

Biliary tract neoplasm Medical treatment

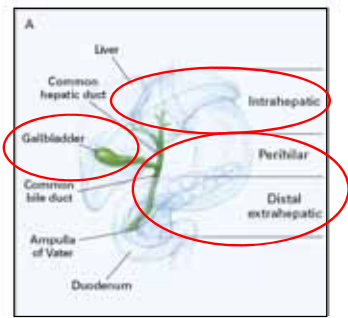


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Institut Gustave Roussy, Villejuif, FRANCE

Biliary tract cancer

- Rare tumor
- Different entities
- Diagnosis sometimes problematic
- Elderly patients with comorbidities
- Cholestasis
- Therapeutic options limited
(mostly phase II trials
potentially curative surgery possible in < 20%)

Different Entities



Incidence (US) / 10⁵

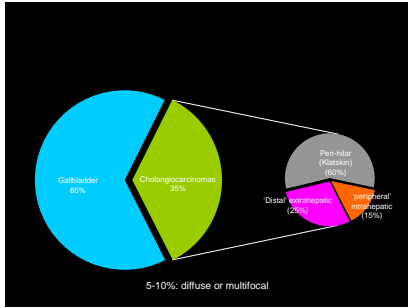
	Incidence/10 ⁵	Relative
Gallbladder (f > m)	1.2	
Biliary tree		
intrahepatic (m ≥ f)	0.9	} 20%
extrahepatic (m ≥ f)	1.6	
perihilar		} 60%
distal		
} 25%		
Pancreas	11	
Esophagus	5	
Colon	54	

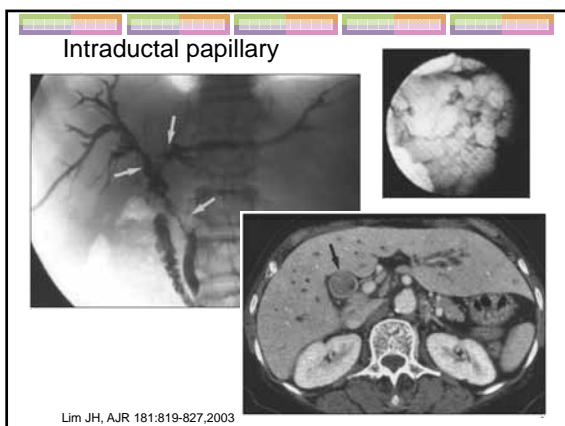
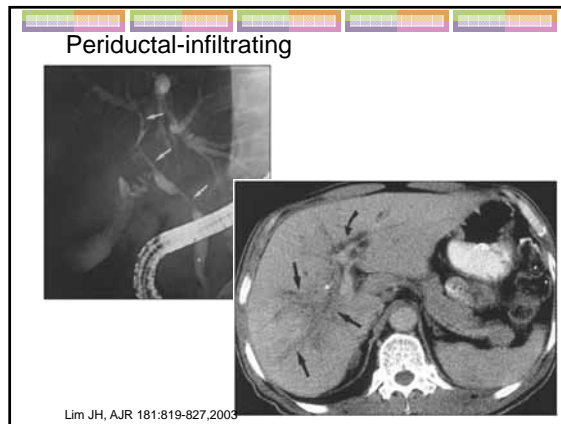
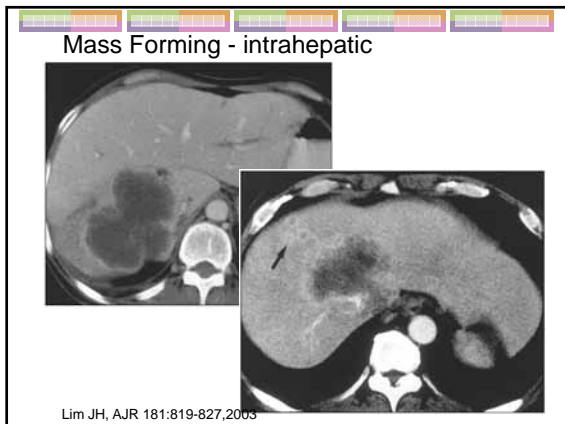
Epidemiology and carcinogenesis

- Rising incidence of cholangiocarcinoma over the past 30 years documented on 3 continents
- Unknown cause
 - Hypothesis : rise in one or several genotoxic environmental agents, causing cholangiocyte DNA damage
 - Khan et al.
 - levels of DNA adducts significantly higher in DNA from 32 patients with intrahepatic cholangiocarcinoma compared with non-cancer patient DNA (n=7), 2.9 ; p = 0.03
 - Hedgehog signalling pathway : role in mature tissue homeostasis

