Understand Tumor Response Heterogeneity in Colorectal Cancer:

Share the similarities, Celebrate the differences.

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Pfizer, Inc.

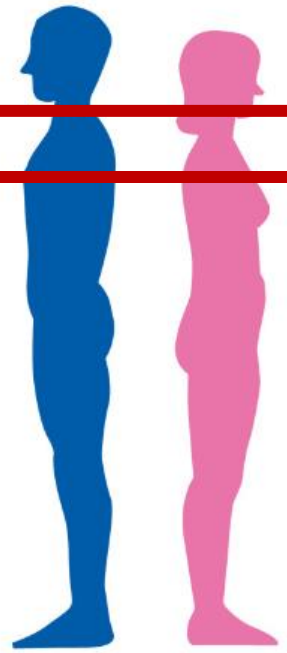
UNC ESHELMAN SCHOOL OF PHARMACY
Advancing medicine for life

Pfizer

Colorectal cancer: 3rd leading cause of cancer deaths

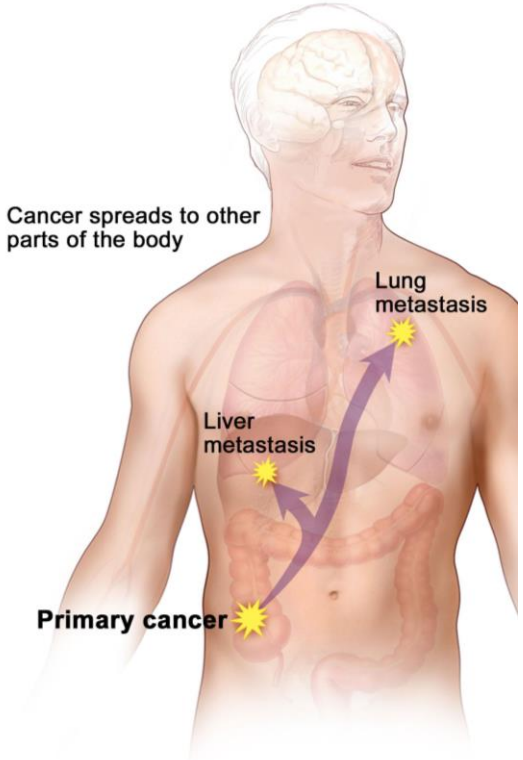
Estimated Deaths

Males				Females		
Lung & bronchus	67,160	21%		Lung & bronchus	59,910	21%
Prostate	34,700	11%		Breast	43,170	15%
Colon & rectum	28,470	9%		Colon & rectum	24,080	8%
Pancreas	26,620	8%		Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%		Ovary	13,270	5%
Leukemia	13,900	4%		Uterine corpus	13,030	5%
Esophagus	12,920	4%		Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%		Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%		Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%		Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**		**All Sites**	**287,740**	**100%**

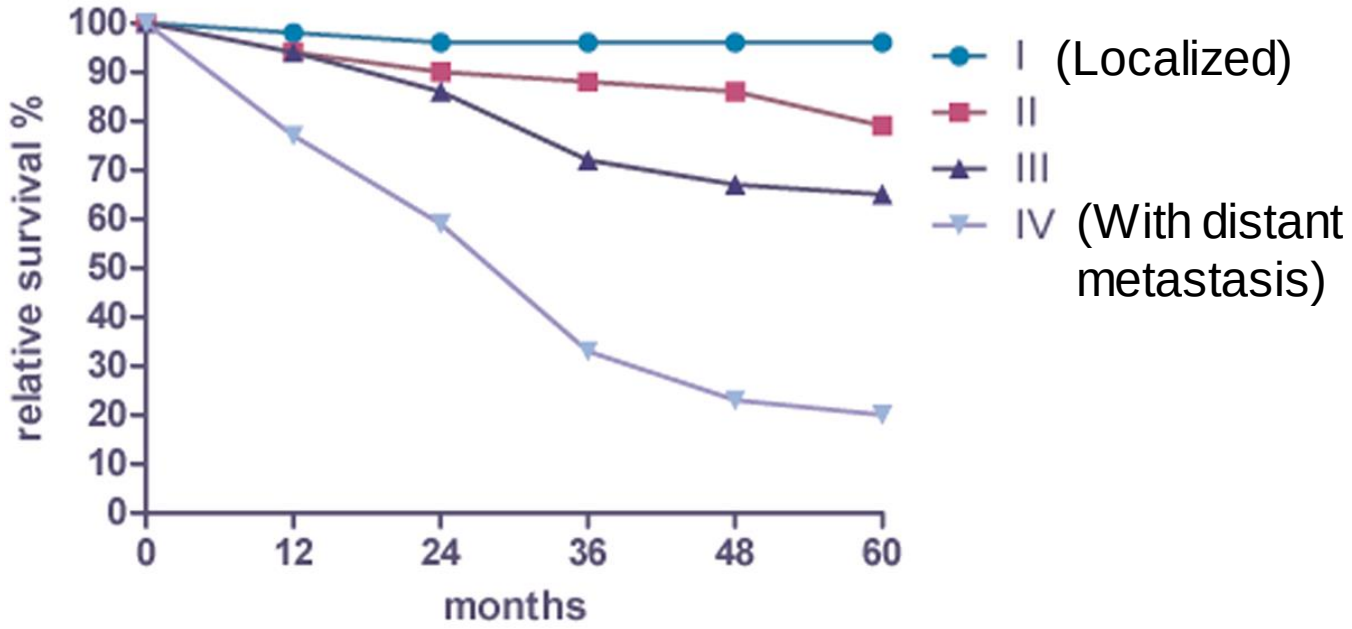


1. Siegel, Rebecca L., et al. "Cancer statistics, 2023." Ca Cancer J Clin 73.1 (2023): 17-48.

Metastasis is the leading cause of CRC mortality.



5-year survival rate for CRC by stage

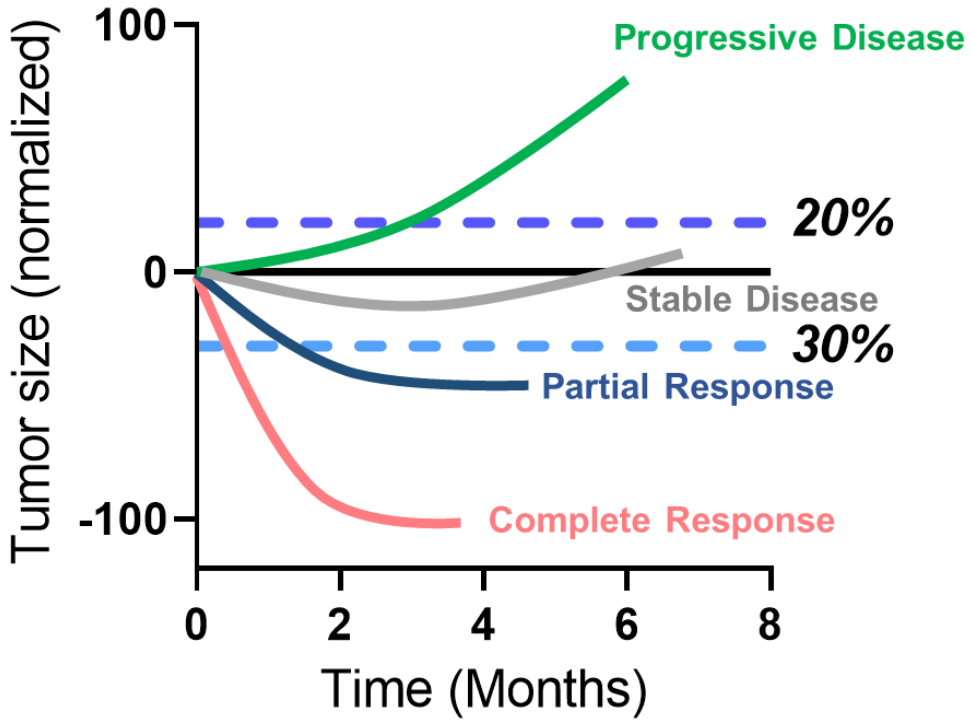


- More than **20%** CRC patients have distant metastasis at diagnosis.

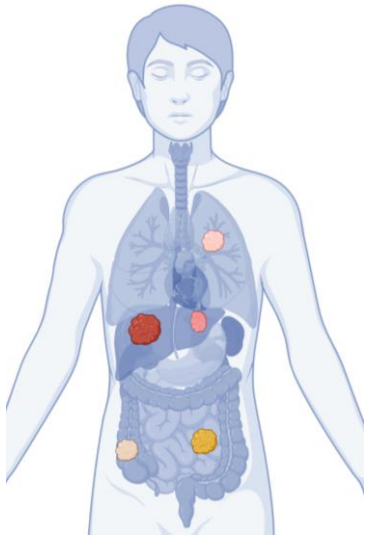
CRC: colorectal cancer

1. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/metastasis
2. Richter, Maximilian, et al. "German oncology certification system for colorectal cancer–relative survival rates of a single certified centre vs. national and international registry data." Innovative surgical sciences 6.2 (2021): 67-73.
3. Biller, Leah H., and Deborah Schrag. "Diagnosis and treatment of metastatic colorectal cancer: a review." Jama 325.7 (2021): 669-685.

RECIST: the criteria to evaluate treatment response.



RECIST: the sum of all target lesions



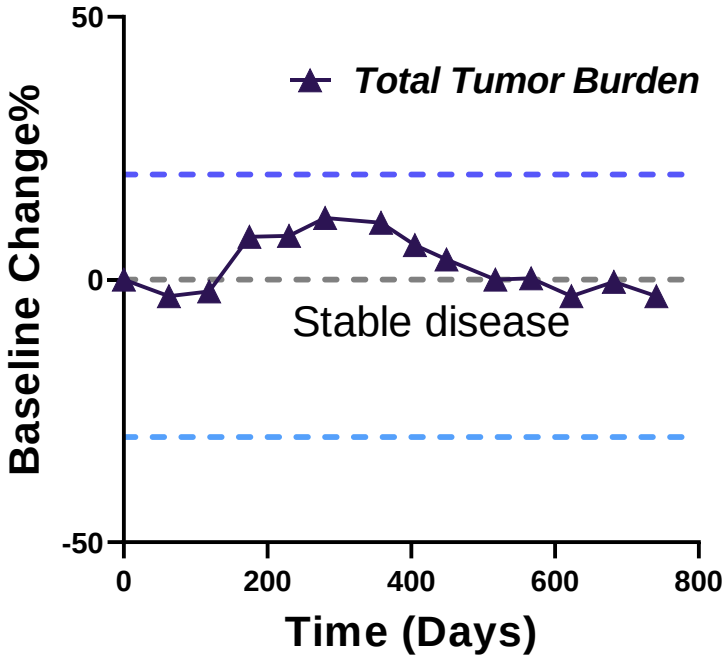
Created with BioRender.com

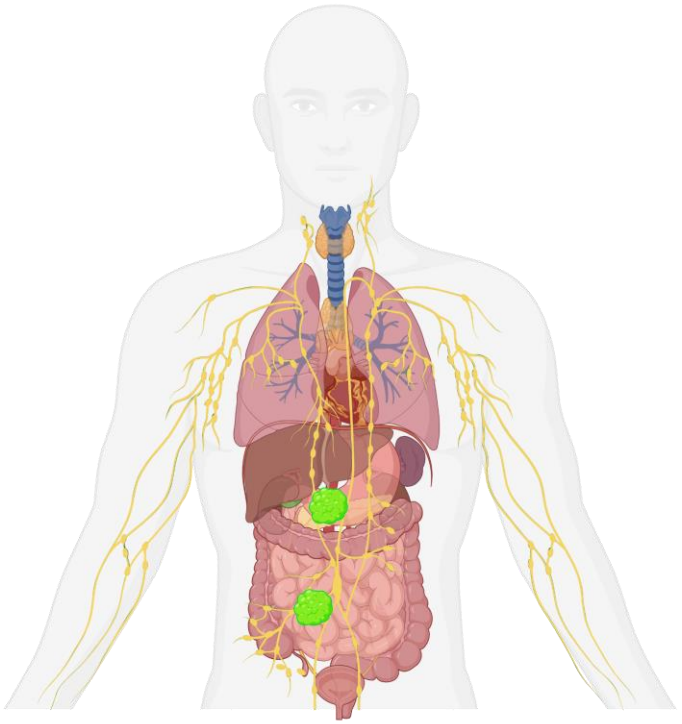
RECIST: Response Evaluation Criteria in Solid Tumors

1. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/metastasis
2. Richter, Maximilian, et al. "German oncology certification system for colorectal cancer–relative survival rates of a single certified centre vs. national and international registry data." Innovative surgical sciences 6.2 (2021): 67-73.
3. Biller, Leah H., and Deborah Schrag. "Diagnosis and treatment of metastatic colorectal cancer: a review." Jama 325.7 (2021): 669-685.

