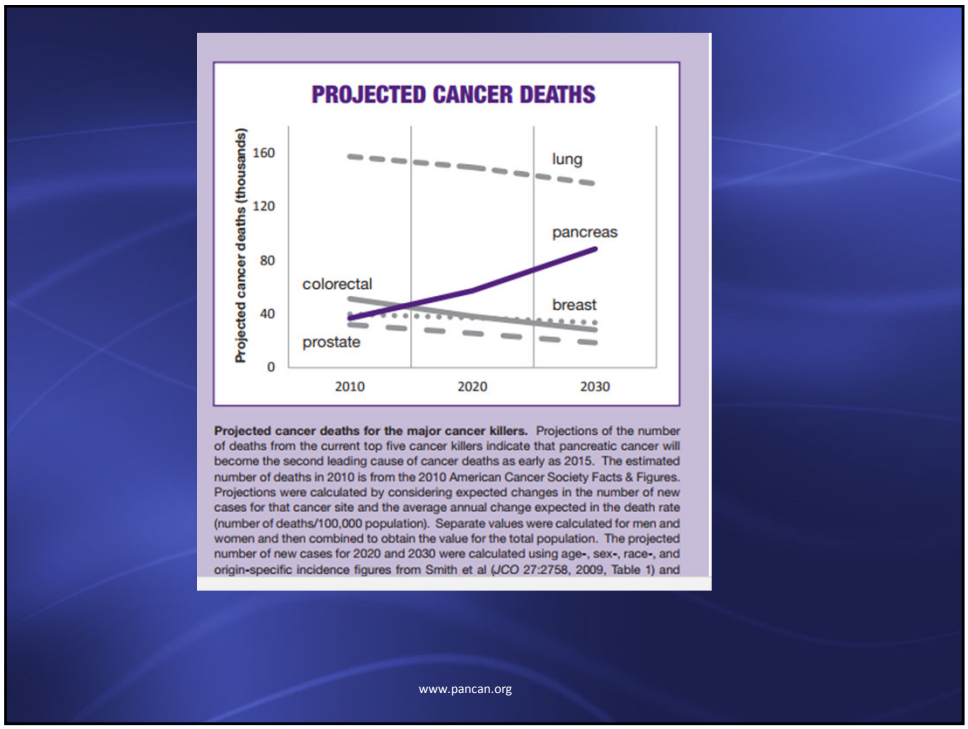
Thrift AP. Cancer Epidemiol 41 (2016) 88–95


Trends in incidence of stomach cancer in selected countries: age-standardised rate (W) per 100,000, men
Denmark
Finland
France*
Slovakia
Spain*
England
China*
India*
Japan*
Philippines*
Singapore
Thailand*
Australia
Canada
Colombia*
Costa Rica
New Zealand
USA*
*Regional data
NORDCAN (www.ancr.nu)
ECO (eco.iarc.fr)
England: www.ons.gov.uk
CI5.iarc.fr
Australia: www.aihw.gov.au
New Zealand: www.health.govt.nz
USA: seer.cancer.gov
Trends in incidence of stomach cancer in selected countries: age-standardised rate (W) per 100,000, women
GLOBOCAN 2012 (IARC) , Section of Cancer Surveillance (29/9/2017)


Trends in incidence of colorectal cancer in selected countries: age-standardised rate (W) per 100,000, men
Denmark
Finland
France*
Slovakia
Spain*
England
China*
India*
Japan*
Philippines*
Singapore
Thailand*
Australia
Canada
Colombia*
Costa Rica
New Zealand
USA*
*Regional data
NORDCAN (www.ancr.nu)
ECO (eco.iarc.fr)
England: www.ons.gov.uk
CI5.iarc.fr
Australia: www.aihw.gov.au
New Zealand: www.health.govt.nz
USA: seer.cancer.gov
GLOBOCAN 2012 (IARC) , Section of Cancer Surveillance
Trends in incidence of colorectal cancer in selected countries: age-standardised rate (W) per 100,000, women
GLOBOCAN 2012 (IARC) , Section of Cancer Surveillance (29/9/2017)

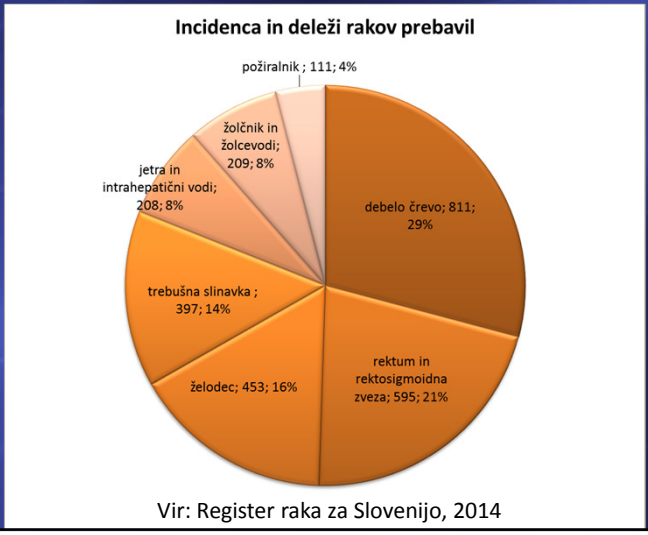

Trends in incidence of liver cancer in selected countries: age-standardised rate (W) per 100,000, men
Denmark
Finland
France*
Slovakia
Spain*
England
China*
India*
Japan*
Philippines*
Singapore
Australia
Canada
Colombia*
Costa Rica
New Zealand
USA*
*Regional data
NORDCAN (www.ancr.nu)
ECO (eco.iarc.fr)
England: www.ons.gov.uk
CI5.iarc.fr
Australia: www.aihw.gov.au
New Zealand: www.health.govt.nz
USA: seer.cancer.gov
GLOBOCAN 2012 (IARC) , Section of Cancer Surveillance (29/9/2017)
Trends in incidence of liver cancer in selected countries: age-standardised rate (W) per 100,000, women


.nature.com/scientificreports/
Incidence, men
Incidence, women
Figure 3. The Average Annual Percentage Change (AAPC) of pancreatic cancer incidence in men (left) and women (right) (1998–2007).
Wong MCS et al. Scientific Reports | 7: 3165 | DOI:10.1038/s41598-017-02997-2

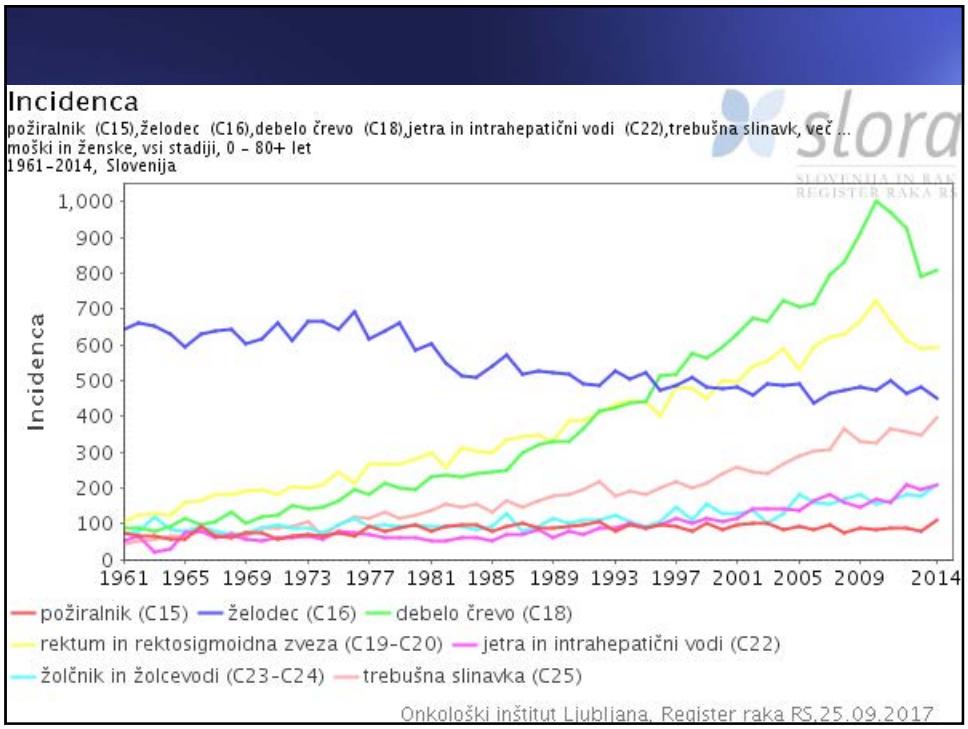


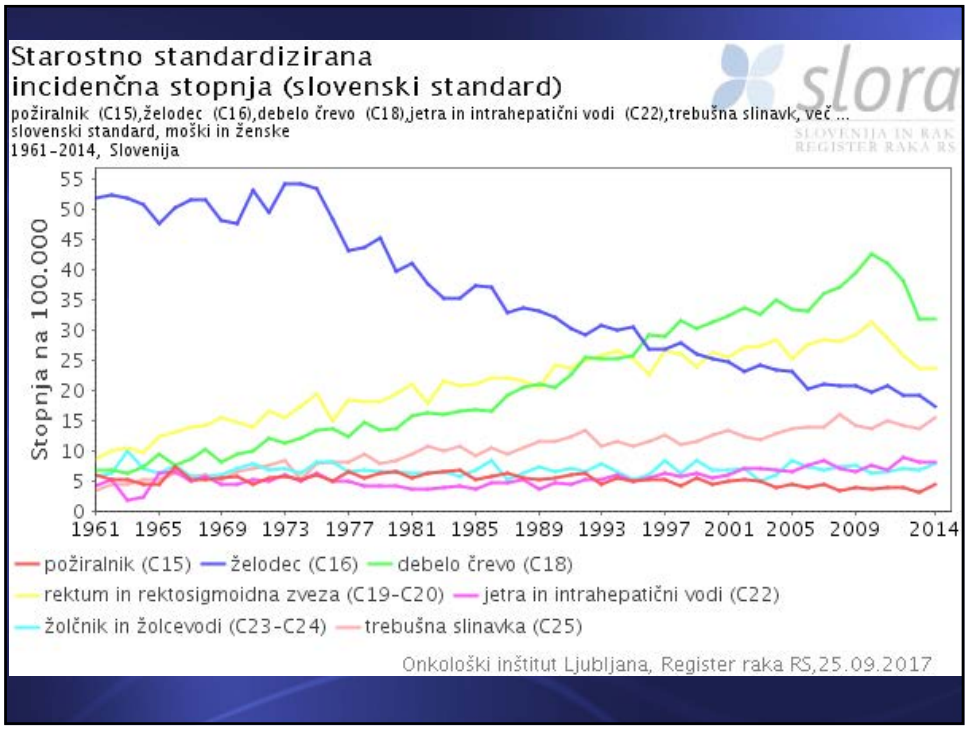
Rak prebavil v Sloveniji 2014

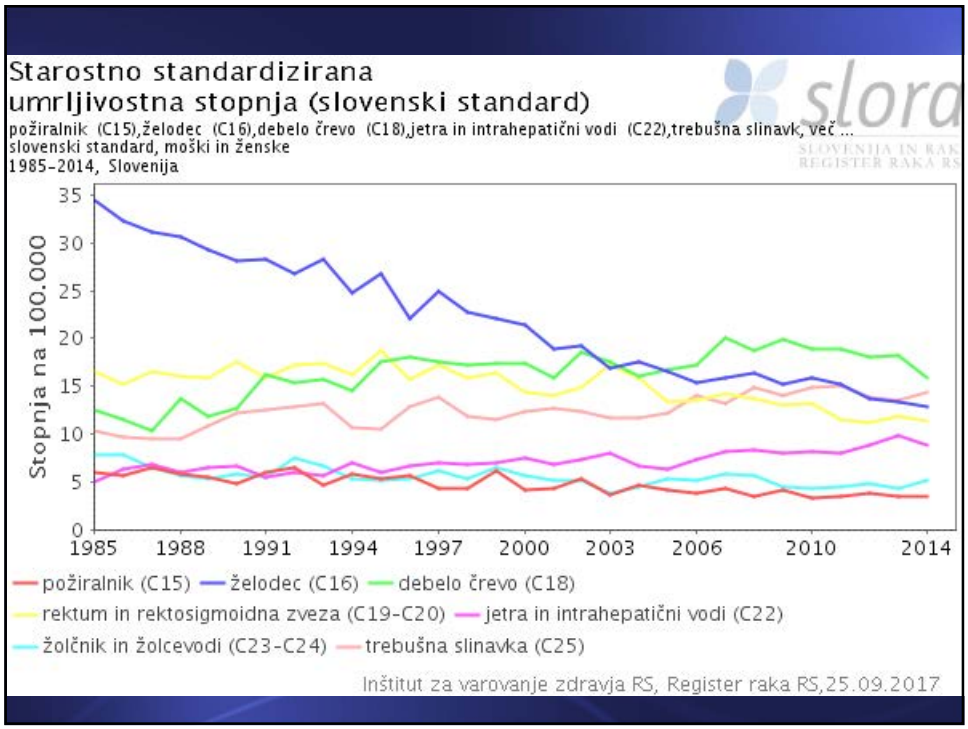
- ~ 20% vseh rakov

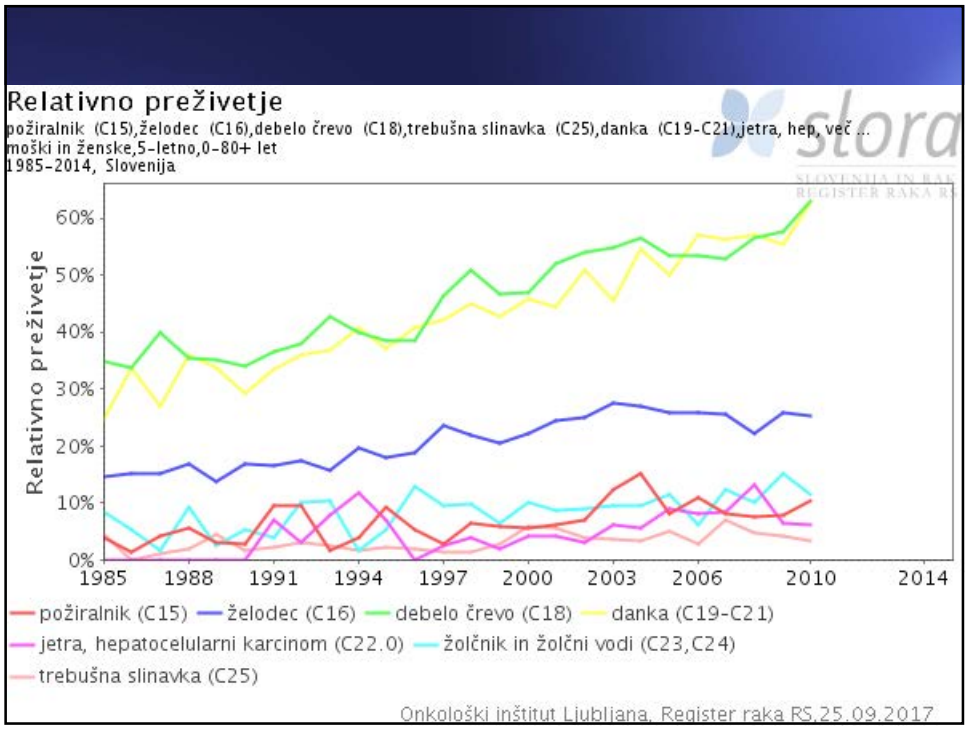


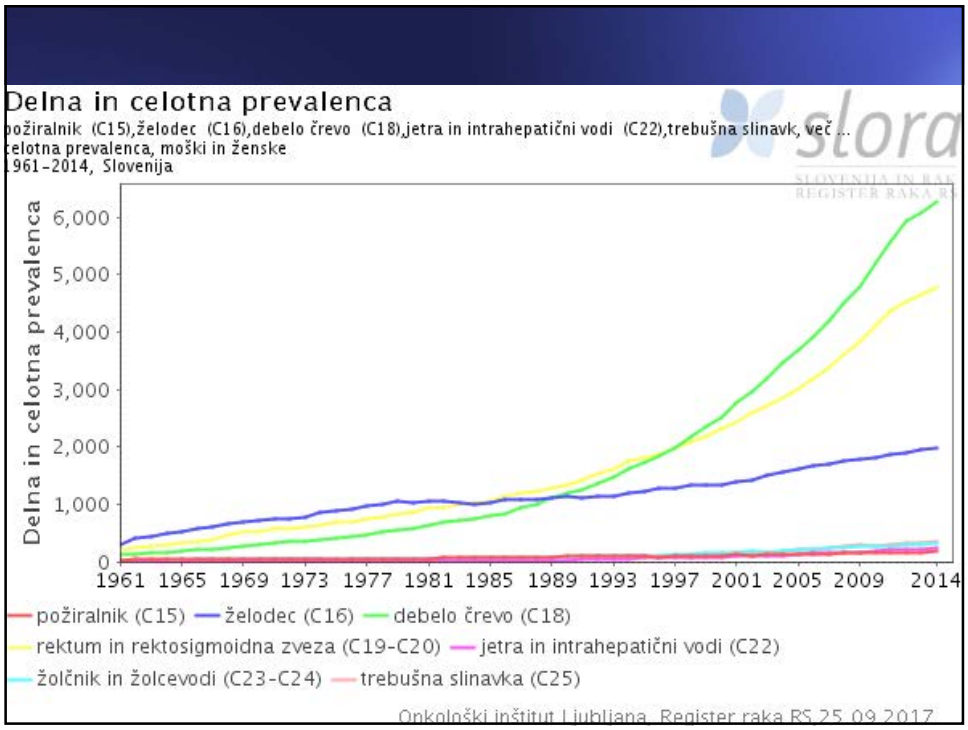
Vir: Register raka za Slovenijo, 2014

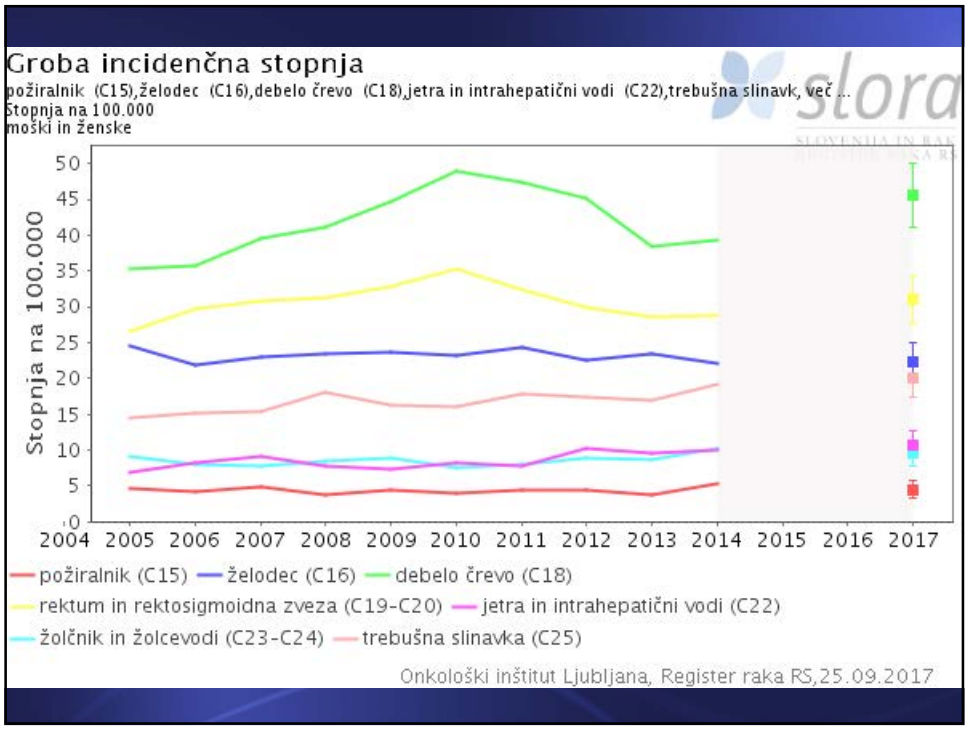

Incidenca
požiralnik (C15),želodec (C16),debelo črevo (C18),jetra in intrahepatični vodi (C22),trebušna slinavk, več ...
moški in ženske, vsi stadiji, 0 - 80+ let
1961-2014, Slovenija
slora
SLOVENIJA IN RAK
REGISTER RAKA RS
Incidenca
1,000
900
800
700
600
500
400
300
200
100
0
1961 1965 1969 1973 1977 1981 1985 1989 1993 1997 2001 2005 2009 2014
požiralnik (C15)
želodec (C16)
debelo črevo (C18)
rektum in rektosigmoidna zveza (C19-C20)
jetra in intrahepatični vodi (C22)
žolčnik in žolcevodi (C23-C24)
trebušna slinavka (C25)
Onkološki inštitut Ljubljana, Register raka RS,25.09.2017


Starostno standardizirana
incidenčna stopnja (slovenski standard)
požiralnik (C15),želodec (C16),debelo črevo (C18),jetra in intrahepatični vodi (C22),trebušna slinavk, več ...
slovenski standard, moški in ženske
1961-2014, Slovenija
slora
SLOVENIJA IN RAK
REGISTER RAKA RS
Stopnja na 100.000
55
50
45
40
35
30
25
20
15
10
5
0
1961 1965 1969 1973 1977 1981 1985 1989 1993 1997 2001 2005 2009 2014
požiralnik (C15)
želodec (C16)
debelo črevo (C18)
rektum in rektosigmoidna zveza (C19-C20)
jetra in intrahepatični vodi (C22)
žolčnik in žolcevodi (C23-C24)
trebušna slinavka (C25)
Onkološki inštitut Ljubljana, Register raka RS,25.09.2017


Starostno standardizirana
umrljivostna stopnja (slovenski standard)
požiralnik (C15),želodec (C16),debelo črevo (C18),jetra in intrahepatični vodi (C22),trebušna slinavk, več ...
slovenski standard, moški in ženske
1985-2014, Slovenija
Stopnja na 100.000
0
5
10
15
20
25
30
35
1985
1988
1991
1994
1997
2000
2003
2006
2010
2014
požiralnik (C15)
želodec (C16)
debelo črevo (C18)
rektum in rektosigmoidna zveza (C19-C20)
jetra in intrahepatični vodi (C22)
žolčnik in žolcevodi (C23-C24)
trebušna slinavka (C25)
Inštitut za varovanje zdravja RS, Register raka RS,25.09.2017


Relativno preživetje
požiralnik (C15),želodec (C16),debelo črevo (C18),trebušna slinavka (C25),danka (C19-C21),jetra, hep, več ...
moški in ženske,5-letno,0-80+ let
1985-2014, Slovenija
Relativno preživetje
0%
10%
20%
30%
40%
50%
60%
1985
1988
1991
1994
1997
2000
2003
2006
2010
2014
požiralnik (C15)
želodec (C16)
debelo črevo (C18)
danka (C19-C21)
jetra, hepatocelularni karcinom (C22.0)
žolčnik in žolčni vodi (C23,C24)
trebušna slinavka (C25)
Onkološki inštitut Ljubljana, Register raka RS,25.09.2017


Delna in celotna prevalenca
požiralnik (C15),želodec (C16),debelo črevo (C18),jetra in intrahepatični vodi (C22),trebušna slinavk, več ...
celotna prevalenca, moški in ženske
1961-2014, Slovenija
Delna in celotna prevalenca
0
1,000
2,000
3,000
4,000
5,000
6,000
1961 1965 1969 1973 1977 1981 1985 1989 1993 1997 2001 2005 2009 2014
požiralnik (C15)
želodec (C16)
debelo črevo (C18)
rektum in rektosigmoidna zveza (C19-C20)
jetra in intrahepatični vodi (C22)
žolčnik in žolcevodi (C23-C24)
trebušna slinavka (C25)
Onkološki inštitut Ljubljana, Register raka RS,25.09.2017


Groba incidenčna stopnja
požiralnik (C15),želodec (C16),debelo črevo (C18),jetra in intrahepatični vodi (C22),trebušna slinavk, več ...
Stopnja na 100.000
moški in ženske
Stopnja na 100.000
0
5
10
15
20
25
30
35
40
45
50
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
požiralnik (C15)
želodec (C16)
debelo črevo (C18)
rektum in rektosigmoidna zveza (C19-C20)
jetra in intrahepatični vodi (C22)
žolčnik in žolcevodi (C23-C24)
trebušna slinavka (C25)
Onkološki inštitut Ljubljana, Register raka RS,25.09.2017

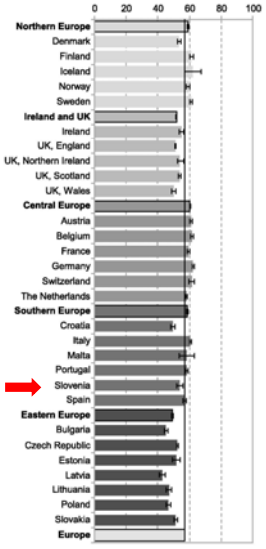
Age-specific and age-standardised relative survival for adult patients with invasive **colon** cancer diagnosed in 2000–2007 by European region, country, gender and overall.

Colon

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	**75,990**	**79.3**	**78.9**	**79.6**	**59.0**	**58.5**	**59.5**	**74.4**	**73.8**	**74.9**
Denmark	18,930	73.7	73.0	74.3	53.6	52.6	54.7	72.8	71.6	74.0
Finland	11,220	80.4	79.6	81.1	61.2	59.9	62.4	76.1	74.8	77.5
Iceland	715	81.2	78.3	84.2	62.0	57.3	67.2	76.4	71.2	82.1
Norway	17,935	79.2	78.5	79.8	59.2	58.2	60.2	74.8	73.6	75.9
Sweden	27,190	82.5	81.9	83.0	61.1	60.3	62.0	74.1	73.2	75.1
Ireland and UK	**186,791**	**72.6**	**72.4**	**72.8**	**51.8**	**51.5**	**52.1**	**71.3**	**70.9**	**71.7**
Ireland	10,113	75.1	74.2	76.0	55.0	53.7	56.3	73.2	71.6	74.7
UK, England	143,713	72.2	72.0	72.5	51.3	51.0	51.7	71.1	70.6	71.5
UK, Northern Ireland	4,961	74.9	73.7	76.2	54.2	52.4	56.2	72.4	70.2	74.7
UK, Scotland	18,188	74.6	73.9	75.3	53.9	52.9	54.9	72.2	71.0	73.4
UK, Wales	9,816	70.4	69.4	71.4	49.9	48.6	51.3	70.9	69.3	72.6
Central Europe	**187,037**	**80.5**	**80.3**	**80.7**	**60.5**	**60.2**	**60.8**	**75.2**	**74.9**	**75.6**
Austria	23,064	79.5	79.0	80.1	61.2	60.3	62.1	76.9	76.0	77.9
Belgium	22,930	82.9	82.4	83.4	61.7	60.8	62.6	74.4	73.5	75.4
France	18,294	81.6	81.0	82.2	59.6	58.8	60.6	73.1	72.2	74.1
Germany	62,210	81.5	81.2	81.9	62.2	61.7	62.8	76.4	75.8	77.0
Switzerland	6,217	82.9	82.0	83.9	61.4	59.8	63.1	74.1	72.3	75.9
The Netherlands	54,322	78.0	77.6	78.4	58.1	57.6	58.7	74.5	73.9	75.2
Southern Europe	**119,671**	**78.6**	**78.4**	**78.9**	**58.5**	**58.1**	**58.8**	**74.4**	**74.0**	**74.8**
Croatia	11,362	66.1	65.2	67.0	49.6	48.3	50.9	74.9	73.3	76.6
Italy	69,971	81.3	81.0	81.6	60.8	60.4	61.3	74.8	74.3	75.3
Malta	857	74.9	72.0	78.0	58.1	53.7	62.7	77.5	72.5	82.8
Portugal	17,908	78.6	78.0	79.3	58.3	57.3	59.2	74.1	73.0	75.1
Slovenia	5,344	73.9	72.7	75.2	54.0	52.2	55.9	73.1	71.0	75.3
Spain	14,229	77.4	76.7	78.2	57.1	56.1	58.1	73.8	72.7	74.8
Eastern Europe	**83,197**	**69.7**	**69.4**	**70.1**	**49.4**	**48.9**	**49.8**	**70.8**	**70.2**	**71.4**
Bulgaria	16,883	65.8	65.1	66.6	45.2	44.1	46.3	68.7	67.2	70.1
Czech Republic	33,404	72.5	72.0	73.0	52.5	51.8	53.3	72.4	71.5	73.3
Estonia	3,310	71.3	69.6	73.0	51.7	49.3	54.3	72.6	69.6	75.7
Latvia	4,213	64.3	62.7	65.8	42.9	40.9	45.1	66.8	64.1	69.7
Lithuania	5,072	66.0	64.7	67.4	47.1	45.3	48.9	71.3	69.1	73.7
Poland	9,012	68.8	67.8	69.8	46.7	45.3	48.1	67.8	66.1	69.6
Slovakia	11,303	72.0	71.1	72.9	51.4	50.2	52.7	71.5	70.0	73.0
Europe	**652,686**	**77.6**	**77.4**	**77.7**	**57.0**	**56.8**	**57.3**	**73.5**	**73.3**	**73.8**

Age-standardised 5-year relative survival (%)



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	17,622	obs	86.4	69.6	64.1
		rel	86.5	69.9	64.7
45-54	45,805	obs	84.2	66.9	59.5
		rel	84.6	67.8	61.0
55-64	116,392	obs	82.7	66.2	58.4
		rel	83.5	68.2	61.6
65-74	201,379	obs	77.0	59.6	50.5
		rel	78.8	64.2	57.7
75+	271,488	obs	61.4	42.0	32.1
		rel	66.5	53.5	49.3
All cases	652,686	obs	75.3	57.6	49.0
		rel	77.6	62.9	57.0
Men (52%)					
15-44	8,701	obs	85.2	69.0	63.9
		rel	85.3	69.4	64.6
45-54	23,971	obs	82.4	65.4	58.0
		rel	82.9	66.6	59.9
55-64	66,181	obs	81.6	64.7	56.5
		rel	82.6	67.3	60.6
65-74	114,310	obs	76.2	58.0	48.1
		rel	78.5	63.6	56.8
75+	123,740	obs	62.1	41.5	30.4
		rel	67.9	54.5	49.2
All cases	336,903	obs	74.8	56.4	47.2
		rel	77.4	62.6	56.4
Women (48%)					
15-44	8,921	obs	87.5	70.1	64.4
		rel	87.6	70.3	64.7
45-54	21,834	obs	86.3	68.7	61.2
		rel	86.5	69.3	62.2
55-64	50,211	obs	84.2	68.1	61.1
		rel	84.7	69.4	63.1
65-74	87,069	obs	78.2	61.9	53.9
		rel	79.3	64.9	58.8
75+	147,748	obs	60.8	42.5	33.4
		rel	65.3	52.7	49.1
All cases	315,783	obs	76.2	59.1	51.2
		rel	77.9	63.3	57.8

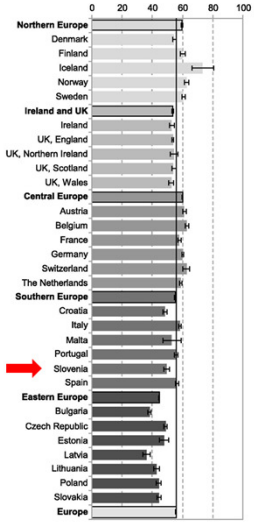
Age-specific and age-standardised relative survival for adult patients with invasive **rectum** cancer (including rectosigmoid junction, anal canal and anus) diagnosed in 2000–2007 by European region, country, gender and overall.

Rectum and anal canal

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	**45,013**	**83.4**	**83.0**	**83.8**	**59.5**	**58.9**	**60.2**	**71.4**	**70.7**	**72.1**
Denmark	11,878	80.3	79.6	81.1	54.6	53.3	55.9	67.9	66.5	69.4
Finland	7,352	82.6	81.6	83.5	60.1	58.6	61.7	72.8	71.2	74.5
Iceland	294	86.7	82.6	91.0	73.2	66.3	80.7	84.4	77.4	91.9
Norway	9,501	84.5	83.7	85.3	62.5	61.2	63.9	74.0	72.5	75.4
Sweden	15,988	85.3	84.7	85.9	60.8	59.7	61.8	71.3	70.1	72.4
Ireland and UK	**115,870**	**78.5**	**78.2**	**78.7**	**53.7**	**53.3**	**54.1**	**68.4**	**68.0**	**68.8**
Ireland	6,111	78.4	77.3	79.4	53.0	51.4	54.7	67.7	65.7	69.6
UK, England	90,879	78.3	78.0	78.6	53.7	53.3	54.2	68.6	68.1	69.1
UK, Northern Ireland	2,834	80.1	78.5	81.6	54.3	51.9	56.9	67.8	65.0	70.8
UK, Scotland	9,957	79.4	78.6	80.2	54.2	52.9	55.6	68.3	66.7	69.8
UK, Wales	6,089	78.6	77.6	79.7	52.6	50.9	54.3	66.9	65.0	68.9
Central Europe	**111,056**	**83.7**	**83.5**	**84.0**	**60.1**	**59.7**	**60.5**	**71.7**	**71.3**	**72.2**
Austria	14,015	83.1	82.5	83.8	61.1	60.0	62.2	73.5	72.3	74.7
Belgium	13,234	86.6	85.9	87.2	62.9	61.8	64.1	72.7	71.5	73.9
France	11,395	83.7	83.0	84.5	57.9	56.8	59.0	69.1	68.0	70.3
Germany	38,685	83.4	83.0	83.8	60.2	59.5	60.9	72.1	71.4	72.9
Switzerland	3,617	87.4	86.3	88.6	62.5	60.3	64.7	71.4	69.2	73.8
The Netherlands	30,110	82.7	82.2	83.2	59.0	58.2	59.8	71.3	70.4	72.2
Southern Europe	**64,777**	**80.4**	**80.1**	**80.7**	**55.4**	**54.9**	**55.9**	**68.9**	**68.3**	**69.4**
Croatia	10,054	71.4	70.5	72.3	48.5	47.1	49.9	67.9	66.2	69.6
Italy	31,143	83.3	82.9	83.7	58.3	57.6	59.0	70.0	69.2	70.7
Malta	505	82.1	78.5	85.8	52.8	47.0	59.3	64.3	57.8	71.6
Portugal	10,705	81.4	80.6	82.2	56.0	54.8	57.3	68.8	67.5	70.2
Slovenia	4,471	76.5	75.2	77.9	49.7	47.7	51.7	64.9	62.6	67.3
Spain	7,899	81.2	80.3	82.1	56.4	55.0	57.7	69.4	68.0	70.9
Eastern Europe	**64,616**	**72.4**	**72.0**	**72.8**	**44.6**	**44.1**	**45.1**	**61.6**	**61.0**	**62.3**
Bulgaria	12,995	67.5	66.7	68.4	38.4	37.2	39.6	56.8	55.2	58.4
Czech Republic	25,592	75.2	74.6	75.8	48.7	47.9	49.6	64.8	63.8	65.8
Estonia	2,232	73.5	71.5	75.5	47.9	45.1	50.9	65.2	61.7	68.8
Latvia	3,401	69.2	67.5	70.9	36.1	33.8	38.5	52.1	49.1	55.3
Lithuania	4,682	67.9	66.5	69.4	43.0	41.2	45.0	63.3	60.9	65.8
Poland	6,734	73.2	72.1	74.4	44.3	42.6	46.0	60.4	58.4	62.5
Slovakia	8,980	73.6	72.6	74.6	44.7	43.3	46.1	60.8	59.1	62.5
Europe	**401,332**	**80.8**	**80.7**	**81.0**	**55.8**	**55.5**	**56.1**	**69.0**	**68.6**	**69.3**

Age-standardised 5-year relative survival (%)

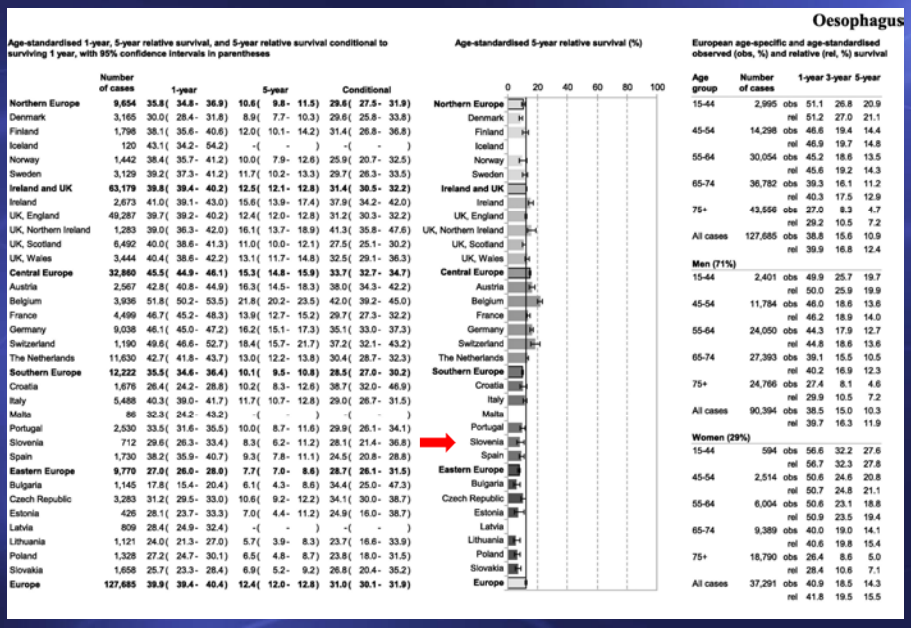


European age-specific and age-standardised observed (obs, %) and relative (rel, %) survival

Age group	Number of cases		1-year	3-year	5-year
15-44	12,325	obs	88.5	70.8	63.3
		rel	88.6	71.1	63.9
45-54	38,495	obs	88.7	70.7	61.2
		rel	89.1	71.7	62.8
55-64	89,207	obs	88.3	68.4	58.7
		rel	87.1	70.6	62.0
65-74	126,720	obs	80.4	61.0	50.2
		rel	82.3	65.7	57.4
75+	134,585	obs	63.8	40.4	29.1
		rel	69.0	51.4	44.3
All cases	401,332	obs	78.5	58.6	48.3
		rel	80.8	63.8	55.8
Men (58%)					
15-44	6,483	obs	87.3	68.4	61.3
		rel	87.4	68.8	62.0
45-54	22,601	obs	87.7	68.8	58.6
		rel	88.2	70.0	60.5
55-64	57,119	obs	85.2	66.2	55.9
		rel	86.3	68.8	59.9
65-74	80,242	obs	79.7	59.5	48.2
		rel	82.0	65.2	56.7
75+	68,255	obs	64.1	40.2	28.2
		rel	70.0	52.5	45.1
All cases	234,700	obs	77.9	57.2	46.3
		rel	80.6	63.2	54.9
Women (42%)					
15-44	5,842	obs	90.0	73.6	65.6
		rel	90.1	73.8	65.9
45-54	15,894	obs	90.2	73.4	65.0
		rel	90.4	74.0	66.0
55-64	32,088	obs	88.2	72.3	63.6
		rel	88.7	73.6	65.7
65-74	46,478	obs	81.7	63.6	53.7
		rel	82.9	66.7	58.5
75+	66,330	obs	63.5	40.6	30.0
		rel	68.2	50.2	43.7
All cases	166,632	obs	79.5	60.8	51.3
		rel	81.4	64.9	57.3

Holleczek B et al.,Eur J Cancer. 2015 Oct;51(15):2158-2168

Age-specific and age-standardised relative survival for adult **oesophageal** cancers diagnosed in 2000–2007, by European region, country, gender and overall.



Oesophagus

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	**9,654**	**35.8**	**(34.8 -**	**36.9)**	**10.6**	**(9.8 -**	**11.5)**	**29.6**	**(27.5 -**	**31.9)**
Denmark	3,165	30.0	(28.4 -	31.8)	8.9	(7.7 -	10.3)	29.6	(25.8 -	33.8)
Finland	1,798	38.1	(35.6 -	40.6)	12.0	(10.1 -	14.2)	31.4	(26.8 -	36.8)
Iceland	120	43.1	(34.2 -	54.2)	-	(-	-)	-	(-	-)
Norway	1,442	38.4	(35.7 -	41.2)	10.0	(7.9 -	12.6)	25.9	(20.7 -	32.5)
Sweden	3,129	39.2	(37.3 -	41.2)	11.7	(10.2 -	13.3)	29.7	(26.3 -	33.5)
Ireland and UK	**63,179**	**39.8**	**(39.4 -**	**40.2)**	**12.5**	**(12.1 -**	**12.8)**	**31.4**	**(30.5 -**	**32.2)**
Ireland	2,673	41.0	(39.1 -	43.0)	15.6	(13.9 -	17.4)	37.9	(34.2 -	42.0)
UK, England	49,287	39.7	(39.2 -	40.2)	12.4	(12.0 -	12.8)	31.2	(30.3 -	32.2)
UK, Northern Ireland	1,283	39.0	(36.3 -	42.0)	16.1	(13.7 -	18.9)	41.3	(35.8 -	47.6)
UK, Scotland	6,492	40.0	(38.6 -	41.3)	11.0	(10.0 -	12.1)	27.5	(25.1 -	30.2)
UK, Wales	3,444	40.4	(38.6 -	42.2)	13.1	(11.7 -	14.8)	32.5	(29.1 -	36.3)
Central Europe	**32,860**	**45.5**	**(44.9 -**	**46.1)**	**15.3**	**(14.8 -**	**15.9)**	**33.7**	**(32.7 -**	**34.7)**
Austria	2,567	42.8	(40.8 -	44.9)	16.3	(14.5 -	18.3)	38.0	(34.3 -	42.2)
Belgium	3,936	51.8	(50.2 -	53.5)	21.8	(20.2 -	23.5)	42.0	(39.2 -	45.0)
France	4,499	46.7	(45.2 -	48.3)	13.9	(12.7 -	15.2)	29.7	(27.3 -	32.2)
Germany	9,038	46.1	(45.0 -	47.2)	16.2	(15.1 -	17.3)	35.1	(33.0 -	37.3)
Switzerland	1,190	49.6	(46.6 -	52.7)	18.4	(15.7 -	21.7)	37.2	(32.1 -	43.2)
The Netherlands	11,630	42.7	(41.8 -	43.7)	13.0	(12.2 -	13.8)	30.4	(28.7 -	32.3)
Southern Europe	**12,222**	**35.5**	**(34.6 -**	**36.4)**	**10.1**	**(9.5 -**	**10.8)**	**28.5**	**(27.0 -**	**30.2)**
Croatia	1,676	26.4	(24.2 -	28.8)	10.2	(8.3 -	12.6)	38.7	(32.0 -	46.9)
Italy	5,488	40.3	(39.0 -	41.7)	11.7	(10.7 -	12.8)	29.0	(26.7 -	31.5)
Malta	86	32.3	(24.2 -	43.2)	-	(-	-)	-	(-	-)
Portugal	2,530	33.5	(31.6 -	35.5)	10.0	(8.7 -	11.6)	29.9	(26.1 -	34.1)
Slovenia	712	29.6	(26.3 -	33.4)	8.3	(6.2 -	11.2)	28.1	(21.4 -	36.8)
Spain	1,730	38.2	(35.9 -	40.7)	9.3	(7.8 -	11.1)	24.5	(20.8 -	28.8)
Eastern Europe	**9,770**	**27.0**	**(26.0 -**	**28.0)**	**7.7**	**(7.0 -**	**8.6)**	**28.7**	**(26.1 -**	**31.5)**
Bulgaria	1,145	17.8	(15.4 -	20.4)	6.1	(4.3 -	8.6)	34.4	(25.0 -	47.3)
Czech Republic	3,283	31.2	(29.5 -	33.0)	10.6	(9.2 -	12.2)	34.1	(30.0 -	38.7)
Estonia	426	28.1	(23.7 -	33.3)	7.0	(4.4 -	11.2)	24.9	(16.0 -	38.7)
Latvia	809	28.4	(24.9 -	32.4)	-	(-	-)	-	(-	-)
Lithuania	1,121	24.0	(21.3 -	27.0)	5.7	(3.9 -	8.3)	23.7	(16.6 -	33.9)
Poland	1,328	27.2	(24.7 -	30.1)	6.5	(4.8 -	8.7)	23.8	(18.0 -	31.5)
Slovakia	1,658	25.7	(23.3 -	28.4)	6.9	(5.2 -	9.2)	26.8	(20.4 -	35.2)
Europe	**127,685**	**39.9**	**(39.4 -**	**40.4)**	**12.4**	**(12.0 -**	**12.8)**	**31.0**	**(30.1 -**	**31.9)**

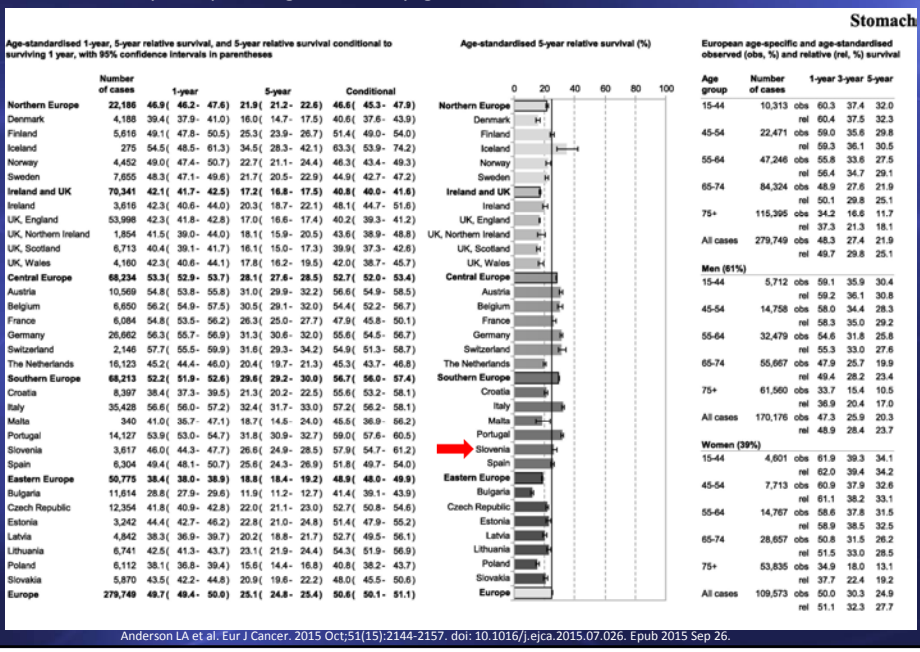
Age-standardised 5-year relative survival (%)

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	2,995	obs	51.1	26.8	20.9
		rel	51.2	27.0	21.1
45-54	14,298	obs	46.6	19.4	14.4
		rel	46.9	19.7	14.8
55-64	30,054	obs	45.2	18.6	13.5
		rel	45.6	19.2	14.3
65-74	36,782	obs	39.3	16.1	11.2
		rel	40.3	17.5	12.9
75+	43,556	obs	27.0	8.3	4.7
		rel	29.2	10.5	7.2
All cases	127,685	obs	38.8	15.6	10.9
		rel	39.9	16.8	12.4
Men (71%)					
15-44	2,401	obs	49.9	25.7	19.7
		rel	50.0	25.9	19.9
45-54	11,784	obs	46.0	18.6	13.6
		rel	46.2	18.9	14.0
55-64	24,050	obs	44.3	17.9	12.7
		rel	44.8	18.6	13.6
65-74	27,393	obs	39.1	15.5	10.5
		rel	40.2	16.9	12.3
75+	24,766	obs	27.4	8.1	4.6
		rel	29.9	10.5	7.2
All cases	90,394	obs	38.5	15.0	10.3
		rel	39.7	16.3	11.9
Women (29%)					
15-44	594	obs	56.6	32.2	27.6
		rel	56.7	32.3	27.8
45-54	2,514	obs	50.6	24.6	20.8
		rel	50.7	24.8	21.1
55-64	6,004	obs	50.6	23.1	18.8
		rel	50.9	23.5	19.4
65-74	9,389	obs	40.0	19.0	14.1
		rel	40.6	19.8	15.4
75+	18,790	obs	26.4	8.6	5.0
		rel	28.4	10.6	7.1
All cases	37,291	obs	40.9	18.5	14.3
		rel	41.8	19.5	15.5

Anderson LA et al. Eur J Cancer. 2015 Oct;51(15):2144-2157. doi: 10.1016/j.ejca.2015.07.026. Epub 2015 Sep 26.

Age-specific and age-standardised relative survival for adult **stomach** cancers diagnosed in 2000–2007, by European region, country, gender and overall.



Stomach

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	**22,186**	**46.9**	**(46.2 -**	**47.6)**	**21.9**	**(21.2 -**	**22.6)**	**46.6**	**(45.3 -**	**47.9)**
Denmark	4,188	39.4	(37.9 -	41.0)	16.0	(14.7 -	17.5)	40.6	(37.6 -	43.9)
Finland	5,616	49.1	(47.8 -	50.5)	25.3	(23.9 -	26.7)	51.4	(49.0 -	54.0)
Iceland	275	54.5	(48.5 -	61.3)	34.5	(28.3 -	42.1)	63.3	(53.9 -	74.2)
Norway	4,452	49.0	(47.4 -	50.7)	22.7	(21.1 -	24.4)	46.3	(43.4 -	49.3)
Sweden	7,655	48.3	(47.1 -	49.6)	21.7	(20.5 -	22.9)	44.9	(42.7 -	47.2)
Ireland and UK	**70,341**	**42.1**	**(41.7 -**	**42.5)**	**17.2**	**(16.8 -**	**17.5)**	**40.8**	**(40.0 -**	**41.6)**
Ireland	3,616	42.3	(40.6 -	44.0)	20.3	(18.7 -	22.1)	48.1	(44.7 -	51.6)
UK, England	53,998	42.3	(41.8 -	42.8)	17.0	(16.6 -	17.4)	40.2	(39.3 -	41.2)
UK, Northern Ireland	1,854	41.5	(39.0 -	44.0)	18.1	(15.9 -	20.5)	43.6	(38.9 -	48.8)
UK, Scotland	6,713	40.4	(39.1 -	41.7)	16.1	(15.0 -	17.3)	39.9	(37.3 -	42.6)
UK, Wales	4,160	42.3	(40.6 -	44.1)	17.8	(16.2 -	19.5)	42.0	(38.7 -	45.7)
Central Europe	**68,234**	**53.3**	**(52.9 -**	**53.7)**	**28.1**	**(27.6 -**	**28.5)**	**52.7**	**(52.0 -**	**53.4)**
Austria	10,569	54.8	(53.8 -	55.8)	31.0	(29.9 -	32.2)	56.6	(54.9 -	58.5)
Belgium	6,650	56.2	(54.9 -	57.5)	30.5	(29.1 -	32.0)	54.4	(52.2 -	56.7)
France	6,084	54.8	(53.5 -	56.2)	26.3	(25.0 -	27.7)	47.9	(45.8 -	50.1)
Germany	26,662	56.3	(55.7 -	56.9)	31.3	(30.6 -	32.0)	55.6	(54.5 -	56.7)
Switzerland	2,146	57.7	(55.5 -	59.9)	31.6	(29.3 -	34.2)	54.9	(51.3 -	58.7)
The Netherlands	16,123	45.2	(44.4 -	46.0)	20.4	(19.7 -	21.3)	45.3	(43.7 -	46.8)
Southern Europe	**68,213**	**52.2**	**(51.9 -**	**52.6)**	**29.6**	**(29.2 -**	**30.0)**	**56.7**	**(56.0 -**	**57.4)**
Croatia	8,397	38.4	(37.3 -	39.5)	21.3	(20.2 -	22.5)	55.6	(53.2 -	58.1)
Italy	35,428	56.6	(56.0 -	57.2)	32.4	(31.7 -	33.0)	57.2	(56.2 -	58.1)
Malta	340	41.0	(36.7 -	47.1)	18.7	(14.5 -	24.0)	45.5	(36.9 -	56.2)
Portugal	14,127	53.9	(53.0 -	54.7)	31.8	(30.9 -	32.7)	59.0	(57.6 -	60.5)
Slovenia	3,617	46.0	(44.3 -	47.7)	26.6	(24.9 -	28.5)	57.9	(54.7 -	61.2)
Spain	6,304	49.4	(48.1 -	50.7)	25.6	(24.3 -	26.9)	51.8	(49.7 -	54.0)
Eastern Europe	**50,775**	**38.4**	**(38.0 -**	**38.9)**	**18.8**	**(18.4 -**	**19.2)**	**48.9**	**(48.0 -**	**49.9)**
Bulgaria	11,614	28.8	(27.9 -	29.6)	11.9	(11.2 -	12.7)	41.4	(39.1 -	43.9)
Czech Republic	12,354	41.8	(40.9 -	42.8)	22.0	(21.1 -	23.0)	52.7	(50.8 -	54.6)
Estonia	3,242	44.4	(42.7 -	46.2)	22.8	(21.0 -	24.8)	51.4	(47.9 -	55.2)
Latvia	4,842	38.3	(36.9 -	39.7)	20.2	(18.8 -	21.7)	52.7	(49.5 -	56.1)
Lithuania	6,741	42.5	(41.3 -	43.7)	23.1	(21.9 -	24.4)	54.3	(51.9 -	56.9)
Poland	6,112	38.1	(36.8 -	39.4)	15.6	(14.4 -	16.8)	40.8	(38.2 -	43.7)
Slovakia	5,870	43.5	(42.2 -	44.8)	20.9	(19.6 -	22.2)	48.0	(45.5 -	50.6)
Europe	**279,749**	**49.7**	**(49.4 -**	**50.0)**	**25.1**	**(24.8 -**	**25.4)**	**50.6**	**(50.1 -**	**51.1)**

Age-standardised 5-year relative survival (%)

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	10,313	obs	60.3	37.4	32.0
		rel	60.4	37.5	32.3
45-54	22,471	obs	59.0	35.6	29.8
		rel	59.3	36.1	30.5
55-64	47,246	obs	55.8	33.6	27.5
		rel	56.4	34.7	29.1
65-74	84,324	obs	48.9	27.6	21.9
		rel	50.1	29.8	25.1
75+	115,395	obs	34.2	16.6	11.7
		rel	37.3	21.3	18.1
All cases	279,749	obs	48.3	27.4	21.9
		rel	49.7	29.8	25.1
Men (61%)					
15-44	5,712	obs	59.1	35.9	30.4
		rel	59.2	36.1	30.8
45-54	14,758	obs	58.0	34.4	28.3
		rel	58.3	35.0	29.2
55-64	32,479	obs	54.6	31.8	25.8
		rel	55.3	33.0	27.6
65-74	55,667	obs	47.9	25.7	19.9
		rel	49.4	28.2	23.4
75+	61,560	obs	33.7	15.4	10.5
		rel	36.9	20.4	17.0
All cases	170,176	obs	47.3	25.9	20.3
		rel	48.9	28.4	23.7
Women (39%)					
15-44	4,601	obs	61.9	39.3	34.1
		rel	62.0	39.4	34.2
45-54	7,713	obs	60.9	37.9	32.6
		rel	61.1	38.2	33.1
55-64	14,767	obs	58.6	37.8	31.5
		rel	58.9	38.5	32.5
65-74	28,657	obs	50.8	31.5	26.2
		rel	51.5	33.0	28.5
75+	53,835	obs	34.9	18.0	13.1
		rel	37.7	22.4	19.2
All cases	109,573	obs	50.0	30.3	24.9
		rel	51.1	32.3	27.7

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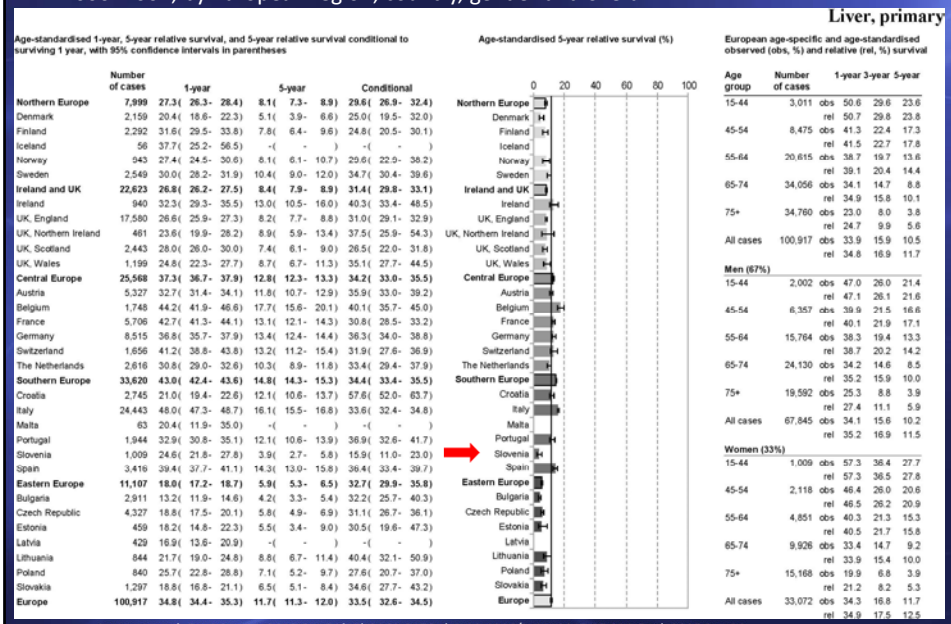
Age-specific and age-standardised relative survival for adult **liver** cancers diagnosed in 2000–2007, by European region, country, gender and overall.



