PARACELSUS
MEDIZINISCHE PRIVATUNIVERSITÄT

UNIVERSITY HOSPITAL
UNIKLINIKUM
SALZBURG

Metastasiertes Kolorektalkarzinom: Verbessertes Überleben durch aggressive Chirurgie und moderne Chemotherapie-Konzepte

Primavesi F, Stättner S, Jäger T, Presl J, Buchner S, Tomanová K, Öfner D, Hutter J, Emmanuel K, Dinnewitzer A

Florian Primavesi

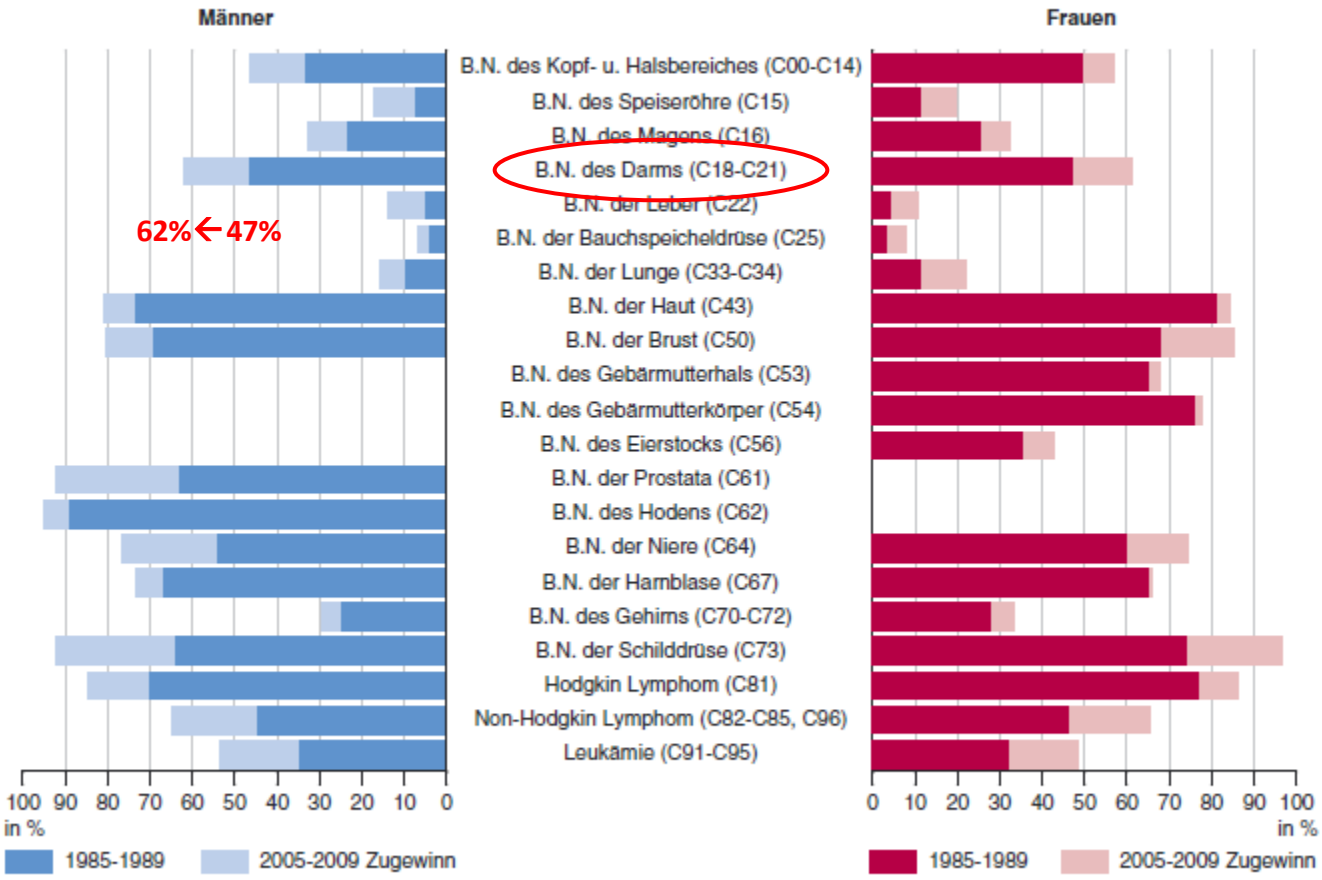
Frühjahrstagung ISDS – 2016 Brac

5-Jahres Überleben Österreich in 20 Jahren

Grafik 18

Relatives 5-Jahres-Überleben im Vergleich 1985-1989 mit 2005-2009 nach Lokalisationen

5-year relative survival 1985-1989 and 2005-2009 by most common cancer sites and sex



Q: STATISTIK AUSTRIA, Österreichisches Krebsregister (Stand 02.10.2015) und Todesursachenstatistik. - Ende des Follow-up 31.12.2014.

UICC IV KRK

- 20% der Patienten haben bei Erstdiagnose Metastasen (UICC IV)
- Weitere 25-30% im Lauf der Erkrankung (metachron)

    - 70% Lebermetastasen[1]
    - 15% Peritoneal- oder Bauchorganmetastasen
    - 10% Lungenmetastasen

1: Chew MH et al. Stage IV colorectal cancers: an analysis of factors predicting outcome and survival in 728 cases. J Gastrointest Surg. 2012 Mar;16(3):603-12.
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- Österreich: 1998-2002 UICC IV – 5a-OS ca. 10%[2]

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- In Österreich müssen metastasierte Patienten nicht einem Zentrum vorgestellt werden.
  -> keine wesentliche systematische Zentrierung
  -> hierdurch ev. Vorenthalt potentiell kurativer Therapieansätze

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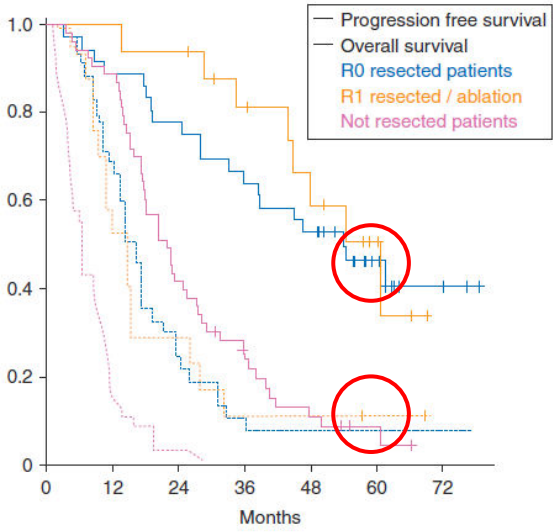
Evolution UICC IV – Bsp: Resektabilität Lebermetastasen

- Vor 20 Jahren: KRK im Stadium UICC IV: 5a-OS < 1%
- Damals wurde nur ein kleiner Anteil als resektabel angesehen
  -> Subgruppe: 30-40% 5a-OS bei liver-limited disease und R0

Durch potente CTX und chirurgische Weiterentwicklung Steigerung der Resektionsraten:

- Beispiel: 2010 CELIM Studie[1]: initial nicht-resektable L-Met (FOLFOX6 + cetuximab vs. FOLFIRI + cetuximab)
  -> 68 bzw 57% Response Rate
  -> 49 % Sekundäre Resektionsrate
  -> Follow-Up-Studie[2]: 5a-OS 46,2%
  -> Vergleichbar mit primär resektablen Patienten



1: Folprecht G, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010 Jan;11(1):38-47.

2: Folprecht G, et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). Ann Oncol. 2014 May;25(5):1018-25.

