Oligometastatic PDAC
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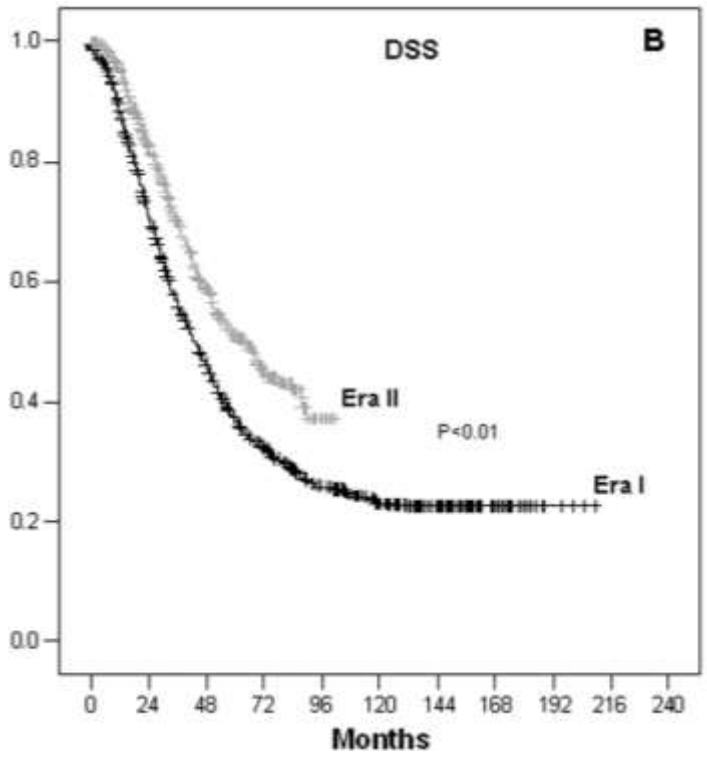
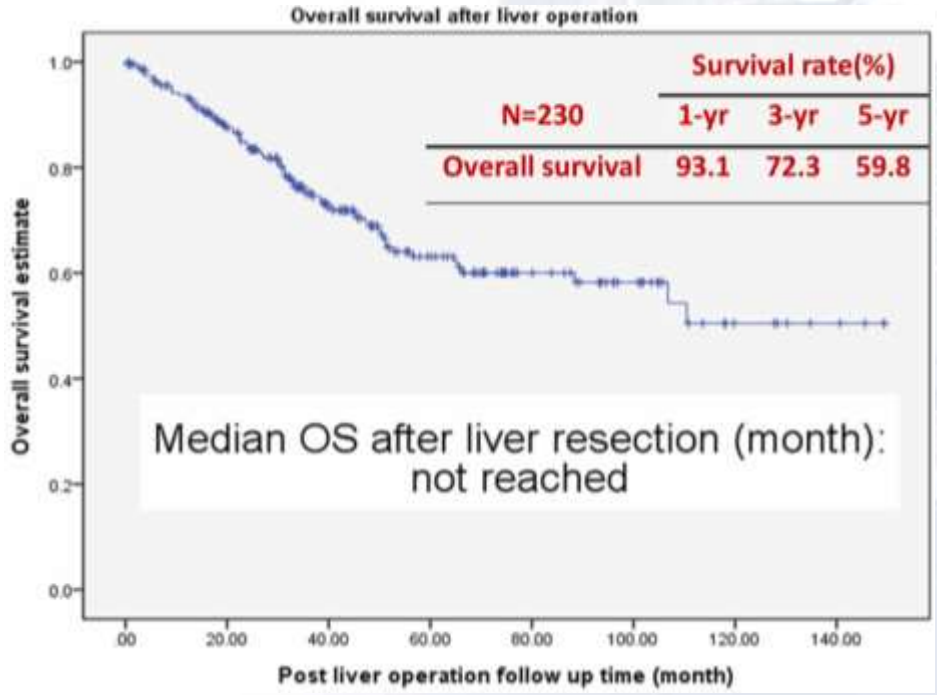
Lessons learned from colorectal cancer

- Modern survival curve for liver-only metastatic colon cancer
- Seed and soil theory of liver metastasis – biology!





House et al. JACS 2010; Hsu et al. JOGS 2024

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Lessons learned from colorectal cancer