Liver, primary

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	**7,999**	**27.3**	**(26.3 -**	**28.4)**	**8.1**	**(7.3 -**	**8.9)**	**29.6**	**(26.9 -**	**32.4)**
Denmark	2,159	20.4	(18.6 -	22.3)	5.1	(3.9 -	6.6)	25.0	(19.5 -	32.0)
Finland	2,292	31.6	(29.5 -	33.8)	7.8	(6.4 -	9.6)	24.8	(20.5 -	30.1)
Iceland	56	37.7	(25.2 -	56.5)	-(	-	)	-(	-	)
Norway	943	27.4	(24.5 -	30.6)	8.1	(6.1 -	10.7)	29.6	(22.9 -	38.2)
Sweden	2,549	30.0	(28.2 -	31.9)	10.4	(9.0 -	12.0)	34.7	(30.4 -	39.6)
Ireland and UK	**22,623**	**26.8**	**(26.2 -**	**27.5)**	**8.4**	**(7.9 -**	**8.9)**	**31.4**	**(29.8 -**	**33.1)**
Ireland	940	32.3	(29.3 -	35.5)	13.0	(10.5 -	16.0)	40.3	(33.4 -	48.5)
UK, England	17,580	26.6	(25.9 -	27.3)	8.2	(7.7 -	8.8)	31.0	(29.1 -	32.9)
UK, Northern Ireland	461	23.6	(19.9 -	28.2)	8.9	(5.9 -	13.4)	37.5	(25.9 -	54.3)
UK, Scotland	2,443	28.0	(26.0 -	30.0)	7.4	(6.1 -	9.0)	26.5	(22.0 -	31.8)
UK, Wales	1,199	24.8	(22.3 -	27.7)	8.7	(6.7 -	11.3)	35.1	(27.7 -	44.5)
Central Europe	**25,568**	**37.3**	**(36.7 -**	**37.9)**	**12.8**	**(12.3 -**	**13.3)**	**34.2**	**(33.0 -**	**35.5)**
Austria	5,327	32.7	(31.4 -	34.1)	11.8	(10.7 -	12.9)	35.9	(33.0 -	39.2)
Belgium	1,748	44.2	(41.9 -	46.6)	17.7	(15.6 -	20.1)	40.1	(35.7 -	45.0)
France	5,706	42.7	(41.3 -	44.1)	13.1	(12.1 -	14.3)	30.8	(28.5 -	33.2)
Germany	8,515	36.8	(35.7 -	37.9)	13.4	(12.4 -	14.4)	36.3	(34.0 -	38.8)
Switzerland	1,656	41.2	(38.8 -	43.8)	13.2	(11.2 -	15.4)	31.9	(27.6 -	36.9)
The Netherlands	2,616	30.8	(29.0 -	32.6)	10.3	(8.9 -	11.8)	33.4	(29.4 -	37.9)
Southern Europe	**33,620**	**43.0**	**(42.4 -**	**43.6)**	**14.8**	**(14.3 -**	**15.3)**	**34.4**	**(33.4 -**	**35.5)**
Croatia	2,745	21.0	(19.4 -	22.6)	12.1	(10.8 -	13.7)	57.6	(52.0 -	63.7)
Italy	24,443	48.0	(47.3 -	48.7)	16.1	(15.5 -	16.8)	33.6	(32.4 -	34.8)
Malta	63	20.4	(11.9 -	35.0)	-(	-	)	-(	-	)
Portugal	1,944	32.9	(30.8 -	35.1)	12.1	(10.6 -	13.9)	36.9	(32.6 -	41.7)
Slovenia	1,009	24.6	(21.8 -	27.8)	3.9	(2.7 -	5.8)	15.9	(11.0 -	23.0)
Spain	3,416	39.4	(37.7 -	41.1)	14.3	(13.0 -	15.8)	36.4	(33.4 -	39.7)
Eastern Europe	**11,107**	**18.0**	**(17.2 -**	**18.7)**	**5.9**	**(5.3 -**	**6.5)**	**32.7**	**(29.9 -**	**35.8)**
Bulgaria	2,911	13.2	(11.9 -	14.6)	4.2	(3.3 -	5.4)	32.2	(25.7 -	40.3)
Czech Republic	4,327	18.8	(17.5 -	20.1)	5.8	(4.9 -	6.9)	31.1	(26.7 -	36.1)
Estonia	459	18.2	(14.8 -	22.3)	5.5	(3.4 -	9.0)	30.5	(19.6 -	47.3)
Latvia	429	16.9	(13.6 -	20.9)	-(	-	)	-(	-	)
Lithuania	844	21.7	(19.0 -	24.8)	8.8	(6.7 -	11.4)	40.4	(32.1 -	50.9)
Poland	840	25.7	(22.8 -	28.8)	7.1	(5.2 -	9.7)	27.6	(20.7 -	37.0)
Slovakia	1,297	18.8	(16.8 -	21.1)	6.5	(5.1 -	8.4)	34.6	(27.7 -	43.2)
Europe	**100,917**	**34.8**	**(34.4 -**	**35.3)**	**11.7**	**(11.3 -**	**12.0)**	**33.5**	**(32.6 -**	**34.5)**

Age-standardised 5-year relative survival (%)

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	3,011	obs	50.6	29.6	23.6
		rel	50.7	29.8	23.8
45-54	8,475	obs	41.3	22.4	17.3
		rel	41.5	22.7	17.8
55-64	20,615	obs	38.7	19.7	13.6
		rel	39.1	20.4	14.4
65-74	34,056	obs	34.1	14.7	8.8
		rel	34.9	15.8	10.1
75+	34,760	obs	23.0	8.0	3.8
		rel	24.7	9.9	5.6
All cases	100,917	obs	33.9	15.9	10.5
		rel	34.8	16.9	11.7
Men (67%)					
15-44	2,002	obs	47.0	26.0	21.4
		rel	47.1	26.1	21.6
45-54	6,357	obs	39.9	21.5	16.6
		rel	40.1	21.9	17.1
55-64	15,764	obs	38.3	19.4	13.3
		rel	38.7	20.2	14.2
65-74	24,130	obs	34.2	14.6	8.5
		rel	35.2	15.9	10.0
75+	19,592	obs	25.3	8.8	3.9
		rel	27.4	11.1	5.9
All cases	67,845	obs	34.1	15.6	10.2
		rel	35.2	16.9	11.5
Women (33%)					
15-44	1,009	obs	57.3	38.4	27.7
		rel	57.3	36.5	27.8
45-54	2,118	obs	46.4	26.0	20.6
		rel	46.5	26.2	20.9
55-64	4,851	obs	40.3	21.3	15.3
		rel	40.5	21.7	15.8
65-74	9,926	obs	33.4	14.7	9.2
		rel	33.9	15.4	10.0
75+	15,168	obs	19.9	6.8	3.9
		rel	21.2	8.2	5.3
All cases	33,072	obs	34.3	16.8	11.7
		rel	34.9	17.5	12.5

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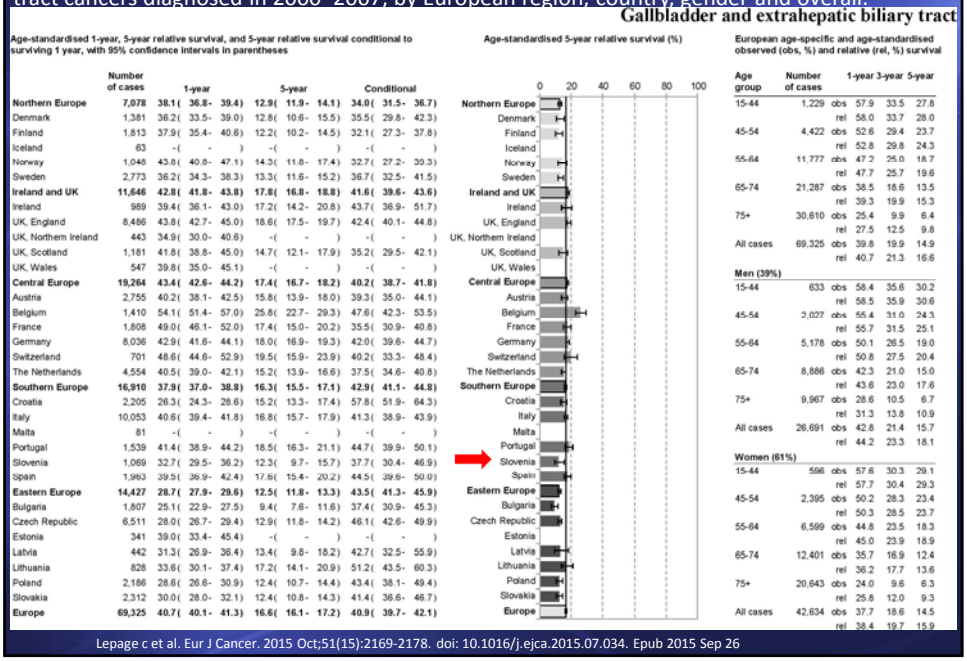
Age-specific and age-standardised relative survival for adult **gallbladder and extrahepatic biliary** tract cancers diagnosed in 2000–2007, by European region, country, gender and overall.



Gallbladder and extrahepatic biliary tract

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	**7,078**	**38.1**	**(36.8 -**	**39.4)**	**12.9**	**(11.9 -**	**14.1)**	**34.0**	**(31.5 -**	**36.7)**
Denmark	1,381	36.2	(33.5 -	39.0)	12.8	(10.6 -	15.5)	35.5	(29.8 -	42.3)
Finland	1,813	37.9	(35.4 -	40.6)	12.2	(10.2 -	14.5)	32.1	(27.3 -	37.8)
Iceland	63	-(	-	)	-(	-	)	-(	-	)
Norway	1,048	43.8	(40.8 -	47.1)	14.3	(11.8 -	17.4)	32.7	(27.2 -	39.3)
Sweden	2,773	36.2	(34.3 -	38.3)	13.3	(11.6 -	15.2)	36.7	(32.5 -	41.5)
Ireland and UK	**11,646**	**42.8**	**(41.8 -**	**43.8)**	**17.8**	**(16.8 -**	**18.8)**	**41.6**	**(39.6 -**	**43.6)**
Ireland	989	39.4	(36.1 -	43.0)	17.2	(14.2 -	20.8)	43.7	(36.9 -	51.7)
UK, England	8,486	43.8	(42.7 -	45.0)	18.6	(17.5 -	19.7)	42.4	(40.1 -	44.8)
UK, Northern Ireland	443	34.9	(30.0 -	40.6)	-(	-	)	-(	-	)
UK, Scotland	1,181	41.8	(38.8 -	45.0)	14.7	(12.1 -	17.9)	35.2	(29.5 -	42.1)
UK, Wales	547	39.8	(35.0 -	45.1)	-(	-	)	-(	-	)
Central Europe	**19,264**	**43.4**	**(42.6 -**	**44.2)**	**17.4**	**(16.7 -**	**18.2)**	**40.2**	**(38.7 -**	**41.8)**
Austria	2,755	40.2	(38.1 -	42.5)	15.8	(13.9 -	18.0)	39.3	(35.0 -	44.1)
Belgium	1,410	54.1	(51.4 -	57.0)	25.8	(22.7 -	29.3)	47.6	(42.3 -	53.5)
France	1,808	49.0	(46.1 -	52.0)	17.4	(15.0 -	20.2)	35.5	(30.9 -	40.8)
Germany	8,036	42.9	(41.6 -	44.1)	18.0	(16.9 -	19.3)	42.0	(39.6 -	44.7)
Switzerland	701	48.6	(44.6 -	52.9)	19.5	(15.9 -	23.9)	40.2	(33.3 -	48.4)
The Netherlands	4,554	40.5	(39.0 -	42.1)	15.2	(13.9 -	16.6)	37.5	(34.6 -	40.8)
Southern Europe	**16,910**	**37.9**	**(37.0 -**	**38.8)**	**16.3**	**(15.5 -**	**17.1)**	**42.9**	**(41.1 -**	**44.8)**
Croatia	2,205	26.3	(24.3 -	28.6)	15.2	(13.3 -	17.4)	57.8	(51.9 -	64.3)
Italy	10,053	40.6	(39.4 -	41.8)	16.8	(15.7 -	17.9)	41.3	(38.9 -	43.9)
Malta	81	-(	-	)	-(	-	)	-(	-	)
Portugal	1,539	41.4	(38.9 -	44.2)	18.5	(16.3 -	21.1)	44.7	(39.9 -	50.1)
Slovenia	1,069	32.7	(29.5 -	36.2)	12.3	(9.7 -	15.7)	37.7	(30.4 -	46.9)
Spain	1,963	39.5	(36.9 -	42.4)	17.6	(15.4 -	20.2)	44.5	(39.6 -	50.0)
Eastern Europe	**14,427**	**28.7**	**(27.9 -**	**29.6)**	**12.5**	**(11.8 -**	**13.3)**	**43.5**	**(41.3 -**	**45.9)**
Bulgaria	1,807	25.1	(22.9 -	27.5)	9.4	(7.6 -	11.6)	37.4	(30.9 -	45.3)
Czech Republic	6,511	28.0	(26.7 -	29.4)	12.9	(11.8 -	14.2)	46.1	(42.6 -	49.9)
Estonia	341	39.0	(33.4 -	45.4)	-(	-	)	-(	-	)
Latvia	442	31.3	(26.9 -	36.4)	13.4	(9.8 -	18.2)	42.7	(32.5 -	55.9)
Lithuania	828	33.6	(30.1 -	37.4)	17.2	(14.1 -	20.9)	51.2	(43.5 -	60.3)
Poland	2,186	28.6	(26.6 -	30.9)	12.4	(10.7 -	14.4)	43.4	(38.1 -	49.4)
Slovakia	2,312	30.0	(28.0 -	32.1)	12.4	(10.8 -	14.3)	41.4	(36.6 -	46.7)
Europe	**69,325**	**40.7**	**(40.1 -**	**41.3)**	**16.6**	**(16.1 -**	**17.2)**	**40.9**	**(39.7 -**	**42.1)**

Age-standardised 5-year relative survival (%)

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	1,229	obs	57.9	33.5	27.8
		rel	58.0	33.7	28.0
45-54	4,422	obs	52.6	29.4	23.7
		rel	52.8	29.8	24.3
55-64	11,777	obs	47.2	25.0	18.7
		rel	47.7	25.7	19.6
65-74	21,287	obs	38.5	18.6	13.5
		rel	39.3	19.9	15.3
75+	30,610	obs	25.4	9.9	6.4
		rel	27.5	12.5	9.8
All cases	69,325	obs	39.8	19.9	14.9
		rel	40.7	21.3	16.6
Men (39%)					
15-44	633	obs	58.4	35.6	30.2
		rel	58.5	35.9	30.6
45-54	2,027	obs	55.4	31.0	24.3
		rel	55.7	31.5	25.1
55-64	5,178	obs	50.1	26.5	19.0
		rel	50.8	27.5	20.4
65-74	8,886	obs	42.3	21.0	15.0
		rel	43.6	23.0	17.6
75+	9,967	obs	28.6	10.5	6.7
		rel	31.3	13.8	10.9
All cases	26,691	obs	42.8	21.4	15.7
		rel	44.2	23.3	18.1
Women (61%)					
15-44	596	obs	57.6	30.3	29.1
		rel	57.7	30.4	29.3
45-54	2,395	obs	50.2	28.3	23.4
		rel	50.3	28.5	23.7
55-64	6,599	obs	44.8	23.5	18.3
		rel	45.0	23.9	18.9
65-74	12,401	obs	35.7	16.9	12.4
		rel	36.2	17.7	13.6
75+	20,643	obs	24.0	9.6	6.3
		rel	25.8	12.0	9.3
All cases	42,634	obs	37.7	18.6	14.5
		rel	38.4	19.7	15.9

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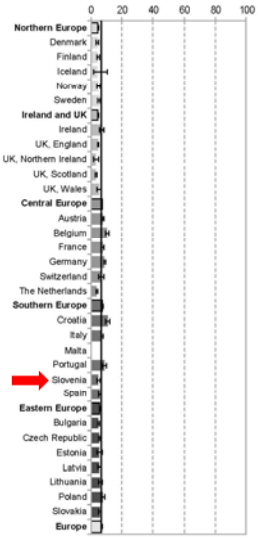
Age-specific and age-standardised relative survival for adult **pancreatic** cancers diagnosed in 2000–2007, by European region, country, gender and overall.

Pancreas

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	**25,083**	**22.5**	**(21.9 -**	**23.1)**	**4.8**	**(4.4 -**	**5.2)**	**21.3**	**(19.6 -**	**23.1)**
Denmark	6,502	18.6	(17.6 -	19.7)	4.2	(3.5 -	5.0)	22.4	(18.9 -	26.5)
Finland	6,604	24.7	(23.5 -	26.0)	4.6	(3.9 -	5.5)	18.7	(15.7 -	22.2)
Iceland	230	25.7	(20.3 -	32.5)	4.5	(1.9 -	10.6)	17.4	(7.6 -	39.9)
Norway	4,933	21.6	(20.2 -	23.0)	5.0	(4.2 -	6.0)	23.2	(19.5 -	27.7)
Sweden	6,814	24.6	(23.5 -	25.7)	5.5	(4.7 -	6.3)	22.3	(19.4 -	25.6)
Ireland and UK	**59,016**	**19.2**	**(18.8 -**	**19.6)**	**4.7**	**(4.4 -**	**4.9)**	**24.3**	**(23.0 -**	**25.6)**
Ireland	3,029	20.6	(19.0 -	22.3)	6.9	(5.8 -	8.2)	33.4	(28.5 -	39.2)
UK, England	46,571	19.5	(19.1 -	19.9)	4.7	(4.4 -	5.0)	23.9	(22.5 -	25.5)
UK, Northern Ireland	1,321	15.3	(13.2 -	17.7)	3.0	(1.8 -	5.0)	19.8	(12.3 -	31.8)
UK, Scotland	4,946	17.4	(16.2 -	18.6)	3.4	(2.8 -	4.3)	19.9	(16.1 -	24.5)
UK, Wales	3,149	18.8	(17.2 -	20.5)	5.4	(4.3 -	6.7)	28.6	(23.4 -	35.0)
Central Europe	**51,395**	**28.3**	**(27.9 -**	**28.7)**	**7.3**	**(7.0 -**	**7.6)**	**25.9**	**(24.9 -**	**26.9)**
Austria	8,295	28.2	(27.1 -	29.3)	7.9	(7.2 -	8.8)	28.1	(25.6 -	30.9)
Belgium	4,826	34.4	(33.1 -	35.9)	10.5	(9.4 -	11.7)	30.4	(27.5 -	33.6)
France	5,347	32.5	(31.2 -	33.9)	7.4	(6.6 -	8.4)	22.8	(20.3 -	25.5)
Germany	17,631	31.8	(31.1 -	32.5)	8.8	(8.2 -	9.3)	27.5	(25.9 -	29.3)
Switzerland	2,277	31.7	(29.6 -	34.0)	6.6	(5.2 -	8.4)	20.9	(16.7 -	26.3)
The Netherlands	13,019	19.0	(18.3 -	19.8)	4.0	(3.6 -	4.6)	21.3	(19.0 -	23.8)
Southern Europe	**35,276**	**25.9**	**(25.4 -**	**26.5)**	**7.5**	**(7.1 -**	**7.9)**	**28.8**	**(27.6 -**	**30.1)**
Croatia	4,441	21.0	(19.8 -	22.3)	10.9	(9.8 -	12.1)	51.7	(47.3 -	56.5)
Italy	22,138	28.3	(27.6 -	29.0)	7.2	(6.7 -	7.7)	25.4	(23.8 -	27.1)
Malta	307	19.7	(15.5 -	25.2)	-	(-	)	-	(-	)
Portugal	2,881	26.3	(24.7 -	28.0)	8.7	(7.6 -	10.0)	33.2	(29.4 -	37.5)
Slovenia	2,016	19.7	(18.0 -	21.6)	5.0	(3.9 -	6.3)	25.3	(20.3 -	31.5)
Spain	3,493	23.3	(21.8 -	24.8)	6.0	(5.1 -	7.0)	25.7	(22.3 -	29.7)
Eastern Europe	**31,814**	**18.0**	**(17.5 -**	**18.4)**	**5.8**	**(5.5 -**	**6.2)**	**32.4**	**(30.7 -**	**34.1)**
Bulgaria	6,690	14.1	(13.2 -	15.0)	5.1	(4.4 -	5.8)	35.9	(31.6 -	40.8)
Czech Republic	11,279	18.1	(17.3 -	18.9)	5.6	(5.0 -	6.2)	30.8	(27.9 -	33.9)
Estonia	1,431	19.5	(17.4 -	21.8)	5.5	(4.2 -	7.4)	28.5	(21.8 -	37.2)
Latvia	2,367	15.9	(14.4 -	17.6)	5.5	(4.4 -	6.9)	34.7	(28.3 -	42.6)
Lithuania	2,918	21.6	(20.1 -	23.2)	6.1	(5.1 -	7.2)	28.1	(24.0 -	32.9)
Poland	3,680	22.2	(20.8 -	23.6)	7.9	(7.0 -	9.1)	35.9	(31.9 -	40.3)
Slovakia	3,449	18.7	(17.4 -	20.1)	5.9	(5.0 -	7.0)	31.6	(27.2 -	36.7)
Europe	**202,584**	**26.0**	**(25.6 -**	**26.3)**	**6.9**	**(6.7 -**	**7.1)**	**26.6**	**(25.8 -**	**27.4)**

Age-standardised 5-year relative survival (%)



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	4,816	obs	45.1	25.3	22.3
		rel	45.2	25.5	22.5
45-54	16,461	obs	35.7	14.3	10.4
		rel	35.9	14.5	10.7
55-64	40,685	obs	30.7	9.8	6.5
		rel	30.9	10.1	6.9
65-74	62,087	obs	24.0	7.0	4.6
		rel	24.5	7.5	5.2
75+	78,535	obs	13.6	3.5	2.1
		rel	14.7	4.4	3.3
All cases	202,584	obs	25.4	8.8	6.3
		rel	26.0	9.3	6.9
Men (50%)					
15-44	2,849	obs	41.3	21.5	19.0
		rel	41.4	21.7	19.3
45-54	10,088	obs	33.0	13.8	9.1
		rel	33.2	13.1	9.4
55-64	24,031	obs	28.6	8.7	5.5
		rel	28.9	9.0	5.9
65-74	33,109	obs	22.8	6.6	4.4
		rel	23.4	7.2	5.2
75+	31,150	obs	13.8	3.5	2.1
		rel	15.0	4.6	3.3
All cases	101,227	obs	24.0	8.0	5.6
		rel	24.7	8.6	6.3
Women (50%)					
15-44	1,967	obs	50.4	30.9	27.2
		rel	50.5	31.0	27.3
45-54	6,373	obs	40.3	16.7	12.6
		rel	40.4	16.9	12.8
55-64	16,654	obs	34.0	11.6	8.1
		rel	34.2	11.8	8.3
65-74	28,978	obs	25.4	7.5	4.9
		rel	25.7	7.8	5.4
75+	47,385	obs	13.5	3.5	2.2
		rel	14.5	4.3	3.2
All cases	101,357	obs	27.4	10.0	7.3
		rel	27.9	10.4	7.9

Lepage c et al. Eur J Cancer. 2015 Oct;51(15):2169-2178. doi: 10.1016/j.ejca.2015.07.034. Epub 2015 Sep 26

Treatment of hepatocellular carcinoma by electrochemotherapy

Results of Phase I study

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Asist. Mihajlo Đokić, MD

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University Medical Centre Ljubljana
Slovenia

1

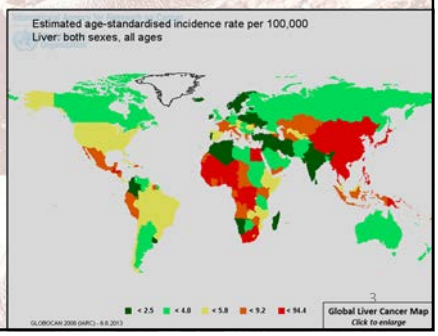
HEPATOCELLULAR CARCINOMA (HCC)

- Primary liver tumors are heterogeneous group that arise from liver cells.
- HCC is the most common (more than 90%).
- With intrahepatic cholangiocarcinoma represent 98.5%.

2

HCC

- Primary liver tumors are the 6th most common cancer in the world.
- The 3rd most common cause of cancer related death.
- The incidence is rising.
- Majority in Asia and Africa.



3

HCC

- The incidence is also rising in the developed world and has tripled in USA in the last 3 decades
- In Slovenia, incidence is 9.3 for males and 4.6/ 100000 for females.

4

What are the reasons behind such situation?

HCC - other etiological factors

1. Aflatoxins
2. Autoimmune hepatitis
3. Hemochromatosis
4. Alpha-1-antitrypsin deficiency
5. Wilson's disease
6. Budd-Chiari syndrome
7. Anabolics.

Patients

- Males : Females 2.5 : 1.
- HCC is uncommon in the first 4 decades of life and increases progressively thereafter with peak incidence in the 7th and 8th decades.

7

Diagnosis of early HCC-curative treatments

Trends in Western countries, 1980-2020

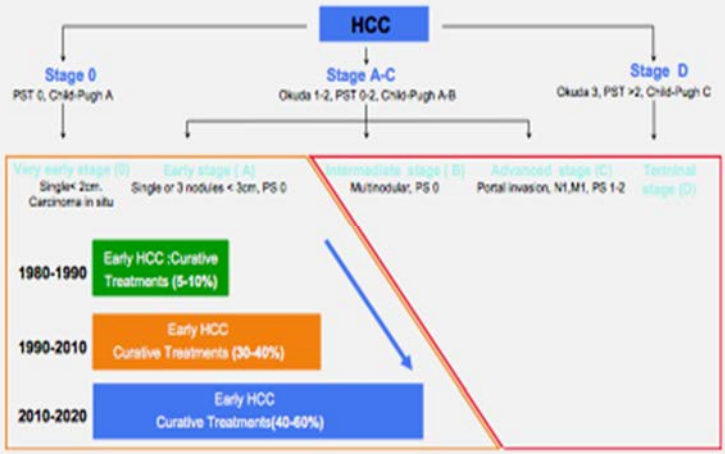
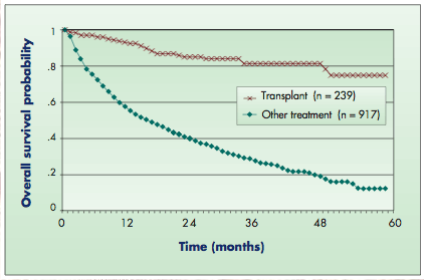


Fig. 1. Representation of the switch in the presentation of HCC in developed countries, as a result of implementation of surveillance among cirrhotic patients. Estimates of applicability of potentially curative therapies have been divided in three periods: until 1990: 5–10% of cases; 1990–2010: 30–40% of cases; 2010–2020: 40–60% of cases.

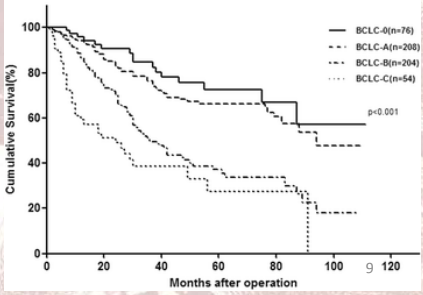
8

HCC - treatment options

- **Surgery**
  - Resection (5y – 50%)
  - Liver transplantation (5y - 80% (up to 100%))
- Ablation
  - RFA, Crio, IRE, **ECT**
- Embolization
  - TACE
  - SIRT (TARE)
- Targeted therapy
- Chemotherapy



Kaplan-Meier Curve



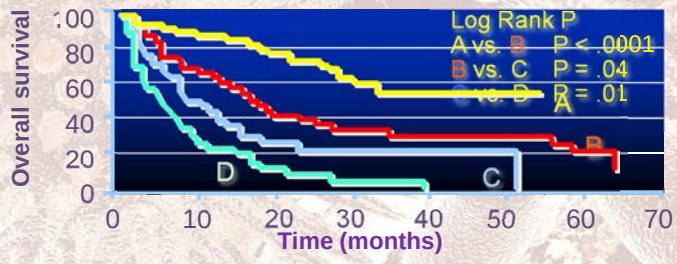
9

BCLC klasifikacija – "thin red surgical line"

Table 1. Barcelona Clinic Liver Cancer Staging System

Stage	Tumor burden	Child–Pugh class	Performance status[a]	Median survival
Very early (0)	Single lesion <2 cm	A	0	°
Early (A)	Single lesion <5 cm or three lesions <3 cm each	A–B	0–2	53 months
Intermediate (B)	Single lesion >5 cm or multiple lesions, with largest >3 cm	A–B	0–2	16 months
Advanced (C)	Any tumor burden	A–B	1–2	7 months
Terminal (D)	Any tumor burden	C	>2	3 months

Adapted from [11].



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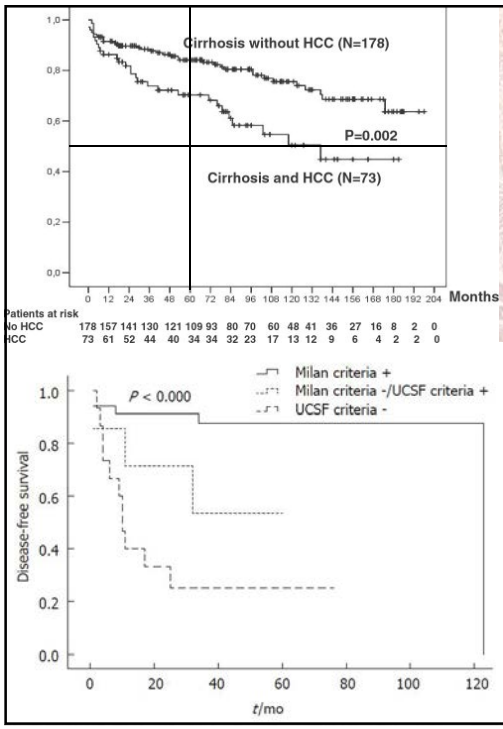


HCC

Milan

1<5cm

3<3cm

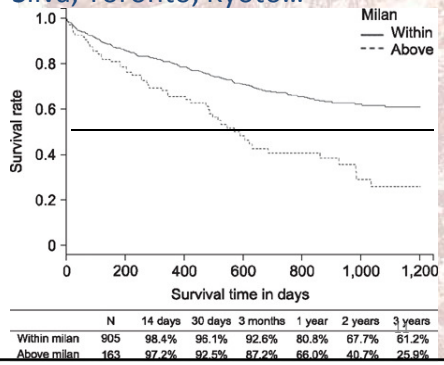
UCSF kriterij

1<6,5cm

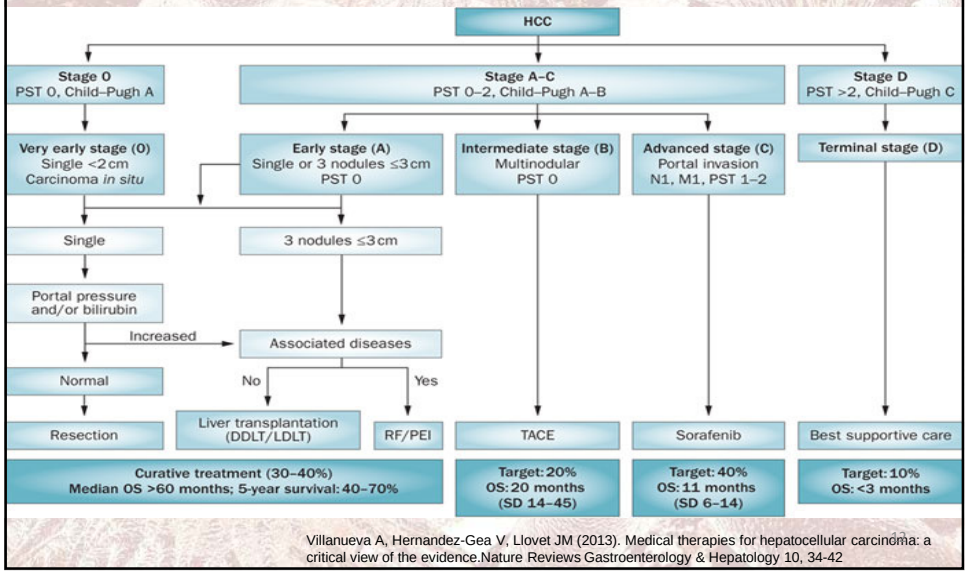
largest 4,5 cm and

overall <8cm

Silva, Toronto, Kyoto…

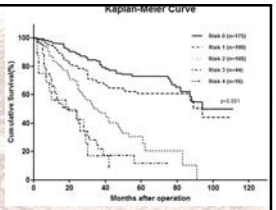


HCC



Villanueva A, Hernandez-Gea V, Llovet JM (2013). Medical therapies for hepatocellular carcinoma: a critical view of the evidence.Nature Reviews Gastroenterology & Hepatology 10, 34-42

HCC



- Most of the patients receive some combination of treatment through the course of their disease, depending on the disease stage.
- Numerous staging systems that are being used worldwide.
- Trying to determine the best treatment option for each patient.

13

HCC

- The proper treatment mainly depends on the following:
- Location
- Number
- Size of tumors
- Quality of liver parenchyma
  - Cirrhosis or absence of it and when present, the stage of cirrhosis

14

HCC

Other important factors to consider include

- Age
- General health
- Patients concerns about treatment and possible side effects.

15

Phase I study????

- Edhemović *et al.* provided evidence of the feasibility, safety and efficacy of electrochemotherapy in the treatment of colorectal liver metastases.
- CRLM are histologically different from primary liver tumors, especially HCC.

16

Phase I study

- Patients with HCC have often poor performance status compared to the patients with other liver malignancies.
- The safety of the method is of outmost importance due to underlying disease (cirrhosis, hepatitis, portal thrombosis, ascites, coagulopathy etc.).

17

Phase I study

- Phase I study was designed at Clinical Department of Abdominal Surgery, University Clinical Center Ljubljana in cooperation with Institute of oncology Ljubljana and with Faculty of Electrical Engineering, University of Ljubljana.
- The study was approved by the National Medical Ethics Committee and registered at the ClinicalTrials.com with approval number NCT02291133.

18

Phase I study

- The main goal was
  - Assess the feasibility and safety
  - To evaluate toxicity and effectiveness of electrochemotherapy with bleomycin in treatment of primary liver tumors.
- Secondary goal was evaluation of treatment by modified Choi criteria (CT/MRI)
  - The local response of treated tumors was expected to be achieved.
  - difference in size and density.

19

Phase I study

- Ten patients were included in phase I study.

20

Phase I study
Inclusion Criteria

- Patients with HCC.
- Patients with tumors not suitable for potentially curative treatment.
  - Patients with smaller (< 5 cm) tumors, unsuitable for resection, liver transplantation and RFA due to position of the tumor

21

Phase I study
Inclusion Criteria

- Treatment was offered to the patients who refused standard treatments.
- HCC confirmed with radiological imaging and/or histology.
- Age more than 18.
- Life expectancy more than 3 months.
- Performance status Karnofsky ≥ 70 or (World Health Organization) WHO < or 2.

22

Phase I study
Inclusion Criteria

- Informed consent.
- Unanimous decision of the multidisciplinary team for liver tumors before entering the trial (surgeon, gastrooncologist and radiologist).

23

Phase I study
Exclusion Criteria

- Synchronous primary tumors,
- Extrahepatic disease,
- Poor performance status,
  - Clinically significant ascites.
- Cumulative dose of 250 mg/m2 bleomycin received ((15mg/m^2) max 30 mg in study)
- Allergic reaction to bleomycin.
- Impaired kidney function (kreatinin > 150 µmol/l).

24

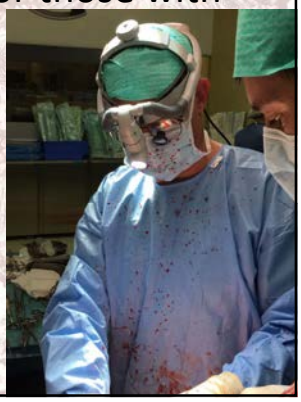
Phase I study

- Before and after electrochemotherapy, primary liver tumor was evaluated by contrast enhanced computed tomography (CE-CT) or magnetic resonance (MRI).
- The treatment response was evaluated by two radiologists, one of them blind for clinical data.

25

Phase I study

- All patients were presented at the MDM meeting.
- A pretreatment plan was made for those with variable electrodes geometry.
- The treatment
  - General Anest
  - open surgery
  - US



TREATMENT PARAMETERS

- Bleomycin 15mg/m2
- Variable electrodes with 3 or 4 cm active part
- Usually 5 electrodes were used according to the pretreatment plan (UL Faculty of Electrical Engineering)
- IO US was used to determine position and size of the tumor

27

RESULTS

- 10 patients
- Median age 69.3 years (57-78)
- 3 females and 7 males
- 1 patient didn‘t reach 4 months follow up
  - pneumonia
- 4/10 histologically proven HCC
- 3/10 had previous treatment (TACE or RFA)
- 1/10 had been operated before and had ECT
- 6/10 had ECT as a primary treatment

28

RESULTS

- 5/10 patients had lesions that were centrally located
- In 10/17 lesions fixed electrodes were used
- 7/17 electrodes with variable geometry were used
- Median diameter for treated lesions was 23mm (10 to 47 mm)

29

RESULTS

- 15/17 showed complete response after 4 months follow up (26 months)
- 2/17 partial response according to the Choi criteria
  - Both lesions were treated with variable electrodes
  - Diameter of lesions with partial response was 45mm + and 39 mm

30

RESULTS

- Hospital stay – 7,6 d (3-21)
- No perioperative mortality
- 2/10 patients perioperative morbidity;
  - Development of ascites due to the transient liver failure
  - Both complications resolved after conservative measures were applied
  - Clavien-Dindo classification 3A. and 3B.

31

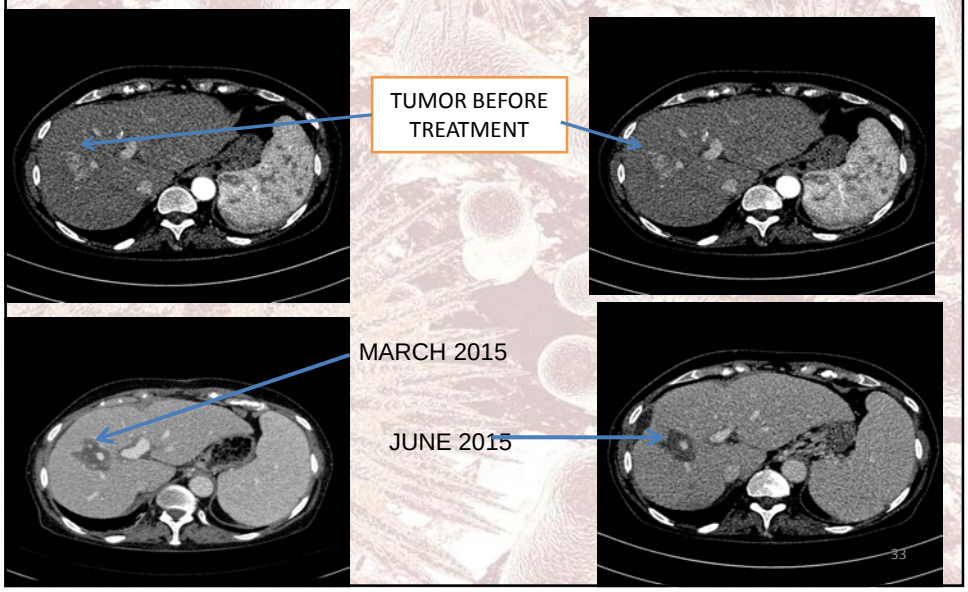
CASE No I
februar 2015

- 73 year old female
- HCC – centrally located
- r = 4cm
- Chirrhosis Child-Pugh B = 6
- Chronic hepatitis C virus
- Pulmonary sarcoidosis
- Hemolitic anemia

Th: medrol

32

CASE no I
ECT februar 2015



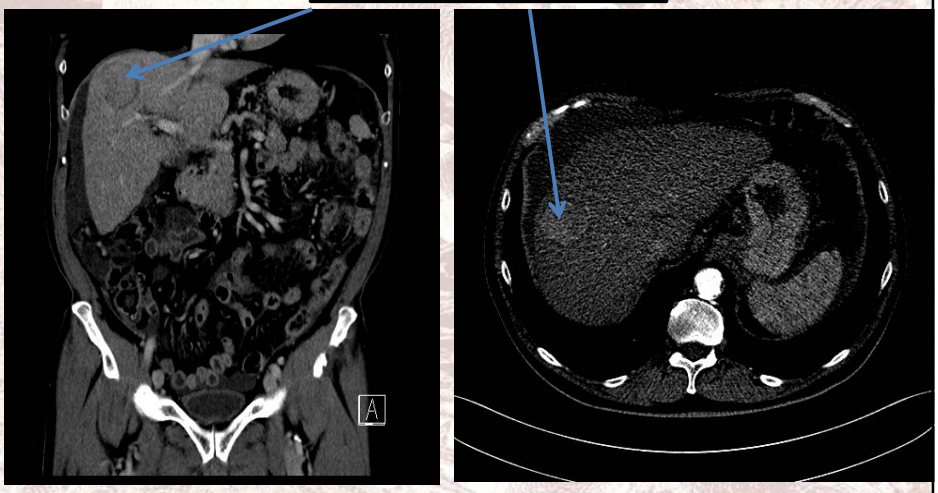
Case No II
april 2015

- 71 year old male
- 1 lesion
- Sg 8 r=4.7cm
- Cirrhosis – Child-PughB= 6
- Art Hipertension
- Astma

34

CASE No II
april 2015

Tumor before treatment



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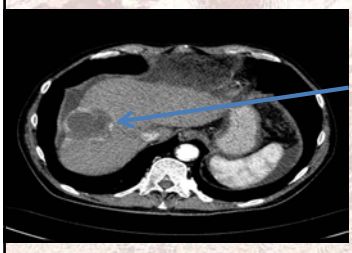
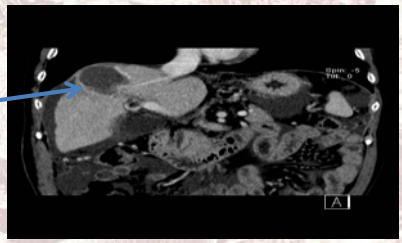
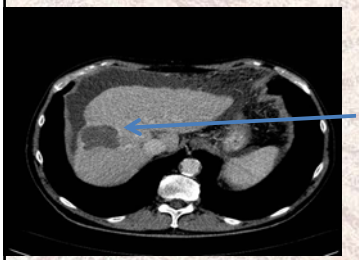
CASE No II

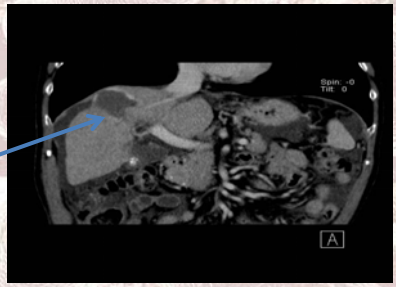


Complete response 1 month after the treatment





Complete response 4 months after the treatment

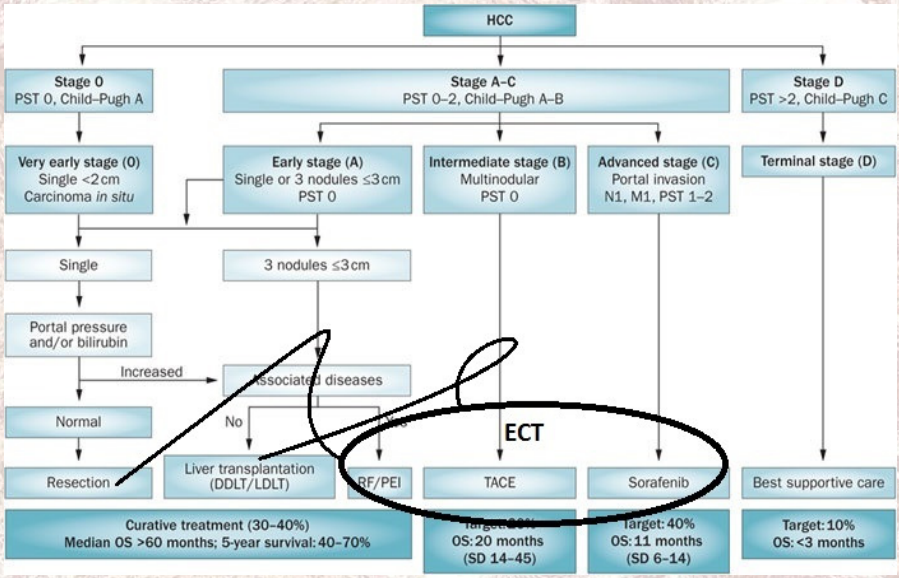


36

Case No III
avgust 2015

- 63 year old female
- Right hemihepatectomy 2009 (57y)
- 2011 limfadenectomy (1 lnn with HCC)
- First ECT 2012 Sg. 4a
- Patohistologically confirmed HCC Sg. 2 2015
  r=2.3cm on LHV (only one)

37



38

Take home

- ECT in HCC is safe and effective.
- Technological development is necessary.
  - Less invasive
  - Imaging
  - Planing
- Phase II has started.

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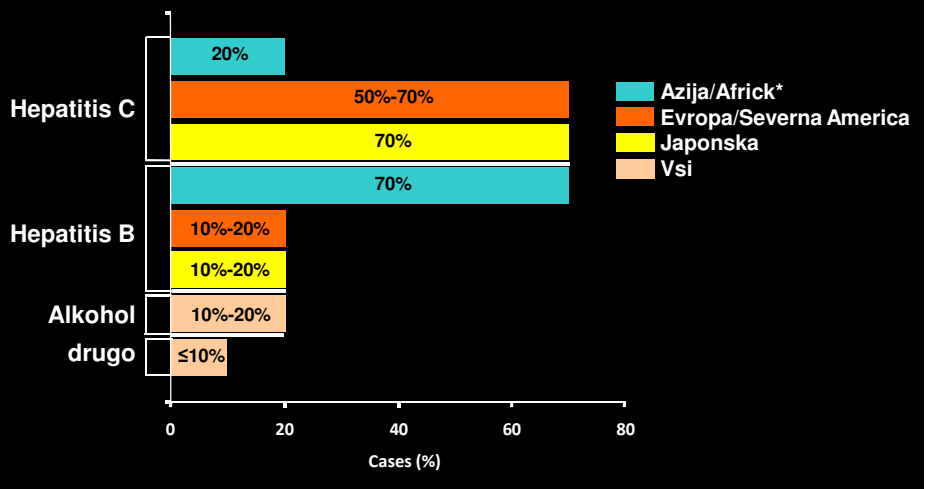
- Mihajlo Đokić, dr. med.
  e-mail: mihajlo.djokic@kclj.si

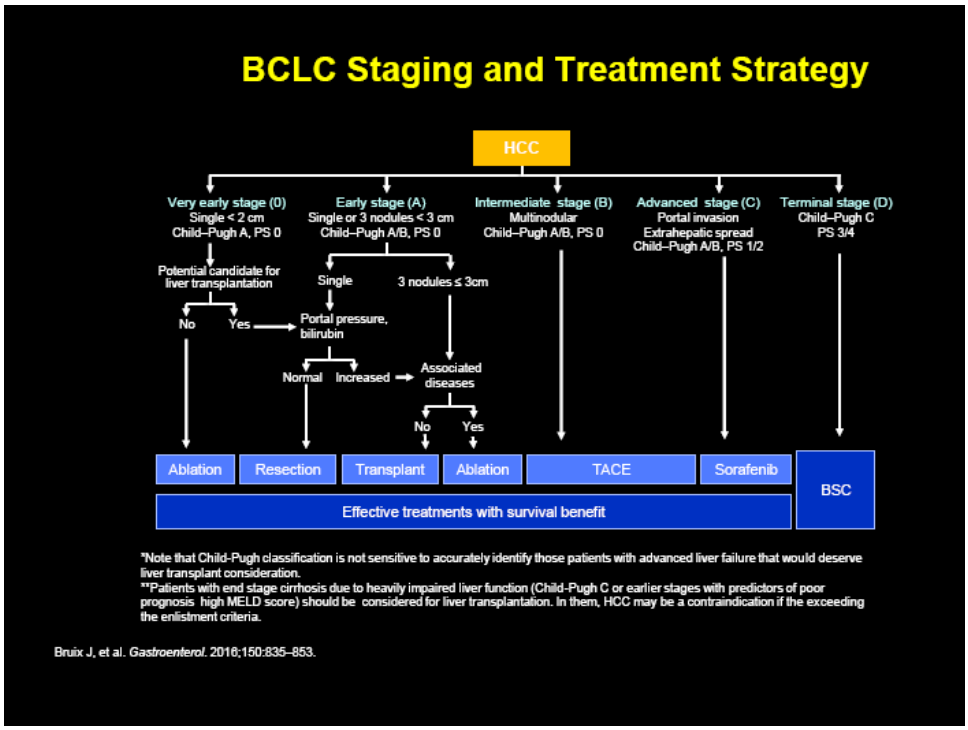
40

Novosti v sistemskem zdarvljenju HCC

Prof.dr.Janja Ocvirk, dr.med.
Onkološki inštitut Ljubljana

Dejavniki tveganja za HCC – po regijah





Kontraindikacije za kirurško zdravljenje

- Izven jetrna bolezen
- Multipli ali bilobarni tumorji
- Napredovala jetrna bolezen
- Zajetje glavnega žolčnega voda
- Prisotnost tromboze debla vene porte ali spodnje vene cave

Predlagane podskupine in zdravljenje bolnikov v vmesnem stadiju

	B1	B2	B3	B4	Quasi-C
Liver function	CPT 5–7	CPT 5–6	CPT 7	CPT 8–9*	CPT-A
ECOG PS	PS 0	PS 0	PS 0	PS 0-1	PS 0
Beyond Milan and within Up to 7*	IN	OUT	OUT	ANY	ANY
PVT	No	No	No	No	Yes†
1st treatment option	TACE	TACE or TARE	- - - - -	BSC	Sorafenib
Alternative	LT TACE+ Ablation	Sorafenib	Research trials TACE Sorafenib	LT**	TACE or TARE

Severe/refractory ascites and/or jaundice; ** only if Up-to-7 IN and PSO; †segmentary or subsegmentary
BSC, best supportive care; LT, liver transplantation; PVT, portal vein thrombosis; TARE, transarterial radioembolization.

Bolondi in L sod. Sem Liv Dis 2012;32:348-359

Absolutne kontraindikacije za cTACE: ESMO priporočila

- Dekompenzirana ciroza (Child–Pugh B ≥8), vključno z:
  - zlatenico
  - klinično encefalopatijo
  - refraktornim ascitesom
- Tumorska masa večjega dela obeh lobusov
- Pomembno zmanjšan portalen venski pretok (npr. Okluzija portalne vene)
- Tehnične kontraindikacije za jetrno intraarterielno zdarvljenje (npr. a-v fistula)
- Bilio-enterična anastamoza ali biliarni stenti
- Ledvična insuficienca (klirens kreatinina <30 mL/min)

- cTACE, conventional transarterial chemoembolization; ESMO, European Society of Medical Oncology.

Verslype C et al. ESMO guidelines. Ann Oncol 23(Suppl 7):vii41–8. – based on Raoul J-L et al. Cancer Treat Rev 2011;37:212–20

Relativne kontraindikacije za cTACE: mnenje ekspertov

- Tumor ≥10 cm
- Komorbiditeta s slabo funkcijo urganov:
  - Aktivne kardiovaskularne bolezni*
  - Aktivne bolezni pljuč†
- Nezdarvljene varice z virokim tveganjem krvavitve
- Okluzije biliarnega sistema ali papile (stent ali po kirurgiji)

Raoul J-L et al. Cancer Treat Rev 2011;37:212–20

Priporočila za TACE za intermediaren HCC

Guideline	Recommendation	Contraindications
AASLD[1]	1st-line non-curative for non-surgical patients with large/multifocal tumours	EHS, vascular invasion
EASL–EORTC[2]	BCLC-B, multi-nodular asymptomatic tumours, without vascular invasion or EHS	Decompensated liver disease, advanced liver dysfunction, macroscopic invasion or EHS
ESMO[3]	BCLC-B, excellent liver function and multinodular asymptomatic tumours without MVI or EHS	Decompensated cirrhosis, MVI, EHS

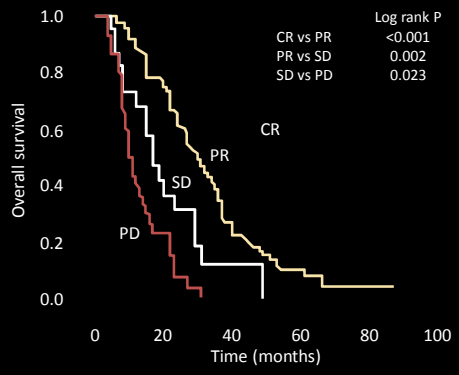
AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Clinic Liver Cancer; EASL, European Association for the Study of the Liver; EHS, extrahepatic spread; EORTC, European Organisation for Research and Treatment of Cancer; ESMO, European Society for Medical Oncology; MVI, microvascular invasion

1. Bruix J, Sherman M. Hepatology 2011;53:1020–2; full guidelines available at: http://www.aasld.org/practiceguidelines/Pages/SortablePracticeGuidelinesAlpha.aspx; 2. EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012;56:908–43; Available at: http://www.easl.eu/assets/application/files/d38c7689f123edf_file.pdf;
3. Verslype C et al. ESMO guidelines. Ann Oncol 23(Suppl 7):vii41–8.