The whole is not the sum of its parts

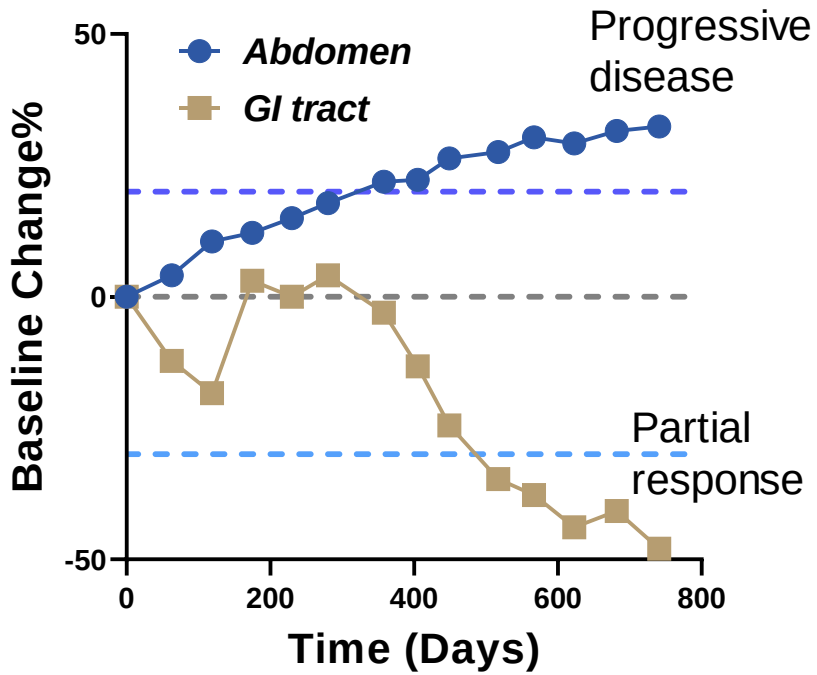
Total Tumor Burden





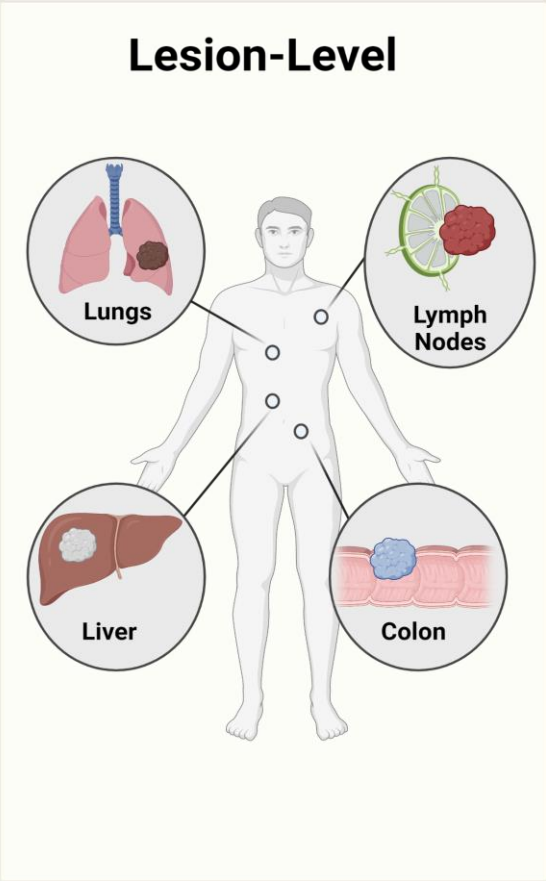
FOLFIRI + Panitumumab

Individual Metastasis



1. Zhou, Jiawei, Quefeng Li, and Yanguang Cao. "Spatiotemporal heterogeneity across metastases and organ-specific response informs drug efficacy and patient survival in colorectal cancer." Cancer research 81.9 (2021): 2522-2533.

Objectives: understand inter-lesion heterogeneity

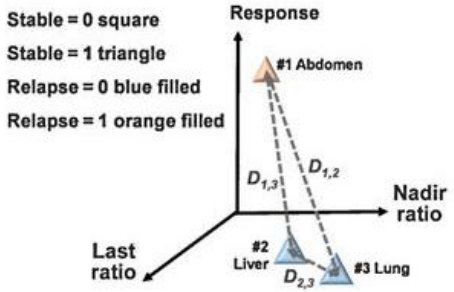


Metastatic tumors in same patient:

- Similar or different growth dynamics?
- How much difference/heterogeneity?
- Is heterogeneity associated with patient survival?

Methods overview

Statistics

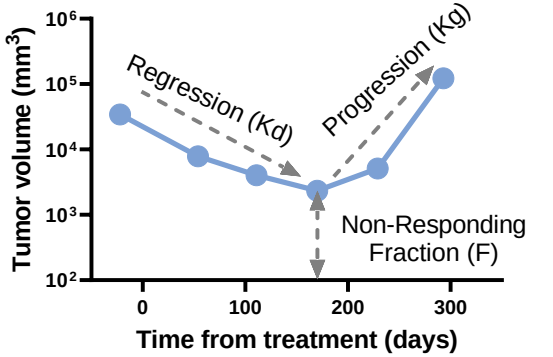


$$\text{Gower Distance for lesion \#1 } D_1 = \Sigma D_{1,n}/n$$

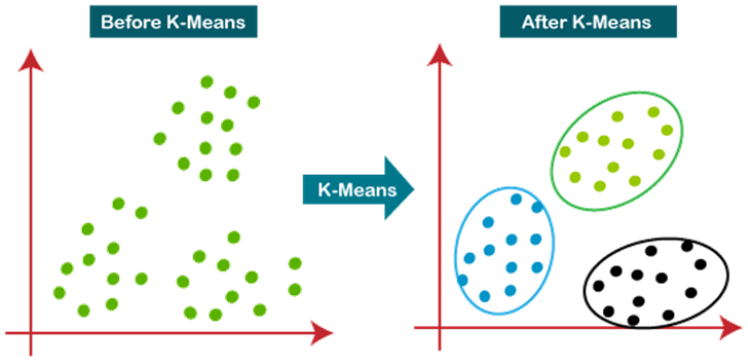
$$\text{Gower Distance for this patient} = \Sigma D_n/n$$

Pharmacometrics

$$V = V0 \bullet [F \bullet \exp(Kg \bullet t) + (1\text{-}F) \bullet \exp(\text{-}Kd \bullet t)]$$



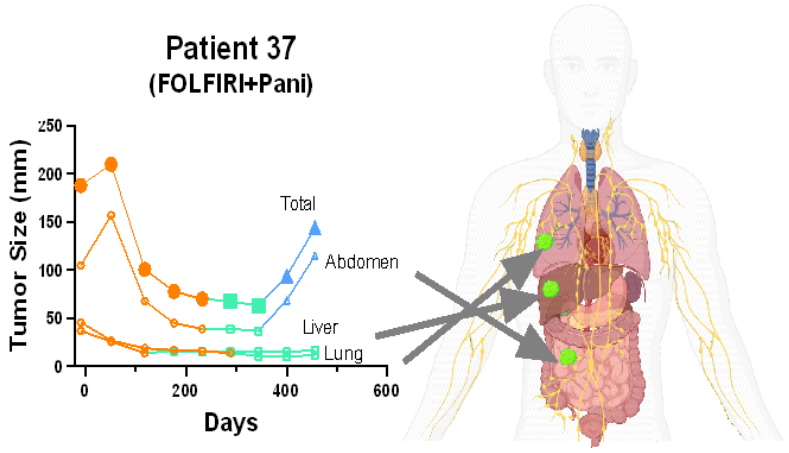
Machine learning



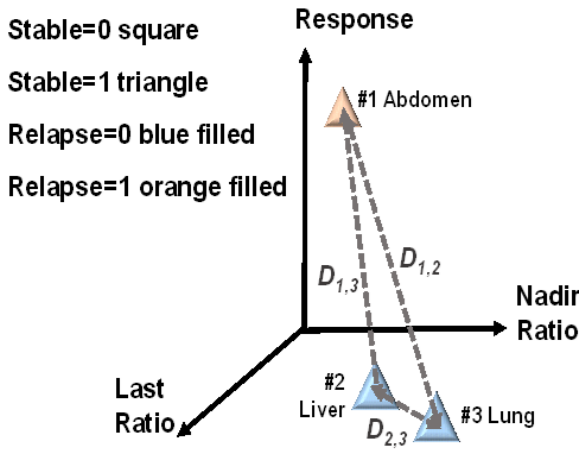
1. https://www.projectdatasphere.org/
2. Zhou, Jiawei, Quefeng Li, and Yanguang Cao. "Spatiotemporal heterogeneity across metastases and organ-specific response informs drug efficacy and patient survival in colorectal cancer." Cancer research 81.9 (2021): 2522-2533.
3. Zhou, Jiawei, et al. "Mapping lesion-specific response and progression dynamics and inter-organ variability in metastatic colorectal cancer." Nature Communications 14.1 (2023): 417.

Gower distance to quantify inter-lesion heterogeneity

- **mCRC data collected**:
  - 11,404 metastatic lesions size
  - 2,802 patients,
  - 5 mCRC clinical trials
  - 6 interventions
- Calculate **Gower distance** for each patient based on all metastatic lesions in this patient.
- Higher Gower distance means higher **inter-lesion heterogeneity**.



