

Computer-Extracted Features of Gland Morphology from Digital Tissue Images is Comparable to Decipher for Prognosis of Biochemical Recurrence Risk Post-Surgery

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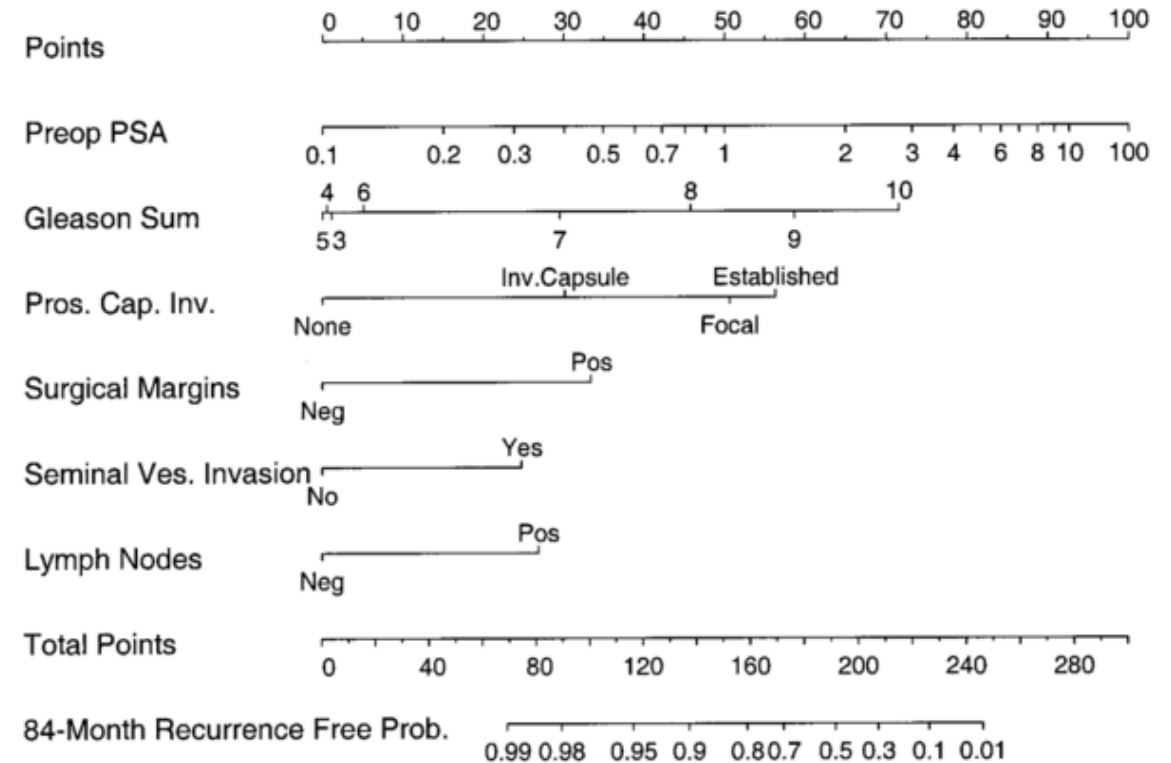
Post-radical prostatectomy treatment

- Adjuvant therapy can extend lives
- Not everyone should get adjuvant therapy
- Precision prescription of adjuvant therapy could reduce deaths and overtreatment



Standard-of-care: Nomograms

- Require a pathologist
- Vulnerable to intra- and inter-reviewer variability
- Do not provide perfect stratification



Companion diagnostics

- Molecular tests of tissue
- Tissue-destructive, no retesting
- Expensive (\$4000)
- Not widely available