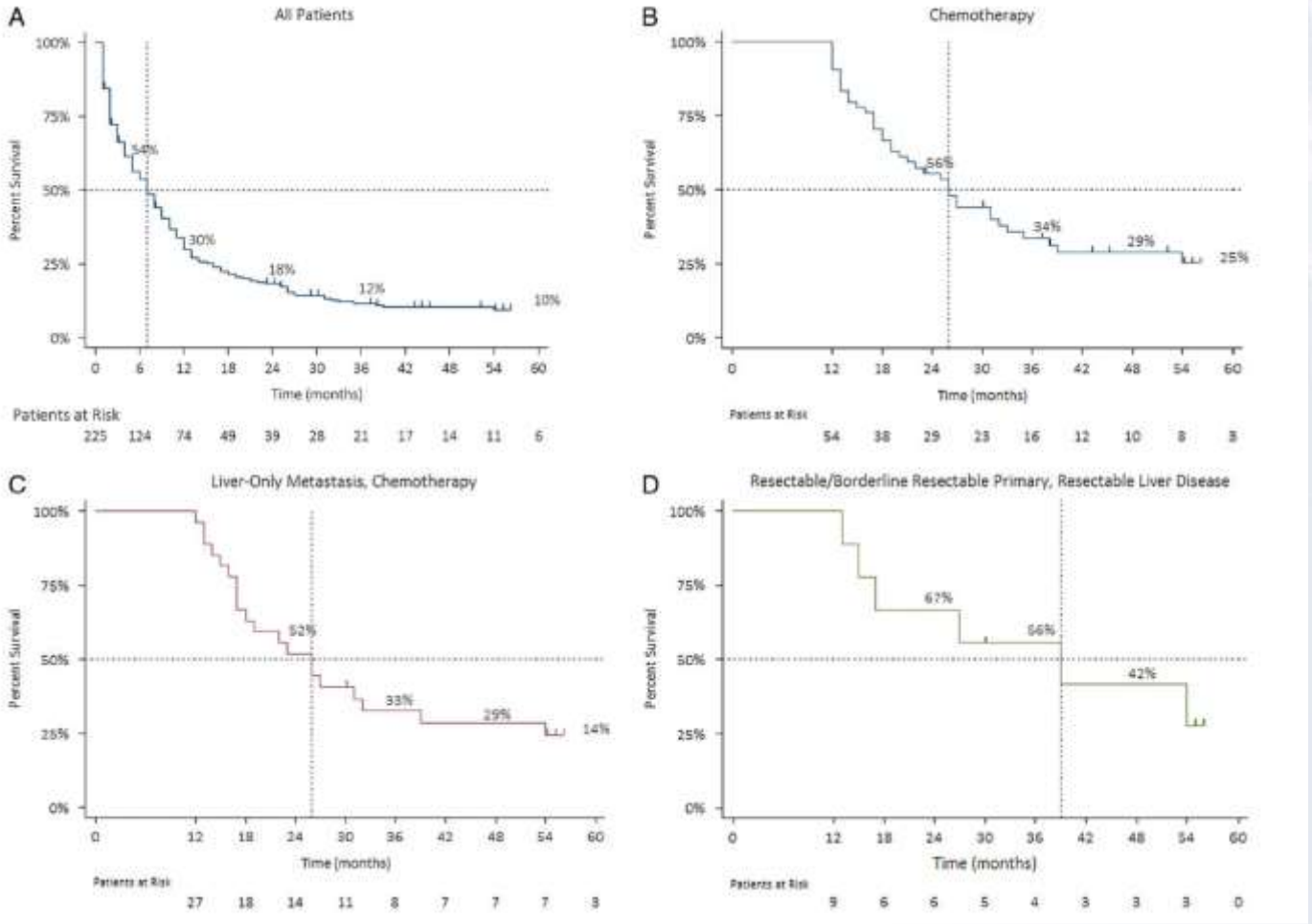
- Identifying the right patient group/selecting out those who don't benefit → working in a multidisciplinary fashion

- Modern experience in this disease justifies utilization of advanced surgical and liver-directed techniques
  - Liver resection
  - ALPPS
  - Hepatic Arterial Infusion Pump
  - Liver Transplantation

- Positive Prognostic Signs:
  - Low tumor burden limited to liver
  - Long disease-free/disease-stable interval
  - Good response to systemic therapies

- Negative Predictors:
  - Tumor location (Right side worse)
  - Undifferentiated or Signet Cell Histopathology
  - Mutation profile: mBRAF, mRAS/mTP53
  - Disease progression on systemic treatment
  - Dominant cancer symptoms (loss of appetite and fatigue)

Where are we now in pancreas cancer?



Kaslow et al. Ann Surg 2023

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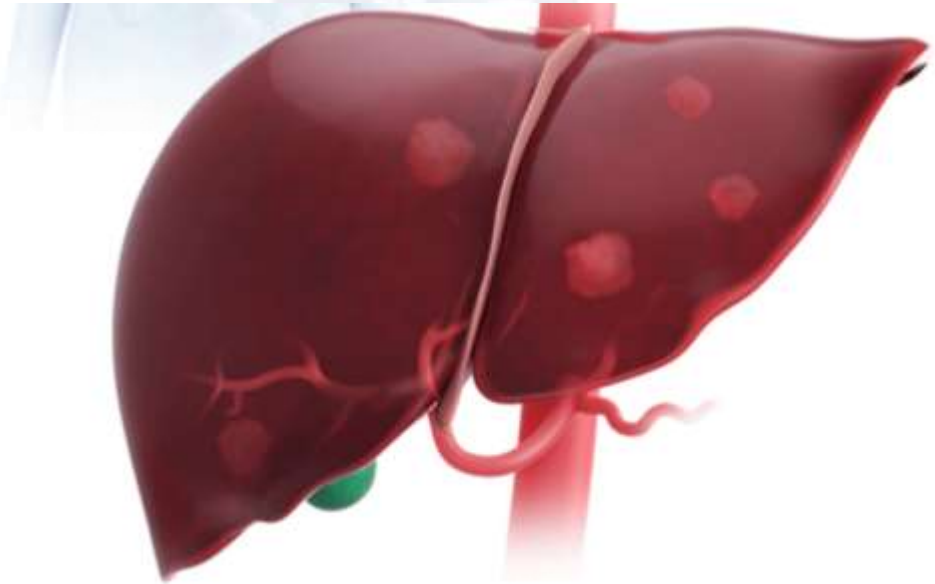
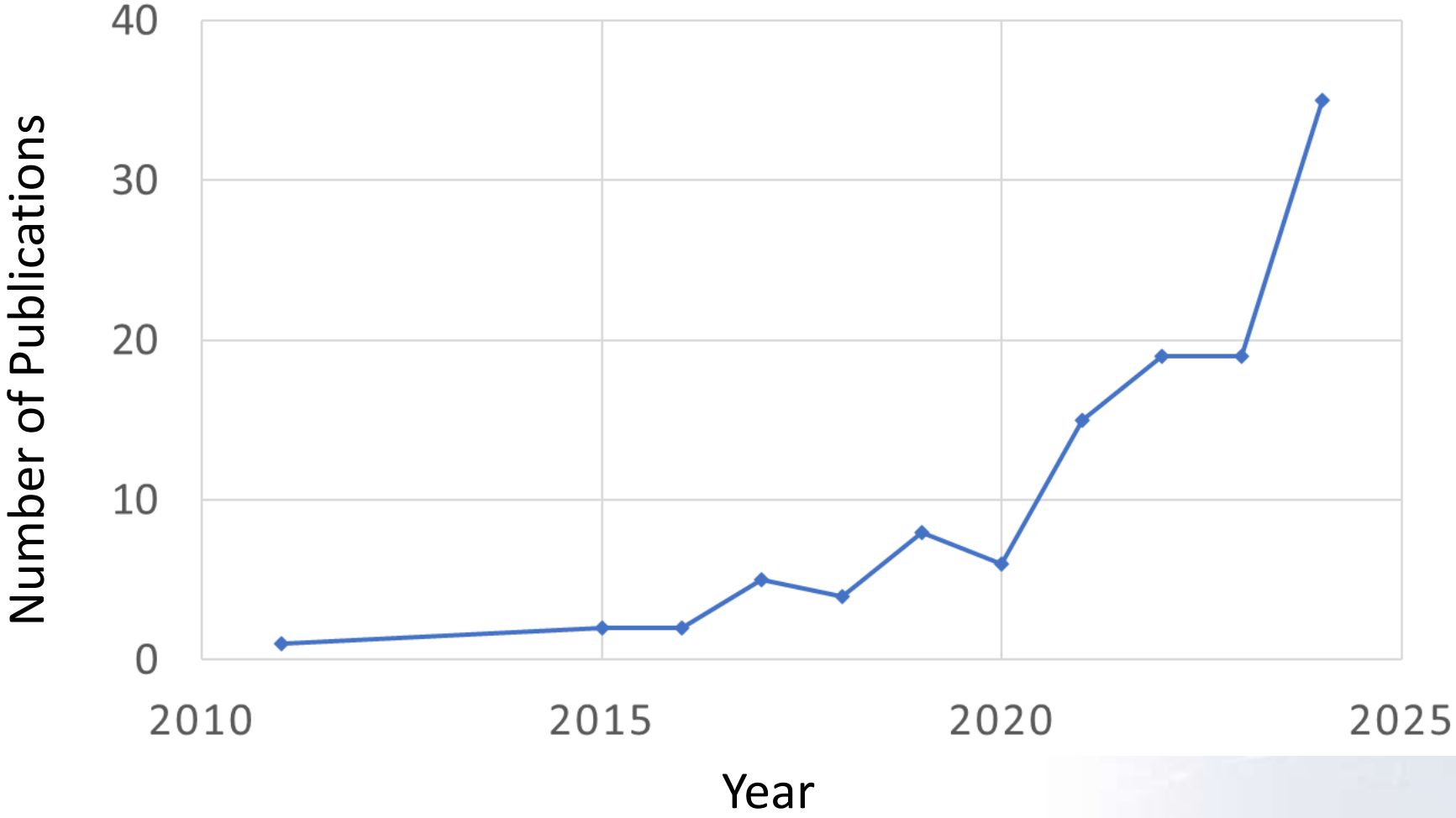
Defining Oligometastasis in PDAC