	Response	Stable	Relapse	Nadir ratio	Last ratio
Abdomen	1	1	1	0.35	1.10
Liver	1	1	0	0.22	0.26
Lung	1	1	0	0.38	0.46



$$Gower\ Distance\ for\ lesion\ \#1\ \ D_1 = \sum D_{1,n}/n$$

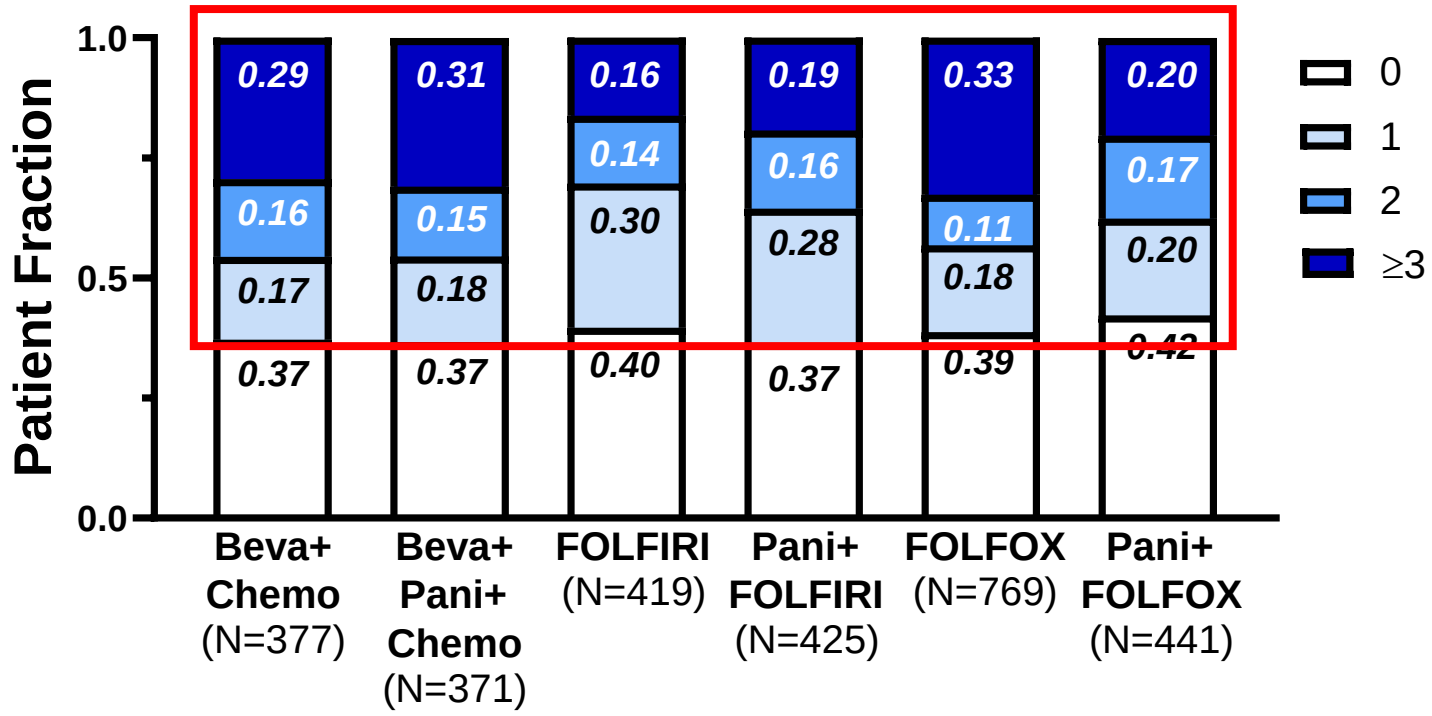
$$Gower\ Distance\ for\ this\ patient = \sum D_n/n$$

mCRC: metastatic colorectal cancer

1. Zhou, Jiawei, Quefeng Li, and Yanguang Cao. "Spatiotemporal heterogeneity across metastases and organ-specific response informs drug efficacy and patient survival in colorectal cancer." Cancer research 81.9 (2021): 2522-2533.

Most patients had heterogeneous metastases.

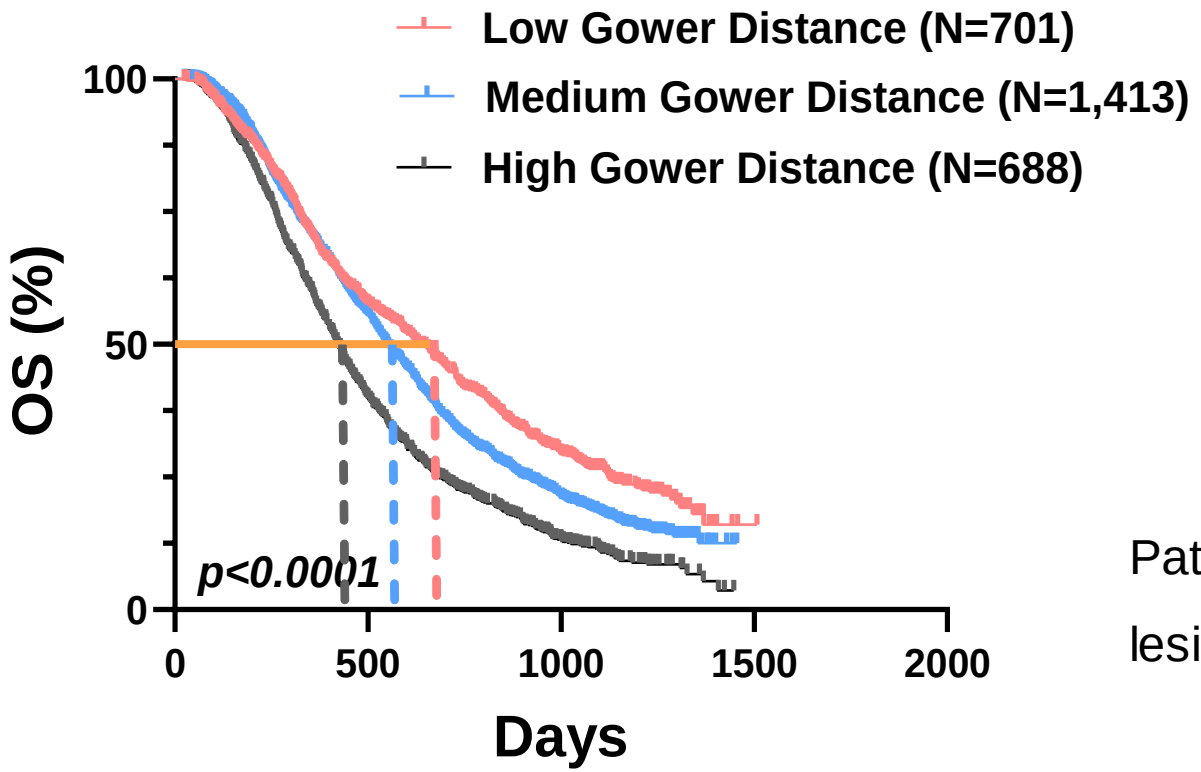
More than **60%** of patients had at least one lesion responding differently from total tumor burden.

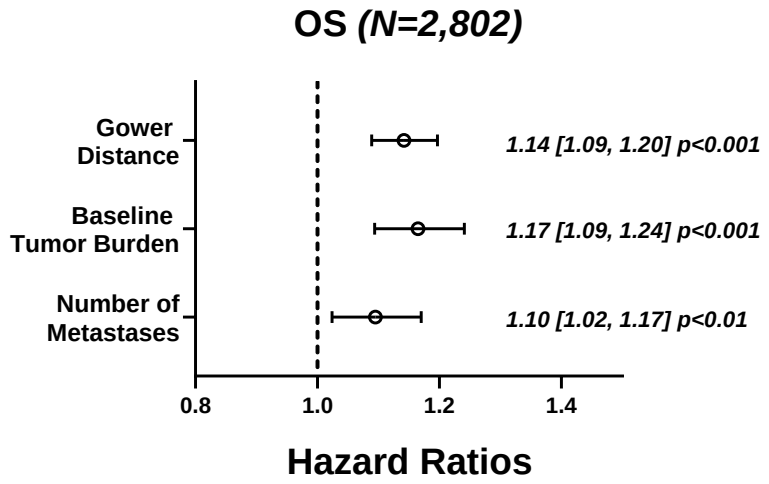


Beva: bevacizumab
Pani: panitumumab
Chemo: chemotherapy (FOLFIRI or FOLFOX)

1. Zhou, Jiawei, Quefeng Li, and Yanguang Cao. "Spatiotemporal heterogeneity across metastases and organ-specific response informs drug efficacy and patient survival in colorectal cancer." Cancer research 81.9 (2021): 2522-2533.

Heterogeneity is associated with survival.



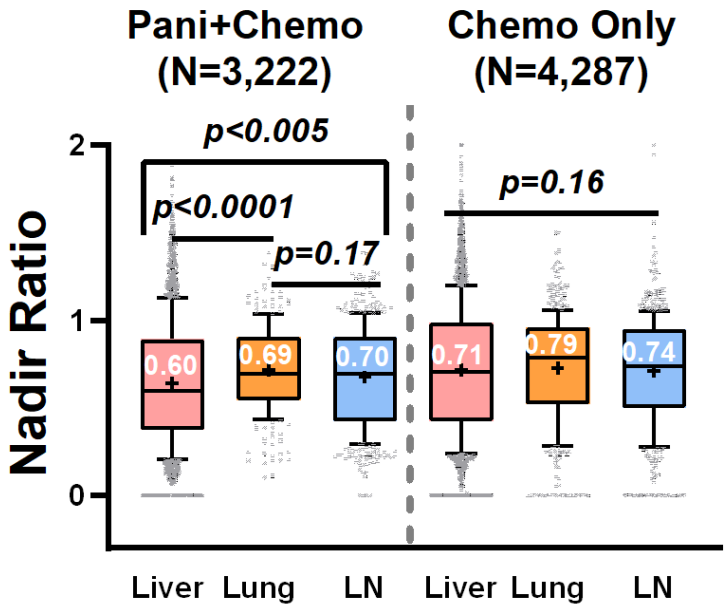


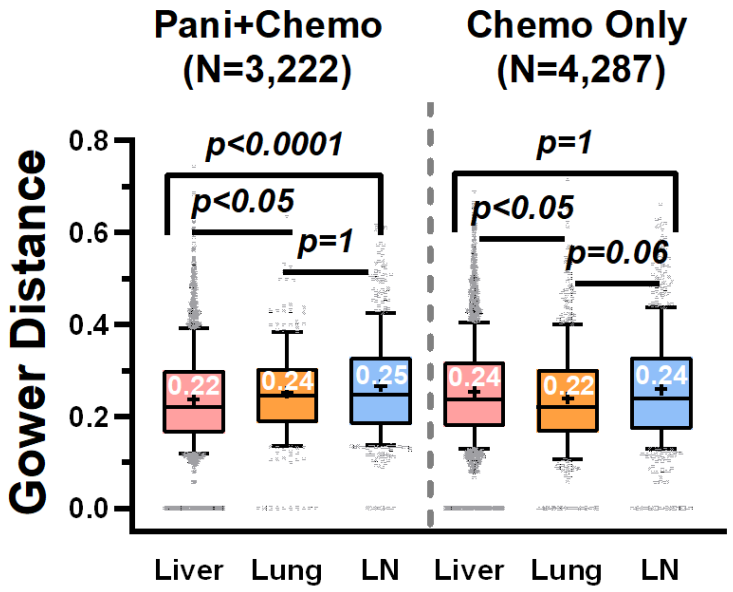
Patients with higher Gower distance (higher inter-lesion heterogeneity) had worse overall survival.

OS: overall survival

1. Zhou, Jiawei, Quefeng Li, and Yanguang Cao. "Spatiotemporal heterogeneity across metastases and organ-specific response informs drug efficacy and patient survival in colorectal cancer." Cancer research 81.9 (2021): 2522-2533.

Targeted therapies showed better efficacy.