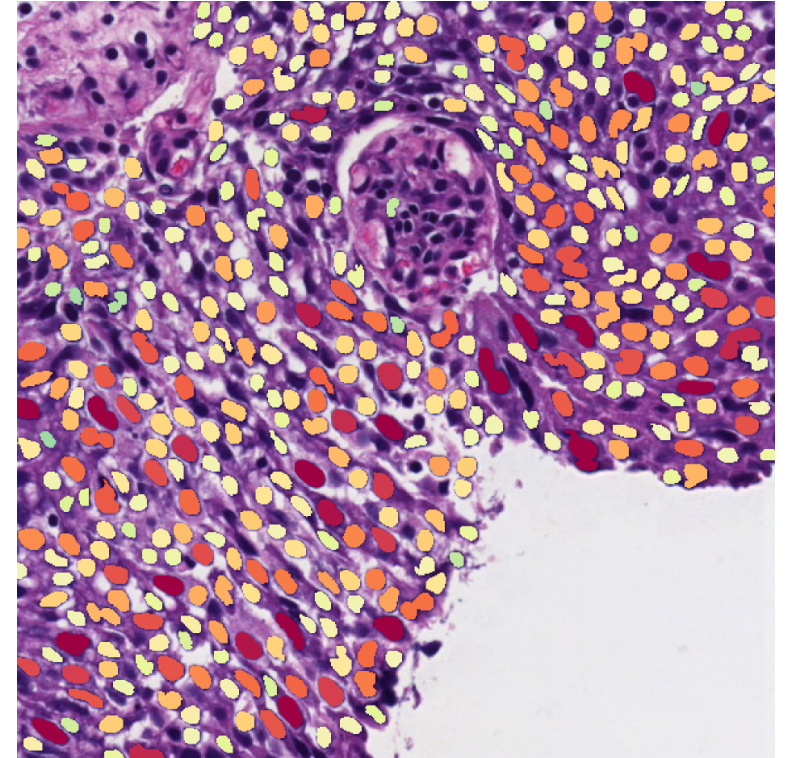
Table 1. Available Tissue-Based Tests for Prostate Cancer Risk Stratification/Prognosis

Test	Platform	Populations Studied	Outcome(s) Reported (Test independently predicts)	Selected References	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post RP, adverse pathology/high-risk features Post RP, biochemical recurrence Post RP, adjuvant, or salvage radiation Biopsy, localized prostate cancer post RP or EBRT	<ul style="list-style-type: none"> • Metastasis • Prostate cancer-specific mortality • PORTOS • Metastasis • Prostate cancer-specific mortality • PORTOS • Metastasis • Prostate cancer-specific mortality • PORTOS • Metastasis • Prostate cancer-specific mortality • Gleason grade ≥ 4 disease at RP • Adverse pathologic features at RP 	136,139,140,234–249	<p>Cover postbiopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment of prostate cancer and are candidates for active surveillance or definitive therapy</p> <p>Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)</p>