- There is significant variation in practitioner impression:
  - Is this defined by a combination of number and size of lesions?
  - Is this defined by the capacity to effectively treat all lesions?
  - Is this defined by anatomic considerations and capacity to resect?
- How should biology and treatment response play a role in this definition?
- Answers to these questions remains elusive.



Pubmed:
Resection in Oligometastatic Pancreatic cancer



Pubmed.gov: Accessed January 2025

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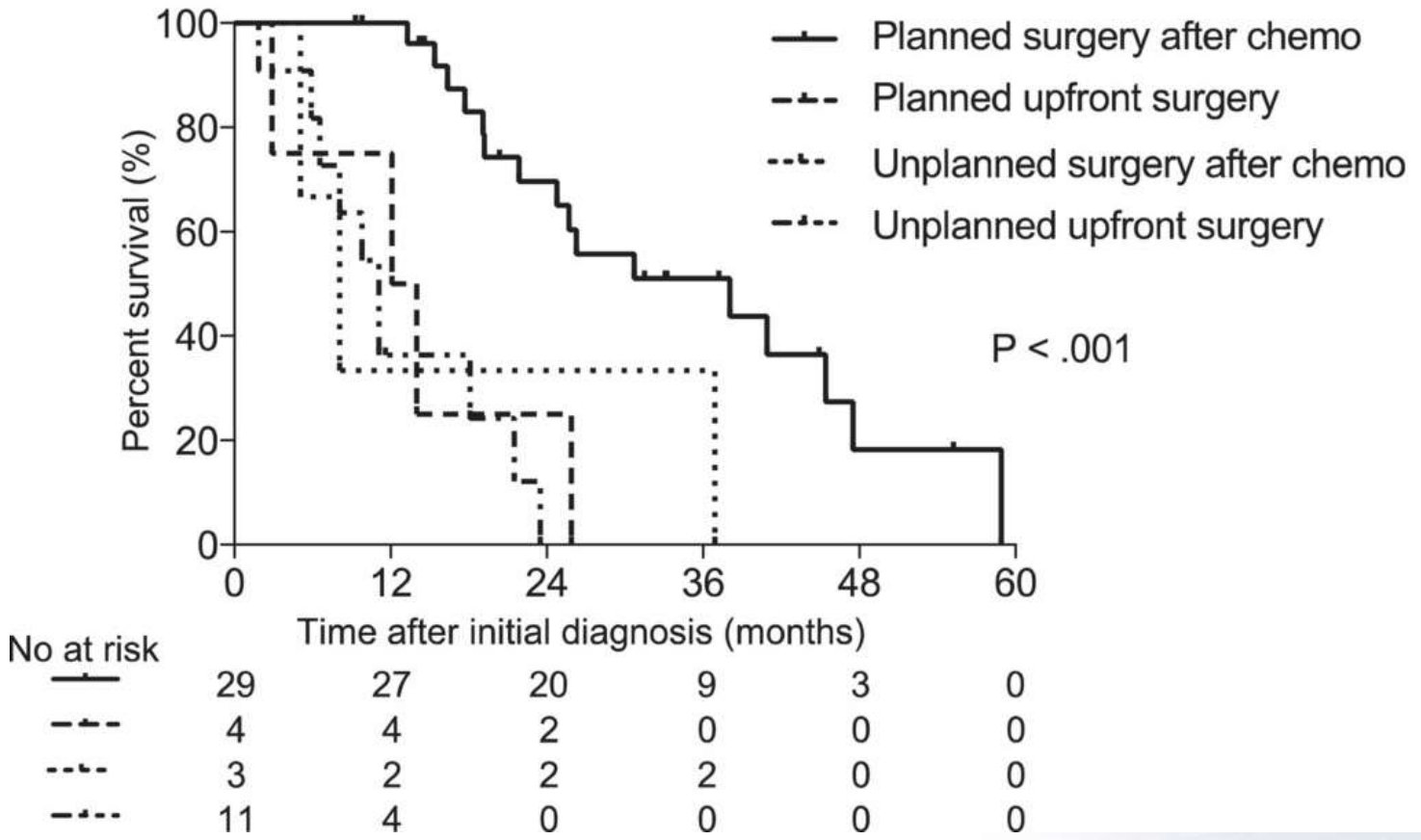
Single-center experiences



