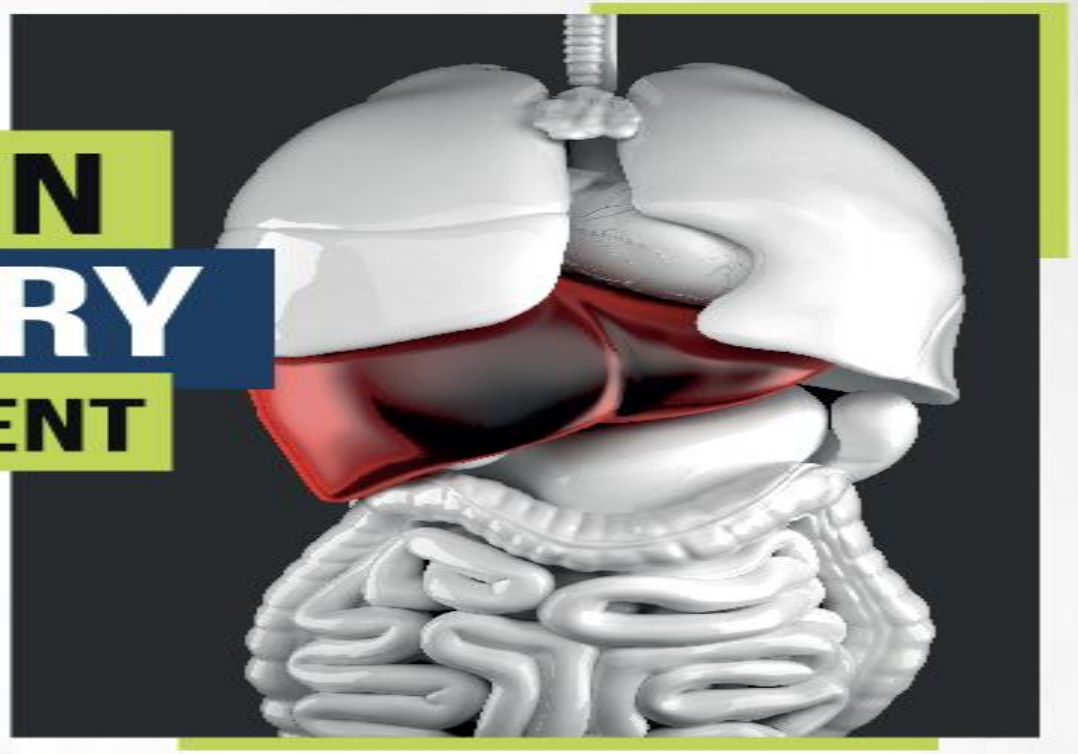
SAUDI SOCIETY OF GI ONCOLOGY
الجمعية السعودية لأورام الجهاز الهضمي
- SSGO -

ADVANCES IN HEPATOBILIARY CANCERS MANAGEMENT



Early biliary tract cancer what is the update ?

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Overview

- Introduction.
- Review Guidelines .
- Evidence -Current standard of care .
- Ongoing –Future trials .

Introduction :