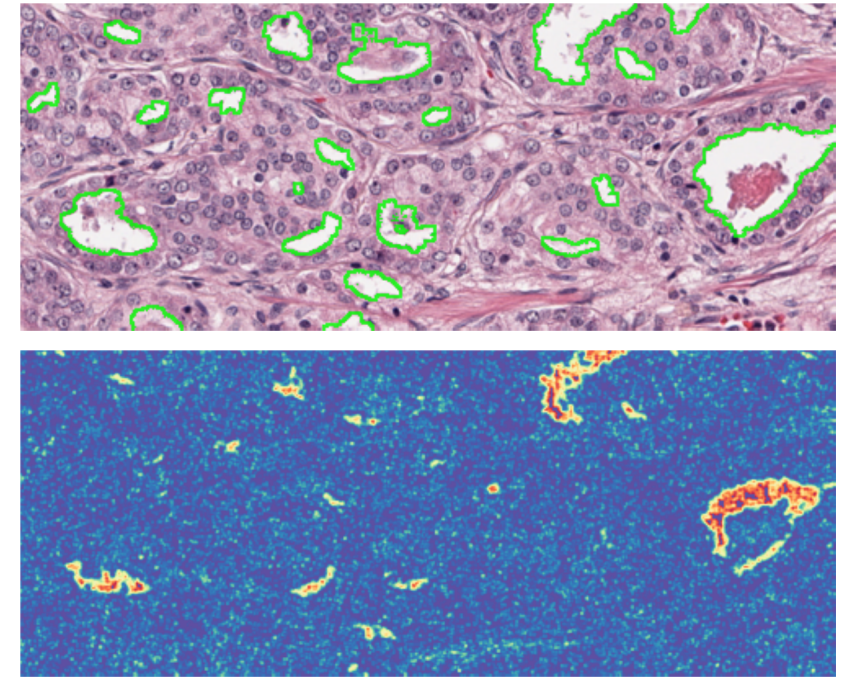
Quantitative histomorphometry

- Digitized H&E specimens
- Sub-visual features
- Useful for
 - Prostate BCR prognosis, grading
 - Prostate, breast, lung cancer detection



Histotyping: A computerized visual assay

- Hypothesis: Quantitative features of lumen morphology are prognostic of BCR
- Computer analysis of digitized slides
- Use both features known to pathologists and those not currently examined
- Compare Histotyping to Decipher companion diagnostic test

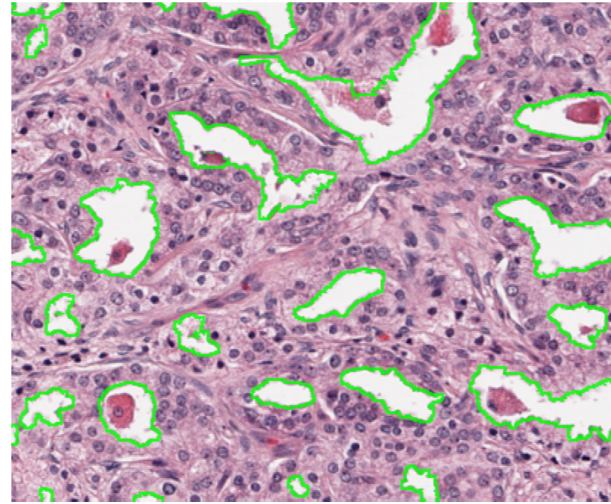


Dataset

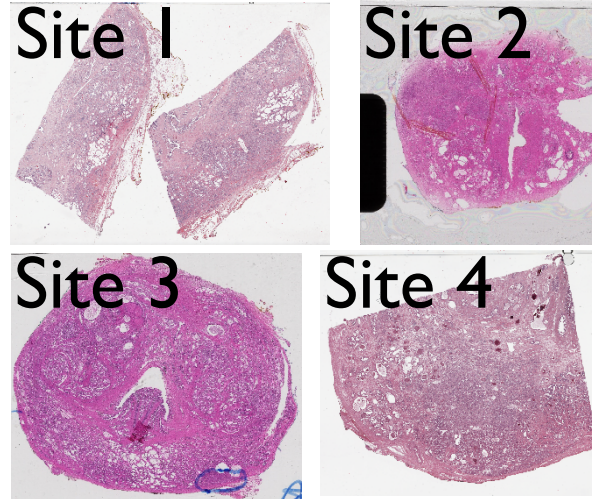
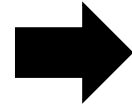
- Radical prostatectomy specimens
- Inclusion criteria: post-surgery PSA testing, no adjuvant therapy
- One slide per patient annotated for tumor region
- N=381 patients split into:
 - n=214 training set from University of Pennsylvania, University Hospitals
 - n=167 validation set from University of Pennsylvania, Mount Sinai