Rolle von HPB-Chirurgen – Beurteilung Resektabilität

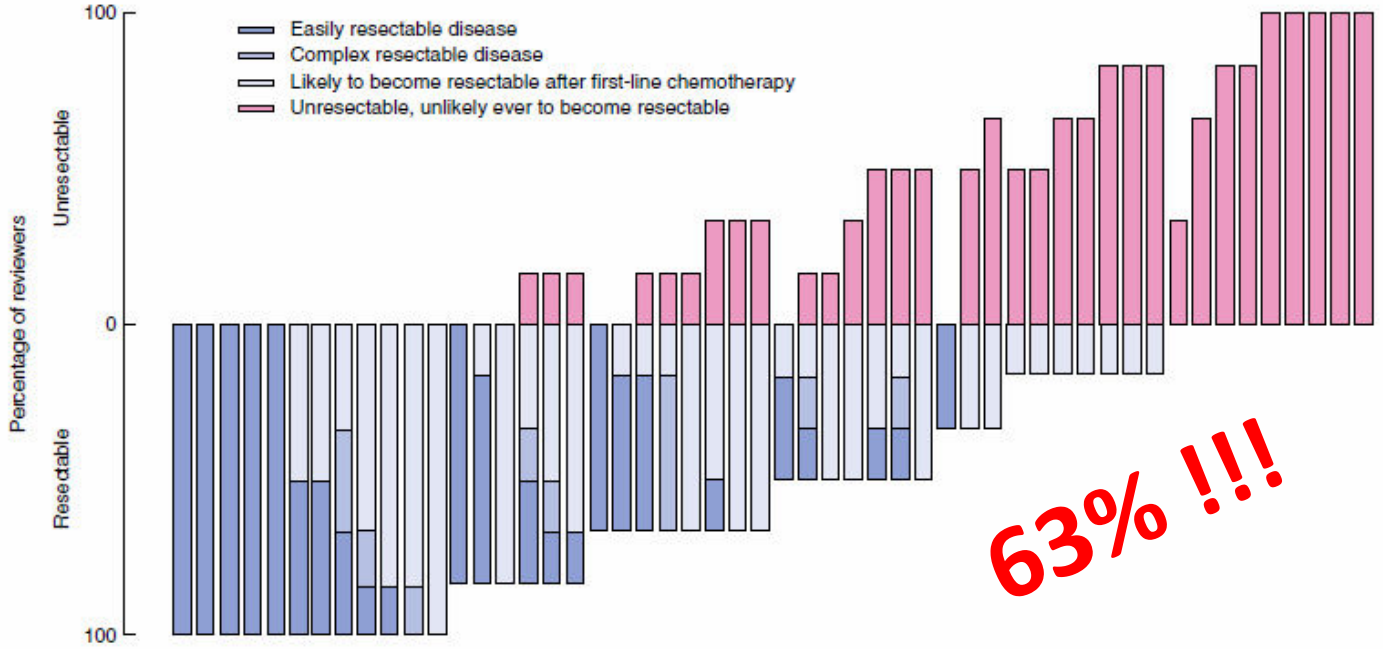


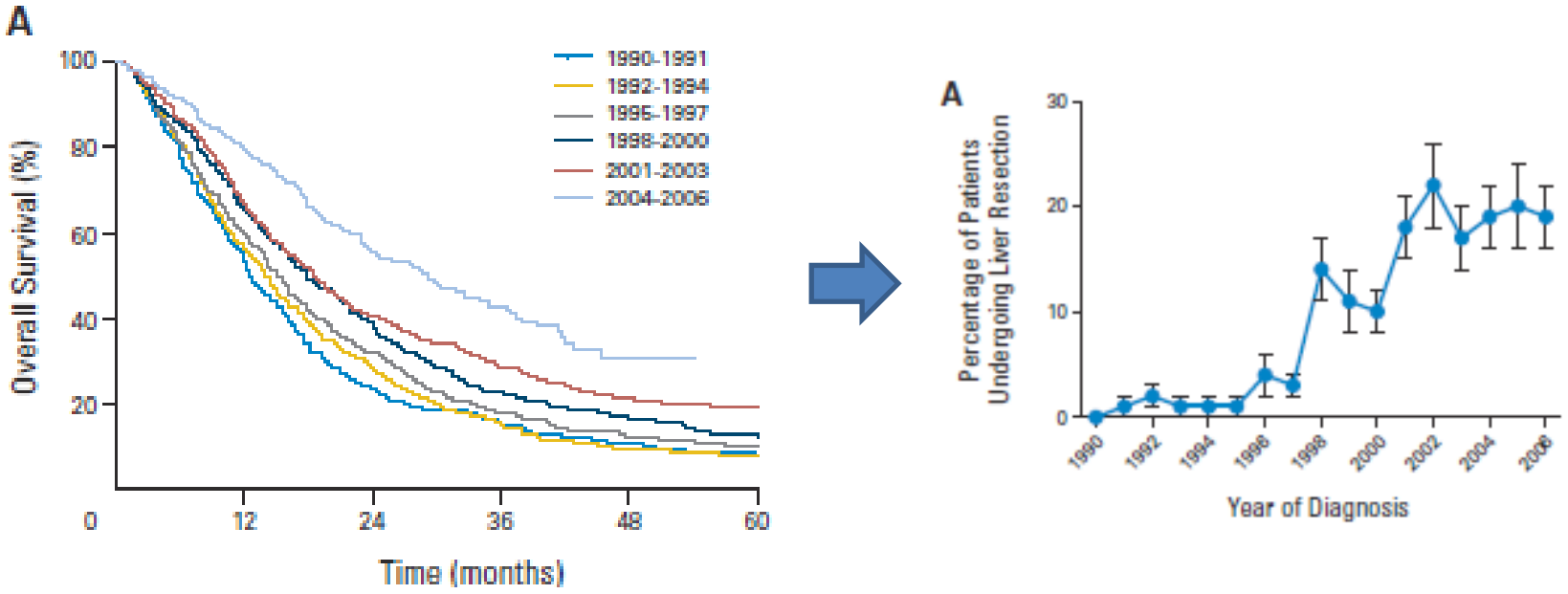
Fig. 2 Forest plot showing decisions on resectability of tumours in 52 patients. Each bar represents one patient. The percentage of reviewers who felt that the tumour was unlikely to ever become resectable (red) or to become resectable (blue) is shown. No colour coding was used when a reviewer felt unable to comment on a scan. In 33 cases (63 per cent), the majority of reviewers felt that the patient had potentially resectable liver disease

Jones RP, et al. Effect of specialist decision-making on treatment strategies for colorectal liver metastases. Br J Surg. 2012 Sep;99(9):1263-9

UICC IV KRK: International

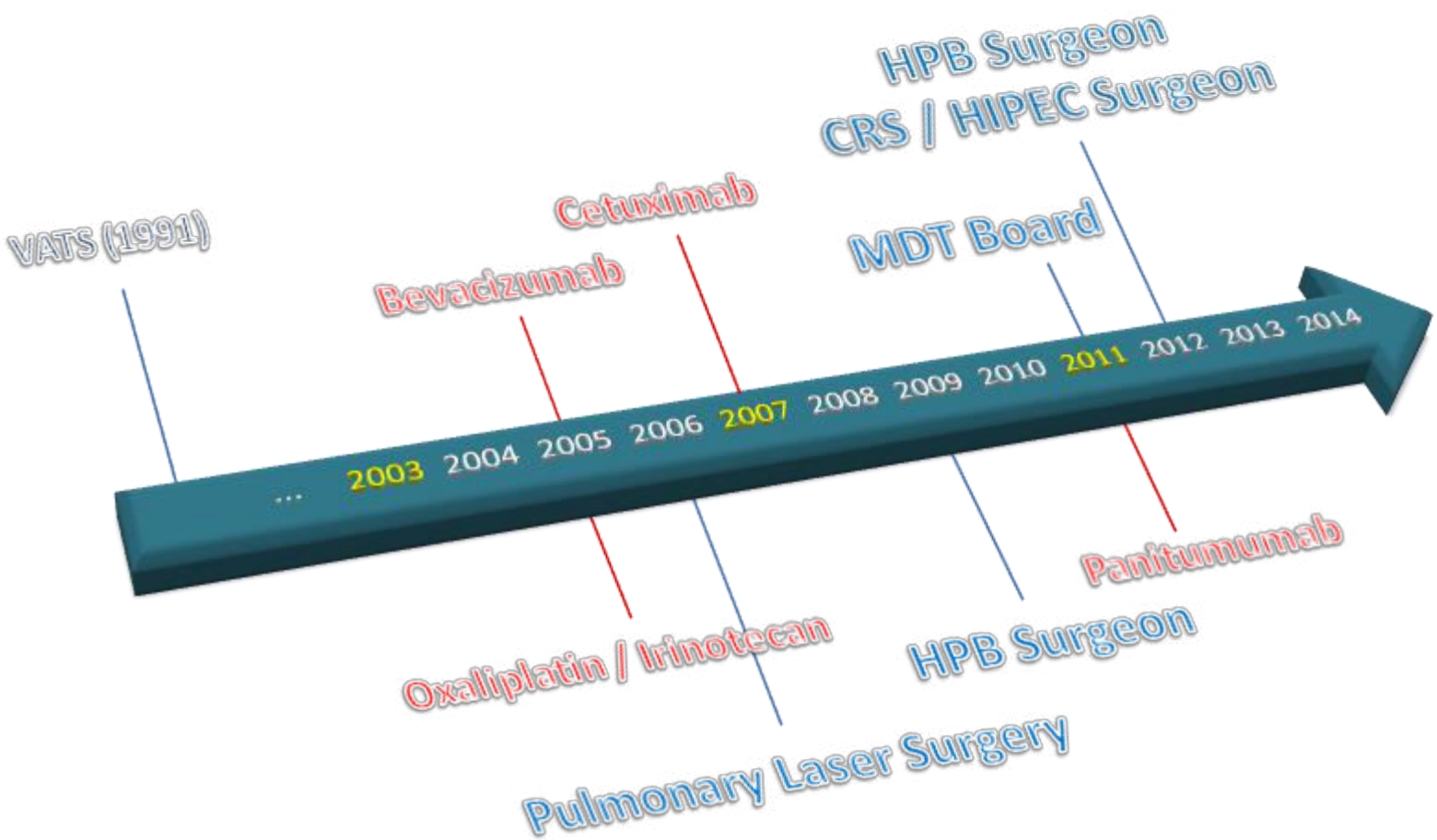
Österreich: 1998-2002 UICC IV – 5a-OS ca. 10%

