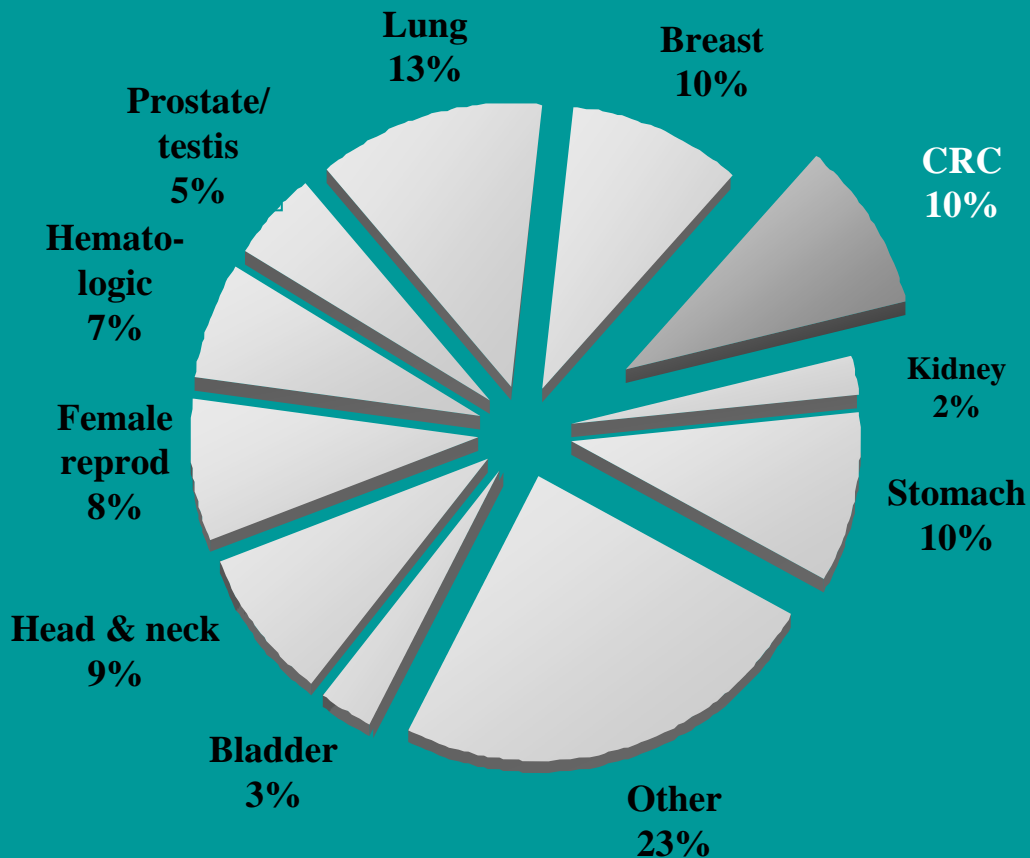


# Chemotherapy in the management of colorectal cancer liver metastases

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# The challenge of colorectal cancer