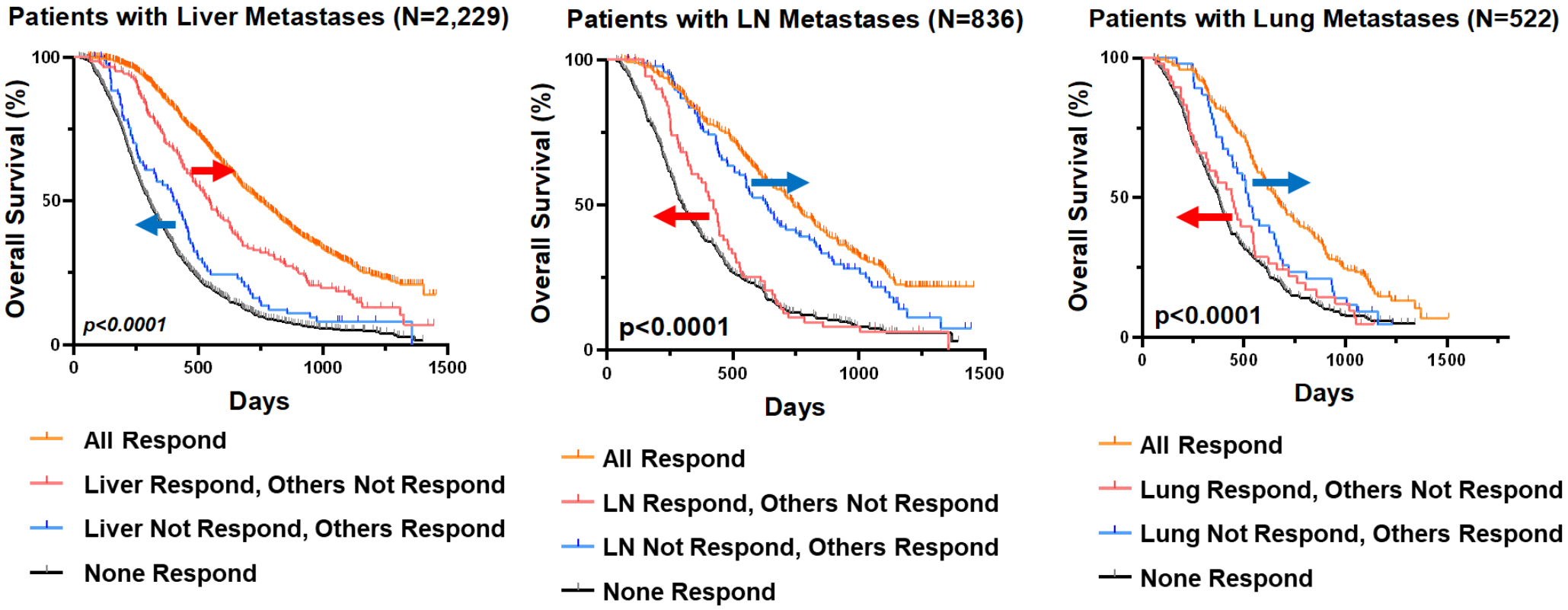


Targeted therapies showed better efficacy (lower nadir) and favored metastases in liver.

LN: lymph nodes

1. Zhou, Jiawei, Quefeng Li, and Yanguang Cao. "Spatiotemporal heterogeneity across metastases and organ-specific response informs drug efficacy and patient survival in colorectal cancer." Cancer research 81.9 (2021): 2522-2533.

Liver lesion responses are more relevant to survival.



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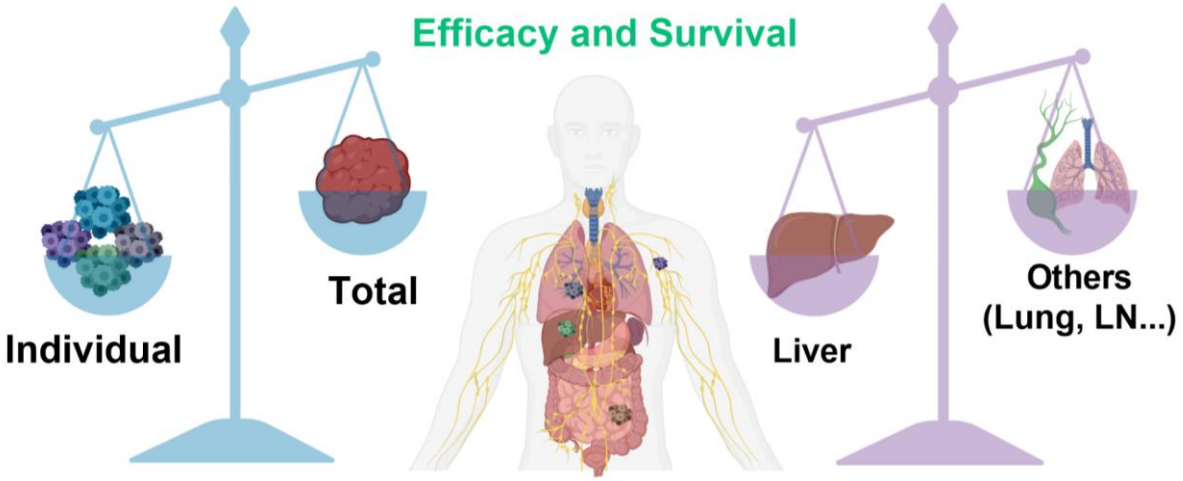
Every lesion matters, liver lesion matter more.



Metastatic tumors in same patient:

- Similar or different growth dynamics?

– Inter-lesion heterogeneity was observed.

- How much difference/heterogeneity?

– Gower distance was applied to quantify inter-lesion heterogeneity.

- Is heterogeneity associated with patient survival?

– Patients with higher inter-lesion heterogeneity had worse survival.

Limitations and next steps

Limitations	Next Step
Observed tumor measurements during the trial were used to determine response and relapse time and efficacy.	How about the tumor size between two sampling time points? And how about those patients who lost follow-up measurements?
Liver, lung, and lymph nodes are the top 3 metastatic organs and were analyzed.	How about other metastatic organs?
Current analyses are hard to be applied in real clinical treatment.	Can we make predictions for patients whose liver lesions might not respond?

Population tumor growth model

Data

- 40,612 lesions from 4,308 metastatic colorectal cancer patients
- Individual tumor size measurements and patient survival

Modeling

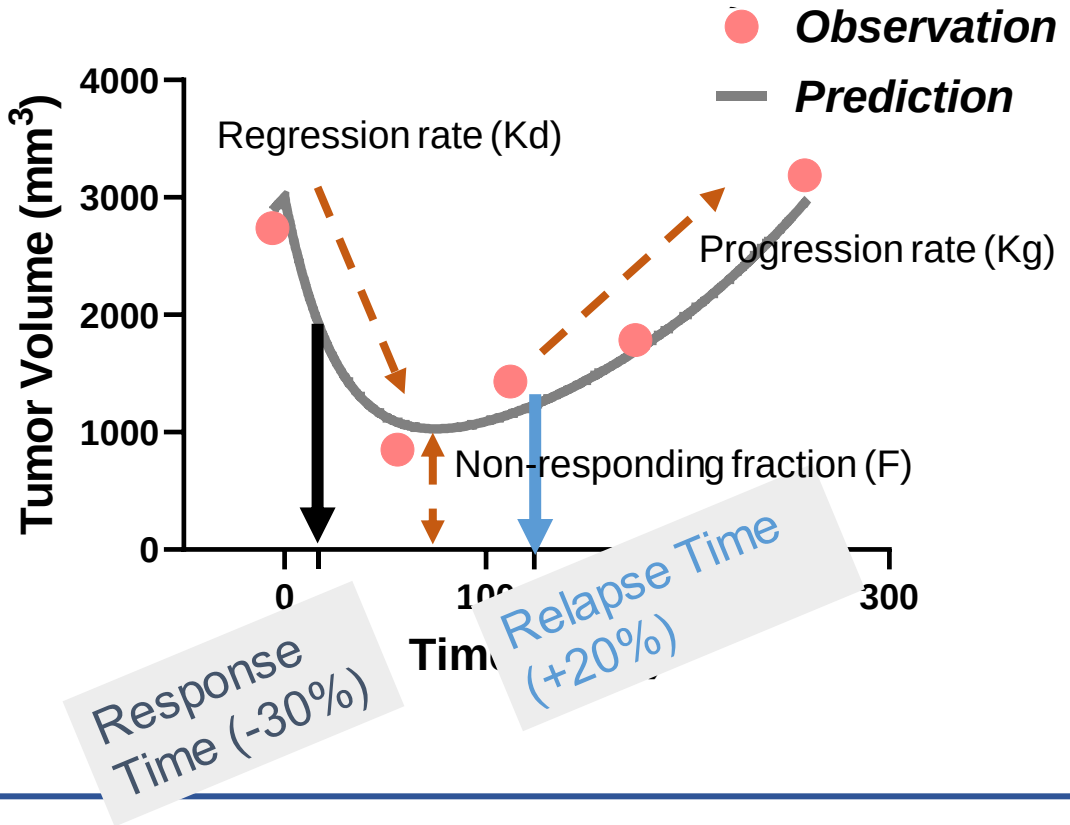
- Non-linear mixed effect estimation

Outcomes

- Model-predicted response and relapse time for each metastasis

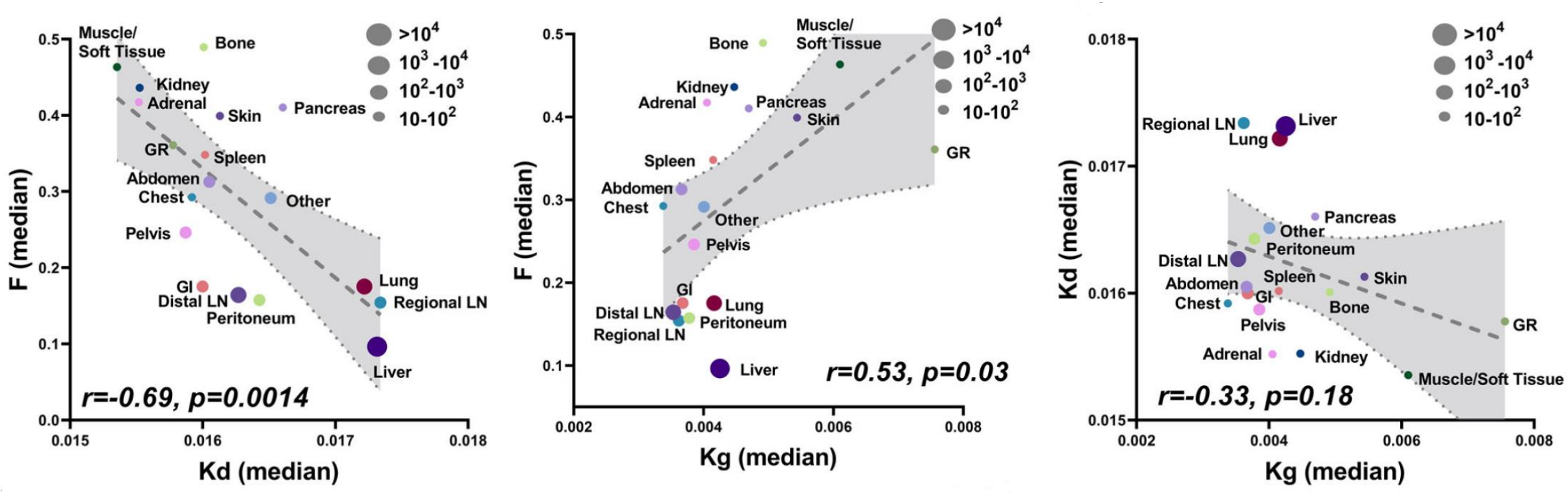
Tumor Growth Model

$$V = V0 \bullet [F \bullet \exp(Kg \bullet t) + (1-F) \bullet \exp(-Kd \bullet t)]$$



1. Zhou, Jiawei, et al. "Mapping lesion-specific response and progression dynamics and inter-organ variability in metastatic colorectal cancer." Nature Communications 14.1 (2023): 417.