UICC IV CRC - MD Anderson + Mayo Clinic (USA)[1]

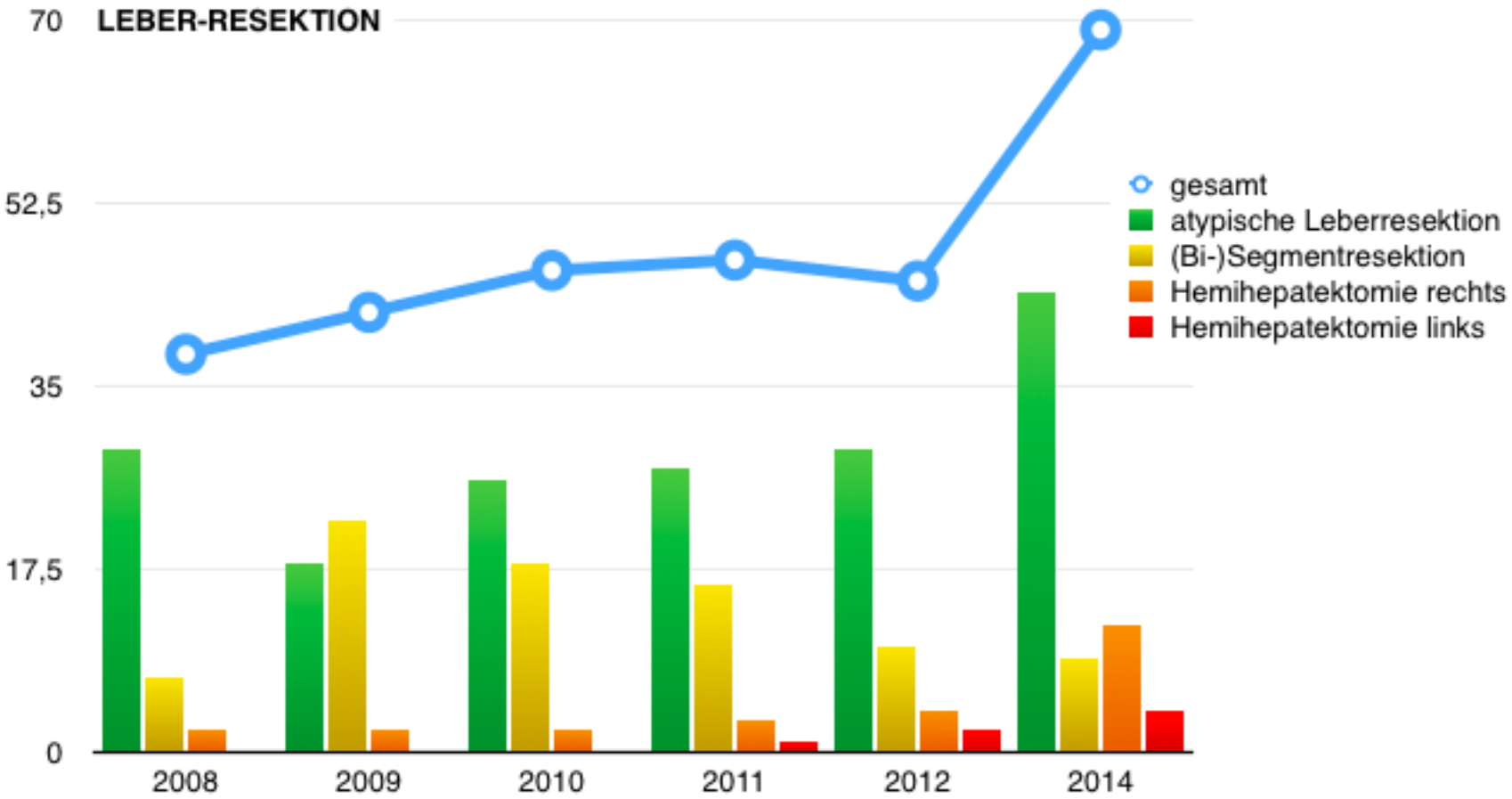


1: Kopetz S, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009 Aug 1;27(22):3677-83.

Key Events CRC Therapy - Salzburg

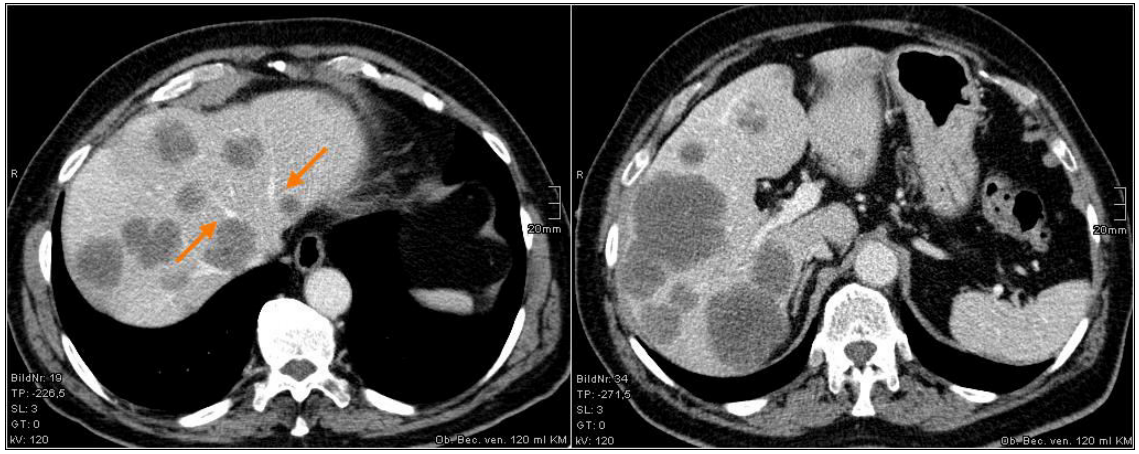


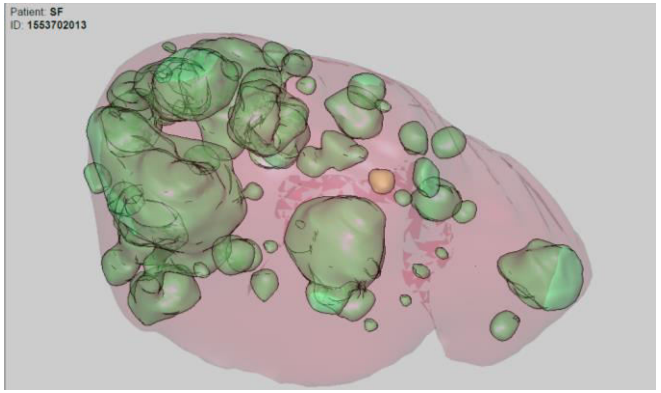
Leberresektionen Salzburg



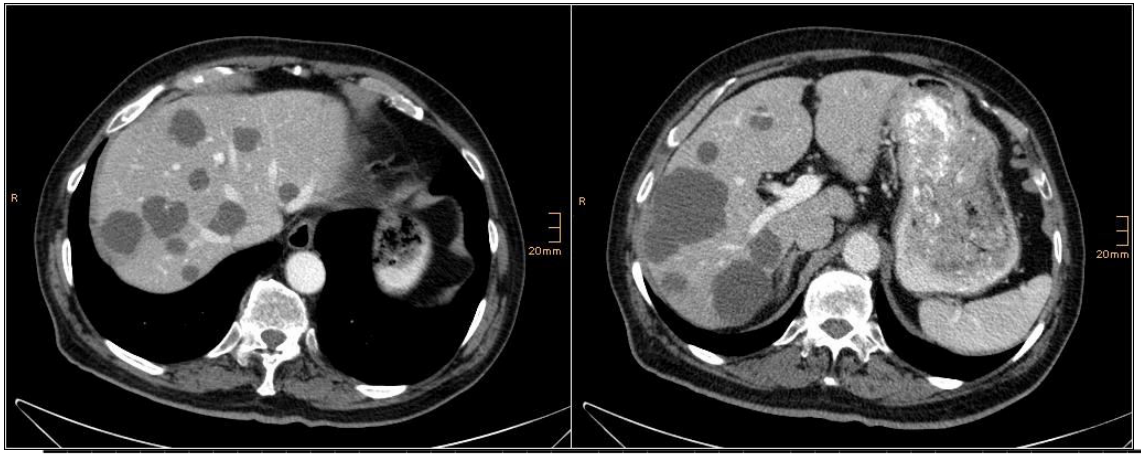
Fallbeispiel – Lebermetastasenchirurgie

72a männlicher Patient, synchron hepatal metastasiertes Ascendens-Ca (2013)