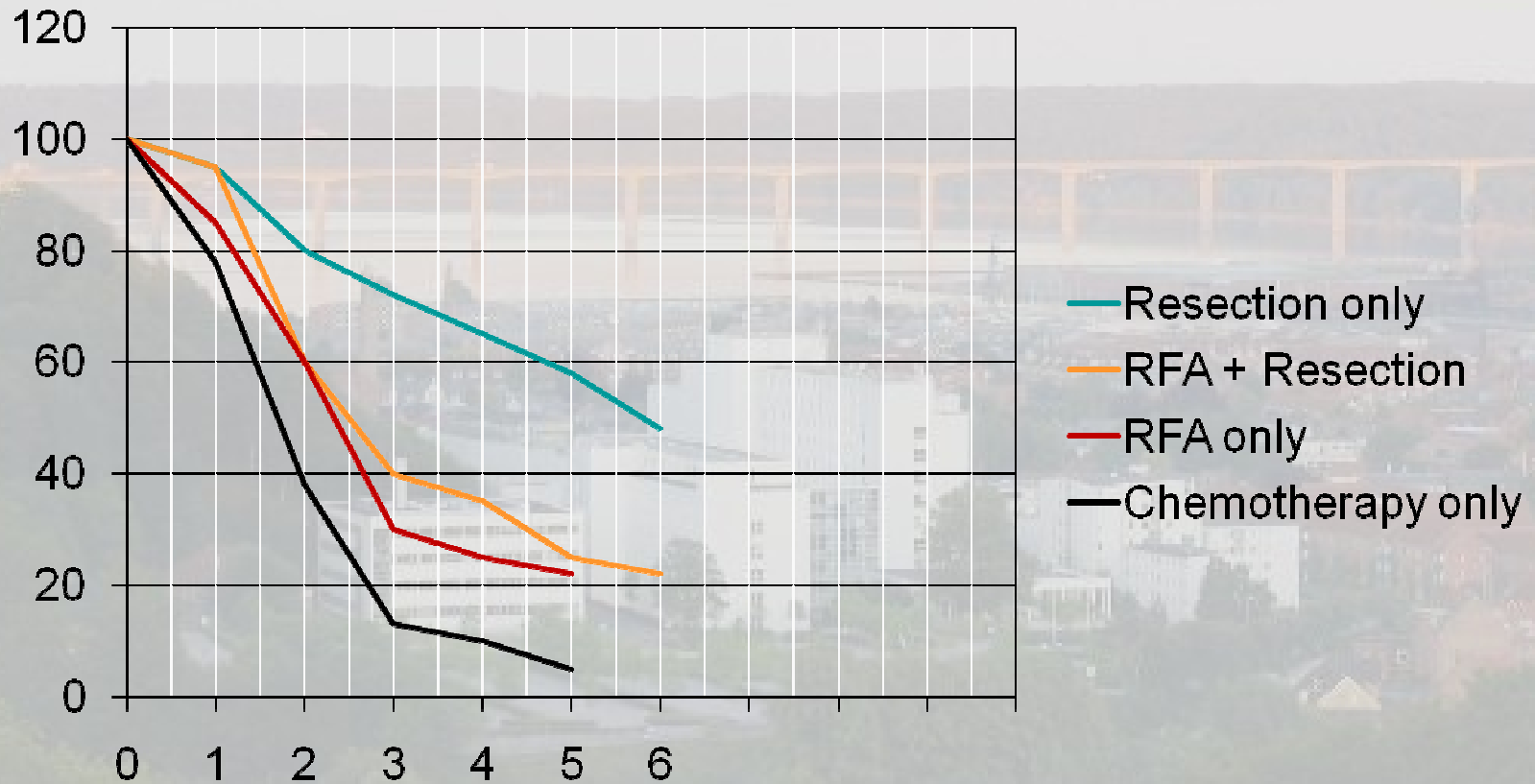
- More than 783,000 worldwide develop CRC each year.
- Mortality in Western Europe from CRC is ~100,000/year.
- About 25% present with metastatic disease.
- 50% of newly diagnosed patients eventually develop metastatic disease, which in 40-50% of cases are confined to the liver.
- 5-year survival rate of patients with liver metastatic disease is 4-40%.

# Treatment modalities and survival

	<u>5 year OS</u>
1. Liversurgery (15 – 25%)	30 - 45%
	20 - 25%
2. <u>R</u> adio- <u>F</u> requency <u>A</u> blation	25 - 30%?
3. Stereotactic Radiation	20 – 25%?
4. Chemotherapy	4 – 9 %

10 Year OS

# Combined Resection and RFA



# Hepatic resection for metastatic colorectal cancer

Study	N	Operative mortality	1-yr Survival %	3-yr Survival %	5-yr Survival %	10-yr Survival %	Median Months
Hughes et al	607	-	-	-	33	-	-
Gayowsk	<i><u>Surgical resection is the only chance for cure!</u></i>						33
Scheele et al	434	4	85	45	33	20	40
Nordlinger et al	1568	2	80	-	28	-	40
Jamison et al	280	4	84	-	27	20	33
Fong et al	1001	2.8	89	57	36	22	42
Minagawa et al	235	0.85	-	51	28	26	-
Choti et al	226	1	93	57	40	26	46
Kato et al	585	0	-	-	33	-	-
Adam et al	335	1	91	66	48	30	52