Model parameter correlations



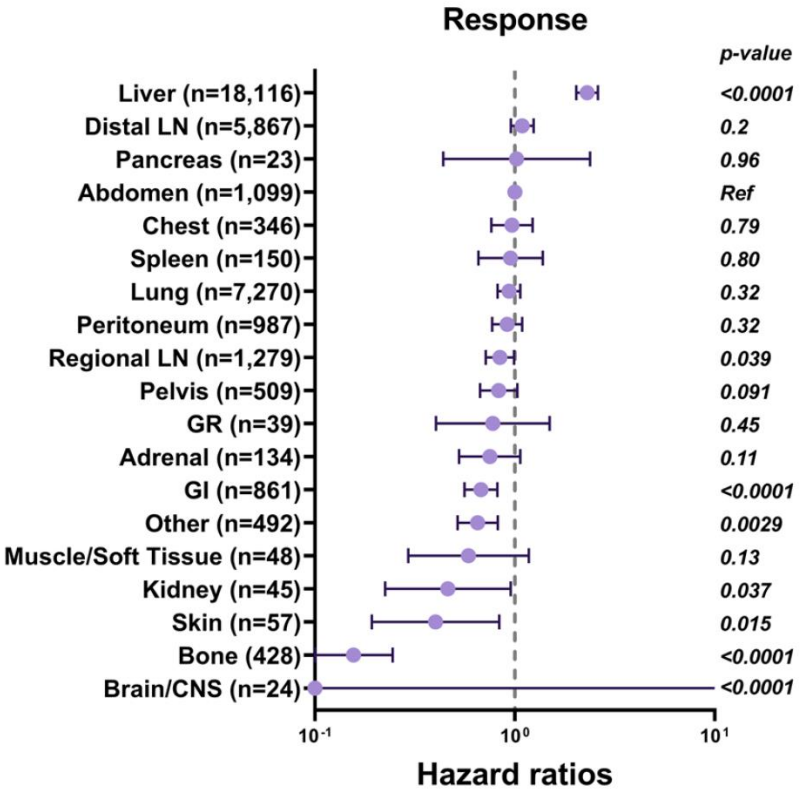
Model parameters have correlations at organ-level.

Kd: regression rate
Kg: progression rate
F: non-responding tumor fraction

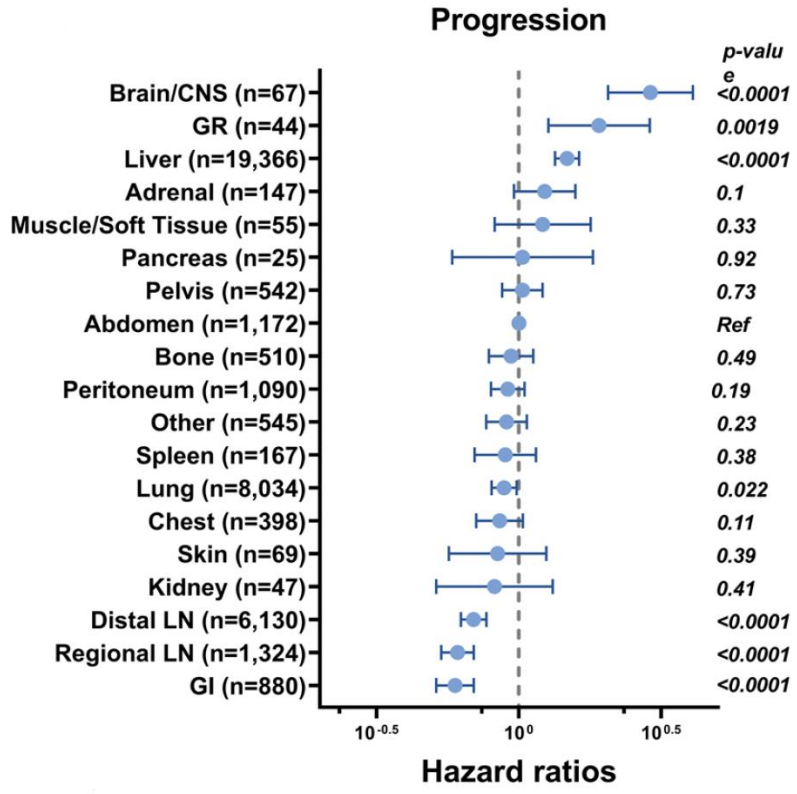
1. Zhou, Jiawei, et al. "Mapping lesion-specific response and progression dynamics and inter-organ variability in metastatic colorectal cancer." Nature Communications 14.1 (2023): 417.

Response and progression probabilities at organ-level

Higher HR, higher response probability



Higher HR, higher progression probability



CNS: central nervous system
GI: gastrointestinal tract
GR: genitourinary reproductive system
LN: lymph nodes

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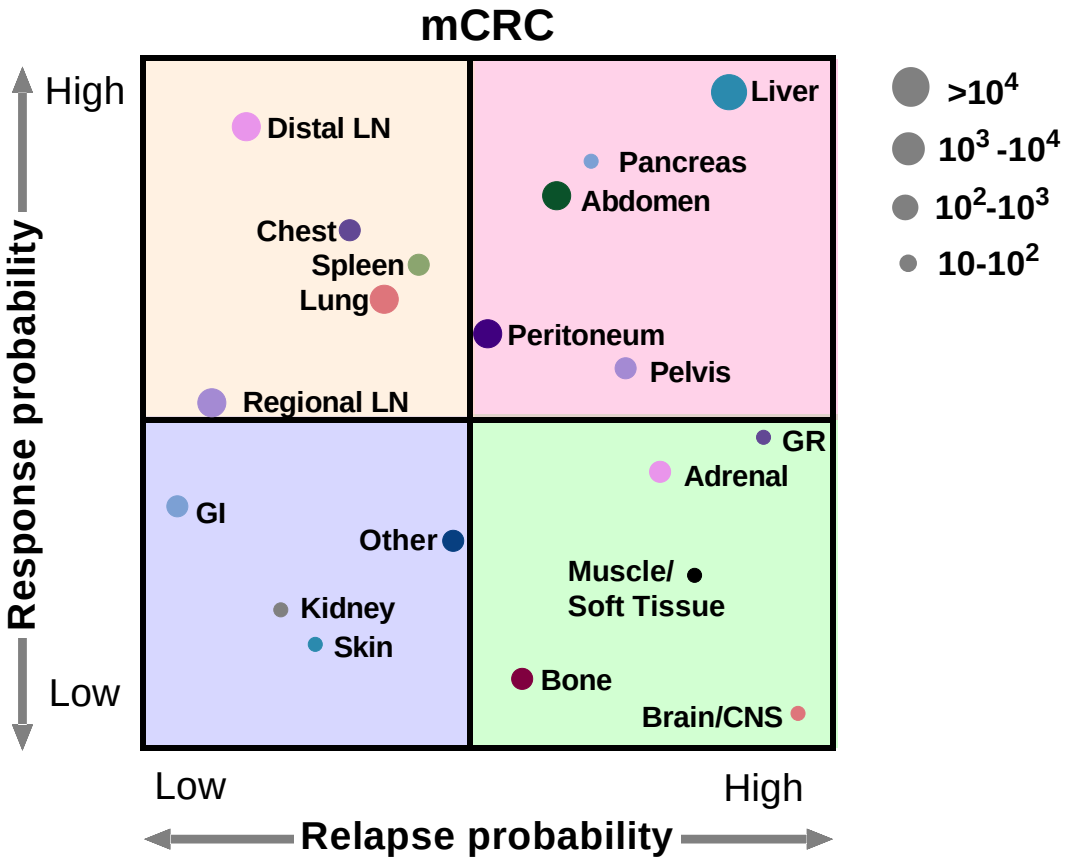
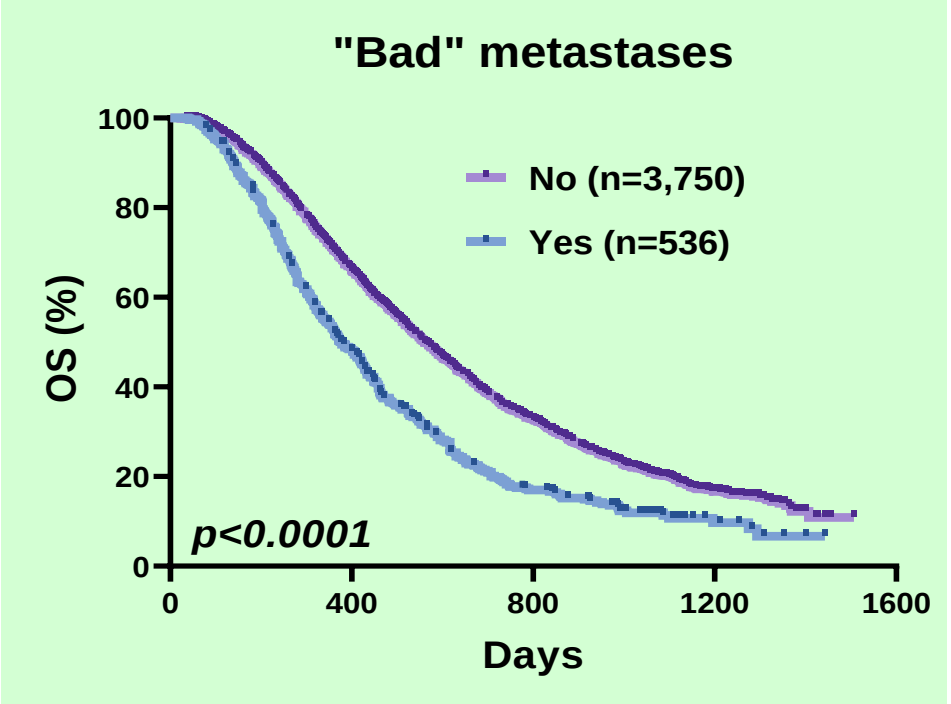
Four types of phenotypic features emerge in mCRC organs





CNS: central nervous system, GI: gastrointestinal tract GR: genitourinary reproductive system , LN: lymph nodes, mCRC: metastatic colorectal cancer