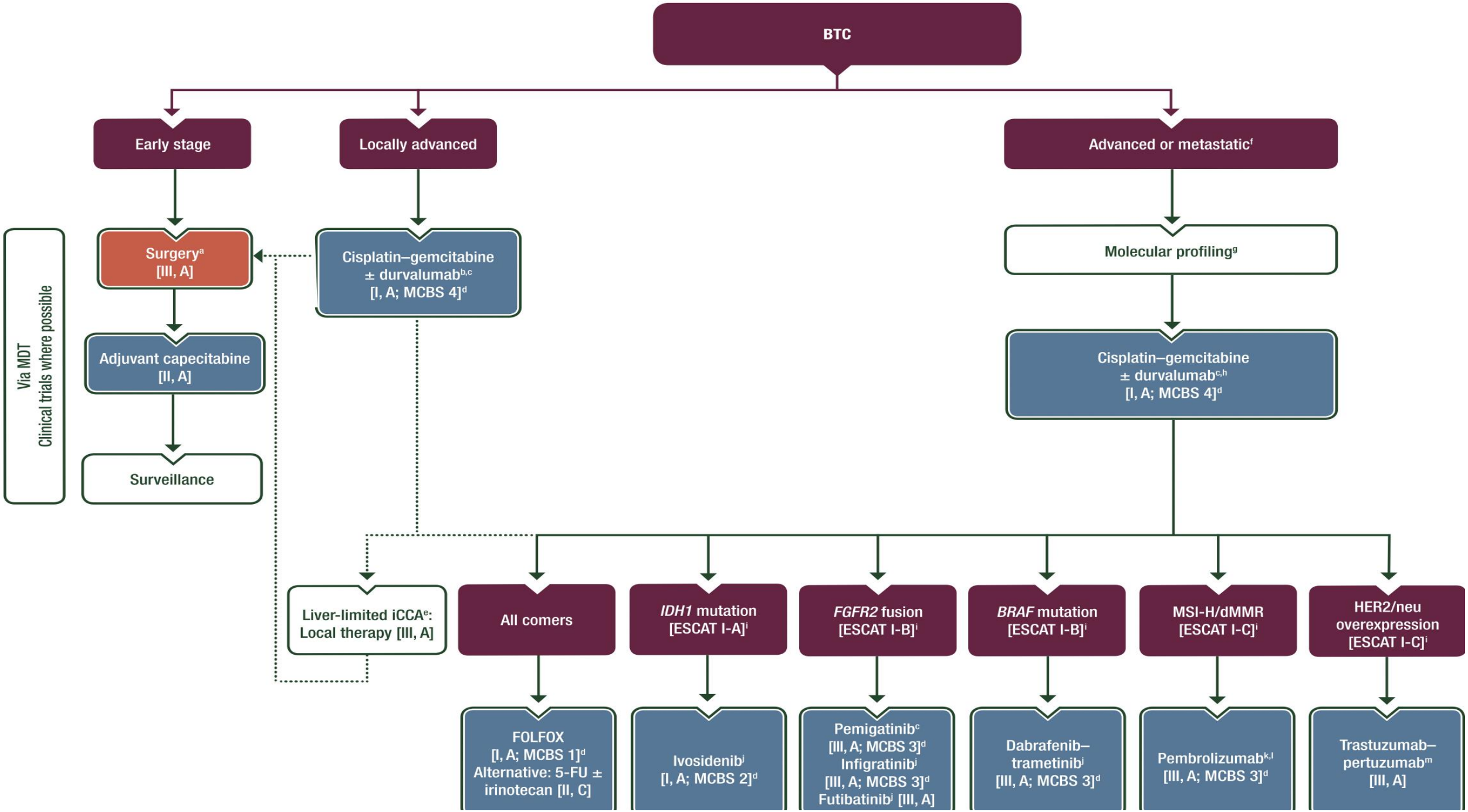
- Only 20% -30% Resectable at diagnosis.

- The 5-year survival remains poor at approximately :

10% for CCA and
19% for GBC

Cancers of the biliary tract include :

- Intrahepatic.
- Perihilar.
- Distal cholangiocarcinoma (CCA).
- Gallbladder cancer (GBC).