# Chemotherapy



# *Difficulties in interpretation of the results of the performed trials.*

- Difference in criterias for resectability between the individual Centers and Countries.
- Which diagnostic examinations has been performed
  - CT
  - US
  - MRI
  - PET-CT
  - LAP-LUS
- Improvement in Surgical techniques and strategies
  - Portal vein embolisation
  - RFA
  - Laparoscopic resection
  - Extended resections
  - 2-stage hepatectomy
  - Extrahepatic tumor eradication
- More effective chemotherapy

# Chemotherapy options

- Preoperative Chemotherapy
  - Neoadjuvant in resectable disease?
  - Downstaging of borderline and unresectable disease
- Adjuvant (after operation)
- Perioperative (before and after operation)

*The optimal use of chemotherapy and biologic agents in the management of CRC liver metastases is not known!*



The management of CRC livermetastases  
is determined by a

## Multi-Disciplinary Team

- Surgeons
- Radiologists
- Oncologists
- Pathologists

# Adjuvant chemotherapy in Stage II and III CRC

		Survival benefit Abs. %
• <u>Colon cancer</u>		
• 1987 – 2003	5-FU monotherapy	5 – 7%
• 2003 -	Oxaliplatin + 5-FU	12 – 14%
• <u>Rectal cancer</u>		
	5-FU monotherapy	3 – 5%
	Oxaliplatin + 5-FU	6 – 10 %

## Randomized adjuvant studies comparing chemotherapy with surgery alone for resectable LM

Study	N	Treatment	4-yr DFS %	P	4-yr OS %	P
Langer et al 2002	107	5-FU/Lv + Surg. Surgery	45 35	.35	57 47	.39
Portier et al 2006	171	5-FU/Lv + Surg. Surgery	42 32	.028	60 52	.13
Ychou et al 2009	306	Iri + 5-FU/Lv + Surg. 5-FU/Lv + Surg.	37.5 37.5	NS	62.5 65	NS
EORTC Trial 40983	364	FOLFOX + S + FOLFOX Surgery	42.4 33.2	.025		

# Retrospective studies of adjuvant chemotherapy

Study	N	Chemotherapy	HR	P value
Parks et al 2007	792	5-FU/Lv (34%)	0.75	< .01
Figueras et al 2007	501	5-FU/Lv based	0.3	< .001
Wang et al 2007	923	5-FU/Lv based (56%)	0.62 (0.50-0.78)	< .01
De Jong et al 2009	1669	5-FU (43%)	0.56 (0.33-0.65)	< .009

***Adjuvant chemotherapy after resection of livermet from CRC is recommended!***

An aerial, slightly hazy photograph of a city. In the background, a large, multi-span bridge with orange-brown supports spans across a valley. The middle ground shows a dense urban area with various buildings, including a prominent white, multi-story building that appears to be a hospital or medical center. The foreground is dominated by lush green trees and foliage. The overall lighting is soft, suggesting an overcast day or early morning/late afternoon.

**Downstaging of  
unresectable or borderline  
liver metastases in CRC**

# **Development of systemic treatments for metastatic colorectal cancer (mCRC)**

- **1957: 5-FU introduced and subsequently dominates the systemic treatment of CRC**
- **1970s – 1980s: various combinations based on 5-FU investigated**
- **End of 1980s: 5-FU/FA accepted as standard 1<sup>st</sup> line treatment for mCRC**
- **1990s: the efficacy of 2<sup>nd</sup> line treatment established**
- **1999: irinotecan + 5-FU/FA approved 1<sup>st</sup> line in EU**
- **1999: oxaliplatin + inf 5-FU/FA approved 1<sup>st</sup> line in EU**
- **2003: Cetuximab + Irinotecan approved as 3<sup>rd</sup> line in EU and USA**
- **2004: Bevacizumab + 5-FU based regimen approved as 1<sup>st</sup> line in USA (EU in 2005)**