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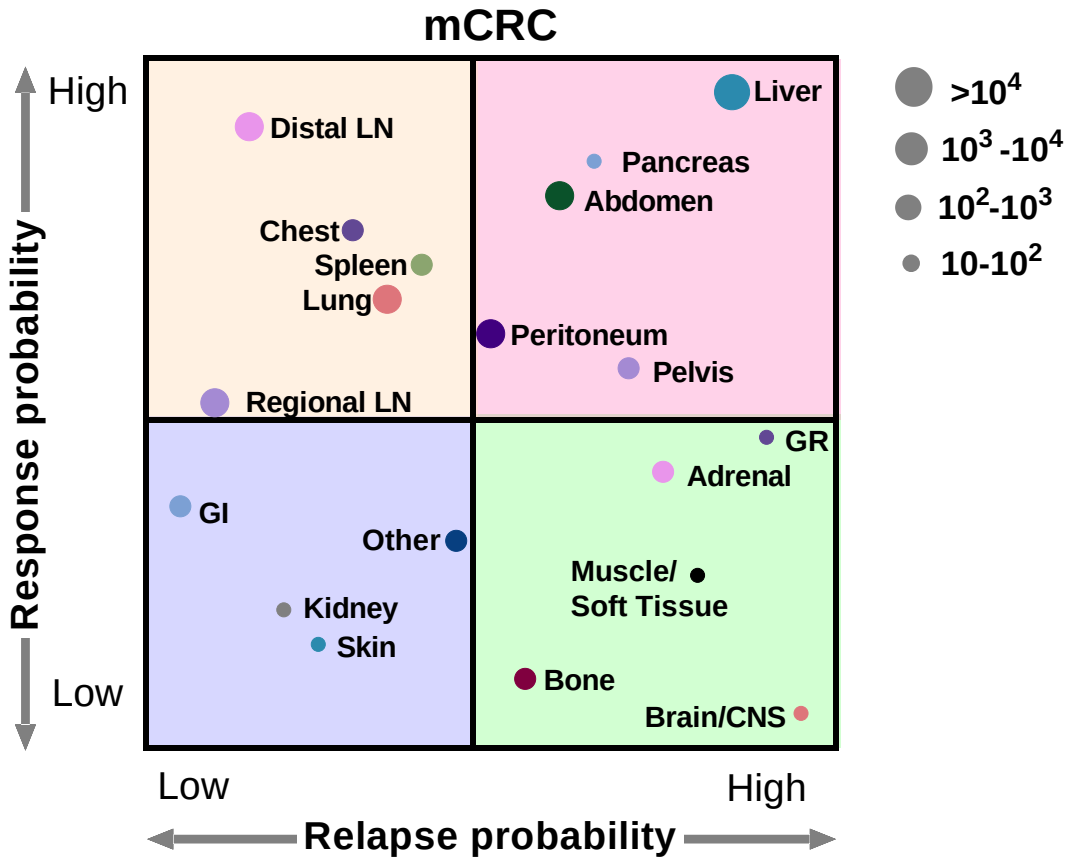

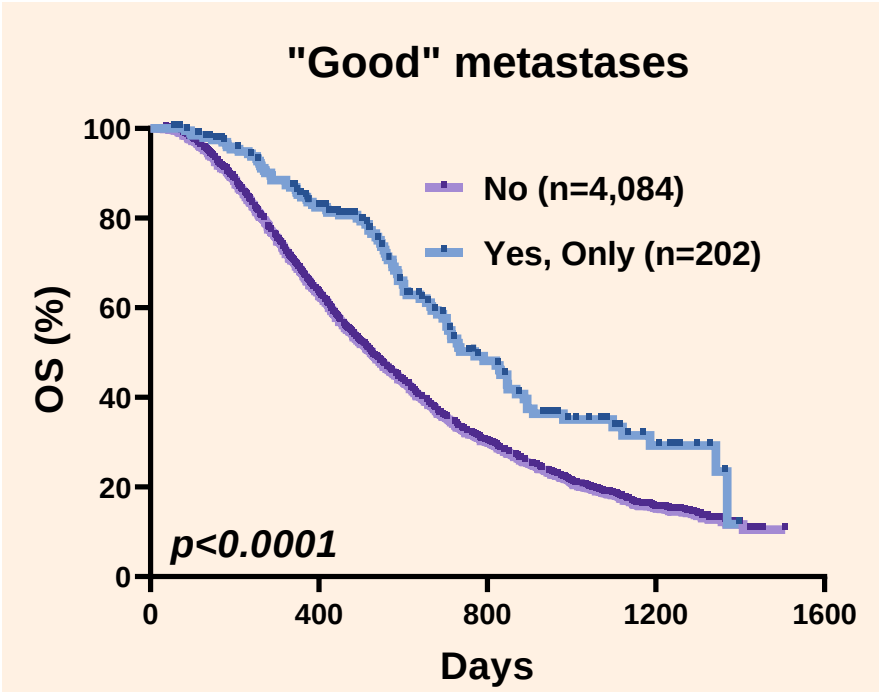

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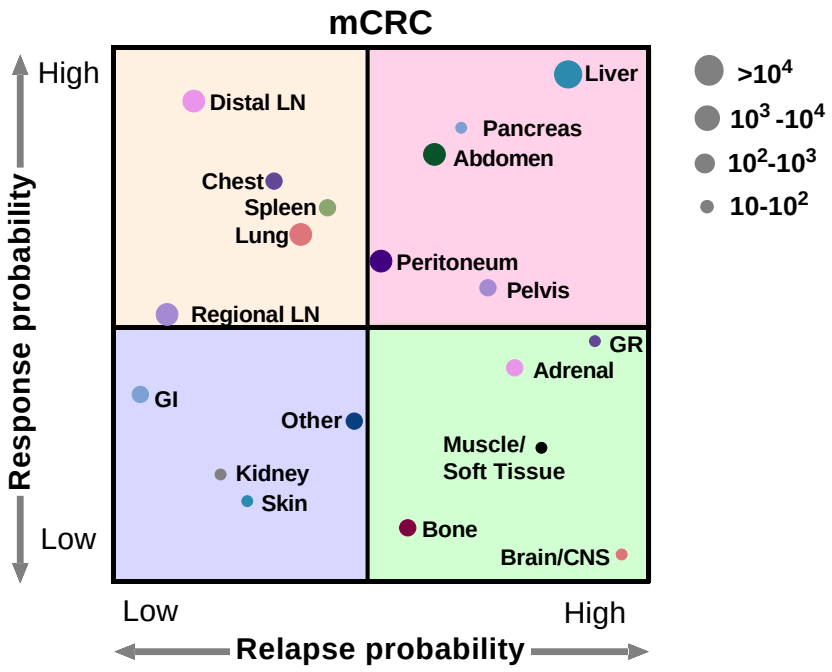
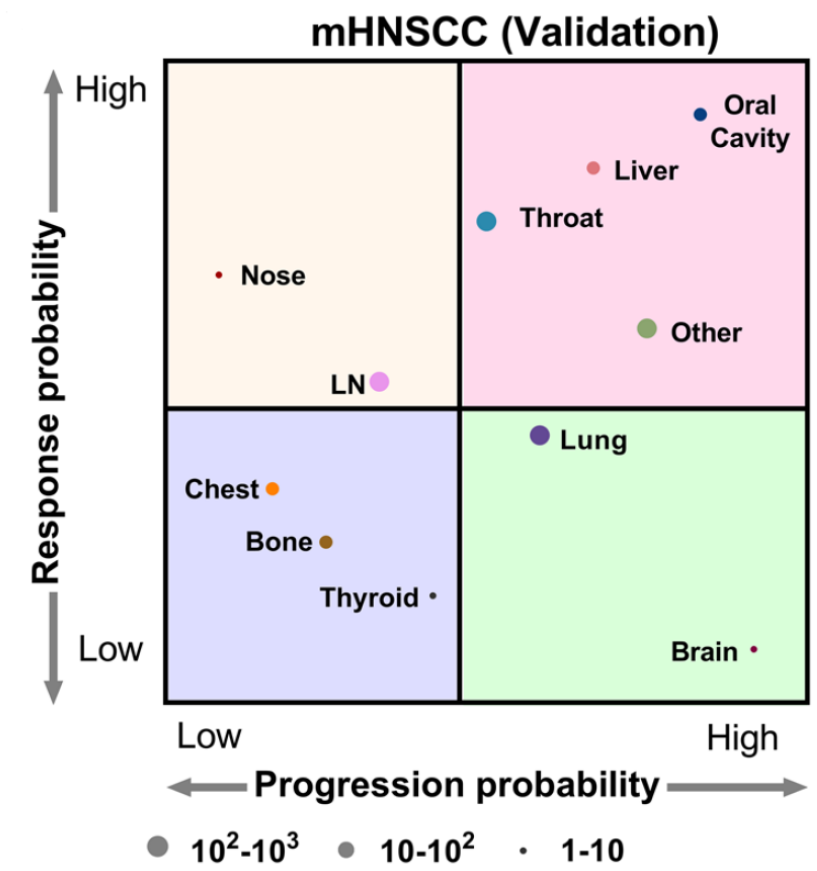
Validate same organ chart in different tumor type

