Localized Potentially Operable CCA: What are the neoadjuvant options?

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MEDICINE

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Cholangiocarcinoma (CCA)

- Highly heterogeneous tumors
  - Incidence is increasing globally

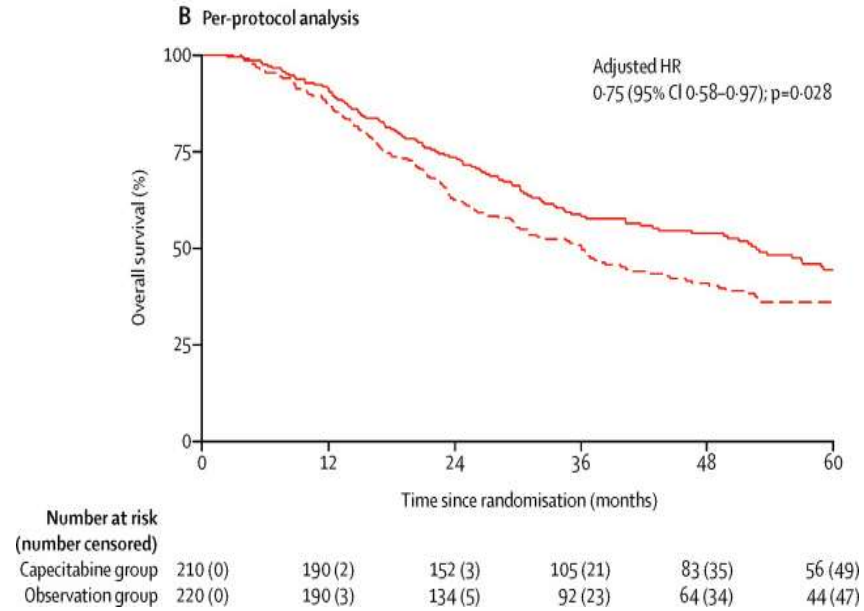
- Typically diagnosed at later stages, up to 70% of CCA is inoperable (upfront)

- **BILCAP**: Randomized open-label phase III study of 6 months adjuvant capecitabine for CCA and muscle-invasive GB
  - Met statistical significance in “pre-protocol analysis” but not intent-to-treat analysis (semi-positive study)
  - In the ITT analysis, the median OS 49.6 months vs 36.1 months (HR 0.84).
  - In a protocol-specified sensitivity analysis, the OS hazard ratio was 0.74

- **SWOG S0809**: Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine
  - Phase 2; EHC and GB, R+ or Node +
  - 2-year survival was 65% (95% CI, 53% to 74%);
  - Median overall survival 35 months