# Metastatic CRC - Survival

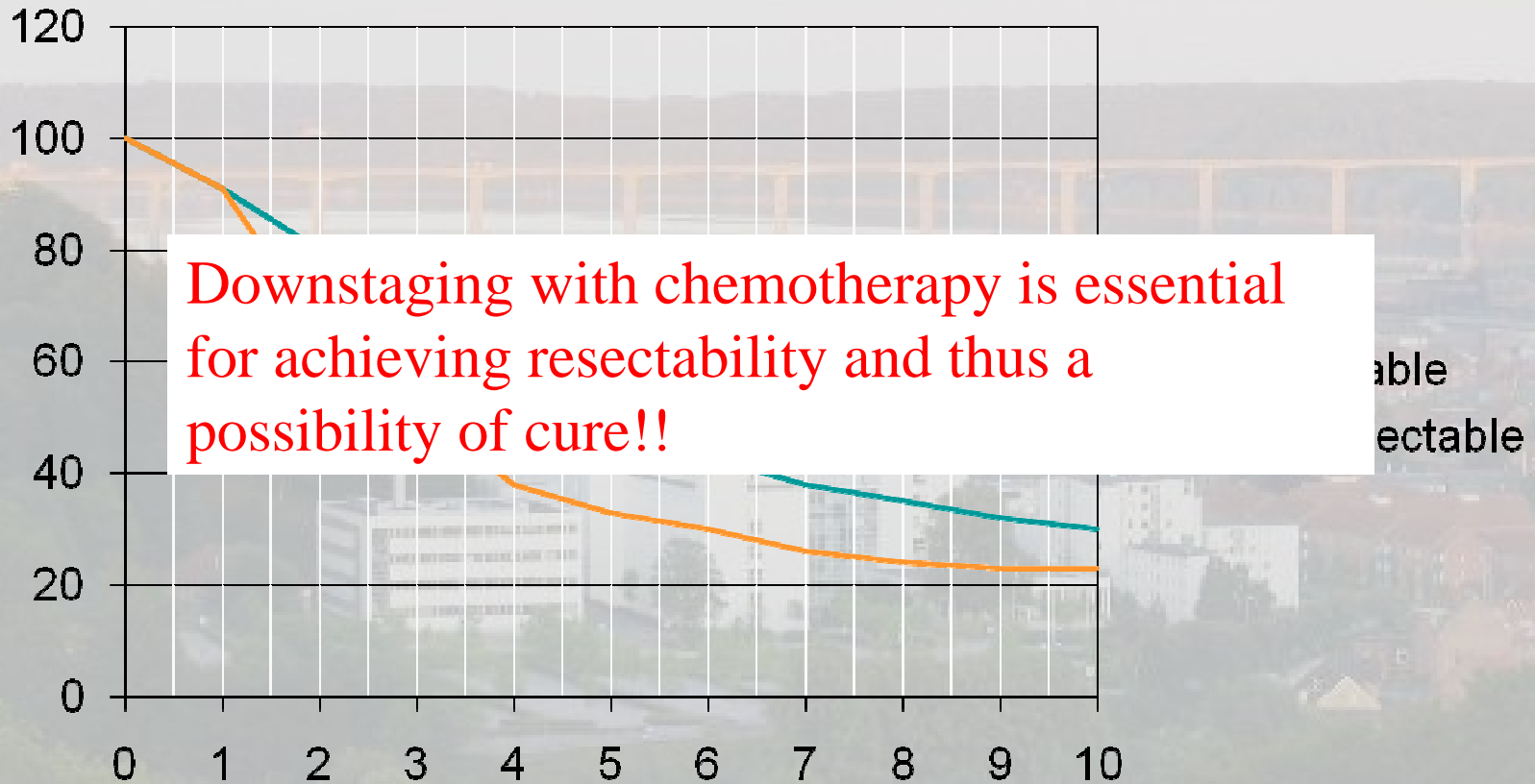
Regimen	RR	Median survival
BSC		6 months
5-FU	25%	12 months
5-FU + Irinotecan	45 – 50%	15 - 18 months
5-FU + Oxaliplatin	50%	16 - 19 months
→ Irinotecan (Iri) +/- 5-FU	30 – 35%	20 - 21 months
→ Iri + Cetuximab (KRAS wt)	40%	23 - 24 months
+ Bevacizumab 1. line	50 – 60%	25 months
5-FU + Iri + Ox	60 – 65%	18 – 20 months