Subtypes

France: Malka 2007





Prognosis

- **Ahmed et al, ASCO GI 2008 #135**
 - OS longer in EHCC (6.0 vs. 3.7 months)
 - OS with surgery similar (13.5 vs. 13.6 months)
 - Surgery more likely in EHCC (26%) vs IHCC (9%)
- **Beg et al. ASCO 2008 #15518**
 - SEER database 1973-2004
 - OS for EHCC: 6 months vs. IHCC: 5 months
- **Survival of intraductal tumors much longer**
 - > 2 years

Different patterns of recurrence

Jarnagin, 2003

177 patients potentially curative resection : 97 gallbladder ; 80 hilar cholangiocarcinoma

- Different median time to disease recurrence:
 - Gallbladder : 11.5 versus 20.3 months
- Different type of recurrence :

	Local	Metastatic
Gallbladder	15%	85%
Cholangiocarcinoma	59%	41%

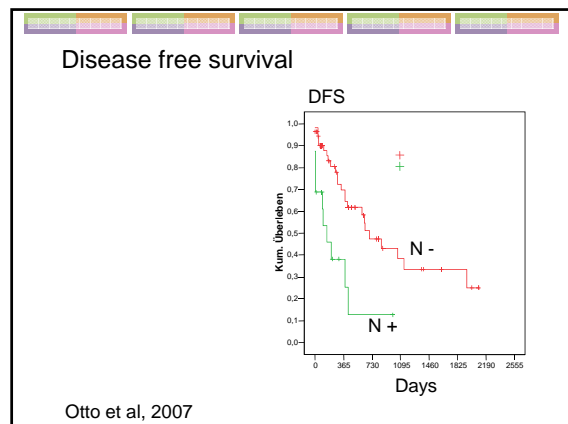
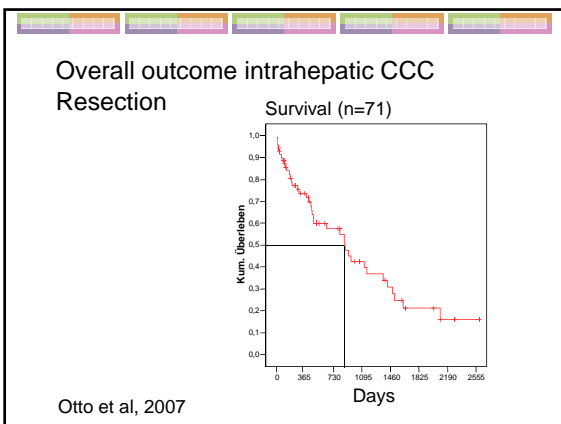
Carcinologic treatments

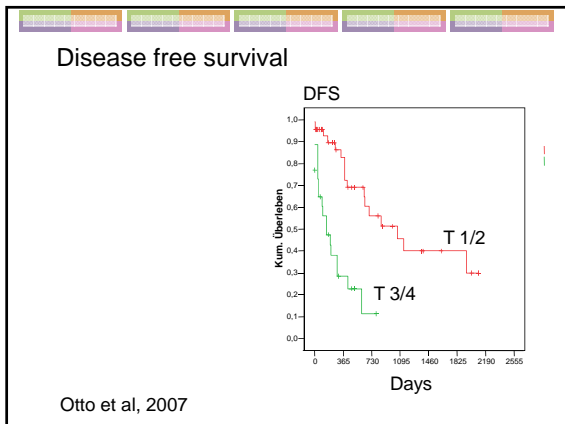
Gallbladder carcinoma

- ### Gallbladder carcinoma
- Surgery with resection of segment IV of the liver
 - Natural venous access from the gallbladder to the liver
 - In case of incidental diagnosis of gallbladder a complementary resection of the liver + lymph node dissection is recommended