Preživetje in odgovor po mRECIST po TACE

PR	2.75 (1.96– 3.87)	<0.001
PD	16.06 (9.76–26.43)	<0.001

- C index for mRECIST criteria was 0.72 (95% CI: 0.68–0.76)

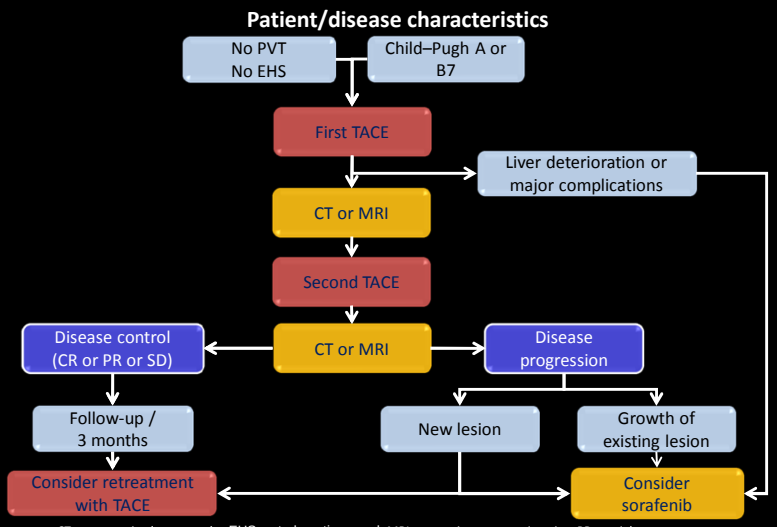


Survival of 332 BCLC stage B patients; tumour responses determined with mRECIST

*Numbers in parentheses are the 95% CIs
†Data were generated from the univariate Cox regression model

Adapted from Shim JH et al. Radiology 2012;262:708–18

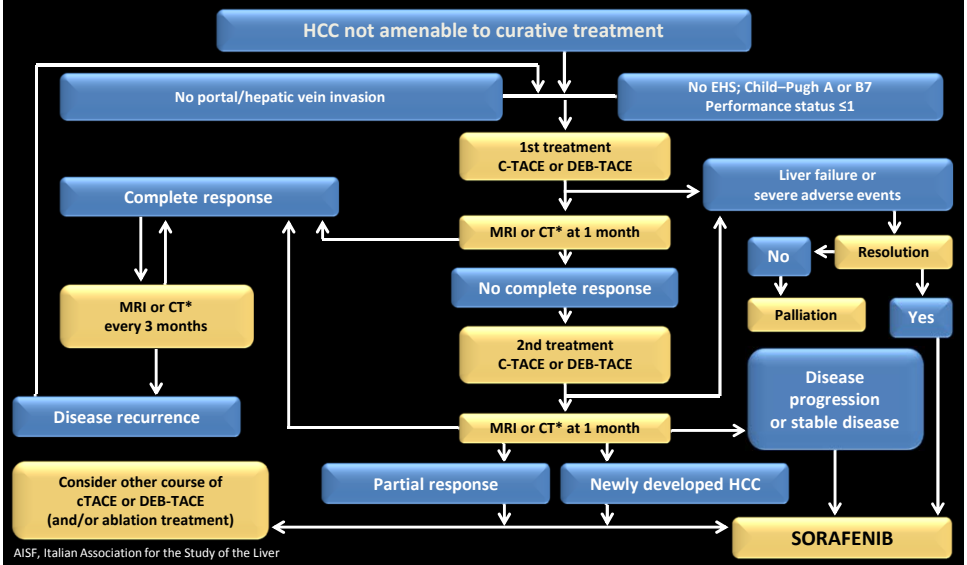
Predlagan algoritem za TACE pri intermediarnih HCC



CR, complete response; CT, computerized tomography; EHS, extrahepatic spread; MRI, magnetic resonance imaging; PR, partial response; PVT, portal vein thrombosis; SD, stable disease; TACE, transarterial chemoembolization
Raoul J-L et al. Cancer Treat Rev 2011;37:212–20

AISF algoritm za TACE (2013)

Digestive and Liver Disease
journal homepage: www.elsevier.com/locate/dld
Progress Report
epub. DOI: 10.1016/j.dld.2013.01.012
Position paper of the Italian Association for the Study of the Liver (AISF): The multidisciplinary clinical approach to hepatocellular carcinoma



AISF, Italian Association for the Study of the Liver
AISF. Dig Liver Dis 2013 (In press)

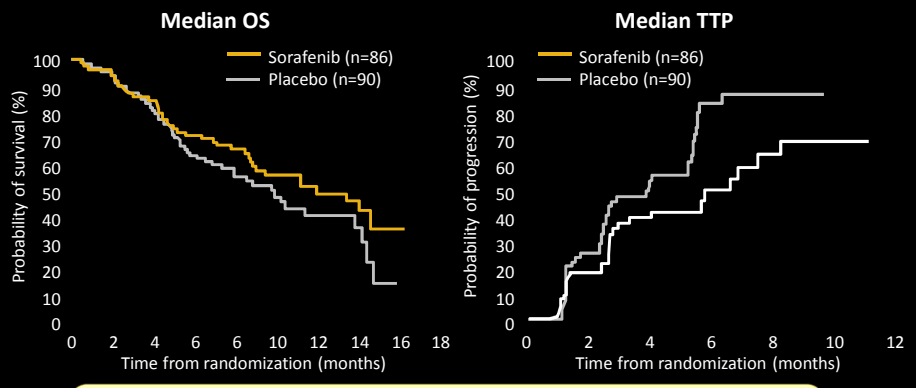
ART točkovnik -Assessment for Retreatment with TACE

- Developed by multivariate regression analysis of
  - baseline characteristics
  - radiological response after 1st TACE (EASL-response criteria)
  - changes of liver function after the 1st TACE
- Determined prior to 2nd TACE in BCLC-A*/B patients, who received ≥ 2x TACE
- Training cohort: n=107 (Vienna), validation cohort: n=115 (Innsbruck)

ART score category	Points
Absence of radiological tumour response	1 (0 if present)
AST increase >25%	4 (0 if absent)
Increase in CP score by 1 point	1.5 (0 if absent)
Increase in CP score by ≥2 points	3 (0 if absent)

*BCLC-A not suitable for liver transplantation/local ablative treatment
AST, aspartate transaminase; BCLC, Barcelona Clinic Liver Cancer; CP, Child–Pugh; EASL, European Association for the Study of the Liver; TACE, transarterial chemoembolization
Sieghart W et al. Hepatology 2013 Jan 12. doi: 10.1002/hep.26256

Učinkovitost sorafeniba pri bolnikih po TACE



Sorafenib: n=86; placebo: n=90
Median OS: 11.9 vs 9.9 months (HR: 0.75; CI: 0.49–1.14)
Median TTP: 5.8 vs 4.0 months (HR: 0.57; CI: 0.36–0.91)

Sorafenib pri bolnikih neprimernih za TACE oz refraktornih na TACE

Intermediaren HCC je zelo raznolika skupina bolnikov

Že izhodiščno niso vsi bolniki primerni za TACE

Bolniku ponudimo naslednjo možno zdarvljenje za isti stadij oz nasleden stadij po BCLC ali nasleden prognostičen stadij

Učinkovitost sorafenib pri BCLC-B bolnikih, ki so neprimerni za TACE ali TACE refraktorni (brez odgovora po 2 TACE)

Odločitev o zdarvljenju temelji na RR in ART točkovniku

Bolniki z radiološkim odgovorjem na zdravljenje na TACE glede na mRECIST/EASL živijo dalj

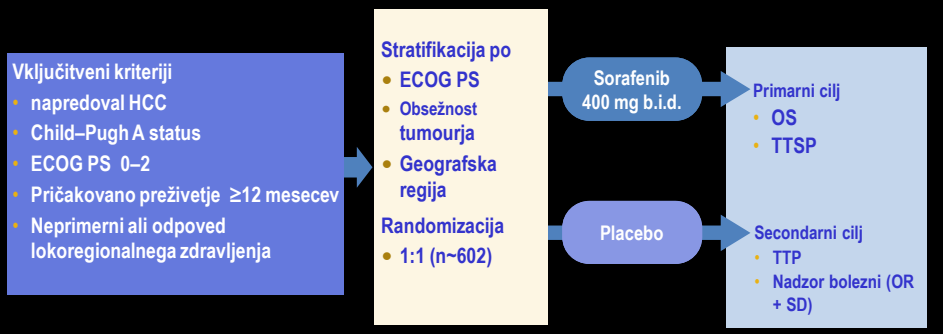
Pri vsaki TACE obstaja tveganje za jetrno počkodbo, ki lahko vpliva na prognozo

Vrednost ≥2.5 točk po ART točkovniku označuje bolnike, ki zelo verjetno ne bodo iemli dobrobita od naslednje TACE

Sorafenib priporočajo za:

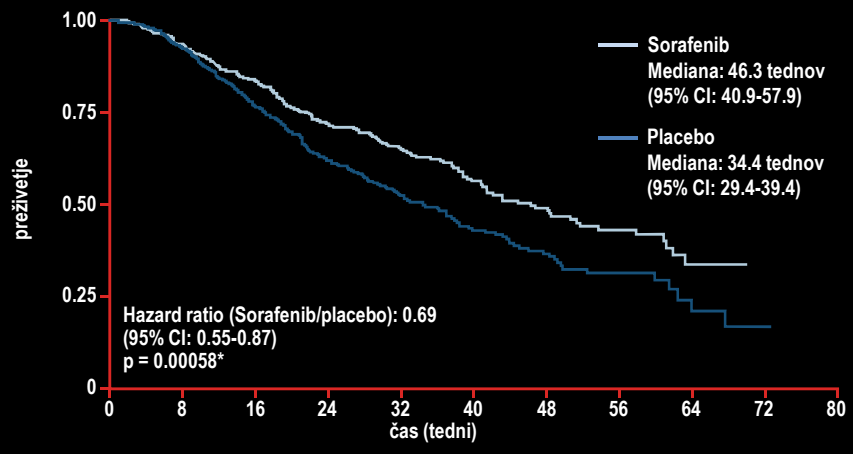
- bolnike z poslabšanjem jetrne funkcije ali pomembnimi NU po 1. TACE
- Progres ali mirovane bolezni po 2. TACE
- delnem odgovoru po 2 TACE

SHARP faza III: Sorafenib vs placebo pri napredovalem HCC



- **Zdravljenje do radiografskega ali simptomatskega progresa ali neželenih učinkov, ki so vodili v prekinitev zdravljenja**
- **Cikel zdravljenja – 6 tednov**

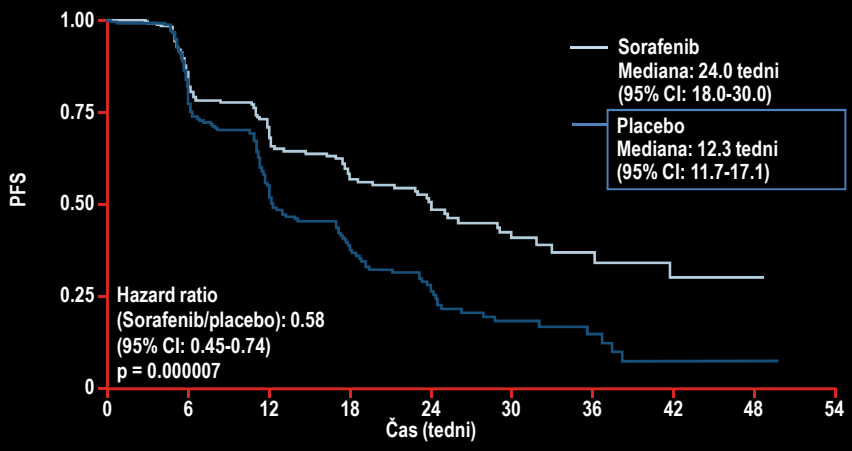
SHARP: vpliv na celokupno preživetje



*O'Brien–Fleming statistično signifikanten p = 0.0077

Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP – vpliv na PFS



Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP - odgovor na zdravljenje

	Sorafenib N = 299	Placebo N = 303
	n (%)	n (%)
Celokupni odgovor		
popoln odg. (CR)	0	0
delni odg. (PR)	7 (2.3)	2 (0.7)
Mirovanje bolezni (SD)	211 (71)	204 (67)
Progres (PD)	54 (18)	73 (24)
Ni bilo določeno	27 (9)	24 (8)
Kontrola bolezni (DCR)**	130 (44)	96 (32)

**DCR = CR + PR + SD vsaj 28 dni od prve evidence

Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP - varnost

	Sorafenib N = 297	Placebo N = 302
Resni neželeni učinki (%)	52	54
Resni neželeni učinki zaradi zdravila (%)	13	9
Neželeni učinki, ki so vodili v ukinitev zdravljenja (%)	32	35

Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP – neželeni učinki

	Sorafenib N = 297		Placebo N = 302	
Neželeni učinki	Vsi (%)	3/4 (%)	vsi (%)	3/4 (%)
Kateri koli	98	39/6	94	24/8
Diareja	55	10/<1	25	2
Bolečina (abdomen)	31	9	26	5/1
Izguba teže	30	2	10	1
Anoreksija	29	3	18	3/<1
Bruhanje	24	1	20	3
Sindrom roka - noga	21	8	3	<1
Izpuščaj	19	1	14	0
Slabost	15	2	11	2
Alopecija	14	0	2	0
Srbečica	14	<1	11	<1
Zaprtje	14	0	10	0
Suha koža	10	0	6	0

Llovet JM. Proc Am Soc Clin Oncol 2007

Sorafenib pri HCC

- Do Sorafeniba je bilo sistemsko zdarvljenje HCC skoraj neučinkovito.
- Rezultati SHARP kažejo, da Sorafenib vpliva na preživetje napredovalega, neresektabilnega HCC.
- Sorafenib je prvo učinkovito sistemsko zdarvljenje, napredovalega neresektabilnega HCC
- Adjuvanto (post-resekcijsko ali post-ablativno zdr.) v fazi raziskovanja

rezultati SHARP in vsakodnevne uporabe sorafeniba pri intermediarnem HCC

SHARP[1] BCLC-B subgroup	• **Increased OS and TTP with sorafenib (n=54) vs placebo (n=51)** – Median OS: 14.5 vs 11.4 months (HR: 0.72; 95% CI: 0.38–1.38) – Median TTP: 6.9 vs 4.4 months (HR: 0.47; 95% CI: 0.23–0.96)
SHARP[1] previous TACE subgroup	• **Increased OS and TTP with sorafenib (n=86) vs placebo (n=90)** – Median OS: 11.9 vs 9.9 months (HR: 0.75; 95% CI: 0.49–1.14) – Median TTP: 5.8 vs 4.0 months (HR: 0.57; 95% CI: 0.36–0.91)
SOFIA[2]	• **Good efficacy demonstrated in BCLC-B HCC** – Longer survival in BCLC-B vs BCLC-C patients: 20.6 vs 8.4 months
INSIGHT[3]	• **Good efficacy demonstrated in BCLC-B HCC** – Longer survival in BCLC-B vs BCLC-C patients: 19.6 vs 14.5 months
GIDEON interim analysis[4]	• **Similar safety profile for sorafenib across BCLC stages**

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; TTP, time to progression
1. Bruix J et al. J Hepatol. 2012;57:821–9; 2. Iavarone M et al. Hepatology 2011;54:2055–63; 3. Ganten TM et al. EMSO 2012;poster 77;
4. Lencioni R et al. Eur J Cancer 2011;47 (Suppl 1):abstract 6500

- Ali ena doza odgovarja vsem?
- NE

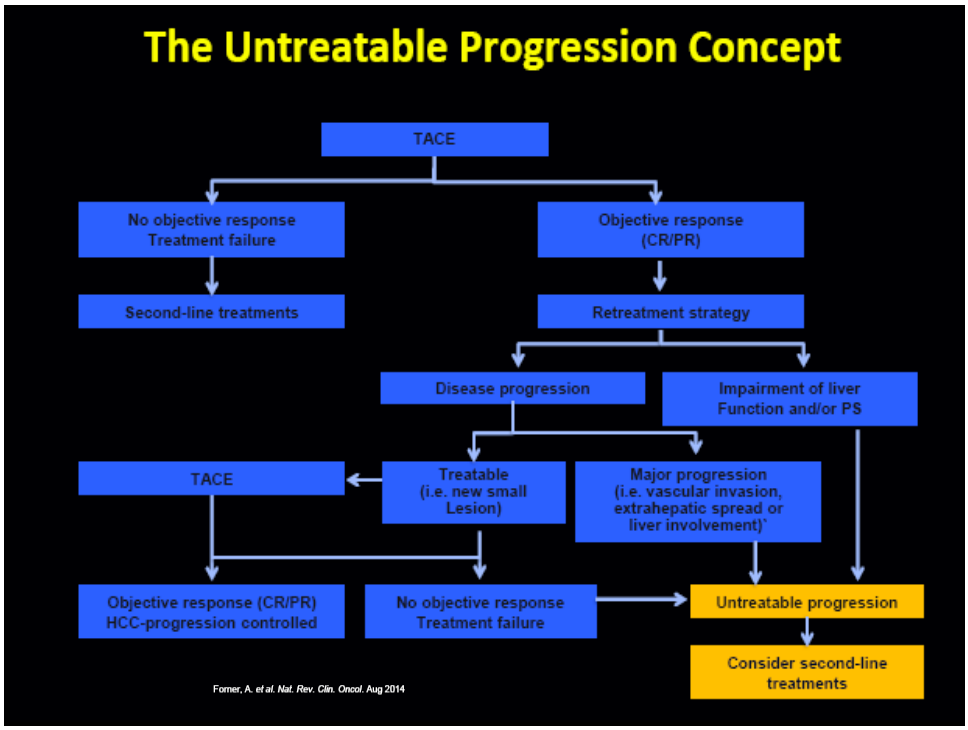
Potencialne možnosti zdrrvlejnja HCC po progresu

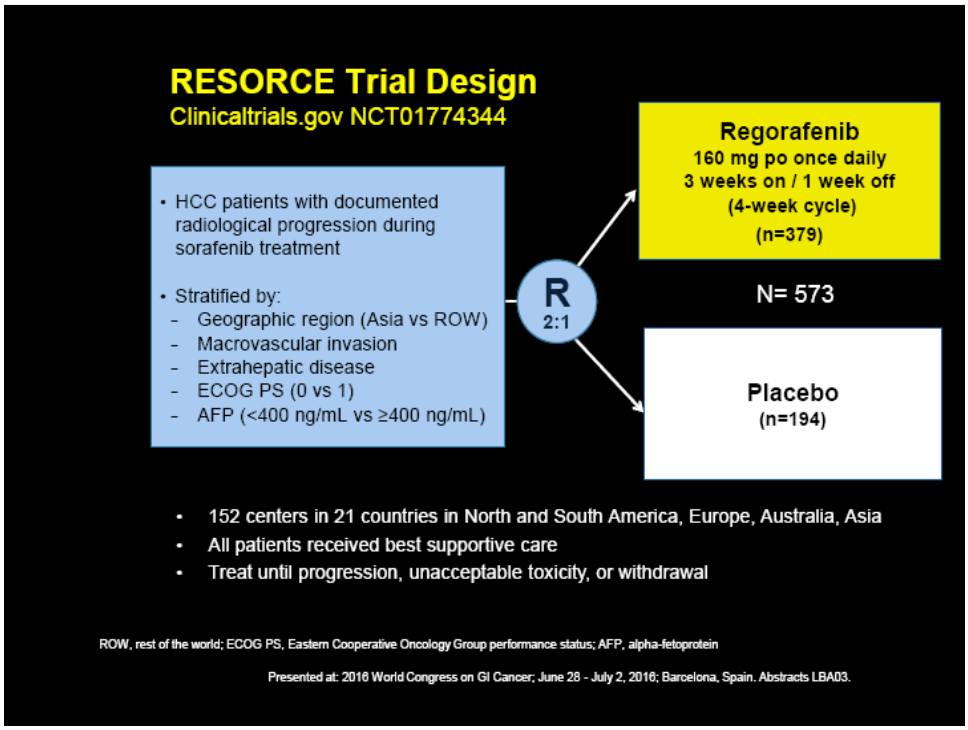
- Nadaljevanje sorafeniba?
- Eskalacija doze sorafenib?
- Kombinirana terapija?
- Klinične raziskave?
- Dobro podporno zdravljenje?

Druga-linija – raziskave faze III pri napredovalem HCC

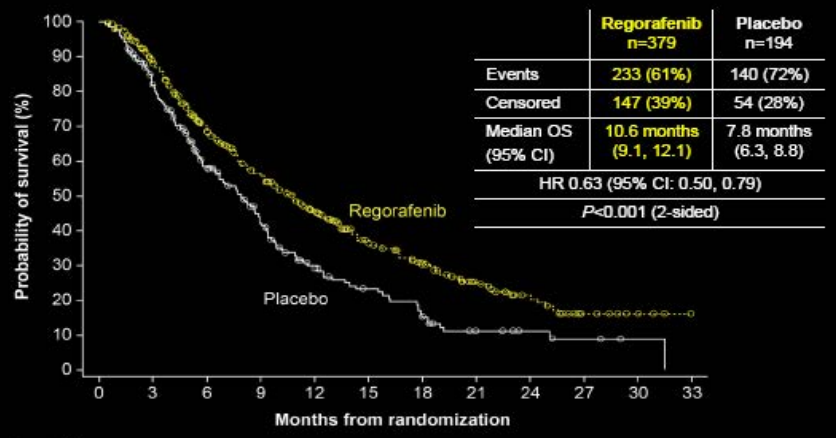
• Brivanibvs. placebo1	• Neg
• •Everolimusvs. placebo2	• Neg
• •Ramucirumabvs. placebo3	• Neg
• •ADI-PEG vs. placebo4	• Neg
• •DoxorubicinTransdrugvs placebo5	
• •Tivantinibvs. placebo6	
• •Regorafenibvs. placebo7	• poz
• •Cabozantinibvs placebo8	

1. LlovetJM, et al. *J ClinOncol*. 2013;31(28):3509-3516; 2. Zhu AX, et al. JAMA. 2014;312(1):57-67; 3. Zhu AX, et al. Lancet Oncol. 2015;16(7):859-870; 4. Abou-Alfa GK, et al. J ClinOncol. 2016;34(suppl): Abstract 4017; 5. Available at: www.clinicaltrials.gov. NCT01655693; 6. Available at: www.clinicaltrials.gov. NCT0175576; 7. BruixJ, et al. Presented at World GI 2016; Abstract LBA-03; 8. Available at: www.clinicaltrials.gov . NCT01908426;
ASCO 2016 WCGIC 2016 **Second-line PhaseIII trialsin advancedHCC**


The Untreatable Progression Concept
TACE
No objective response
Treatment failure
Objective response
(CR/PR)
Second-line treatments
Retreatment strategy
Disease progression
Impairment of liver
Function and/or PS
TACE
Treatable
(i.e. new small
Lesion)
Major progression
(i.e. vascular invasion,
extrahepatic spread or
liver involvement)`
Objective response (CR/PR)
HCC-progression controlled
No objective response
Treatment failure
Untreatable progression
Consider second-line
treatments
Forner, A. et al. Nat. Rev. Clin. Oncol. Aug 2014


RESORCE Trial Design
Clinicaltrials.gov NCT01774344
• HCC patients with documented radiological progression during sorafenib treatment
• Stratified by:
- Geographic region (Asia vs ROW)
- Macrovascular invasion
- Extrahepatic disease
- ECOG PS (0 vs 1)
- AFP (<400 ng/mL vs ≥400 ng/mL)
R
2:1
Regorafenib
160 mg po once daily
3 weeks on / 1 week off
(4-week cycle)
(n=379)
N= 573
Placebo
(n=194)
• 152 centers in 21 countries in North and South America, Europe, Australia, Asia
• All patients received best supportive care
• Treat until progression, unacceptable toxicity, or withdrawal
ROW, rest of the world; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein
Presented at: 2016 World Congress on GI Cancer; June 28 - July 2, 2016; Barcelona, Spain. Abstracts LBA03.

Regorafenib vs Placebo in Second Line Overall Survival (OS)



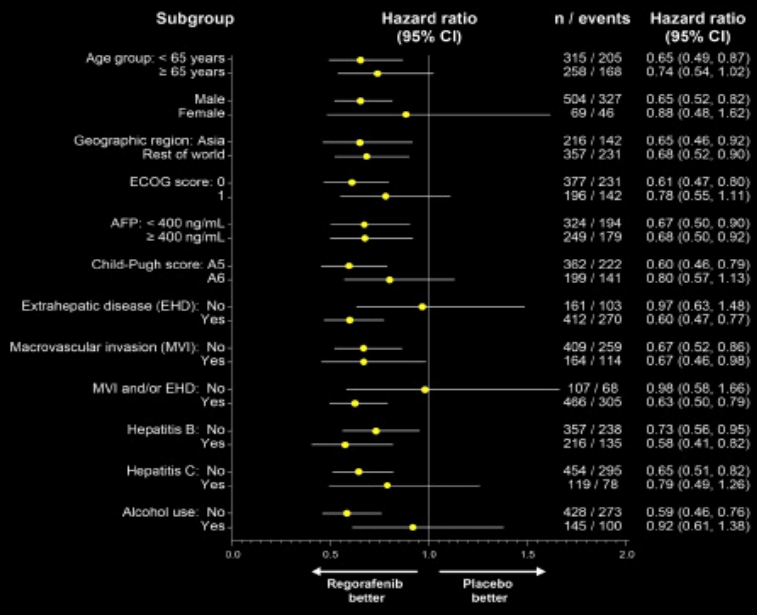
	Regorafenib n=379	Placebo n=194
Events	233 (61%)	140 (72%)
Censored	147 (39%)	54 (28%)
Median OS (95% CI)	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
HR 0.63 (95% CI: 0.50, 0.79)		
P<0.001 (2-sided)		

Number at risk

Regorafenib	379	316	224	170	122	78	54	34	21	10	4	0
Placebo	194	149	95	62	37	26	16	8	5	3	1	0

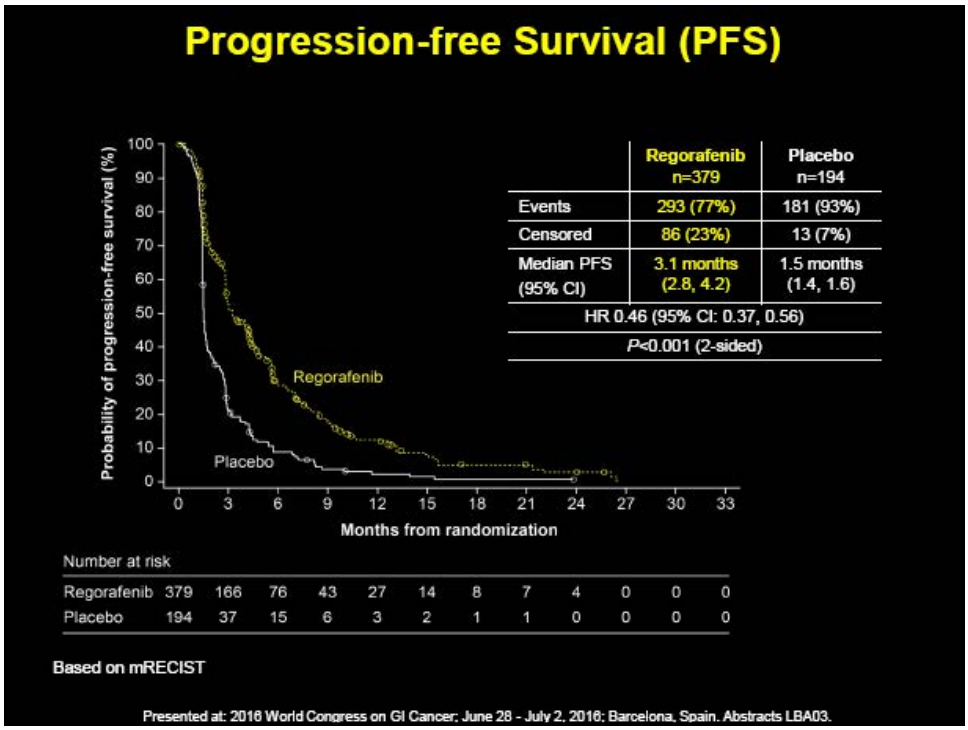
Presented at: 2016 World Congress on GI Cancer; June 28 – July 2, 2016; Barcelona, Spain. Abstracts LBA03.

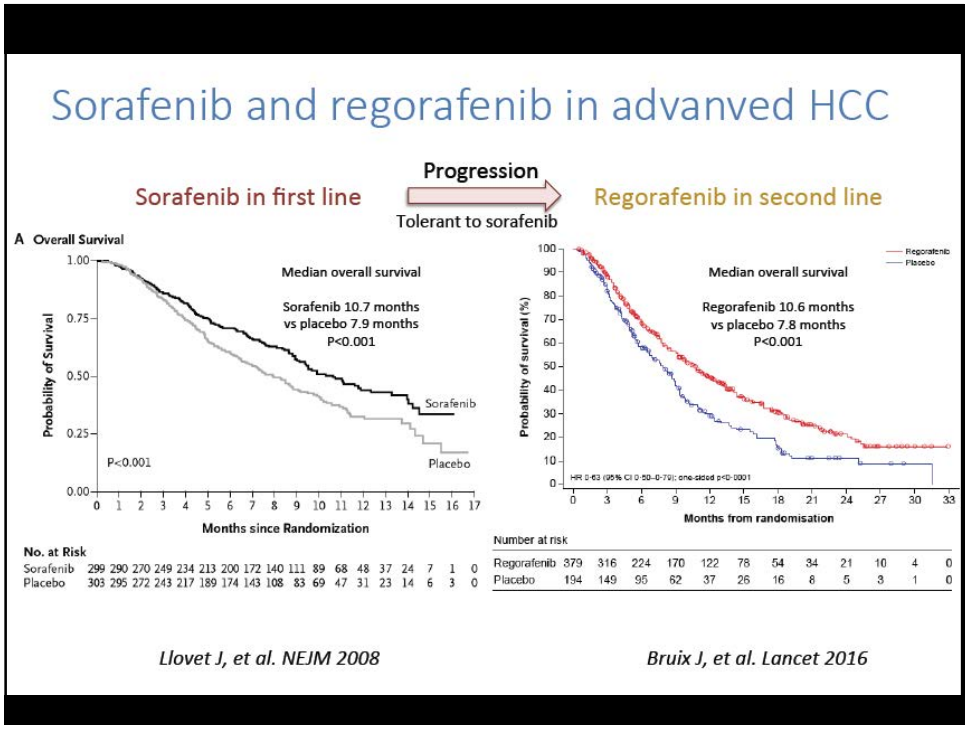
Subgroup Analysis of OS

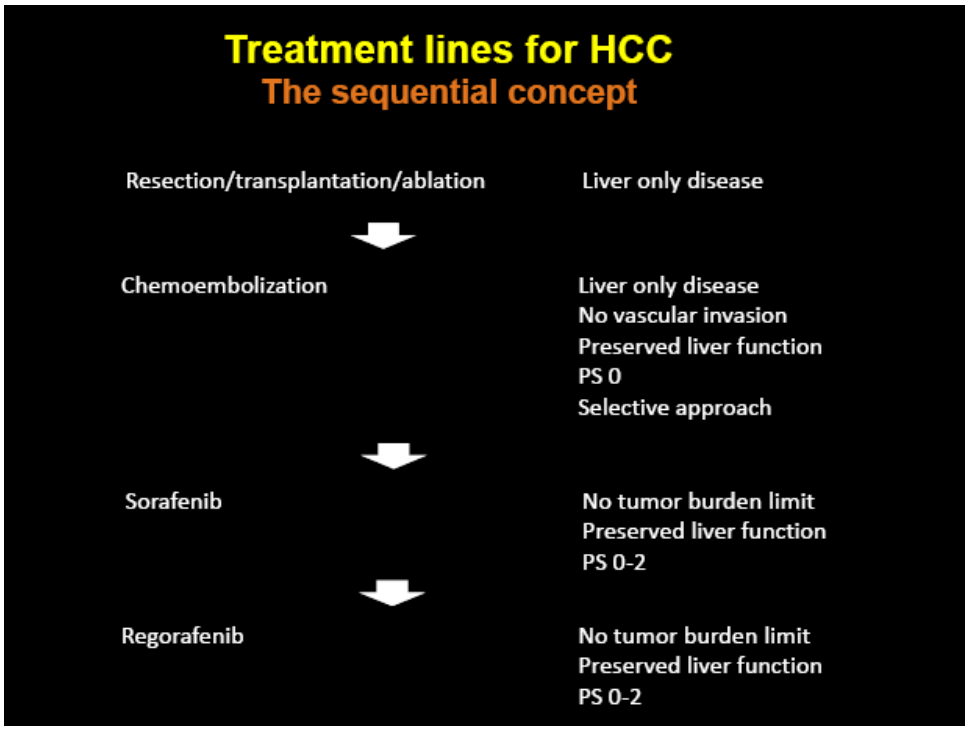


AFP, alpha-fetoprotein.

Presented at: 2016 World Congress on GI Cancer; June 28 – July 2, 2016; Barcelona, Spain. Abstracts LBA03.


Progression-free Survival (PFS)
Probability of progression-free survival (%)
Regorafenib
Placebo
Months from randomization
Regorafenib n=379
Placebo n=194
Events 293 (77%) 181 (93%)
Censored 86 (23%) 13 (7%)
Median PFS (95% CI) 3.1 months (2.8, 4.2) 1.5 months (1.4, 1.6)
HR 0.46 (95% CI: 0.37, 0.56)
P<0.001 (2-sided)
Number at risk
Regorafenib 379 166 76 43 27 14 8 7 4 0 0 0
Placebo 194 37 15 6 3 2 1 1 0 0 0 0
Based on mRECIST
Presented at: 2016 World Congress on GI Cancer; June 28 - July 2, 2016; Barcelona, Spain. Abstracts LBA03.


Sorafenib and regorafenib in advanved HCC
Sorafenib in first line
Progression
Tolerant to sorafenib
Regorafenib in second line
A Overall Survival
Median overall survival
Sorafenib 10.7 months
vs placebo 7.9 months
P<0.001
Probability of Survival
Sorafenib
Placebo
P<0.001
Months since Randomization
No. at Risk
Sorafenib 299 290 270 249 234 213 200 172 140 111 89 68 48 37 24 7 1 0
Placebo 303 295 272 243 217 189 174 143 108 83 69 47 31 23 14 6 3 0
Median overall survival
Regorafenib 10.6 months
vs placebo 7.8 months
P<0.001
Probability of survival (%)
Months from randomisation
Number at risk
Regorafenib 379 316 224 170 122 78 54 34 21 10 4 0
Placebo 194 149 95 62 37 26 16 8 5 3 1 0
Llovet J, et al. NEJM 2008
Bruix J, et al. Lancet 2016



Nivolumab in sorafenib-experienced patients with advanced hepatocellular carcinoma with or without chronic hepatitis: CheckMate 040 study

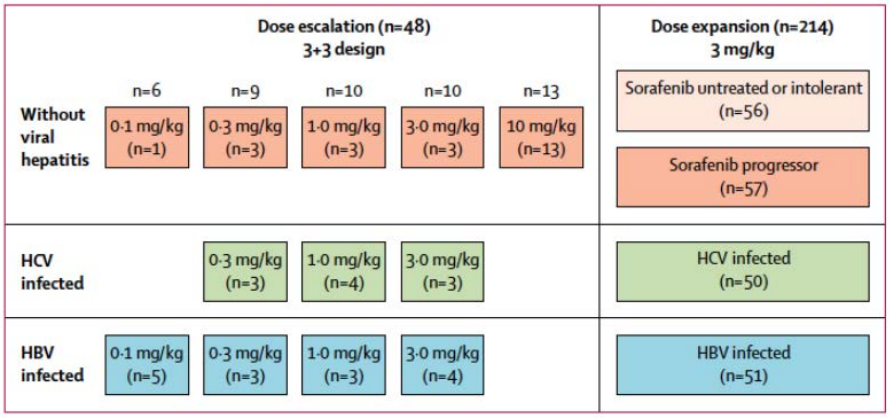
- Phase 1 / 2 using nivolumab 3 mg/kg every 2 weeks in patients with advanced HCC progressor or intolerant to sorafenib
- Primary endpoint: objective response rate

Inclusion criteria
Child Pugh A patient
Advanced HCC
Progression after 1 prior line of systemic therapy or intolerant to sorafenib

Exclusion criteria
Any history of hepatic encephalopathy
Prior or current clinically significant ascites

El Khoueiry AB, et al. Lancet 2017

Nivolumab in sorafenib-experienced patients with advanced hepatocellular carcinoma with or without chronic hepatitis: CheckMate 040 study

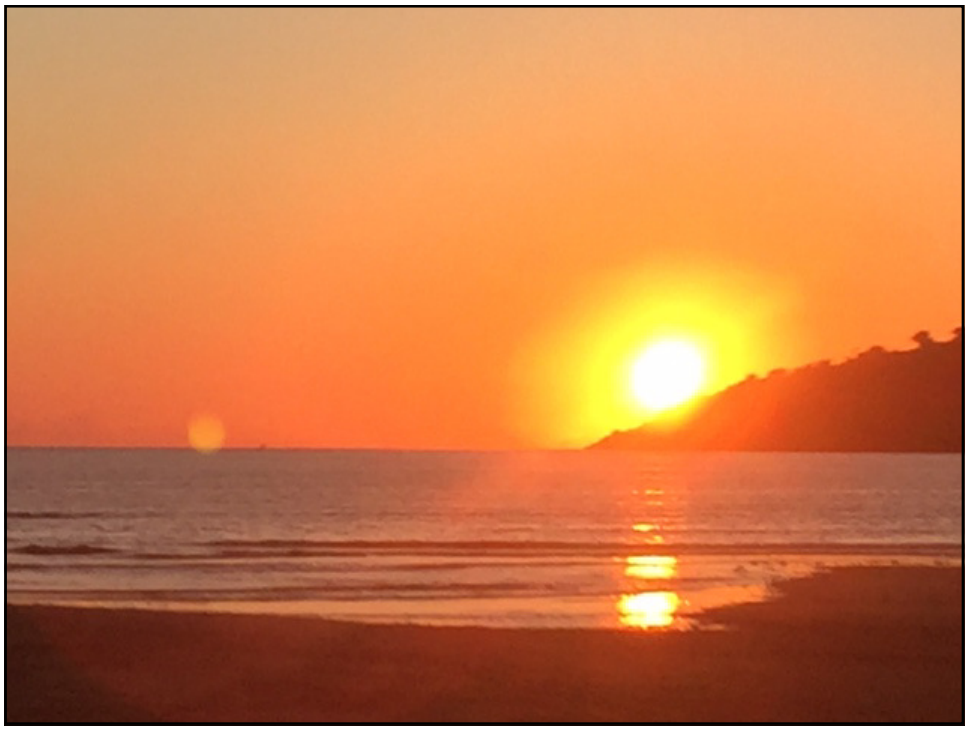


El Khoueiry AB, et al. Lancet 2017

Checkmate 040 : nivolumab pri napredovalem HCC

- Nivolumab 3 mg/kg vodi v objektivne odgovore pri 16% bolnikov po RECIST 1.1 (15% of PR and 1% of CR)
- Nadzor boelzni -68%
- Srednje preživetje 15 mesecev
- Sprejemljiv varnostni profil
- Randomizirane raziskave faze III – primerjava sorafeniba in nivolumaba pri napredovalem HCC (Checkmate 459)

El Khoueiry AB, et al. Lancet 2017



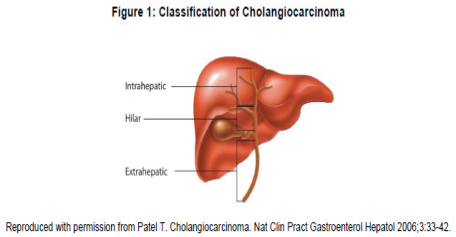
Novosti v sistemskem zdravljenju karcinoma žolčnika in žolčevodov

ASIST.DR.MARTINA REBERŠEK, DR.MED.
SEKTOR INTERNISTIČNE ONKOLOGIJE
ONKOLOŠKI INŠTITUT LJUBLJANA, 20.10.2017

Klasifikacija

Razdelitev:

- **Karcinom žočnika**
- **Intrahepatični holangiokarcinom**
- **Perihilarni holangiokarcinom (Klatskinov tumor)**
- **Distalni (ekstrahepatični) holangiokarcinom**



Reproduced with permission from Patel T. Cholangiocarcinoma. Nat Clin Pract Gastroenterol Hepatol 2006;3:33-42.

- **1% vseh GIT tumorjev**
- **Karcinom žolčnega epitelija, ki lahko vznikne kjerkoli v žolčnem vejevju**
- **HISTOLOŠKO: 90% adenoCa, 10% SCC**

Epidemiologija (1)

Tabela 8: Incidenca raka (brez primerov registriranih samo iz zdravniških poročil o vzroku smrti) po stadiju, lokaciji in spolu, Slovenija 2014.

Table 8: Cancer incidence (without cases registered from death certificates only) by stage, by site and by sex, Slovenia 2014.

Šifra MKB ICD code	Primarna lokacija Primary site	Spol Sex	Število novih primerov Number of new cases	Stadij							
				Omejen		Razširjen		Razsejan		Neznan	
				Število	%*	Število	%*	Število	%*	Število	%*
				Stage							
				Localized		Regional		Distant		Unknown	
				Number	%*	Number	%*	Number	%*	Number	%*
C22	Jetra in intrahepatični vodi	M	141	57	40,4	40	28,4	37	26,2	7	5,0
	Liver and intrahepatic bile ducts	Ž	67	20	29,9	13	19,4	33	49,3	1	1,5
C23	Žolčnik	M	22	8	36,4	5	22,7	9	40,9	0	0
	Gallbladder	Ž	46	12	26,1	12	26,1	22	47,8	0	0
C24	Drugi in neopredeljeni deli biliarnega trakta	M	74	17	23,0	35	47,3	19	25,7	3	4,1
	Billiary tract, other and unspecified parts	Ž	67	11	16,4	36	53,7	19	28,4	1	1,5

Rak v Sloveniji 2014. Ljubljana: Onkološki inštitut Ljubljana, Epidemiologija in register raka, Register raka Republike Slovenije, 2017.

Epidemiologija (2)

Tabela 11a: Število in deleži bolnikov (brez primerov registriranih samo iz zdravniških poročil o vzroku smrti), v Sloveniji zbolelih leta 2014, ki so bili v okviru prvega kurativnega zdravljenja operirani, zdravljeni s sistemskim zdravljenjem ali obsevani.

Table 11a: Number of patients (without cases registered from death certificates only) diagnosed in Slovenia in 2014, that were treated by primary curative surgery, systemic therapy or radiotherapy during their first treatment.

Šifra MKB ICD code	Primarna lokacija Primary site	Število novih primerov Number of new cases	Število kakorkoli zdravljenih* Number of all treated*		Število operiranih Number of treated by surgery		Število zdravljenih s sistemskim zdravljenjem Number of treated sistemic therapy		Število obsevanih Number of treated by radiotherapy	
			Število Number	%**	Število Number	%**	Število Number	%**	Število Number	%**
C00–C96	Vse lokacije All sites	13728	11109	80,9	8514	62,0	3994	29,1	3102	22,6
C00–C14	Usta in žrelo Mouth and pharynx	352	328	93,2	190	54,0	21	6,0	256	72,7
C15	Požiralnik Oesophagus	111	73	65,8	20	18,0	32	28,8	52	46,8
C16	Želodec Stomach	452	284	62,8	216	47,8	149	33,0	79	17,5
C18	Debelo črevo Colon	809	708	87,5	687	84,9	185	22,9	9	–
C19–C20	Rektum in rektosigmoidna zveza	592	517	87,3	472	79,7	193	32,6	199	33,6
C22	Jetra in intrahepatični vodi Liver and intrahepatic bile ducts	208	64	30,8	31	14,9	33	15,9	3	–
C23–C24	Žolčnik in žolčevodi Gallbladder and billiary tract	209	86	41,1	79	37,8	12	–	3	–
C25	Pancreas	392	140	35,7	76	19,4	87	22,2	13	–

Rak v Sloveniji 2014. Ljubljana: Onkološki inštitut Ljubljana, Epidemiologija in register raka, Register raka Republike Slovenije, 2017.

KLINIČNA SLIKA

SIMPTOMI

Pruritus (66%)

Bolečina pod DRL (30-50%)

Hujšanje (30-50%)

Povišana tel. T(20%)

Temen urin, belo blato

Redko holangitis

ZNAKI

Zlatenica (90%)

Hepatomegalija (25-40%)

Masa pod DRL (10%)

Courvoisier-jev znak (redko)

Onkološko specifično zdravljenje

- kirurško
- radioterapija
- sistemska terapija

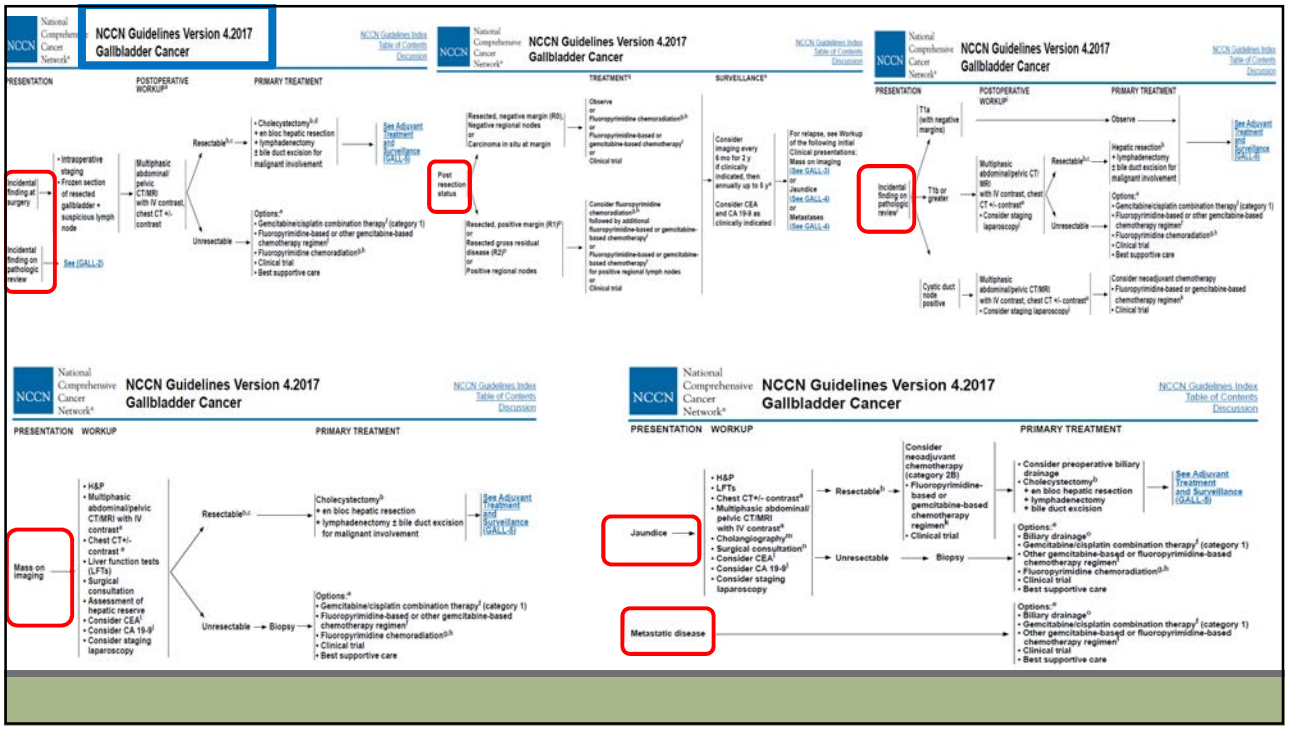
J. W. Valle, et al. On behalf of the ESMO Guidelines Committee Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up- TNM AJCC

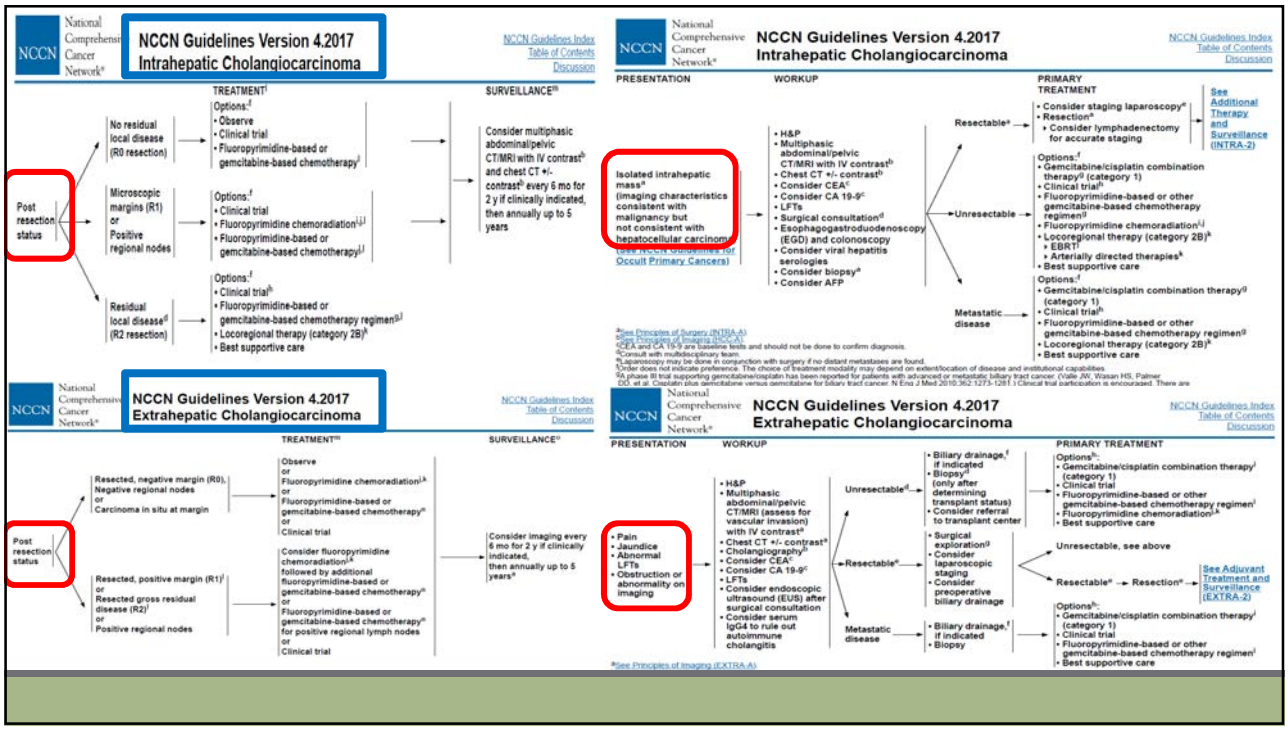
Table 1. *Continued*

Cholangiocarcinoma															
Cholangiocarcinoma - intrahepatic Primary tumour (T)				Cholangiocarcinoma - perihilar Primary tumour (T)				Cholangiocarcinoma - distal Primary tumour (T)				Gallbladder cancer Gallbladder cancer Primary tumour (T)			
Stage grouping			Distant metastasis present	Stage grouping				Stage grouping				Stage grouping			
Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0
Stage I	T1	N0	M0	Stage I	T1	N0	M0	Stage IA	T1	N0	M0	Stage I	T1	N0	M0
Stage II	T2	N0	M0	Stage II	T2a–b	N0	M0	Stage IB	T2	N0	M0	Stage II	T2	N0	M0
Stage III	T3	N0	M0	Stage IIIA	T3	N0	M0	Stage IIA	T3	N0	M0	Stage IIIA	T3	N0	M0
Stage IVA	T4	N0	M0	Stage IIIB	T1–3	N1	M0	Stage IIB	T1	N1	M0	Stage IIIB	T1–3	N1	M0
	Any T	N1	M0	Stage IVA	T4	N0–1	M0		T2	N1	M0	Stage IVA	T4	N0–1	M0
Stage IVB	Any T	Any N	M1	Stage IVB	Any T	N2	M0		T3	N1	M0	Stage IVB	Any T	N2	M0
					Any T	Any N	M1	Stage III	T4	Any N	M0		Any T	Any N	M1
								Stage IV	Any T	Any N	M1				

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control.
Edge et al. [20]. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, IL, USA. The original source for this material is the AJCC Cancer Staging Handbook, 7th edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Annals of Oncology 27 (Supplement 5): v28–v37, 2016 doi:10.1093/annonc/mdw324





SISTEMSKO ZDRAVLJENJE

- adjuvantno sistemsko zdravljenje
- sistemsko zdravljenje metastatske bolezni

Sistemska terapija

KEMOTERAPIJA:

- gemcitabin
- derivati platine
- fluoropirimidini

Adjuvantna sistemska terapija (1)

- redki raki
- podatki iz retrospektivnih analiz, kliničnih primerov in klin.raziskav faze II

Only Older Randomized Adjuvant Therapy Trial

- Japanese study, randomly assigned patients with: extrahepatic biliary cancer, gallbladder cancer, periampullary cancer or pancreas cancer to chemotherapy post-op vs surgery alone
  - Chemotherapy was 5FU and MMC x 1 dose then oral 5FU
  - Only gallbladder came out positive
  - Problem: were these 5 trials or 5 subset analyses?

Adjuvantna sistemska terapija (2)

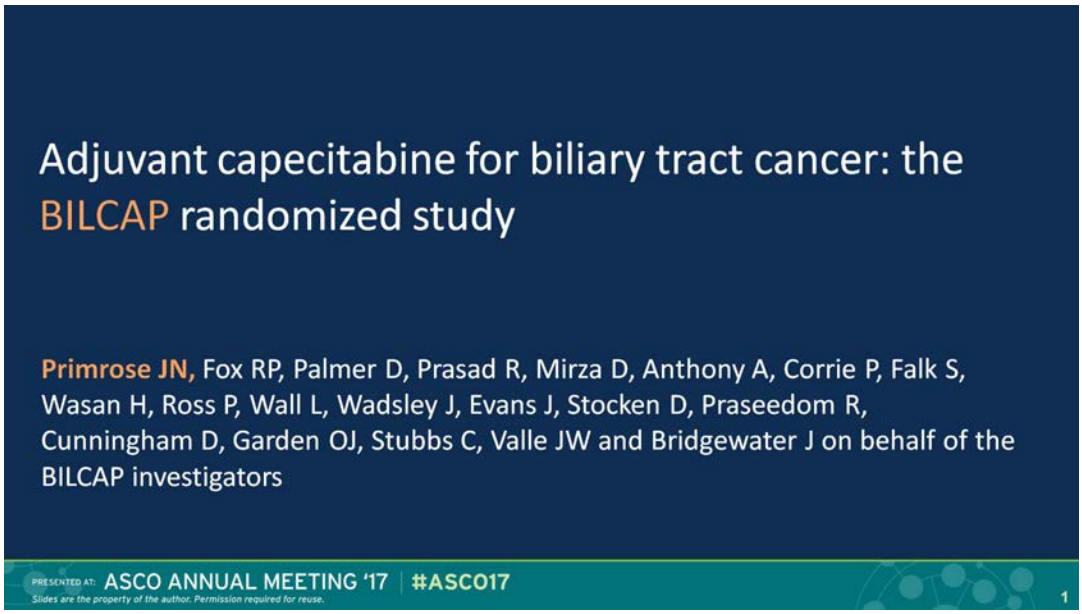
Adjuvantna kemoterapija:

- BILCAP faza III: kapecitabin vs. kontrola
- Prodige-12 faza III: GEMOX vs. kontrola
- ACTICCA-1 faza III: gem/cis vs. kontrola

Adjuvantna kemoradioterapija lahko izboljša preživetje v primerjavi z BSC (drenaža žolča)[1]

- mOS 9m vs. 3 m
- Rezultati retrospektivnih analiz

1.Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol 2012; 30: 1934–1940.