# Downstaging with chemotherapy

Study	N	Chemotherapy	Converted to resection	5-yr Survival
Bismuth et al	330	Oxa + 5-FU	53 (16%)	40%
Adam et al	701	Oxa + 5-FU	95 (13.5%)	35%
Adam et al	1104	Oxa + 5-FU (70%) Iri + 5-FU (7%) Oxa + Iri + 5-FU (4%)	138 (12.5%)	33%
Alberts et al	42	Oxa + 5-FU	17 (40%)	<26 months>
Barone et al	40	Iri + 5-FU	19 (47%)	62%
Clavien et al	23	FUDR (HAI)	6 (26%)	<30 months>
Kemeny et al	49	Oxa + Iri + 5-FUDR(HAI)	23 (47%)	<39 months>



# Downstaging with chemotherapy and Survival



Boring??



# At diagnosis



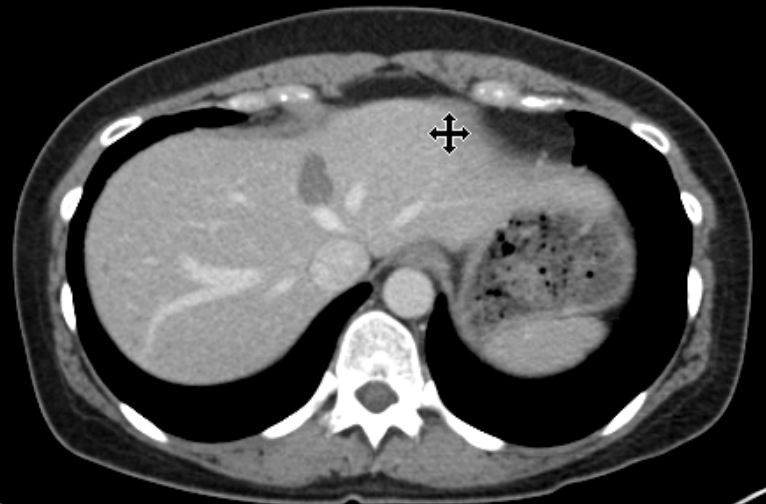
Body



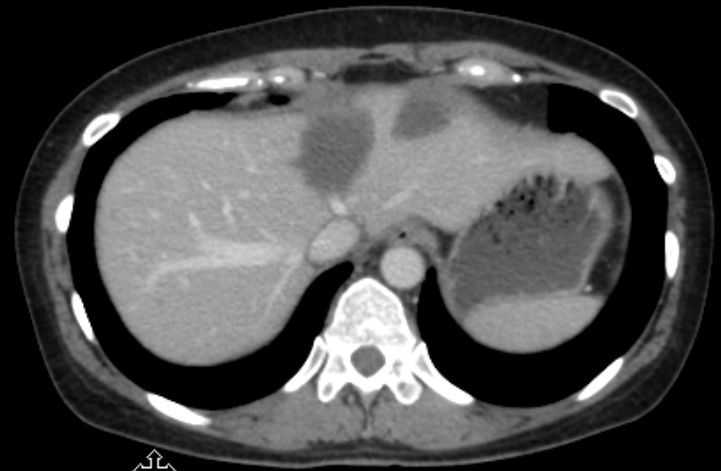
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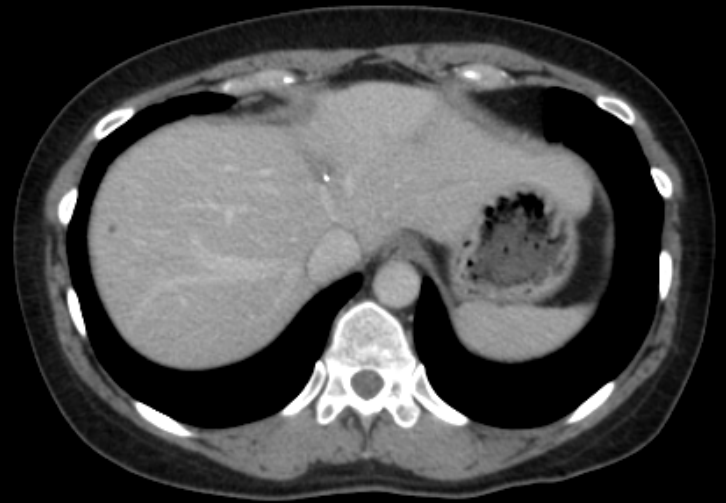
# Just before resection