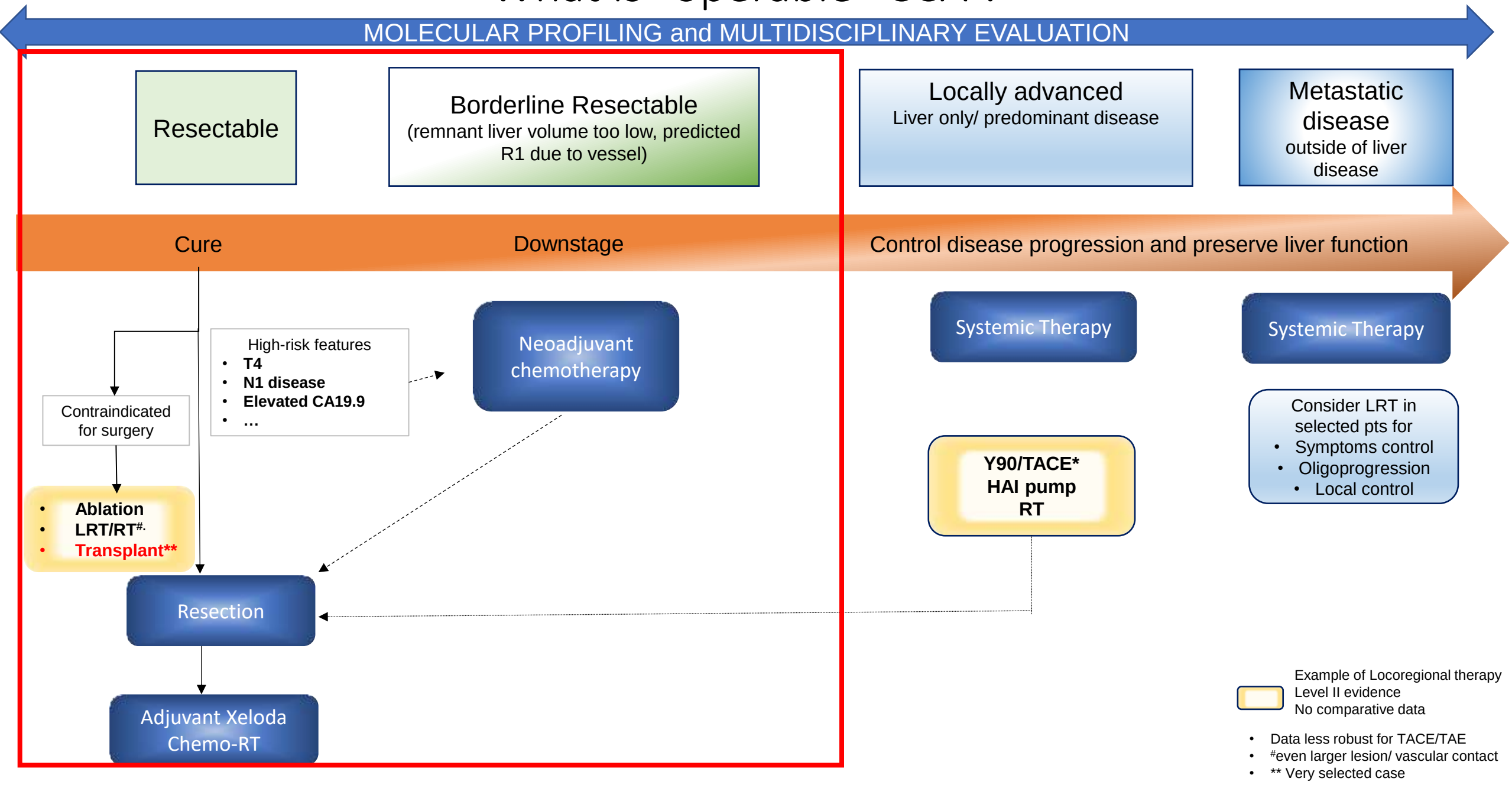
Presentation a Time of Diagnosis

■ resectable ■ unresectable □ liver only mets



Banales et al., Nat Rev Gastroenterol Hepatol. 2020; Primrose J. et al. Lancet Oncol 2019; Ben-Josef et al. J Clin oncol 2015,

What is “operable” CCA ?



Time to Rethink Upfront Surgery for Potentially Resectable CCA?

Theoretical advantages to neoadjuvant chemotherapy

- More patient receive systemic therapy
- Progression avoids 'unnecessary' surgery
- Response is a biomarker
- ↑ chance of R0 and negative nodes

Examples of disease showing superiority of Neoadjuvant Systemic tx

Tumor Type	Neoadjuvant Benefit
Non-Small Cell Lung Cancer (NSCLC)	Improved survival, better downstaging, higher pCR rates
Breast Cancer (Triple-Negative, HER2+)	Increased pCR, better response to immunotherapy + chemo
Rectal Cancer	Organ preservation, reduced recurrence
Melanoma (Stage III, High risk)	Improved relapse-free survival, better immune response

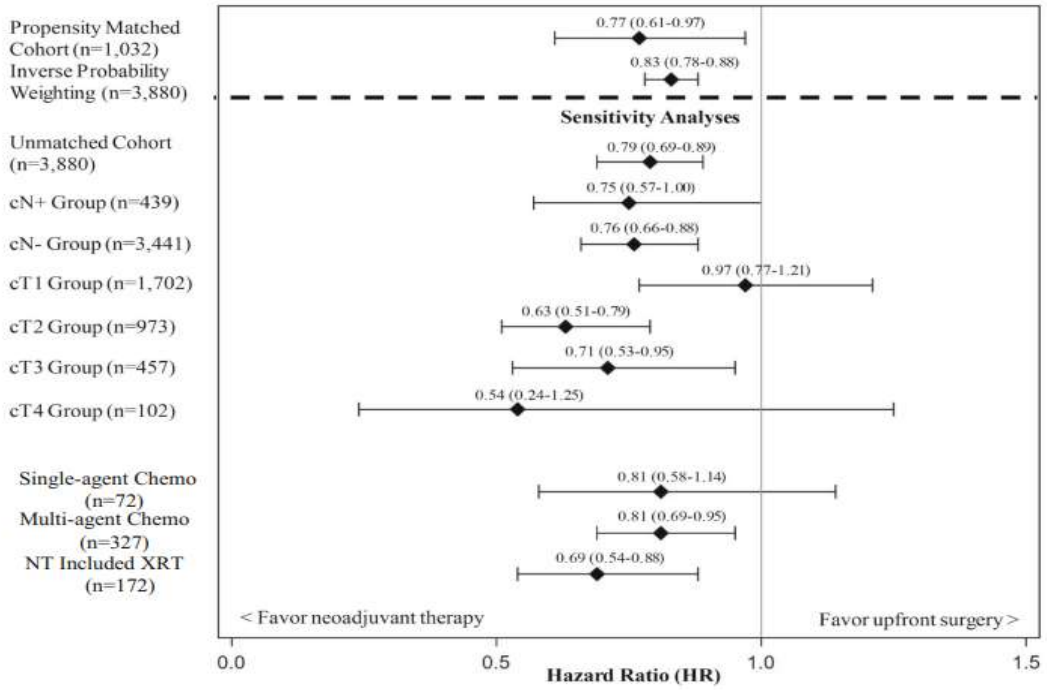
But….

- Chemotherapy has real toxicities
- Loss of window for surgical benefit
- Multimodality therapy can be challenging

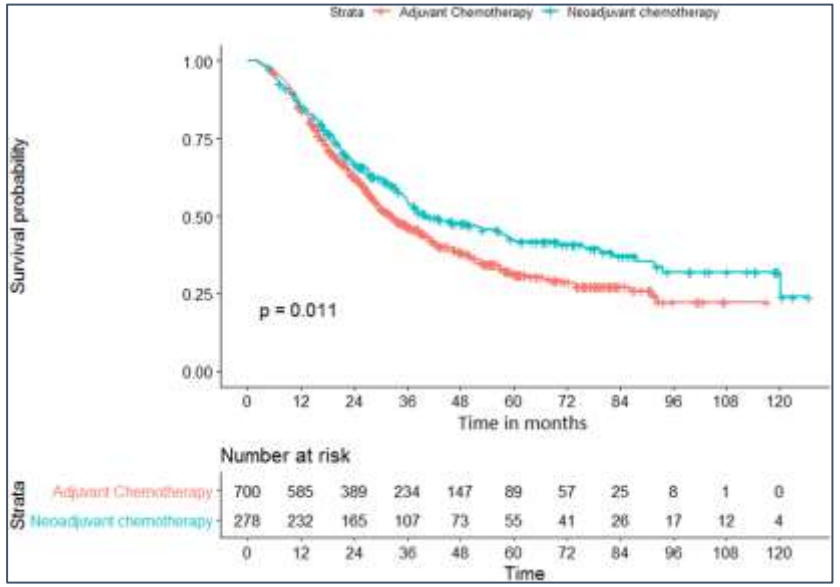
Banales et al., Nat Rev Gastroenterol Hepatol. 2020; Primrose J. et al. Lancet Oncol 2019; Ben-Josef et al. J Clin oncol 2015,

Neoadjuvant Therapy (NT) Is Feasible & Safe

- Retrospective cohort study of 4456 surgically resected patients within National Cancer Data Base (2006–2016).
  - After propensity matching, **NT associated with 23% decreased risk of death vs upfront surgery** (HR 0.77, 95% CI 0.61–0.97).