Nagai et al. J HPB Sci. 2023

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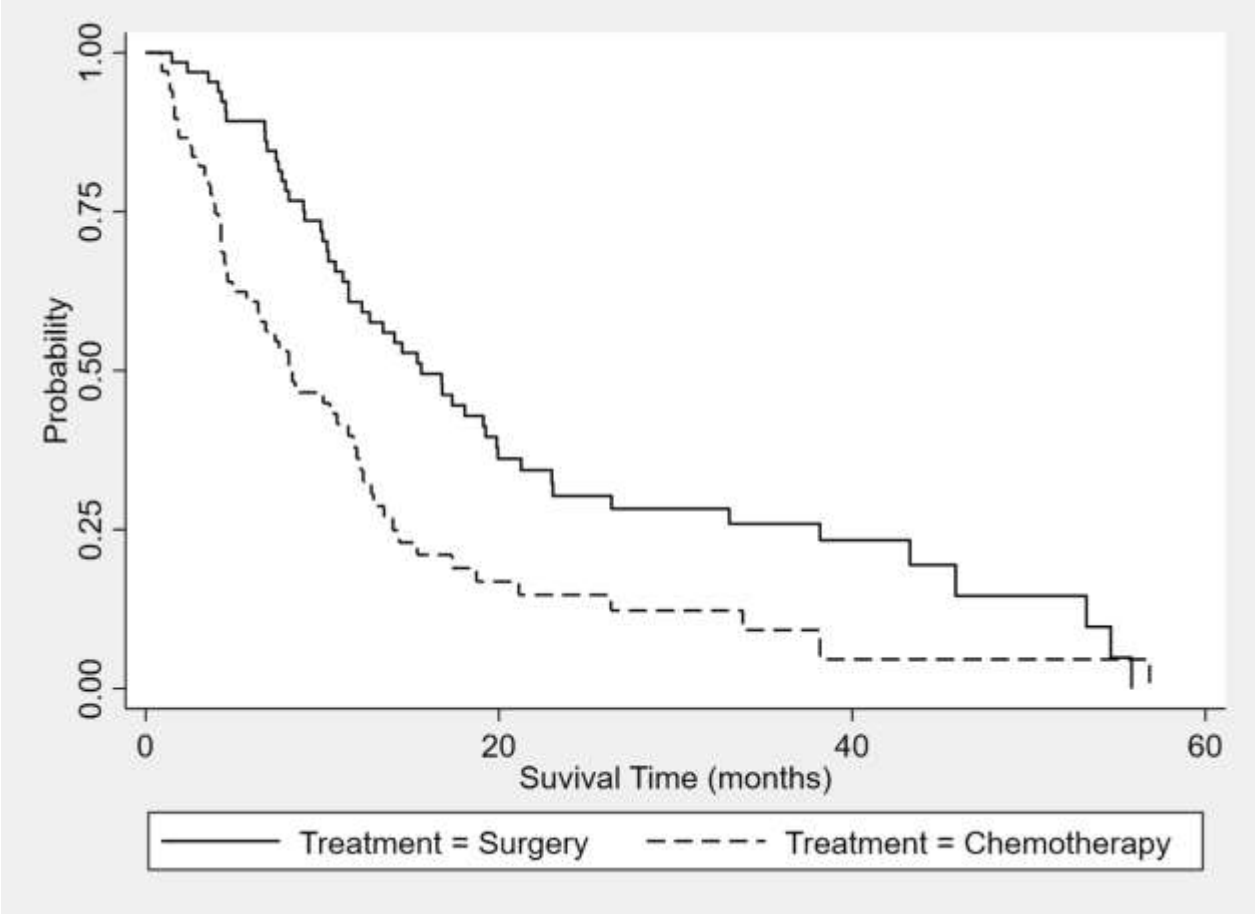
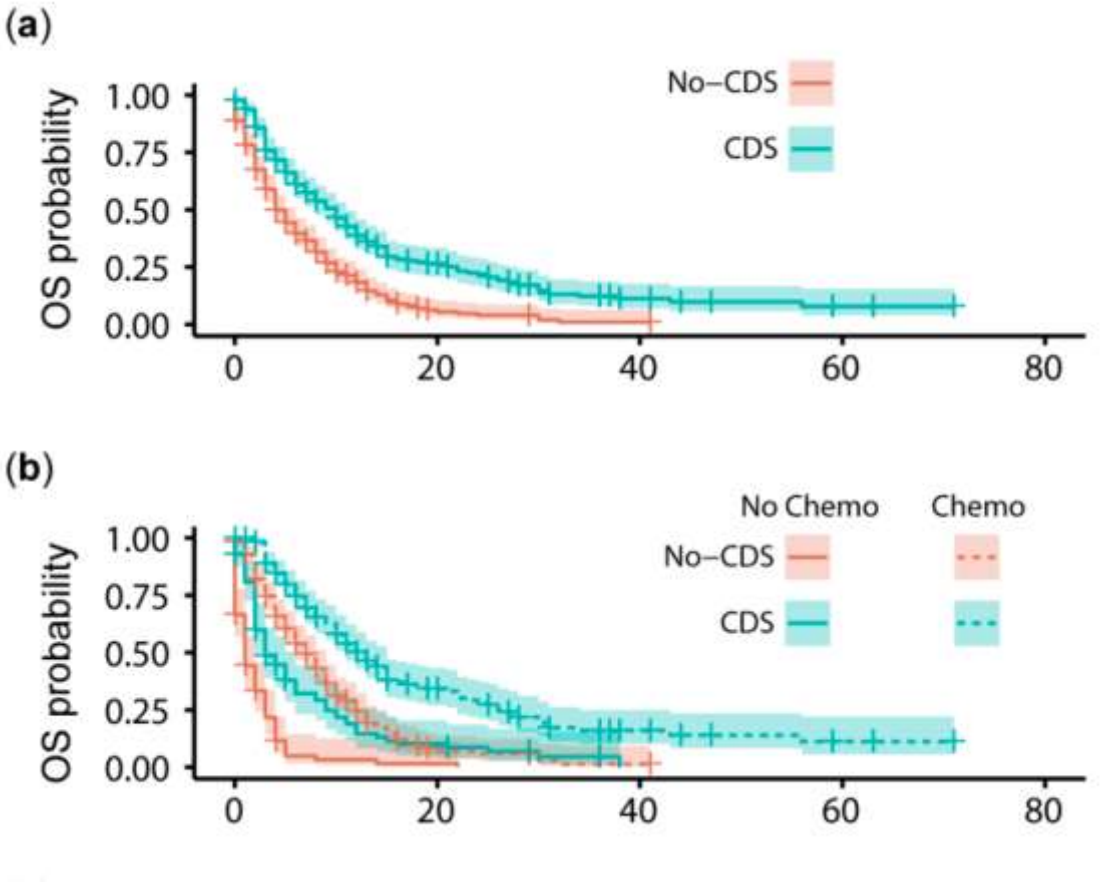
Evaluating the National Cancer Database and SEER