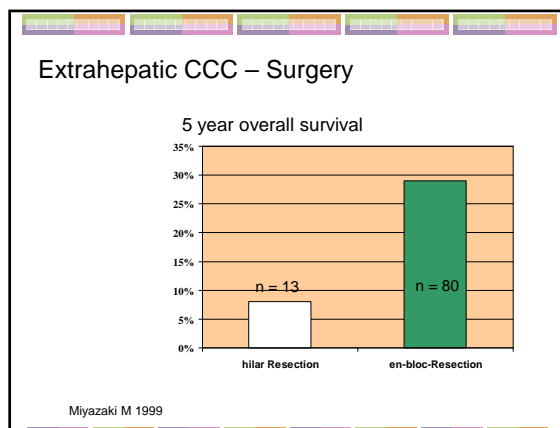
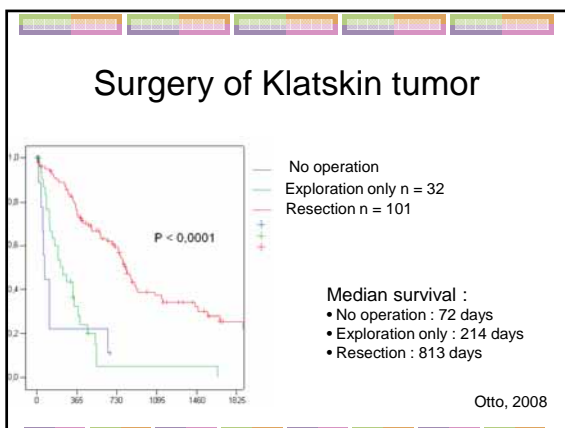
- ### Adjuvant chemotherapy ???
- Takada, 2002
 - 508 patients : 139 bile duct, 140 gallbladder, 56 ampullomas
 - 5FU + MMC followed by oral 5FU versus control
 - 112 gallbladder eligible : 5-year survival 26% versus 14% (p = 0.0367)
 - Subgroup analysis... A lot of non eligible patients...

Intrahepatic bile duct cancer





Central bile duct cancer (Klatskin Tumor)



- **Resection Treatment of choice for 'normal'**
 - **Klatskin tumors:**
 - En Bloc resection
 - + portal vein resection
 - + lymph node dissection
 - **Extrahepatic tumors:**
 - + Pancreaticoduodenectomy
- **Resection yields dismal results in PSC**
 - often multifocal CCC
 - 10 % of pts with CCC have PSC

Liver Transplantation

Liver transplantation – Two periods

Institution	Year	n	Patient survival (%)		
			1-yr	3-yr	5-yr
European Transplant Registry ⁽¹⁾	1987	38	40	16 (2-yr)	0
Kings College, London, UK ⁽²⁾	1988	13	30	10	10
Hochschule Hannover, Germany ⁽³⁾	1996	25	60	21.4	17.1
University of Pittsburgh, USA ⁽⁴⁾	1998	27 (LT)	59.3	36.2	36.2
		11 (Cluster)	54.6	9.1	9.1
Humboldt University, Berlin, Germany ⁽⁵⁾	1999	15 (LTTP)	-	-	38

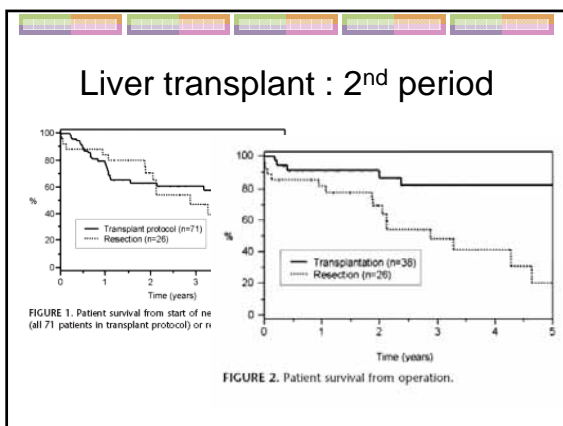
LT: liver transplantation; Cluster: abdominal cluster transplantation; LTTP: LT with partial pancreatectomy.

Institution	Year	n	Patient survival (%)		
			1-yr	3-yr	5-yr
Mayo Clinic, Rochester, USA ⁽⁶⁾	2000	11	100	-	-
University of California, LA, USA ⁽⁷⁾	2001	9	86	31	-
University of Nebraska Medical Center, Omaha, USA ⁽⁸⁾	2002	11	-	-	45
Spanish experience (multicenter) ⁽⁹⁾	2004	36	82	57	30
Mayo Clinic, Rochester, USA ⁽⁶⁾	2005	38	92	82	82