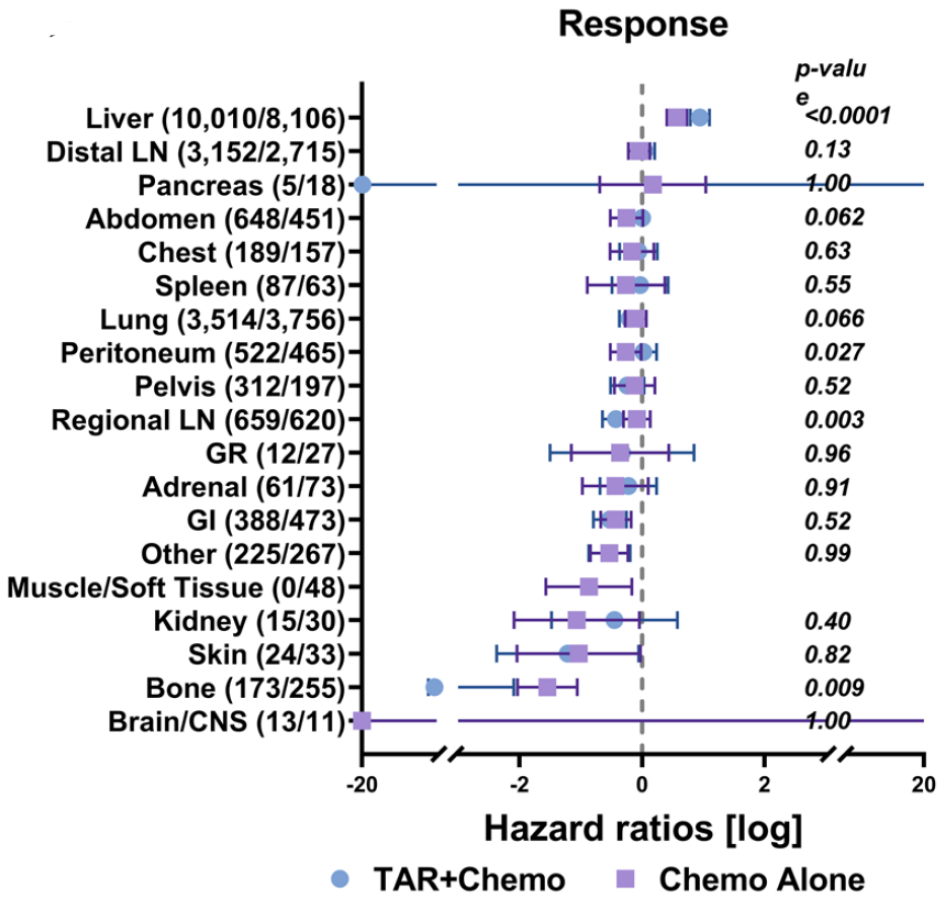


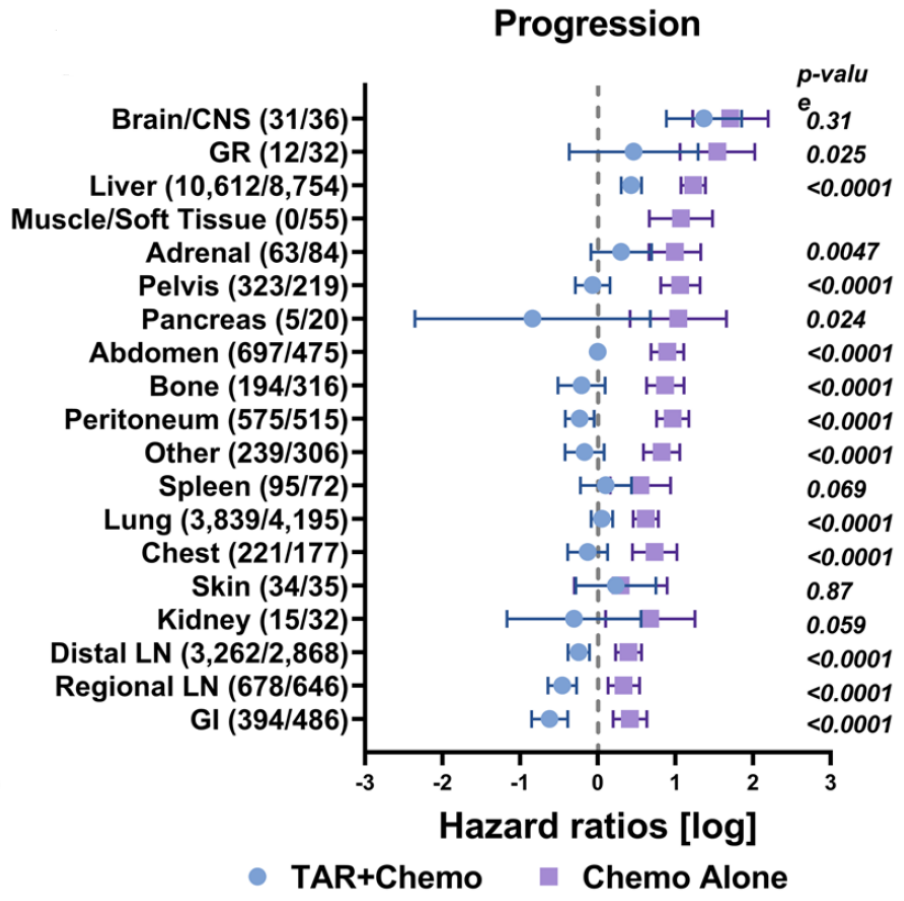


CNS: central nervous system, GI: gastrointestinal tract
GR: genitourinary reproductive system , LN: lymph nodes,
mCRC: metastatic colorectal cancer
mHNSCC: metastatic head and neck squamous cell carcinoma

1. Zhou, Jiawei, et al. "Mapping lesion-specific response and progression dynamics and inter-organ variability in metastatic colorectal cancer." Nature Communications 14.1 (2023): 417.

Targeted therapies primarily decreased lesion progression.





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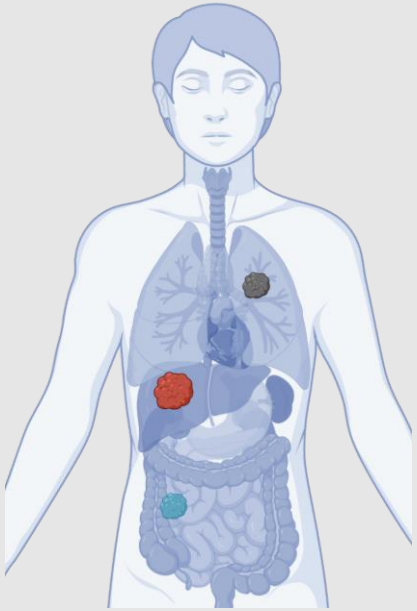
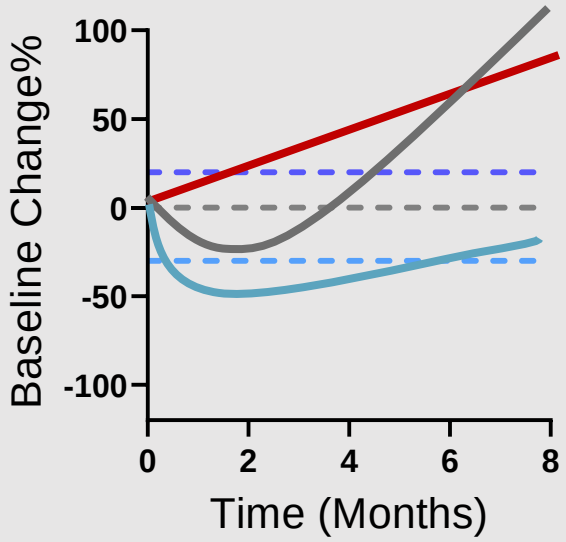
Classify relapse sequence using ML

Model-informed tumor growth dynamics

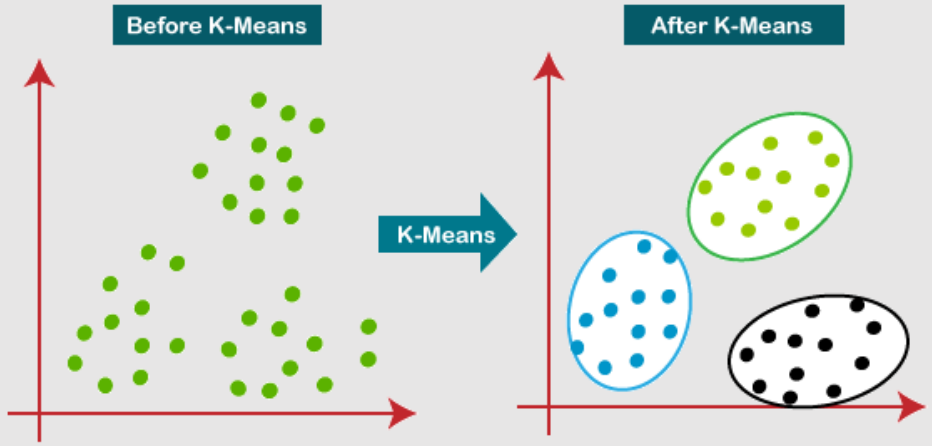




Relapse sequence: Liver → Lung → GI Tract

K-means cluster patient relapse sequence

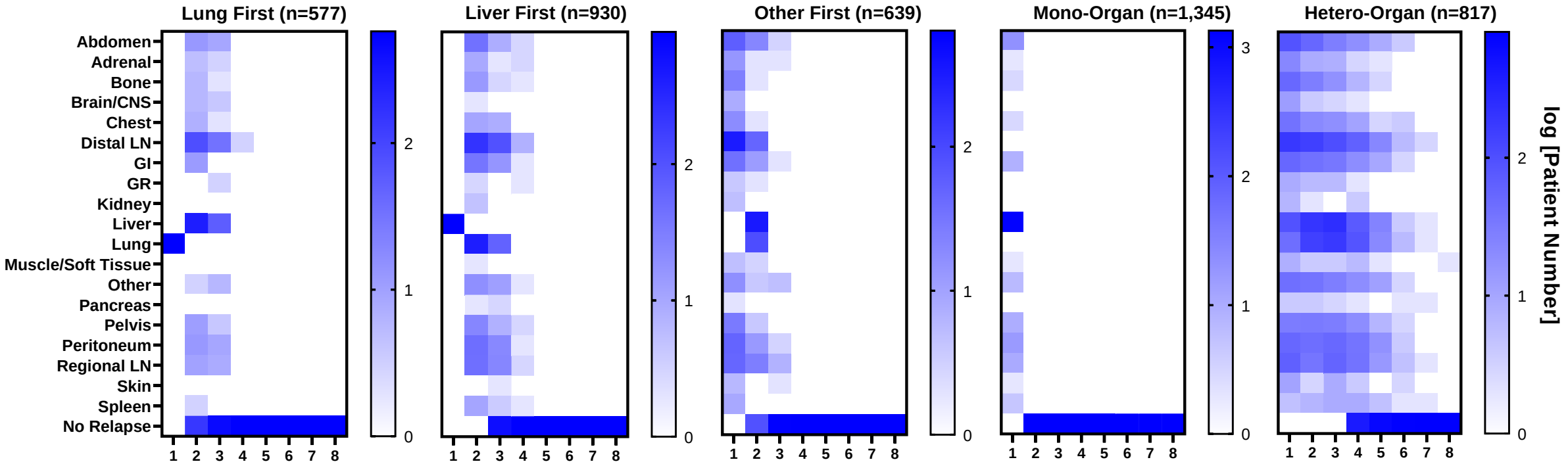
Relapse sequence for
all 4,308 patients



GI: gastrointestinal tract
ML: machine learning

1. https://www.analyticsvidhya.com/blog/2021/04/k-means-clustering-simplified-in-python/

Five clusters of relapse sequence



- Heatmap column: the sequence of the lesion had relapse, e.g., 1 means the first relapsed organ
- Heatmap row: the metastatic organs

CNS: central nervous system, GI: gastrointestinal tract
GR: genitourinary reproductive system , LN: lymph nodes,

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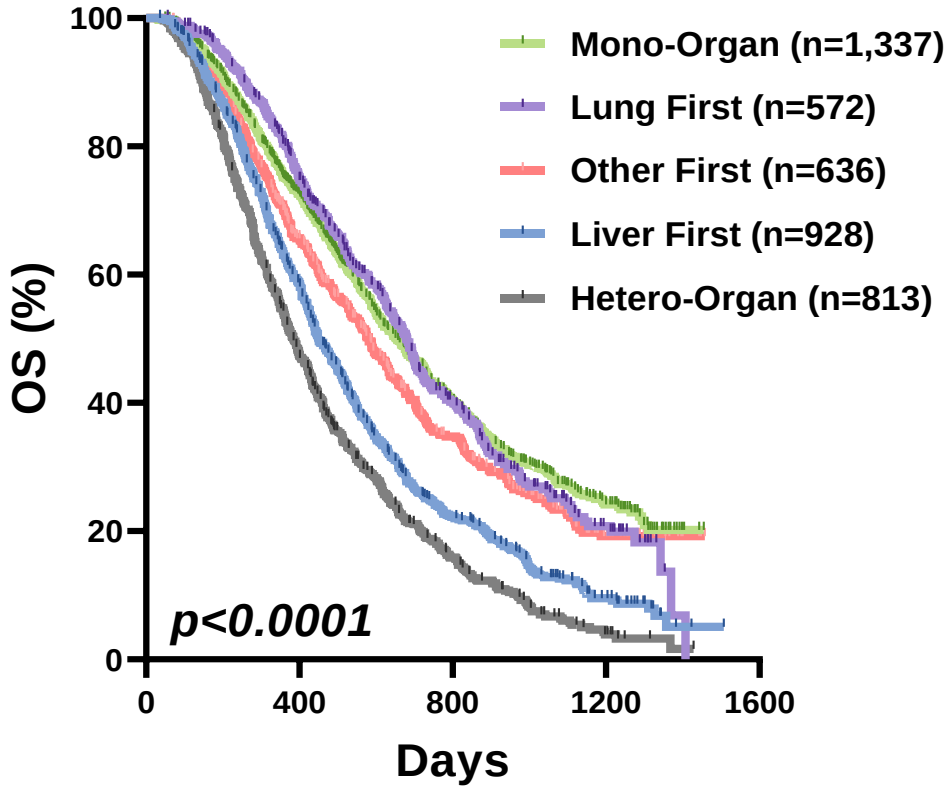
Relapse sequence is associated with survival.



1. Hetero-Organ patients have worse survival than Mono-Organ patients.
2. For patients with similar relapsed organ number: ***Liver First*** patients have worse survival than ***Other First*** and ***Lung First***.

1. Zhou, Jiawei, et al. "Mapping lesion-specific response and progression dynamics and inter-organ variability in metastatic colorectal cancer." Nature Communications 14.1 (2023): 417.