- Retrospective Propensity matched analysis patients who underwent surgery and chemotherapy for stage I-III CCA between 2006 and 2014 (N=1450).
  - **Patients who underwent NT had significantly longer OS compared to those who received adjuvant chemotherapy** (median OS: 40.3 vs. 32.8 months, HR: 0.78, 95% CI: 0.64–0.94, p = 0.01)

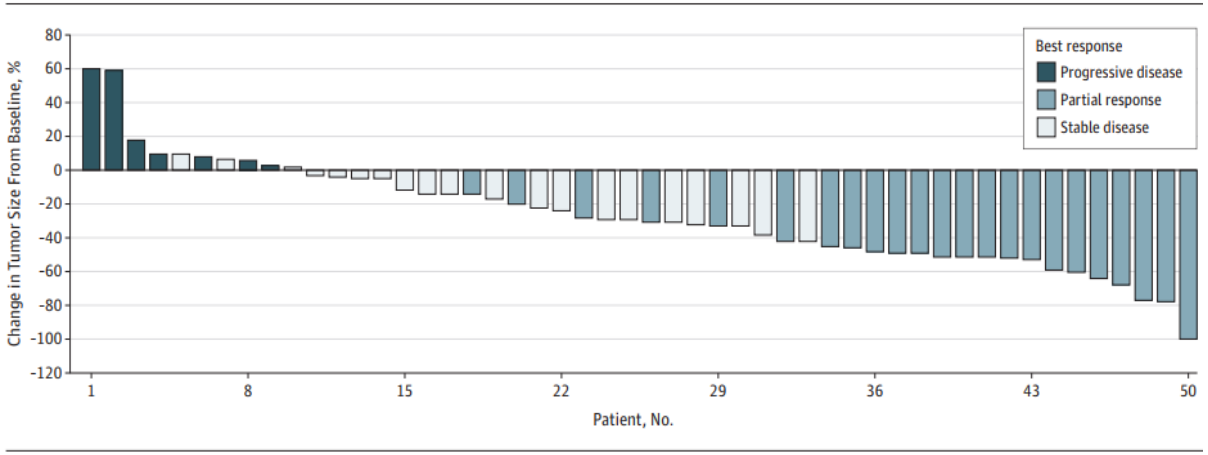


Mason MC et al., Ann Surg Oncol. 2021; Yadav S et al., Eur J Surg Oncol. 2019

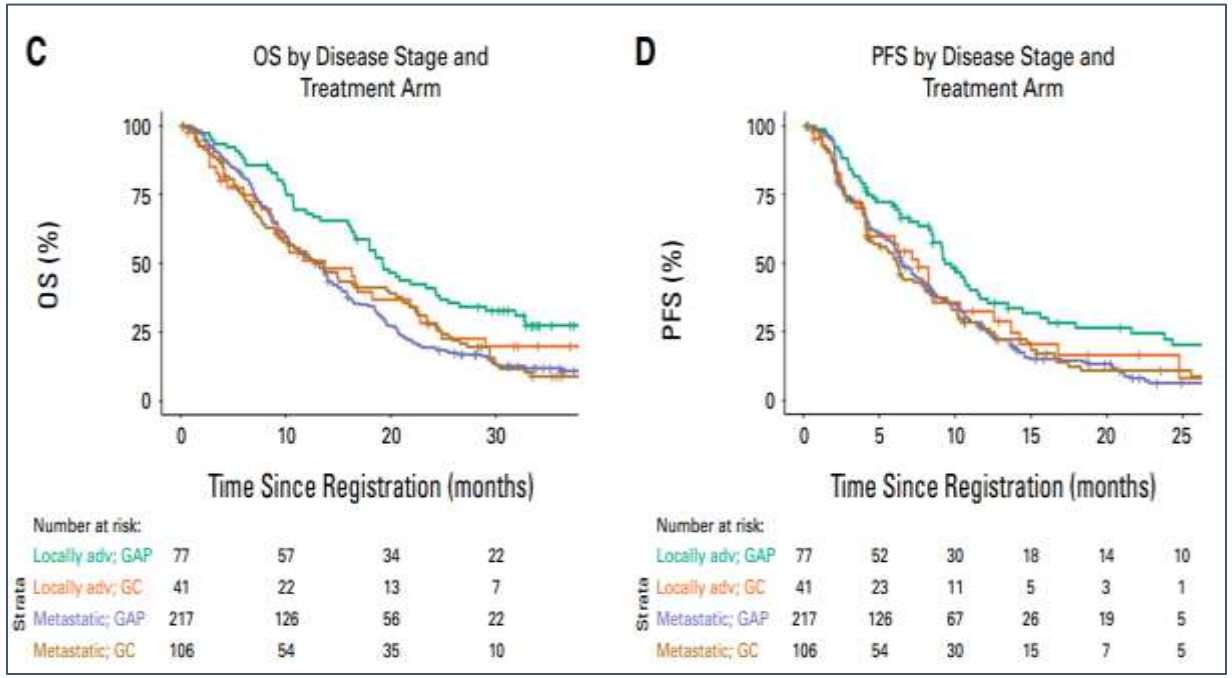
What regimen do we use?