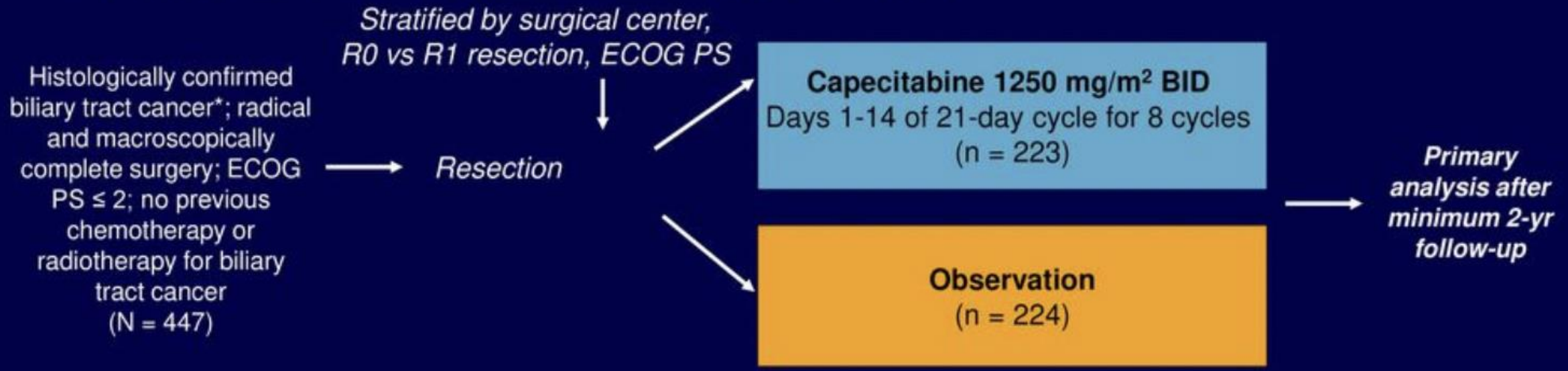

BTC
Early stage
Locally advanced
Advanced or metastatic[f]
Via MDT
Clinical trials where possible
Surgery[a] [III, A]
Adjuvant capecitabine [II, A]
Surveillance
Cisplatin–gemcitabine ± durvalumab[b,c] [I, A; MCBS 4][d]
Molecular profiling[g]
Cisplatin–gemcitabine ± durvalumab[c,h] [I, A; MCBS 4][d]
Liver-limited iCCA[e]: Local therapy [III, A]
All comers
IDH1 mutation [ESCAT I-A][i]
FGFR2 fusion [ESCAT I-B][i]
BRAF mutation [ESCAT I-B][i]
MSI-H/dMMR [ESCAT I-C][i]
HER2/neu overexpression [ESCAT I-C][i]
FOLFOX [I, A; MCBS 1][d] Alternative: 5-FU ± irinotecan [II, C]
Ivosidenib[j] [I, A; MCBS 2][d]
Pemigatinib[c] [III, A; MCBS 3][d] Infigratinib[j] [III, A; MCBS 3][d] Futibatinib[j] [III, A]
Dabrafenib–trametinib[j] [III, A; MCBS 3][d]
Pembrolizumab[k,l] [III, A; MCBS 3][d]
Trastuzumab–pertuzumab[m] [III, A]

Is there any role for adjuvant chemotherapy ?

BTC 5 Adjuvant RCT	n	BTC Tumor Sites	Treatment	Primary endpoint	Comments
Recent Completed Studies					
PRODIGE Edeline et al. 2017	196	All	GemOx vs observation	RFS	Negative trial
BILCAP Primrose et al. 2017	447	All	Capecitabine vs observation	OS	Practice changing positive trial. Std of Care
BCAT Ebata et al. 2018	225	Extrahepatic:	Gemcitabine vs observation	OS	Negative trial
ASCOT Ikeda et al. 2022	440	Extrahepatic:	S1 vs observation	OS	Positive Practice changing trial
STAMP Yoo et al. 2022	101	Extrahepatic node pos	GemCis vs Capecitabine Phase 2	DFS	Negative

BILCAP: Study Design

- Open-label, randomized, controlled phase III trial



*Included: intrahepatic CC, hilar CC, muscle-invasive gallbladder cancer, and lower common bile duct CC
Excluded: pancreatic, ampullary, mucosal (T1a) gallbladder cancers; incomplete recovery from prior surgery

- Primary endpoint: OS
- Secondary endpoints: RFS, toxicity, QoL, health economics

Primrose JN , et al. ASCO 2017. Abstract 4006.