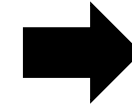
Histotyping model construction







Feature extraction

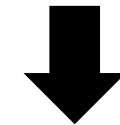


Stability filtering

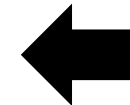


Patient X	Risk score
Feature 1	
Feature 2	
Feature 3	
Feature 4	

Cox regression



Histotyping score



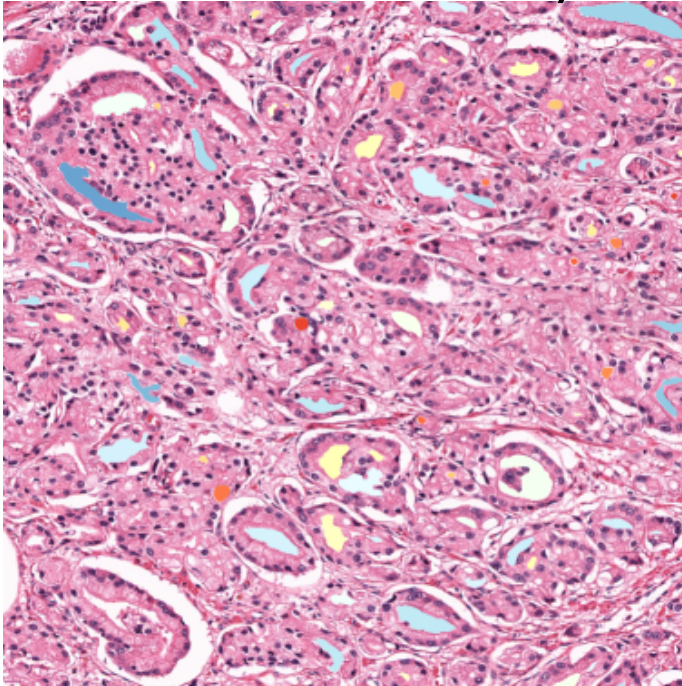
Include Gleason grade and PSA for Histotyping+



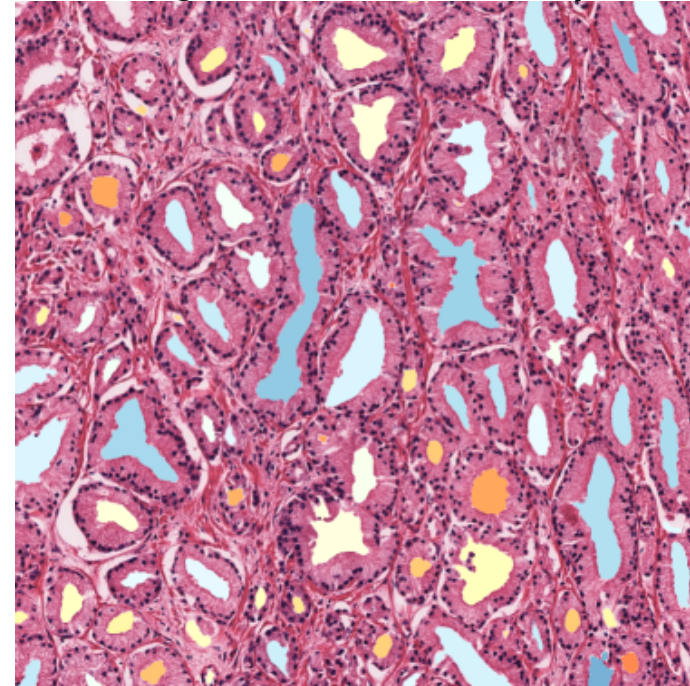
Features used in Histotyping

- 5 features of lumen shape, 1 feature of lumen arrangement
- Prevalence of disk-shaped lumen associated with worse outcomes