CisGem + NabPaclitaxel

- Phase 2 trial, (N=60 patients)
  - mPFS of 11.8 months
  - mOS of 19.2 months
  - ORR 45%; DCR 84% > Downstaging strategy



- Phase III trial (SWOG1815), (N=452) randomly *no significant difference in OS*
  - mOS with GAP was 14.0 months (95% CI, 12.4 to 16.1) and 13.6 months with GC (95% CI, 9.7 to 16.6); HR, 0.91 (95% CI, 0.72 to 1.14);
  - In exploratory subset analyses, OS and PFS benefits of GAP were greater in *locally advanced disease* compared with metastatic disease, although not statistically significant (interaction P = .14 for OS and P = .17 for PFS)



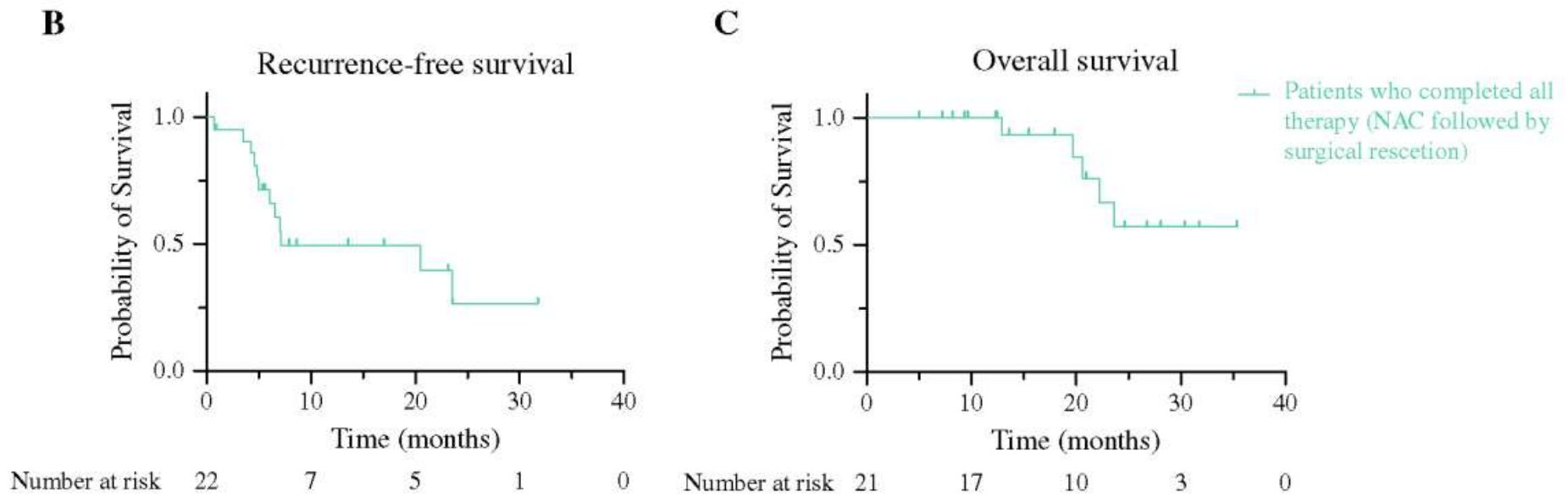
Shroff R. et al. Jama Oncol 2019; Shroff R et al., J Clin Oncol. 2024

NEO-GAP: A Single-Arm, Phase II Feasibility Trial of Neoadjuvant GAP for Resectable, High-Risk Intrahepatic Cholangiocarcinoma

- Single-arm, phase II trial was conducted for patients with resectable, high-risk IHCC (n=30)
  - tumor size > 5 cm, multiple tumors, presence of radiographic major vascular invasion, or lymph node involvement

- Twenty-two patients (73%) completed all chemotherapy and surgery.
  - Median RFS was 7.1 months.
  - Median OS for the entire cohort was 24 months and was not reached in patients who underwent surgical resection.

- Ten patients (33%) experienced Grade ≥ 3 treatment-related AEs. No grade 5 events