CANCER RESEARCH UK

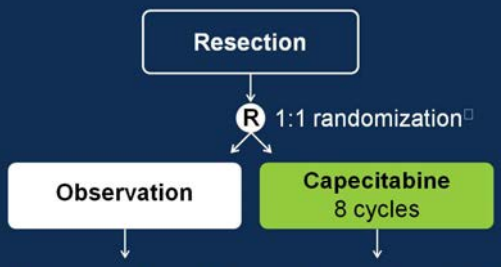
Study overview

BILCAP

- Two arm, open label, randomized, controlled clinical trial

Interventions
- Observation
- Capecitabine (1250mg/m²) twice a day on day 1 to 14 of a 3 weekly cycle for 24 weeks (8 cycles)

Outcome measures
- Primary; overall survival (OS)
- Secondary;
  - Relapse free survival (RFS)
  - Toxicity
  - Quality of life*
  - Health economics



Primary analysis after a minimum 2 year follow-up

*EORTC QLQ-C30 & LMC-21 (latter for patients with colorectal liver metastasis)
□Minimized on surgical centre, tumour site, type of resection (RO/RI) & performance status (ECOG PS 0-2)

CANCER RESEARCH UK

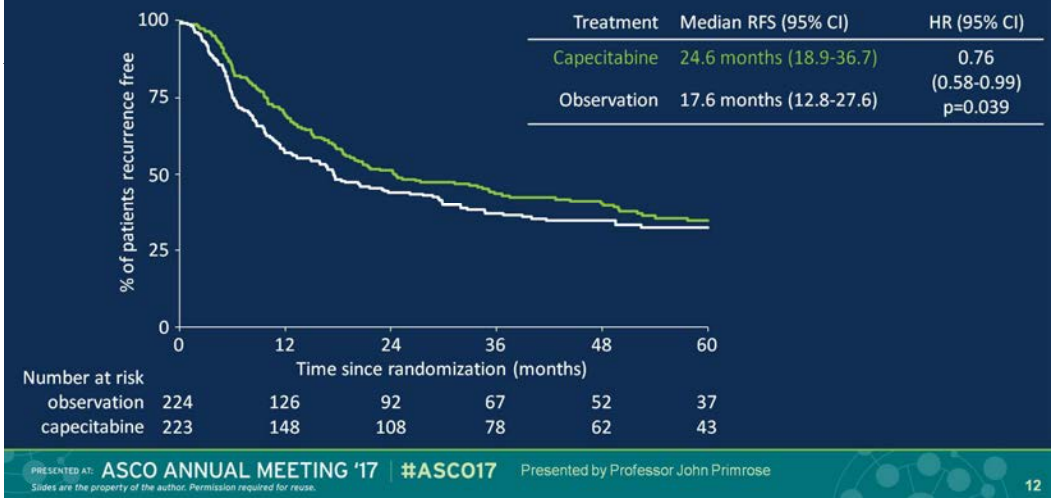
Baseline characteristics

BILCAP

		Observation arm (n=224)	Capecitabine arm (n=223)
Gender	Male	113 (50%)	111 (50%)
Age	Median years (inter-quartile range)	64 (55-69)	62 (55-68)
Tumour site	Intrahepatic CC	41 (18%)	43 (19%)
	Hilar CC	63 (28%)	65 (29%)
	Muscle invasive gall bladder carcinoma	40 (18%)	39 (17%)
	Lower common bile duct CC	80 (36%)	76 (34%)
Resection status	R0	140 (63%)	139 (62%)
	R1	84 (38%)	84 (38%)
ECOG performance status	0	101 (45%)	100 (45%)
	1	116 (52%)	116 (52%)
	2	7 (3%)	7 (3%)
Tumour size	Median mm (inter-quartile range)	25 (20-44)	25 (19-45)
Lymph node status	N0	108 (48%)	100 (45%)
	N1	102 (46%)	108 (48%)
	NX	14 (6%)	15 (7%)

Values shown are n (%) for categorical data, and median (IQR) for continuous measures

RFS in the ITT population



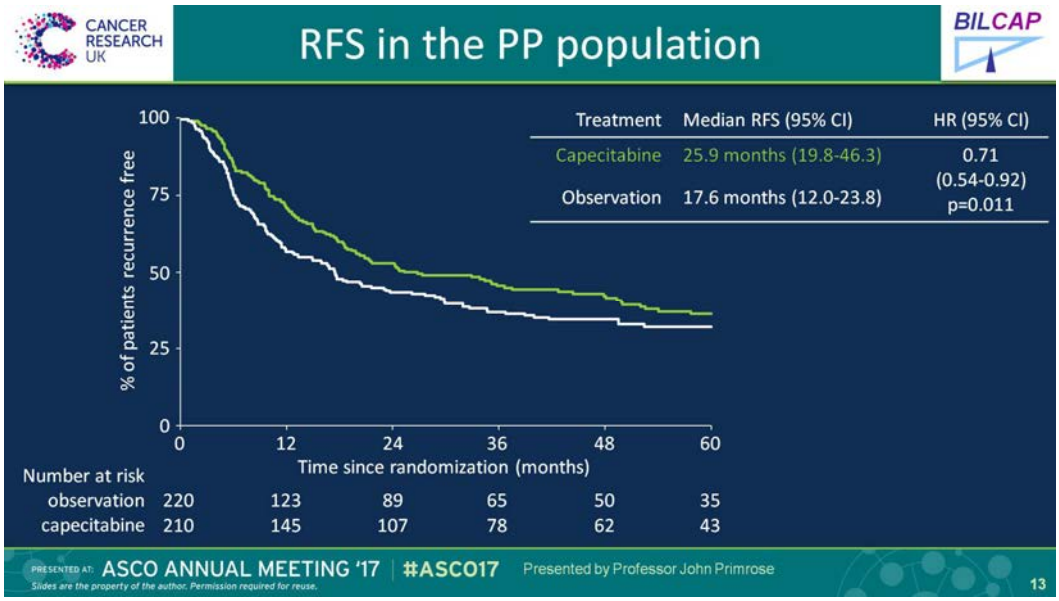
Treatment	Median RFS (95% CI)	HR (95% CI)
Capecitabine	24.6 months (18.9-36.7)	0.76 (0.58-0.99) p=0.039
Observation	17.6 months (12.8-27.6)	

12

OS in the PP population

Treatment	Median OS (95% CI)	HR (95% CI)
Capecitabine	52.7 months (40.3-NR)	0.75 (0.58-0.97) p=0.028
Observation	36.1 months (29.6-44.2)	

11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RFS in the PP population
BILCAP
Treatment | Median RFS (95% CI) | HR (95% CI)
Capecitabine | 25.9 months (19.8-46.3) | 0.71 (0.54-0.92) p=0.011
Observation | 17.6 months (12.0-23.8)
% of patients recurrence free
100
75
50
25
0
0 12 24 36 48 60
Time since randomization (months)
Number at risk
observation 220 123 89 65 50 35
capecitabine 210 145 107 78 62 43
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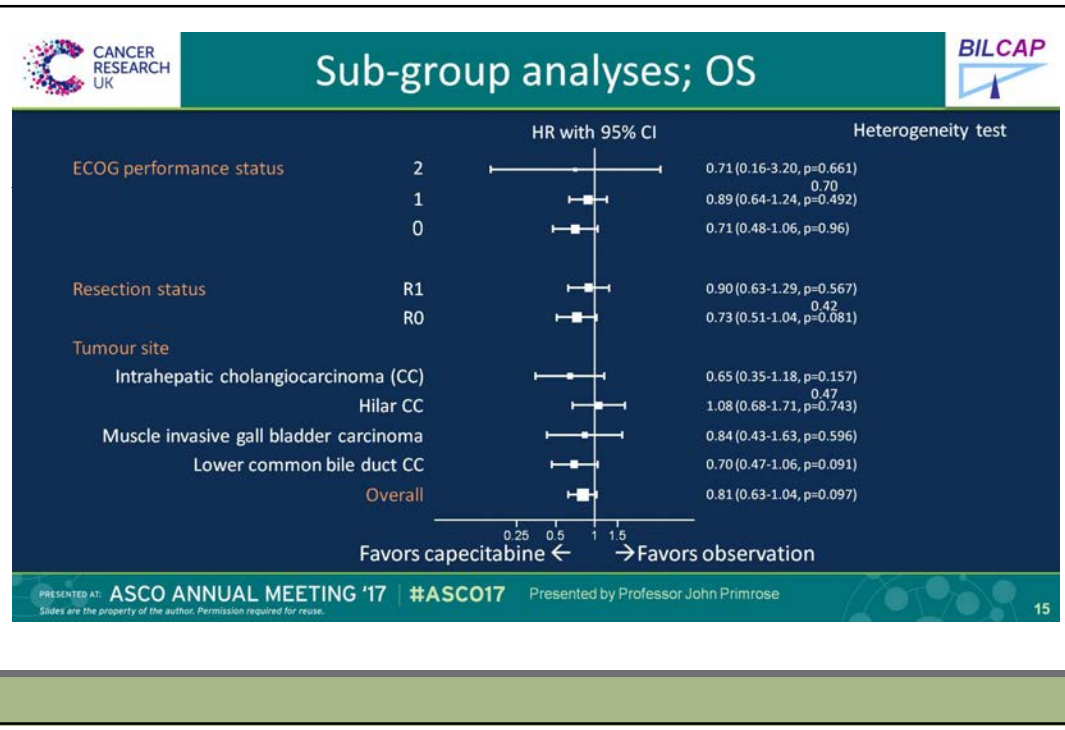
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Sub-group analyses; OS
BILCAP
HR with 95% CI
Heterogeneity test
ECOG performance status
2 0.71 (0.16-3.20, p=0.661)
1 0.89 (0.64-1.24, p=0.492)
0 0.71 (0.48-1.06, p=0.96)
0.70
Resection status
R1 0.90 (0.63-1.29, p=0.567)
R0 0.73 (0.51-1.04, p=0.081)
0.42
Tumour site
Intrahepatic cholangiocarcinoma (CC) 0.65 (0.35-1.18, p=0.157)
Hilar CC 1.08 (0.68-1.71, p=0.743)
Muscle invasive gall bladder carcinoma 0.84 (0.43-1.63, p=0.596)
Lower common bile duct CC 0.70 (0.47-1.06, p=0.091)
Overall 0.81 (0.63-1.04, p=0.097)
0.47
0.25 0.5 1 1.5
Favors capecitabine ← →Favors observation
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Toxicity

The safety population was conditional on receiving capecitabine (n=213)

There were no deaths related to chemotherapy

Toxicity type	Grade 3/4
Fatigue	16 (7.5 %)
Plantar palmar erythrema	44 (20.7 %)
Diarrhea	16 (7.5 %)
Nausea	2 (0.9 %)
Mucositis/stomatitis	2 (0.9 %)
Vomiting	1 (0.5 %)
Neutropenia	4 (1.9 %)
Bilirubin	3 (1.4 %)
Thrombocytopenia	1 (0.5 %)
Alopecia	0

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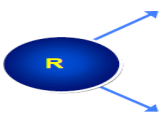
Adjuvant GEMOX: Study Design

Prodige 12- Accord 18 (UNICANCER GI)



Observation

GEM-OX
Gemcitabine 1,000 mg/m2 day 1
Oxaliplatin 85Mg/m2 day2, both every other week x 12

Randomized phase III design

Edeline, J, et al. ASCO GI, 2017, abstract 225

AIM: whether GEMOX would improve RFS vs surveillance while maintaining health-related quality of life.

One hundred and ninety-six patients were enrolled; median follow-up was 44.3 months. Relapse events occurred in 54 patients with GEMOX and in 64 patients under surveillance. Median RFS was 30.4 months with GEMOX vs 22 months with surveillance; 4-year RFS rates were 39.3% and 33.2%, respectively. The differences were not significant.

Edeline J, Bonnetain F, Phelip JM, et al. Gemox versus surveillance following surgery of localized biliary tract cancer: Results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial. *J Clin Oncol*. 2017;35(suppl):4S. Abstract 225.

Baseline Characteristics

Characteristic	GEMOX N= 94	Surveillance N = 99
M:F	59.6%/40.4%	50.5%/49.5%
ECOG PS: 0 1 2	53.2% 39.4% 5.3%	63.6% 31.3% 2.0%
IHC Perihilar Extrahepatic Gallbladder	43.6% 10.6% 27.7% 18.1%	45.5% 5.1% 28.3% 21.2%
Pre-op Tx: Portal vein Embo Biliary drain	20.2% 11.7%	23.2% 9.1%
Tumor characteristics: Node + R1 Perineural invasion	37.2% 13.8% 54.3%	36.4% 12.1% 45.5%
Vascular Emboli	26.6%	29.3%

Edeline, J, et al. ASCO GI, 2017, abstract 225

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Outcomes

- Primary endpoint, RFS
  - HR 0.83, p = 0.31
  - Median Gem-OX 30.4 months vs 22.0 Months for surveillance
  - 4-year RFS: 39.3% vs 33.2%
  - Forrest Plot
    - All subsets to left of 1 except Extrahepatic cholangiocarcinoma which was wildly to the right

Edeline, J, et al. ASCO GI, 2017, abstract 225

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- Health-related quality of life scores did not differ at 1-year and 2-year time points.
- Grade 4 adverse events occurred among 17% of patients receiving GEMOX and 9.1% of patients under surveillance. One patient died from each group.

Edeline J, Bonnetain F, Phelip JM, et al. Gemox versus surveillance following surgery of localized biliary tract cancer: Results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial. *J Clin Oncol*. 2017;35(suppl):4S. Abstract 225.

Sistemsko zdravljenje metastatske bolezni (1)

Gemcitabine

Reference	Schedule	# of patients	Response Rate	TTP	Overall Survival
Penz, et al	2200/m2 Q o week	32	22%	5.6 mos	11.5 mos
Valencak, et al	1200/m2 Qw x3	24	4%	3.5 mos	6.8 mos
Kubicka, et al	1000/m2 qw x3	23	30%	4.4 mos	N/A
Arroyo, et al	1000/m2 qw x3	39	36%	N/A	6.5 mos

These and other trials are all summarized in Scheitauer W. Semin Oncol 29:6 (suppl 20). 40-45. 2002

Sistemsko zdravljenje metastatske bolezni (2)

Gemcitabine + 5-FU

Reference	Gemcitabine +_____	# of pts	Response Rate	TTP or PFS	Overall Survival
Murad (Am J Clin Oncol 26: 151-4, 2003	Bolus 5-FU	9 pts	33%	TTP	9 months
Jacobson D ASCO 2003	Bolus 5-FU with LV	42 pts	9.5%	3.8 months	6.8 months
Hsu C, et al ASCO 2003	Bolus 5-FU	26 pts	19%	4.2 months	7.3 months
Knox J, et al GI Symposium, 2004	Capecitabine	35 pts	26%	6.8 months	10.3 months

2nd study of gem-cape in 57 pts, RR18%, OS 7 months

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Sistemsko zdravljenje metastatske bolezni (3)

Gemcitabine + platinums

Reference	Type of platinum	# of pts	RR	Survival
Thengprasert, et al GI ASCO	Cisplatin	24	33%	13 mos
Reyes-Vidal, et al GI ASCO (GOCCHI trial)	Cisplatin	42	48%	7 mos
ASCO 2003	Carboplatin	13	30%	N/A
EORTC	Oxaliplatin	33 (1st line)	36%	14.3 months

Sistemsko zdravljenje metastatske bolezni (4)

Sistemska terapija:

- **Faza III UK ABC-02**: cisplatin/gemcitabine vs. gemcitab- mOS: 11.7 mesecev cisplatin/

Gemcitabin vs. 8.1 mesecev gemcitabin (95% CI: 0.53-0.79; P<0.001)

- **Meta-analiza** [1]: kombinacija kemoterapije učinkovitejša od monokemoterapije neodvisno od starosti (<65 vs≥65 let), spola, mesta primarnega tumorja (intrahepatični vs ekstrahepatični vs karcinom žolčnika), stadija bolezni (lokoregionalni vs metastatski) in predhodne terapije (operacija vs stent), razen v primeru PS ECOG 2 vs 0,1→ gemcitabin monoterapija, v primeru led.insuficience oksaliplatin

[1] Valle JW, Furuse J, Jitlal M et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. Ann Oncol 2014; 25: 391–398.

ABC-02 - Study schema

Eligible patients (n=400*)

+ QoL

Randomized 1:1

(stratified by centre, primary site, PS, prior therapy and locally advanced vs. metastatic)

Arm A	Arm B
Gem *1000 mg/m²* *D1,8,15 q 28d*	Cisplatin *25 mg/m²* + Gem *1000 mg/m²* *D1,8 q 21d*
24 weeks (6 cycles)	24 weeks (8 cycles)

Upon disease progression, management will be on clinician's discretion (mostly best supportive care)

* *Including 86 patients in ABC-01*

Valle, et al NEJM 362:1273-81, 2010

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ABC-02 statistical methods

Primary endpoint:	**OVERALL SURVIVAL:** ITT analysis (pre-planned ABC-01 and ABC-02)
Secondary endpoints:	• Progression-free survival • Toxicity • Quality of life (EORTC QLQ C-30)
Sample size:	• Powered to detect increase in median survival from 8 to 11 months • n=354 patients (315 OS events), n=400 to allow for drop-out • Log-rank test with 80% power and two-sided α 5% level

Valle, et al NEJM 362:1273-81, 2010

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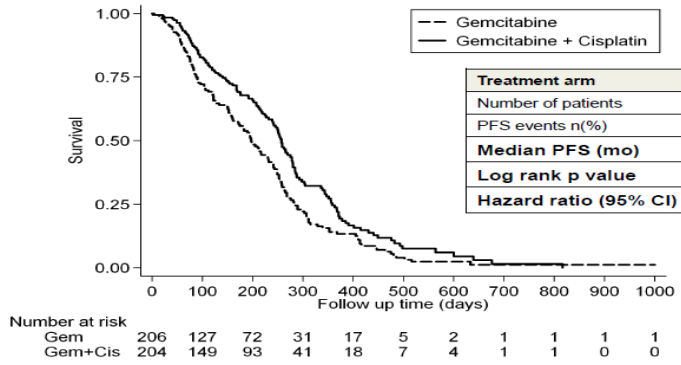
ABC-02 Results: Progression-free survival (ITT)



Treatment arm	Gem	Gem + Cis
Number of patients	n=206	n=204
PFS events n(%)	155 (75.2)	135 (66.2)
Median PFS (mo)	**6.5**	**8.4**
Log rank p value	**0.003**	
Hazard ratio (95% CI)	**0.72 (0.57, 0.90)**	

Valle, et al NEJM 362:1273-81, 2010

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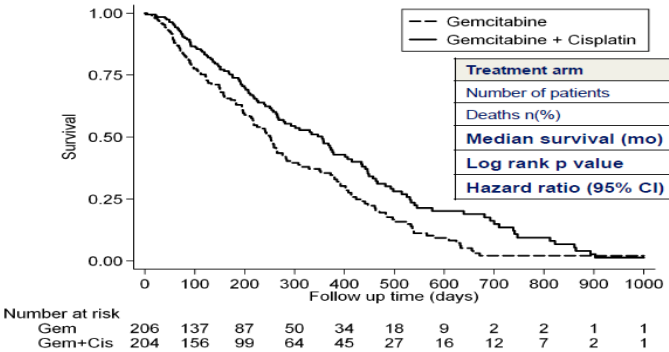
ABC-02 - Results: Overall Survival (ITT)



Treatment arm	Gem	Gem + Cis
Number of patients	n=206	n=204
Deaths n(%)	141 (68.5)	122 (59.8)
Median survival (mo)	**8.3**	**11.7**
Log rank p value	**0.002**	
Hazard ratio (95% CI)	**0.70 (0.54, 0.89)**	

Valle, et al NEJM 362:1273-81, 2010

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NOVOSTI v sistemskem zdravljenju

- Tarčna zdravila ?
- Imunoterapija ?

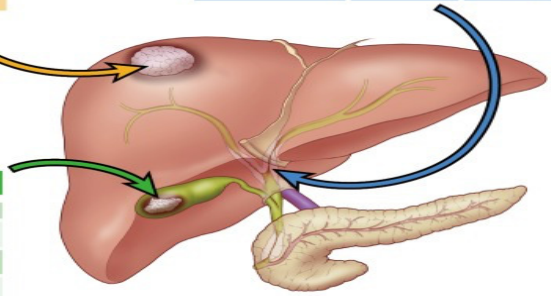
Biliary Tract Cancers are Heterogeneous

IHCCA

Specific Targetable GAs	Prevalence	Targeted Therapies
FGFR2 Fusions	10% to 20%	BGJ398, Ponatinib, JNJ42756493, PRN1371, TAS-120, FGFR antbodies and FGFR trap molecules
IDH1/2	22% to 28%	AG-120, AG-881
BAP1	15% to 25%	Histone Deacetylase (HDAC) inhibitors like vorinostat and panobinostat

EHCCA

Specific Targetable GAs	Prevalence	Targeted Therapies
HER2/neu (mutation)	11% to 20%	Tyrosine Kinase Inhibitors like afatinib, neratinib, and dacomitinib
PRKACA and *PRKACB*	9%	Protein Kinase A inhibitors under development
ARID1A	5% to 12%	Histone Deacetylase (HDAC) inhibitors like vorinostat and panobinostat



GBC

Specific Targetable GAs	Prevalence	Targeted Therapies
EGFR	4% to 13%	Erlotinib, Cetuximab
HER2/neu (amplification)	10% to 15%	Trastuzumab, Lapatinib, Pertuzumab, T-DM1
ERBB3	0% to 12%	Seribantumab (MM-121), Pertuzumab, Trastuzumab, T-DM1
PTEN	0% to 4%	mTOR inhibitors like Everolimus, AKT inhibitor like MK2206, PI3K inhibitors like BKM120, BYL719 and SF1126
PIK3CA	6% to 13%	mTOR inhibitors like Everolimus, AKT inhibitor like MK2206, PI3K inhibitors like BKM120, BYL719 and SF1126

Tarčna zdravila

Anti EGFR zaviralci:

- cetuksimab+ GEMOX →63% ORR, v 30% op.

- random. BINGO faza II: cetuksimab+ GEMOX vs GEMOX→ neg.

- erlotinib+GEMOX, panitumumab+ GEMOX → neg.

Anti VEGF zaviralci:

- sorafenib+ gemcitabin (faza II)→ neg.

- cediranib+ gemcitabin+ cisplatin→ neg.

O-019

Ramucirumab plus pembrolizumab in previously treated advanced or metastatic biliary tract cancer: A multi-disease phase 1 study

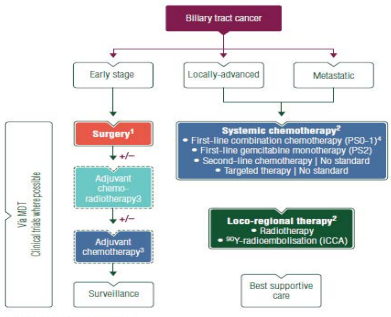
Hendrik-Tobias Arkena HT, et al.

- Ramucirumab 8 mg/kg i.v. 1. in 8. dan

- Pembrolizumab 200 mg i.v. 1.dan/3 tedne

“The primary objective was to assess the safety and tolerability of ramucirumab plus pembrolizumab; preliminary efficacy will be examined. ”

J. W. Valle, et al. On behalf of the ESMO Guidelines Committee Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up



[1] Special considerations:
- Need for pre-operative biliary drainage
- Avoid percutaneous biopsy in resectable disease
- Assess Future Liver Remnant
- Assess need for Portal Vein Embolisation
- Neoadjuvant approach (selected cases)
- Completion surgery for incidental gallbladder cancer of T-stage T1b and above

[2] Option of salvage surgery should be considered in responding patients with initially inoperable disease
[3] Level of recommendation IV,C
[4] Cisplatin and gemcitabine [category IA], other gemcitabine-based combination [category IIB]

Figure 1. Algorithm for the management of patients with biliary tract cancer. MDT, multidisciplinary team; PS, performance status; iCCA, intrahepatic cholangiocarcinoma.

Annals of Oncology 27 (Supplement 5): v28–v37, 2016 doi:10.1093/annonc/mdw324

Zaključki (1)

- slaba prognoza
- pomen diagnostike
- prvo zdravljenje kiruško

Zaključki (2)- vloga sistemske terapije

- **Adjuvantna kemoterapija:**

- kapecitabin novo standardno sistemsko zdravljenje

- vloga radioterapije v kombinaciji s sistemsko kemoterapijo- prospektivne klin.raziskave

- **Metastatska bolezen:**

- gemcitabin+cisplatin v 1.redu

- ni standardne terapije za 2.red

- **Imunoterapija:** prve klinične raziskave v poteku

HVALA ZA POZORNOST

DIAGNOSTIKA KARCINOZE PERITONEJA

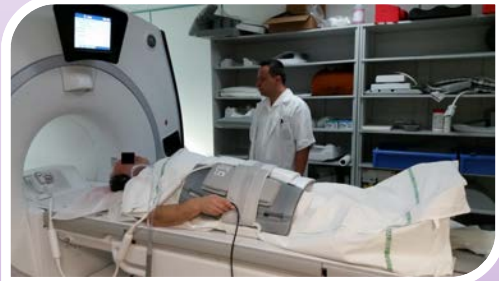
Nina Boc, dr.med.
Oddelek za radiologijo
Onkološki inštitut Ljubljana
Ljubljana, 20.10.2017

PCI – OCENA KARCINOZE PERITONEJA

- Low RN, 2012 – n=32 – DWI+DCE-MRI: senz.88%, spec.74%
  - Ujemanje PCI in laparoskopije 29 od 33 bolnikov
- Espade et al, 2013 – n=34 – DWI: 91% natančen za napoved suboptimalne kirurgije v primerjavi z eksplorativno laparotomijo
- Michielsen et al, 2014 – n=32 – WB-DWI: 91% natančen staging in PCI
  - CT: 75% natančen
  - FDG PET-CT 71% natančen
- Na OI – vsaj 20 bolnikov od maja 2016

Metode in materiali za slikanje karcinoze peritoneja

- MR – GE Optima 450w GEM 1,5T
- Tuljave:
  - GEM Posterior Array (40 elementov),
  - GEM Anterior Array (36 elementov).



- Pulzna zaporedja:
  - 3 plane localiser
  - AX T2 FRFSE fs zgoraj
  - AX T2 FRFSE fs spodaj

  Navigator, debelina reza 6 mm, razmak med rezi 1,5 cm, FOV 38 cm
  - AX LAVA zgoraj
  - AX LAVA spodaj

  V zadržanem dihu, debelina reza 4 mm, FOV 35 cm
  - AX DWI zgoraj
  - AX DWI spodaj

  Debelina reza 8 mm, razmak med rezi 1 mm, FOV 36 cm

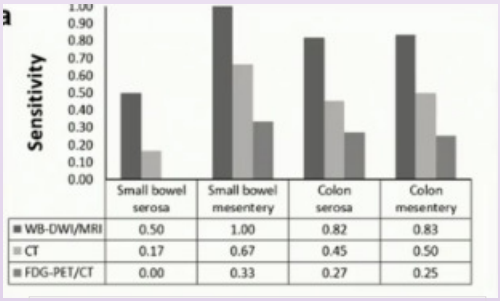
Kontrastno sredstvo

- +C AX LAVA zgoraj
- AX LAVA spodaj

V zadržanem dihu, debelina reza 4 mm, FOV 35 cm

OCENA KARCINOZE PERITONEJA

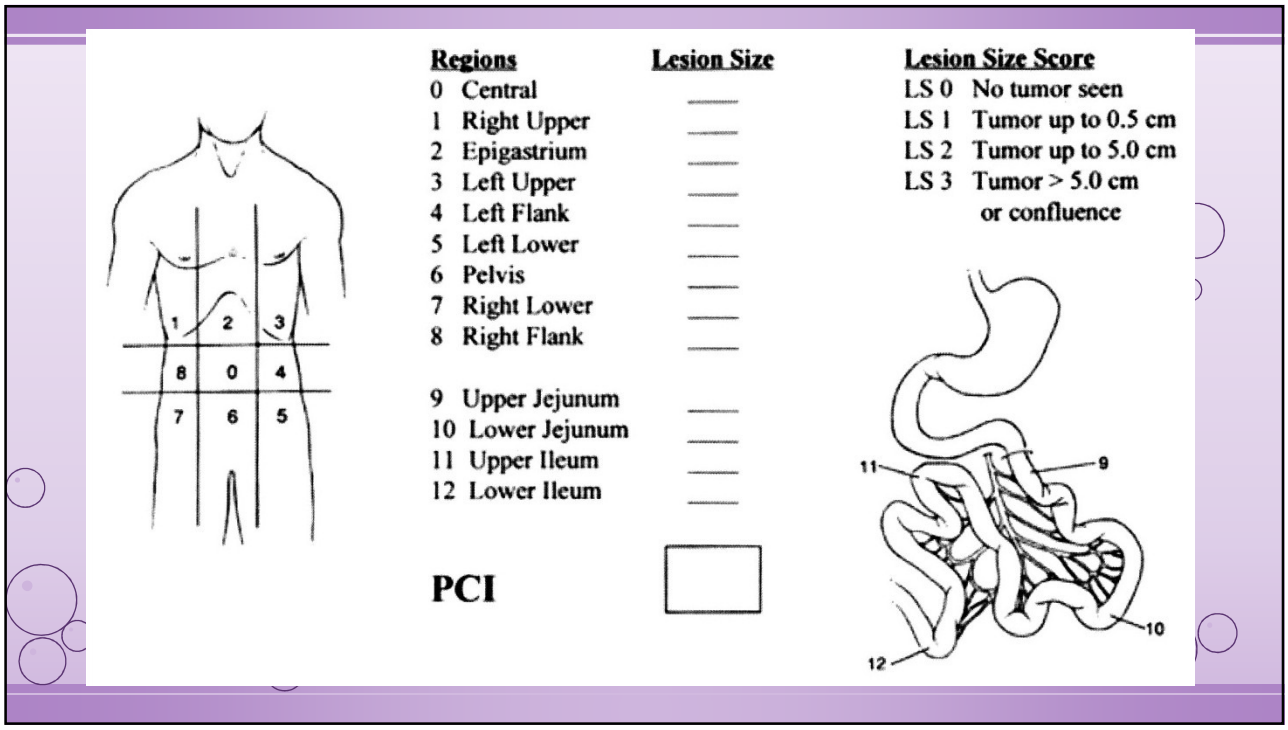
It may surprise you that the most modern radiologic technology, MRI, CT, PET CT are very inaccurate for low volume cancer. [cancer with small-size but numerous metastases]

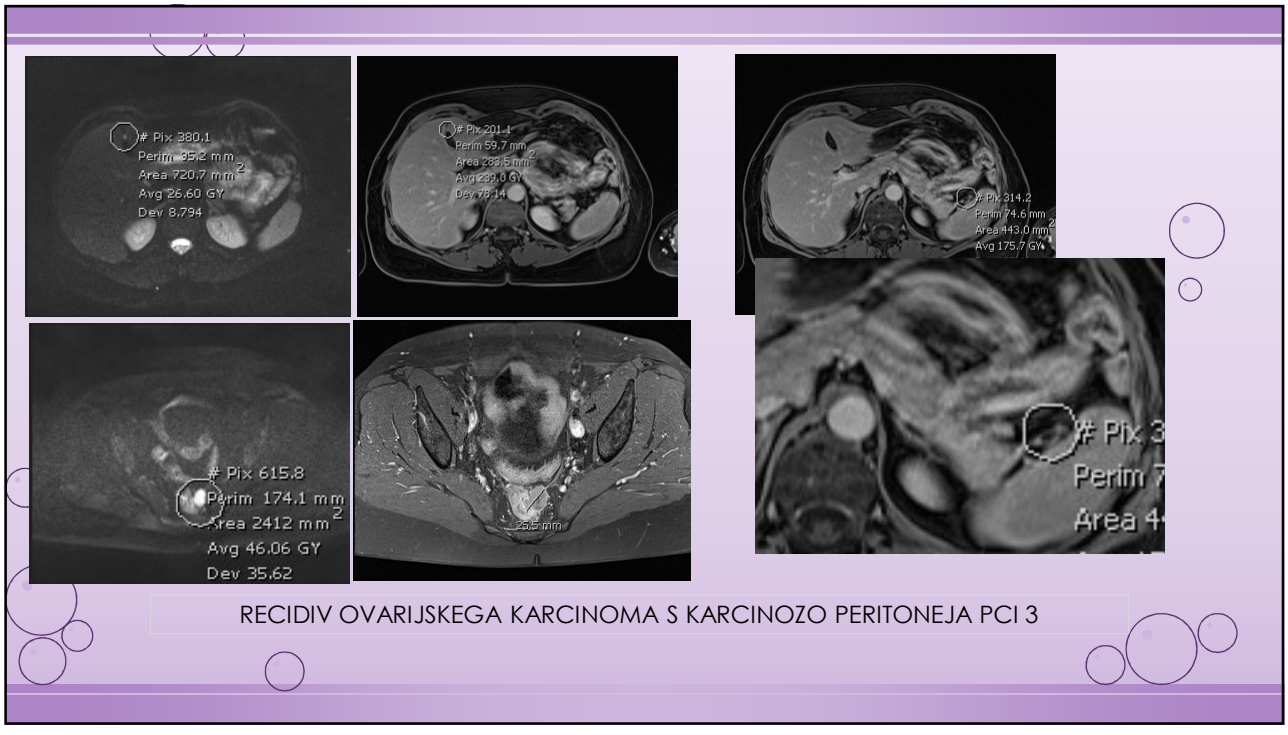


	Small bowel serosa	Small bowel mesentery	Colon serosa	Colon mesentery
WB-DWI/MRI	0.50	1.00	0.82	0.83
CT	0.17	0.67	0.45	0.50
FDG-PET/CT	0.00	0.33	0.27	0.25

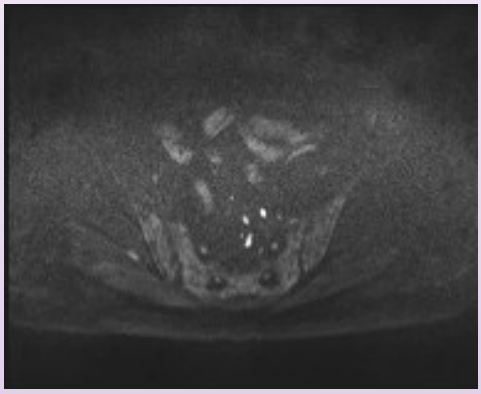
Michielsen K et al, Eur 2014

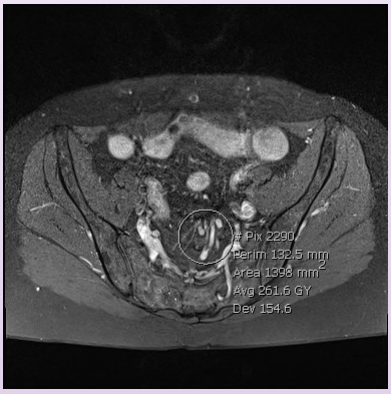
Restrikcija difuzije fiziološko
Izguba signala DWI – fiziološke razmere
Izguba signala DWI – karakteristike tumorja



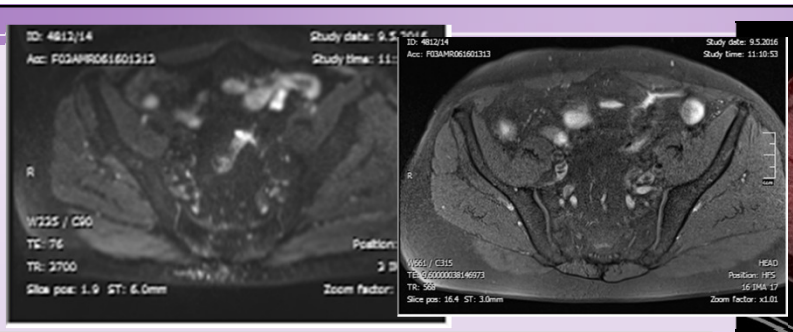


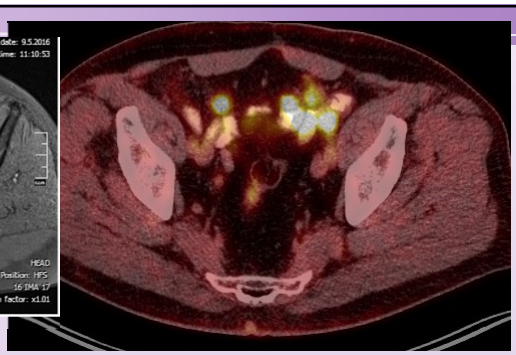
RECIDIV OVARIJSKEGA KARCINOMA S KARCINOZO PERITONEJA PCI 3



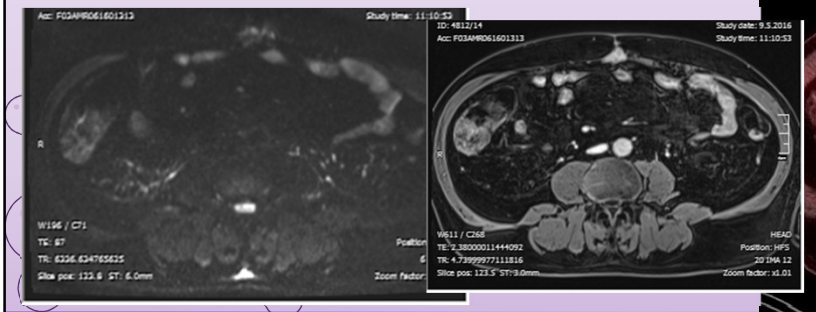


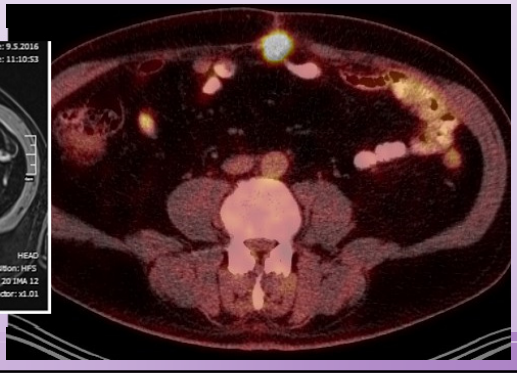
RECIDIV OVARIJSKEGA KARCINOMA S KARCINOZO PERITONEJA PCI 3





CRC – KARCINOZA PERITONEJA PCI 12 (OP.10)





ZAKLJUČEK

- MRI predstavlja dobro možnost ocene PCI pred HIPEC terapijo pri bolnikih s karcinozo peritoneja pred posegom

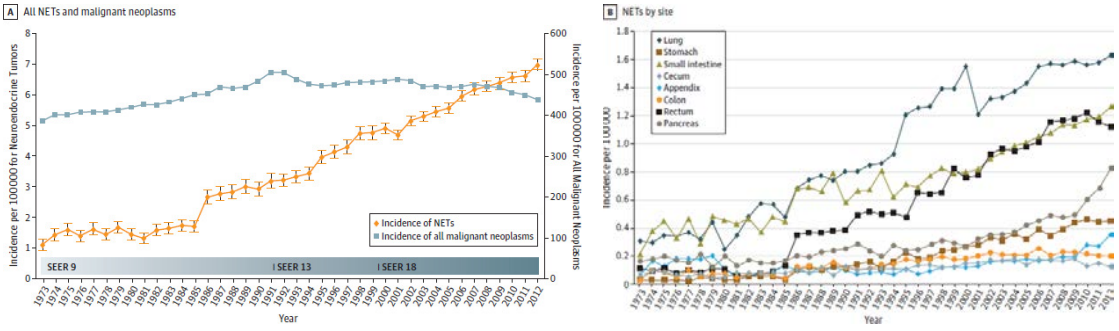
Smernice obravnave bolnikov z nevroendokrinimi neoplazmami (NEN)

Prof. Dr. Janja Ocvirk, dr. med.

Ljubljana 20.10. 2017

Nevroendokrine neoplazme (NEN) bolezen v porastu

- Celotna incidenca NEN vseh lokalizacij v letu 2012
  - 6,98/100.000 prebivalcev[1]



1. Dasari A, Shen C, Halperin D et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol.* 2017;3(10):1335-1342.

Multidisciplinarni pristop h zdravljenju bolnikov z NEN

- Celovit pristop, kjer so potrebna znanja in izkušnje s področja:
  - Kirurgije
  - Patologije
  - Radiologije
  - Internistične onkologije
  - Gastroenterologije
  - Endokrinologije
  - Nuklearne medicine

ENETS consensus guidelines 2016

- NEN želodca in dvanajstnika
- NEN tankega črevesa (jejunum in ileum)
- NEN debelega črevesa in danke
- NEN trebušne slinavke
- NEN slepega črevesa
- Zdravljenje metastatskih NEN
- Zdravljenje NEN visokega gradusa (NEC G3)

NEC- nevroendokrini karcinom

NEN želodca in dvanajstnika

- Incidenca- 1,2/100.000 prebivalcev[1]
- Klasifikacija NEN želodca (g- NEN)[2]

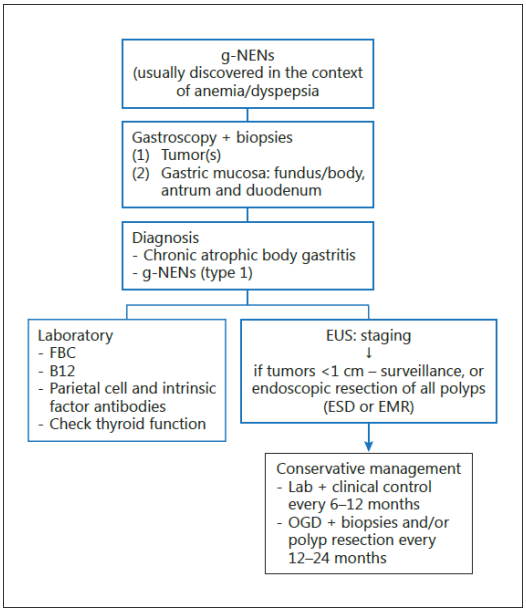
	Tip 1	Tip 2	Tip 3
Delež med g-NEN, %	70-80	5-6	14-25
Lastnosti tumorja	Pogosto majhni (< 1-2cm), multipli v 65% primerov in polipoidni v 78% primerov	Pogosto majhni (<1-2cm), multipli, polipoidni	Svojevrstni, pogosto veliki (>2cm), polipoidni in ulcerajoči
Pridružena stanja	Atrofični gastritis	Gastrinom/MEN-1	Brez
Patologija	G1-G2 NET	G1-G2 NET	G3 NEC
Raven serumskega gastrina	↑	↑	Normalna
pH želodca	↑↑	↓↓	Normalna
Zasevki, %	2-5	10-30	50-100
Delež smrti povezanih s tumorjem, %	0	<10	25-30

1. Dasari A, Shen C, Halperin D et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol.* 2017;3(10):1335-1342.
2. Delle Fave G, O'Toole D, Sundin A et al. ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. Neuroendocrinology. 2016;103:119–124

NEN želodca (gNEN)[1]

- Obravnava Tip 1 gNEN
  - Klasična obravnava z gastroskopijo/resekcijo
- Obravnava Tip 2 gNEN
  - V sklopu MEN-1 ob prisotnosti NEN drugih lokalizacij
- Obravnava Tip 3 gNEN
  - Endoskopska resekcija manjših tumorjev
  - Kirurška resekcija kot pri adenokarcinomu želodca

  (delna ali popolna gastrektomija z limfadenektomijo)
  - Stadij 4 ali inoperabilna bolezen- sistemsko zdravljenje



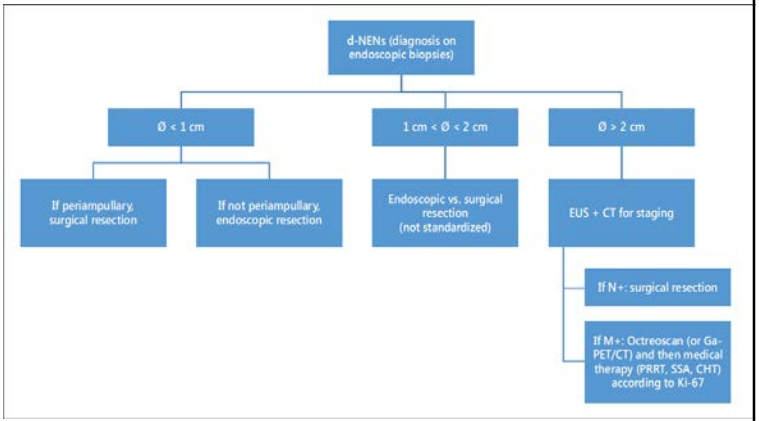
EUS- endoskopski UZ, FBC-krvna slika, OGD- ezofagealna gastroduodenalna endoskopija, ESD- endoskposka submukozna disekcija, EMR- endoskopska mukozna resekcija

1. Delle Fave G, O'Toole D, Sundin A et al. ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. Neuroendocrinology. 2016;103:119–124

NEN dvanajstnika (dNEN)- diagnostika in zdravljenje[1]

- Obravnava dNEN
  - <1cm- Endoskopska obravnava
  - 1-2cmEndoskopska obravnava/kirurgija

  - individualno
  - EUZ in CT za opredelitev stadija
    - N+- kirurgija
    - M+- sistemsko zdravljenje



EUS- endoskopski UZ, N+-zasevki v bezgavkah, M+-sistemski zasevki, CHT- kemoterapija, SSA- analogi somatostatina, PRRT- radionuklidno obsevanje s peptidnimi receptorji

1. Delle Fave G, O'Toole D, Sundin A et al. ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. Neuroendocrinology. 2016;103:119–124

NEN tankega črevesa(jejunum in ileum)

- Incidenca 0,81/100.000 prebivalcev[1]
- 21,3 % funkcionalnih (karcinoidni sindrom)[2]
- 30-50% vseh neoplazem tankega črevesa[2]
- 5- letno preživetje odvisno od stadija[2]
  - Vse stopnje 50-60%
  - Lokalno napredovala bolezen- 80-100%
  - Stadij I-IIIa z zasevki v bezgavkah- 70-80%
  - Stadij IV- 35-80%

1. Dasari A, Shen C, Halperin D et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol.* 2017;3(10):1335-1342.

2. Niederle B, Pape UF, Costa F et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. Neuroendocrinology. 2016;103:125–138

NEN tankega črevesa (jejunim in ileum)

- Diagnostični algoritem[1]

<table>
<tr><td colspan="6">Klinična diagnoza: naključna, simptomatska</td></tr>
<tr><td colspan="4">Abdominalna kirurgija
(vključno z urgenco)</td><td>Abdominalni UZ</td><td>Endoskopija</td></tr>
<tr><td colspan="4">Primarni tumor in/ali zasevki v bezgavkah</td><td>Biopsija jetrnih sprememb</td><td>(Jejuno-) ilealni primarni tumor</td></tr>
<tr><td colspan="6">Histopatološka diagnoza</td></tr>
<tr><td colspan="6">HE barvanja
Imunohistokemijsko barvanje: kromogranin A (CgA), sinaptofizin- pozitiven za NEN trnkega črevesa: serotonin, cdx-2
Gradus: Ki 67 indeks, mitotski indeks</td></tr>
<tr><td colspan="4">Klinični stadiji</td><td colspan="2">Funkcionalnost</td></tr>
<tr><td colspan="4">Slikovne preiskave
CT, MR ali funkcionalno slikanje
(G1 in G2: SSR-PET-CT; G3- FDG-PET-CT</td><td colspan="2">Biokemija
CgA
5-HIAA</td></tr>
<tr><td colspan="3">Primarni tumor z ali brez zasevkov</td><td>Primarni tumor ni viden</td><td>Normalni izvidi</td><td>Povišane vrednosti
Asimptomatski / Simptomatski</td></tr>
<tr><td rowspan="2">Samo primarni tumor</td><td rowspan="2">Zasevki v bezgavkah</td><td rowspan="2">Oddaljeni zasevki
(oddaljene bezgavke, jetra, kosti, pljuča)</td><td rowspan="2">Kapsulna endoskopija
Dvojna balonska enteroskopija
Kolonoskopija</td><td>Nefunkcionalni</td><td>Funkcionalni</td></tr>
<tr><td colspan="2">EKG
NT-pro-BNP
(za izključitev ali potrditev):
Karcinoidna srčna bolezen
(Hedingerjev sindrom)</td></tr>
</table>

1. Niederle B, Pape UF, Costa F et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. Neuroendocrinology. 2016;103:125–138

NEN tankega črevesa (jejunum in ileum)

- Kirurška obravnava[1]

Bolezen	Lokalizirana	Regionalna	Oddaljeni zasevki		
Stadij	I/II	III	IV		
TNM	T1-3N0M0	T4N0M0 T1-4N1M0	TxNxM1		
Kirurško zdravljenje	Radikalna resekcija		Radikalna resekcija z namenom ozdravljenja	Paliativna resekcija	Brez resekcije
	Lokalna radikalna odprta/laparoskopksa resekcija: primarnega/multiplih primarnih tumorjev bezgavk (resekcija vzdolž zgornjega mezeterijskega korena)		Lokalna odprta radikalna resekcija: primarnih tumorjev bezgavk (resekcija vzdolž zgornjega mezeterijskega korena) V kombinaciji resekcije zasevkov (jetra)	Lokalna odprta/laparoskopska radikalna resekcija: primarnega/multiplih primarnih tumorjev bezgavk (resekcija vzdolž zgornjega mezeterijskega korena)	Zaradi: lokalne neoperabilnosti tumorja komorbiditet
Cilj	Popolna odstranitev bolezni		Popolna odstranitev bolezni	Preprečevanje lokalnih zapletov (obstrukcij, krvavitev itd.) Morebitno izboljšanje prognoze	

1. Niederle B, Pape UF, Costa F et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. Neuroendocrinology. 2016;103:125–138

NEN debelega črevesa in danke

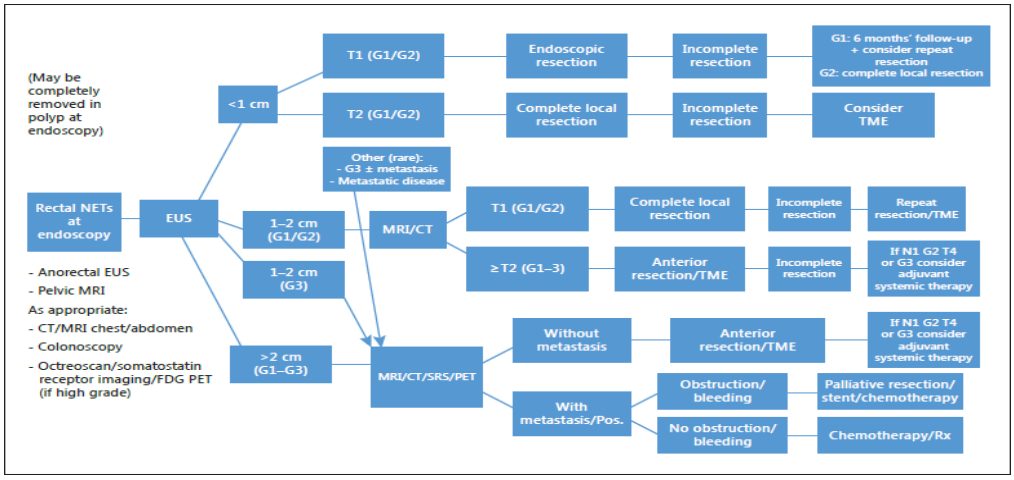
- Incidenca 1/100.000 prebivalcev[1]
- Največkrat odkriti hitro pri presejalnih testih (npr. SVIT) s kolonoskopijo[2]
- NEC debelega črevesa in danke imajo slabšo prognozo (srednje preživetje z regionalno razširjeno boleznijo manj kot 10 let, in manj kot 1 leto pri bolnikih z oddaljenimi zasevki)[1]

1. Dasari A, Shen C, Halperin D et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol.* 2017;3(10):1335-1342.

2. Ramage JK, De Herder WW, Delle Fave G et al. ENETS Consensus Guidelines Update for Colorectal Neuroendocrine Neoplasms. Neuroendocrinology. 2016;103:139–143

NEN debelega črevesa in danke

- Algoritem obravnave NEN danke- endoskopska/kirurška resekcija[1]



1. Ramage JK, De Herder WW, Delle Fave G et al. ENETS Consensus Guidelines Update for Colorectal Neuroendocrine Neoplasms. Neuroendocrinology. 2016;103:139–143

NEN trebušne slinavke (pNEN)

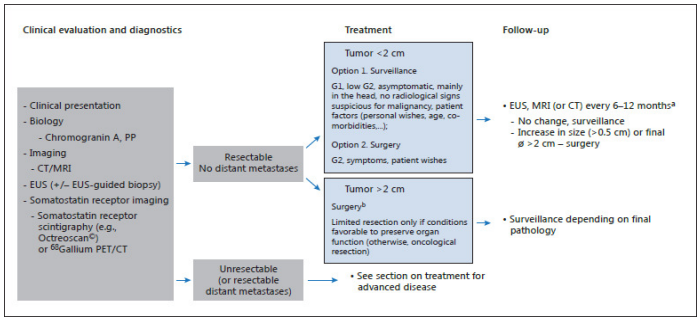
- Incidenca 0,86/100.000 prebivalcev[1]
- 60—80% jih je nefunkcionalnih[2]
- Funkcionalni pNEN povzročajo široko paleto hormonsko pogojenih sindromov (Insulinomi, Glukagonomi, Zollinger Ellisonov sindrom, VIPomi...)[2]
  - Potrebna endokrinološka obravnava[2]

1. Dasari A, Shen C, Halperin D et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol.* 2017;3(10):1335-1342.

2. Falconi M, Eriksson B, Kaltsas G et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016;103:153–171

NEN trebušne slinavke pNEN

- Obravnava nefunkcionalnih pNEN[1]
- Kirurška obravnava
- Sistemsko zdravljenje
  - SSA, tarčno zdravljenje, kemoterapija, PRRT.



1. Falconi M, Eriksson B, Kaltsas G et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016;103:153–171

NEN slepega črevesa

- Incidenca 0,53/100.000 prebivalcev[1]
- Najpogostejše neoplazme slepega črevesa (30-80%)[2]
- Dobra prognoza tumorjev v zgodnjih stadijih (5-letno preživetje skoraj 100%[2]
- 5-letno preživetje metastatske bolezni 12-28%[2]
- Brez specifičnih kliničnih znakov, naključna najdba po apendektomijah, ki so pogosto kirurško kurativne[2].