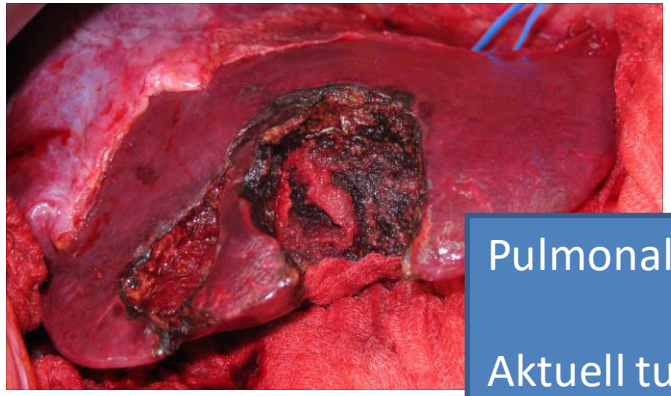
Auswärtig: palliative CTX 5 Zyklen XELOX + Bevacizumab

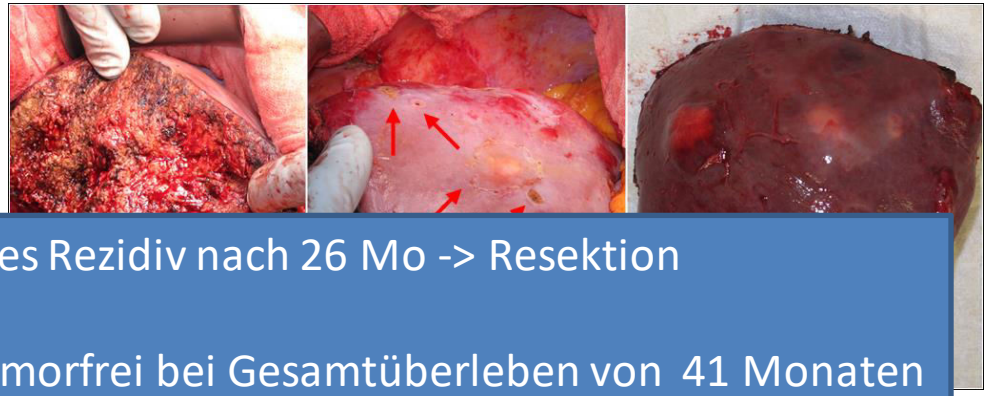


Fallbeispiel – Lebermetastasenchirurgie

Zweizeitiges Vorgehen:

1. Atyp Res (7x) Seg II/III & I, PVL, Hemikol re
2. (erw. HH re geplant) -> HH re, MWA Seg IV

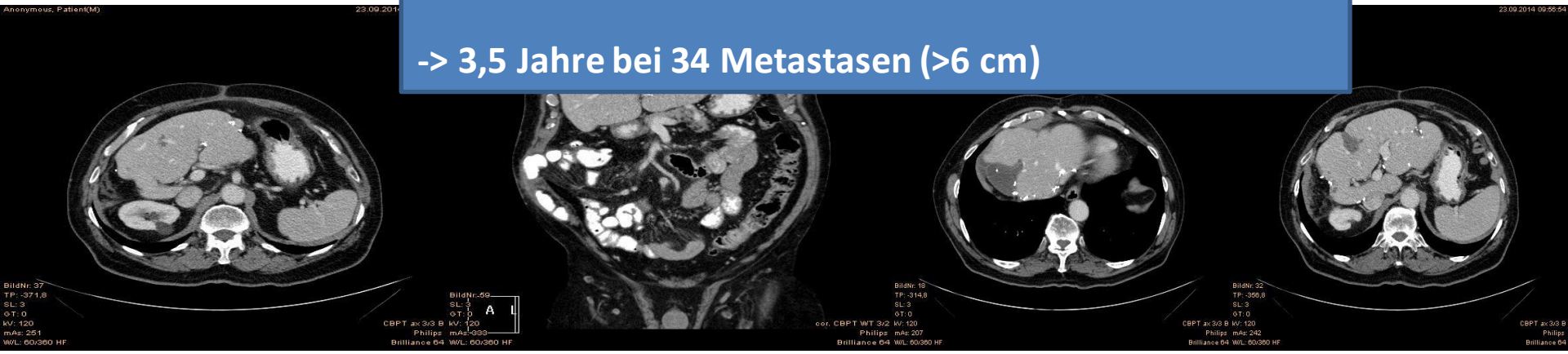




Pulmonales Rezidiv nach 26 Mo -> Resektion

Aktuell tumorfrei bei Gesamtüberleben von 41 Monaten

-> 3,5 Jahre bei 34 Metastasen (>6 cm)