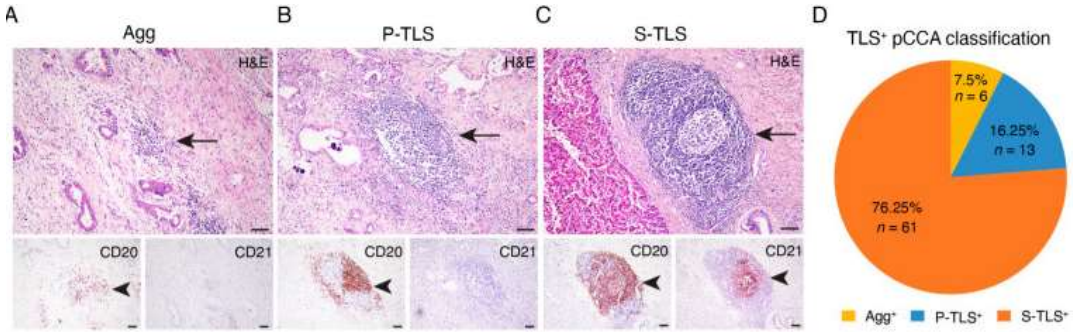
Maithel SK et al., Ann surg Oncol 2023

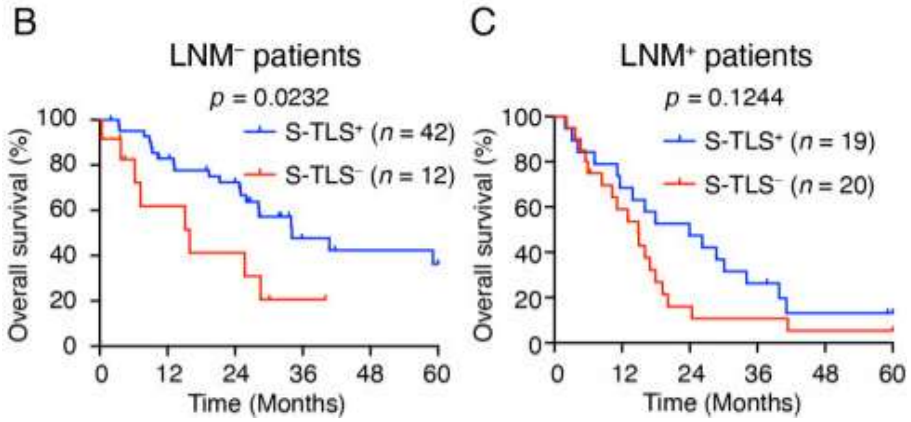
Immunotherapy plus chemo provides some benefit in unselected CCA

- **Administering immunotherapy preoperatively** is a biologically sound approach:
  - can generate the optimal immune response
  - high rates of pathologic response
  - improved long-term survival/immune memory.
  - Less disease burden (less immunosuppression)

- Understanding the **underlying immune mechanisms** of successful neoadjuvant immunotherapy is key to enhance patient selection
  - Antitumor immunity impacted by immune cells in the TME
  - Landmark studies demonstrate the importance of TLS and B cells to ICB response

Presence of tertiary lymphoid structures (TLS) correlated with improved CCA prognosis

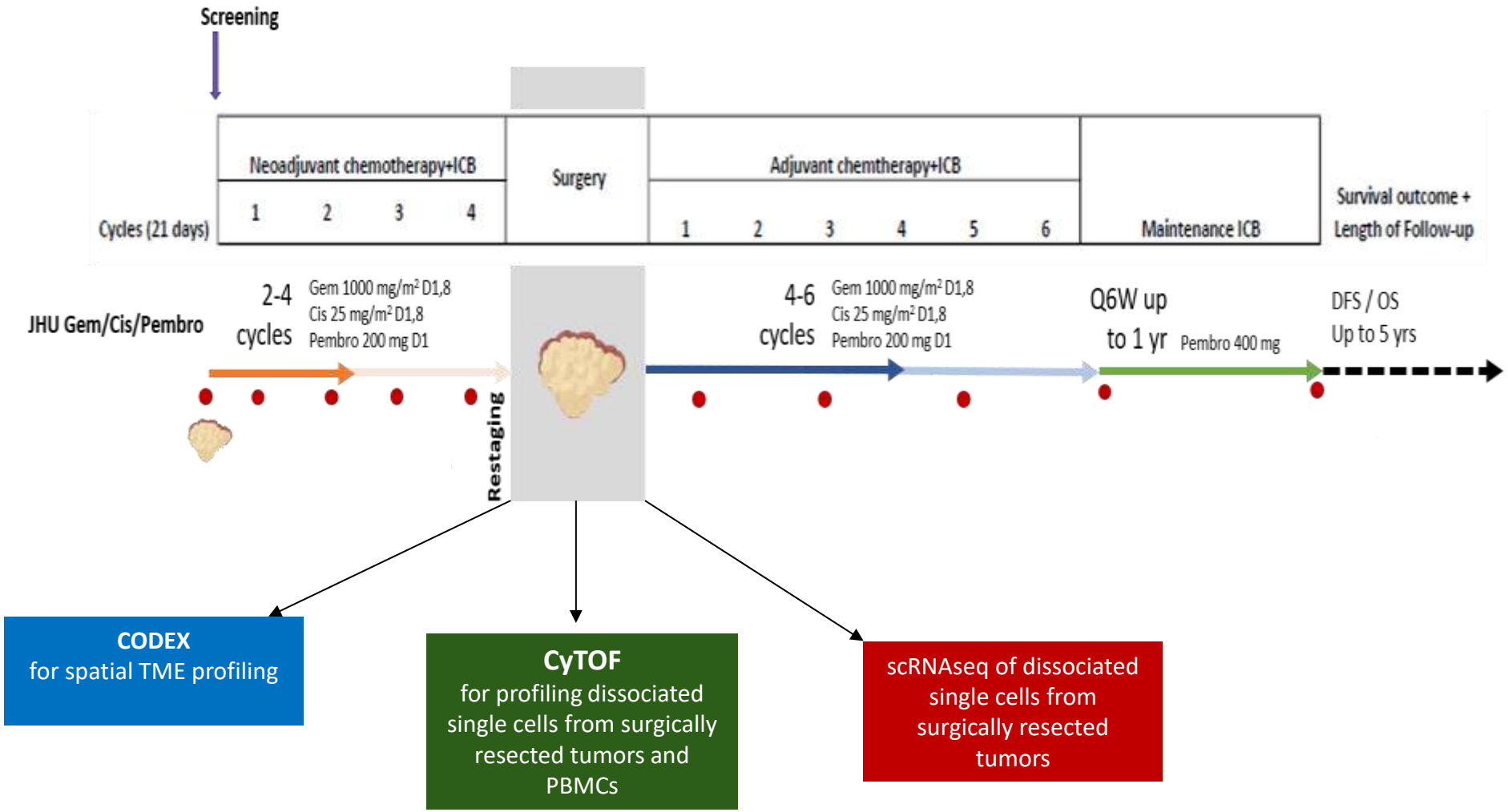




Ho W et al. Nature Cancer 2021: Zhang et al, Cancers (Basel) 2022

Study of perioperative gem/cis/pembro in resectable CCA to investigate mechanisms of response and immune resistance

ClinicalTrials.gov Identifier: NCT06001658




Laura Courtright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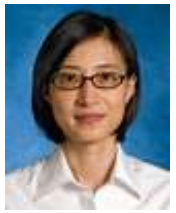
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Translational connection between genomics and clinical care