Hamad et al. Surgery 2022; Pausch et al. Cancers 2022

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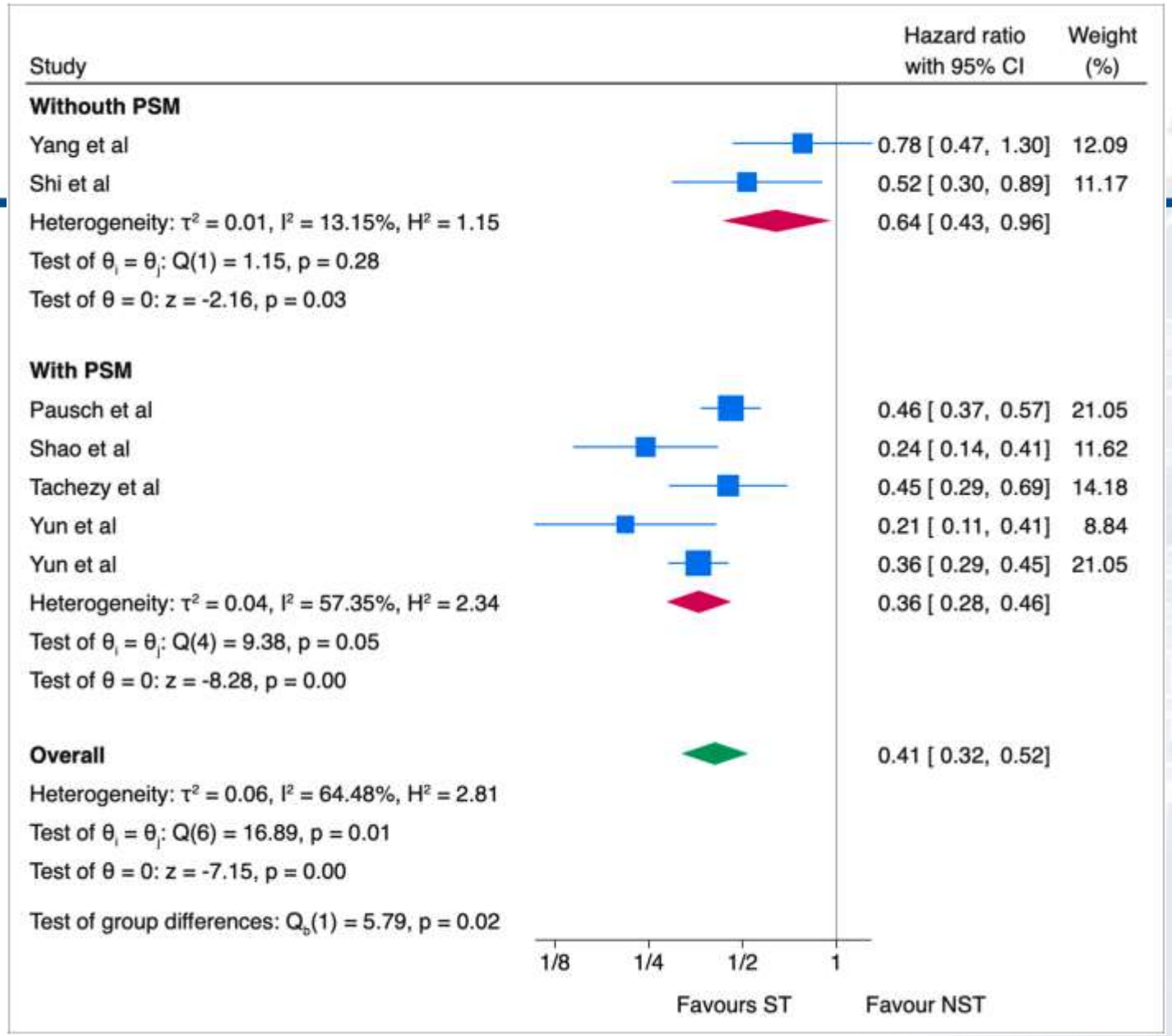

D'Ambra et al. Eur J Surg Onc. 2025

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Re-examining lessons learned in CRC – and applying these lessons in PDAC

- Long disease free and disease stable intervals can partially define disease biology and portend favorable outcomes.
- The capacity of systemic therapies to control disseminated disease appears paramount for defining the group that may benefit from aggressive surgical therapy.
- Both histopathologic factors (nodal status) and molecular diagnostics (sequencing) will play a further role in patient selection in the near future.