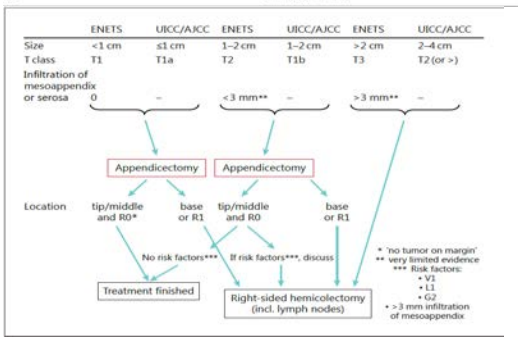
1. Dasari A, Shen C, Halperin D et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol.* 2017;3(10):1335-1342.
2. Pape UF, Niederle B, Costa F et al. ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas). Neuroendocrinology. 2016;103:144–152

NEN slepega črevesa

- Laboratorijske preiskave[1]
  - CgA (predvsem za diferenciacijo karcinoma čašastih celic in spremljanje morebitnega napredovanja metastatske bolezni), 5-HIAA
- Kirurško zdravljenje[1]
  - Tumorji <1cm(T1)- kurativna apendektomija
  - Tumorji >1cm in <2cm (T1b)- individualna presoja
  - >2 cm(T2 in več)- razširjena operacija

Table 2. TNM staging for appendiceal NEN according to either the ENETS guidelines or the UICC/AJCC classification

	ENETS guidelines	UICC/AJCC classification
T – primary tumor		
x	primary tumor not assessed/assessable	
0	no evidence of any primary tumor	
1	tumor ≤1 cm with infiltration of the submucosa and muscularis propria	
1a		tumor ≤1 cm
1b		tumor >1 cm but ≤2 cm
2	tumor ≤2 cm with infiltration of the submucosa, muscularis propria and/or minimal (≤3 mm) infiltration of the subserosa and/or mesoappendix	tumor >2 cm but ≤4 cm or with extension into the cecum
3	tumor >2 cm and/or extensive (>3 mm) infiltration of the subserosa and/or mesoappendix	tumor >4 cm or with extension into the ileum
4	tumor with infiltration of the peritoneum and/or other neighboring organs	tumor with perforation of the peritoneum or invasion of other adjacent structures
N – regional lymph node metastasis		
Nx	regional lymph nodes not assessed/assessable	
N0	no regional lymph node metastasis	
N1	locoregional lymph node metastasis/-es	
M – distant metastasis		
Mx	distant metastasis not assessed/assessable	
M0	no distant metastasis	
M1	distant metastasis/-es	



1. Pape UF, Niederle B, Costa F et al. ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas). Neuroendocrinology. 2016;103:144–152

Metastatski NEN

- Več kot 50% vseh NEN ob ima ob postavitvi diagnoze regionalne ali oddaljene zasevke[1]
- NEN najpogosteje zasevajo v jetra[1]
- Cilji zdravljenja metastatskih NEN[1]:
  - Obravnava primarnega tumorja in zasevkov
    - Kirurška resekcija za zmanjševanje tumorskega bremena
    - Zaviranje hormonske aktivnosti funkcionalnih tumorjev
    - Zaviranje napredovanja bolezni

1. Pavel M, O'Toole D, Costa F et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology. 2016;103:172–185

Metastatski NEN- obravnava zasevkov v jetrih[1]

- Kirurgija
  - Resekcija jetrnih režnjev
  - Lokalne ablativne metode
  - Transplantacija jeter (v redkih primerih ob odstranjenem primarnem tumorju in zasevkih omejenih na jetra)
- Sistemsko zdravljenje
  - Analogi somatostatina (IFN)
  - PRRT
  - Tarčna terapija (everolimus, sunitinib)

PRRT- peptidna receptorska radionuklidna terapija, IFN- interferon

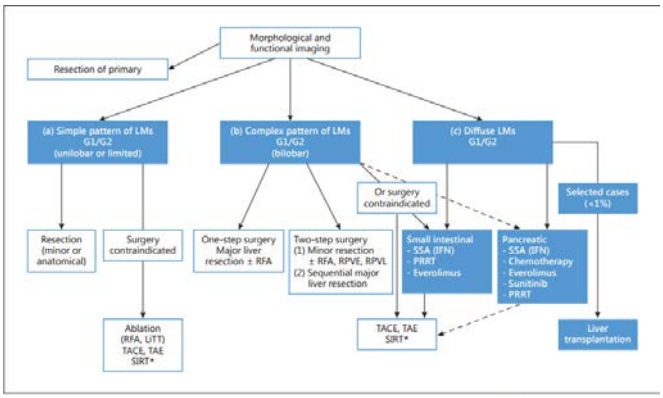


Fig. 1. Management of liver metastases without extrahepatic disease in G1/G2 NEN. * SIRT (selective internal radiation therapy) is still an investigational method. LiTT = Laser-induced thermotherapy; LMs = liver metastases; RFA = radiofrequency ablation; RPVE = right portal vein embolization; RPVL = right portal vein ligation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

1. Pavel M, O'Toole D, Costa F et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology. 2016;103:172–185

Metastatski NEN- sistemsko zdravljenje[1]

- Zaradi heterogenosti NEN, priporočljiva obravnava bolnikov na multidisciplinarnem konziliju.
- Analogi somatostatina (oktreotid in lanreotid) zlati standard zdravljenja prvega reda G1 in G2 NEN
- Drugi red zdravljenja po individualni obravnavi in ni strogo določen

Terapevtske možnosti in pogoji za priporočeno prvo linijo zdravljenja pri napredovalih NEN

Zdravilo	Funkcionalen	Gradus	Lokacija primarnega tumorja	SSTR status	Dodatno za razmislek
Oktreotid	+ / -	G1	srednje črevo	+	nizko tumorsko breme
Lanreotid	+ / -	G1/G2 (-10%)	srednje črevo treb. slinavka	+	nizko in visoko (>25%) tumorsko breme v jetrih
IFN-α 2b	+ / -	G1/G2	srednje črevo		če SSTR -
STZ/5-FU	+ / -	G1/G2	treb. slinavka		hitro napredovanje bolezni* ali visoko tumorsko breme ali simptomatska bolezen;
TEM/CAP	+ / -	G2	treb. slinavka		hitro napredovanje bolezni* ali visoko tumorsko breme ali simptomatska bolezen; STZ kontraindiciran ali ni na voljo
Everolimus	+ / -	G1/G2	pljuča		atipični karcinoid in/ali SSTR -
			treb. slinavka		inzulinom ali kontraindicirana CTX
			srednje črevo		če SSTR -
Sunitinib	+ / -	G1/G2	treb. slinavka		kontraindicirana CTX
PRRT	+ / -	G1/G2	srednje črevo	+ (nujno potrebni)	
Cisplatin/etopozid	+ / -	G3	vsi		

SSTR- receptorji za somatostatin; STZ- streptozotocin; 5-FU- fluorouracil; CAP- kapecitabin;
TEM- temozolomid; CTX- kemoterapija; *-≤ 6-12 mesecev; PRRT- peptidna receptorska radionuklidna terapija;
Cisplatin lahko zamenja karboplatin

1. Pavel M, O'Toole D, Costa F et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology. 2016;103:172–185

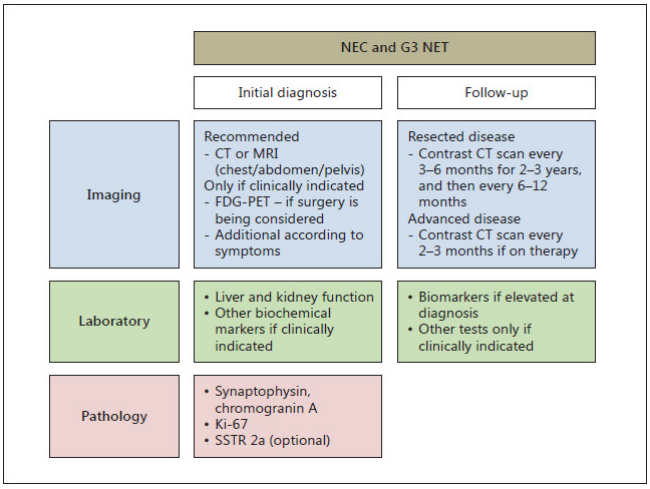
NEN visokega gradusa (G3 NEC)[1]

- NEC prebavnega trakta relativno redke (5% vseh NEN)
- Pogostejše NEC v pljučih v obliki drobnoceličnega karcinoma (35-55% vseh NEN v pljučih)
- G3 zelo širok razpon Ki67- (od 20 do 100%)- heterogeni odzivi na zdravljenje s kemoterapijo (boljši odzivi na KT pri NEC Ki67 >55%)
- Principi zdravljenja enaki kot pri zdravljenju drobnoceličnega karcinoma pljuč
- Srednje preživetje bolnikov z NEC do 38 mesecev (lokalizirana bolezen) do samo 5 mesecev pri bolnikih z metastatsko boleznijo (razpon od 1 meseca pri bolnikih samo s paliativno oskrbo do 12 mesecev pri bolnikih, ki imajo na voljo vsa sistemska zdravljenja)

1. Garcia- Carbonero R, Sorbye H, Baudin E et al. ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. Neuroendocrinology. 2016;103:186–194

NEC- diagnostični algoritem[1]

- Laboratorijske preiskave
  - CgA, NSE
- Slikovna diagnostika
  - Endoskopija
  - MR
  - FDG PET

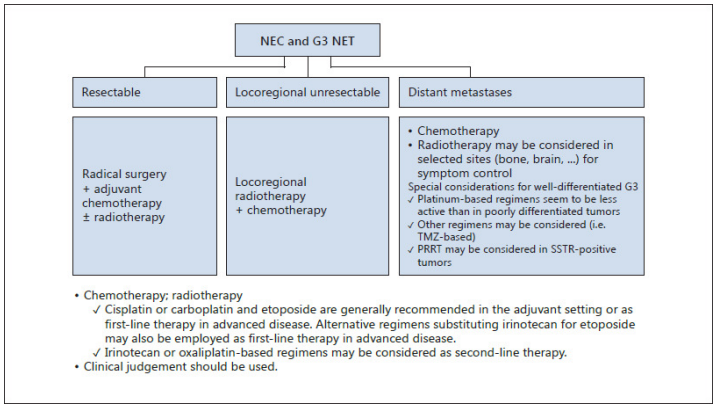


NSE- nevron specifična enolaza

1. Garcia- Carbonero R, Sorbye H, Baudin E et al. ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. Neuroendocrinology. 2016;103:186–194

NEC- zdravljenje[1]

- Kirurgija pri lokalizirani bolezni (redko kurativna)
  - Adjuvantna KT na osnovi platine
- Inoperabilna bolezen
  - Kombinacija KT in RT
  - KT prvega reda cisplatin/karboplatin + etopozid/irinotekan
  - KT drugega reda irinotekan ali KT na osnovi oksaliplatina



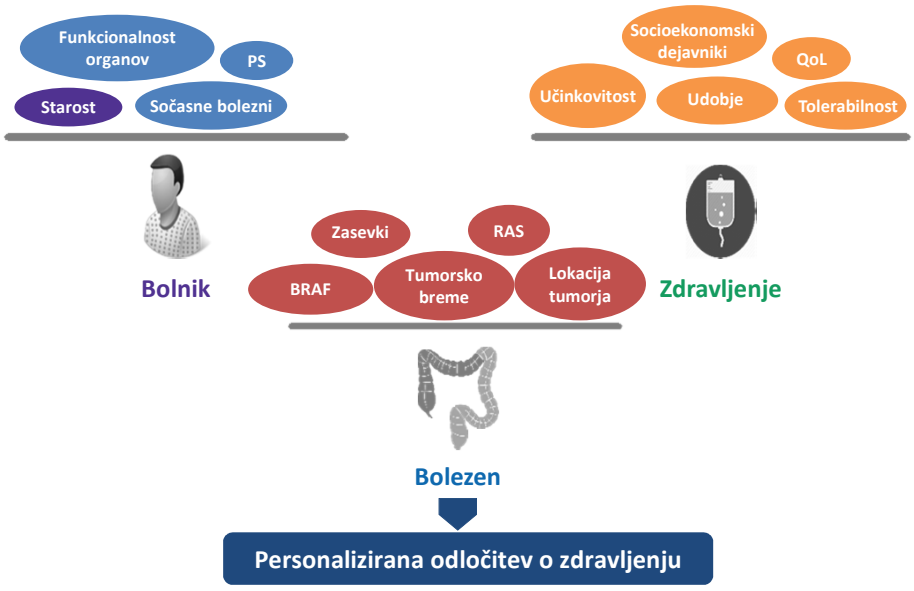
1. Garcia- Carbonero R, Sorbye H, Baudin E et al. ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. Neuroendocrinology. 2016;103:186–194

Levi ali desni rak črevesa: Kje so razlike in kako ga zdravimo?

Izr. prof. dr.Janja Ocvirk ,dr. med.
Onkološki Inštitut Ljubljana

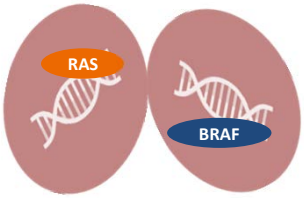
Šola tumorjev prebavil
20. Oktober 2017

PERSONALIZACIJA JE POMEMBNA: KAJ VSE MORAMO UPOŠTEVATI

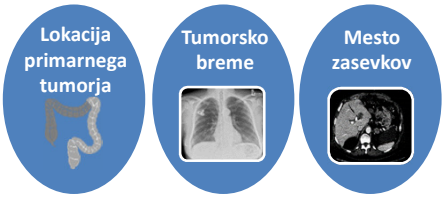


PROGNOSTIČNI DEJAVNIKI RDČD: KAKŠEN VPLIV IMAJO NA NAŠO KLINIČNI PRAKSO?

Genski dejavniki



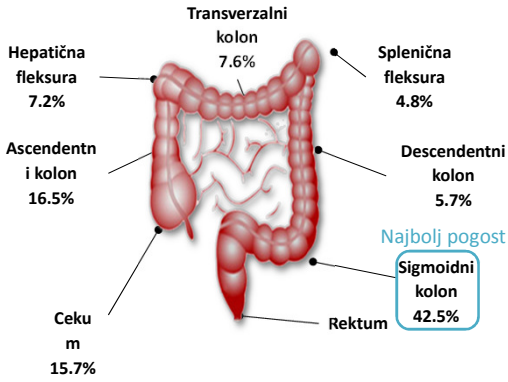
Tumorski dejavniki



Heterogenost RDČD: Mesto nastanka primarnega tumorja

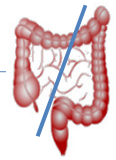
- **RDČD je heterogena bolezen: primarni tumorji, ki nastanejo v različnih področjih kolona so klinično in molekularno različni**

Desna stran **Leva stran**



4

Primarni tumorji kolona desne in leve strani so biološko in anatomsko različni[1]



Desni		Levi (z rektumom)
Lower Increasing Female	Incidence	Higher Decreasing Male
Higher TNM stage Larger tumors More mucinous type	Presentation	Lower TNM stage Smaller tumors
MUTYH-associated polyposis	Genetics	Familial adenomatous polyposis
More active immune cells promoting immunogenicity	Immunology	Immunologically less active, promoting tolerogenesis
CIMP/MSI/BRAF positive tumors predominate	Molecular pathway	Chromosomal instability tumors predominate
Worse	Survival	Better

CIMP, cytosine-guanosine (CpG) island methylation phenotype; MSI, microsatellite instability; TNM, American Joint Committee on Cancer tumor–node–metastasis stage.

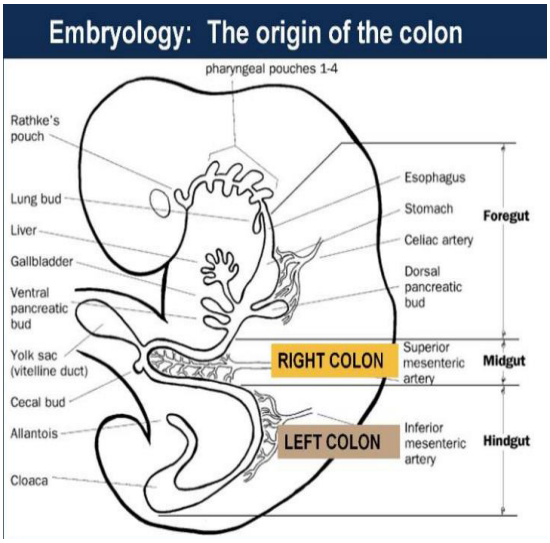
1. Figure adapted from Lee GH, et al. Eur J Surg Oncol 2015;41:300–308.

Zakaj je pomembna lokacija primarnega tumorja?

Razlike med desnim in levim kolonom

1. Embriološko/ Anatomsko

Desni in levi kolon sta z embriološkega stališča "različna" organa



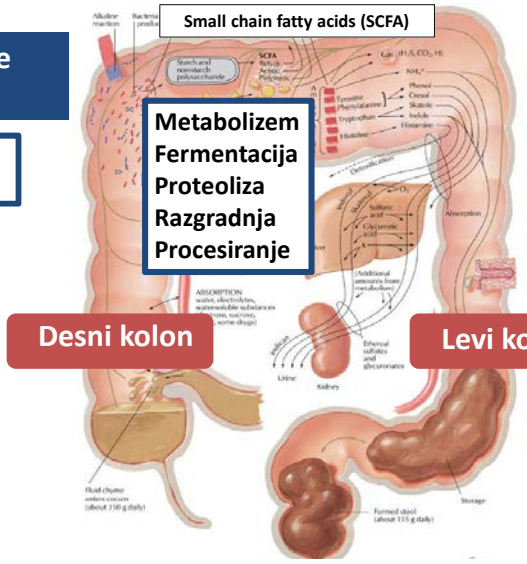
Venook A et al. ASCO 2016. Abstract 3504. Oral presentation at ASCO 2016.

Zakaj je pomembna lokacija primarnega tumorja?

Razlike med desnim in levim kolonom

2. Različne funkcije

Metabolična aktivnost



Floch M & Netter F. (2010). Netter's gastroenterology. Philadelphia: Saunders/Elsevier.

Zakaj je pomembna lokacija primarnega tumorja

Tumorji desne strani sopogosteje povezani z bakterijskimi biofilmi

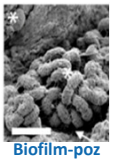
3. Mikrobiom

Proliferacija IL6
Preživetje STAT-3
Spremenjena imunost

Microbiota organization is a distinct feature of proximal colorectal cancers

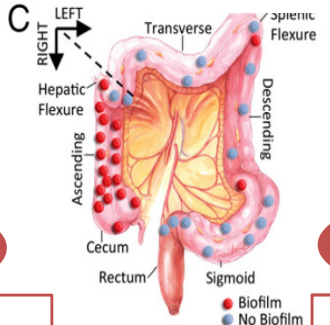
PNAS | December 23, 2014 | vol. 111 | no. 51 | 18321–18326

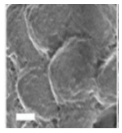
Vzrok za razliko v patogenezi med adenomom in karcinomom desnostr. vs levostr. tumorjev



Biofilm-poz desno-stranski tumor

87% biofilm-poz





Biofilm-neg levo-stranski tumor

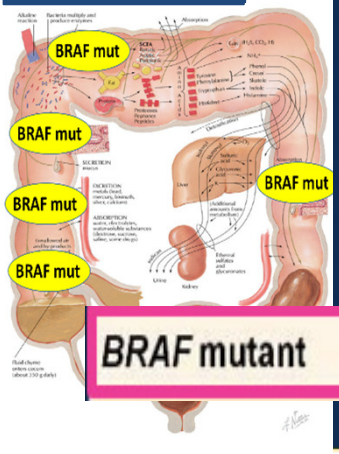
13% biofilm-poz

p=0.0001

Dejea CM, et al. Proc Natl Acad Sci USA 2014;111:18321–18326.

Zakaj je pomembna lokacija primarnega tumorja?

4. Genetika



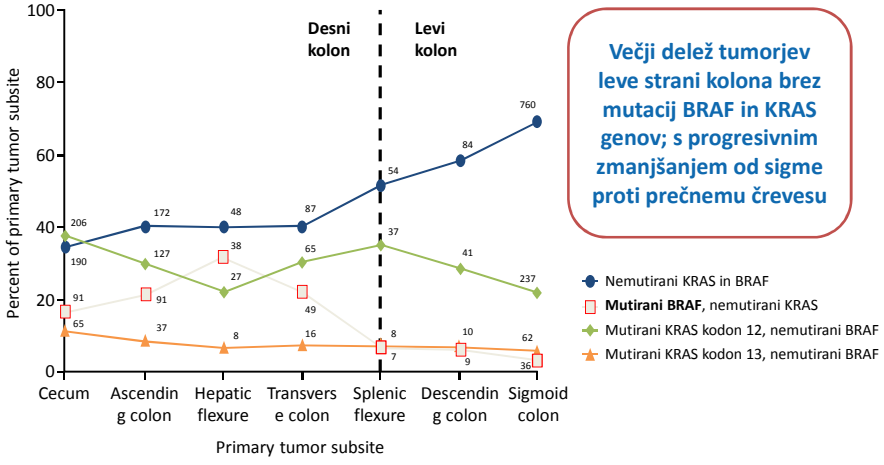
Age, MSI, *BRAF*, and Methylation (CIMP) are associated with right-sided primaries

	Right-Sided n=63 (32%)	Left-Sided n=135 (68%)	Odds Ratio	P-value
Median age	62 (30-81)	56 (24-76)	1.05 (1.02-1.08)	0.001
Male sex	37/63 (58.7%)	84/135 (62.2%)		0.64
White race	55/63 (87.3%)	103/135 (76.3%)		0.09
MSI-High	5/31 (16.1%)	2/71 (2.8%)	6.63 (1.21-36.3)	0.026
PIK3CA mutant	7/51 (13.7%)	19/112 (17.0%)		0.65
BRAF mutant	**22/61 (36.1%)**	**12/116 (10.3%)**		
CIMP High	24/63 (38.1%)	28/135 (20.7%)	2.35 (1.22-4.54)	0.015

ASCO ANNUAL MEETING '16 Presented by: Michael S. Lee, MD

1. Clarke CN & Kopetz ES. J Gastrointest Oncol 2015;6(6):660–667.
2. Lee MS et al. ASCO 2016. (Abstract 3506).

Pogostost molekularnih alteracij glede na mesto primarnega tumorja kolona (stadij III)[1]

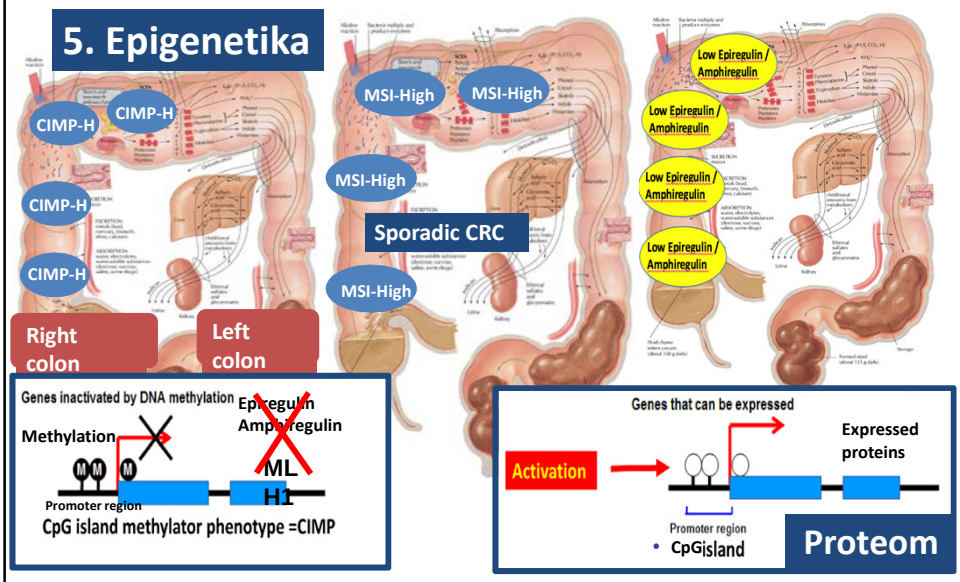


Večji delež tumorjev leve strani kolona brez mutacij BRAF in KRAS genov; s progresivnim zmanjšanjem od sigme proti prečnemu črevesu

Data are shown for KRAS and BRAFV600E mutation status as a combined variable. Separation of KRAS mutations into those located in codon 12 versus codon 13 of exon 2 is shown by tumor subsite.

1. Figure adapted from Sinicrope FA, et al. Clin Cancer Res 2015;21:5294–5304.

Epigenetske spremembe prevladujejo na desni strani kolona–„CIMP high“

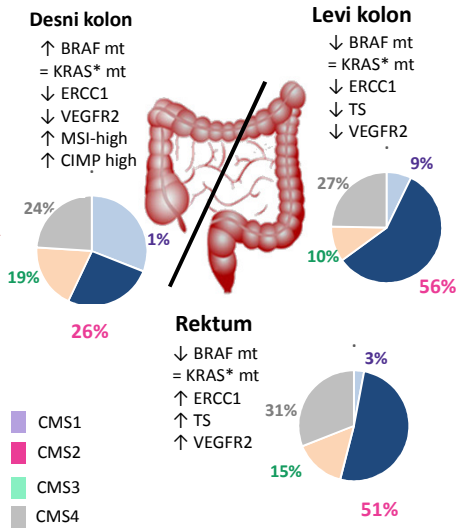


1. Floch M & Netter F. (2010). Netter's gastroenterology. Philadelphia: Saunders/Elsevier.
2. Clarke CN & Kopetz ES. J Gastrointest Oncol 2015;6(6):660–667;
3. Bettington M, et al. Histopathology 2013;62:367–386;
4. Lee M.S, et a. BJC 2016;114:1352–1361.

Ključno za razumevanje učinkov zdravljenja je poznavanje molekularne zgradbe, še posebej pri desnostranskem RDČD[1,2]

Desnostranski tumorji so povezani z:

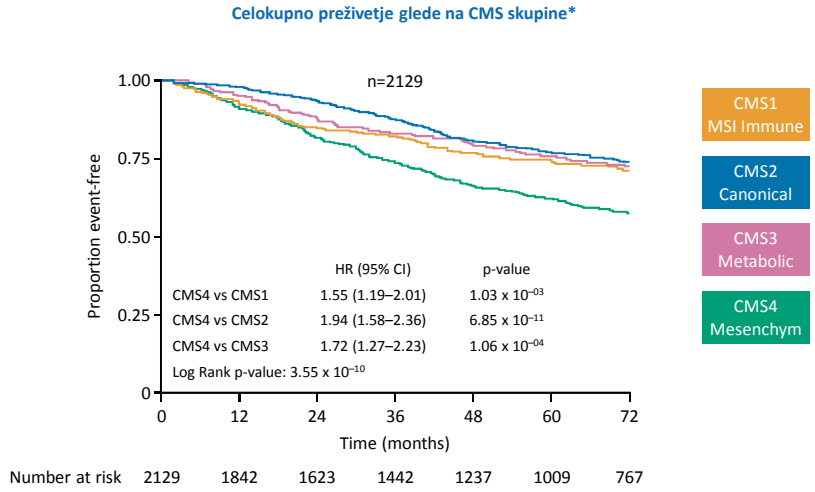
- BRAF mutacijami
- Hipermetilacijami
  - Močno regulirajo izražanje velikega števila genov, kot so EREG in AREG
- Izrazitimi vzorci izražanja genov
  - „Consensus molecular subtypes“ (CMS) 1 & 3



*No extended RAS mutation analysis was reported.
Analysis of FFPE tumor samples from 431 patients with advanced CC.
ERCC1, excision repair cross complement group 1 (low levels associated with sensitivity to platinum chemotherapy agents);
FFPE, formalin-fixed paraffin-embedded; TS, thymidylate synthase (low levels associated with sensitivity to fluoropyrimidines); VEGFR2, vascular endothelial growth factor receptor 2.

This figure has been created for illustrative purposes only using data from:
1. Maus MK, et al. Pharmacogenomics J 2015;15:354–362;
2. Guinney J, et al. Nat Med 2015;21:1350–1356.

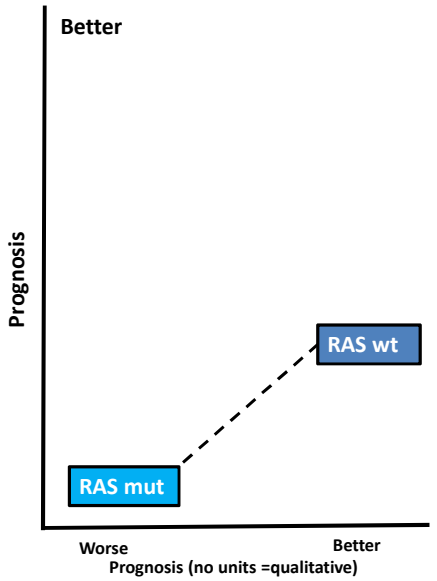
Molekularni podtipi RDČD imajo različne stopnje celokupnega preživetja[1]



CMS, Consensus Molecular Subtype.
*Central repository of 18 data sets (n=4151). Cox Proportional Hazards modelling performed in the aggregated data sets after confirming proportionality of hazards across patient cohorts. OS models included all stage I–IV patients

1. Guinney J, et al. NatMed 2015;21:1350–1356.

Kako se "biologija tumorja" izraža kot prognostični marker?



***KRAS* Mutation Status Is Predictive of Response to Cetuximab Therapy in Colorectal Cancer**

Astrid Lièvre,[1,2] Jean-Baptiste Bachet,[2] Delphine Le Corre,[1] Valérie Boige,[4] Bruno Landi,[2] Jean-François Emile,[3] Jean-François Côté,[1,2] Gorana Tomasic,[1] Christophe Penna,[3] Michel Ducreux,[4] Philippe Rougier,[5] Frédérique Penault-Llorca,[3] and Pierre Laurent-Puig[1,2]

Cancer Res 2006; 66: (8). April 15, 2006

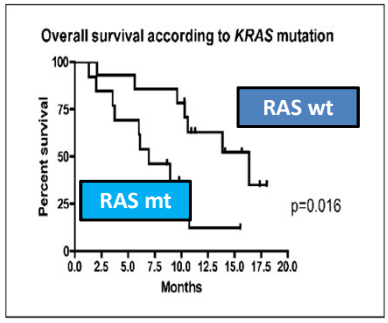
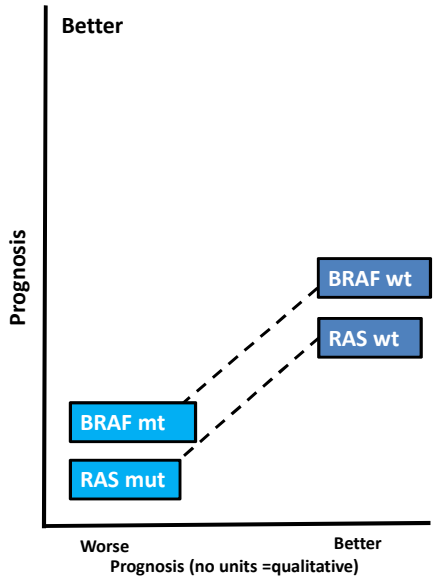


Figure 2. Overall survival curves of patients with a *KRAS*-mutated and nonmutated tumor.

1. Lievre A, et al. Cancer Res 2006;66(8):3992–3995;
2. Van Cutsem E, et al. Ann Oncol 2016;27:1386–1422;
3. Erbitux SmPC June 2014

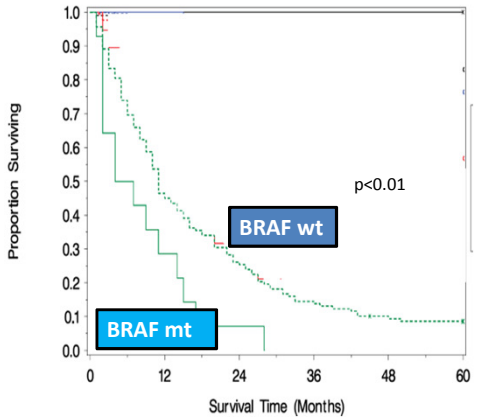
Kako se "biologija tumorja" izraža kot prognostični marker?



Poor Survival Associated with the *BRAF* V600E Mutation in Microsatellite-Stable Colon Cancers

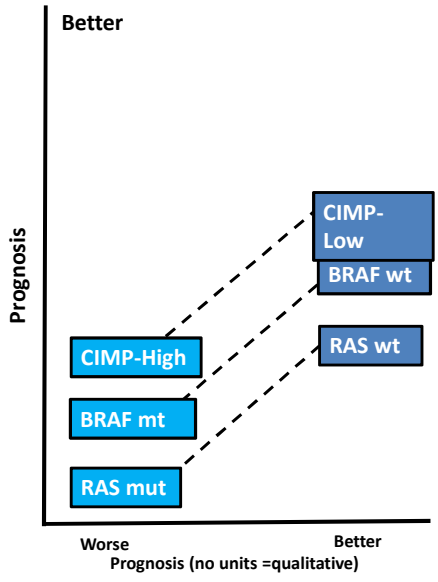
Wade S. Samowitz,[1] Carol Sweeney,[2] Jennifer Herrick,[2] Hans Albertsen,[2] Theodore R. Levin,[3] Maureen A. Murtaugh,[2] Roger K. Wolff,[2] and Martha L. Slattery[2]

6063 Cancer Res 2005; 65: (14). July 15, 2005



1. Lievre A, et al. Cancer Res 2006;66(8):3992–3995;
2. Samowitz WS, et al. Cancer Res 2005;65(14):6063–6069;
3. Erbitux SmPC June 2014.

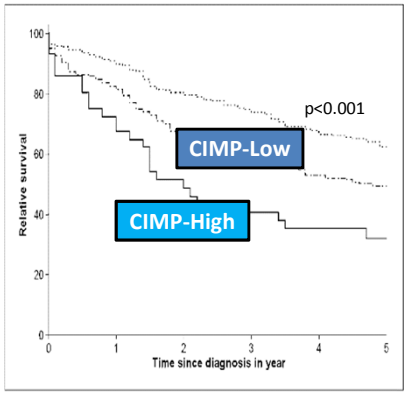
Kako se "biologija tumorja" izraža kot prognostični marker?



Hypermethylator Phenotype in Sporadic Colon Cancer: Study on a Population-Based Series of 582 Cases

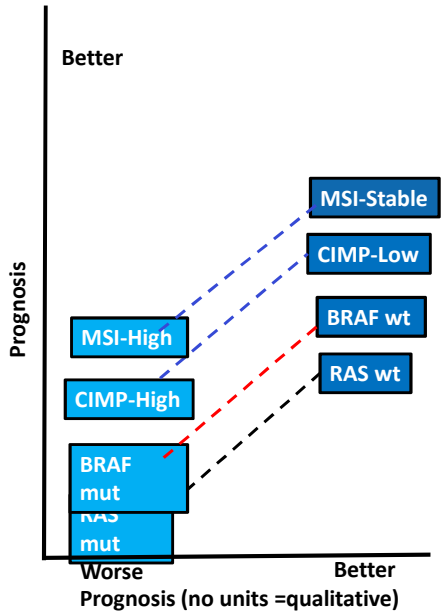
Ludovic Barault,[1,2] Céline Charon-Barra,[1,2] Valérie Jooste,[1,3] Mathilde Funes de la Vega,[2] Laurent Martin,[2] Patrick Roignot,[1] Patrick Rat,[5] Anne-Marie Bouvier,[1,3,6] Pierre Laurent-Puig,[7] Jean Faivre,[1,3,6] Caroline Chapusot,[1,2] and Francoise Piard[1,2]

8541 Cancer Res 2008; 68: (20). October 15, 2008



1. Lievre A, et al. Cancer Res 2006;66(8):3992–3995;
2. Samowitz WS, et al. Cancer Res 2005;65(14):6063–6069;
3. Barault L, et al. Cancer Res 2008;68(20):8541–8546;
4. Erbitux SmPC June 2014.

Kako se "biologija tumorja" izraža kot prognostični marker?



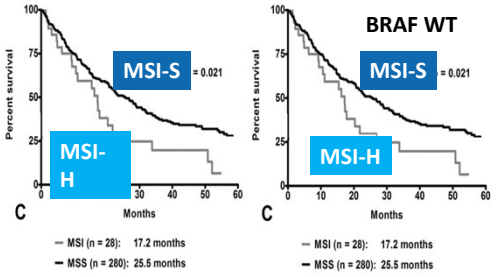
Impact of BRAF Mutation and Microsatellite Instability on the Pattern of Metastatic Spread and Prognosis in Metastatic Colorectal Cancer

Ben Tran, MBBS[1]; Scott Kopetz, MD[2]; Jeanne Tie, MBBS, MD[3]; Peter Gibbs, MBBS, MD[3,4]; Zhi-Qin Jiang, MD[2]; Christopher H. Lieu, MD[2]; Atin Agarwal, MD[5]; Dipen M. Maru, MD[5]; Oliver Sieber, PhD[3,4]; and Jayesh Desai, MBBS[3,4]

MSI tumors were observed to have significantly poorer survival compared with MSS tumors (11.1 months vs 22.1 months, $P < .001$).

....contrary to the early stage colon

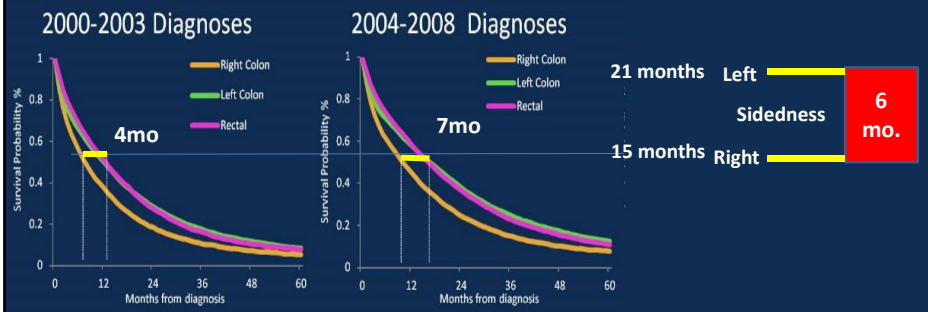
Metastatic disease



1. Tran, B. et al., Cancer. 2011;117(20):4623-32

Overall Survival for Stage IV CRC

All RAS wt + mt by Primary Tumor Location and Year of Diagnosis

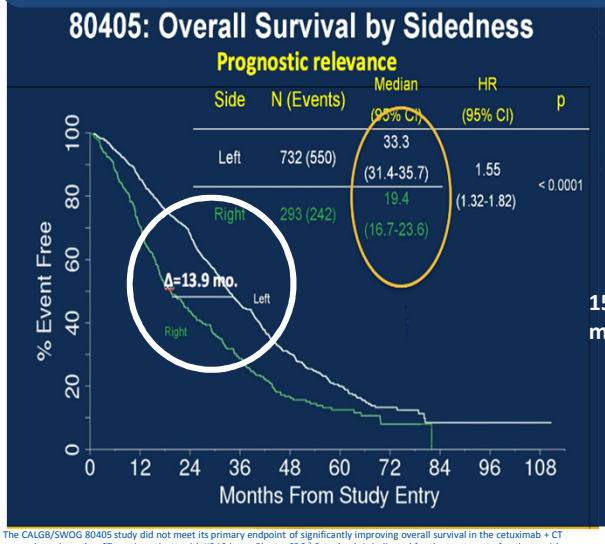


Pred uvedbo tarčnih zdravil, je *LOKACIJA TUMORJA* prispevala 4–7 mesecev razlike (povp. 6 m) v *srednjem preživetju* med desnim in levim kolonom (ob zdravljenju s *KEMOTERAPIJO)*

Right vs. Left Colon	0.82	0.78-0.85	0.84	0.82-0.87
Rectal vs. Left Colon				

1. Schrag D, et al. ASCO 2016 (Abstract No. 3505).

***Po uvedbi tarčnih zdravil*, je *LOKACIJA TUMORJA na levi strani, postala še bolj prepričljiv* PROGNOSTIČNI marker, izražen kot PREDIKTIVNI marker odgovora na tarčna zdravila**

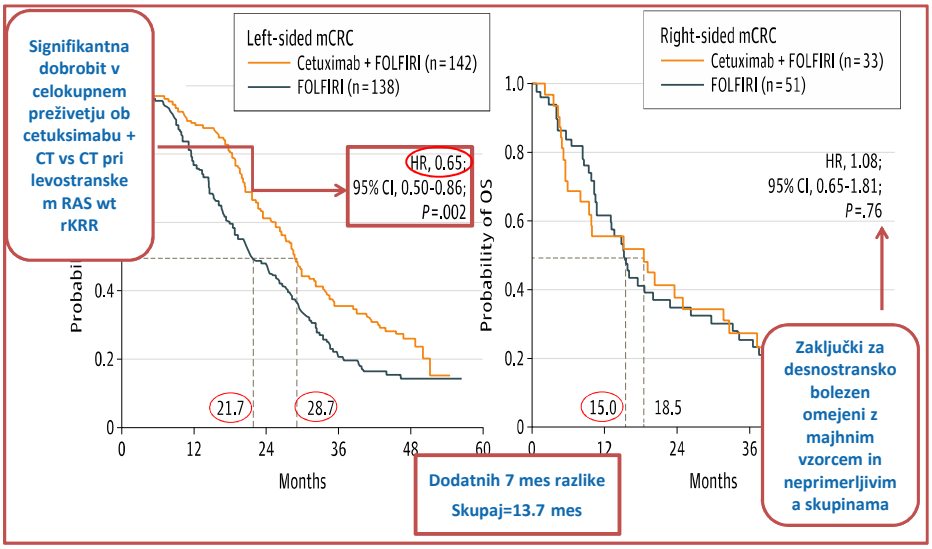


The CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving overall survival in the cetuximab + CT arm vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC.[2] Cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX and as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan[3]

1. Venook AP, et al. ASCO 2016 (Abstract No. 3504);
2. Venook A, et al JAMA. 2017;317:2392-2401;
3. Erbitux SmPC June 2014.

Podatki iz randomizirane raziskave faze III: cetuksimab + KT vs KT

CRYSTAL: podatki o celokupnem preživetju glede na lokacijo tumorja

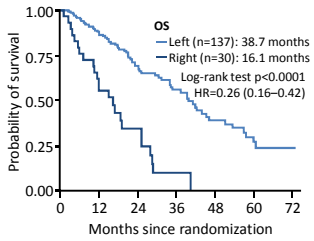


1. Tejpar S, et al. JAMA Oncol 2016; epub 10 Oct 2016;
2. Van Cutsem E, et al. Oral presentation at ESMO 2016

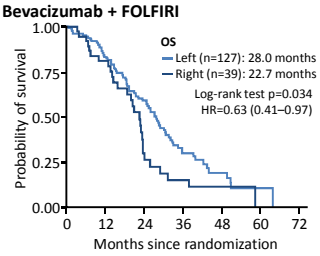
Lokacija primarnega RDČD je uveljavljen prognostični dejavnik

FIRE-3* raziskava (RAS wt)

OS: Cetuximab + FOLFIRI



OS: Bevacizumab + FOLFIRI



- Slabši izidi zdravljenja pri tumorjih desne strani, neglede na prejeto zdravljenje

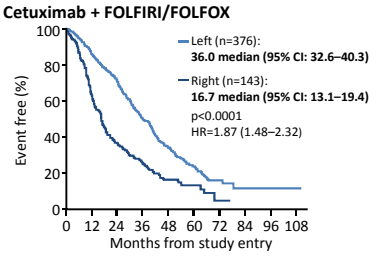
Interpretacija je omejena z:
- Retrospectivno analizo
- Majhnim številom desnostranskih tumorjev
- Možno neprimerljivostjo značilnosti bolnikov

1. Figures adapted from Heinemann V, et al. ASCO 2014 (Abstract No. 3600), updated information presented at meeting: http://meetinglibrary.asco.org/content/96810?media=vm&poster=1 (accessed June 22 2016); 2. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075.

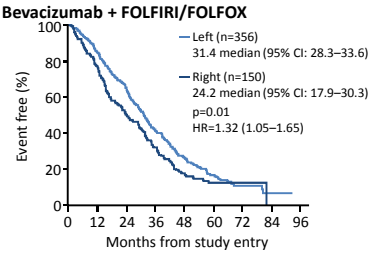
Lokacija primarnega RDČD je uveljavljen prognostični dejavnik

CALGB/SWOG 80405* raziskava (KRAS exon 2 wt):[1]

OS: Cetuximab + FOLFIRI/FOLFOX



OS: Bevacizumab + FOLFIRI/FOLFOX



- Slabši izidi zdravljenja pri tumorjih desne strani, neglede na prejeto zdravljenje

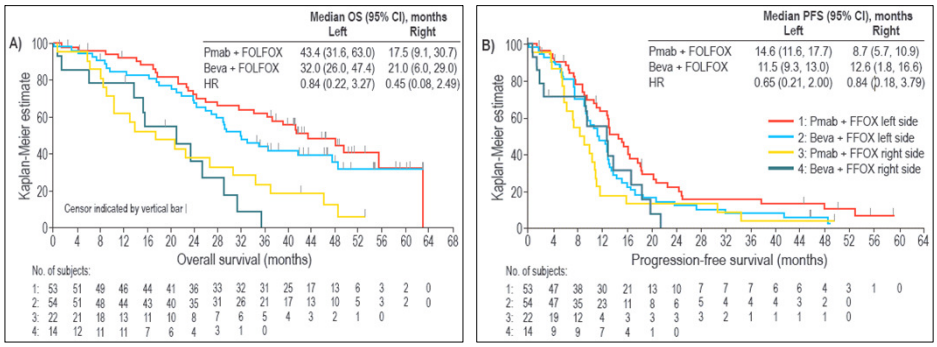
Interpretacija je omejena z:
- Pomanjkanjem podatkov glede RAS statusa
- Retrospectivno naliza
- Majhnim število desnostranskih tumorjev

1. Figure adapted from Venook A, et al. ASCO 2016 (Abstract No. 3504); updated data presented at the meeting: http://meetinglibrary.asco.org/content/123617?media=sl (accessed June 22 2016); 2. Venook AP, et al. ASCO 2014 (Abstract No. LBA3), updated information presented at meeting: http://meetinglibrary.asco.org/content/94399?media=sl (accessed June

Boeckx N, et al. Primary Tumor Sidedness Impacts on Prognosis and Treatment Outcome

A) OS in B) PFS glede na lokacijo tumorja - PEAK raziskava (*RAS* WT populacija)

OS **PFS**



Beva = bevacizumab; CI = confidence interval; FFOX = FOLFOX; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; Pmab = panitumumab.

Boeckx N, et al. Primary Tumor Sidedness Impacts on Prognosis and Treatment Outcome

RAS/BRAF WT Disease

- Prognosis remained poor for patients with right-sided tumors after excluding those with *BRAF* mutant disease
  - There were no significant changes compared with results for the *RAS* WT population

Table 5. OS, PFS and Response Rate by Tumor Side (*RAS/BRAF* WT Population)

	Patients, n (L/R)	Median OS (95% CI), months		Median PFS (95% CI), months		CR + PR, %	
		Left	Right	Left	Right	Left	Right
PRIME (1st line)							
Pmab + FOLFOX	156/26	32.5 (27.5, 37.6)	22.5 (8.1, 30.8)	12.9 (10.0, 14.9)	8.9 (5.5, 11.3)	70.3	52.0
FOLFOX	148/32	23.6 (18.2, 27.7)	21.5 (10.8, 26.0)	9.3 (7.7, 10.8)	7.3 (4.2, 11.1)	54.8	41.4
HR (95% CI)		0.67 (0.52, 0.86)	0.94 (0.53, 1.67)	0.69 (0.54, 0.88)	0.71 (0.4, 1.27)		
PEAK (1st line)							
Pmab + FOLFOX	52/13	43.4 (34.2, 63.0)	22.5 (8.4, 36.9)	14.6 (11.6, 18.1)	10.3 (6.1, 11.6)	63.5	69.2
Beva + FOLFOX	53/13	32.0 (26.9, 48.5)	23.3 (6.0, 29.0)	11.5 (9.3, 13.0)	12.6 (1.8, 18.4)	58.5	46.2
HR (95% CI)		0.77 (0.46, 1.28)	0.63 (0.26, 1.54)	0.67 (0.44, 1.02)	0.88 (0.39, 2.02)		
181 (2nd line)							
Pmab + FOLFIRI	143/22	20.1 (16.6, 21.7)	11.9 (6.4, 16.0)	8.0 (7.3, 9.3)	6.8 (3.7, 10.3)	50.7	19.0
FOLFIRI	144/26	16.9 (15.1, 22.2)	10.9 (6.7, 13.0)	6.6 (5.3, 7.4)	3.7 (2.0, 5.9)	13.5	3.8
HR (95% CI)		0.97 (0.76, 1.26)	0.84 (0.46, 1.54)	0.89 (0.70, 1.14)	0.62 (0.34, 1.13)		

DoR = duration of response; n = number of patients; NE = not evaluable.

Zaključki:

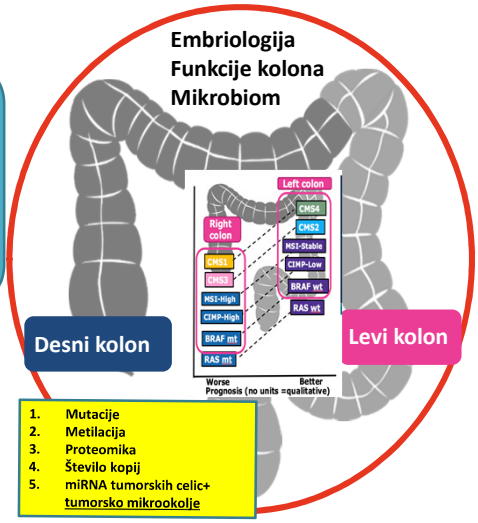
1. Lokacija tumorja združuje vse prognostične označevalce povezane z rakom kolona kot "master" prognostični dejavnik.

$$F(x) = \int f(x)\,dx.$$

prognostični dejavniki = LOKACIJA TUMORJA ("master" prognostični marker)

Lokacija tumorja (D + L), PROGNOSTIČNI DEJAVNIKI

Embriologija
Funkcije kolona
Mikrobiom



Desni kolon

Levi kolon

1. Mutacije
2. Metilacija
3. Proteomika
4. Število kopij
5. miRNA tumorskih celic+ tumorsko mikrookolje

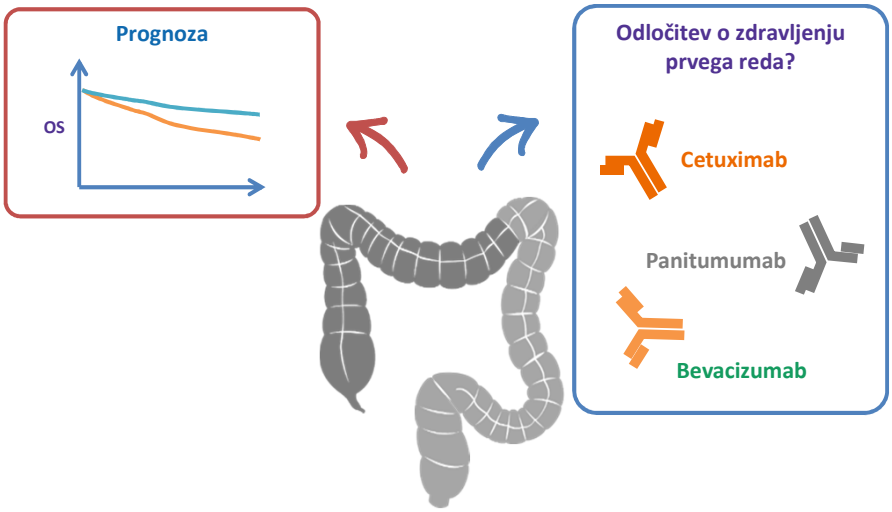
1. Lievre A, et al. Cancer Res 2006;66(8):3992–3995.
2. Samowitz WS, et al. Cancer Res 2005;65(14):6063–6069.
3. Barault L, et al. Cancer Res 2008;68(20):8541–8546.
4. Messersmith W, et al. ASCO 2017. oral presentation;
5. Tran B, et al. Cancer 2011;117:4623–32;
6. Heinemann V et al. Lancet Oncol 2014;15:1065–1075;
7. Venook A, et al JAMA. 2017;317:2392-2401.

2. Leva in desna stran tumorja sta PROGNOSTIČNI marker
   - LEVA stran TUMORJA pomeni najboljši PREDIKTIVNI marker boljšega odgovora na anti-EGFR tarčna zdravila

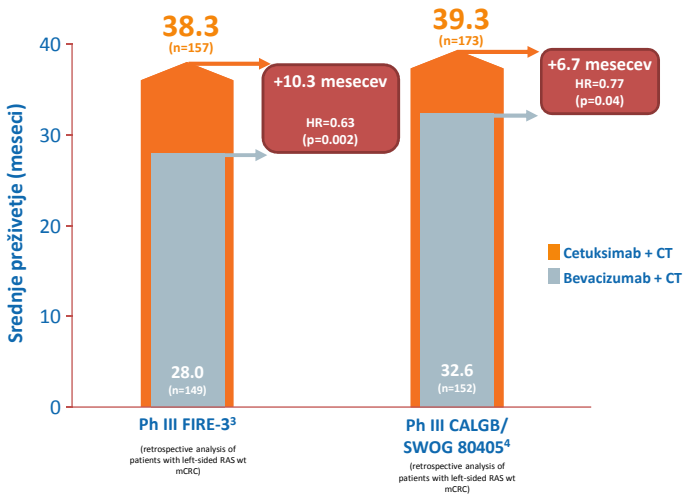
Lokacija tumorja (D + L), PROGNOSTIČNI DEJAVNIK

PROGNOSTIČNO

VPLIV LOKACIJE PRIMARNEGA TUMORJA NA PROGNOZO IN ODLOČITEV O ZDRAVLJENJU: KAJ JE PRAVILNA ODLOČITEV?

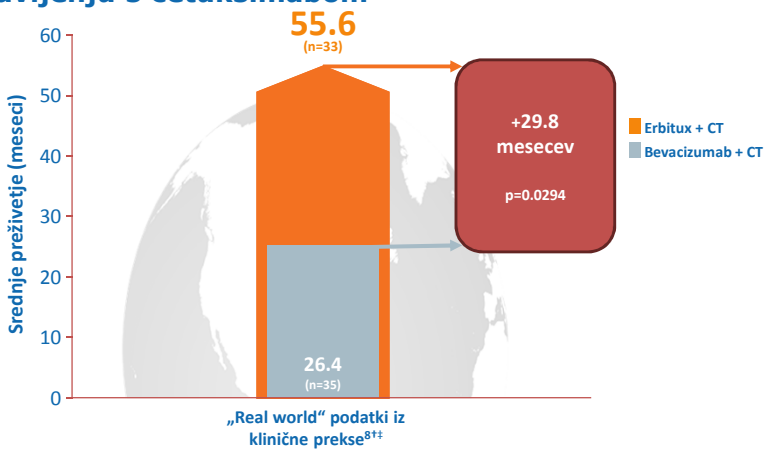


- Podatki iz randomiziranih raziskav faz III:
- pri bolnikih z RAS wt RDČD cetuksimab dosledno zagotavlja dobrobit v preživetju napram bevacizumabu [3,4]



28

Podatki iz klinične prakse: več kot 55 mesecev srednjega preživetja pri bolnikih z levostranskimi tumorji ob zdravljenju s cetuksimabom[8†‡]



†In this Japanese single-institution, retrospective, case-control study, all Erbitux-treated patients had KRAS wt mCRC, whereas those who received bevacizumab had KRAS wt or KRAS mt tumor status[8].‡Erbitux is currently indicated for patients with EGFR-expressing, RAS wt mCRC: in combination with irinotecan-based chemotherapy, or in 1st line in combination with FOLFOX, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. Erbitux should not be used in the treatment of CRC patients whose tumors have RAS mutations or for whom RAS tumor status is unknown.[9]

29

Izidi zdarvljenja s pomočjo analize lokacije tumorja? Rezultati učinkovitosti po lokaciji tumorja pri bolnikih z RAS WT boleznijo

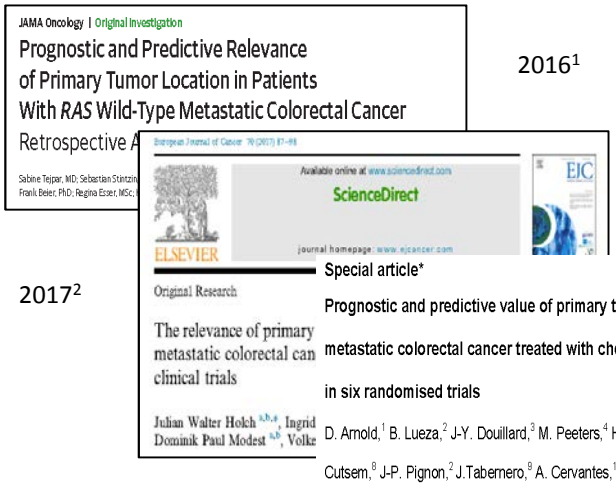
	PRIME		PEAK		Study 181	
WT *RAS*	**Pmab + FOLFOX**	**FOLFOX**	**Pmab + FOLFOX**	**Bev + FOLFOX**	**Pmab + FOLFIRI**	**FOLFIRI**
Pts, n (left/right)	169/39	159/49	53/22	54/14	150/31	148/39
Median OS, months						
Left	30.3	23.6	43.4	32.0	20.1	16.6
HR (95% CI)	0.73 (0.57–0.93)		NA†		0.96 (0.74–1.23)	
Right	11.1	15.4	17.5	21.0	10.3	8.1
HR (95% CI)	0.87 (0.55–1.37)		NA†		1.14 (0.68–1.89)	
Median PFS, months						
Left	12.9	9.2	14.6	11.5	8.0	5.8
HR (95% CI)	0.72 (0.57–0.90)		NA†		0.88 (0.69–1.12)	
Right	7.5	7.0	8.7	12.6	4.8	2.4
HR (95% CI)	0.80 (0.50–1.26)		NA†		0.75 (0.45–1.27)	
CR + PR, %						
Left	68	53	64	57	50	13
Right	42	35	64	50	13	3

Boeckx N, et al. Ann Oncol 2016;27(Suppl 6):abstract 89P (and poster).

†Updated values will be included in the full publication.