- ❑ Genomic studies have highlighted the molecular heterogeneity of BTCs

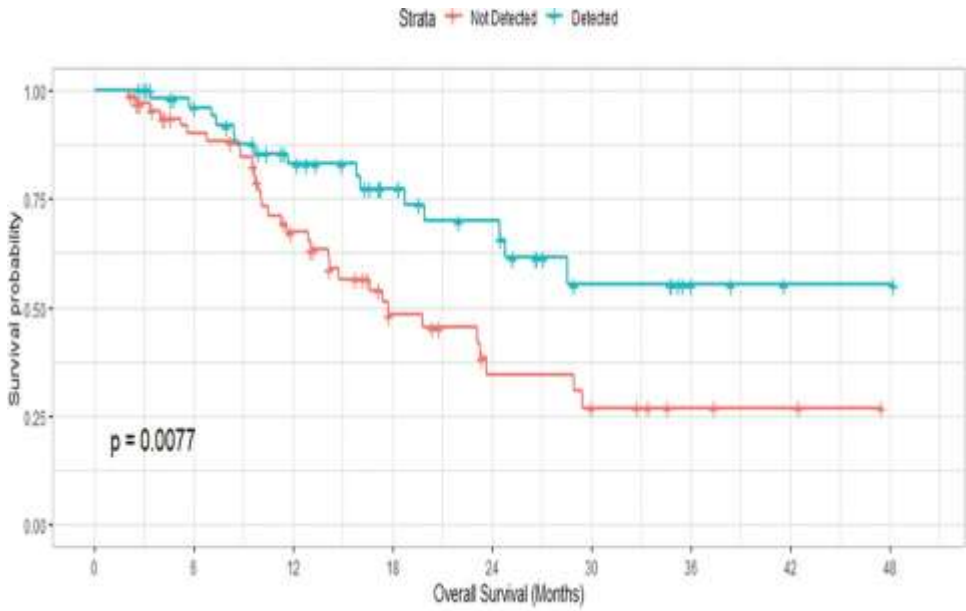
- ❑ Up to 40% of patients with CCA harbor genomic alterations for which molecularly targeted therapies are available.

- ❑ Improved survival and Higher Response rate

❖ FGFR2 fusion/rearrangement
  Pemigatinib ORR 35.5%
  Futibatinib ORR 43%

❖ HER2 amplification
  Zanidatamab ORR 41.3%

❖ BRAF V600E
  Dabrafenib/trametinib ORR %51



For patients with nonmetastatic CCA the detection of an actionable molecular alteration was associated with improved OS

Kendre G et al., Journal of Hepatology 2023; Abou-alfa G et al., Lancet oncol; Goyal L et al NEJM 2023; Harding et al. Lancet oncol 2024; Purchla et al. . J Am Coll Surg 2024

Complexities/Area of Research

- The search for a better way to manage CCA patients has revealed important avenues of investigation; however, this **disease remains difficult to manage**
  - Higher their tendency for intrahepatic spread & distant metastasis
  - Need to optimize treatment in patients at high risk of both local & distant failure

- **Optimal use and sequencing of therapies** (stage, patient population, and combinations) are still unknown
  - Need for larger, prospective studies for this niche patient group
  - We must refine patient selection—who truly benefits?
  - Integrating molecular profiling could enhance response prediction and patient selection
  - Novel approaches like immunotherapy warrant exploration, and ongoing trials will be very informative

- Moving forward, a precision medicine approach—leveraging genomics, immune profiling, and multidisciplinary expertise—will be key to optimizing neoadjuvant strategies in cholangiocarcinoma.

Thank you!

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A role for neoadjuvant radiation therapy for potentially resectable cholangiocarinoma

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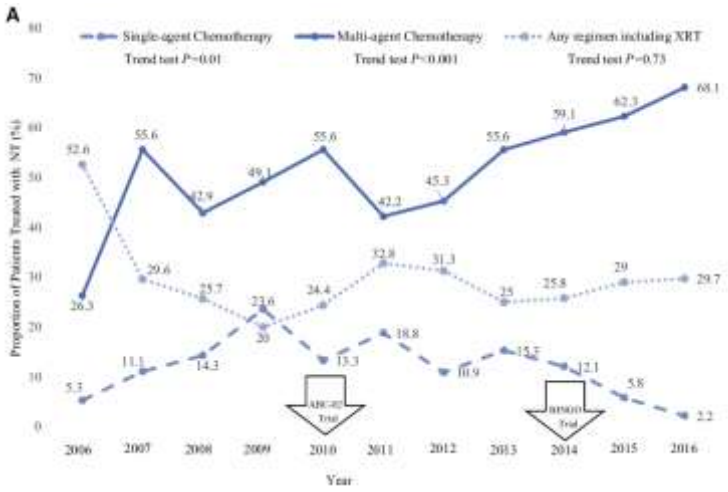
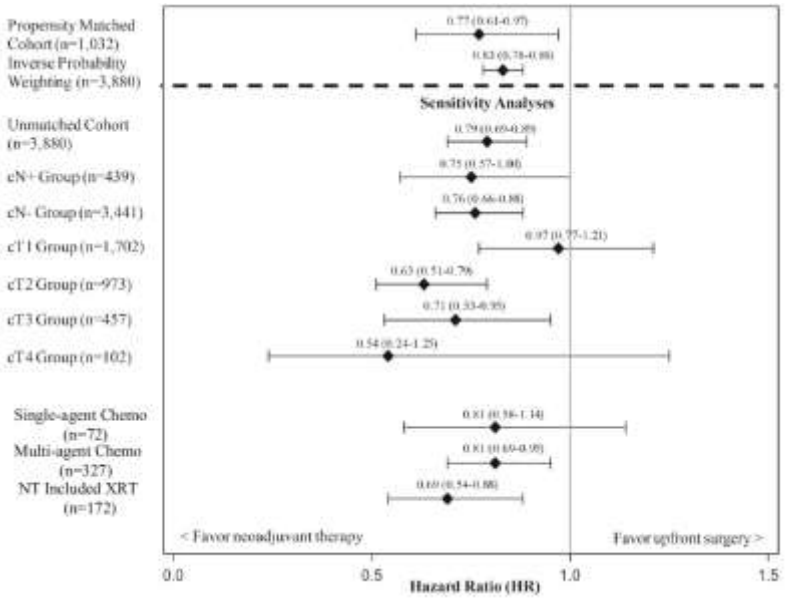
Neoadjuvant therapy (NT) for resected intrahepatic cholangiocarcinoma (IHC)