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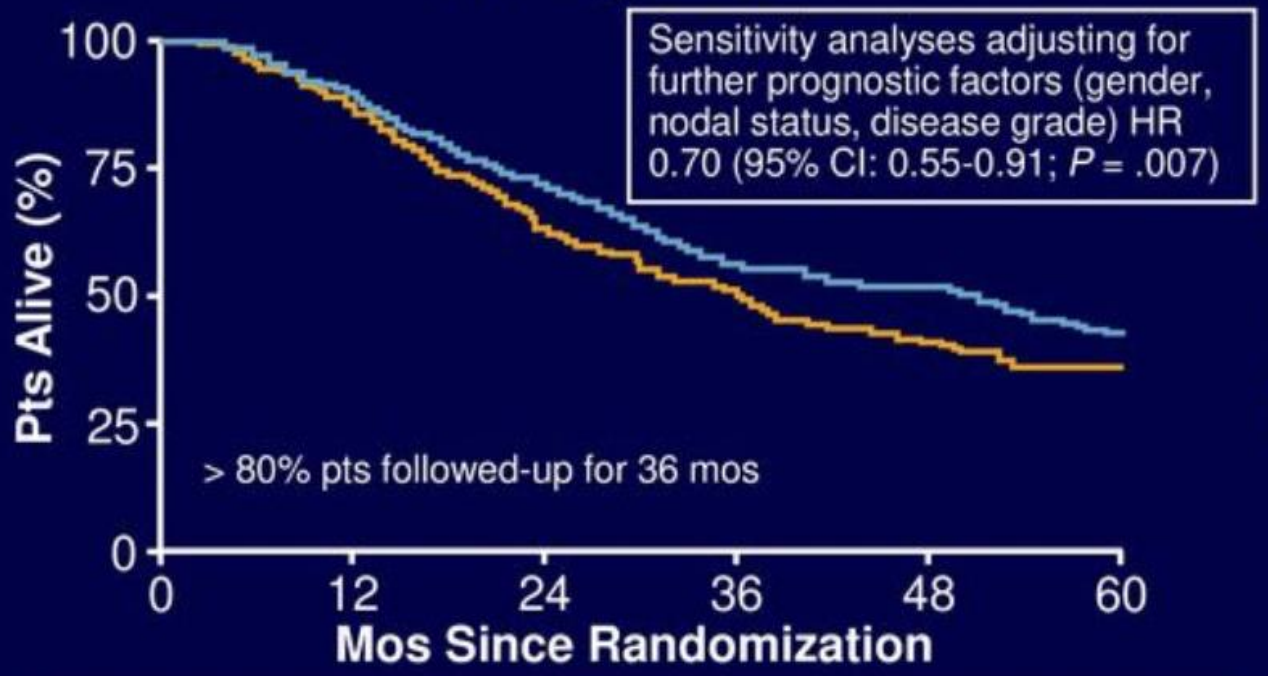
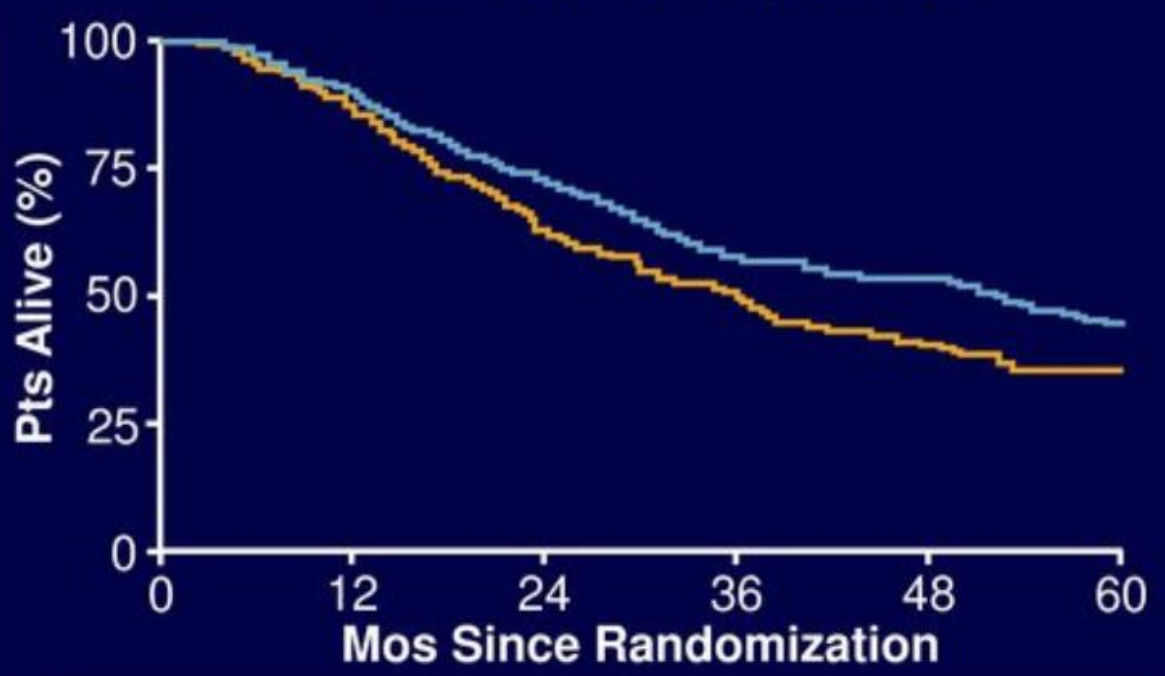
BILCAP: OS

ITT Population



Treatment	Median OS, Mos (95% CI)	HR (95% CI)
Capecitabine	51.1 (34.6-59.1)	0.81 (0.63-1.04) P = .097
Observation	36.4 (29.7-44.5)	

Per Protocol Population



Treatment	Median OS, Mos (95% CI)	HR (95% CI)
Capecitabine	52.7 (40.3-NR)	0.75 (0.58-0.97) P = .028
Observation	36.1 (29.6-44.2)	

Primrose JN , et al. ASCO 2017. Abstract 4006. Reproduced with permission.