Pomen lokacije primarnega tumorja kolona

Nove publikacije retrospektivnih meta analiz


JAMA Oncology | Original Investigation

Prognostic and Predictive Relevance of Primary Tumor Location in Patients With *RAS* Wild-Type Metastatic Colorectal Cancer Retrospective A

Sabine Tejpar, MD; Sebastian Stintzi
Frank Beier, PhD; Regina Esser, MSc;

2016[1]

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

EJC

Original Research

The relevance of primary metastatic colorectal can clinical trials

Julian Walter Holch [a,b,*], Ingrid
Dominik Paul Modest [a,b], Volke

2017[2]

Special article*

Prognostic and predictive value of primary tumour side in patients with *RAS* wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomised trials

D. Arnold,[1] B. Lueza,[2] J-Y. Douillard,[3] M. Peeters,[4] H-J. Lenz,[5] A. Venook,[6] V. Heinemann,[7] E. Van Cutsem,[8] J-P. Pignon,[2] J.Tabernero,[9] A. Cervantes,[10] F. Ciardiello[11]

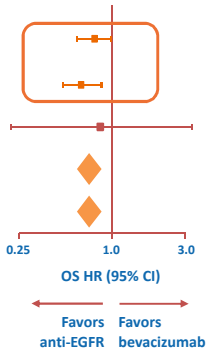
2017[3]

1. Tejpar S, et al. JAMA Oncol 2016;3797;
2. Holch JW, et al. EJC 2017;87-98
3. Arnold D, et al. Ann of Onc, epub 2017

META-ANALIZA HOLCH ET AL.: STATISTIČNO POMEMBNA DOBROBIT V CELOKUPNEM PREŽIVETJU OB ANTI-EGRF+ KT (NAPRAM BEVACIZUMABU + CT) V 1. REDU ZDRAVLJENJA LEVOSTRANSKIH RAS WT RDČD[1]

Trial	Weight, %	OS HR (95% CI)	p-value
CALGB/SWOG 80405 (n=325)	53.8	0.77 (0.59–0.99)	
FIRE-3 (n=306)	44.2	0.63 (0.48–0.85)	
PEAK (n=107)	2.0	0.84 (0.22–3.27)	
Summary (fixed effects)		0.71 (0.58–0.85)	0.0003
Summary (random effects)		0.71 (0.58–0.85)	0.0003

Heterogeneity: I^2=0% (95% CI: 0–95.1)
p=0.575 (chi-squared test)



85% bolnikov iz analize je bilo v raziskavah faz III zdravljenih s cetuksimabom

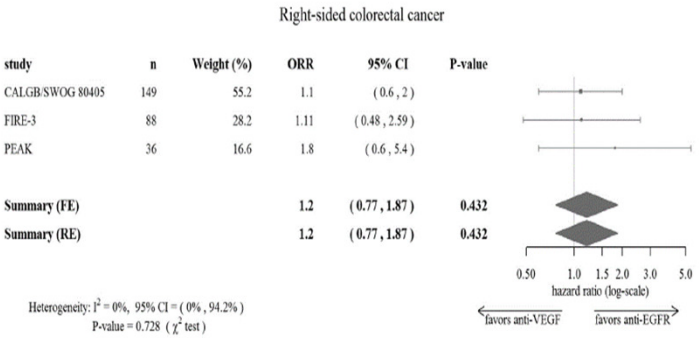
Zaključek *Holch meta-analize: RAS wt rKRR bolniki s tumorji leve strani bi morali biti zdravljeni z anti-EGFR tarčnimi zdravili*[1]

FIRE-3 did not meet its primary endpoint of significantly improving overall response rate (ORR) based on investigators' read in patients with KRAS (exon 2) wt mCRC.[2] The CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving overall survival in the cetuximab + CT arm vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC[3]

1. Figure adapted from Holch JW, et al. Eur J Cancer 2017;70:87–9;
2. Heinemann V et al. Lancet Oncol 2014;15:1065–1075;
3. Venook A, et al JAMA. 2017;317:2392-2401

HOLCHOVA META-ANALIZA: ANTI-EGFR ZDRAVILA POVEČAJO ODGOVOR NA ZDRAVLJENJE PRI DESNOSTRANSKIH RAS WT RDČD[1]

1. red zdravljenja: anti-EGFR + CT napram anti-VEGF + CT



1. Holch JW, et al. Eur J Cancer 2017;70:87–9;
2. Heinemann V et al. Lancet Oncol 2014;15:1065–1075;
3. Venook A, et al JAMA. 2017;317:2392-2401

ARNOLD META-ANALIZA: ANTI-EGFR ZDRAVILA POVEČAJO ODGOVOR NA ZDRAVLJENJE PRI DESNOSTRANSKIH RAS WT RDČD[1]

1/2. red zdravljenja: anti-EGFR + CT vs CT ± bevacizumab pri desno stranskih RAS wt rKRR

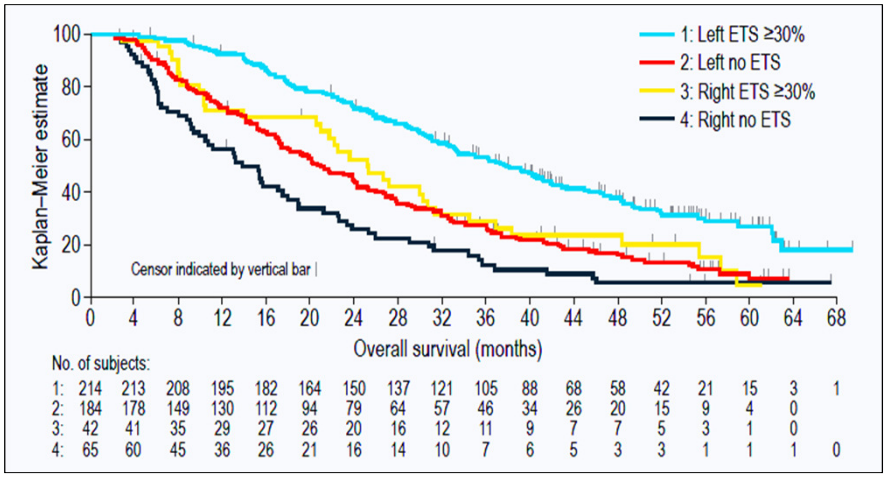
	Odds ratio (95% CI)
ORR	1.47 (0.94–2.29)

"Ko gre za bolnike s RAS wt rKRR tumorji desne strani, je po podatkih o stopnjah odgovora iz predstavljenje analize, dvojček KT z anti-EGFR zdravilom primerna izbira"[1]

Table created with data from:
1. Arnold D, et al. Ann Oncol 2017; epub Apr 12;
2. Heinemann V et al. Lancet Oncol 2014;15:1065–1075;
3. Venook A, et al JAMA. 2017;317:2392-2401.

Peeters M, et al. Impact of Primary Tumour Location on Outcomes in Patients with mCRC Undergoing First-Line Treatment

Vpliv lokacije primarnega tumorja in zgodnjega zmanjšanja tumorja na celokupno preživetje **(Pooled Analysis)**



PRIPOROČILA ZA DESNOSTRANSKE RAS WT RDČD IZ HOLCHOVE TER ARNOLDOVE META-ANALIZE: POTRJENA Z NEDAVNO ANALIZO RAZISKAVE FAZE III-FIRE-3[1]

Učinkovitost pri desnostranskih RAS wt RDČD, ki so imeli ETS* ≥20%[1]

	Cetuximab + CT (n=17)	Bev + CT (n=16)	HR/OR (p-value)
Median PFS, months	7.8	13.4	1.72 (p=0.14)
Median OS, months	27.9	23.2	1.05 (p=0.90)
DpR, %	58	41	N/A (p=0.30)
ORR, %	88	94	0.5 (p=0.99)

Primerljiva učinkovitost cetuksimaba in bevacizumaba pri bolnikih z desnostranskimi RAS wt RDČD, ki so imeli ETS*

Ko je cilj zdravljenja citoredukcija, je anti- EGFR + KT učinkovita izbira 1. reda zdravljenja za desnostranske RAS wt RDČD[2,3]

*ETS, Early tumor shrinkage

1. Holch JW, et al. ASCO 2017 (Abstract No. 3586);
2. Arnold D, et al. Ann Oncol 2017; epub Apr 12; 3. Holch JW, et al. Eur J Cancer 2017;70:87–98;
4. Heinemann V et al. Lancet Oncol 2014;15:1065–1075.

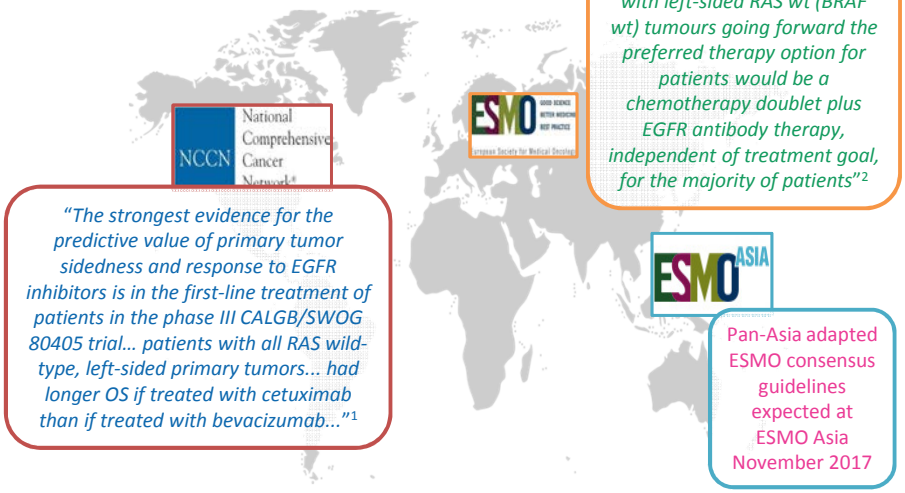
Izidi zdarvljenja s pomočjo analize lokacije tumorja? Rezultati učinkovitosti po lokaciji tumorja pri bolnikih z RAS WT/ BRAF WT boleznijo

	PRIME		PEAK		Study 181	
WT *RAS*/ WT *BRAF*	**Pmab + FOLFOX**	**FOLFOX**	**Pmab + FOLFOX**	**Bev + FOLFOX**	**Pmab + FOLFIRI**	**FOLFIRI**
Pts, n (left/right)	156/26	148/32	52/13	53/13	143/22	144/26
Median OS, months						
Left	32.5	23.6	43.4	32.0	20.1	16.9
HR (95% CI)	0.67 (0.56–0.86)		0.77 (0.46–1.28)		0.97 (0.76–1.26)	
Right	22.5	21.5	22.5	23.3	11.9	10.9
HR (95% CI)	0.94 (0.53–1.67)		0.63 (0.26–1.54)		0.84 (0.46–1.54)	
Median PFS, months						
Left	12.9	9.3	14.6	11.5	8.0	6.6
HR (95% CI)	0.69 (0.54–0.88)		0.67 (0.44–1.02)		0.89 (0.70–1.14)	
Right	8.9	7.3	10.3	12.6	6.8	3.7
HR (95% CI)	0.71 (0.4–1.27)		0.88 (0.39–2.02)		0.62 (0.34–1.13)	
CR + PR, %						
Left	70.3	54.8	63.5	58.5	50.7	13.5
Right	52.0	41.4	69.2	46.2	19.0	3.8

Boeckx N, et al. Ann Oncol 2016;27(Suppl 6):abstract 89P (and poster).

Mednarodne smernice za zdravljenje rKRR: Glede na lokacijo primarnega tumorja

"For the treatment of patients with left-sided RAS wt (BRAF wt) tumours going forward the preferred therapy option for patients would be a chemotherapy doublet plus EGFR antibody therapy, independent of treatment goal, for the majority of patients"[2]

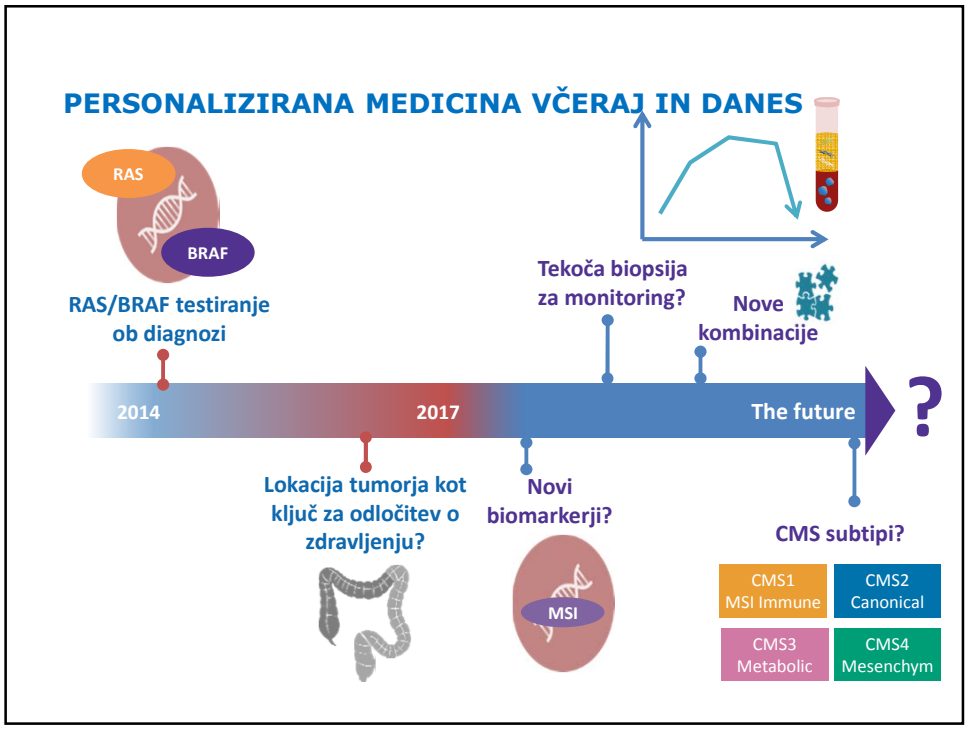


"The strongest evidence for the predictive value of primary tumor sidedness and response to EGFR inhibitors is in the first-line treatment of patients in the phase III CALGB/SWOG 80405 trial… patients with all RAS wild-type, left-sided primary tumors... had longer OS if treated with cetuximab than if treated with bevacizumab..."[1]

Pan-Asia adapted ESMO consensus guidelines expected at ESMO Asia November 2017

The CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving overall survival in the cetuximab + CT arm vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC[3] Cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX and as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan[4]

1. NCCN guidelines. Colon Cancer Version 2.2017;
2. Arnold D, et al. Ann Oncol 2017;28:1713–1729;
3. Venook A, et al JAMA. 2017;317:2392-2401;
4. Erbitux SmPC June 2014.



HVALA ZA POZORNOST!

40

NOVOSTI V ADJUVANTNEM ZDRAVLJENJU RAKA TREBUŠNE SLINAVKE

mag. Zvezdana Hlebanja, dr. med. spec. internistične onkologije

RAK TREBUŠNE SLINAVKE

- Pogost (7. najpogostejši v Evropi, je 4. najpogostejši vzrok smrti zaradi raka, incidenca narašča)
- V Sloveniji cca. 400 bolnikov na leto (več žensk)
- 5 letno preživetje le 5-6%
- Ob radikalni kirurgiji cca. 10%
- 15-20% resektabilnih
- Po R0 resekciji: > 80% metastazira (MS 3-6 mesecev), > 20% lokalnih ponovitev (MS 8-12 mesecev)

ZAHRBTEN, POZNO ODKRIT, HITRO POTEKAJOČ, SMRTEN

Stage	Description	Possible Treatments	Stage at Diagnosis	5 Year Survival Rate
Stage 0	Local, abnormal cells yet to be formed into tumor	None needed	7%	20%
Stage I	Tumor about 2 cm, found in pancreas only	Surgery, Surgery with chemo and radiation		
Stage II	Spread to nearby tissues and organs and possibly lymph nodes	Surgery, Surgery with chemo and radiation	26%	8.2%
Stage III	Spread to major blood vessels near pancreas and possibly lymph nodes	Surgery with chemo and radiation, chemo with Gemzar, clinical trial therapies		
Stage IV	Cancer of any size that has spread to distant organs	Chemo with Gemzar, Treatments for pain, Clinical trial therapies	52%	1.8%
Recurrent Cancer	Cancer thought to be removed has return and spread throughout the body	Chemo with Gemzar, Treatments for pain, Clinical trial therapies	N/A	<1%

RAK TREBUŠNE SLINAVKE

- 95% neoplazem trebušne slinavke so eksokrini raki
- Simptomi bolezni nastopijo pozno (bolečina, zlatenica, izguba teže)
- Prva diagnostična metoda je običajno UZ (odkrije tu > 3cm)
- ERCP diagnostična in terapevtska metoda za razrešitev zlatenice
- Za določitev stadija bolezni CT prsnega koša in CT trebuha (ali MRI trebuha)
- Pred zdravljenjem določitev TM CA 19-9
- Histološka potrditev (ni vedno nujna)

ZDRAVLJENJE

- Zahteva multidisciplinarni pristop
- Edino kurativno zdravljenje je kirurško
- Odvisno od razširjenosti bolezni, PS bolnika, komorbidnosti in preferenc bolnika
- Nujno je agresivno zdravljenje bolečine in drugih z rakom povezanih simptomov – zgodnja vključitev v paliatvno oskrbo!
- Zdravljenje je:
  - adjuvantno/R0 resekcija
  - zdravljenje napredovale bolezni (metastatska ali lokalno napredovala)

PS BOLNIKA!

WHO/ ECOG/ ZUBROD	Karnofsky	Status bolnika
0	100	aktiven, brez znakov bolezni
1	90	aktiven, minimalni znaki bolezni
1	80	zmanjšana aktivnost, zmerni znaki bolezni
2	70	ni normalne aktivnosti, skrbi zase
2	60	potrebuje občasno pomoč
3	50	pogosto potrebuje pomoč in zdravniško oskrbo
3	40	prizadet, potrebuje posebno oskrbo
4	30	močno prizadet, indicirana hospitalizacija
4	20	zelo bolan, nujna hospitalizacija, aktivna terapija
4	10	moribunden
5	0	smrt

ADJUVANTNO ZDRAVLJENJE

- Proporočeno za vse bolnike po R0 resekciji (tudi T_1N_0)
- Začne naj se 8-12 tednov po operaciji (do primernega okrevanja po operaciji)
- Traja naj 6 mesecev
- Pred začetkom adjuvantne kemoterapije opravimo:
  - Restaging CT
  - Določimo tumorski marker (CA 19-9)
- Nivo CA 19-9 je prognostični, ne prediktivni glede dobrobiti ADJ th (<= 180 kU/L, sicer obravnavamo kot napredovalo bolezen)

IZBIRA ADJUVANTNE TERAPIJE

- Bolnikom informacije o potekajočih kliničnih študijah
- PRIPOROČAMO 6M KOMBINACIJE GEM+CAP ZA VEČINO BOLNIKOV
- GEMZAR MONO JE RAZUMNA IZBIRA PRI PS>1, OZ KO GRE ZA KOMORBIDNOST, KI PREPREČUJE AGRESIVNO TERAPIJO
- Vloga adjuvantne radiokemoterapije ostaja kontraverzna, večina EU le KT, ZDA bodisi RT/KT ali KT

SMERNICE

- **ESMO smernice:**
  - RT/KT adjuvantno le v sklopu randomiziranih kontroliranih študij
- **Japonski pristop:** KT, S_1, Gemzar
- **ZDA, NCCN smernice:**
  - adjuvantna KT
  - adjuvantna RT/KT – visoka možnost lokalne ponovitve, visok odstotek pozitivnih retroperitonealnih robov (R1 resekcija), izboljšano preživetje (GITSG študija)
- **ASCO smernice:**
  - adjuvantna KT (Gemzar), ki ji sledi KT/RT (5-FU), za bolnike z N+ tumorji in za bolnike po R1 resekciji
  - nosilci BRCA1/BRCA 2, se adjuvantno zdravijo enako kot ostali
  - močnejši bolniki naj dobijo polni odmerek izračunan na površino

DOBROBIT ADJUVANTNE KEMOTERAPIJE

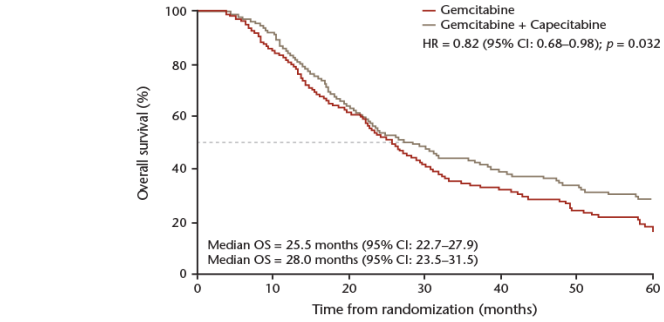
- Številne randomizirane študije so pokazale dobrobit adjuvantne kemoterapije po R0 in R1 resekcijah

- Kemoterapija, ki temelji na **preparatih 5-FU**:
  - *ESPAC-1:* signifikantna dobrobit adjuvantne kemoterapije (MS 19,7M vs 14M), ni signifikantne dobrobiti RT/KT v primerjavi s KT (celo nekoliko slabše preživetje)
  - Norveška študija: potrdi dobrobit adjuvantne kemoterapije (MS 23M vs 11M) – FAM
- Kemoterapija, ki temelji na **Gemcitabinu**:
  - *CONKO-001:* potrdi signifikantno izboljšanje OS in 5 let OS (Gemzar vs kontrola, 21% vs 10%)
- **Gemzar vs 5-FU:**
  - *ESPAC-3:* MS podoben (23.6M vs 23M), PFS podoben, vendar 5-FU bolj toksičen (več G3,4), stomatitis, diareja, hospitalizacije

DOBROBIT ADJUVANTNE KEMOTERAPIJE

- **NOVO!**
  Gemcitabin + Kapecitabin vs Gemcitabin:

ESPAC-4:
- 730 bolnikov,
- R0 in R1(60%), N+(80%)
- Gem vs GemCap
- OS 25,5M vs 28M
- 5 letni OS = 9% vs 19%



Number at risk							
Gemcitabine	366	302	207	109	61	27	9
Gemcitabine + Capecitabine	364	328	219	139	83	50	19

CI = confidence interval; HR = hazard ratio; OS = overall survival

POTEKAJOČE ŠTUDIJE

- Potekajo nove študije z agresivnimi kombinacijami citostatikov v adjuvantnem zdravljenju
- Trenutno dve:
  - APACT (Gem vs Nab Pacli/Gem)
  - PRODIGE (Gem vs Folfirinox)

POVZETEK IN PRIPOROČILA

- Primarna resekcija je indicirana pri bolnikih z rakom trebušne slinavke, ki:
  - nimajo oddaljenih metastaz (CT, MRI pred operacijo CA 19-9),
  - so v primernem PS,
  - nimajo radioloških znakov vraščanja tumorja v mezenterične žile
- Adjuvantna kemoterapija se priporoča za vse bolnike po R0 resekciji, tudi za T_1N_0 (1A)
- Ni dorečenega konsenza gleda optimalne adjuvantne strategije, pristop v EU nekoliko drugačen kot v ZDA
- Priporočajo 6M kombinirane kemoterapije GemCap, raje kot Gem-mono (2B)
- Gem-mono ostaja terapija izbora za PS>1 in za komorbidnost

- Če se odločimo za adjuvantno radiokemoterapijo, naj se za radiosenzibilizacijo uporabijo preparati 5-FU (raje od Gemcitabina)
- Zaporedje RT in KT ni dorečeno, zaenkrat priporočajo 6M KT (Gemzar), ki mu sledi RT/KT (5-FU)
- Neoadjuvantno zdravljenje je indicirano pri mejno-resektabilnih tumorjih, zaenkrat ni dokazov, da izboljša OS pri jasno resektabilnih
- Nujno je zgodnje vključevanje paliativnih metod in agresivno zdravljenje simptomov povezanih z napredovanjem bolezni
- Sledenje po adjuvantnem zdravljenju ni povsem dorečeno, večina NE priporoča rutinskega CT, razen ob nastopu simptomov oz ob dvigu CA 19-9 (NCCN: CT na 3-6M, prvi 2 leti)

ELEKTROKEMOTERAPIJA PRI ZDRAVLJENJU METASTAZ RAKA DEBELEGA ČREVESA IN DANKE

Erik Brecelj

ONKOLOŠKI INŠTITUT LJUBLJANA

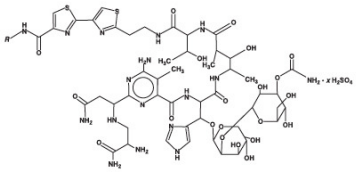
ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ABLACIJSKE METODE

- **radiofrekvenčna ablacija**
- **krioterapija**
- **stereotaksija**
- **elektrokemoterapija**
- **…**

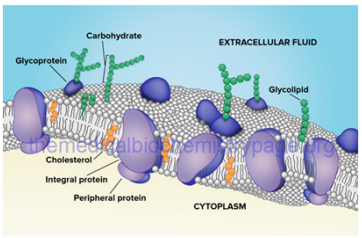
ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

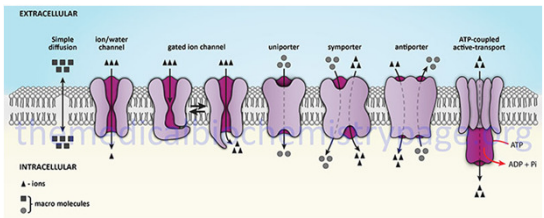
- N'-[3-(dimethylsulphonio)propyl]**Bleomycin**-amide (Bleomycin A2) and N'-[4-(guaniodobutyl)]Bleomycin-amide (Bleomycin B2).



- natančen mehanizem delovanja ni poznan, zavira sintezo DNA, poškoduje DNA, zadrži celico v G2 fazi in mitozi celičnega ciklusa
- **INDIKACIJE**: limfom, rak testisov, planocelularni rak, **NE** rak črevesja
- **PRITI MORA V CELICO**

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

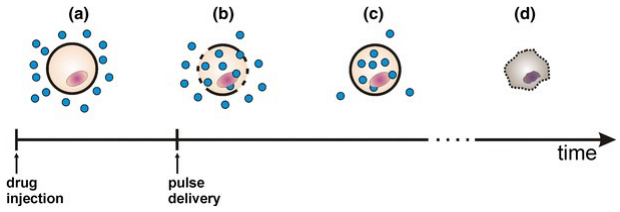




ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

- **ELEKTROPORACIJA**: izpostavljenost celice električnemu polju ustrezne jakosti in trajanja poveča prepustnost celične membrane (elektropermeabilizacija)
- **Reverzibilna elektroporacija**: vnos npr. citostatika v celico (tudi če ta v normalnih pogojih ne prehaja preko celične membrane)
- **Ireverzibilna elektroporacija**: uniči membrano

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH



Electrochemotherapy: technological advancements for efficient electroporation-based treatment of internal tumors.
Miklavčič D1, Serša G, Brecelj E, Gehl J, Soden D, Bianchi G, Ruggieri P, Rossi CR, Campana LG, Jarm T
Med Biol Eng Comput. 2012 Dec;50(12):1213-25.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

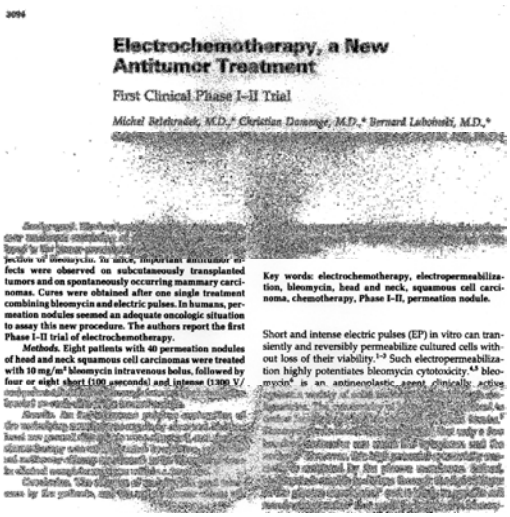
Mol Biother. **1990** Sep;2(3):165-8.

Inhibition of SA-1 tumor growth in mice by human leukocyte interferon alpha combined with low-level direct current.

Sersa G, Miklavcic D.

A preliminary study of the antitumor effect of partially purified human interferon alpha (IFN-alpha) and low-level direct current (DC) was carried out using a murine subcutaneous SA-1 experimental tumor model. Tumor-bearing animals were treated with 5 x 10(4) IU IFN-alpha peritumorally, or with 0.6 mA DC current for 15 minutes daily, for 6 consecutive days. Antitumor effect was manifested 2 days after the beginning of each treatment modality. Combined treatment with DC current applied immediately after IFN-alpha application was more effective than IFN-alpha treatment alone (P less than 0.005), but not significantly better than DC current treatment (P less than 0.5). The results indicate that the combined treatment with IFN-alpha and DC current can be effective in tumor therapy; however, further work is required to determine optimal scheduling.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH



3094

Electrochemotherapy, a New Antitumor Treatment

First Clinical Phase I–II Trial

Michel Belehradek, M.D., Christian Domenge, M.D.,* Bernard Luboinski, M.D.,**

Key words: electrochemotherapy, electropermeabilization, bleomycin, head and neck, squamous cell carcinoma, chemotherapy, Phase I–II, permeation nodule.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

[CANCER RESEARCH 55, 3450–3455, August 1, 1995]

Antitumor Effectiveness of Electrochemotherapy with *cis*-Diamminedichloroplatinum(II) in Mice[1]

Gregor Serša,[2] Maja Čemažar, and Damijan Miklavčič

Department of Tumor Biology, Institute of Oncology, Zaloška 2 Tržaška 25 [G. S., M. Č.], and Faculty of Electrical and Computer Engineering, University of Ljubljana, [D. M.], SI-61000 Ljubljana, Slovenia

ABSTRACT

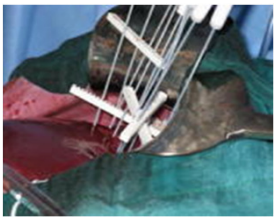
One of the ways to increase drug delivery into cells and tissues is by a local application of short, intense electric pulses, *i.e.*, electropermeabilization. This approach is used in electrochemotherapy to potentiate antitumor effectiveness of chemotherapeutic drugs. To determine whether electropermeabilization can potentiate antitumor effectiveness of *cis*-diamminedichloroplatinum(II) (CDDP), electrochemotherapy with CDDP was tested *in vitro* and *in vivo* on s.c. SA-1, EAT, and melanoma B16 tumors in mice. Electric pulses were applied to the tumors by percutaneously placed electrodes after i.v. injection of CDDP. Severalfold potentiation of CDDP antitumor effectiveness with electric pulses was obtained, inducing partial or complete responses in tumor growth. Electrochemotherapy was CDDP dose dependent, as well as dependent upon the amplitude of electric pulses. Also important was the sequencing and the interval of CDDP administration, relative to application of electric pulses. Specifically, a good antitumor effect without side effects was obtained with eight electric pulses (electric pulse amplitude, 1040 V; repetition frequency, 1 Hz; pulse width, 100 μs; electrode distance, 8 mm; 1300 V/cm) applied 3 min after i.v. injection of 4 mg/kg CDDP. With a higher CDDP dose (8 mg/kg), some long-term complete responses were obtained (14%) be greatly potentiated with EP, inducing partial and complete responses of the tumors. Furthermore, the treatment requires such a low amount of bleomycin that it is ineffective without EP and does not induce side effects (18–23).

Whether electropermeabilization of the tumors *in vivo* also potentiates the antitumor effectiveness of CDDP is not known. If electrochemotherapy with CDDP is effective in the treatment of tumors, it is not known how the antitumor effect depends upon the electric field intensity, the sequencing and timing of CDDP administration, and the CDDP dose. To answer these questions, we studied the antitumor effects of electrochemotherapy with CDDP on different s.c. tumors in mice.

MATERIALS AND METHODS

Chemicals. CDDP (Pliva, Zagreb, Croatia) was prepared in sterile H_2O to obtain a concentration of 1 mg/ml. The final concentration was prepared in EMEM (Sigma Chemical Co., St. Louis, MO) for *in vitro* experiments or in 0.9% NaCl solution for *in vivo* experiments. For each experiment, a fresh

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH



POSAMEZNE ELEKTRODE V IN OKROG TUMORJA

GENERATOR ELEKTRIČNIH IMPULZOV

HEKSAGONALNA ELEKTRODA

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ELEKTROKEMOTERAPIJA

- elektroporacija deluje na vsa tkiva
- poveča koncentracijo citostatika v celici; ne glede na histološki tip
- poveča učinkovitost citostatika (bleomicin, cisplatin)
- lokalna terapija; zdrava tkiva v okolici niso poškodovana
- ne povzroča denaturacije proteinov; imunski anti- tumorski odgovor
- prve klinične študije na kožnih tumorjih- na površini (kompleten odgovor do 60%)

Electrochemotherapy: technological advancements for efficient electroporation-based treatment of internal tumors
Miklavčič D, Serša G, Brecelj E, Gehl J, Soden D, Bianchi G, Ruggieri P, Rossi CR, Campana LG, Jarm T.
Med Biol Eng Comput. 2012 Dec;50(12):1213-25. Review.

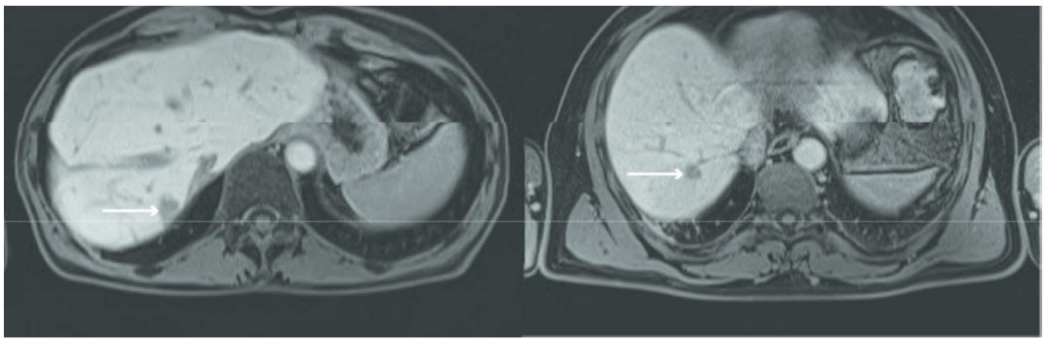
ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

akad. prof. dr. Gregor Serša

prof. dr. Damijan Miklavčič

prof. dr. Eldar Gadžijev, dr. med.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH



INDIKACIJE

- **TEŽKO DOSTOPNE METASTAZE**
- **METASTAZE OB ŽILAH; radiofrekvenčna ablacija ni uspešna zahtevajo obsežno odstranitev dela jeter**

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ZDRAVLJENJE JETRNIH ZASEVKOV Z ELEKTROKEMOTERAPIJO

Poteka na OI od leta 2008

- **FAZA I in II**
  - **načrtovanje zdravljenja**
  - **preučevanje in ugotavljanje stranskih učinkov zdravljenja ter uspešnosti zdravljenja**

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

INŽENIRSKI DEL

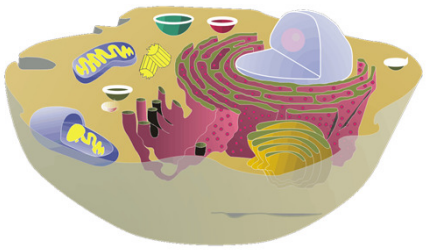
NAČRTOVANJE ZDRAVLJENJA

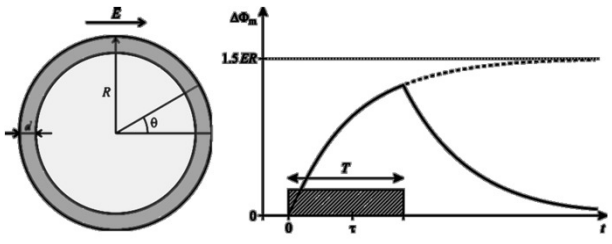
dr. Denis Pavliha

SRC Infonet
(do 2013 Fakulteta za elektrotehniko Univerze v Ljubljani)

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

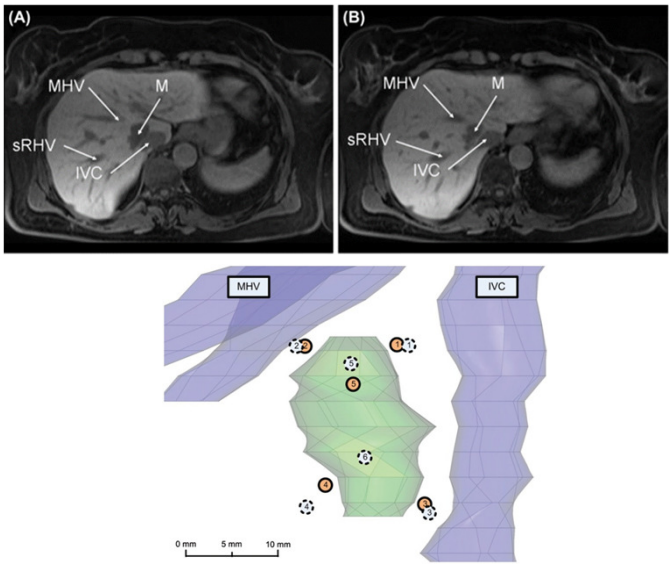
RAZLIČNI POGLEDI NA BIOLOŠKO CELICO





$$\Delta\Phi_m(t) = \frac{3}{2} ER\cos\theta \left[1 - \exp\left(-\frac{t}{\tau}\right)\right]$$

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH



ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

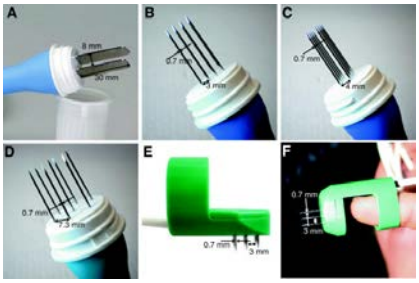
ZAKAJ MORAMO ZDRAVLJENJE NAČRTOVATI

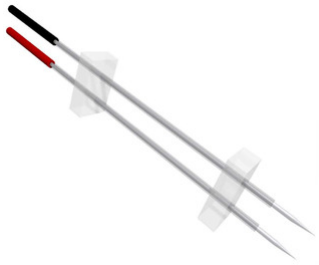
- pokritost celotnega tumorja z električnim poljem zadostne (ustrezne) jakosti.
- upoštevanje omejitev naprave (elektroporatorja).
- električno polje nad reverzibilnim in pod ireverzibilnim pragom.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ZAKAJ MORAMO ZDRAVLJENJE NAČRTOVATI

- razlika med površinskimi in globoko ležečimi tumorji.





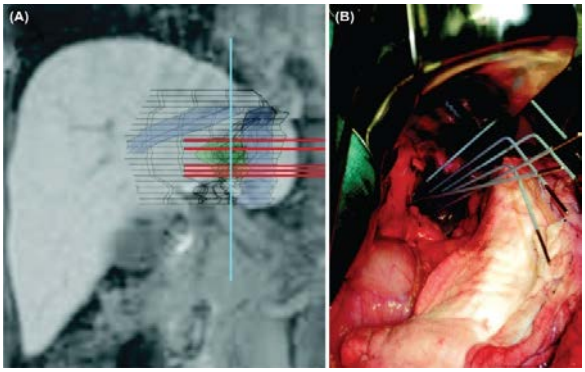
ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

NAČRTOVANJE ZDRAVLJENJA

- izhajamo iz medicinskih slik pacienta.
- izdelava 3D modela organa, ki ga obravnavamo.
- segmentacija tumorja(ev).
- izračun porazdelitve električne poljske jakosti z uporabo numeričnega modeliranja.
- vizualizacija z načrtom zdravljenja (napetosti elektrod).

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

Electrode pair	Delivered voltage[V]	Delivered No.of pulses	Measured current[A]
1-5	1300	20	32.3
1-6	2100	8	45.2
2-5	1700	21	44.7
2-6	2100	8	48.3
3-5	2100	8	48.9
3-6	1900	8	48.8
4-5	2100	8	47.5
4-6	1700	16	41.2
5-6	1700	8	48.9
Total		105	



Electrochemotherapy: a new technological approach in treatment of metastases in the liver.
Edhemovic I, Gadzijev EM, Brecelj E, Miklavcic D, Kos B, Zupanic A, Mali B, Jarm T, Pavliha D, Marcan M, Gasljevic G, Gorjup V, Music M, Vavpotic TP, Cemazar M, Snoj M, Sersa G. **Technol Cancer Res Treat. 2011 Oct;10(5):475-85.**

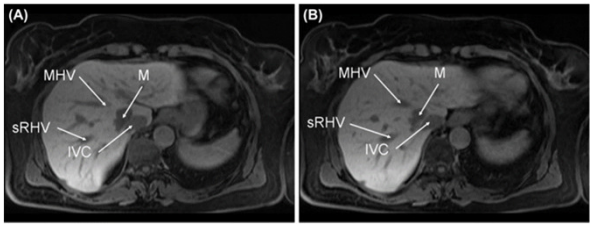
ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

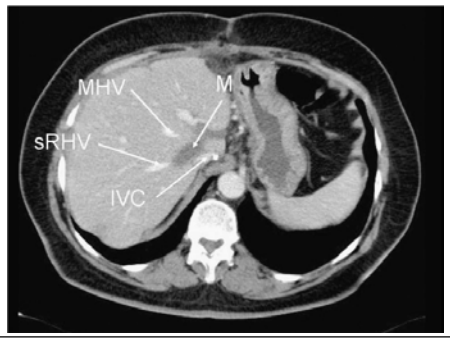
VPLIV NA EKG

- **APLIKACIJA ELEKTRIČNIH PULZOV BLIZU SRCA (3000 V, 30 A)**
  - EKG ?
  - DELOVANJE SRCA ?
  - ISHEMIJA SRCA ?
- **SINHRONIZACIJA Z ELEKTRIČNO AKTIVNOSTJO SRCA**
  - ELEKTRIČNI PULZI V ČASU NE-VURNELABILNE FAZE
  - MINIMALEN UČINEK, KLINIČNO NEPOMEMBNE SPREMEMBE V EKG-ju

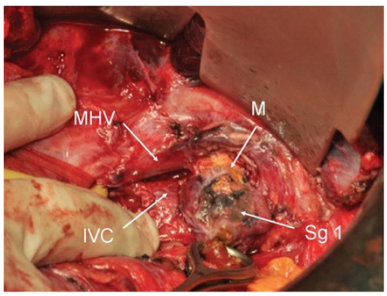
Electrochemotherapy of colorectal liver metastases--an observational study of its effects on the electrocardiogram.
Mali B, Gorjup V, Edhemovic I, Brecelj E, Cemazar M, Sersa G, Strazisar B, Miklavcic D, Jarm T.
Biomed Eng Online. 2015;14 Suppl 3

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH





PRVO ZDRAVLJENJE METASTAZE Z EKT



ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

HISTOPATOLOŠKE ZNAČILNOSTI

- regresivne spremembe v celotnem tretiranem področju
- jasna meja z zdravim parenhimom, pseudokapsula
- v bližini elektrod hujša destrukcija tkiva (ireverzibilna elektroporacija), koagulacijska nekroza

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

Histopathological findings in colorectal liver metastases after electrochemotherapy.
Gasljevic G, Edhemovic I, Cemazar M, Brecelj E, Gadzijev EM, Music MM, Sersa G.
PLoS One. 2017 Jul 7;12(7):e0180709.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

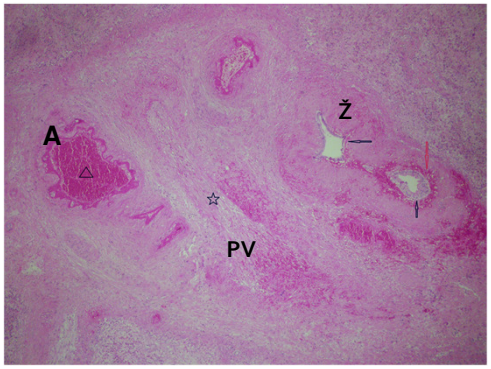
HISTOPATOLOŠKE ZNAČILNOSTI

- poškodba manjših žil
- **večje žile > 5mm niso pomembno poškodovane**
- okrog večjih žil nismo našli vitalnih tumorskih celic

OHRANITEV VEČJIH ŽIL - POMEMBNO ZA TRETIRANJE METASTAZ OB VELIKIH ŽILAH, METODA JE VARNA

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

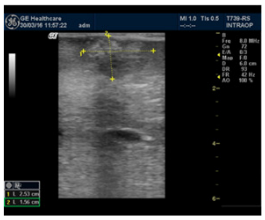
HISTOPATOLOŠKE ZNAČILNOSTI

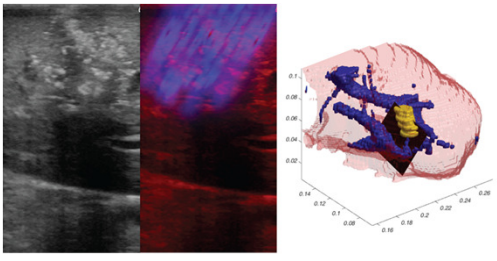


- najbolj **vulnerabilne** venule, manj arteriole, najmanj žolčni vodi

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

- **SPREMLJANJE USPEŠNOSTI EKT MED OPERACIJO - UZ**
- spremljanje učinka EKT



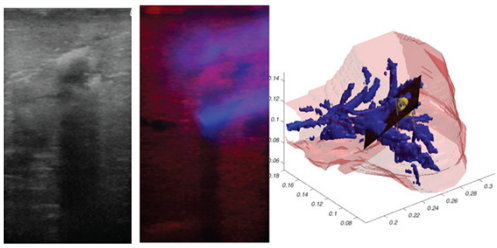


Ultrasonographic verification of tumor coverage with electric field for effective electrochemotherapy.
Boc N, Edhemovic I, Kos B, Music M, Brecelj E, Trotovsek B, Bosnjak M, Djokic M, Miklavcic D, Cemazar M, Sersa G

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

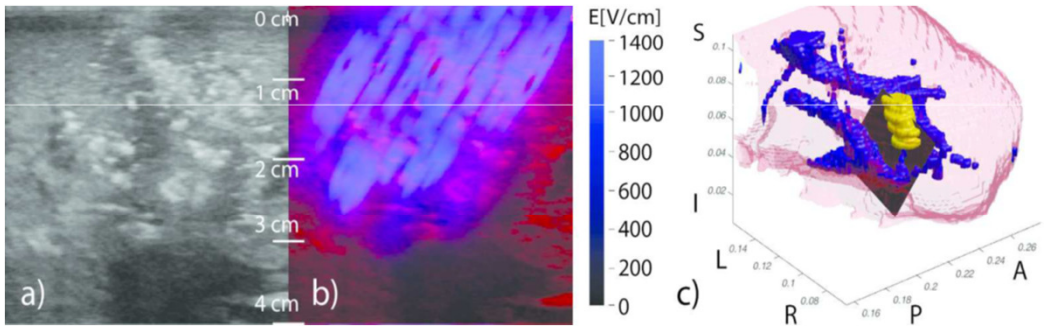
SPREMLJANJE USPEŠNOSTI EKT MED OPERACIJO - UZ

- spremljanje postavitve elektrod



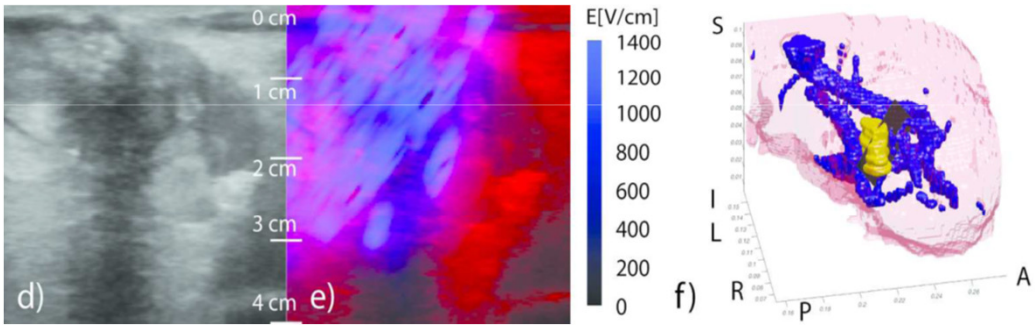
Ultrasonographic verification of tumor coverage with electric field for effective electrochemotherapy.
Boc N, Edhemovic I, Kos B, Music M, Brecelj E, Trotovsek B, Bosnjak M, Djokic M, Miklavcic D, Cemazar M, Sersa G

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH



SPREMEMBE **5 MIN** PO TRETIRANJU Z EKT

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH



SPREMEMBE **15 MIN** PO TRETIRANJU Z EKT

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ELEKTROKEMOTERAPIJA

- izvaja se lahko tudi na globoko ležečih tumorjih
- ni termična- vpliv ohlajanja zaradi pretoka skozi žile ni pomemben
- izvaja lahko na težko dostopnih mestih
- zdravljenje inoperabilnih metastaz ali metastaz, ki zahtevajo obsežne resekcije jeter
- pri bolnikih, ki niso sposobni radikalnega zdravljenja
- histološki tip tumorja verjetno ni pomemben

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ELEKTROKEMOTERAPIJA VERJETNO DELUJE NA VSE HISTOLOŠKE TIPE TUMORJEV

- BRECELJ, Erik, GADŽIJEV, Eldar, EDHEMOVIĆ, Ibrahim, MAROLT-MUŠIČ, Maja, GAŠLJEVIĆ, Gorana, ČEMAŽAR, Maja, MIKLAVČIČ, Damijan, SERŠA, Gregor. **ELECTROCHEMOTHERAPY (ECT) OF RECURRENT HEPATOCELLULAR CARCINOMA (HCC) : A CASE REPORT**. V: ***Programme***, 10th Congress European-African Hepato Pancreato Biliary Association, Belgrade, 29-31 May 2013. Belgrade: E-AHPBA. 2013, str. P98

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ZDRAVLJENJE METASTAZ KOLOREKTALNEGA RAKA (16 BOLNIKOV, 29 METASTAZ)

- **brez hudih zapletov povezanih z elektrokemoterapijo**
- **brez pomembnega vpliva na delovanje srca**

Intraoperative electrochemotherapy of colorectal liver metastases.
Edhemovic I, Brecelj E, Gasljevic G, Marolt Music M, Gorjup V, Mali B, Jarm T, Kos B, Pavliha D, Grcar Kuzmanov B, Cemazar M, Snoj M, Miklavcic D, Gadzijev EM, Sersa G.
J Surg Oncol. 2014 Sep;110(3):320-7.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ZDRAVLJENJE METASTAZ KOLOREKTALNEGA RAKA (16 BOLNIKOV, 29 METASTAZ)

- **85 % kompleten odgovor radiološko**
- **15% delni odgovor**

Intraoperative electrochemotherapy of colorectal liver metastases.
Edhemovic I, Brecelj E, Gasljevic G, Marolt Music M, Gorjup V, Mali B, Jarm T, Kos B, Pavliha D, Grcar Kuzmanov B, Cemazar M, Snoj M, Miklavcic D, Gadzijev EM, Sersa G.
J Surg Oncol. 2014 Sep;110(3):320-7.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ZDRAVLJENJE METASTAZ KOLOREKTALNEGA RAKA (16 BOLNIKOV, 29 METASTAZ)

- **7 BOLNIKOV OPERIRANO 6-12 TEDNOV po EKT**
  - Primerjava 13 metastaz tretiranih z EKT z 22 ne-tretiranimi metastazami
    - **EKT metastaze 9,9 % ±12,2 % vitalnega tkiva**
    - **Ne-EKT metastaze 34,1% ± 22,5 % vitalnega tkiva (p 0,001)**

Intraoperative electrochemotherapy of colorectal liver metastases.
Edhemovic I, Brecelj E, Gasljevic G, Marolt Music M, Gorjup V, Mali B, Jarm T, Kos B, Pavliha D, Grcar Kuzmanov B, Cemazar M, Snoj M, Miklavcic D, Gadzijev EM, Sersa G.
J Surg Oncol. 2014 Sep;110(3):320-7..

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ZDRAVLJENJE METASTAZ KOLOREKTALNEGA RAKA (16 BOLNIKOV, 29 METASTAZ)

- 8 bolnikov (14 metastaz) zdravljeno samo z EKT:
  - **po 1 mesecu**
    - kompleten odgovor v **12** metastazah (86%), 2 metastazi delen odgovor
  - **po povprečno 3 mesecih**
    - kompleten odgovor **10** metastaz (71%), 4 metastaze progres

Intraoperative electrochemotherapy of colorectal liver metastases.
Edhemovic I, Brecelj E, Gasljevic G, Marolt Music M, Gorjup V, Mali B, Jarm T, Kos B, Pavliha D, Grcar Kuzmanov B, Cemazar M, Snoj M, Miklavcic D, Gadzijev EM, Sersa G.
J Surg Oncol. 2014 Sep;110(3):320-7.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ZDRAVLJENJE METASTAZ KOLOREKTALNEGA RAKA (15 BOLNIKOV, 9 METASTAZ)

- **KOMPLETEN ODGOVOR** PO 30 DNEH; 55,5%
- stabilna bolezen 45.5%

Safety and feasibility of electrochemotherapy in patients with unresectable colorectal liver metastases: A pilot study.
Coletti L, Battaglia V, De Simone P, Turturici L, Bartolozzi C, Filipponi F.
Int J Surg. 2017 Aug;44:26-32.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

Table 4 Radiological evaluation (MRI) (# 9 lesions).

Pt	CLM	30-day MRI	6M MRI	30-day responsea	6M responsea	30-day intensity (T2-weighted)b	6M intensity (T2-weighted)b
1	S8, 30 mm	22 mm	20 mm	SD	SD	Hyper-intense	Isointense
2	S4, 6 mm	3 mm	2 mm	SD	CR	Hyper-intense	Isointense
3	S8-S1, 24 mm	24 mm	22 mm	SD	CR	Hyper-intense	Isointense
4	S4, 7 mm	6 mm	3 mm	SD	CR	Hyper-intense	Isointense
	S2, 32 mm	23 mm	66 mm	PR	Progression	Hyper-intense	Hyper-intense
	S3, 25 mm	19 mm	71 mm	PR	Progression	Hyper-intense	Hyper-intense
5	S3, 25 mm	18 mm	77 mm	PR	Progression	Hyper-intense	Hyper-intense
	S3, 25 mm	17 mm	57 mm	PR	Progression	Hyper-intense	Hyper-intense
	S4, 11 mm	11 mm	35 mm	PR	Progression	Hyper-intense	Hyper-intense

Safety and feasibility of electrochemotherapy in patients with unresectable colorectal liver metastases: A pilot study.
Coletti L, Battaglia V, De Simone P, Turturici L, Bartolozzi C, Filipponi F.
Int J Surg. 2017 Aug;44:26-32.

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

VEČ KOT JE IZKUŠENJ, VEČ JE VPRAŠANJ IN NEZNANK

- testiranje učinka elektrokemoterapije na živalih (Veterinarska fakulteta)
- prenos terapije na druge lokacije po telesu ?
- zakaj metoda ni 100% uspešna ?
- navigacija in planiranje ?

ELEKTROKEMOTERAPIJA ZASEVKOV V JETRIH

ZAKLJUČEK

ELEKTROKEMOTERAPIJA

- varna metoda
- uspešna
- primerna za težko dostopne, inoperabilne metastaze
- lahko se izvaja v bližini večjih žil

ZDRAVLJENJE RAKA POŽIRALNIKA

7. ŠOLA TUMORJEV PREBAVIL

MARKO BOC, DR.MED.
SEKTOR ZA INTERNISTIČNO ONKOLOGIJO
ONKOLOŠKI INŠTITUT LJUBLJANA

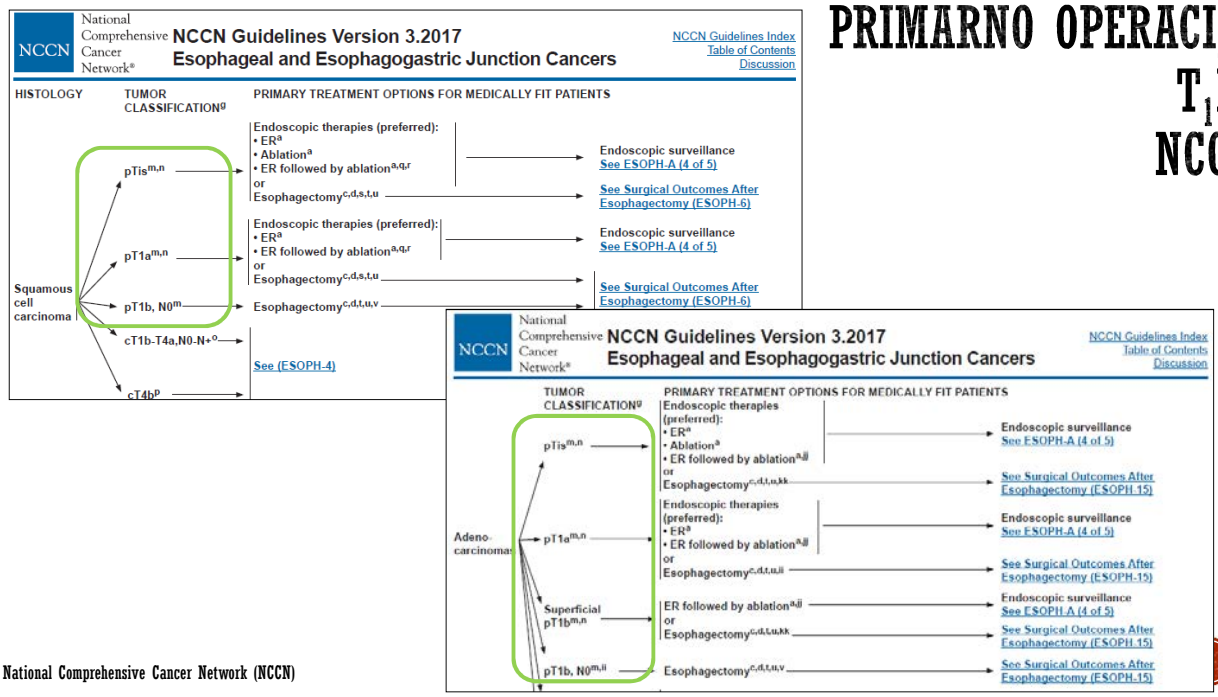
LJUBLJANA, 20.10.2017

PRIMARNO OPERACIJA

- 30-40% BOLNIKOV IMA PRIMARNO POTENCIALNO RESEKTABILNO BOLEZEN
- SAMA KIRURGIJA → SLABA PREŽIVETJA
  - 5-LETNO PREŽIVETJE < 50%,
  - SAMO 15% PRI N+ BOLEZNI[1]
  - 5-LETNO PREŽIVETJE > 50% LE PRI STADIJU T_1N_0
- T3 R0 50%
- T4 R0 30%

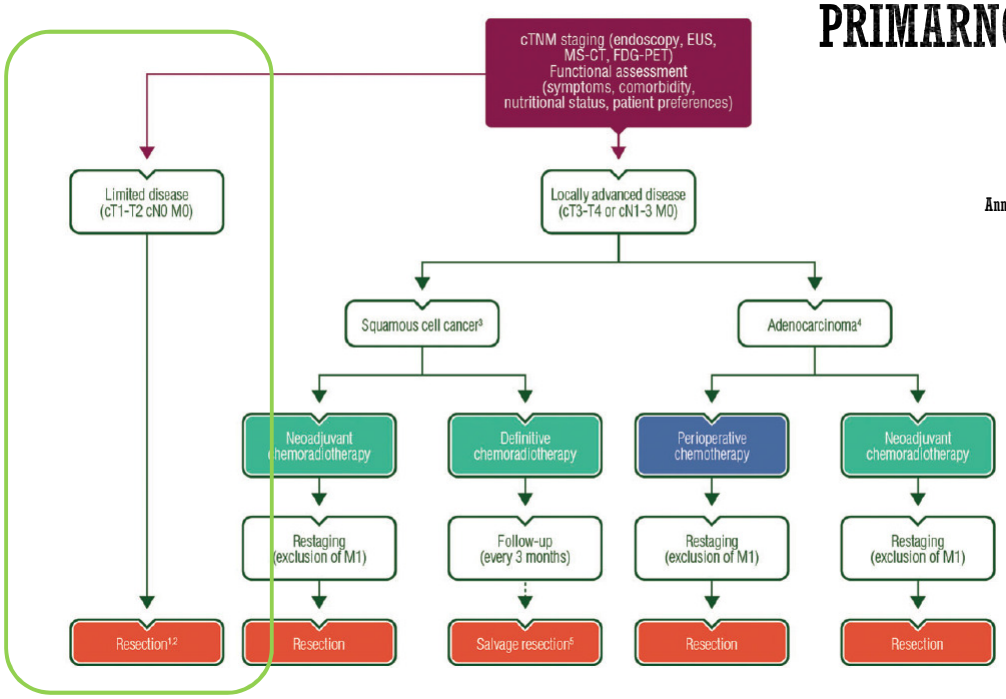
1. Dis Esophagus. 2009;22(1):1.