- NCDB retrospective analysis 2006-2016 of 4456 IHC who underwent resection
- 14% received NT
  - 30% NT includes radiation therapy
- NT associated with advanced T and N stage
- 46% had no lymph nodes removed
- After propensity matching NT with agent chemotherapy or RT associated with decreased risk of death (HR 0.81 [0.69-0.95], HR 0.69 [0.54-0.88], respectively)

Mason. Ann Surg Onc. 2021

Neoadjuvant therapy (NT) for resected extrahepatic cholangiocarcinoma

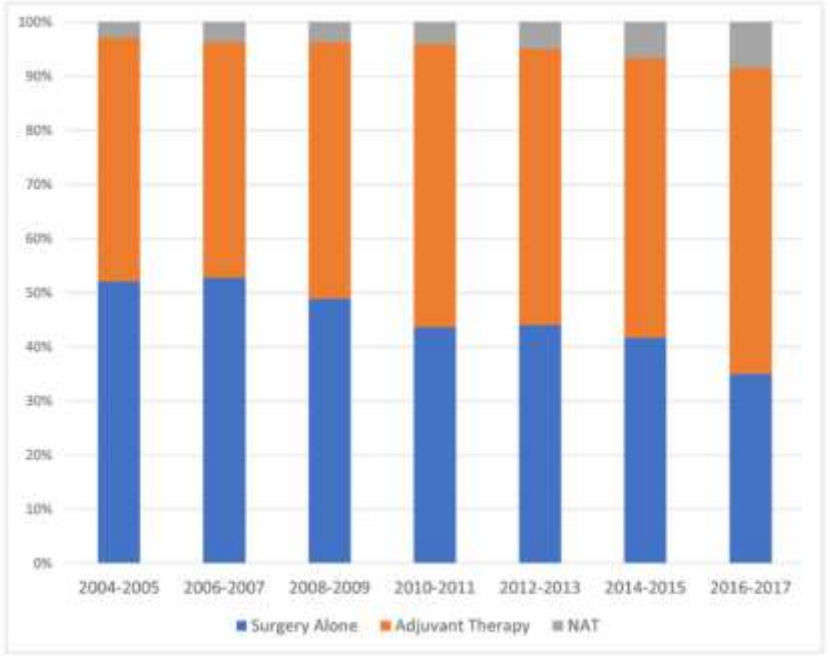
NCDB 2004-2017, 8040 patients, excluding distal duct cancers, underwent resection

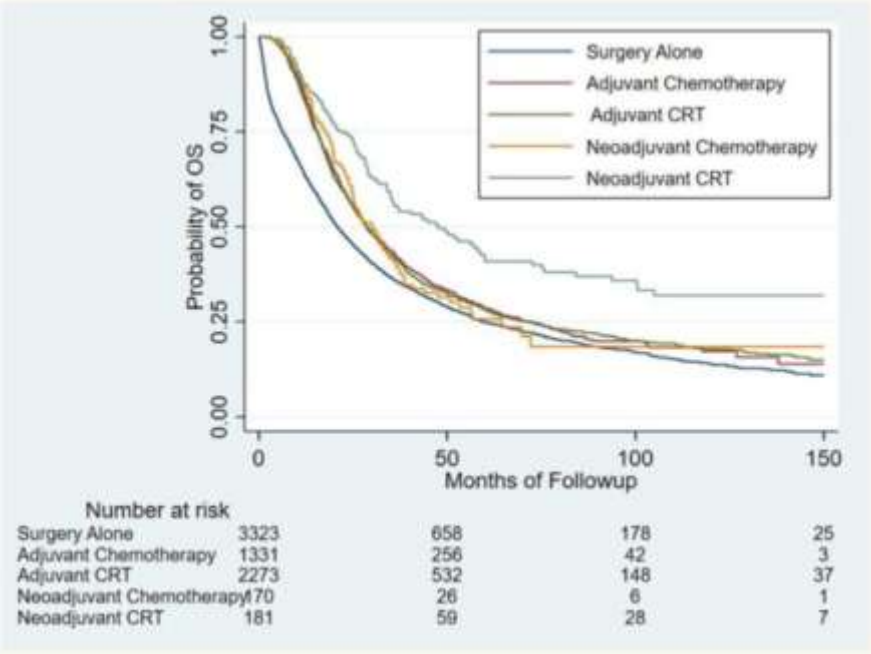
5% underwent neoadjuvant

49% received chemoradiation

Neoadjuvant CRT was associated with improvement in R0 resection (OR 3.52, <0.001) and median survival (47.8 vs. 25.3 months, log-rank < 0.001) compared to surgery first