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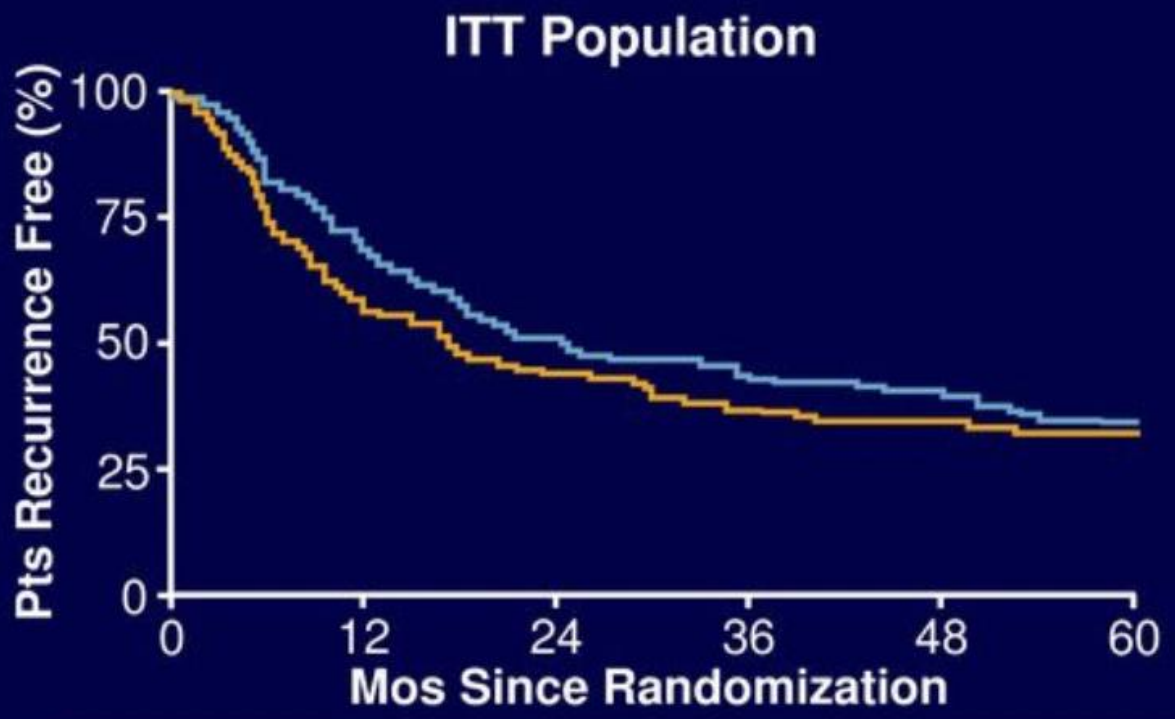
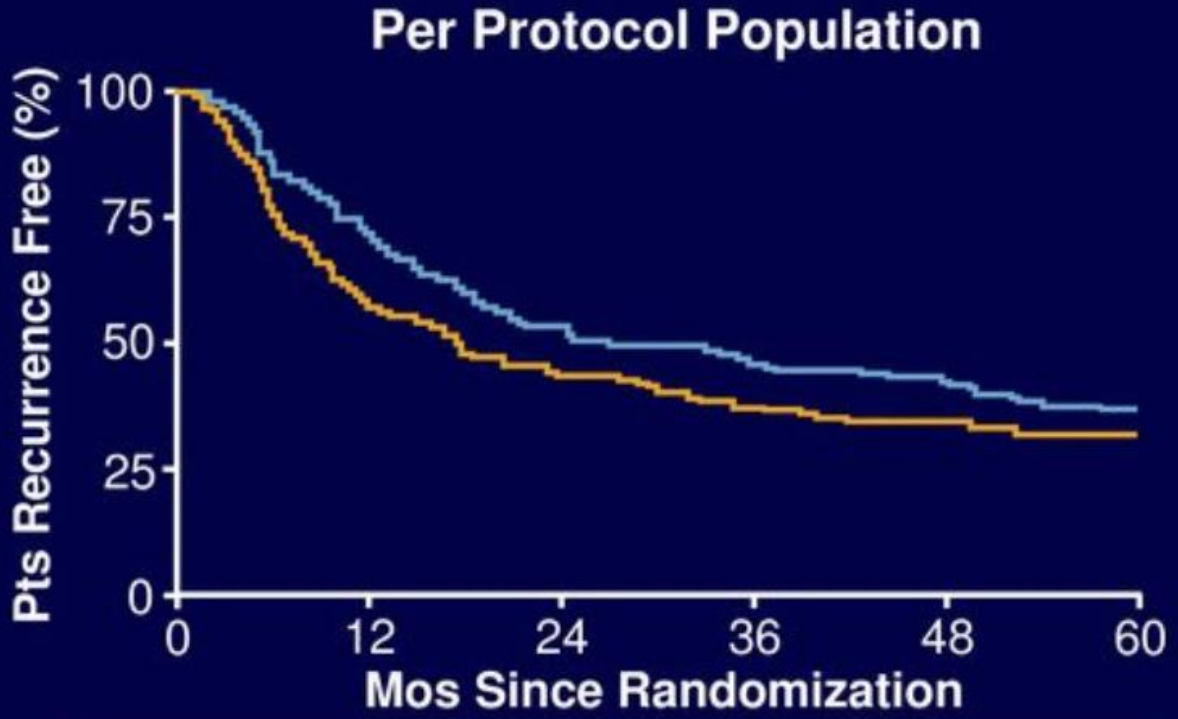
BILCAP: Relapse-Free Survival



Treatment	Median RFS, Mos (95% CI)	HR (95% CI)
Capecitabine	24.6 (18.9-36.7)	0.76 (0.58-0.99) *P* = .039
Observation	17.6 (12.8-27.6)	



Treatment	Median RFS, Mos (95% CI)	HR (95% CI)
Capecitabine	25.9 (19.8-46.3)	0.71 (0.54-0.92) *P* = .011
Observation	17.6 (12.0-23.8)	

Primrose JN , et al. ASCO 2017. Abstract 4006. Reproduced with permission.