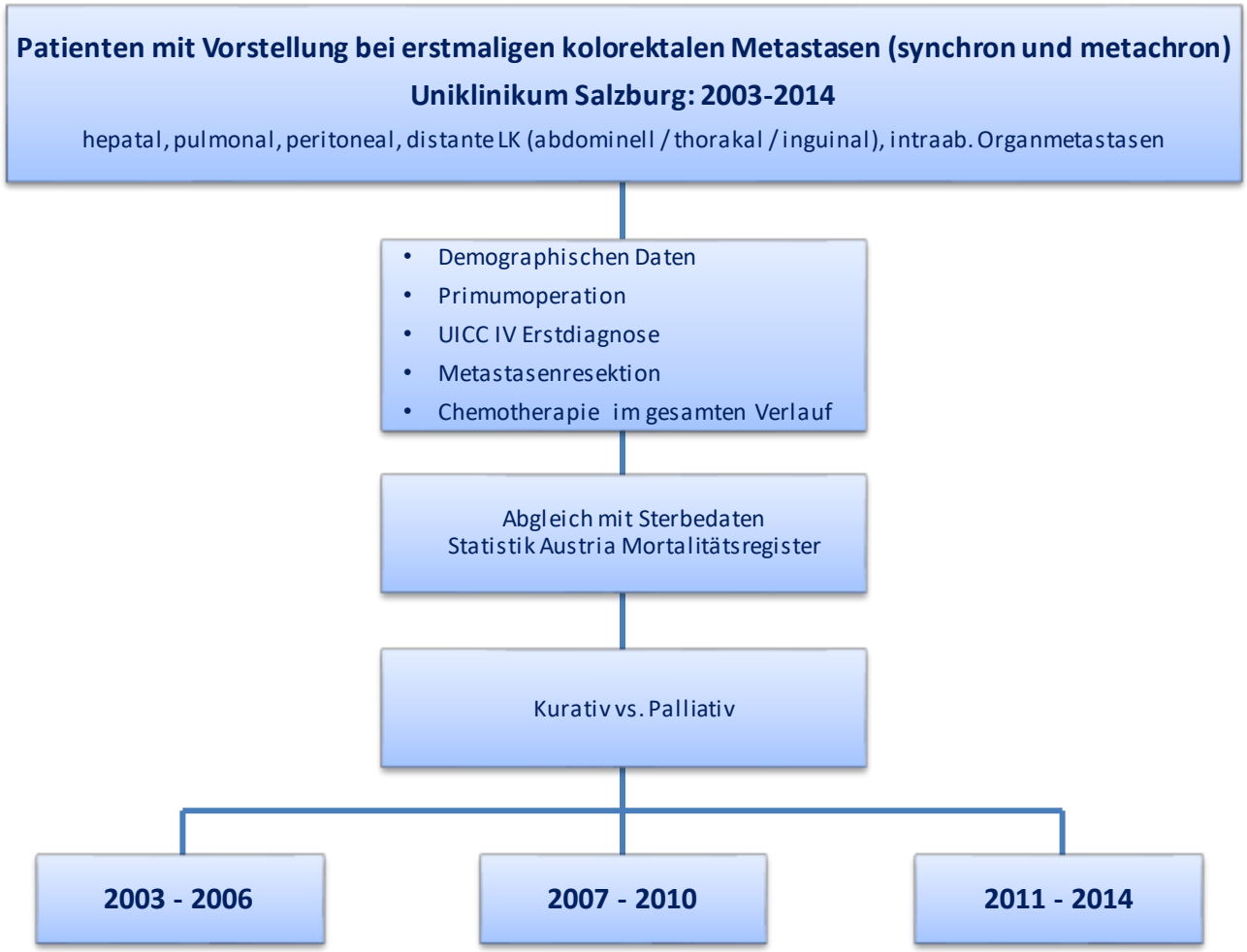


Fragestellung unserer Arbeit

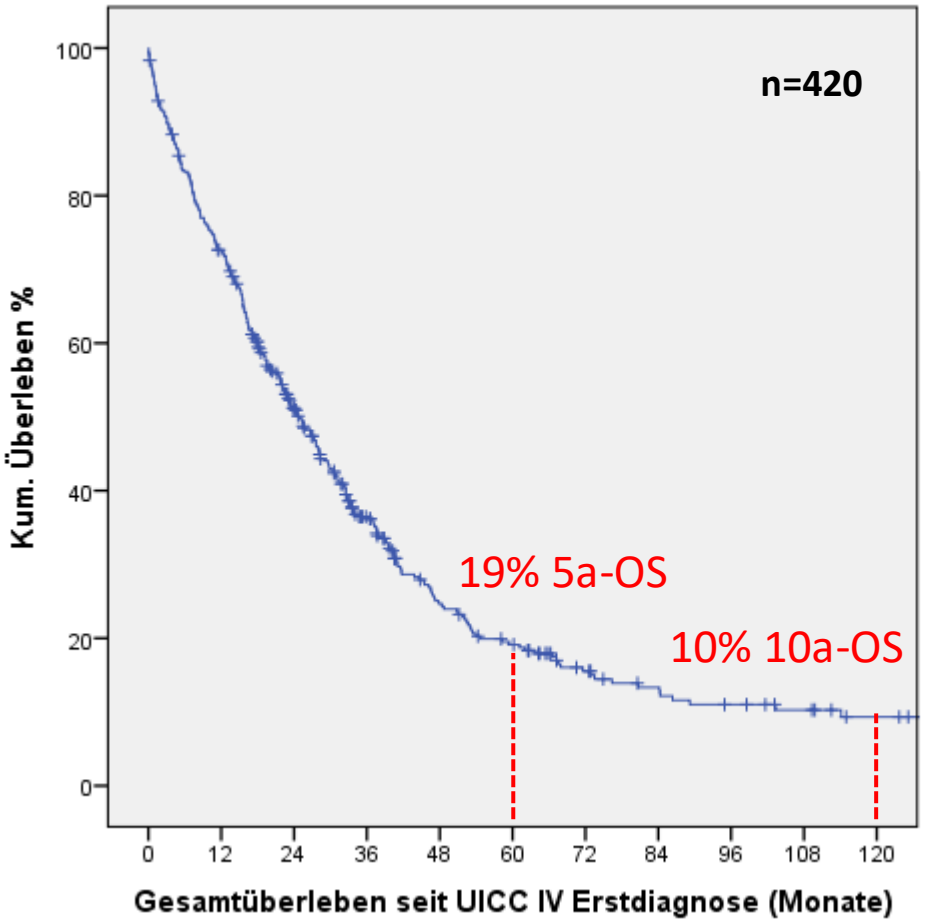
Wie ist die Prognose von Patienten mit erstmalig diagnostizierten Metastasen bei kolorektalem Karzinom am Uniklinikum Salzburg?

- Profitieren Patienten von einem aggressiven chirurgischen Vorgehen?
- Entwicklung des Gesamtüberlebens innerhalb der letzten Jahre
- Einfluss verschiedener Faktoren (Entwicklung der Chirurgie, neue Chemotherapien, etc.)
- Vergleich der Behandlungsqualität international

Methodik

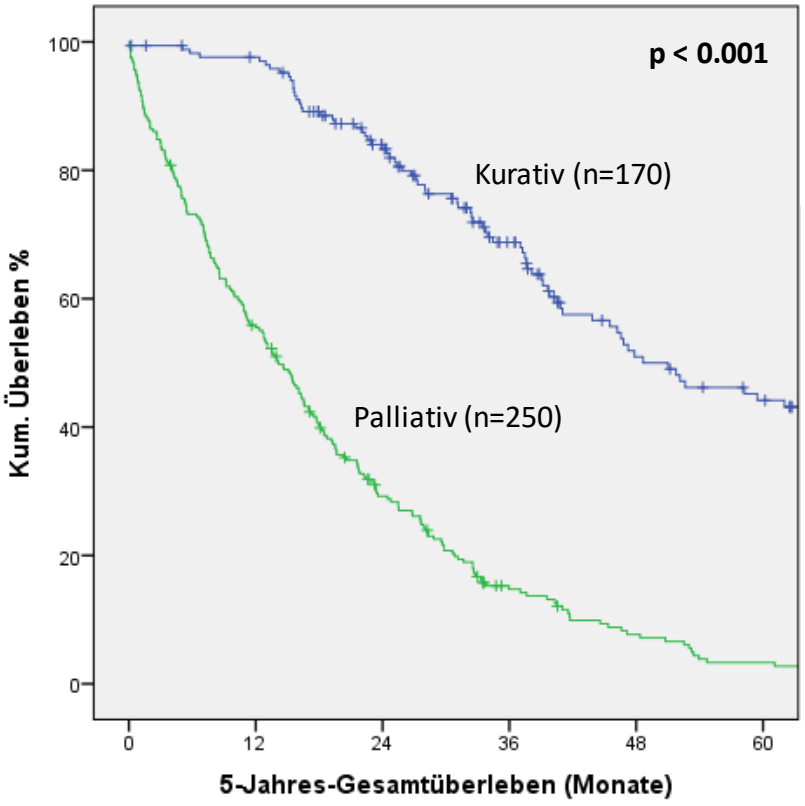

Patienten mit Vorstellung bei erstmaligen kolorektalen Metastasen (synchron und metachron)
Uniklinikum Salzburg: 2003-2014
hepatal, pulmonal, peritoneal, distante LK (abdominell / thorakal / inguinal), intraab. Organmetastasen
• Demographischen Daten
• Primumoperation
• UICC IV Erstdiagnose
• Metastasenresektion
• Chemotherapie im gesamten Verlauf
Abgleich mit Sterbedaten
Statistik Austria Mortalitätsregister
Kurativ vs. Palliativ
2003 - 2006
2007 - 2010
2011 - 2014