Pandey et al. Hepatobil Pancreat Dis Int, 2007

Liver transplantation and adjuvant treatment

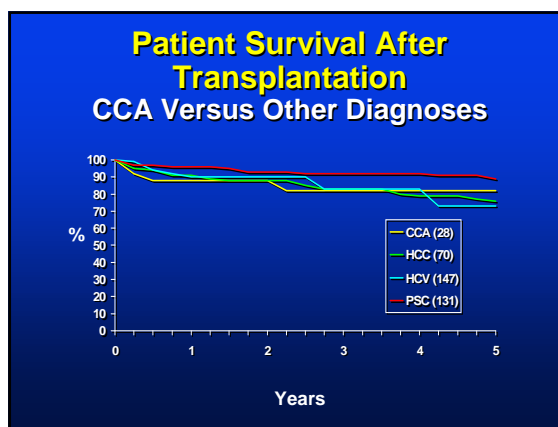
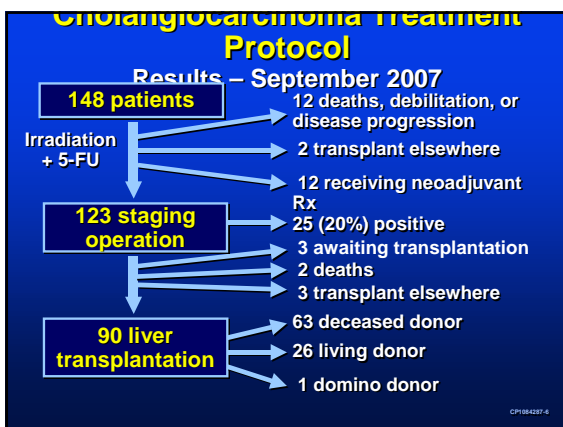
- Mayo Clinic experience
 - Rea, 2005
 - 71 patients selected for transplantation
 - 38 underwent LT
 - Neoadjuvant therapy : RT 45 Gy, 5FU IV CI + brachytherapy 20 – 30 Gy, followed by 5FU or capecitabine
 - 26 resections
 - 28 unresectable disease



Criteria for LTx

- Unresectable, perihilar
- Mass, radial diameter <3 cm, no cut off for longitudinal diameter
- If PSC, any ductal tumor <3 cm

G. Gores 2008



Palliative treatments

One problem of the medical treatment :

- Palliation of biliary obstruction



Methods = Plastic Stents



- Plastic stents => **stent occlusion** develops after 3-5 months
- ⇒ biliary obstruction and cholangitis
- ⇒ requires stent exchange

Due to a multifactorial process = deposition of a material containing bacterial biofilm, calcium bilirubinate and calcium palmitate crystals

Metal Stents

- Composed of either stainless steel or nitinol
- Delivered into bile duct while constrained by a sheath allowing insertion as a small circumference delivery system (7.5-10 French). When the sheath is retracted, the wire mesh stent expand to a diameter up to 10 mm

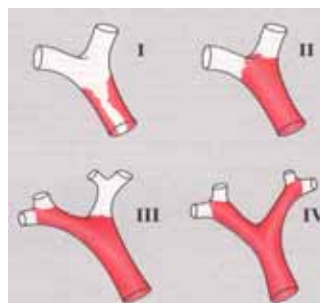


Plastic vs Metal Stents ?

5 comparative trials

- **Longer patency** of metal vs plastic stents 273 vs 126 days (Davids Lancet 1992;340:1488)
 - 28 % reduction in ERC
 - Survival duration did not differ
- Cost-effectiveness analysis = placement of a metal stent more economical than plastic stent only in patients with a **survival > 4-6 months**
- Identification of factors that reliably predict patient survival : multivariate analysis
 - Prat, Gut 1998 = **tumor size > 3 cm** (3.2 vs 6.6 months)
 - Kaassis, GIE 2003 = liver metastases (2.7 vs 5.7)

Malignant Hilar Obstruction Bismuth-Corlette Classification



Hilar Cholangiocarcinoma

- Endoscopic management of malignant hilar obstruction of **stage II to IV** is controversial with respect to optimal types of stents and extent of drainage
- Drainage of 25 % of the liver volume can achieve adequate palliation
(Dowsett Gastroenterology 1989;96:1180)
- But high risk of cholangitis in patients with opacified biliary ducts without drainage
(Ducreux Dig Dis Sci 1992;37:778)

2 Stents for Stage II

Plastic Metal

Partial drainage ?

**A = 1 lobe opacified
same lobe drained**

**B = 2 lobes opacified
and drained**

**C = 2 lobes opacified,
1 lobe drained**

Figure 3. Kaplan-Meier survival curves for groups A, B, and C. Significant differences were noted for group A vs. C and group B vs. C ($p < 0.0001$).

Table 5. Survival days of drainage groups in bismuth types II and III tumors

Bismuth type	Group A N = 32	Group B N = 29	Group C N = 37
II	150 (n = 24)	242 (n = 18)	58* (n = 16)
III	127 (n = 8)	165 (n = 11)	45* (n = 21)
II + III	145	225	66