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BILCAP: Conclusions

- Adjuvant capecitabine associated with improved OS in pts with resected biliary tract cancer
  - Authors suggest capecitabine should become standard of care in this setting
- Capecitabine treatment produced modest toxicity
- QoL in capecitabine arm comparable to observation arm
- Authors recommend using capecitabine control arm in future adjuvant trials in biliary tract cancer

Primrose JN , et al. ASCO 2017. Abstract 4006.

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Is there any role for CCRT ? Phase 2

SWOG 0809

- Eligibility
  - Gallbladder cancer or EHCC
  - At least one of the following:
    - T2-T4
    - N1
    - Positive margins

Gemcitabine 1000 mg/m2 IV over 30 min D1 and D8
+ Capecitabine 750 mg/m2 PO BID x 14 days

X

4 cycles

Concurrent EBRT with Capecitabine 665 mg/m2 BID x 7 days for 6 weeks

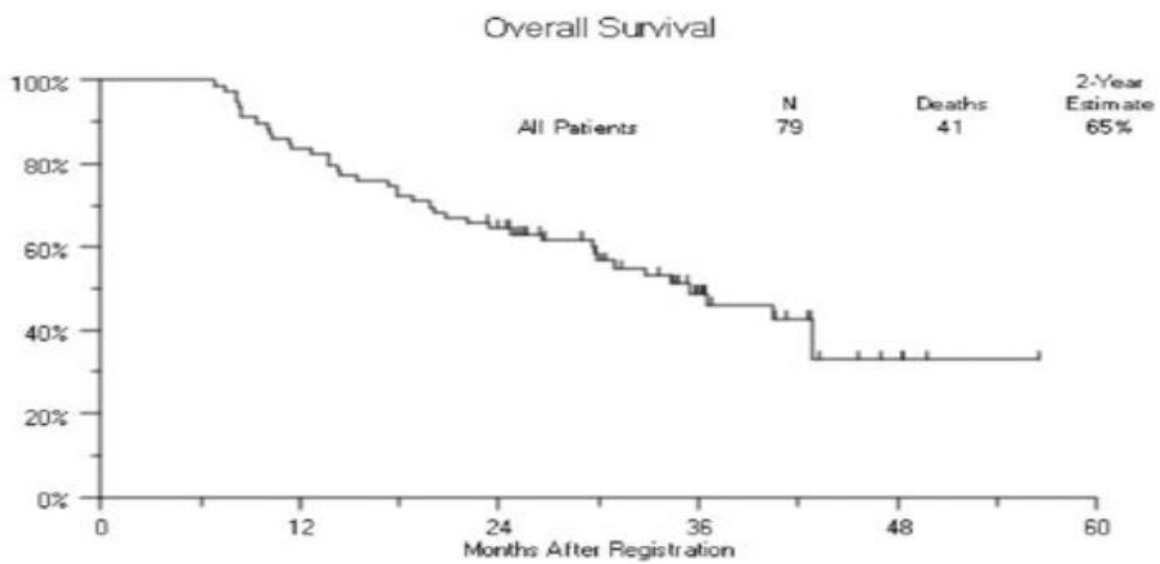
(45 Gy to regional lymphatics, 54-59.4 Gy to the tumor bed)

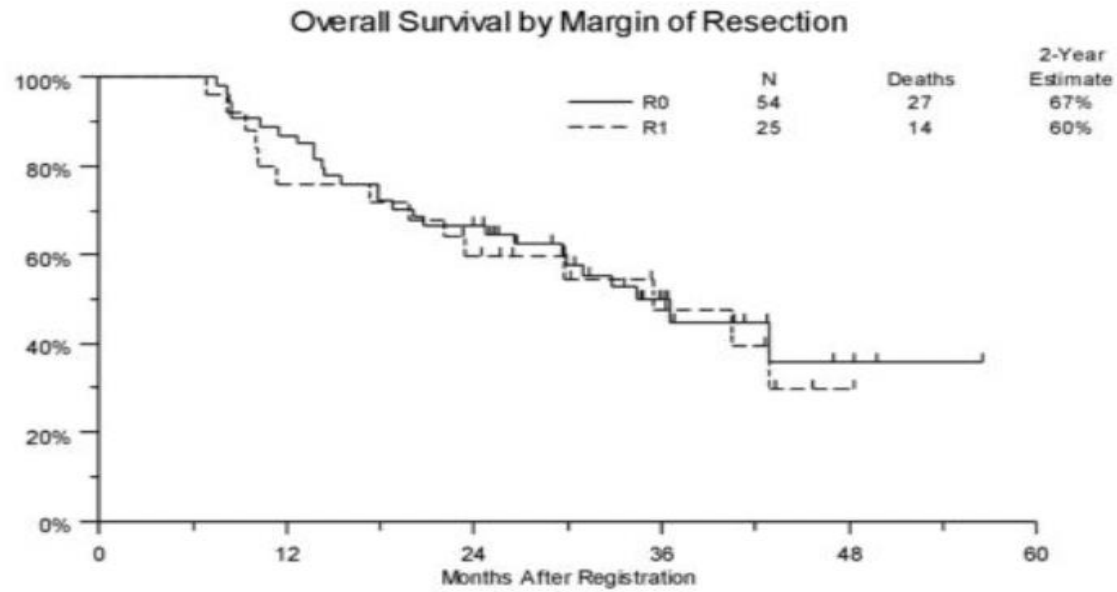
SWOG 0809 Results

- 2 year OS=65%, median OS=35 months
- 79 eligible; 54 R0, 25 R1
- 68% EHBD, 32% GB
- 86% completed treatment
- Grade 3-4 toxicities included neutropenia (44%), hand-foot (11%), diarrhea (8%)
- One death due to duodenal bleed