Low lumen circularity

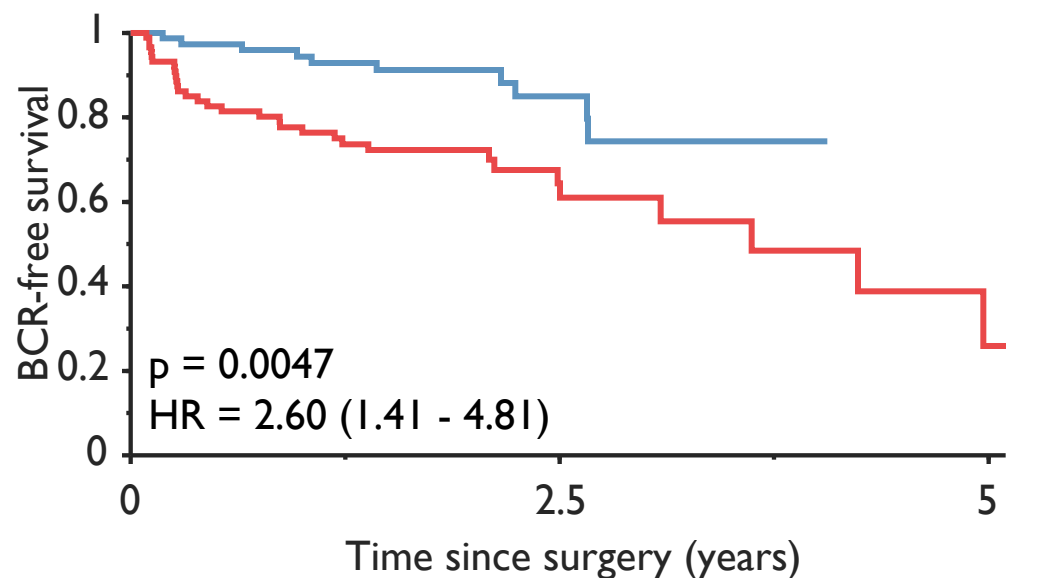


High lumen circularity



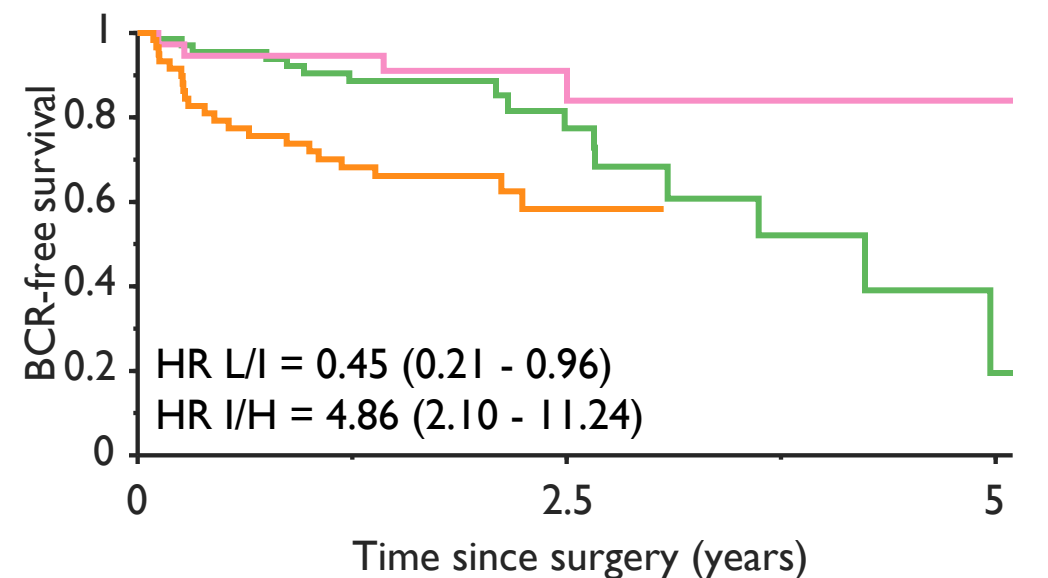
Results: Histotyping vs. Decipher

Histotyping (c-index = 0.68)



	Number at risk (number censored)		
Low-risk	79 (0)	19 (52)	0 (69)
High-risk	88 (0)	19 (43)	2 (55)

Decipher (c-index = 0.70)