Overall Survival – Gesamte Kohorte 2003-2014

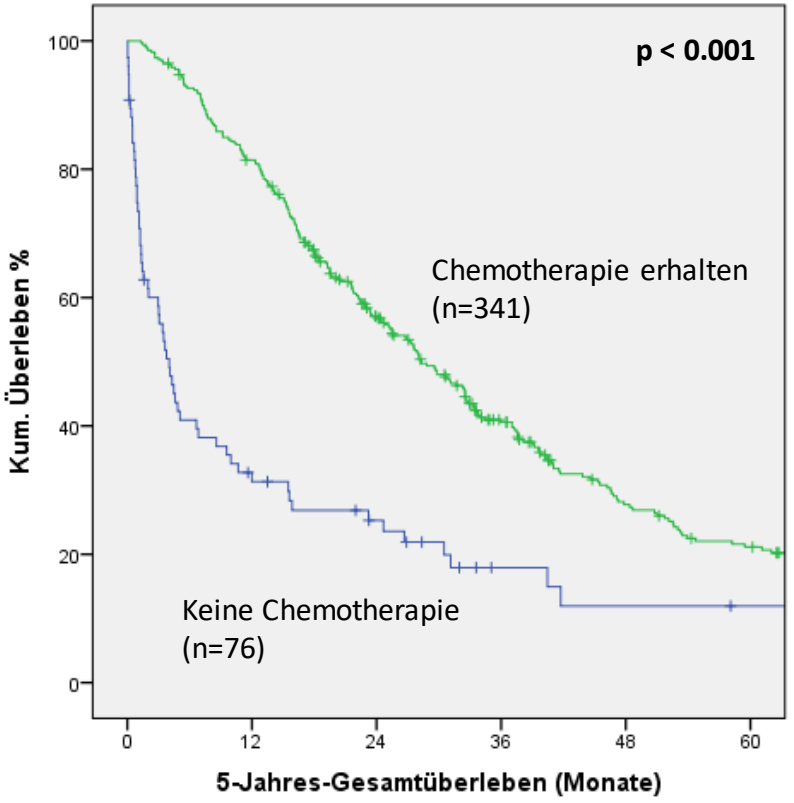


5a-Überleben– Gesamte Kohorte (n=420) 2003-2014

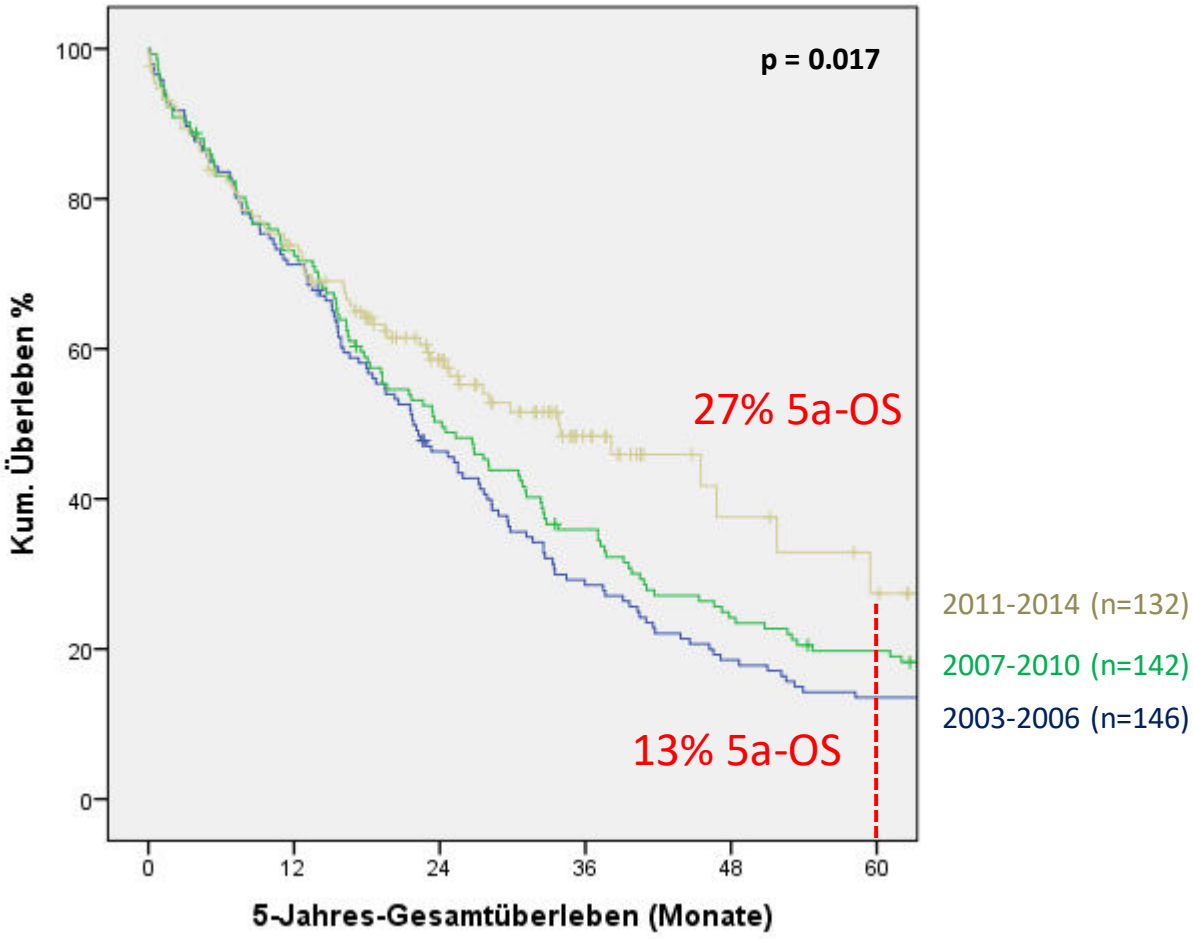
Palliativ vs. kurativ



Chemotherapie ja / nein



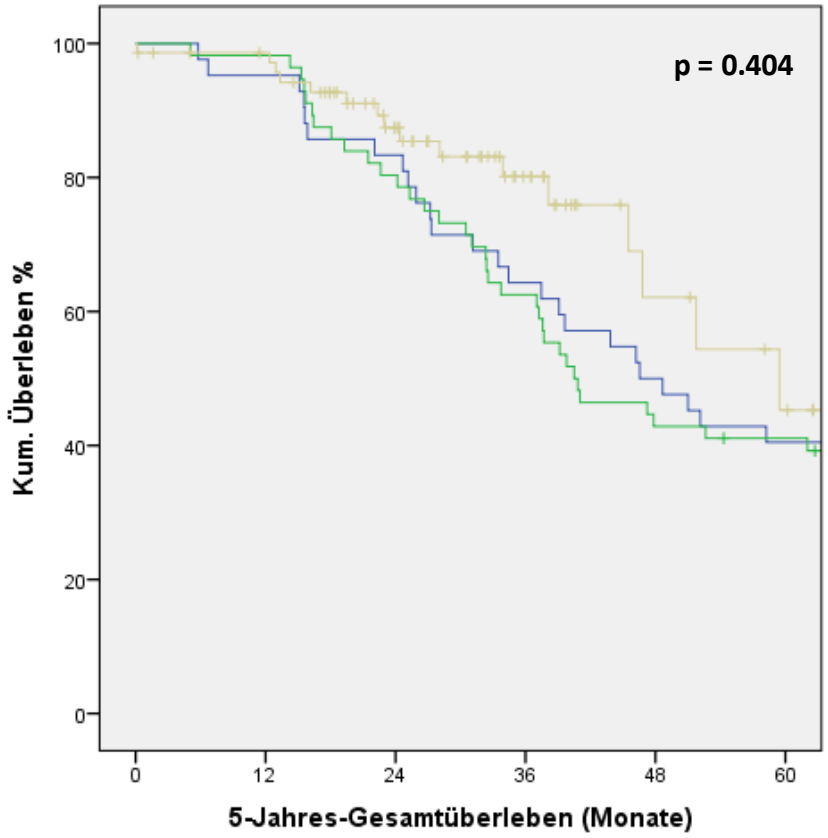
5a-Überleben– gruppiert nach Zeitraum



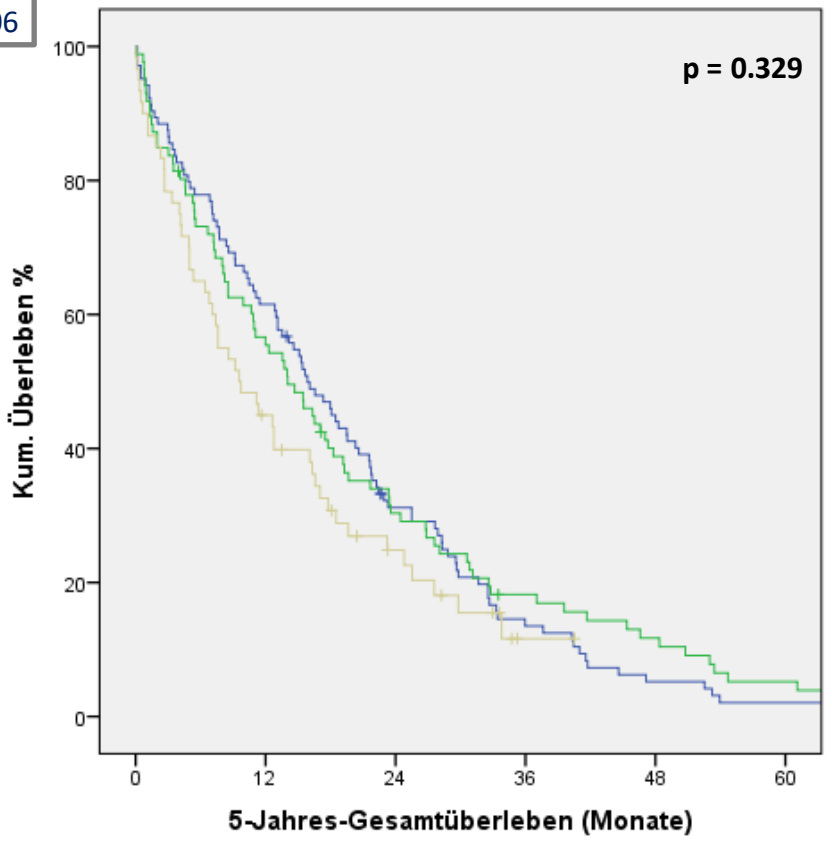
5a-Überleben– gruppiert nach Zeitraum

2011-2014
2007-2010
2003-2006

Kurativ

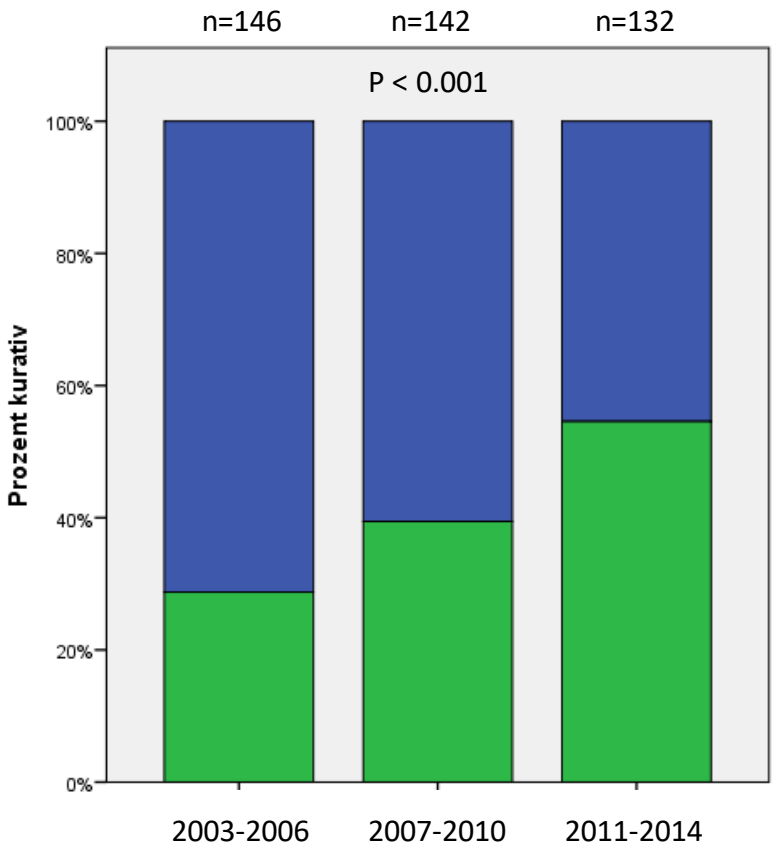


Palliativ

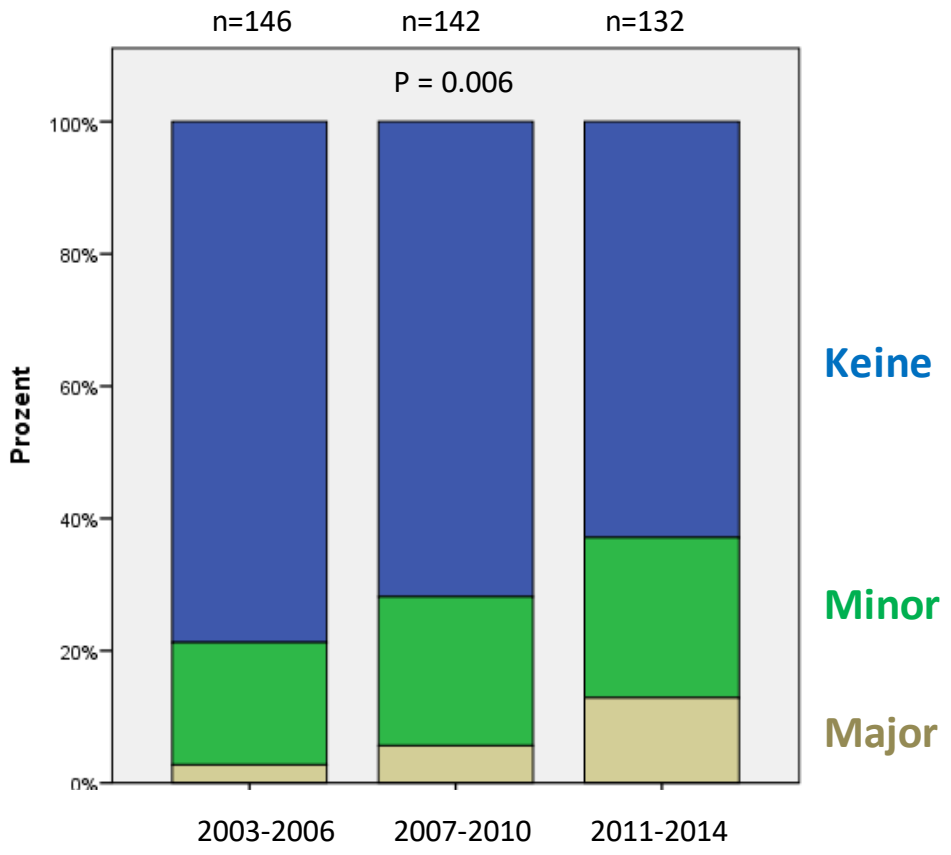


Resektionsraten über 3 Zeiträume

Kurativ | Palliativ



Zunahme Major-Leberresektionen



Demographische & Klinikopathologische Charakteristika

	Total Cohort				Curative Group				Palliative Group			
Factor	2003-2006 n=146	2007-2010 n=142	2011-2014 n=132	p-value	2003-2006 n=42	2007-2010 n=56	2011-2014 n=72	p-value	2003-2006 n=104	2007-2010 n=86	2011-2014 n=60	p-value

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Age:												
- Primary OP (Mean)	66.0	67.6	67.5	**0.418**	65.0	64.4	62.7	**0.445**	**66.4**	**69.7**	**73.4**	**0.001**
- UICC IV Diagnosis (Mean)	66.7	68.1	68.4	**0.403**	66.0	65.0	63.7	**0.507**	**67.0**	**70.2**	**74.0**	**0.001**
BMI: Mean	25.5	25.5	25.0	**0.550**	25.9	24.9	25.2	**0.487**	25.3	25.9	24.7	**0.276**
Gender: Male	100 (68.5%)	84 (59.2%)	78 (59.1%)	**0.168**	32 (76.2%)	32 (57.1%)	44 (61.1%)	**0.130**	68 (65.4%)	52 (60.5%)	34 (56.7%)	**0.524**
ASA				**0.530**				**0.378**				**0.133**