- There are, at least, two ongoing prospective trials evaluating surgical resection as a prospectively-selected treatment strategy for patients presenting with hepatic oligometastatic pancreatic cancer.

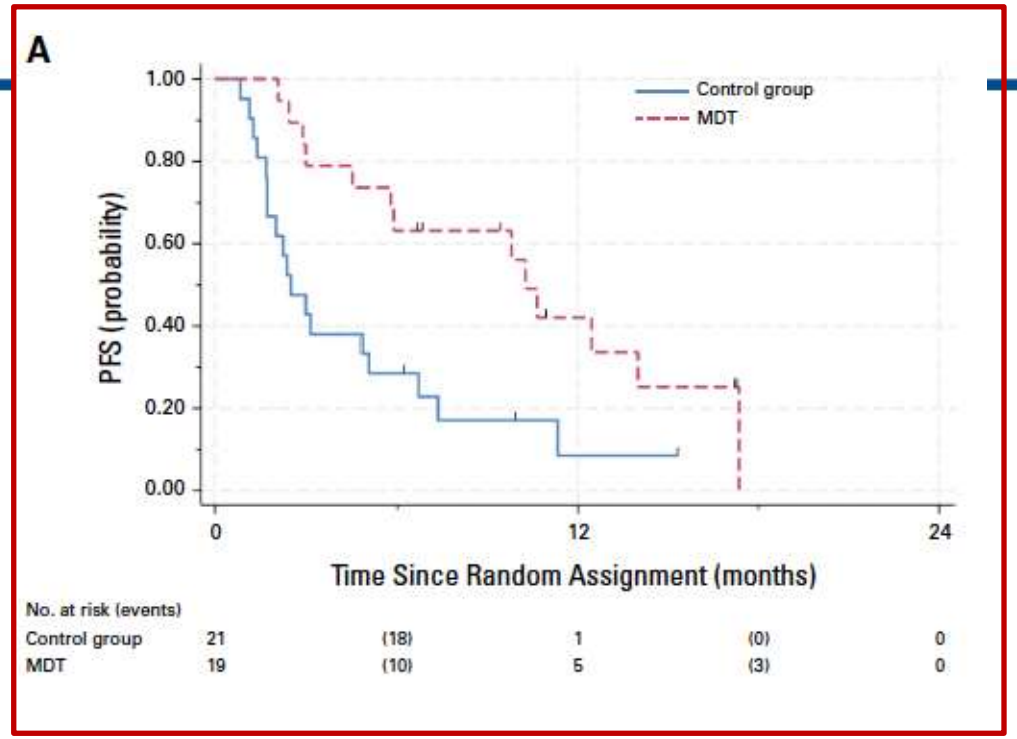
Multi-agent chemotherapy has led to improved systemic and local control

- Multi-agent chemotherapy has increased OS in the metastatic setting.
  - mFOLFIRINOX: Median OS 11.1 mo (PRODIGE)
  - Gem/nab-paclitaxel: Median OS 8.5 mo (MPACT)
  - NALIRIFOX: Median OS 11.1 mo (NAPOLI-1)

- Multi-agent chemotherapy has converted previously unresectable disease into resectable disease.
  - Borderline resectable data: Katz *et al*, JAMA Surgery 2016, Murphy *et al*, JAMA Oncol 2018.

But 60-70% recur even after chemo even with localized disease -> better systemic therapies will be required to treat oligometastatic disease

Benefits of Multi-Modal Approach: EXTEND TRIAL (EXTernal beam radiation to Eliminate Nominal Metastatic Disease)



Stage IV PDAC
≤ 5 mets
RT per Investigator
N= 41 (55)

RANDOMIZE

SOC+Metastasis Directed Therapy
N= 20

SOC
N= 21

Stratify: Mets 1-2 vs 3-5; Lines of therapy 0-1 vs ≥ 2; Ca 19-9 <90 vs ≥ 90
Primary endpoint: median PFS (~N= 40; HR 0.47)
Secondary endpoint: median OS

- Multi-center, randomized Ph II trial combining MDT (metastases-directed therapy) to SOC systemic therapy
- ≤ 5 Mets, RT per investigator -> 20 SOC + MDT, 21 SOC – most had 1-2 metastatic sites
- Improvement in PFS 10.3 months (95% CI, 4.6 to 14.0) in the MDT+SOC arm vs 2.5 months (95% CI, 1.7 to 5.1) in SOC arm
- CD8 T cell activation was only seen in MDT + SOC Arm and correlated with improved PFS. Potential for systemic effect beyond local disease control through release of neoantigens.

Ludmir *et al*, JCO 2024

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But deeper, more robust, and durable responses are needed to extend this benefit

Current SOC

Chemotherapy
FOLFIRINOX
Gem/nab-paclitaxel
NALIRIFOX

Systemic therapies on the horizon

New biomarker-directed therapies
RAS inhibitors beyond G12C

Vaccines/Immunotherapy
Antigen-targeted vaccines
KRAS vaccines
Checkpoint antagonists
Checkpoint agonists
TME Remodulating agents

Best combinations, sequencing, and synergies?