Chang Gastrointest Endosc 1998;47:354

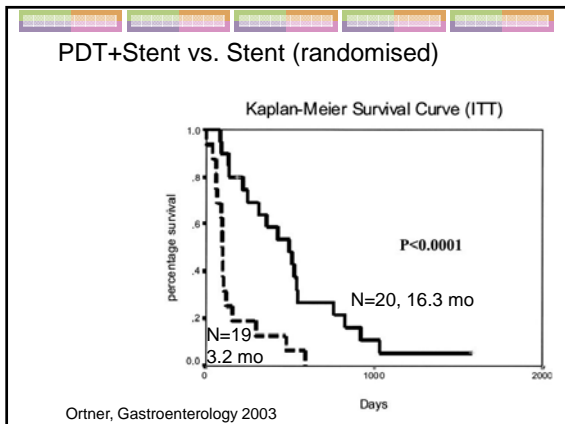
Guidelines for the Endoscopic Drainage

- Distal cholangiocarcinomas**
 - Plastic stents in patients with poor prognosis (large tumor, metastasis, poor general status)
 - Metal stents in the others
- Hilar tumors**
 - Evaluation with MRCP
 - Planning of optimal drainage
 - Limited opacification during ERC and insertion of the guidewire in preselected bile ducts

Photodynamic therapy

- Ablative Treatment for malignant/premalignant lesions
- Application of photosensitizing drug
- Irradiation with laser light (630 nm)
- Intracellular activation of photosensitizer
- Cellular injury
- additional effects: peritumoral thrombosis, immune resp.

Rumalla et al. Gastrointestinal Endoscopy 2001



- ### Photodynamic therapy
- Clearly successful in several trials
 - Excellent option for advanced unresectable ca.
 - Available in few centers only
 - Complex, time consuming procedure
 - Suboptimal photosensitizer
 - Suboptimal fibers
 - Comparison with CT or RCT ?

Is it useful to perform a chemotherapy ?

Only one phase III trial

Glimelius, 1995

- 93 patients with pancreatic or biliary metastatic cancer
- Improvement of survival and quality of life in the treated group (global analysis)

Treatment	n patients	Survival	p
BSC	19	2.5 months	
5FU-LV or ELF	18	6 months	NS

BSC vs FUFOL vs GEMOX in gallbladder K

- Randomised monocentric study
- Main endpoint : overall survival
- Non resectable or metastatic gallbladder cancer
- ECOG 0-2, age 18-70 years (median age : 50)

	BSC	FUFOL 5FU bolus 425 mg/m ² + AF 20 mg/m ² weekly	GEMOX GEM 900 mg/m ² + OXA 80 mg/m ² d1 + d8, d1 = d21	p
n	27	28	26	
PFS (months)	2.8	3.5	8.5	0.001
SG (months)	4.5	4.6	9.3	0.039

- ➔ Methodological problems ?
- ➔ Confirm efficacy of combination treatment

AD Dwyer et al., ASCO 2009, A 4521

Metastatic biliary tract cancer

Monochemotherapy with old drugs : not very active !

Drug	n patients	OR
5FU	70	14 %
Mitomycin C	49	20 %
Cisplatine	13	8 %
Methyl-CCNU	17	6 %
Amsacrine	23	9 %
Streptozotocin	14	17 %

- ### Metastatic biliary tract cancer : New drugs
- Irinotecan : Alberts 2002
 - 39 patients with gallbladder carcinoma
 - 125 mg/m² weekly for 4 weeks, two weeks of rest
 - ORR : 8%
 - Tegafur : 16 patients : 0 response
 - S1 : 19 patients : ORR = 21%, OS = 8.3 months
 - Paclitaxel : Jones, 1996
 - 15 patients : no response
 - Docetaxel : Souglakos, 2001
 - 25 patients : ORR = 20%

Classical Combination – EORTC 40955 not very active

Efficacy	5FU n = 27	5FU + FA + P n = 26
CR	0%	4%
PR	7%	15%
ORR [CI]	7.1% [1 - 30]	18.5% [8 - 35]
Early toxic death	0	1 (4%)
Median survival	n = 29	n = 29
Overall (months)	5.0 [4.0 - 7.4]	8.0 [5.8 - 11.8]
Progression free	3.3 [1.7 - 4.7]	3.3 [2.3 - 6.7]

Gemcitabine monotherapy

Trial	Schedule	Patients	ORR (%)	PFS (months)	OS (months)
Kubicka, 1999 (A)	Gemcitabine	23	30	4.4	-
Gelber, 2005	Gemcitabine FDR	11	0	-	5.0
Eng, 2004	Gemcitabine	15	0	2.0	5.0
Dobriša-Dintrićana, 2000	Gemcitabine	18	60	-	6.3
Arroyo, 2001 (A)	Gemcitabine	39	36	-	6.5
Raderer, 1999	Gemcitabine	19	16	2.5	6.5
Valencak, 1999	Gemcitabine	24	17	3.5	6.8
Valencak, 1999	Gemcitabine	14	29	-	10.5
Valle, 2006 (IIR)	Gemcitabine	44	15	4.0	-
Lin, 2003	Gemcitabine	24	12	2.5	7.2
von Delius, 2005	Gemcitabine	19	6	3.6	7.5
Okusaka, 2006	Gemcitabine	40	17	2.6	7.6
Gebbia, 2001 (IIR)	Gemcitabine	18	22	3.4	8.0
Penz, 2001	Gemcitabine	32	22	5.6	11.5
Park, 2005	Gemcitabine	23	26	8.1	13.1
Tsavaris, 2004	Gemcitabine	30	30	7.0	13.5
Medzger, 1998	Gemcitabine	13	8	7.0	16.0