1 month after resection



1 year after resection



# Conclusions 1

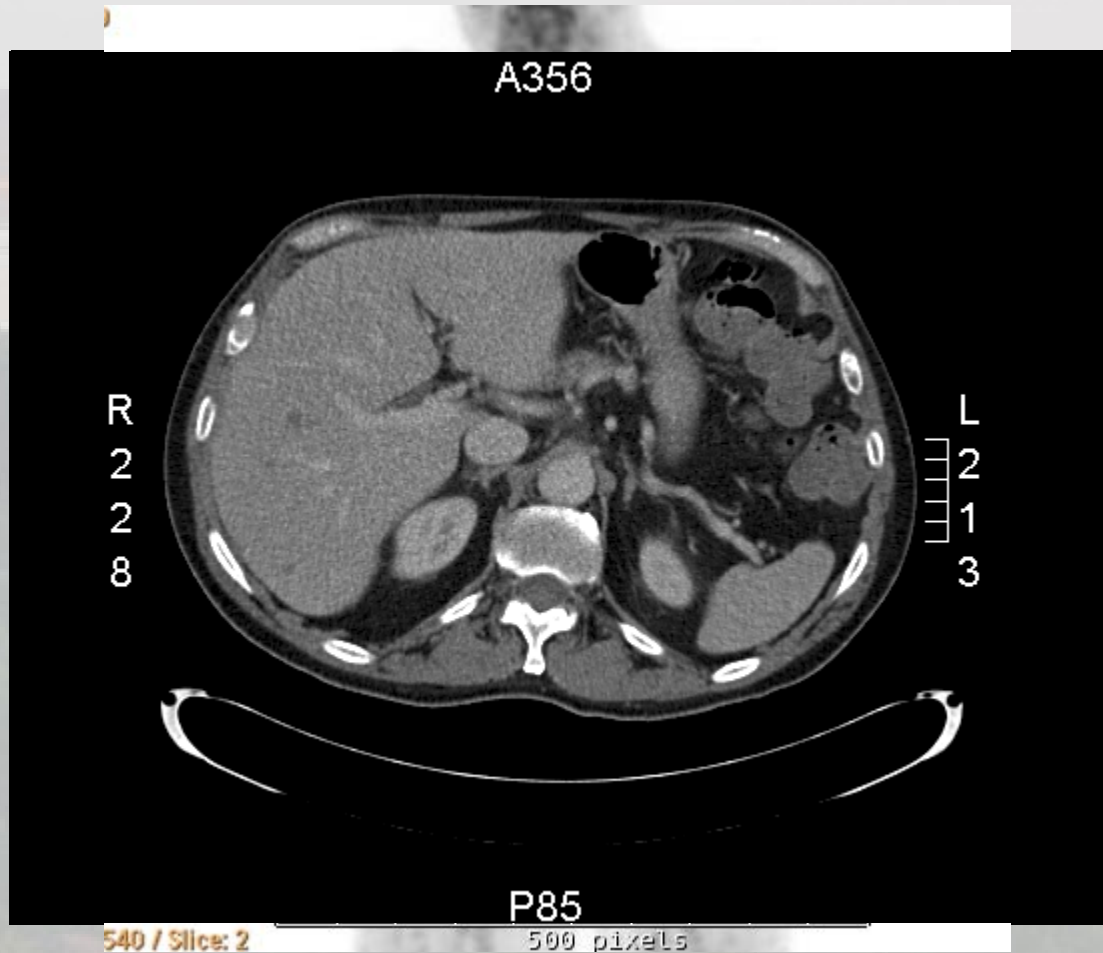
- Resectable liver metastases
  - There is an urgent need for randomized trials comparing peri-operative vs. Adjuvant chemotherapy
- Unresectable or borderline metastases
  - Randomized trials
    - Comparing the downstaging ability of modern chemotherapy and biological modifiers (EGF og VEGF inhibitors) to obtain resectability
    - +/- HAI.
    - Postoperative optimal adjuvant treatment scedule (selection of agents and proper length of treatment).