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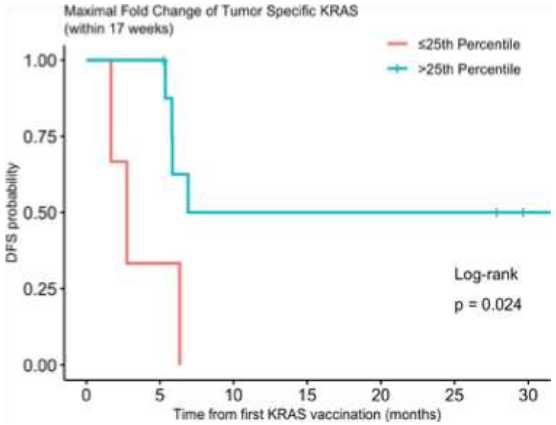
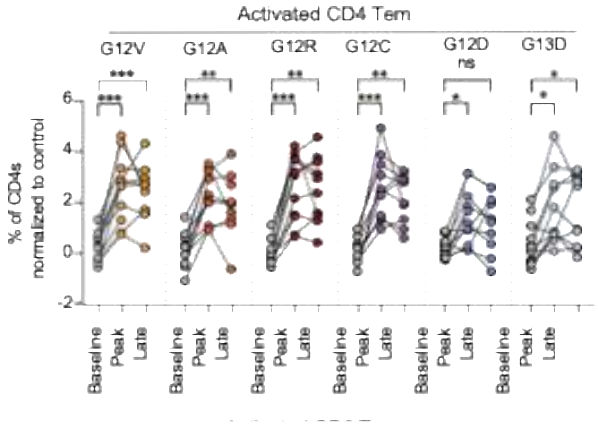
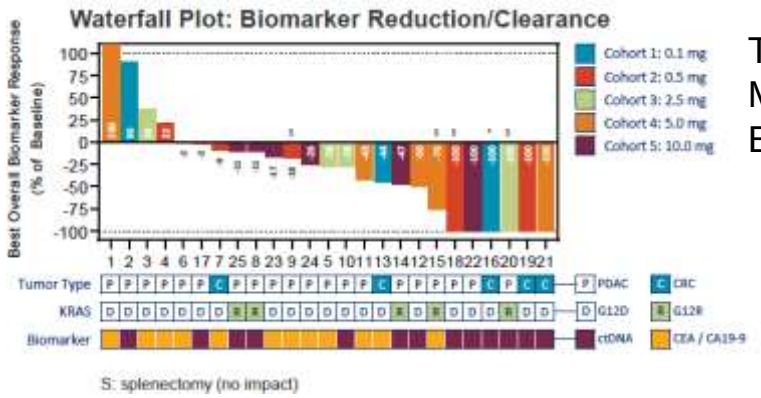
Systemic control after localized treatment: Minimally Residual Disease (MRD)

Oncogene (mKRAS) vaccines

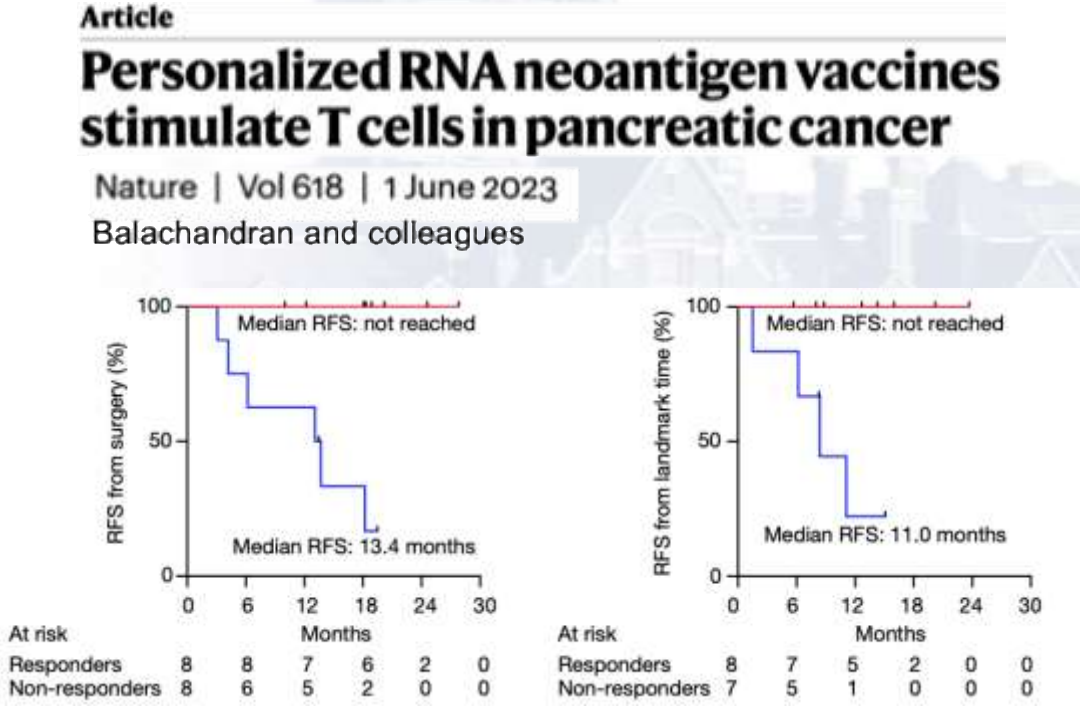






Top panel: Huff *et al,* AACR 2023, Manuscript under review
Bottom panel: Pant *et al,* Nat Med 2024