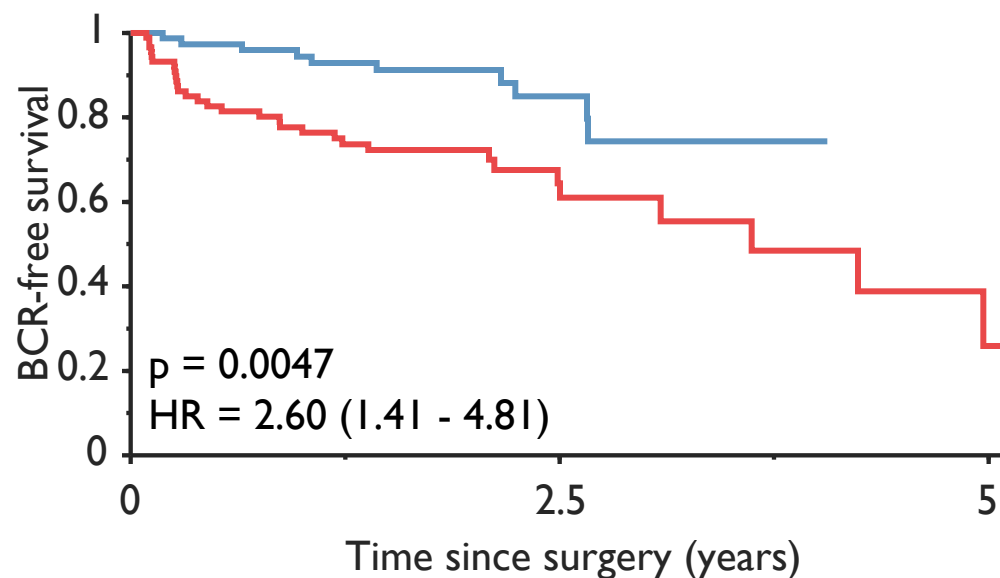


	Number at risk (number censored)		
Low-risk	71 (0)	19 (42)	1 (54)
Inter.-risk	37 (0)	13 (21)	1 (32)
High-risk	59 (0)	6 (32)	0 (38)



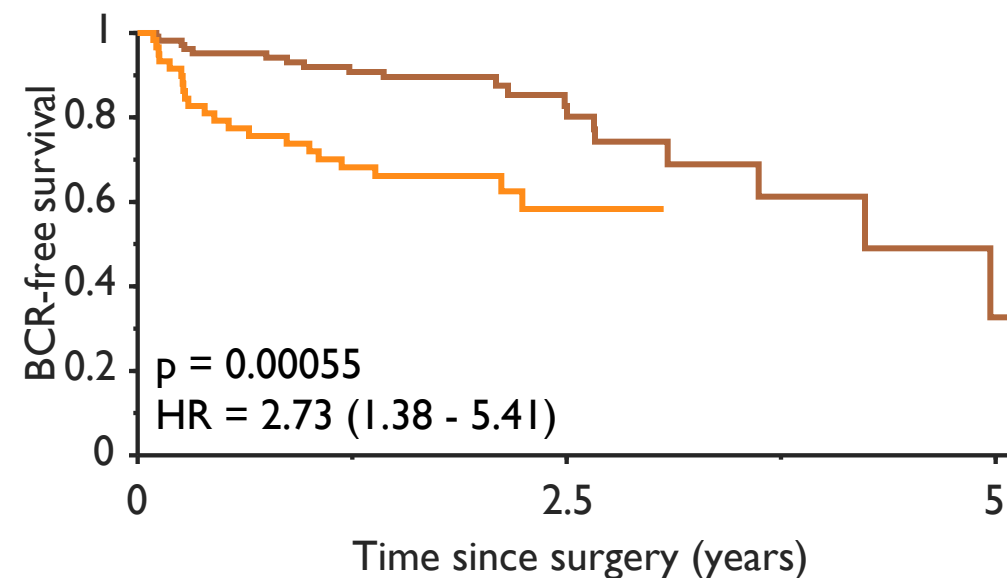
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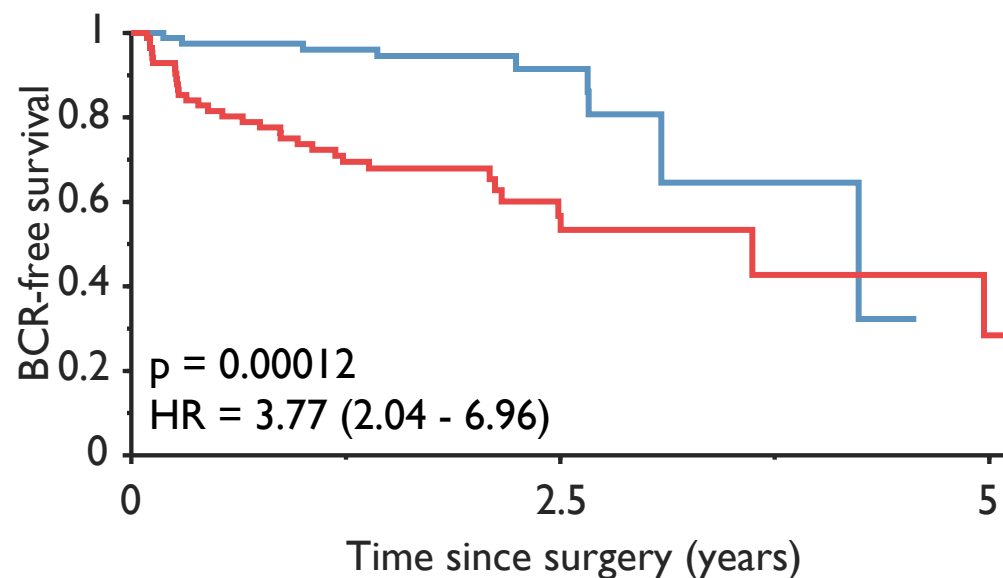