# Conclusions 2 - Recommendation

- Resectable liver metastases
  - Synchronous and metachronous: should be resected directly and postoperative adjuvant chemotherapy with Oxaliplatin and 5-FU should be given.
- Unresectable or borderline metastases should be downstaged with combination chemotherapy with:
  - 5-FU + Oxaliplatin or Irinotecan + Bevacizumab or Cetuximab/Panitumumab (only KRAS *wt*) to obtain high response rates. As soon as resectability is obtained the pt. should be operated to minimize postoperative complications due to accumulating liver toxicity (steatosis and steatohepatitis from Irinotecan and 5-FU or Sinusoidal obstruction syndrome from Oxaliplatin).
  - Liver resection should be followed by further adjuvant treatment with 5-FU +/- Oxaliplatin.

# Downstaging



An aerial, slightly hazy photograph of a city. In the background, a large, long stadium with a prominent orange roof structure is visible. The foreground shows a dense residential area with green trees and various buildings. The overall tone is soft and somewhat muted.

It is essential that we improve in our ability to identify the group of patients that indeed are resectable!!!

Fortunately we have you!



Thank you for your attention!





# Clinical risk score (CRS) Prognostic score

- Node positive primary tumor
  - Disease-free interval < 12 months
  - Size of largest lesion > 5 cm
  - > 1 lesion
  - CEA > 200 ng/dl
- 
- Ptt. with 2 or more of these prognostic factors should receive preoperative chemotherapy.