Personalized vaccines



Induction of immunologic memory

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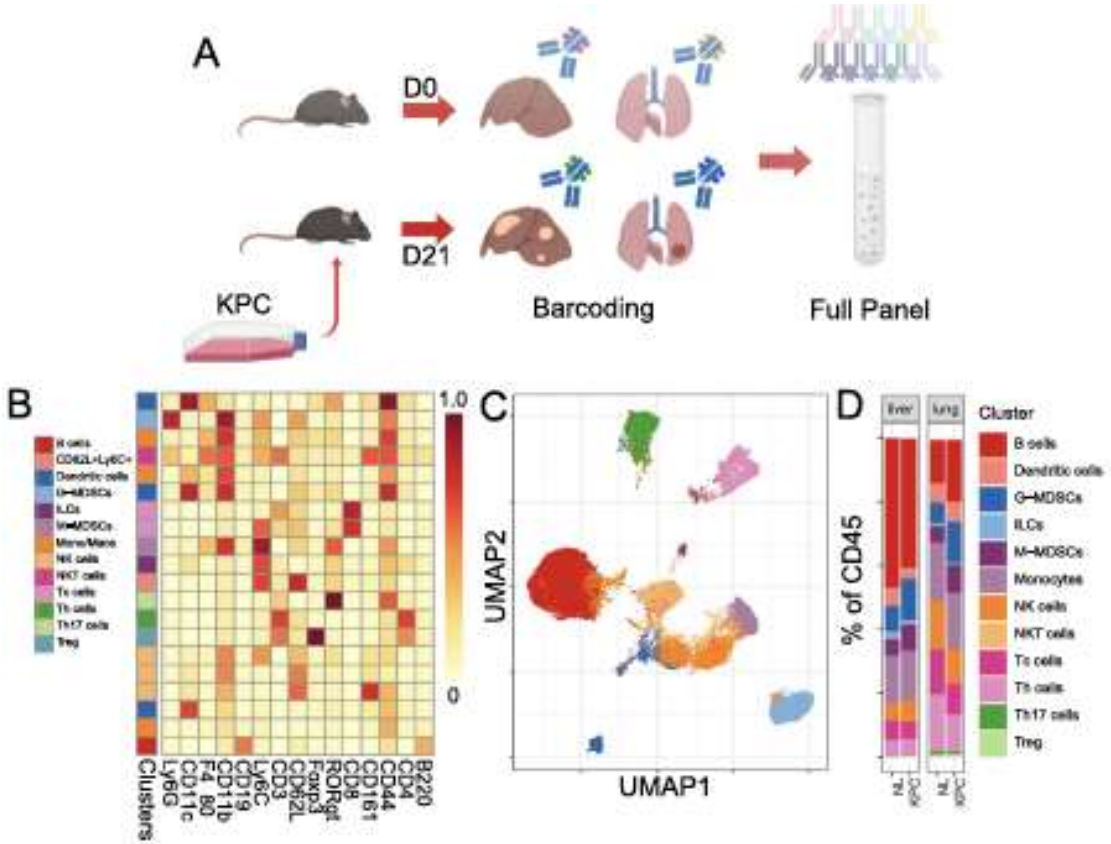
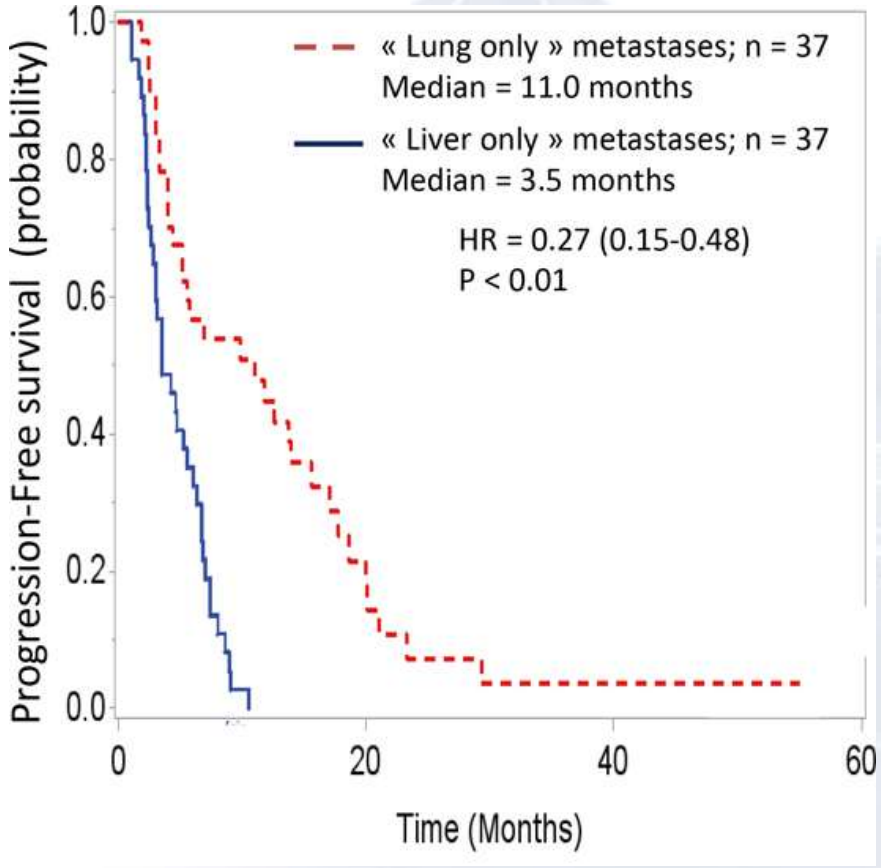
Liver metastases have distinct tumor microenvironments and may respond to novel therapies differently

PDAC murine model comparing liver vs lung mets



Ho *et al.*, Genome Medicine 2021.



Decoster *et al.*, Oncotarget 2016.

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Is curative intent multi-modal treatment for oligometastatic PDAC really a reality?

- Thus far, there have been some reports of locoregional therapy may result in favorable outcomes for highly selected cases with further prospective trials ongoing

- Improved systemic control will be required beyond current standard-of-care chemotherapy to extend meaningful benefit to oligometastatic disease
  - Biomarker directed therapy may offer improved systemic control
  - Vaccines in MRD/low burden disease setting shows early promise

- Liver metastasis portend a worse prognosis and have a distinct tumor microenvironment that may respond to treatment differently.
  - Clinical trials will need to assess on treatment biopsies of liver mets

How will we get there?

Better upfront systemic control

- Patient selection
  - Low tumor burden limited to liver
  - Long disease-free/stable-disease interval
  - Good response to systemic therapies
- Biomarker driven agents may improve systemic control
- Integration of RT for localized control may be synergistic

Integration of localized treatments (optimal timing and sequencing?)

MRD space to decrease recurrence rate

- Need for **durable** control
  - Oncogene targeted vaccines
  - Personalized vaccines

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Thank you!

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