Combination chemotherapy with Gemcitabine (excluding platinum analogs)

Trial	Schedule	Patients	ORR (%)	PFS (months)	OS (months)
Knox, 2004	Gem, 5FU	27	33	3.7	5.3
Murad, 2003	Gem, 5FU	26	31	-	9.0
Hsu, 2004	Gem, 5FU, LV	30	21	3.7	4.7
Jacobson, 2003 (A)	Gem, 5FU, LV	42	9.5	3.8	6.8
Alberts, 2005	Gem, 5FU, LV	42	9.5	4.6	9.7
Gebbia, 2001 (IIR)	Gem, 5FU, LV	22	36	4.1	11.0
Iqbal, 2006 (A)	Gem FDR, Cap	52	10	-	7.0
Knox, 2005	Gem, Cap	45	31	7.0	14.0
Cho, 2005	Gem, Cap	44	32	6.0	14.0
Bhargava, 2003	Gem, irinotecan	14	14	-	-
Kornek, 2004 (IIR)	Gem, MMC	25	20	4.2	6.7
Kuhn, 2002	Gem, docetaxel	43	9	5.2	11.0

Gemcitabine + platinum analogs

Trial	Schedule	Patients	ORR (%)	PFS (months)	OS (months)
Doval, 2004	Gem, cisplatin	30	37	-	4.6
Thongprasert, 2005	Gem, cisplatin	40	27	4.8	8.3
Kim, 2006	Gem, cisplatin	29	34	3.0	11.0
Carraro, 2001 (A)	Gem, cisplatin	10	50	5.5	11.3
Valle, 2006 (IIR)	Gem, cisplatin	42	24	8.0	-
Tan, 2004 (A)	Gem, carboplatin	13	31	-	-
Harder, 2006 (A)	Gem, oxaliplatin	31	26	6.5	10.4
André, 2004	Gem, oxaliplatin (GEMOX)	33	36	5.7	15.4
André, 2006 (A)	Gem, oxaliplatin (GEMOX)	70	24	3.1	9.5
	- Vésicule / autres	23/43	17/28	1.8/3.8	6.2/11.2

Palliative chemotherapy :

Systematic review (1985-2005) :

TRIALS	Patients	ORR (%)	IC ₉₅ (%)	Range (%)	PFS (months)	OS (months)
88	2137	23.3	21.5-25.2	0-83	4.1	8.0

- Taxanes, irinotecan : negative impact on ORR
- Gemcitabine : ↗ (non significant) OR with 5FU (or CAP) (22% vs 17%)
- Platinum analogues : significant ↗ OR with 5FU (27% vs 17%) or GEM (42% vs 22%)
- Gemcitabine-platinum analogues :
 - Promising results should be evaluated in randomised trials
 - Good option for standard care

Eckel ASCO 2006:14036

Multicentric Gemox gallbladder : to be or not to be ?

André, 2006

70 patients

- Cholangiocarcinoma + gallbladder tumours
- Locally advanced and metastatic disease

Location	n	%RO	PFS	OS
Gallbladder	25	4	1.8	6.2
Non gallb.	35	21	3.8	11.2

The same for Gem-Cap

Knox, 2006

- 23 Cholangiocarcinoma + 22 gallbladder tumours
- Locally advanced and metastatic disease