PRIMARNO OPERACIJA T_1N_0 NCCN



National Comprehensive Cancer Network (NCCN)

PRIMARNO OPERACIJA T_1N_0 ESMO



Ann Oncol. 2016 Sep;27(suppl 5):v50-v57.

PRIMARNO OPERACIJA T_2N_0??

Medline ® Abstract for Reference 123 of 'Radiation therapy, chemoradiotherapy, neoadjuvant approaches, and postoperative adjuvant therapy for localized cancers of the esophagus'

123 PubMed

TI Treatment of clinical T2N0M0 esophageal cancer.

AU Hardacker TJ, Ceppa D, Okereke I, Rieger KM, Jalal SI, LeBlanc JK, DeWitt JM, Kesler KA, Birdas TJ

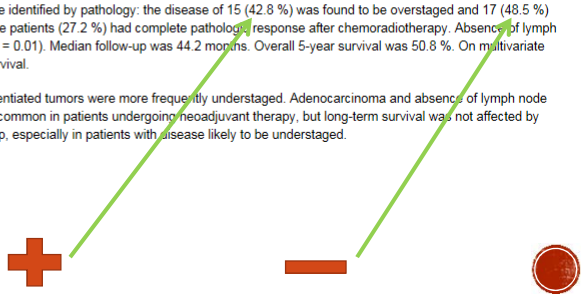
SO Ann Surg Oncol. 2014;21(12):3739.

BACKGROUND: Management of clinical T2N0M0 (cT2N0M0) esophageal cancer remains controversial. We reviewed our institutional experience over 21 years (1990-2011) to determine clinical staging accuracy, optimal treatment approaches, and factors predictive of survival in this patient population.

METHODS: Patients with cT2N0M0 esophageal cancer determined by endoscopic ultrasound (EUS) were identified through a prospectively collected database. Demographics, perioperative data, and outcomes were examined. Cox regression model and Kaplan-Meier plots were used for statistical survival analysis.

RESULTS: A total of 731 patients underwent esophagectomy, of whom 68 cT2N0M0 patients (9 %) were identified. Fifty-seven patients (84 %) had adenocarcinoma. Thirty-three patients (48.5 %) were treated with neoadjuvant chemoradiation followed by surgery, and 35 underwent surgical resection alone. All resections except one included a transthoracic approach with two-field lymph node dissection. Thirty-day operative mortality was 2.9 %. Only 3 patients (8.5 %) who underwent surgery alone had T2N0M0 disease identified by pathology: the disease of 15 (42.8 %) was found to be overstaged and 17 (48.5 %) understagedafter surgery. Understaging was more common in poorly differentiated tumors (p = 0.03). Nine patients (27.2 %) had complete pathologic response after chemoradiotherapy. Absence of lymph node metastases (pN0) was significantly more frequent in the neoadjuvant group (29 of 33 vs. 21 of 35, p = 0.01). Median follow-up was 44.2 months. Overall 5-year survival was 50.8 %. On multivariate analysis, adenocarcinoma (p = 0.001) and pN0 after resection (p = 0.01) were significant predictors of survival.

CONCLUSIONS: EUS was inaccurate in staging cT2N0M0 esophageal cancer in this study. Poorly differentiated tumors were more frequently understaged. Adenocarcinoma and absence of lymph node metastases (pN0) were independently predictive of long-term survival. pN0 status was significantly more common in patients undergoing neoadjuvant therapy, but long-term survival was not affected by neoadjuvant therapy. A strategy of neoadjuvant therapy followed by resection may be optimal in this group, especially in patients with disease likely to be understaged.



PRIMARNO OPERACIJA – VIŠJI T±N

- 30-40% BOLNIKOV IMA PRIMARNO POTENCIALNO RESEKTABILNO BOLEZEN
- SAMA KIRURGIJA → SLABA PREŽIVETJA
  - 5-LETNO PREŽIVETJE < 50%,
  - SAMO 15% PRI N+ BOLEZNI[1]
  - 5-LETNO PREŽIVETJE > 50% LE PRI STADIJU T_1N_0

- T3 R0 50%
- T4 R0 30%

1. Dis Esophagus. 2009;22(1):1.

KEMORADIOTERAPIJA VS. RADIOTERAPIJA

RTOG 85-01
90% SCC,

RT (64Gy) vs. CISPLATIN/5FU/RT

S_{5L} 27m vs. 0
signifikantno večja lokalna in sistemska kontrola bolezni
vseeno 46% lokalnih ponovitev/ostanka bolezni pri 12m
JAMA. 1999;281(17):1623.

IMRT + CISPLATIN/DOCETAKSEL

LAHKO IZBOLJŠA LOKALNO KONTROLO IN PODALJŠA PREŽIVETJE
VEČ TOKSIČNOSTI
Zhonghua Wei Chang Wai Ke Za Zhi. 2013 Sep;16(9):842-5.

INT 0123
SCC in AC

CISPLATIN/5FU/50.4Gy vs. CISPLATIN/5FU/64.8Gy

VIŠJA DOZA RT BREZ VPLIVA NA PREŽIVETJE IN LOKALNO PONOVITEV
VEČJA TOKSIČNOST (PRED 3D)
J Clin Oncol. 2002;20(5):1167.

KEMORADIOTERAPIJA+OPERACIJA VS. OPERACIJA

FFCD 9102: T_3N_{0-1}: 89% SCC & 11% AC

CISPLATIN/5FU/RT → OP
CISPLATIN/5FU/RT

PODOBNO PREŽIVETJE (17.7m vs. 19.3m)
BOLJŠA LOKALNA KONTROLA V ROKI Z OP
BOLJŠE PREŽIVETJE PRI BOLNIKIH KI SE NISO ODZVALI NA KT/RT IN BILI OPERIRANI (17m vs. 5.5m)
Ann Oncol. 2006;17(5):827. Epub 2006 Mar 8.
Eur J Cancer. 2015 Sep;51(13):1683-93. Epub 2015 Jul 7.

FFCD 9901, POŽIRALNIK OZ. EG PREHOD, $T_{1-2}N_{+}$, T_3N_0

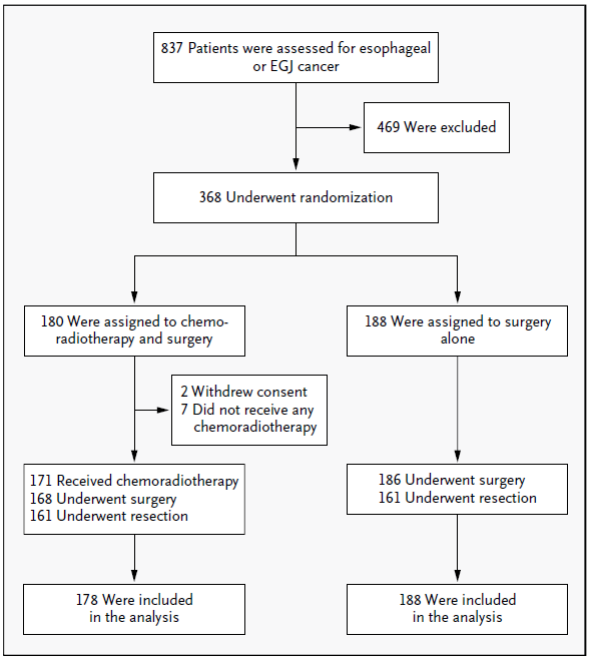
CISPLATIN/5FU/RT + OP vs. OP

KT/RT NE IZBOLJŠA 3-LETNO PREŽIVETJE (47.5% vs. 53%)
KT/RT NE IZBOLJŠA R0
VEČJA UMRLJIVOST V ROKI Z KT/RT (11.1% vs 3.4%)
J Clin Oncol. 2014 Aug;32(23):2416-22. Epub 2014 Jun 30.

META-ANALIZA
12 RANDOMIZIRANIH RAZISKAV
KT/RT + OP vs OP

ABSOLUTNA DOBROBIT NA PREŽIVETJE 8.7% V 2 LETIH
11 ZDRAVLJENIH BOLNIKOV DA PREPREČIŠ ENO SMRT
HISTOLOGIJA NIMA VPLIVA
Lancet Oncol. 2011;12(7):681. Epub 2011 Jun 16.

KEMORADIOTERAPIJA+OPERACIJA VS. OPERACIJA RAZISKAVA CROSS



- KLINIČNA RAZISKAVA FAZE III
- VKLJUČENIH 368 BOLNIKOV Z OPERABILNIM KARCINOMOM POŽIRALNIKA IN GEP PREHODA (T1N1,T2-3, N0-1, M0)
- ADENOKARCINOM V 75%, SCC V 23 %, 2% VELIKOCELIČNI NEDIFERENCIRAN KARCINOM

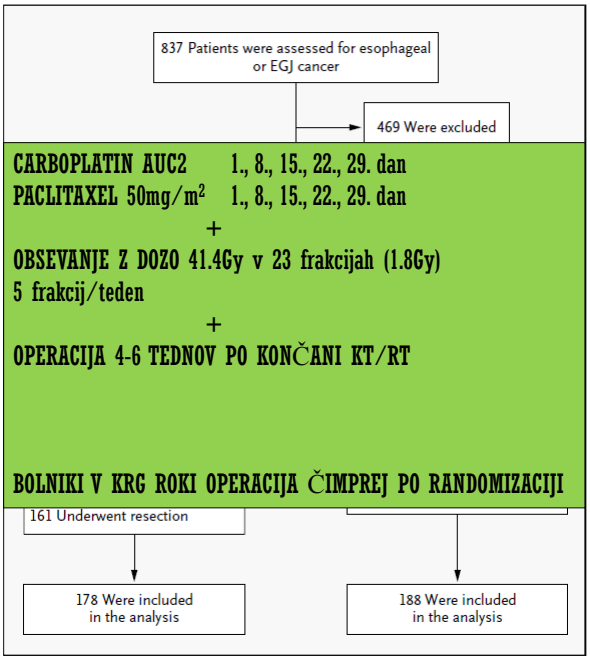
KARBOPLATIN/PACLITAKSEL/OBSEVANJE + OPERACIJA

VS.

SAMO OPERACIJA

N ENGL J MED 2012;366:2074-2084.

KEMORADIOTERAPIJA+OPERACIJA VS. OPERACIJA RAZISKAVA CROSS



- KLINIČNA RAZISKAVA FAZE III
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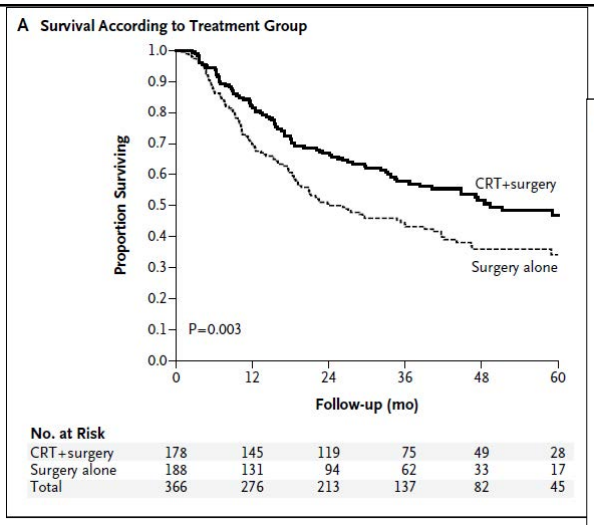
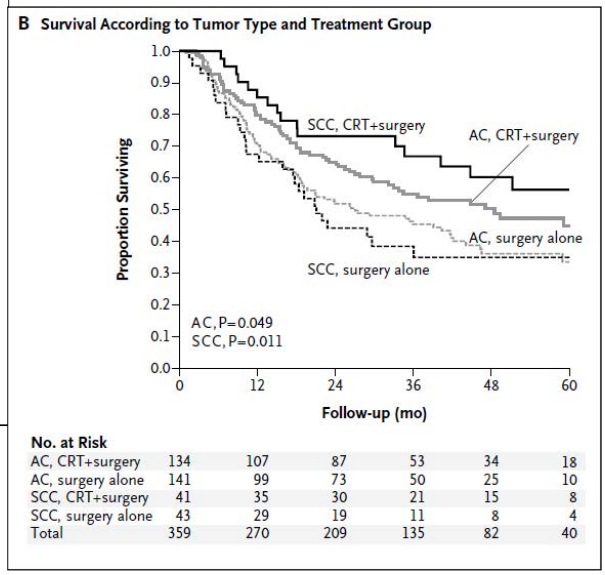
VS.

SAMO OPERACIJA

N ENGL J MED 2012;366:2074-2084.

NEOADJUVANTNO ZDRAVLJENJE CROSS – OS + RR





ITT

mOS 49.4 m. vs. 24.0 m. p=0.003 HR 0.65 (95%CI 0.495-0.871)

S_{1L}=82% vs. 70%

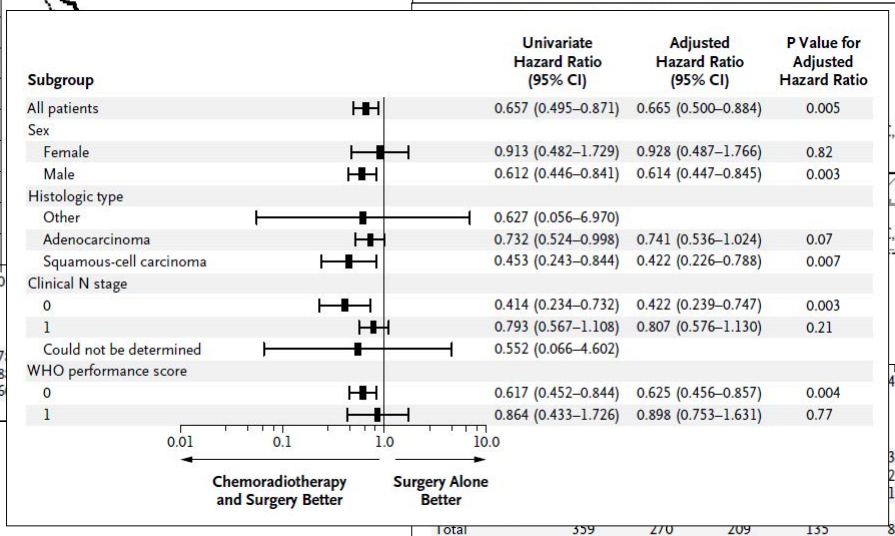
S_{2L}=67%, vs. 50%

S_{3L}=58% vs. 44%

S_{5L}=47% vs. 43%

N ENGL J MED 2012;366:2074-2084.

NEOADJUVANTNO ZDRAVLJENJE CROSS – OS + RR



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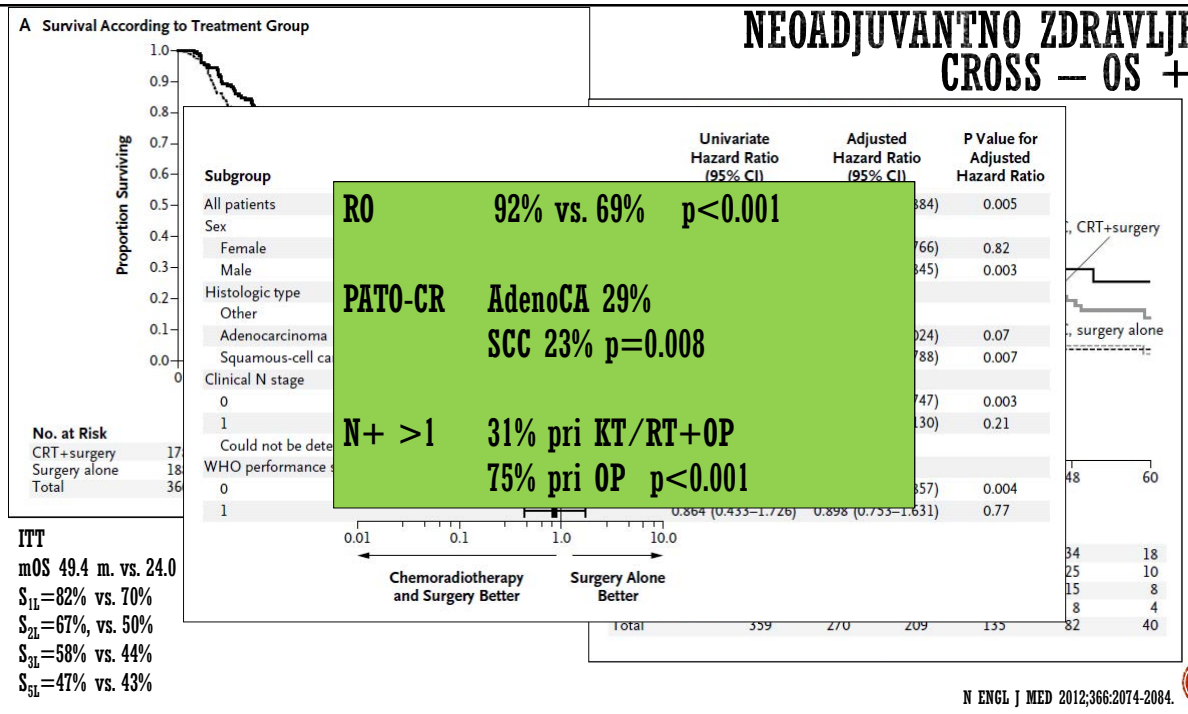
N ENGL J MED 2012;366:2074-2084.

NEOADJUVANTNO ZDRAVLJENJE CROSS – OS + RR



RO 92% vs. 69% p<0.001

PATO-CR AdenoCA 29%
SCC 23% p=0.008

N+ >1 31% pri KT/RT+OP
75% pri OP p<0.001

ITT
mOS 49.4 m. vs. 24.0
S_{1L}=82% vs. 70%
S_{2L}=67%, vs. 50%
S_{3L}=58% vs. 44%
S_{5L}=47% vs. 43%

N ENGL J MED 2012;366:2074-2084.

NEOADJUVANTNO ZDRAVLJENJE CROSS - TOKSIČNOST

Event	Chemoradiotherapy and Surgery (N=171)	Surgery Alone (N=186)
Postoperative events — no. of patients/total no. (%)†		
Pulmonary complications‡	78/168 (46)	82/186 (44)
Cardiac complications§	36/168 (21)	31/186 (17)
Chylothorax¶	17/168 (10)	11/186 (6)
Mediastinitis‖	5/168 (3)	12/186 (6)
Anastomotic leakage**	36/161 (22)	48/161 (30)
Death		
In hospital	6/168 (4)	8/186 (4)
After 30 days	4/168 (2)	5/186 (3)
Events of any grade during chemoradiotherapy — no. of patients (%)		
Anorexia	51 (30)	
Alopecia	25 (15)	
Constipation	47 (27)	
Diarrhea	30 (18)	
Esophageal perforation	1 (1)	
Esophagitis	32 (19)	
Fatigue	115 (67)	
Nausea	91 (53)	
Neurotoxic effects	25 (15)	
Vomiting	43 (25)	
Leukopenia	103 (60)	
Neutropenia	16 (9)	
Thrombocytopenia	92 (54)	

- 91% BOLNIKOV JE PREJELO VSO KT
- 92% BOLNIKOV JE PREJELO VSO RT

- 94% BOLNIKOV V ROKI Z KTRT JE BILO OPERIRANIH
- 99% BOLNIKOV V ROKI Z OP JE BILO OPERIRANIH

N ENGL J MED 2012;366:2074-2084.

DEFINITVINA KEMORADIOTERAPIJA:

- PRI KARCINOMU VRATNEGA DELA POŽIRALNIKA OZIROMA ZGORNJE TRETJINE POŽIRALNIKA ZARADI ZAHTEVNOSTI KIRURŠKE REKONSTRUKCIJE PO RESEKCIJI TUMORJA – **ODLOČITEV MULTIDISCIPLINARNEGA KONZILIJA!**
- PRI BOLNIKIH S KARCINOMOM SREDNJE IN SPODNJE TRETJINE POŽIRALNIKA OZIROMA EG PREHODA:
  - KJER OPERACIJA IZ KAKRŠNEGAKOLI RAZLOGA NI IZVEDLJIVA
  - PRI TISTIH KI OPERACIJO ZAVRNEJO, ČEPRAV JE TA S STRANI KONZILIJA INDICIRANA
  - PRI TISTIH, KI IMAJO VELIKE TUMORJE, KI VRAŠČAJO V SOSEDNJE ORGANE IN SO TEHNIČNO NERESEKTABILNI (T_{4B} TUMORJI)

PREDOPERATIVNA KEMORADIOTERAPIJA ➔ OPERACIJA

- STANDARDNO ZDRAVLJENJE PRI BOLNIKIH S PLOŠČATOCELIČNIM KARCINOMOM POŽIRALNIKA V SREDNJI IN SPODNJI TRETJINI STADIJA > $T_{1B}N_0$
- STANDARDNO ZDRAVLJENJE PRI BOLNIKIH ADENOKARCINOM STADIJA > $T_{1B}N_0$
- PERIOPERATIVNA SISTEMSKA KEMOTERAPIJA JE ALTERNATIVNA MOŽNOST ZDRAVLJENJA PRI IZBRANIH BOLNIKIH Z RESEKTABILNO BOLEZNIJO, KI BODISI ZAVRAČAJO ALI IZ KAKRŠNEGAKOLI DRUGEGA RAZLOGA NISO KANDIDATI ZA OBSEVANJE

POOPERATIVNO ZDRAVLJENJE - SCC

- RADIKALNA (R0) RESEKCIJA PO PRIMARNI OPERACIJI ALI PO OPERACIJI, KI SLEDI PREDOPERATIVNI RADIOKEMOTERAPIJI

  ➔ DODATNO SPECIFIČNO ONKOLOŠKO ZDRAVLJENJE NI POTREBNO (ZA VSE T IN N STADIJE)

- NERADIKALNA (R1/2) RESEKCIJA

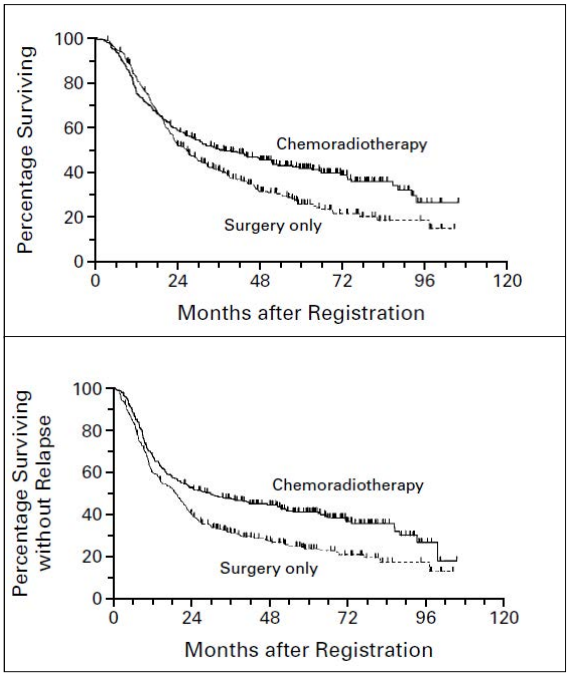
  ➔ ODLOČITEV NA MULTIDISCIPLINARNEM KONZILIJU ZA VSAKEGA BOLNIKA POSEBEJ NA PODLAGI NJEGOVEGA PREDHODNJEGA ZDRAVLJENJA, SPLOŠNO STANJE, PRIDRUŽENE BOLEZNI IN EVENTUELNE PERIOPERATIVNE ZAPLETE

  ➔ KIRURŠKA RERESEKCIJA, POOPERATIVNA RT/KT ALI KT, PODPORNO ZDRAVLJENJE

POOPERATIVNO ZDRAVLJENJE - ADENOCA

- RADIKALNA RESEKCIJA PO PREDOPERATIVNI KEMOTERAPIJI
  - ➔ POOPERATIVNA KEMOTERAPIJA, RAZEN V PRIMERU PATOLOŠKE POPOLNE REMISIJE
- RADIKALNA (R0) RESEKCIJA V STADIJU > pT_2N_0 ALI pN+ PO PREDOPERATIVNI RADIOKEMOTERAPIJI
  - ➔ POOPERATIVNA KEMOTERAPIJA
- RADIKALNA (R0) RESEKCIJA PO PRIMARNI OPERACIJI
  - ➔ PRI BOLNIKIH Z **NEGATIVNIMI BEZGAVKAMI (pN_0) V STADIJU pT_{IS-2}**
    - ➔ SLEDENJE
  - ➔ PRI **STADIJU $pT_{3-4}N_0$ ALI $pT_{1-4}N+$**
    - ➔ POOPERATIVNA RADIOKEMOTERAPIJA

POOPERATIVNO ZDRAVLJENJE - ADENOCA



- ADENOKARCINOM GE PREHODA IN ŽELODCA V STADIJU $pT_{3-4}pN_0$ ALI $pT_{1-4}pN+$
- OPERACIJA vs OPERACIJA + KT/RT
- mOS 27m vs. 36m, p=0.005,
- mRFS 19m vs. 30m, p<0.001

N ENGL J MED, VOL.345, NO.10, 2001

POOPERATIVNO ZDRAVLJENJE - ADENOCA

- RADIKALNA RESEKCIJA PO PREDOPERATIVNI KEMOTERAPIJI
  - ➔ POOPERATIVNA KEMOTERAPIJA, RAZEN V PRIMERU PATOLOŠKE POPOLNE REMISIJE
- RADIKALNA (R0) RESEKCIJA V STADIJU > pT_2N_0 ALI pN+ PO PREDOPERATIVNI RADIOKEMOTERAPIJI
  - ➔ POOPERATIVNA KEMOTERAPIJA
- RADIKALNA (R0) RESEKCIJA PO PRIMARNI OPERACIJI
  - ➔ PRI BOLNIKIH Z **NEGATIVNIMI BEZGAVKAMI (pN_0) V STADIJU pT_{IS-2}** PRIHAJA V POŠTEV LE SLEDENJE
  - ➔ PRI **STADIJU $pT_{3-4}N_0$ ALI $pT_{1-4}N+$** POOPERATIVNA RADIOKEMOTERAPIJA
- **POOPERATIVNA RADIOKEMOTERAPIJA EVENTUELNO PRIHAJA V POŠTEV TUDI PRI BOLNIKIH V STADIJU pT_2, KI IMAJO PRISOTNE NEGATIVNE PATOHISTOLOŠKE NAPOVEDNE DEJAVNIKE (GRADUS 3, STAROST <50 LET, LIMFOVASKULARNA ± PERINEVRALNA INVAZIJA)**

PERIOPERATVINA SISTEMSKA KEMOTERAPIJA- ADENOCA

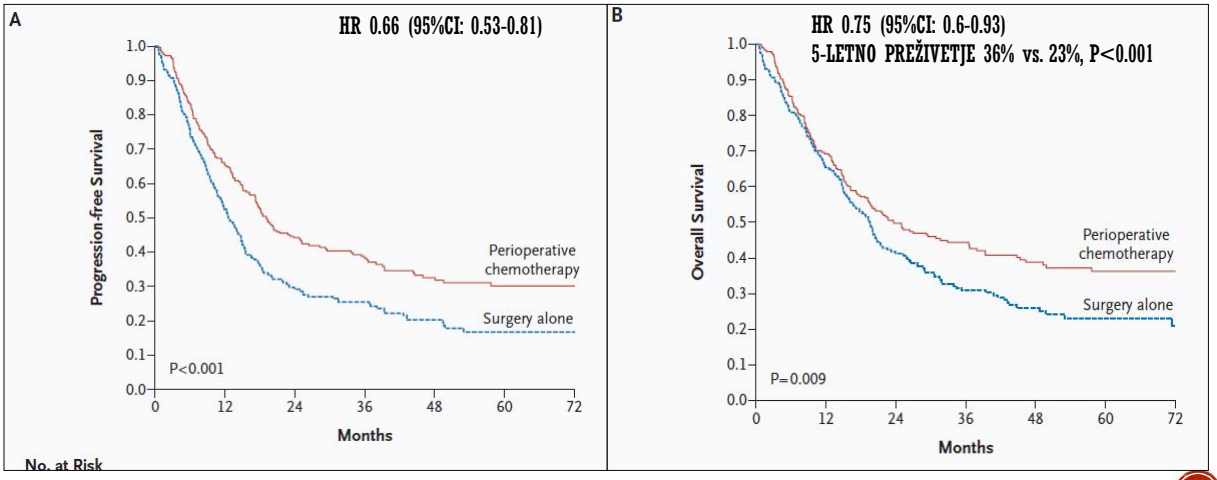
- **PRI BOLNIKIH Z OPERABILNIM ADENOKARCINOMOM EG PREHODA IN ADENOKARCINOMOM SPODNJE TRETJINE POŽIRALNIKA ($cT_{2-4}N_0$ ALI $cT_{1B-4}N+$)**
- **MAGIC – FIII**
  - **3X ECF ➔ OP ➔ 3X ECF**

1	81 (32.4)	80 (31.6)
Site of tumor — no. (%)		
Stomach	185 (74.0)	187 (73.9)
Lower esophagus	37 (14.8)	36 (14.2)
Esophagogastric junction	28 (11.2)	30 (11.9)
Maximum tumor diameter		
0.0–3.9 cm — no. (%)‡	50 (30.9)	61 (33.3)
4.0–7.9 cm — no. (%)‡	79 (48.8)	87 (47.5)

N ENGL J MED, 2006;355:11-20

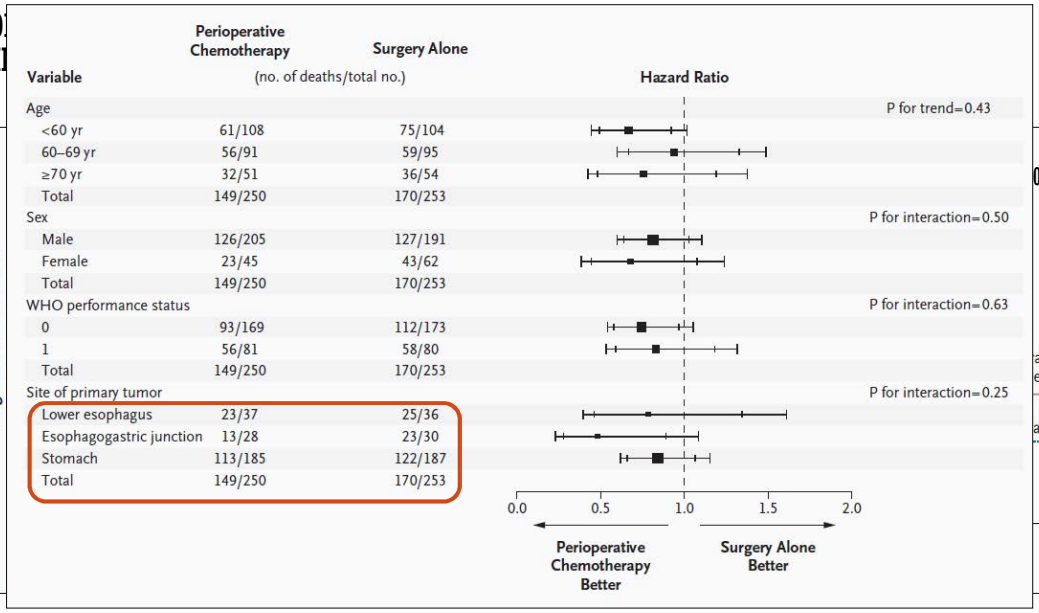
PERIOPERATVINA SISTEMSKA KEMOTERAPIJA- ADENOCA

- PRI BOLNIKIH Z OPERABILNIM ADENOKARCINOMOM EG PREHODA IN ADENOKARCINOMOM SPODNJE TRETJINE POŽIRALNIKA ($cT_{2-4}N_0$ ALI $cT_{1B-4}N+$)
- MAGIC – FIII



N ENGL J MED, 2006;355:11-20

PERIOPERATVINA SISTEMSKA KEMOTERAPIJA- ADENOCA



N ENGL J MED, 2006;355:11-20

METASTATSKA BOLEZEN

- SISTEMSKA TERAPIJA PRIHAJA V POŠTEV LE:
  - PRI BOLNIKIH Z DOBRIM PS WHO 0-2, KARNOVSKY > 80%
  - PRI BOLNIKIH Z UREJENIM PREHRANJEVANJEM
  - PRI BOLNIKIH BREZ KAHEKSIJE
  - PRI BOLNIKIH BREZ RELEVANTNIH PRIDRUŽENIH BOLEZNI
  - BREME BOLEZNI!!!
- DRUGAČE JE BOLNIK KANDIDAT ZA BSC
- 1.RED:
  - KOMBINACIJA 2 CITOSTATIKOV,
  - KOMBINACIJA 3 CITOSTATIKOV V PRIMERU DOBREGA PS → VEČJA TOKSIČNOST
- 2.RED:
  - STANDARDNEGA ZDRAVLJENJA NI, PRIMERNO ZA BOLNIKE V DOBREM PS, KI SO ODGOVORILI NA 1.RED SISTEMSKEGA ZDRAVLJENJA

METASTATSKA BOLEZEN KT

	Treatment	n	Histology	RR	Median OS
Phase II	Cisplatin/5-FU	44	SCC	35%	8.25 months
Phase II	Paclitaxel/5-FU/cisplatin	60	SCC/AC	48%	10.8 months
Phase II	Cisplatin/irinotecan	35	SCC/AC	57%	14.6 months
Phase II	Cisplatin/vinorelbine	71	SCC	34%	6.8 months
Phase II	Oxaliplatin/5-FU	35	SCC/AC	40%	7.1 months
Phase II	Docetaxel/capecitabine	16	SCC/AC+ GEJ	56%	15.8 months
Phase II	Docetaxel/cisplatin	76	GEJ +	26%	10.5 months
	Docetaxel/cisplatin/5-FU	79	GASTRIC	43%	9.6 months
Phase II	Docetaxel/capecitabine	44	GEJ + GASTRIC	39%	9.4 months
Phase II	Oxaliplatin/capecitabine	43	AC +GEJ +GASTRIC	35%	6.4 months
Phase II (first, second I)	Oxaliplatin/capecitabine	51	SCC/AC+ GEJ	39%	8 months
Phase II	Docetaxel/capecitabine/carboplatin	25	AC +GEJ +GASTRIC	48%	8 months
Phase II	Docetaxel/cisplatin/5-FU	60	GEJ + GASTRIC	47%	17.9 months
Phase III	ECF	249	SCC+	41%	9.9 months
	ECX	241	AC+	46%	9.9 months
	EOF	235	GEJ+	42%	9.3 months
	EOX	239	GASTRIC	48%	11.2 months
Phase II	Cisplatin/paclitaxel	35	SCC	49%	13 months
Phase II	Capecitabine/cisplatin	45	SCC	58%	11.2 months
Phase III	Cisplatin/S-1Cisplatin/5-FU	8288	GEJ +GASTRIC	29%/32%	8.6 months/7.9 months
Phase II	Docetaxel/cisplatin/5-FU	50	SCC+ AC +GEJ +GASTRIC	47%	11.2 months
Phase II (first, second I)	Paclitaxel/capecitabine	32	SCC	75%/45%	14.3 months/8.4 months
Phase II	Cisplatin/paclitaxel	46	SCC	57%	17 months

1.RED

mOS 7-17m
RR 35-50%

Notes: *P, 0.05; **P, 0.01.
Abbreviations: 5-FU, 5-fluorouracil; AC, adenocarcinoma; ECF, epirubicin/cisplatin/5-FU; ECX, epirubicin/capecitabine/5-FU; EOF, epirubicin/oxaliplatin/5-FU; EOX, epirubicin/oxaliplatin/capecitabine; GASTRIC, gastric cancer; GEJ, gastroesophageal junction carcinoma; S-1, oral fluoropyrimidine; SCC, squamous cell carcinoma; OS, overall survival; RR, response rate.

Wiedman MW, et al:Cancer Management and Research 2013:5

METASTATSKA BOLEZEN KT

	Treatment	n	RR	Median OS
Phase II	Vinorelbine	16	6%	6 months
Phase II	Docetaxel	11++	0%	4 months
Phase II	Docetaxel/irinotecan	24+++	12.5%	6.5 months
Phase II	Paclitaxel	13+++	0%	NA
Phase II	Docetaxel	38+++	16%	8.1 months
Phase II	Docetaxel/capecitabine	8+++	25%	6.2 months
Phase II	Docetaxel/nedaplatin	28+++	39.3%	8.5 months
Phase II	Docetaxel/nedaplatin	12+	25%	NA
Phase II	Irinotecan	13++	15.4%	5 months
Phase II	Docetaxel/cisplatin/5-FU	20+++	35%	8 months
Phase II	Docetaxel/cisplatin/5-FU	32+++	50%	NA
Phase II	Mitomycin/ifosfamide/cisplatin	19+	12.5%	5.2 months
Phase II	Docetaxel/nedaplatin	20+	25%	6.5 months
Phase II	Docetaxel/irinotecan	15++	20%	11.4 months
Phase II	Docetaxel/nedaplatin	46+	27.1%	5.9 months
Phase II	Docetaxel/cisplatin	35+	34.2%	7.4 months
Phase III	Docetaxel vs BSC	84#84#	7%#0%#	5.2 months#,*3.6 months#

Notes: *P , 0.05; +squamous cell carcinoma; ++adenocarcinoma; +++squamous cell carcinoma/adenocarcinoma; #including stomach cancer.
Abbreviations: 5-FU, 5-fluorouracil; RR, response rate; OS, overall survival; NA, nonapplicable; BSC, best supportive care.

Wiedman MW, et al:Cancer Management and Research 2013:5

2 .RED

mOS 4-11m
RR do 35%

METASTATSKA BOLEZEN TARČNA TERAPIJA

	Treatment	n	RR	Median OS
Phase II (2nd line)	Erlotinib	44++	9%	6.7 months
Phase II (2nd line)	Gefitinib	36+++	3%	5.5 months
Phase II (1st/2nd)	Gefitinib	27++	11%	4.5 months
Phase II	Irinotecan/5-FU/cetuximab	38++,#	44%#	16 months#
Phase II	Cisplatin/5-FU/cetuximab versus cisplatin/5-FU	32+30+	19% vs 13%	9.5 months vs 5.5 mont
Phase II	Cisplatin/docetaxel/cetuximab	13++	41%#	9 months
Phase II	Oxaliplatin/5-FU/cetuximab	25++	77%	9.5 months#
Phase II (2nd line)	Cetuximab	55++	6%	4.0 months
Phase III	5-FU (capecitabine)/cisplatin ± trastuzumab	58++48++	47%#35%#	13.8 months#,**11.1 months#
Phase II (2nd line)	Cetuximab/irinotecan	50++	14%	5.5 months
Phase II (2nd line)	Erlotinib	13+/17++	15%/0%	8.2 months/11.2 months
Phase II(2nd line)	Cetuximab	35++	3%	3.1 months
Phase II	Irinotecan/5-FU/cetuximab	13++	46%#	16.5 months#
Phase II	5-FU/oxaliplatin/erlotinib	33++	52%	11.0 months
Phase II/III	Epirubicin/oxaliplatin/capecitabine ± panitumumab	278#275#	46%42%#	8.8 months#11.3 months#
Phase II	Lapatinib	16++	6%	NA
Phase III (2nd line)	Ramucirumab/BSC	238++,#117++,#	3.4%#2.6%#	5.2 months#,**3.8 months#

Notes: **P ,0.01; +squamous cell carcinoma; ++adenocarcinoma; +++squamous cell carcinoma/adenocarcinoma; #including gastric cancer patients.
Abbreviations: 5-FU, 5-fluorouracil; BSC, best supportive care; NA, non-applicable; RR, response rate; OS, overall survival.

Wiedman MW, et al:Cancer Management and Research 2013:5

METASTATSKA BOLEZEN TARČNA TERAPIJA

- REGARD[1]
- KLINIČNA RAZISKAVA FAZE III (2.RED) - REGARD
  - ADENOCA ŽELODCA IN GEP (25%)
- RAMUCIRUMAB vs. PLACEBO,
- SREDNJE PREŽIVETJE 5.2m vs. 3.8m, p=0.047

- RAINBOW[2]
- KLINIČNA RAZISKAVA FAZE III
  - ADENOCA ŽELODCA IN GEP (20%)
- PAKLITAKSEL ± RAMUCIRUMAB
- SREDNJE PREŽIVETJE 9.6m vs. 7.4m, p=0.017
- ORR 28% vs. 17%
- DCR 80% vs. 64%

1. LANCET 2014;383: 31-39.
2. LANCET ONCOL 2014;15:1224-35.

- KLINIČNA RAZISKAVA FAZE III (1.RED) – TOGA
  - ADENOCA ŽELODCA IN GEP (20%)
- BOLNIKI Z ADENOKARCINOMOM, HER2 POZITIVNI
- 5-FU (KAPECITABIN)/CISPLATIN ± TRASTUZUMAB
- RR 47% vs. 35%
- SREDNJE PREŽIVETJE 13.8m vs. 11.1m, p=0.046

LANCET 2010;376: 687-97.

METASTATSKA BOLEZEN

Management of advanced/metastatic disease

Ann Oncol. 2016 Sep;27(suppl 5):v50-v57.

Patients with metastatic oesophageal cancer can be considered for different options of palliative treatment depending on the clinical situation. Single-dose brachytherapy may be a preferred option even after external RT, since it provides better long-term relief of dysphagia with fewer complications than metal stent placement [I, B].
Chemotherapy is indicated for palliative treatment in selected patients, particularly for patients with AC who have a good PS [III, B].
In squamous cell oesophageal cancer, the value of palliative combination chemotherapy is less proved. Therefore, BSC or palliative monotherapy should also be considered [II, B].

Personalised medicine

HER2-positive metastatic AC should be treated with a trastuzumab-containing treatment [II, B].

METASTATSKA BOLEZEN

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES††

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

FIRST-LINE THERAPY

Trastuzumab (with chemotherapy)
Trastuzumab 8 mg/kg IV loading dose on Day 1 of cycle 1, then
Trastuzumab 6 mg/kg IV every 21 days[19]
or
Trastuzumab 6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg IV every 14 days

PREFERRED REGIMENS

Fluoropyrimidine and cisplatin
Cisplatin 75–100 mg/m² IV on Day 1
Fluorouracil 750–1000 mg/m² IV continuous infusion over 24 hours daily on Days 1–4
Cycled every 28 days[20]

Cisplatin 50 mg/m² IV daily on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2000 mg/m² IV continuous infusion over 24 hours daily on Day 1
Cycled every 14 days[21,22]

Cisplatin 80 mg/m² IV daily on Day 1
Capecitabine 1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[23]

PREFERRED REGIMENS--continued

Fluoropyrimidine and oxaliplatin
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[24]

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2600 mg/m² IV continuous infusion over 24 hours on Day 1
Cycled every 14 days[21]

Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[25]

PREFERRED REGIMENS--continued

DCF modifications
Docetaxel 40 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV on Day 1
Fluorouracil 1000 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cisplatin 40 mg/m² IV on Day 3
Cycled every 14 days[26]

Docetaxel 50 mg/m² IV on Day 1
Oxaliplatin 85 mg/m² IV on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[27]

Docetaxel 75 mg/m² IV on Day 1
Carboplatin AUC 6 IV on Day 2
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1–3
Cycled every 21 days[28]

National Comprehensive Cancer Network (NCCN)

METASTATSKA BOLEZEN

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES††

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

FIRST-LINE THERAPY; OTHER REGIMENS

Paclitaxel with cisplatin or carboplatin
Paclitaxel 135–200 mg/m² IV on Day 1
Cisplatin 75 mg/m² IV on Day 2
Cycled every 21 days[29]

Paclitaxel 90 mg/m² IV on Day 1
Cisplatin 50 mg/m² IV on Day 1
Cycled every 14 days[30]

Paclitaxel 200 mg/m² IV on Day 1
Carboplatin AUC 5 IV on Day 1
Cycled every 21 days[31]

Docetaxel and cisplatin
Docetaxel 70–85 mg/m² IV on Day 1
Cisplatin 70–75 mg/m² IV on Day 1
Cycled every 21 days[32,33]

Fluoropyrimidine
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[22]

Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 28 days[34]

Capecitabine 1000–1250 mg/m² PO BID on Days 1–14
Cycled every 21 days[35]

OTHER REGIMENS--continued

Taxane
Docetaxel 75–100 mg/m² IV on Day 1
Cycled every 21 days[36,37]

Paclitaxel 135–250 mg/m² IV on Day 1
Cycled every 21 days[38]

Paclitaxel 80 mg/m² IV on Day 1 weekly
Cycled every 28 days[39]

Fluorouracil and irinotecan
Irinotecan 180 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days
(only for adenocarcinoma)[40]

Irinotecan 80 mg/m² IV on Day 1
Leucovorin 500 mg/m² IV on Day 1
Fluorouracil 2000 mg/m² IV continuous infusion over 24 hours on Day 1
Weekly for 6 weeks followed by 2 weeks off treatment[61]

OTHER REGIMENS--continued

ECF
Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days[41]

ECF modifications
Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days[10,11]

Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days[10,11]

Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days[10,11]

††Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.

National Comprehensive Cancer Network (NCCN)

ZAKLJUČKI

PRIMARNA OPERACIJA

- BOLNIKI STADIJA $T_{1b}N_0$

DEFINITIVNA KEMORADIOTERAPIJA

- SCC ZGORNJE TRETJINE POŽIRALNIKA
- SREDNJA IN SPODNJA TRETJINA OZ. EG PREHOD, ČE OPERACIJA NI MOŽNA

ZAKLJUČKI

BOLNIKI PRED OPERACIJO (SCC+ADENO)

- BOLNIKI STADIJA > $T_{1b}N_0$ ALI N+ SREDNJE IN SPODNJE 1/3 ➔ PREDOPERATIVNA KEMORADIOTERAPIJA
- OPERABILNI BOLNIKI ADENOCA GEP ➔ PERIOPERATIVNA KEMOTERAPIJA (KT-OP-KT)

BOLNIKI PO OPERACIJI

- SCC NE GLEDE NA STADIJ IN PREDOPERATIVNO ZDRAVLJENJE
  - ČE R0 RESEKCIJA ➔ SLEDENJE
  - ČE R1/2 RESEKCIJA ➔ MULTIDISCIPLINARNI KONZILIJ
- BOLNIKI STADIJA pN_0 in pT_{is-1} SREDNJE IN SPODNJE 1/3 POŽIRALNIKA ➔ SLEDENJE
- BOLNIKI STADIJA $pT_{3-4}N_0$ ALI $pT_{1-4}N+$ SREDNJE IN SPODNJE 1/3 POŽIRALNIKA ➔ POOPERATIVNA KEMORADIOTERAPIJA

ZAKLJUČKI

METASTATSKA BOLEZEN, I. LINIJA

- BOLNIKI V DOBREM STANJU (PS <2)
- BOLNIKI BREZ PRIDRUŽENIH OBOLENJ IN KAHEKSIJE
- GEP, HER2+ ➔ DVOJČEK + TRASTUZUMAB
- ZELO DOBRA KONDICIJA + MLADI ➔ TROJČEK, DRUGAČE DVOJČEK (MANJ TOKSIČNOSTI)

METASTATSKA BOLEZEN, II. LINIJA

- STANDARDNEGA ZDRAVLJENJA NI
- BOLNIKI KI SO ODGOVORILI NA PRVI RED ZDRAVLJENJA, BOLNIKI V DOBREM STANJU (PS <2), BOLNIKI BREZ PRIDRUŽENIH OBOLENJ IN KAHEKSIJE
- GEP, ADENO ➔ RAMUCIRUMAB + PAKLITAKSEL
- VEČINOMA DVOJČEK ALI MONOTERAPIJA (MANJ TOKSIČNOSTI)
- IZBIRA TERAPIJE ODVISNA OD PREDHODNEGA ZDRAVLJENJA

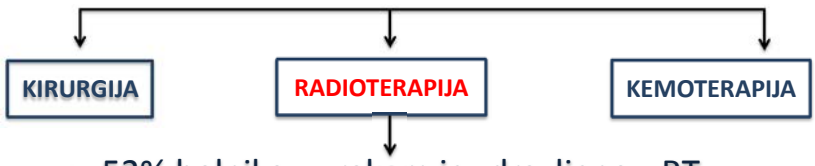
OSTALI BOLNIKI, KI NISO PRIMERNI ZA KT ➔ PALIATIVNO PODPORNO ZDRAVLJENJE

Stranski učinki obsevanja pri zdravljenju tumorjev prebavil in obvladovanje

Vaneja Velenik

Modalitete zdravljenja raka

- 14.1 mio/l novoobolelih, 8.2 mio/l smrti zaradi raka; 63% smrti je v deželah v razvoju

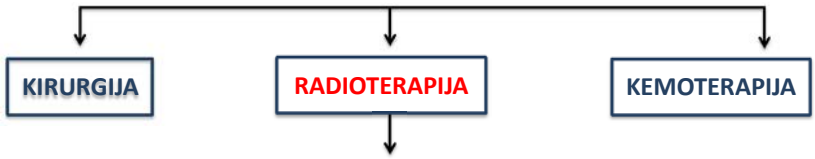


- 52% bolnikov z rakom je zdravljeno z RT
- Ozdravljeni: 49% s kirurgijo
  40% z radioterapijo
  11% s kemoterapijo

The Royal College of radiologists UK

Modalitete zdravljenja raka

- 14.1 mio/l novoobolelih, 8.2 mio/l smrti zaradi raka; 63% smrti je v deželah v razvoju

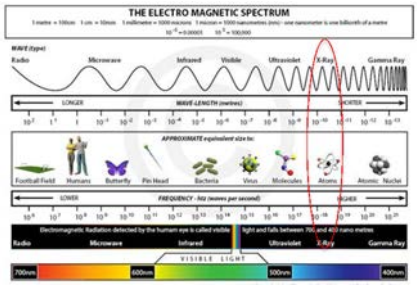


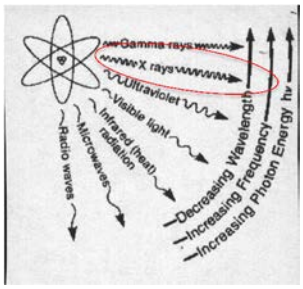
- Radikalno (definitivno,predop, postop, intraop, konsolidacijsko), paliativno
- Teleterapija, brahiradioterapija
- le 5% celotne cene zdravljena raka

Ringborg U et al. Acta Oncol 2001

Kaj je obsevanje?