Neoadjuvant CT was not associated with outcomes





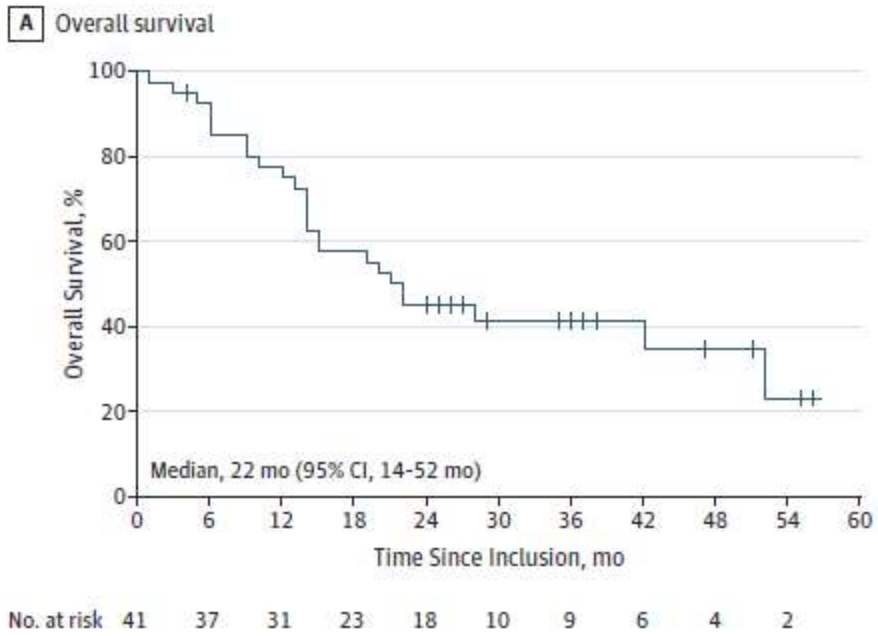
Silver. Ann Surg Onc. 2021

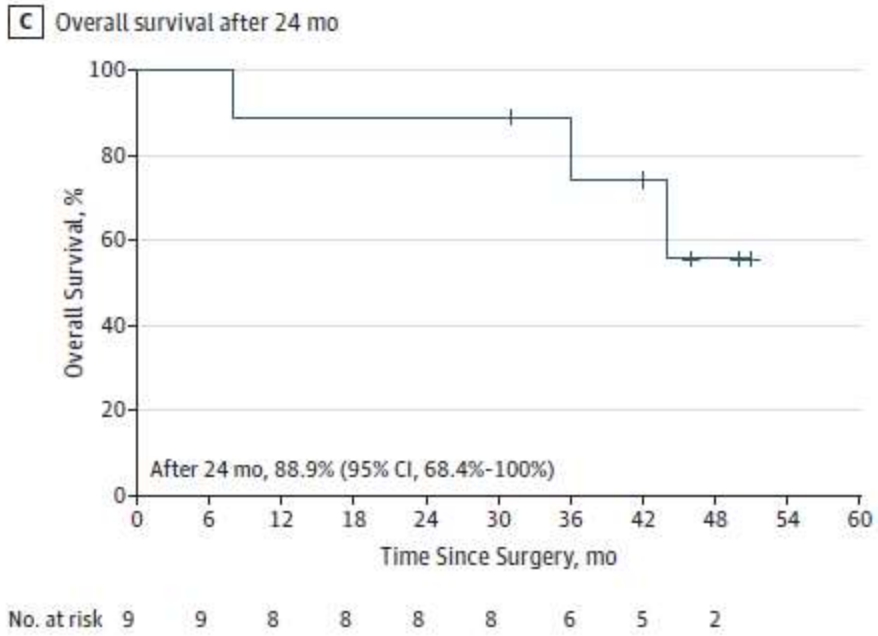
Retrospective series of Resection after radiation therapy for initially unresectable or “downstaging” IHC/EHC

Series	N	Treatment	% Resection	Outcome
Sumiyoshi. W J Surg. 2018	15 IHC/EHC	50 Gy and S-1	73% (11/15)	Median OS for resected: 37 months 82% R0 rate
Cloyd. Am J Surg. 2018	21Distal cholangiocarcinoma	Chemoradiation (n=16) or chemotherapy alone (n=5)	N/A	Median OS 40.3 months
Sarwar. J Vasc Int Radiol. 2021	31 IHC	Chemotherapy +Y-90	35% (11/31) 52% NT cohort (11/21)	Median OS: 22 months 73% R0 rate
Rayar et al. Ann Surg Oncol. 2015	45 IHC	Y-90 + chemotherapy	18% (8/45) 80% (8/10 downstaged)	Median DFS: 19.1 months 100% R0 rate
Adamus. JHEP. 2025	88 IHC	Y90 + gemcitabine and platinum chemotherapy	18.7% (16/88)	Median OS: 22.5 months

Phase 2 of Yt-90 and chemotherapy for unresectable IHC (MISPHEC)

- 41 patients with unresectable, recurrent, liver only IHC enrolled, <50% tumor burden enrolled on multi-institutional phase 2
- Cisplatin, 25 mg/m2, and gemcitabine, 1000 mg/m2, on days 1 and 8 of a 21-day cycle for 8 cycles. Selective internal radiotherapy was administered during cycle 1 (1 hemiliver disease) or cycles 1 and 3 (disease involving both hemilivers)
- Primary endpoint was response rate at 3 months by RECIST: 39%
- Median follow up 36 months, median overall survival was 22 months
- 9 of 41 patients (22%) underwent resection
  - 8 of 9 had R0 resection
  - 24-month PFS: 67%





Edeline. JAMA Oncol. 2019

Summary

- While upfront surgery remains the standard of care for resectable IHC and EHC, patients with unfavorable anatomy, aggressive biology, or advanced disease should be consider for NT
- For patients with risk factors for locoregional recurrence, neoadjuvant external beam can be considered on case-by-case basis for EHC based on extrapolation of other paradigms
- Yt-90 selective internal radiation therapy is an emerging option for incorporation into systemic therapy for locally advanced IHC

THANK YOU!