	Number at risk (number censored)		
Low/inter.-risk	108 (0)	32 (63)	2 (86)
High-risk	59 (0)	6 (32)	0 (38)



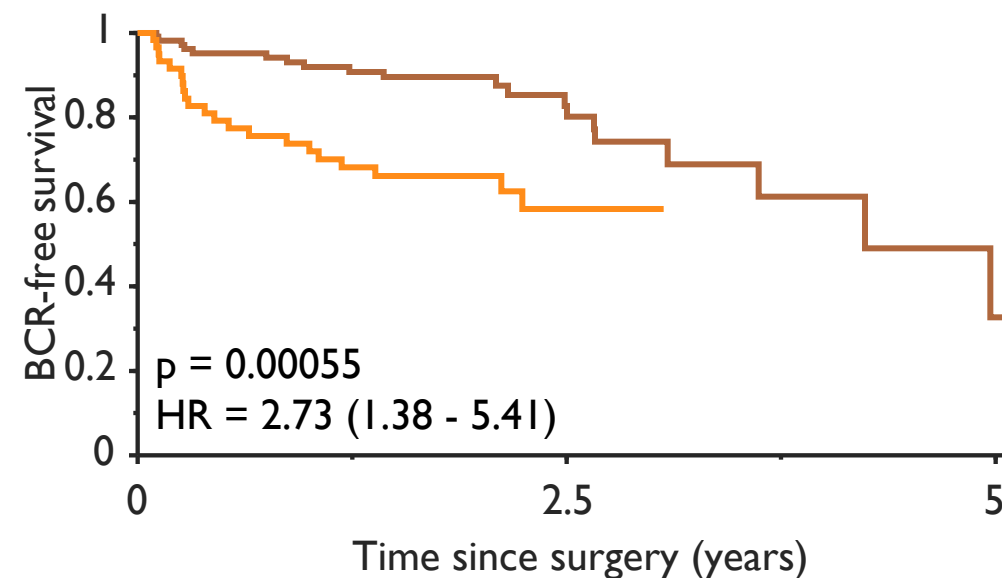
Results: Histotyping+ vs. Decipher

Histotyping+ (c-index = 0.75)



	Number at risk (number censored)		
Low-risk	83 (0)	21 (57)	0 (74)
High-risk	84 (0)	17 (38)	2 (50)

Decipher (c-index = 0.70)



	Number at risk (number censored)		
Low/inter.-risk	108 (0)	32 (63)	2 (86)
High-risk	59 (0)	6 (32)	0 (38)



Conclusions

- Histotyping was prognostic of BCR
- Performance similar to Decipher
- Computer analysis of morphology could supplement existing prognostic tools
- Future work: Predictive of treatment response, metastasis outcome



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