- 1	13 (9.0%)	15 (10.6%)	6 (4.5%)		3 (7.1%)	7 (12.5%)	5 (6.9%)		10 (9.7%)	8 (9.3%)	1 (1.7%)	
- 2	71 (49.0%)	65 (45.8%)	70 (53.0%)		25 (59.5%)	34 (60.7%)	47 (65.3%)		46 (44.7%)	31 (36.0%)	23 (38.3%)	
- 3	52 (35.9%)	55 (38.7%)	47 (35.6%)		14 (33.3%)	13 (23.2%)	20 (27.8%)		38 (36.9%)	42 (48.8%)	27 (45.0%)	
- 4	9 (6.2%)	6 (4.2%)	9 (6.8%)		0 (0.0%)	2 (3.6%)	0 (0.0%)		9 (8.7%)	4 (4.7%)	9 (15.0%)	
- 5	0 (0.0%)	1 (0.7%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (1.2%)	0 (0.0%)	

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Primary TU Location				**0.677**				**0.821**				**0.085**
- Colon	86 (58.9%)	89 (62.7%)	84 (63.6%)		22 (52.4%)	30 (53.6%)	37 (51.4%)		64 (61.5%)	59 (68.6%)	47 (78.3%)	
- Rectum	59 (40.4%)	51 (35.9%)	45 (34.1%)		19 (45.2%)	26 (46.4%)	33 (45.8%)		40 (38.5%)	25 (29.1%)	12 (20.0%)	
- Both	1 (0.7%)	2 (1.4%)	3 (2.3%)		1 (2.4%)	0 (0.0%)	2 (2.8%)		0 (0.0%)	2 (2.3%)	1 (1.7%)	
- Double primary TU	5 (3.4%)	3 (2.1%)	4 (3.0%)	**0.792**	1 (2.4%)	0 (0.0%)	2 (2.8%)	**0.467**	4 (3.8%)	3 (3.5%)	2 (3.3%)	**0.983**
Primary TU UICC stage				**0.603**				**0.116**				**0.885**
- I	6 (4.1%)	5 (3.5%)	6 (4.5%)		2 (4.8%)	3 (5.4%)	4 (5.6%)		4 (3.8%)	2 (2.3%)	2 (3.3%)	
- II	14 (9.6%)	13 (9.2%)	9 (6.8%)		5 (11.9%)	8 (14.3%)	4 (5.6%)		9 (8.7%)	5 (5.8%)	5 (8.3%)	
- III	42 (28.8%)	29 (20.4%)	29 (22.0%)		19 (45.2%)	12 (21.4%)	20 (27.8%)		23 (22.1%)	17 (19.8%)	9 (15.0%)	
- IV	84 (57.5%)	95 (66.9%)	88 (66.7%)		16 (38.1%)	33 (58.9%)	44 (61.1%)		68 (65.4%)	62 (72.1%)	44 (73.3%)	