Ben-Josef et al, in press, JCO

Overall Survival: SWOG 0809





2-year estimate of OS=65%

OS not significantly different by margin status:
2-year OS 67% vs 60%

Ongoing trial (Adjuvant)

Table 2. Adjuvant chemotherapy clinical trials in progress

Trial ID/name	Location	Trial type	Tumor site	No. of patients	Intervention	Primary outcome	Status
NCT02170090; EudraCT 2012-005078-70 (ACTICCA-1)	Germany	Phase III	CCA, GBC	781	Cisplatin + gemcitabine + *vs.* capecitabine	DFS at 2 year	Recruiting
NCT03779035	China	Phase III	CCA, GBC	460	Gemcitabine + capecitabine *vs.* capecitabine	DFS at 2 year	Recruiting
UMIN000011688 (JCOG1202: ASCOT)[70]	Japan	Phase III	CCA, GBC, ampulla of Vater	440	S-1 24 weeks *vs.* surveillance	OS	Recruiting
NCT02548195	China	Phase III	iCCA	286	Cisplatin + gemcitabine *vs.* capecitabine	DFS	Unknown
NCT02798510	China	Phase III	GBC, pCCA, dCCA	140	Gemcitabine/capecitabine → CRT (capecitabine) → gemcitabine/capecitabine *vs.* gemcitabine/capecitabine	OS at 2 year	Unknown
NCT03079427	Korea	Phase II	pCCA + dCCA with regional LN metastases	100	Cisplatin + gemcitabine *vs.* capecitabine	2 year DFS	Recruiting
EudraCT 2010-020480-21	Germany	Phase II	iCCA	45	Gemcitabine post liver transplantation	Completion rate	Recruiting
NCT04333927	China	Phase II	CCA, GBC	92	Camrelizumab + CRT(capecitabine) *vs.* surveillance	OS 2 year	Active, not recruiting
NCT04295317	China	Phase II	iCCA	65	Anti-PD-L1 (SHR-1210) + capecitabine	DFS 2 year	Recruiting
NCT04077983	China	Phase II	iCCA	40	Gemcitabine + Nab-paclitaxel	DFS	Not yet recruiting
NCT04782804	China	Phase I-II	iCCA	30	Tislelizumab + capecitabine	DFS	Recruiting
NCT02778308	India	N/A	GBC	100	Cisplatin + gemcitabine *vs.* surveillance	DFS	Completed, not reported

Ongoing trial (Adjuvant)

- Cisplatin + gemcitabine vs capecitabine (**ACTICCA)**
- Gemcitabine plus nab-paclitaxel
- The benefit of adjuvant gemcitabine following liver transplantation
- Combination of an anti-PD-1/PD-L1
- Monoclonal antibody with chemotherapy

- ACTICCA-1 also includes a second randomization in R1 patients whereby chemoradiation is introduced to the treatment, replacing the final two (of eight) cycles of chemotherapy.

- This design has the potential to answer the chemo-intensification question and whether more tailored treatment for R1 cases improves outcomes.

Neoadjuvant data :

Neoadjuvant data :

There has been a steady shift to neoadjuvant and perioperative chemotherapy in some gastrointestinal malignancies, including:

- Gastric.
- Locally advanced rectal carcinoma.
- Pancreatic adenocarcinoma(improved R0 rate, DFS, and locoregional failure-free interval , no OS) with neoadjuvant FOLFIRINOX in borderline resectable

- There are no completed phase III randomized-control trials determining the survival benefit of neoadjuvant or downstaging chemotherapy, with evidence predominately obtained from retrospective analyses…

- A review of 1450 patients with stage I-III CCA in the United States National Cancer Database by Yadav *et al* indicated that :

- Those who received neoadjuvant chemotherapy were more likely to attain an R0 resection compared to those who had upfront surgery followed by adjuvant chemotherapy (71.2% *vs*. 61.6%, $P = 0.02$).