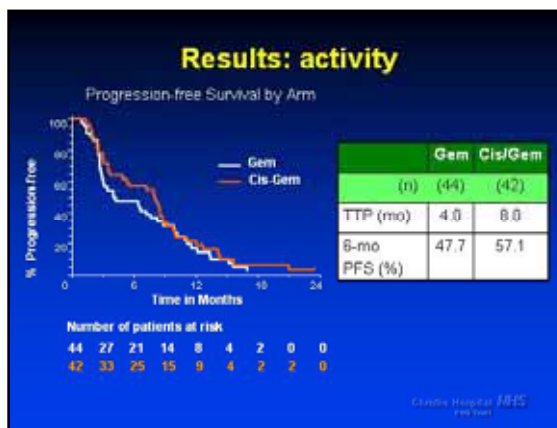
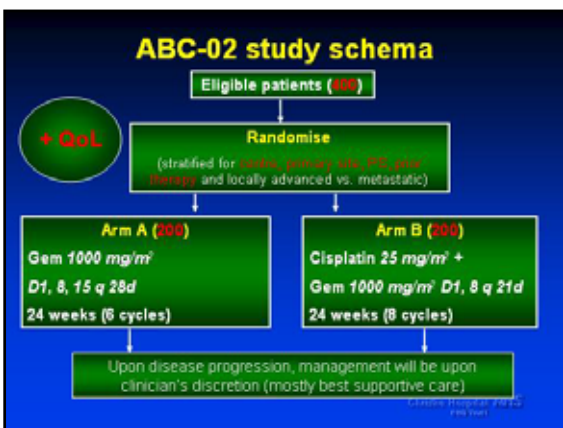
Location	n	%RO	PFS	OS
Gallbladder	22	28%	4.4	6.6
Non gallb.	23	34%	9.0	19

Completely different with Xelox

Nehls, ASCO 2006

- Xelox
 - 65 patients, median number of cycles = 5
 - Good tolerance

	CR / PR	SD	Median OS
Gallbladder (n=27)	4 / 23%	45%	12.8 m
Intra-hepatic CC (n=18)	0 / 0%	28%	5.8 m
Extra-hepatic CC (n=20)	5 / 20%	45%	12.8 m



GEM vs GEMCIS - UK-ABC 02 trial

- ABC 01**
 - Randomised phase II, 86 patients (ASCO GI 2006)
 - PFS : GEM-CDDP > GEM
- ABC 02**
 - Phase III, 324 pts, 34 centres
 - Main endpoint : overall survival
 - Locally advanced disease or metastatic, age ≥18 years, WHO 0-2

Stratification: Stage, Tumoral site, General status WHO, Centre

GEMCIS x 8 (GEM 1000 mg/m² J1-8 + CDDP 25 mg/m² J1-8, J1=J21)

GEM x 6 (GEM 1000 mg/m² J1-8-15, J1=J28)

JW Valle et al., ASCO 2009, A 4503

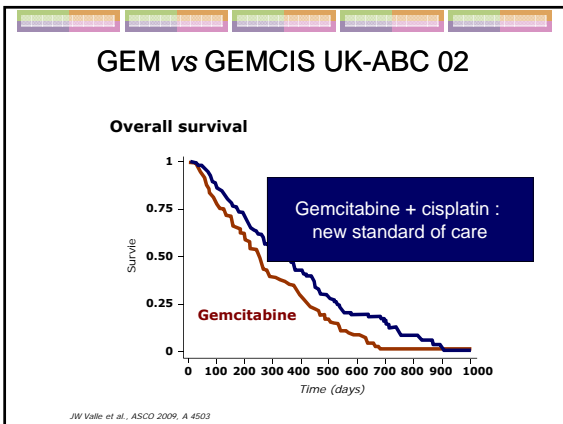
GEM vs GEMCIS UK-ABC 02

Intermedaite analysis of ABC 01 and 02

- 410 patients, median age 64 (23-85)
- LAD 25% / M+ 75%
- ECOG 0-1 87% / 2 13%
- Gallbladder 36% / Biliary tree 59% / Ampulloma 5%
- Comparable toxicity (Gr 3-4: 65.5 vs 64.2%)

	GEMCIS	GEM	HR (95%CI)	p
n	206	204		
OS (months)	11.7	8.3	0.70 (0.54-0.89)	0.002
PFS (months)	8.4	6.5	0.72 (0.57-0.90)	0.003

JW Valle et al., ASCO 2009, A 4503



- ### Targeted therapies Anti-angiogenic?
- Bevacizumab
 - Clark, ASCO 2007
 - Gemcitabine + oxaliplatin + bevacizumab
 - 19 patients, 10 biliary tract, 9 gallbladder
 - 3 PR, 5 stable disease
 - Low toxicity profile
 - No survival results

- ### Targeted therapies : lapatinib
- Oral tyrosine kinase inhibitor of EGFR and HER2
 - Phase II study :
 - Biliary tract carcinomas or HCC (2 groups of 17 patients)
 - One previous line of CT was allowed
 - 1500 mg/d
 - 49 pts (biliary tract : 19 ; HCC : 30)
 - Grade 3/4 toxicity : 19 pts (fatigue : 4, liver enzymes : 4, diarrhea : 2, nausea, vomiting, rash, anemia, thrombocytopenia : 1)
 - 17 evaluable pts with biliary tract cancer : 0 OR, 5 SD → closure of the biliary tract cohort
 - 17 first pts with HCC: 2 OR, 8 SD
 - PFS : 1.8 months (mix biliary and HCC)
- Ramanathan ASCO 2006;4010