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- 5	0 (0.0%)	1 (0.7%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (1.2%)	0 (0.0%)	
Primary TU Location				**0.677**				**0.821**				**0.085**
- Colon	86 (58.9%)	89 (62.7%)	84 (63.6%)		22 (52.4%)	30 (53.6%)	37 (51.4%)		64 (61.5%)	59 (68.6%)	47 (78.3%)	
- Rectum	59 (40.4%)	51 (35.9%)	45 (34.1%)		19 (45.2%)	26 (46.4%)	33 (45.8%)		40 (38.5%)	25 (29.1%)	12 (20.0%)	
- Both	1 (0.7%)	2 (1.4%)	3 (2.3%)		1 (2.4%)	0 (0.0%)	2 (2.8%)		0 (0.0%)	2 (2.3%)	1 (1.7%)	
- Double primary TU	5 (3.4%)	3 (2.1%)	4 (3.0%)	**0.792**	1 (2.4%)	0 (0.0%)	2 (2.8%)	**0.467**	4 (3.8%)	3 (3.5%)	2 (3.3%)	**0.983**
Primary TU UICC stage				**0.603**				**0.116**				**0.885**
- I	6 (4.1%)	5 (3.5%)	6 (4.5%)		2 (4.8%)	3 (5.4%)	4 (5.6%)		4 (3.8%)	2 (2.3%)	2 (3.3%)	
- II	14 (9.6%)	13 (9.2%)	9 (6.8%)		5 (11.9%)	8 (14.3%)	4 (5.6%)		9 (8.7%)	5 (5.8%)	5 (8.3%)	
- III	42 (28.8%)	29 (20.4%)	29 (22.0%)		19 (45.2%)	12 (21.4%)	20 (27.8%)		23 (22.1%)	17 (19.8%)	9 (15.0%)	
- IV	84 (57.5%)	95 (66.9%)	88 (66.7%)		16 (38.1%)	33 (58.9%)	44 (61.1%)		68 (65.4%)	62 (72.1%)	44 (73.3%)	
Timing of metastasis:												
- synchronous (12 mo)	106 (72.6%)	115 (81.0%)	99 (75.0%)	**0.230**	25 (59.5%)	43 (76.8%)	52 (72.2%)	**0.165**	81 (77.9%)	72 (83.7%)	47 (78.3%)	**0.566**
CEA at UICC IV diagnosis (mean)	277.6	218.6	267.6	**0.846**	128.4	116.3	98.0	**0.946**	335.4	276.3	461.0	**0.585**
- > 200 ng/ml	26 (19.0%)	23 (18.9%)	20 (16.4%)	**0.836**	2 (5.1%)	4 (9.1%)	4 (6.2%)	**0.747**	24 (24.5%)	19 (24.4%)	16 (28.1%)	**0.860**
Initial metastatic site												
- Hepatic	108 (74.0%)	102 (71.8%)	97 (73.5%)	**0.241**	31 (73.8%)	39 (69.6%)	47 (68.8%)	**0.596**	77 (74.0%)	63 (73.3%)	50 (83.3%)	**0.126**
- Pulmonary	35 (24.0%)	47 (33.1%)	50 (37.9%)	**0.163**	9 (21.4%)	20 (35.7%)	23 (31.9%)	**0.644**	26 (25.0%)	27 (31.4%)	27 (45.0%)	**0.101**
- Peritoneal	29 (19.9%)	28 (19.7%)	27 (20.5%)	**0.476**	**0 (0.0%)**	**2 (3.6%)**	**10 (13.9%)**	**0.002**	29 (27.9%)	26 (30.2%)	17 (28.3%)	**0.603**
- Distant lymph nodes	19 (13.0%)	12 (8.5%)	6 (4.5%)	**0.120**	4 (9.5%)	2 (3.6%)	3 (4.2%)	**0.707**	15 (14.4%)	10 (11.6%)	3 (5.0%)	**0.325**
- Other (abd. Org., Bone, Brain)	14 (9.6%)	12 (8.5%)	13 (9.8%)	**0.230**	1 (2.4%)	2 (3.6%)	5 (6.9%)	**0.094**	12 (12.5%)	10 (11.6%)	8 (13.3%)	**0.783**

Kurative Resektionen (n=170)

	2003-2006	2007-2010	2011-2014	p-value
Curative patients (% of total)	42 (28.8%)	56 (39.4%)	72 (54.5%)	<0.001

Kurative Resektionen (n=170)

	2003-2006	2007-2010	2011-2014	p-value
Curative patients (% of total)	42 (28.8%)	56 (39.4%)	72 (54.5%)	**<0.001**
Liver resections (% of total)	**31 (21.2%)**	**40 (28.1%)**	**46 (34.8%)**	**0.008**
- Liver first concept	0 (0.0%)	5 (12.5%)	6 (13.0%)	0.122
- Major resections	**4 (12.9%)**	**8 (20.0%)**	**17 (37.0%)**	**0.039**
- Laparoscopic resection	0 (0.0%)	3 (7.5%)	6 (13.0%)	0.109
- Bilobar metastasis	**6 (19.4%)**	**10 (25.0%)**	**24 (52.2%)**	**0.004**
- Number of metastasis : mean (range)	**2.2 (1-8)**	**2.45 (1-9)**	**5.5 (1-40)**	**0.005**
- Diameter of largest lesion (cm): mean (range)	2.9 (0.9-5.7)	2.6 (0.4-7.0)	3.0 (0.4.16.0)	0.807
- Fong score: mean (range)	1.8 (0-4)	1.8 (0-4)	1.8 (0-3)	0.969
- Length of stay (days): mean (range)	11.2 (3-34)	14.7 (2-126)	12.4 (4-50)	0.514
- Complications	**9 (29%)**	**9 (22.5%)**	**19 (43.5%)**	**0.024**
- Mild (Clavien-Dindo 1-3a)	4 (12.9%)	4 (10.0%)	17 (37.0%)	
- Severe (Clavien-Dindo 3b-4b)	5 (16.1%)	5 (12.5%)	2 (4.3%)	
- Mortality (In-hospital)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0.459

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Lung resections (% of total)	**9 (6.2%)**	**20 (14.3%)**	**23 (17.9%)**	**0.051**
- Thoracoscopic resection (VATS)	4 (44.4%)	4 (20.0%)	10 (43.5%)	0.215
- Bilateral metastasis	0 (0.0%)	3 (15.0%)	5 (21.7%)	0.308
- Number of metastasis : mean (range)	1.2 (1-2)	2.5 (1-12)	2.3 (1-8)	0.359
- Diameter of largest lesion (cm): mean (range)	1.9 (0.5-3.1)	1.8 (0.4-5.0)	1.4 (0.3-6.0)	0.496
- Length of stay (days): mean (range)	7.4 (2-18)	6.1 (1-15)	6.0 (2-20)	0.719
- Complications	2 (22.2%)	3 (15.0%)	6 (26.1%)	0.216
- Mild (Clavien-Dindo 1-3a)	1 (11.1%)	1 (5.0%)	6 (26.1%)	
- Severe (Clavien-Dindo 3b-4b)	1 (11.1%)	2 (10.0%)	0 (0.0%)	
- Mortality (In-hospital)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-

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- Mild (Clavien-Dindo 1-3a)	4 (12.9%)	4 (10.0%)	17 (37.0%)	
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- Severe (Clavien-Dindo 3b-4b)	1 (11.1%)	2 (10.0%)	0 (0.0%)	
- Mortality (In-hospital)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Peritonectomy (% of total)	**0 (0.0%)**	**2 (1.4%)**	**10 (7.6%)**	**0.001**
- Including HIPEC	0 (0.0%)	0 (0.0%)	5 (50%)	-

Kurative Patienten: Chemotherapie

	2003-2006	2007-2010	2011-2014	p-value
Chemotherapy received since UICC IV ED	37 (90.2%)	52 (92.9%)	62 (86.1%)	0.460
- Number of ctx cycles (months) received: mean (range)	11.5 (0-31)	9.3 (0-23)	8.8 (0-33)	0.147
- Pseudoneoadjuvant before metastasectomy	16 (38.1%)	21 (37.5%)	27 (38.0%)	0.998
- Adjuvant / palliative after metastasectomy	33 (78.6%)	44 (78.6%)	59 (81.9%)	0.694

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- Adjuvant / palliative after metastasectomy	33 (78.6%)	44 (78.6%)	59 (81.9%)	0.694
Type of ctx scheme				
- 5-FU-Mono based	11 (28.9%)	12 (21.8%)	21 (29.2%)	0.609
- Oxaliplatin / Irinotecan based dual				0.733
- One agent	13 (34.2%)	23 (41.1%)	34 (47.2%)	
- Both agents (sequentially)	18 (47.4%)	22 (39.3%)	27 (37.5%)	
- Oxaliplatin / Irinotecan based triple (FOLFOXIRI)	0 (0.0%)	2 (3.6%)	3 (4.2%)	0.456
- Antibody based (Bevacizumab, Panitumumab, Cetuximab, Tivozanib, Matuzumab)	21 (55.3%)	38 (67.9%)	46 (63.9%)	0.457
- Other agents (3rd/4th/5th line; Aflibercept, Regorafenib, Mitomycin C, TAS-102/Lonsurf, Phase I study agents)	**0 (0.0%)**	**2 (3.6%)**	**11 (15.3%)**	**0.007**

Conclusio zur Fragestellung

Wie ist die Prognose von Patienten mit erstmalig diagnostizierten Metastasen bei kolorektalem Karzinom am Uniklinikum Salzburg?

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- Entwicklung des Gesamtüberlebens innerhalb der letzten Jahre?
  - **-> Verdoppelung des 5a-OS (13%->27%)** zwischen 2003-2006 und 2011-2014.

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Wie ist die Prognose von Patienten mit erstmalig diagnostizierten Metastasen bei kolorektalem Karzinom am Uniklinikum Salzburg?

- Entwicklung des Gesamtüberlebens innerhalb der letzten Jahre?
  - **-> Verdoppelung des 5a-OS (13%->27%)** zwischen 2003-2006 und 2011-2014.

- Ursache?
  - **Anstieg der Resektionsraten** in erster Linie leberchirurgisch, aber auch durch CRS+HIPEC und weitere Zunahme der Lungenchirurgie **(TEAM APPROACH!)**
  - Nur möglich durch konsequente Vorstellung im **TU-Board** mit spezialisierten Chirurgen
  - Keine signifikante Veränderung der CTX-Raten im Zeitraum der Untersuchung

Vielen Dank für die Aufmerksamkeit!