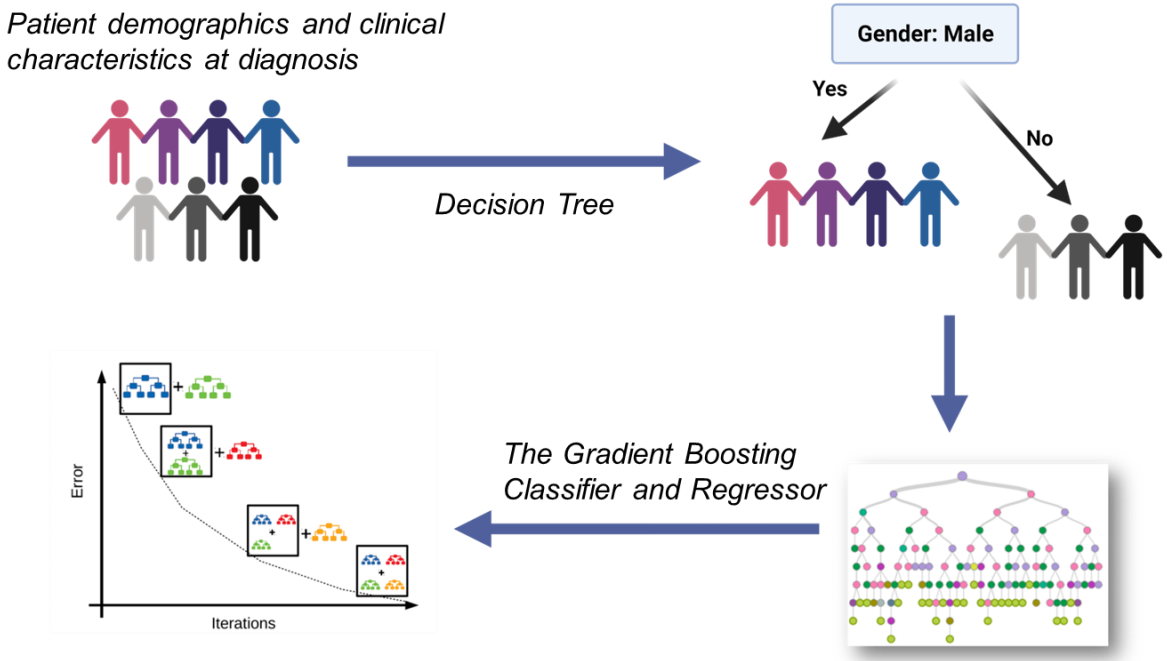
Clinical applications

Can we predict patient cluster at diagnosis?

A mCRC patient at diagnosis

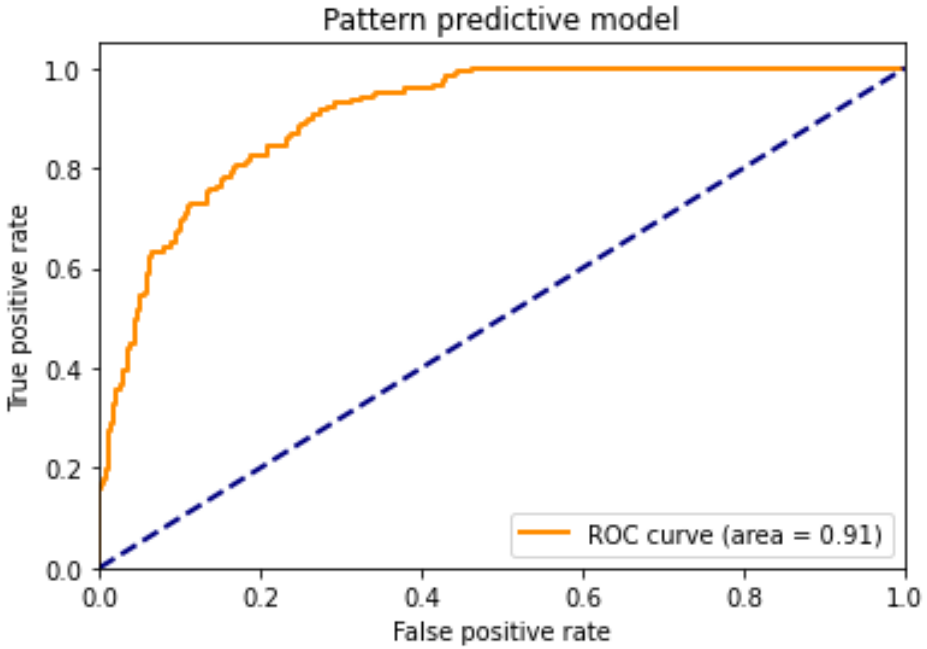
Liver-first cluster

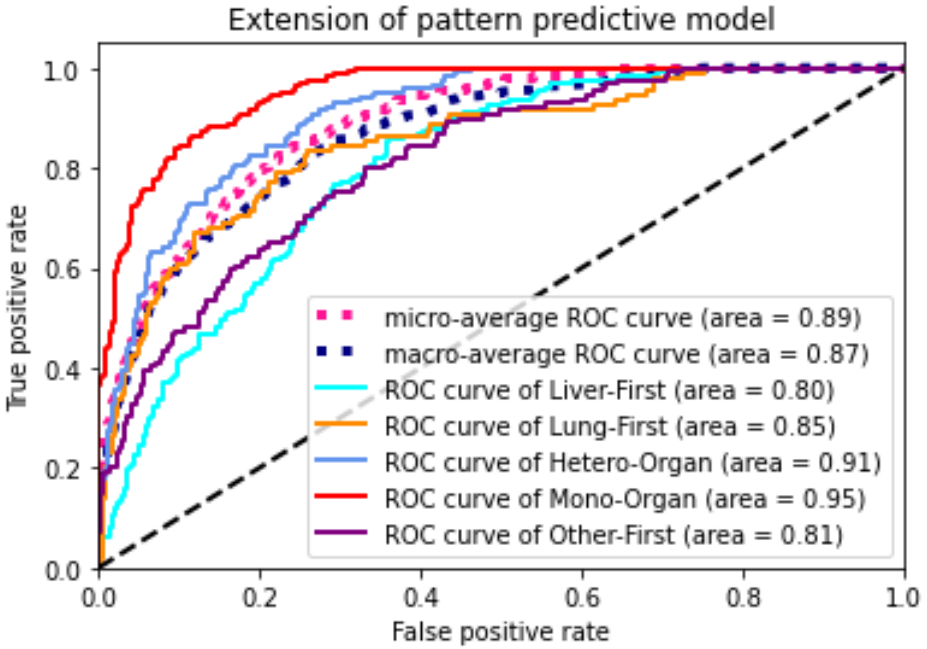
Liver-specific treatment to prevent liver metastases relapse



1. Courtesy of Dr. Gang Fang's machine learning lecture slides

ML gradient boosting model to predict relapse sequence

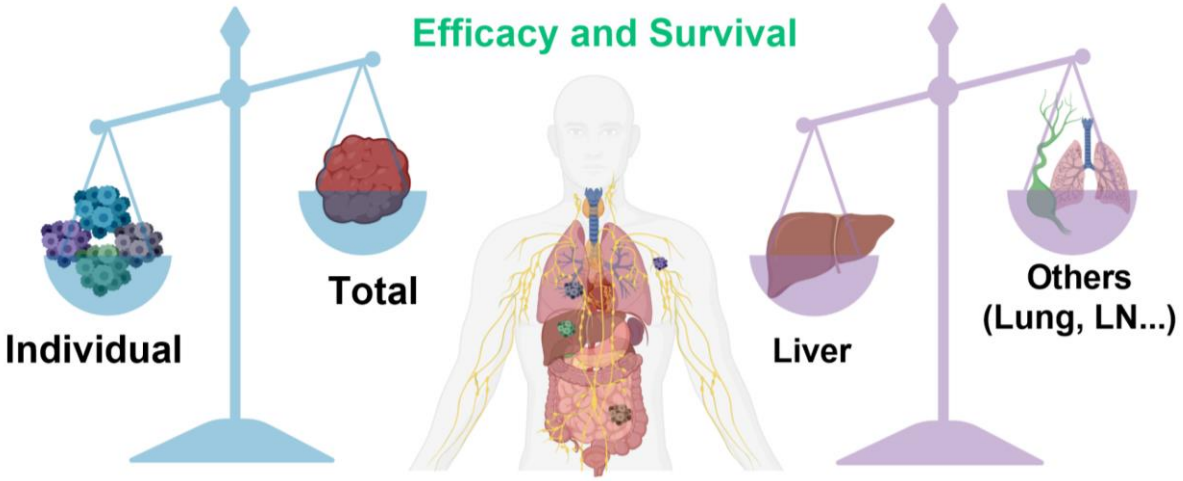




- We built a gradient boosting model to predict patient relapse sequence category using their baseline clinical characteristics.
- AUC under ROC curve = 0.91 means our model has good performance.

ML: machine learning

Every lesion matters, liver lesion matter more.



- We created an anatomical chart to tell organs **similarities** and **differences**.
- Organ-level relapse sequence was closely associated with patient survival.
- Patients with the first relapses in the **liver** often had worse survival.

Acknowledgments

Project Data Sphere

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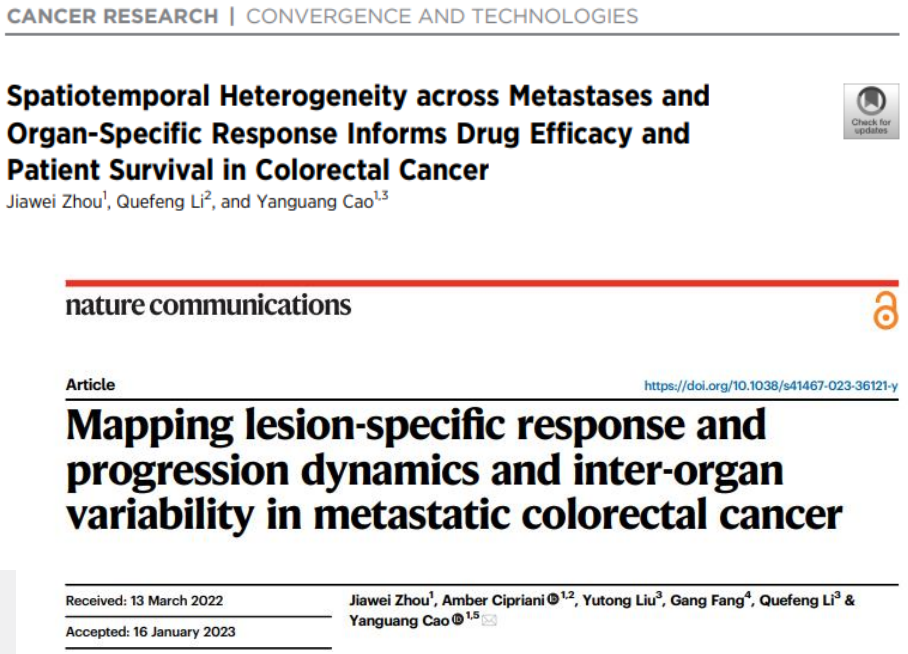

CANCER RESEARCH | CONVERGENCE AND TECHNOLOGIES

Spatiotemporal Heterogeneity across Metastases and Organ-Specific Response Informs Drug Efficacy and Patient Survival in Colorectal Cancer

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Mapping lesion-specific response and progression dynamics and inter-organ variability in metastatic colorectal cancer

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