- ### Targeted therapies Anti-angiogenic?
- Sorafenib ???,
 - Elkhoueiry ASCO 2007
 - 36 patients
 - 400 mg x 2 / day
 - Leucoencephalitis 1 pt, perforation 1 pt, haemorrhage 1 pt
 - Median PFS : 2 months
 - Overall survival : 6 months
- Non encouraging results*

Targeted therapies Anti-EGFR

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JOURNAL OF CLINICAL ONCOLOGY

Phase II Study of Erlotinib in Patients With Advanced Biliary Cancer

Philip A. Philip, Michelle R. Mahoney, Cristine Albner, James Thomas, Henry C. Pitot, George Kim, Ross C. Donehower, Tom Fitch, Joel Picus, and Charles Erlichman

Targeted therapies Anti-EGFR

Characteristic	No.	%
Age, years		
Median	57	
Range	35-82	
Sex		
Male	22	52
Female	20	48
Performance status, ECOG		
0	22	52
1	17	40
2	3	7
Site of primary disease		
Gall bladder	16	38
Intrahepatic bile duct	15	36
Extrahepatic bile duct	8	21
Unspecified	2	5
Site of disease		
Liver metastases	23	55
Perihilar metastases	16	38
Lymph node disease	8	21
EGFR protein expression in tumor cells	20 of 36	55
0	7	17
1+	12	30
2+	6	17
3+	11	31
Not evaluable	2	5
Yes	24	57
No	18	43

End Point	Estimate	95% CI
Partial response, No. of patients	0	2 to 20%
%	0	
Stable disease, No. of patients	17	27 to 59%
%	43	
Duration of stable disease, months	4.4	—
Median	3.20	
Range	—	
Disease control (partial response + stable disease)	50%	34% to 66%
Duration of disease control, months	5.1	—
Median	2.20	
Range	—	
24-week progression-free rate	7	7% to 31%
%	17	
Overall survival, months	7.5	5-12
Median	6	39-70%
Range	—	19-48%
Time to disease progression, months	2.6	2.4
Median	3	43%
Range	6	9-33%
95% CI	9	5-27%

BINGO: international, multicenter, open-label, randomized phase 2 trial

ABC
 1st line
 Stratification
 • Stage (LA vs M+)
 • Type (gallbladder vs other)
 • Center
 • Previous treatments (Y/N)*

R

Gemcitabine 1000 mg/m² in 100 min (10 mg/m²/min) IV – D1
 Oxaliplatin 100 mg/m² in 120 min IV – D2 Every 2 weeks

Until disease progression or limiting toxicity

Gemcitabine 1000 mg/m² in 100 min (10 mg/m²/min) IV – D1
 Oxaliplatin 100 mg/m² in 120 min IV – D2
 Cetuximab 500 mg/m² in 150 min IV – D1 or D2 Every 2 weeks

Endpoints

- Primary: 4-month PFS rate (RECIST)
- Secondary:
 - Toxicity
 - ORR, DCR, resectability rate
 - PFS, OS
- Exploratory: identification of predictive biomarkers for efficacy
 - Biological study (blood, tumor): EGFR pathway analyses
 - Functional imaging study (PET)

* Surgery, radiotherapy, brachytherapy, photodynamic therapy, adjuvant chemotherapy
 Tumor measurement every 8 weeks (RECIST)

Grade 3/4 toxicity

Severe toxicity (% patients) ^a	GEMOX (n=17)	GEMOX + cetuximab (n=18)
Total	76	67
Hematologic	43	39
Anemia	6	0
Neutropenia (febrile)	25 (0)	28 (6)
Thrombocytopenia	31	6
Peripheral neuropathy^b	31	33
Fatigue	6	22
Gastrointestinal	12	17
Rash / hypersensitivity	0	17

^a NCI-CTC v3.0, grade 3-4
^b Modified Levi scale, grade 2-3

Efficacy

	GEMOX (n=18)	GEMOX-Cetuximab (n=18)
4-month PFS	44%	61%
95% CI	[20-70]	[36-83]

Median follow-up: 5 months

- ### Conclusion
- Medical treatment of biliary tract carcinoma remains difficult
 - Jaundice should be treated and photodynamic therapy seems to be an improvement
 - Gallbladder carcinoma and other cholangiocarcinomas are very different tumours
 - Gemcitabine + cisplatin in a new CT standard
 - Gemox + cetuximab : next step???
 - Specific evaluation of new molecules should be done with stratification factors