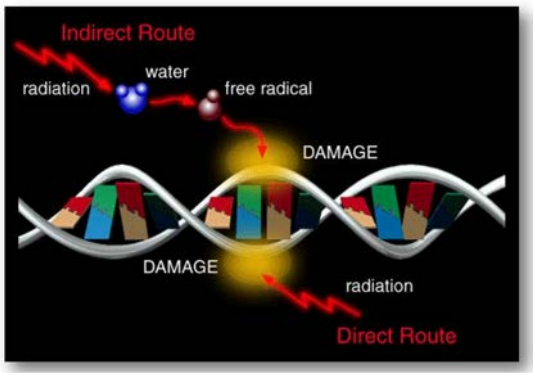
- Je lokalno zdravljenje
- uporaba visokoenergijske radiacije iz fotonov (X žarki, gama žarki), delcev (elektroni, neutroni, protoni) za uničenje rakavih celic in zmanjšanje tumorjev





Učinek obsevanja

- Je rezultat prenosa W na gradnike celičnih struktur v tkivu (→ionizacija →poškodba)



Učinek obsevanja

- Najobčutljivejša je DNA

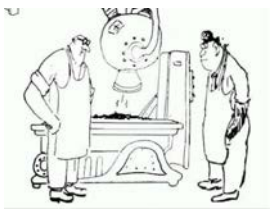
V mlg celicah je več DNA kot v normalnih
Mlg celice se množijo hitreje
Mehanizmi popravila so okvarjeni

⇩

Poškodba je v mlg celici močneje izražena

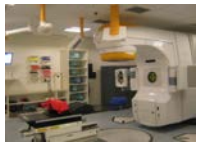
⇩

Uničenje rakavega tkiva in manj izražena poškodba zdravih tkiv, ki je še lahko popravljiva in ne ogroža življenja



Načini dovajanja obsevanja

- Linearni pospeševalnik

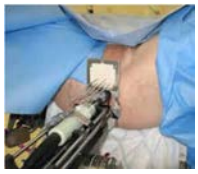


- CyberKnife

- Tomoterapija

- Gamma Knife

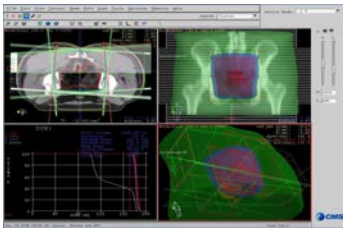
- Brahiterapija

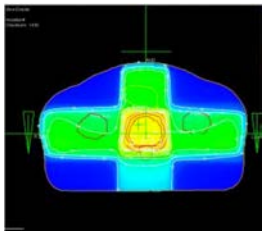


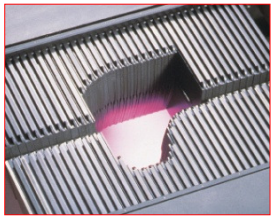
Planiranje obsevanja

(maks. doza na tumor in min. toksičnost)

- Moderne obsevalne tehnike GIT tumorjev
  - **3D- konformno obsevanje**
    - Računalniško planiranje
    - Uporaba CT ali MRI posnetkov za tvorbo 3D slike tumorja
    - Žarki so natančno usmerjeni, da se izognemo RT zdravih tkiv

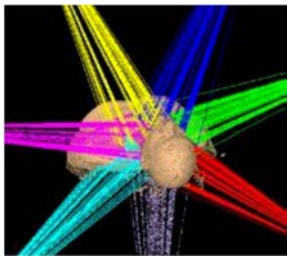






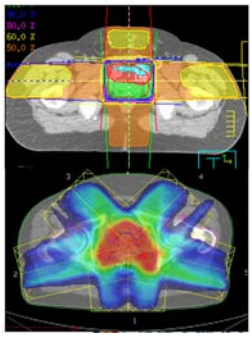
Planiranje obsevanja
(maks. doza na tumor in min. toksičnost)

- Moderne obsevalne tehnike
  - **Intenzitetno modulirano obsevanje (IMRT)**
    - Oblika 3D obsevanja
    - sevanje se razdeli na številne žarke in intenzivnost vsakega se lahko individualno prilagodi
    - Večja radiacijska doza, manj sopojavov



3D

IMRT



Planiranje obsevanja
(maks. doza na tumor in min. toksičnost)

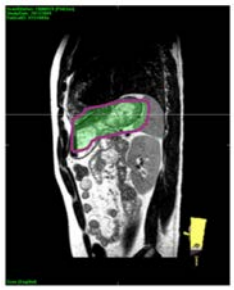
- Moderne obsevalne tehnike
  - **Slikovno vodeno obsevanje (IGRT)**

    modificira obsevalno polje pred vsakim obsevanjem glede na anatomske ali fiziološke spremembe

    Intrafrakcijske
    - Dihanje
    - Pulzacije srca
    - Peristaltika

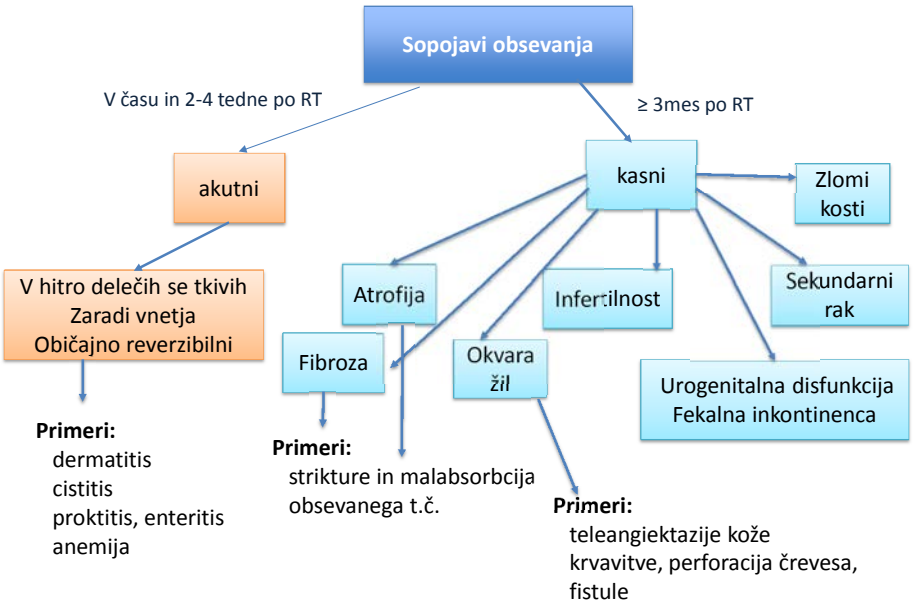
    Interfrakcijske
    - Napolnjenost želodca

slikanje → registracija → prilagoditev plana obsevanja (premik isocentra ali mize)



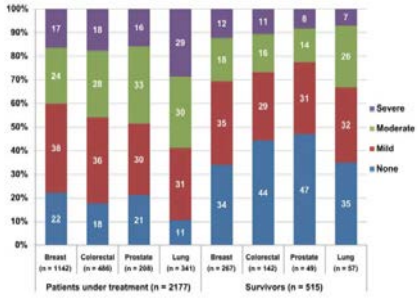
Zapleti pri RT so odvisni od

- Dejavniki tveganja – zdravljenje
  - velikosti obsevalnega polja
  - celokupne obsevalne doze
  - doze na frakcijo
  - Obsevano področje
  - Tip obsevanja in energija
- Dejavniki tveganja – bolnik
  - Komorbiditeta (anemija, diabetes, supresija imun.sistema)
  - Kajenje
  - Starost
  - BMI



Utrujenost (fatigue)

- Pri 80 % obsevancev
- Posledica razpadlih produktov rakave celice
- vrh v 2. tednu, izzveni cca 4 tedne po zaključku
- V 30% preide v koronično obliko



- Ukrepi: ostati čim bolj aktiven

Jereczek-Fossa BA et al. Crit Rev Oncol Hematol 2002
Minyon O et al. Cancer 2013
Ahmad SS et al. BMJ 2012

Rektum

- ≥G 3 ne-hemato akutna toksičnost pri 27% pts
  - Najpogosteje diareja
  - in dermatitis
- ≥G 3 pozna toksičnost pri 14% pts.
  - Najpogosteje diareja
  - Obstrukcija/strikture
  - Inkontinenca
  - Seksualna disfunkcija(erektilna pri 63%)

Sauer et al. NEJM 2004
Azria D et al. Acta Oncol 2017

Anus

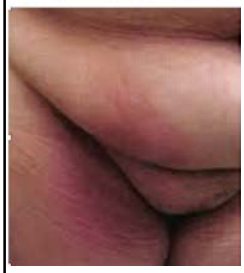
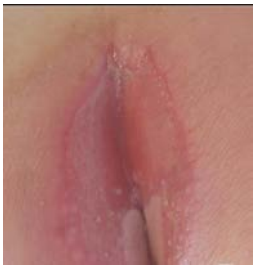
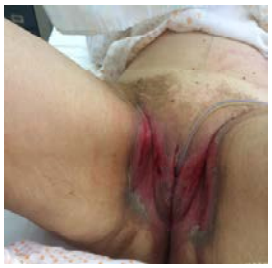
- ≥G 3 ne-hemato akutna toksičnost pri 74% pts
  - Najpogosteje dermatitis
  - in diareja
- ≥G 3 pozna toksičnost pri 11% pts.
  - Najpogosteje anorektalni ulkus
  - analne strikture, anorektalna fistula
  - Analna bolečina, inkontinenca

Ajani JA et al. JAMA 2008

Radiacijski dermatitis

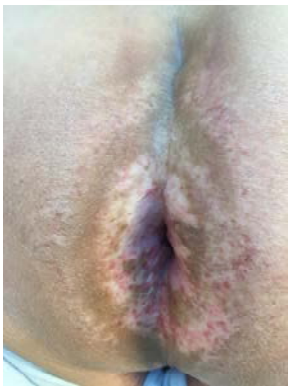
- Je kombinacija radiacijske okvare in posledičnega vnetnega odgovora
- To ni opeklina!

Radiacijski dermatitis

RD I	RD II	RD III	RD IV
Blaga rdečina ali suho luščenje, v gubah, edem	Zmerna rdečina ali neenotno luščenje, v gubah, edem	Vlažno luščenje ne le v gubah, izrazitejši edem	Ulceracija ali nekroza kože, spontano krvavi
			
Krema za regeneracijo, ki vlaži, hladi, daje prožnost, 1% gentiana tiolet	Krema +čiščenje s FR + hidrogel + poliuretanska pena ali silikonska mrežica	Kot RD II + ev. sistemski antibiotik ob okužbi, Abound ali Cubitan v prehrano	Prekinemo RT, hospitalizacija, oskrba kot RD III + Ca-alginatne obloge pri krvavitvi

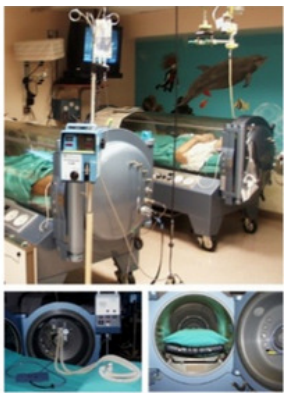
Pozni zapleti

Atrofija, teleangiektazije



Fistula

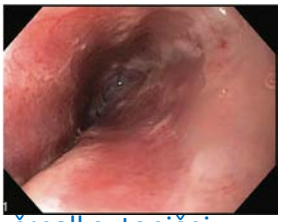
Hiperbarična komora



Radiacijski enteritis

- Akutna toksičnost
  - Diareja, bolečina, slabost, bruhanje, anoreksija
  - V 3.tednu, pogostnost 20-70%
  - Ukrepi: antidiaroiki, hidracija, dieta brez vlaknin, ev. test na C.difficile
- Pozna toksičnost (8-12 mes po RT)
  - TD 5/5 pri RT dela t.č.je 50 Gy
  - Diareja in malabsorbija
  - Ukrepi: probiotiki, izogibanje laktozi; pri malabsorbciji dieta z malo maščob, holestiramin, prehranska podpora
  - Pri kroničnem proktitisu: argon plazma koagulacija, hidrokortizonske klizme, instalacija formalina, laser, hiperbarični kisik

Ezofagitis



- ≥ G 3 akutna toksičnost pri 71% pts
  - Disfagija, odinofagija, izguba teže
  - Ukrepi-simptomatski: inhibitor protonske črpalke, topični analgetiki (Mo-sulfat, lidokain), antibiotik, NG sonda, parenteralna prehrana
- ≥ G 3 pozna toksičnost pri 37% pts
  - Progresivna disfagija
  - Fibroza z ezofagealnimi strikturami (v 26% pri CRT 58 Gy, 1% pri RT)
  - Perforacija, krvavitev
  - Ukrepi: dilatacija, krg

Murro D et al. Arch Patol Lab Med 2015
Minsky BD et al. JCO 2002

Radiacijski gastritis

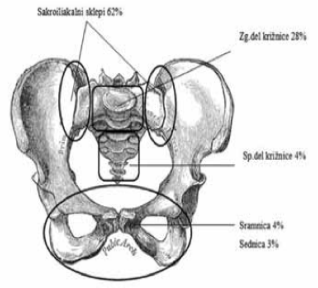
- Akutna toksičnost
  - Slabost, bruhanje v 24 urah, dispepsija, anoreksija, abd.bolečina..
  - 2/3 pts občuti slabost
  - Ukrepi – simptomatski: antiemetiki, analgetiki, inhibitor prot. črpalke
- Pozna toksičnost
  - TD 5/5 pri RT celega želodca je 50 Gy
  - 5-FU ne poveča toksičnosti
  - Abdominalna bolečina zaradi dispepsija, ulceracije, antralne stenoze

Emami B et al. IJRPBP 1991
Minsky BD et al. JCO 2002
Bentzen SM et al. IJRBP 2010

Pozni zapleti

Sekundarni zlomi kosti

Author (yr)	Primary tumor	RT site	No. of patients	Imaging study	The incidence of IF	Sites	Comments
Baxter et al. (2005) [11]	Anal cancer Cervical cancer Rectal cancer	Not demonstrated	399 1,139 1,317	Not demonstrated	14.0% 8.2% 11.2% (all at 5 years)	Pelvic bone Femur neck	SEER registry data Most fractures (90%) were hip fracture
Oh et al. (2008) [8]	Cervical cancer	Whole pelvis	557	BS, CT, & MRI	19.7% at 5 years (symptomatic: 57.8% of patients)	Pelvic bone	Risk factors: RT dose ≥50.4 Gy and low body weight (<55 kg)
Kwon et al. (2008) [10]	Cervical cancer	Whole pelvis	510	MRI	45.2% at 5 years (symptomatic: 43% of patients)	Pelvic bone Lumbar spine Femur neck	Osteolysis and AVN of femur neck is also reported
Igdem et al. (2010) [13]	Prostate cancer	Whole pelvis	134	BS, CT and MRI	6.8% at 5 years (all symptomatic)	Pelvic bone	-
Kim et al. (2012) [14]	Rectal cancer	Whole pelvis	582	CT and MRI	9% at 4 years	Sacrum	Risk factors: old age (>60 years), female gender, and history of osteoporosis
Tokumaru et al. (2012) [12]	Cervical cancer	Whole pelvis	59	CT and MRI	36.9% at 2 years (symptomatic: 16.1% at 2 years)	Pelvic bone Lumbar spine	Multi-institutional prospective study



Dongrvul O et al. Radiat Oncol J 2014
Tai P et al. Radiother Oncol. 2000

Zaključki

- RT je ena najučinkovitejših in najcenejših modalitet zdravljenja raka
- Zapleti ob/po obsevanju tumorjev prebavil so pogosti
- Moderne obsevalne tehnike povečajo homogenost dozne razporeditve v tarči in zmanjšajo dozo na zdrava tkiva
- Tehnike omogočajo prilagajanje obsevanja posamezniku, zmanjšanje toksičnosti in izboljšanje QOL
- Pomembna je multidisciplinarna obravnava za prevencijo, diagnozo in zdravljenje sopojavov

Pomen paliativne kirurgije v zdravljenju tumorjev prebavil

dr. Gašper Pilko, dr.med.
Onkološki inštitut Ljubljana

„Paliativna kirurgija je poseg, katerega primarni cilj je izboljšanje kvalitete življenja in blažitev simptomov neozdravljive bolezni“

- Balfour Mount 1973

"Paliativna kirurgija je poseg, katerega primarni cilj je izboljšanje kvalitete življenja in blažitev simptomov neozdravljive bolezni„

≠

R1,R2 resekcija

- podaljševanje preživetja ni primarni cilj

PROBLEMI

- s kirurškim posegom lahko simptome še poslabšamo in skrajšamo preživetje
- v poteku medicinskega izobraževanja in v kirurških učbenikih namenjeno le malo pozornosti (1 %)
- kirurgi pogosto pravilno ocenijo pričakovano življensko dobo bolnika, podcenijo pa pomen paliativnega posega na kvaliteto življenja

Smith DD, et al. Predicting life expectancy and symptom relief following surgery for advanced malignancy. Ann surg oncol 2008.

PROBLEMI

- multidisciplinaren pristop
- upoštevati pričakovano preživetje (2-3 mesece)
- tip tumorja
- odgovor na predhodno terapijo
- seruski albumin in telesna teža

MCCahill LE, et al. A prospective evaluation of palliative outcomes for surgery of advanced malignancies. AnnSurg Oncol 2003.

„Uspešen“ paliativen poseg: bolnik zapusti bolnišnico in se po 30 - 60 dneh lahko hrani per os

Turnbull AD, et al. Results of surgery for obstructing carcinomatosis of gastrointestinal, pancreatic, or biliary origin. J Clin Oncol 1989.

NAJPOGOSTEJŠI SIMPTOMI

- obstrukcija prebavne cevi
- krvavitev
- hujšanje
- bolečina

OBSTRUKCIJA PREBAVNE CEVI

- pri 15 % paliativnih bolnikov
- benigni vzroki 3 - 48 %
- peritonitis, prosti zrak v trebuhu, močno povišani vnetni parametri, znaki ishemije – hitro ukrepanje
- večinoma ne gre za nujne primere – temeljit razmislek in pogovor z bolnikom in svojci
- 5 – 32 % perioperativna umrljivost
- najprej poiskus konzervativne terapije (NGS, i.v. tekočine, analgetiki, karenca)

FeuerDJ, et al. Systematic review of surgery in malignant bowel obstruction in advanced gynecological and gastrointestinal cancer. Gynecol Oncol 1999.

OBSTRUKCIJA PREBAVNE CEVI

- absolutne kontraindikacije za operacijo:
  - ascites
  - tipne številne intraabdominalne mase
  - multiple stenoze
  - predhodna operacija, ki je pokazala difuzno karcinozo
  - prizadetost proksimalnega želodca

FeuerDJ, et al. Systematic review of surgery in malignant bowel obstruction in advanced gynecological and gastrointestinal cancer. Gynecol Oncol 1999.

OBSTRUKCIJA PREBAVNE CEVI

- relativne kontraindikacije za operacijo:
  - številni tumorji
  - nizek albumin < 35
  - predhodno obsevano črevo
  - slab splošni status
  - starost > 65 let
  - jetrni in oddaljeni zasevki

FeuerDJ, et al. Systematic review of surgery in malignant bowel obstruction in advanced gynecological and gastrointestinal cancer. Gynecol Oncol 1999.

OBSTRUKCIJA PREBAVNE CEVI

- simptomi in posegi odvisni od višine obstrukcije
- požiralnik, proksimalni želodec

  nezmožnost hranjenja, hujšanje

  hranilna gastrostoma, jejunostoma

OBSTRUKCIJA PREBAVNE CEVI

- distalni želodec, pankreas

  visoki ileus z bruhanjem, ikterus

  gastrostoma, gastro-entero anastomoza,

  holedoho-jejuno anastomoza

OBSTRUKCIJA PREBAVNE CEVI

- tanko in debelo črevo

ileus, bolečine

resekcija, obvod, stoma

OBSTRUKCIJA PREBAVNE CEVI

- parenteralna prehrana
- nekirurške metode
- oslabeli bolniki
- manj zapletov, nižja smrtnost, krajša hospitalizacija
- stenti, PEG

KRVAVITEV

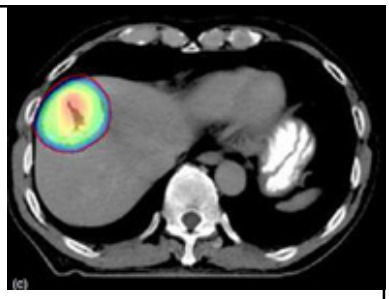
- pogosto simptom napredovale bolezni
- okultna, manifestna
- želodec, debelo črevo
- paliativna resekcija

MCCahill LE, et al. Indications and use of palliative surgery. AnnSurg Oncol 2002.

- pri zdravljenju bolečine in hujšanja so danes v ospredju bolj nekirurške metode

ZAKLJUČKI

- primarni cilj izboljšanje kvalitete življenja
- „Primum non nocere“
- multidisciplinaren pristop
- skrben pogovor z bolnikom in svojci
- dolžina preživetja, tip tumorja, stanje bolnika
- nekirurške metode



SBRT TU prebavil

Irena Oblak

STEREOS= RIGIDEN, FIKSEN

TAXIS= PREDPIS

SBRT = stereotaktična radioterapija ali stereotaktična radioablacija.

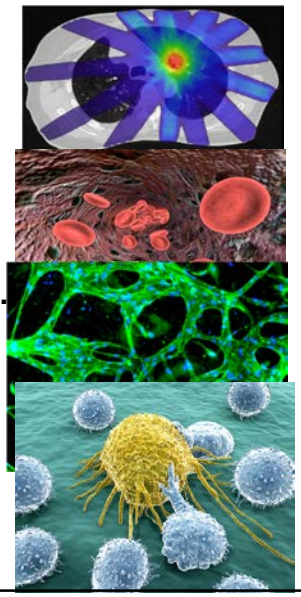
Gre za novejšo tehniko RT, ki omogoča precizno posredovanje visoke doze sevanja na TU z minimalno dozno obremenitvijo sosednjih zdravih tkiv.

SBRT

- 1 ali nekaj frakcij obsevanja;
- posredujemo ↑ D na TU;
- povzročimo ablativen učinek.
-
- Predpogoj:
- a). ustrezna strojna in programska opremljenost;
- b). usposobljen kader.

Radiobiologija SBRT

a). Ablativni učinek RT;
b). Okvara endotelija;
c). Okvara žilja;
d). Aktivacija imunskega sistema.



Primerjava doz konvencionalne RT in SBRT

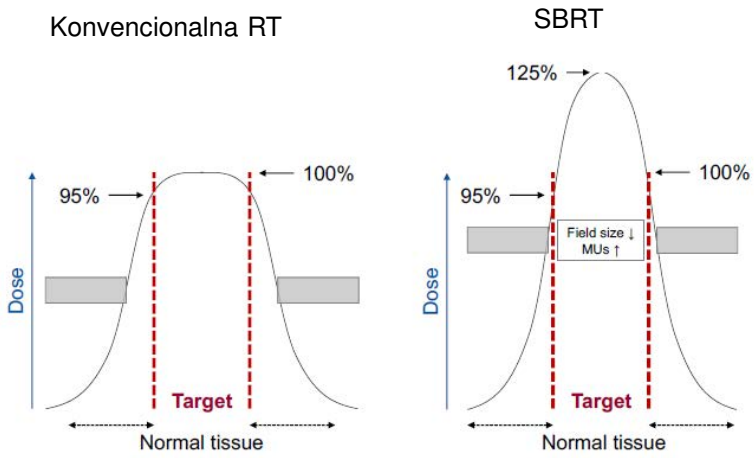
- 30 x 2Gy = 60Gy (konvencionalna RT)

≠

- 3 x 20Gy = 60Gy (SBRT)

Fizikalne doze so enake, vendar nikakor ne biološke!

Primerjava načrtovanja konvencionalne RT in SBRT



SBRT je bolnikom prijazna metoda

- Neinvazivna;
- Neboleča;
- Bolniki jo dobro prenašajo;
- Ne potrebuje anastezije;
- Izvaja se ambulantno.

Stereotaktična radioterapija indikacije-1

- Standardno zdravljenje možganskih TU in zasevkov, ki niso za OP;
- Standardno zdravljenje pri zgodnjem pljučnem raku, ki ni za OP;
- Standardno zdravljenje pri HCC, ki ni za OP;
- Rak prostate;
- Recidivi v področju lobanjske baze;
- Ponovno obsevanje lokalnega recidiva pljučnega raka;
- Recidivi v bezgavkah.

Stereotaktična radioterapija indikacije-2

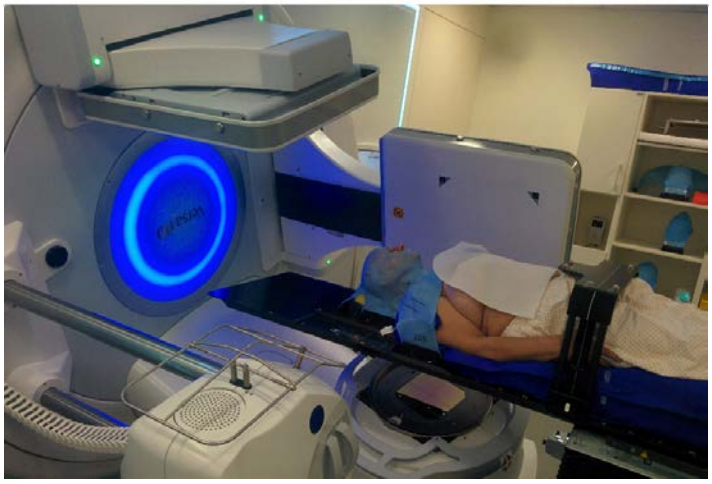
- Pljučni zasevki različnih rakov, ki niso primerni za OP;
- Zasevki v hrbtenici;
- Jetrni zasevki različnih rakov, ki niso primerni za OP;
- Zasevki v nadledvičnici;
- Paliativno ali predoperativno pri raku trebušne slinavke.
- ….

Stereotaktično obsevanje na OIL

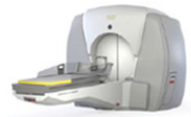
- 10 let TU in zasevke v CŽS;
- Dobro leto TU in zasevke v pljučih;
- 1 leto TU in zasevke v hrbtenici;
- Pričenjamo z zasevki v jetrih, nadaljujemo z primarnimi TU jeter in drugih GIT lokalizacij.

Linearni akcelerator (aparat 8)

Linearni akcelerator (aparat 4)



Primerjava različnih obsevalnih naprav



	Mechanical accuracy	Overall treatment accuracy
Gamma Knife Perfexion♮	0.30 mm	0.93 mm
Dedicated Linac: Novalis°	0.31 mm	0.50 – 1.5 mm
Cyberknife*	0.50 mm	0.85 mm

* Hoogeman 2008 & Murphy 2009
♮ Wu & Maitz & Massagier 2007
° Verellen 2003

ESTRO SBRT 2017

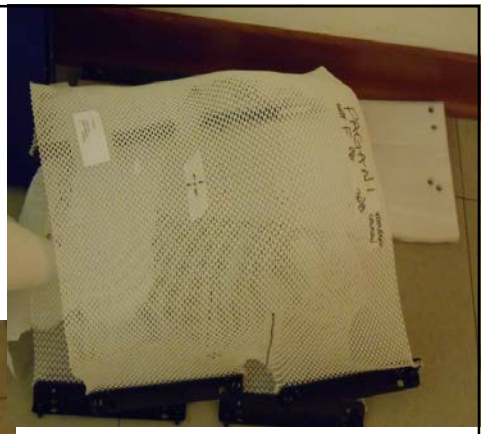
Uvajanje SBRT

- Intrakranialno stereotaktično RT;
- Ekstrakranialno stereotaktično RT: zahtevnejše zaradi težje imobilizacije in zagotavljanja enakih pogojev med načrtovanjem in izvajanjem RT:

- Intrafrakcijski in interfrakcijski premiki struktur (dihanje, polnjenost organov,…);
- Dodatna oprema (kontrola dihanja, abdominalna kompresija, vstavitev fiducialnih markerjev za sledenje).

FIKSACIJA BOLNIKA:
MASKA ZA TREBUH

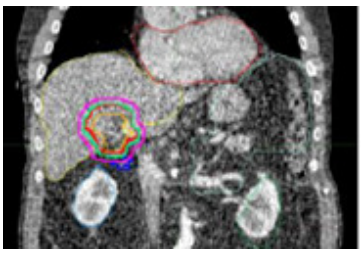
trebušna slinavka

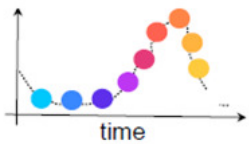


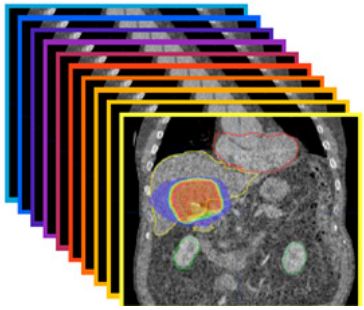
jetra (kompresija)

FIKSACIJA BOLNIKA

4D –CT: vpliv dihanja (10 faz)

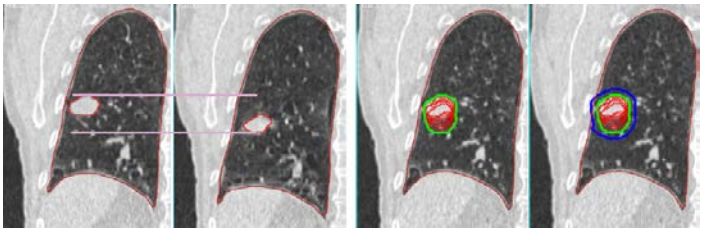






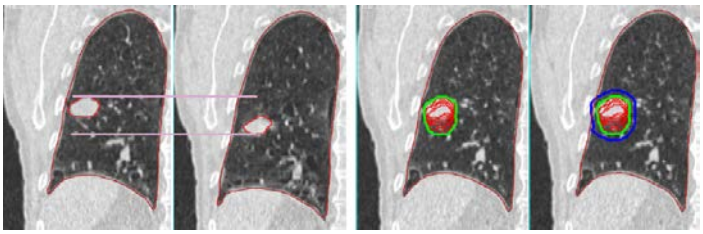
KONTROLA DIHANJA

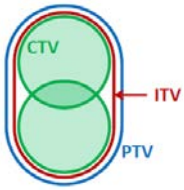
- Aktivna (obsevanje v določeni fazi dihalnega cikla;
- Pasivna (zadrževano dihanje).



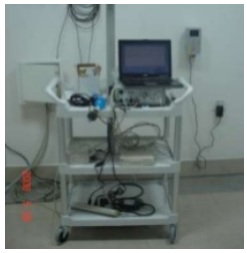
KONTROLA DIHANJA

- Aktivna (obsevanje v določeni fazi dihalnega cikla;
- Pasivna (zadrževano dihanje).

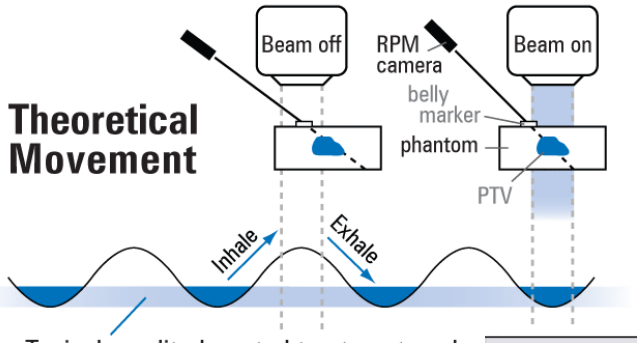




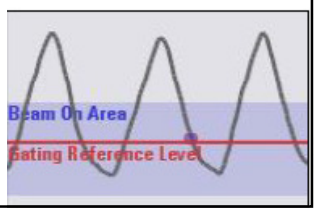
Kontrola respiratorne gibljivosti



Dihalno proženje

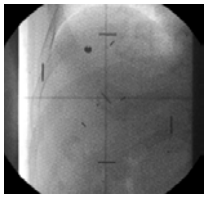


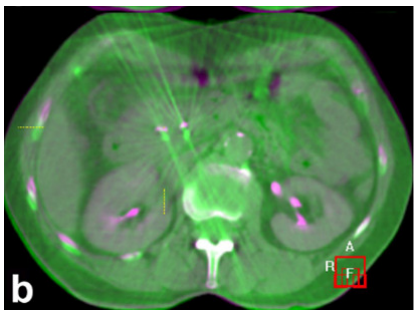
RPM = Real-time Position Management



Abdominalna kompresija

Vstavitev fiducialnih markerjev





SBRT JETER

- V preteklosti klasično RT jeter le izjemoma v paliativne namene;
- Vzrok je bila nizka toleranca celotnih jeter na obsevanje;
- Jetra imajo paralelno organiziranost: tolerirajo visoke doze na majhen volumen.

SBRT JETER

- *Tehnično zahtevnejša zaradi:*

1. večje gibljivosti zaradi dihanja (predvsem L jetrni lobus lahko celo 39.5mm (mean 17.6mm);
2. različne polnjenosti sosednjih organov (želodec, črevo);
3. slabe vidljivosti zasevkov na CT-ju (vstavitev fiducialnih markerjev);
4. potrebnega zdravega jetrnega parenhima (>700 cm^3).

Raziskave faze I–II SBRT jetrnih zasevkov

Study	No. Pts	Primary Cancer (No. Patients)	Tumor Size	Dose (No. #)	Local Control	Survival
Herfarth 2001	35	NR	1-132 cc	14-26 Gy (1)	1 yr 71%	NR
Mendez-Romero 2006	17	CRC (14) Other (3))	1.1-322 cc	30-37.5 Gy (3)	1 yr 100% 2 yr 82%	1 yr 85% 2 yr 62%
Hoyer 2006	44	CRC (44)	1-8.8 cm	45 Gy (3)	NR	NR
Lee 2009	68	CRC (40) Breast (12) Other (16)	1.2 – 3090 cc	27.7-60 Gy (6)	1 yr 71%	Med surv 17.6 mo
Rusthoven 2009	47	CRC (15) Lung (10) Other (22)	0.8-98.0 cc	60 Gy (3)	1 yr 95% 2 yr 92%	Med surv 20.5 mo
Goodman 2010	22 47	CRC (5) Other (17)	7.5-146 cc	18-36 Gy (1)	1 yr 77%	Med surv 28.6 mo
Rule 2011	27	CRC (12) Other (15)	1-135 cc	30-60 Gy (5)	1 yr 100% (60Gy)	Med surv 37 mo

Uspešnost SBRT jeter

- 1-letna lokalna kontrola: 70-100%;
- 2-letna lokalna kontrola: 60-90%;
- 2-letno preživetje bolnikov: 30-85%

Scorsetti M, et al. Stereotactic body radiation therapy for liver metastases. J Gastrointest Oncol 2014.

SBRT JETER

- Za izbrane bolnike, ki niso za OP zaradi medicinskih ali tehničnih razlogov ali OP odklonijo.
- (zasevki blizu velikih žil, diafragme, žolčnik izvodil in žolčnika, s portalno karcinomsko vensko trombozo,…).

Ostali kriteriji za SBRT-1

- Pričakovana življenjska doba bolnika> 6 mesecev oz. 1 leto;
- PS 0-2 po lestvici SZO;
- Največ 4 zasevke;
- Premer zasevka ≤ 6 cm;
- ≥700 cm^3 zdravega jetrnega parenhima (>1000 cm^3).

Ostali kriteriji za SBRT-2

- Jetrna funkcija po Child-Pugh A-B;
- Zasevek oddaljen ≥5- 8mm od požiralnika, želodca, duodenuma in črevesja;
- Brez izven jetrne bolezni ali gre za omejeno bolezen, ki jo je možno zdraviti.

SBRT kriteriji

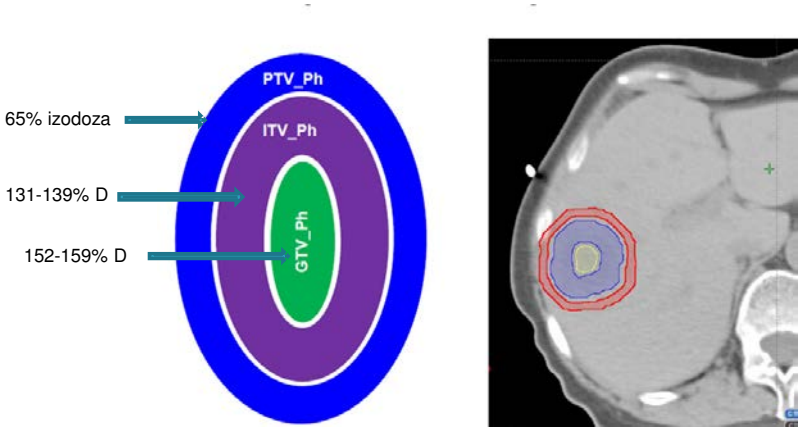
Bolniki/ Kriteriji	Primerni	Mejni	Neprimerni
Št. zasevkov	<3	4	<4
Premer zasevka (cm)	1-3	3-6	>6
Oddaljenost do rizičnih organov (mm)	>8 (od GTV)	5-8	<5
Funkcija jeter	Child A	Child B	Child C
Volumen N jeter (cm^3)	<1000	700-1000	<700

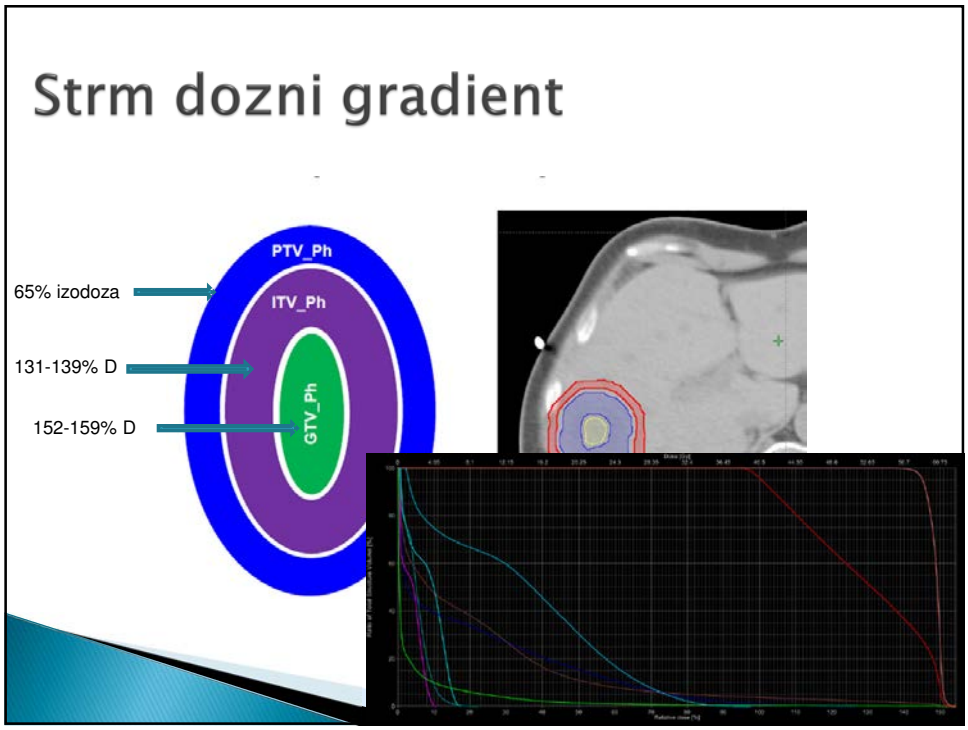
Scorsetti M, et al. Stereotactic body radiation therapy for liver metastases. J Gastrointest Oncol 2014.

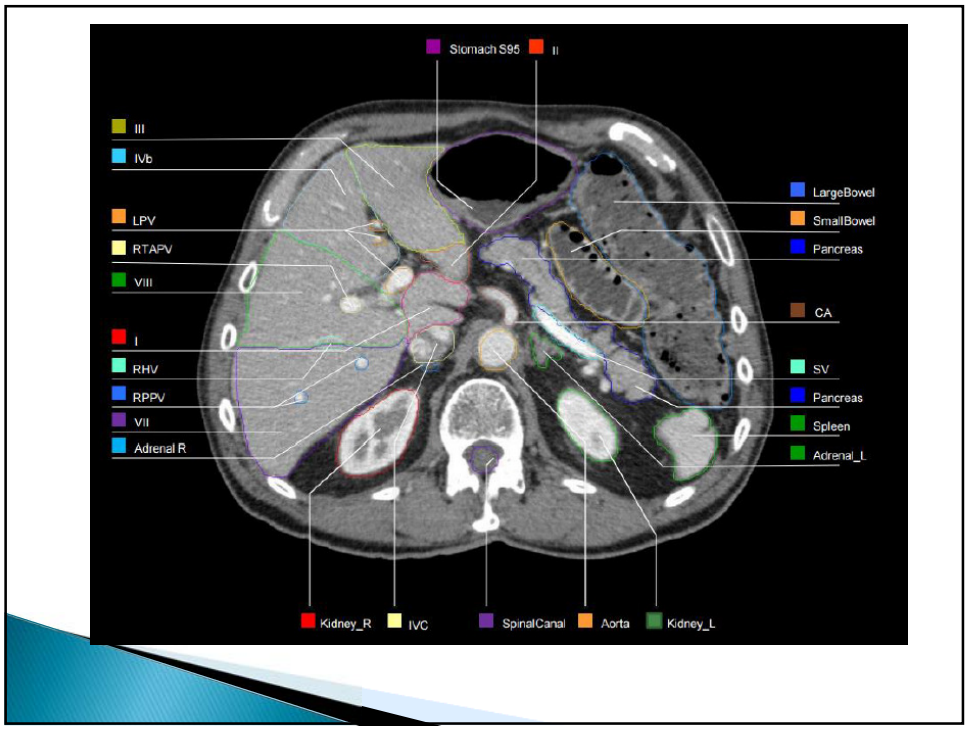
Režimi SBRT JETER

<u>3 frakcije:</u>
a). zasevki <3 cm: TD 60 Gy;
b). zasevki 3-6 cm: TD 75 Gy.
<u>5 frakcij:</u>
TD 55-60Gy.

Strm dozni gradient




Strm dozni gradient
65% izodoza
131-139% D
152-159% D
PTV_Ph
ITV_Ph
GTV_Ph


Stomach S95
II
III
IVb
LPV
RTAPV
VIII
I
RHV
RPPV
VII
Adrenal R
LargeBowel
SmallBowel
Pancreas
CA
SV
Pancreas
Spleen
Adrenal_L
Kidney_R
IVC
SpinalCanal
Aorta
Kidney_L

Predpisane doze in restrikcije za RT jeter

	Doza/fr	Št. fr	Srednja doza	ORGAN	Dose-Volume omejitve	Drugo
Standardna D	25Gy	3	75 Gy	Zdrava jetra)	> 700 cc pri < 15 Gy v 3 fr	Volumen zdravih jeter> 1000 cc
Zmanjšanje D 10%	22.5 Gy	3	67.5 Gy	Hrbtenjača	< 18 Gy v 3 fr	
				Ledvica (R+L)	V15 Gy < 35%	
Zmanjšanje D 20%	20. 63 Gy	3	61.89 Gy	želodec, duodenum, tanko črevo	< 21 Gy v 3 fr	Bolniki z GTV < 8 mm od srca, želodca, duodenuma in tankega črevesa so izključeni
Zmanjšanje D 30%	18.75 Gy	3	56.25 Gy			
				Srce	<30 Gy v 3fr	

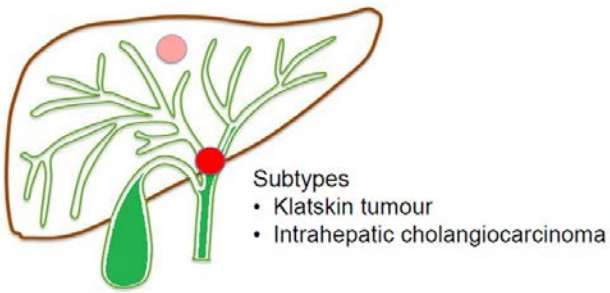
Neželjeni učinki SBRT jeter in TU v zgornjem abdomnu

- Z obsevanjem povzročena okvara jeter (RILD) (anikterični ascites, ↑AF, ↑transaminaze→odpoved jeter);
- Krvavitve, ulkusi, perforacije cevastih organov;
- Bolečine v prsnem košu, zlomi reber;
- Stenoza žolčnih vodov;
- Okvara ledvic.

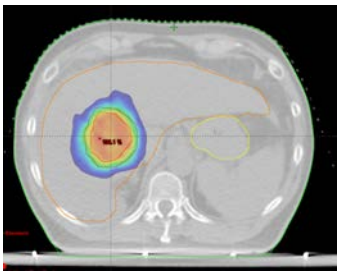
SBRT pri HCC

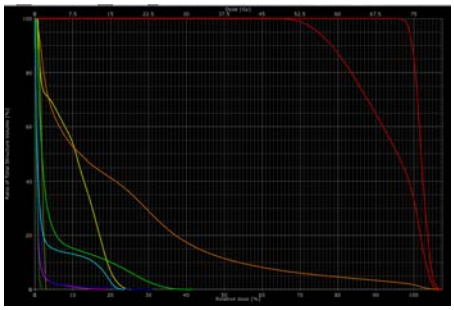
- Zelo zahtevna zaradi okvare normalnega jetrnega tkiva (hepatitis, ciroza,..);
- Za izbrane bolnike, kjer OP ni možna;
- Kot premostitveno TH pri bolnikih,ki čakajo transplantacijo;
- Ob 2 letih po SBRT:LC 95%, OS 69%, PFD 34% (Kwon JH, 2010).

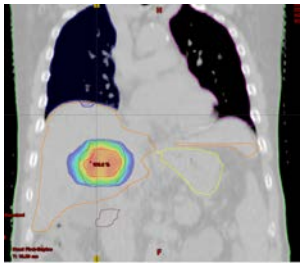
SBRT pri holangiokarcinomu

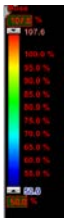


SBRT JETER : 25Gy x 3;

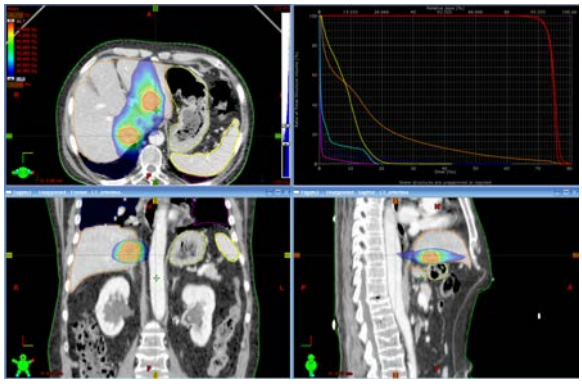


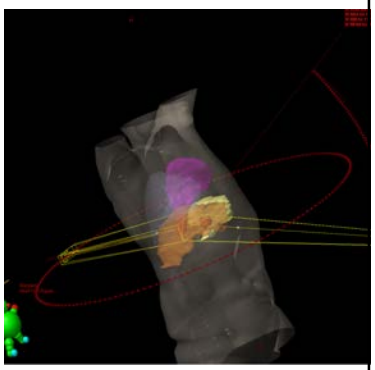






SBRT JETER: 25Gy x 3

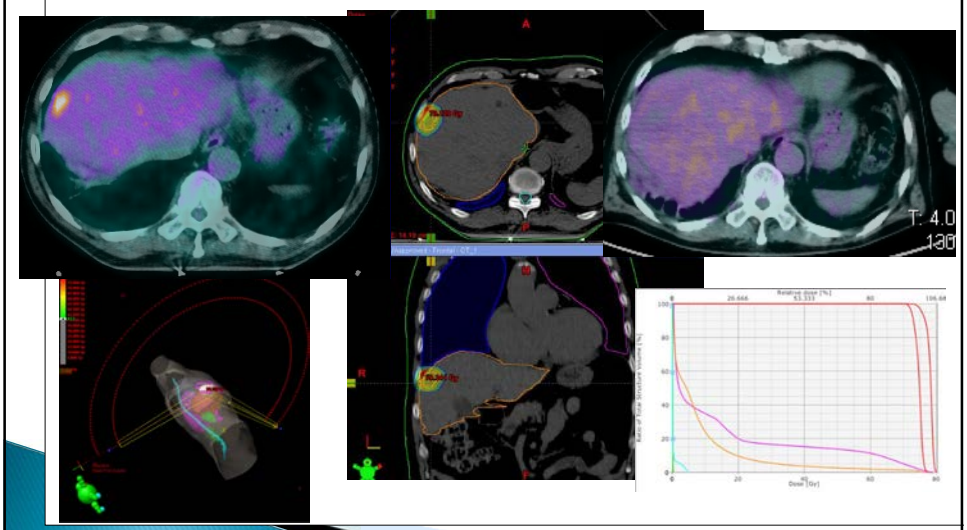




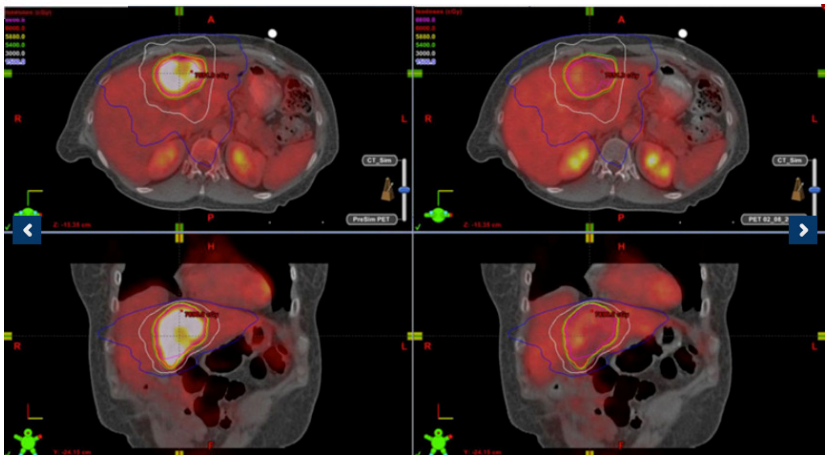
SBRT JETER: 25Gy x 3

PET pred zdravljenjem

PET po 6 mesecih



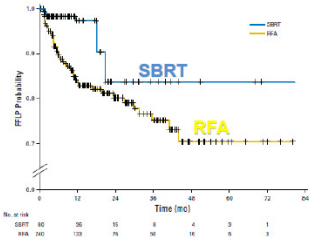
HCC



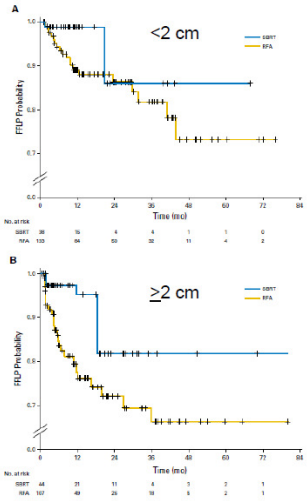
SBRT in RFA

SBRT versus RFA

Inoperable HCC wo. PVT



	SBRT	RFA
FFLP (1-yr)	97%	84%
OS (1-yr)	84%	80%
Gr 3+ tox	5%	11%



Wahl et al JCO 2016; 34(5): 452

RFA in SBRT

RFA:

- Zasevki<3cm;
- Stran od žolčnika in žolčnih vodov;
- Stran od diafragme;
- Stran od večjih žil.

SBRT

- Zasevki<6cm;
- Stran od želodca, dvanajstnika, črevesja;
- Vsaj 700cm^3 zdravih jeter.

SBRT INOPERABILNEGA CA PANKREASA

2013

RESEARCH Open Access

SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience

Angelo Tozzi[1], Tiziana Comito[1], Filippo Alongi[1,3*], Pierina Navarria[1], Cristina Iftode[1], Pietro Mancosu[1], Giacomo Reggiori[1], Elena Clerici[1], Lorenza Rimassa[1], Alessandro Zerbi[1], Antonella Fogliata[2], Luca Cozzi[2], Stefano Tomatis[1] and Marta Scorsetti[1]

- Januarjem 2010 - oktober 2011;
- **30 bolnikov** z **inoperabilnim ali recidivivnim adenocarcinomom pancreasa;**
- KT z gemcitabinom pred SBRT;
- predpisana doza **45Gy v 6 frakcijah po 7.5Gy.**

Rezultati

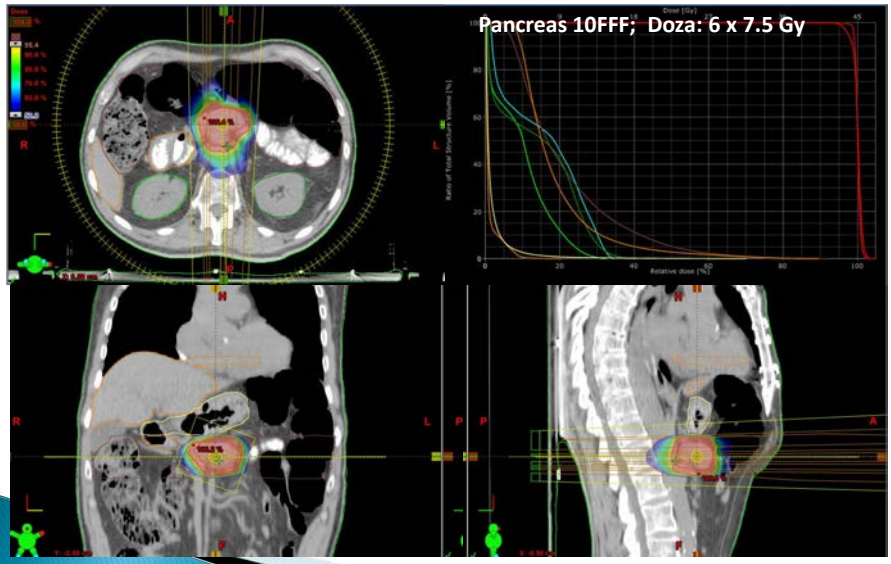
•Srednji čas sledenja 11 mesecev (2–28 mesecev);

•LC 91% pri 6 mesecih, 85% pri 1 letu.

Restrikcije

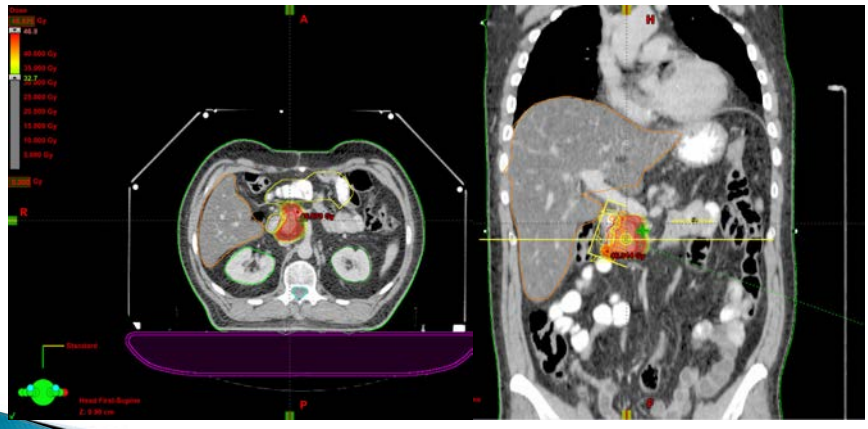
MEDULA	D1cc<18 Gy
LEDVICA	V15Gy <35%
DUODENUM	V36Gy<1cc
ŽELODEC	V36Gy<1cc
TANKO ČREVO	V36Gy<3cc
JETRA	(Vcela jetra – V21Gy)>700cc

SBRT KARCINOMA PANCREASA



SBRT KARCINOMA PANCREASA

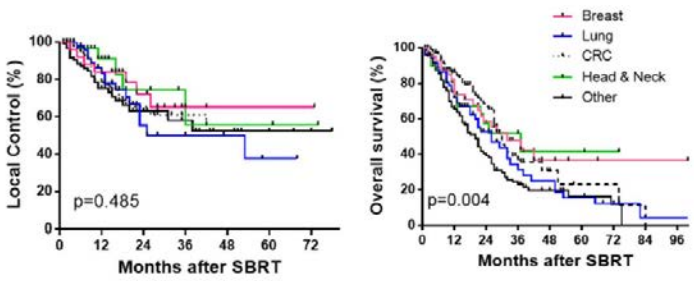
Bolnik: 56 let. Neresektabilni adenokarcinom pankreasa;
GEM + FOLFIRI in RT (**45Gy v 6 frakcijah**) -> OP (R0).



Ugotovitve nekaterih raziskovalcev

- Lee 2009: 68 bolnikov z neresektabilnimi zasevki v jetrih CRC raka, raka dojke, žolčnika,…
- *rak dojke ima daljše preživetje v primerjavi z ostalimi raki :*
- Swaminath 2011:
- *nekateri bolniki z 1-5 zasevkov v jetrih po SBRT živijo 5-10 let brez bolezni ;*
- Scorsetti 2013: 61 bolnikov z 76 zasevki v jetrih CRC, raka dojke, 36% bolnikov stabilno extrahepatično bolezen;
- **LC 94%, mediano preživetje 19 mesecev. Tu <3 cm imajo↑LC, kot TU >3cm (zvišana TD za TU > 3cm)**

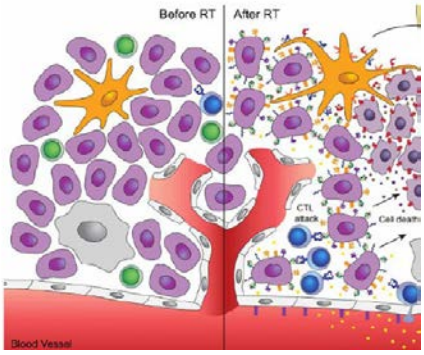
LC in preživetje po SBRT jetrnih zasevkov glede na vrsto malignoma



Multi-institutional database; 702 pts.

Ricco et al. Radiat Oncol 2017; 12: 35

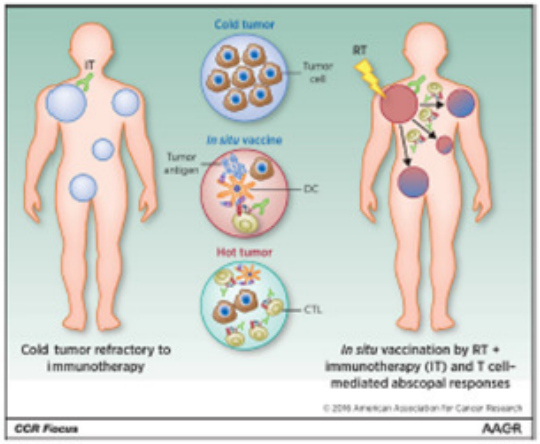
RT aktivira imunski odgovor



CD8/Treg ratio

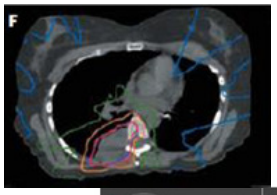
PD-L1 expression

ACSCOPAL efekt: sprožen sistemski odgovor na lokalno zdravljenje z RT

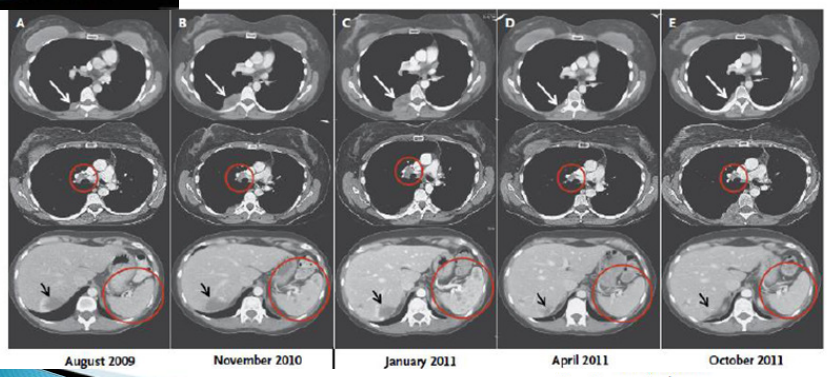


Whiteside TL, Clin Cancer Res 2016

Abcopal imunski odgovor



RT: 3 x 9.5Gy



Postow et al:
NEJM 2012;366:925

ZAKLJUČEK

- SBRT jeter in zgornjega trebuha je tehnično in strokovno najzahtevnejša v primerjavi z ostalimi SBRT lokalizacijami;
- Za izbrane bolnike z oligometastatsko boleznijo ali primarnimi TU;
- Omogoča 70-100% lokalno kontrolo in ob pravilni izbiri bolnikov tudi dolgo preživetje.

SIMPOZIJ SO PODPRLE NASLEDNJE DRUŽBE:

SERVIER

ELI LILLY

BAYER

MERCK

CELGENE

MSD

ROCHE

DR. FALK FARMACIJA

MEDIAS

AMGEN

SANOFI AVENTIS