Table 3. Selected completed clinical trials of neoadjuvant or downstaging chemotherapy in biliary tract cancers

Study author	Year	Study type	Study arms	Tumor site	No. of patients	Resectability status presentation	Results			
							% RO	ORR	DFS	OS
McMasters *et al.*[51]	1997	Prospective (non-randomized)	EBRT (fluorouracil)	dCCA pCCA	4 5 (total 9)	Unresectable	100%	3 pCR	NA	NA
Nelson *et al.*[71]	2009	Retrospective	EBRT (fluorouracil) +/- brachytherapy	pCCA, dCCA	12	Unresectable	91.7%	3 pCR	NA	34 months
Jung *et al.*[72]	2017	Retrospective	Fluorouracil/gemcitabine + EBRT	pCCa	12	Unresectable	83.3%	NA	NA	NA
Katayose *et al.*[52]	2015	Prospective (non-randomized)	Gemcitabine + EBRT	dCCA, pCCA	24	Resectable	80.9%	NA	NA	NA
Kobayashi *et al.*[73]	2017	Retrospective	EBRT (gemcitabine) → surgery v surgery	pCCA, dCCA, GBC	106 (27 neoadjuvant CRT)	Resectable	NA	70%	3 year DFS 78% *vs.* 57%	3 year OS 85% *vs.* 69%
Kato *et al.*[35]	2013	Retrospective	Gemcitabine	iCCA	22	Unresectable	18%	37%	NA	45 months (resected)
Kato *et al.*[74]	2015	Retrospective	Cisplatin + gemcitabine	iCCA	39	Unresectable	26%	23%	NA	NA
Le Roy *et al.*[75]	2018	Retrospective	Gemcitabine + oxaliplatin	iCCA	74 (39 received surgery)	Unresectable	31%	24%	NA	24.1 months
Lunsford *et al.*[76]	2018	Prospective case series	Gemcitabine → liver transplant	iCCA	6	Unresectable	NA	NA	1 year 50%	5 year 83.3%
Chaudhari *et al.*[53]	2018	Prospective (non-randomized)	Cisplatin + gemcitabine OR gemcitabine + oxaliplatin	GBC	160	Unresectable	95% (63/66)	52.5%	25 months	49 months
Sumiyoshi *et al.*[34]	2018	Retrospective	IMRT (S-1)	iCCA pCCA	7 8	Unresectable	9/11 (both) (82%)	57% 37%	mDFS 21.5 months (4-40)	mOS 37 months (surgical pt)

Ongoing trial (Neoadjuvant)

Table 4. Neoadjuvant and downstaging clinical trials in progress

Trial ID/name	Location	Trial type	Tumor site	Resectability status	No. of patients	Intervention	Primary outcomes	Status
NCT03673072; EudraCT 2017-004444-38 (GAIN)[56]	Germany	Phase III	GBC, CCA	Incidental diagnosis post cholecystectomy	300	Cisplatin + gemcitabine v nil (×3 cycles) → surgery → +/- adjuvant cisplatin + gemcitabine (×3 cycles)	OS	Recruiting
CTRI/2016/08/007199; NCT02867865 (POLCAGB)[57]	India	Phase II-III	GBC	Unresectable without evidence of distant metastases	314	Cisplatin + gemcitabine v CRT (gemcitabine) → cisplatin + gemcitabine	OS	Recruiting
NCT03603834	Thailand	Phase II	CCA	Resectable OR potentially resectable	25	mFOLFOXIRI	ORR	Recruiting
NCT04308174 (DEBATE)	Korea	Phase II	CCA, GBC	Resectable	45	Durvalumab + cisplatin + gemcitabine v cisplatin + gemcitabine	R0 rate	Recruiting
NCT04546828	Korea	Phase II	iCCA with high risk recurrence features	Resectable	34	Cisplatin + gemcitabine + nab-paclitaxel	RO rate	Not yet recruiting
NCT04669496	China		iCCA with high risk recurrence features	Resectable	178	Gemcitabine + oxaliplatin + lenvatinib + toripalimab → surgery → adjuvant capecitabine	Event-free survival	Recruiting
NCT04559139	USA	Phase II-III	Incidental GBC	Incidental diagnosis post cholecystectomy	186	+/- neoadjuvant cisplatin + gemcitabine → revision surgery → adjuvant cisplatin + gemcitabine	OS (5 year)	Recruiting
NCT04727541	Germany	Phase II	CCA, GBC	Resectable	24	Bintrafusp-alfa ×2 doses	Pathologic response rate	Not yet recruiting
NCT04378023	Spain	Phase IV	pCCA	Unresectable	34	EBRT + capecitabine → cisplatin + gemcitabine until transplant	OS at 1, 3 and 5 year	Recruiting
NCT04523402	China	Phase II	iCCA with high-risk LN metastases	Resectable	100	Gemcitabine + oxaliplatin	Event-free survival (24 months)	Not yet recruiting

Future

- Molecular testing in adjuvant –Perioperative setting ?
- Role of Targeted therapy in Adjuvant or perioperative ?
- Immunotherapy ??

THANK YOU