*Nordlinger et al, Cancer 1996; Vol 77: 985-992*

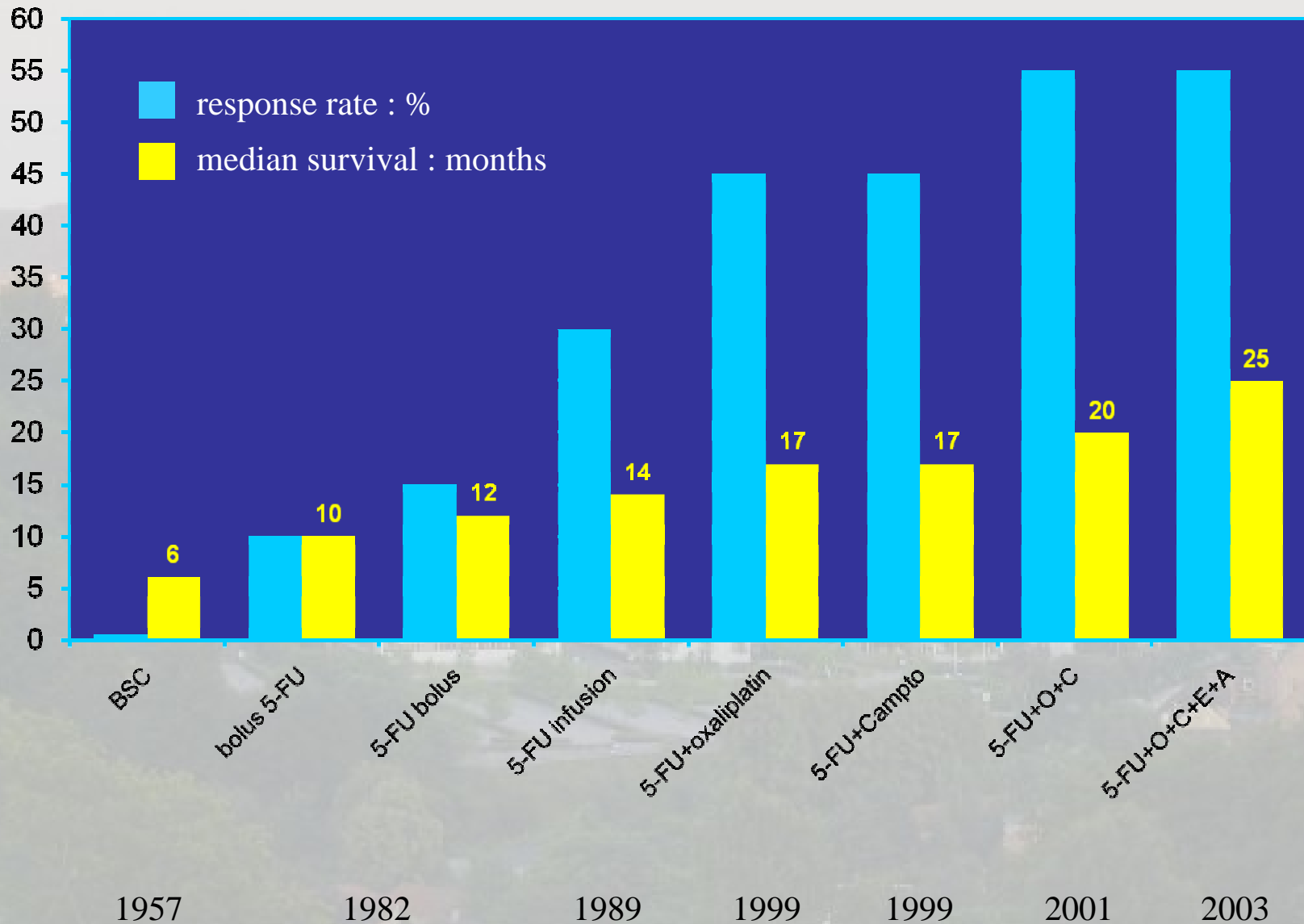
Conventional indications	Modern aggressive approach
< 4 metastases in one lobe	No limits. Multiple/bilobar metastases acceptable, using neoadjuvant chemotherapy, staged resection and resection + ablative therapy.
Size < 5 cm	No limits
No extrahepatic disease	Pulmonary metastases can be resected or ablated
Resection margin < 1 cm	Resection margin < 1 cm managed with ablative treatment of narrow margin
Adequate remnant liver parenchyma	Perioperative PVE to increase remnant liver volume
Absence of vena cava and hepatic vein confluence invasion	No limits. Resection with reconstruction can be performed
Absence of hepatic pedicle lymph node metastases	In absence of celiac axis metastases, hepatic pedicle lymph node metastases may be resected for improved 3-year survival.



# Randomized adjuvant studies of adjuvant HAI +/- systemic chemotherapy vs Surgery +/- systemic Chemotherapy

Study	N	Treatment	4-yr DFS %	P	4-yr OS %	P
ECOG 2002	75	S + FUDR + Syst. 5-FU Surgery	46 25	.04	61.5 52.7	.6
Lorenz et al 2006	226	Surg. + 5-FU/Lv Surgery	14.2 13.7	NS	34.9 40.8	NS
MSKCC	156	S + FUDR + Syst. 5-FU Surgery + Syst. 5-FU	48 33	.045	41 27	.10
Lygidakis et al 2009	122	S + Immun/Mito/FU + Syst. Mito/FU S + Syst. Immuno/Mito/FU	58 33	.002	78 64	.05

# Chemotherapy in metastatic CRC



”The optimal use of systemic chemotherapy combined with surgical techniques for the management of Colorectal cancer liver metastases has yet to be determined.”

*Surgical resection is the only chance for  
cure!*