Supplementary Online Content

L'Imperio V, Wulczyn E, Plass M, et al. Pathologist validation of a machine learning–derived feature for colon cancer risk stratification. *JAMA Netw Open.* 2023;6(3):e2254891. doi:10.1001/jamanetworkopen.2022.54891

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. TAF Scoring per Pathologist
Gray boxes represent cases with agreement on the TAF extent between the two observers.

TAF Scoring (Path 2)	**TAF Scoring (Path 1)**				*Total*
	Not observed	*Unifocal*	*Multifocal*	*Widespread*	
Not observed	120	13	6	2	141
Unifocal	11	15	15	9	50
Multifocal	-	2	10	6	18
Widespread	2	3	4	40	49
Total	133	33	35	57	258

Additional TAF scoring information
There was initial disagreement on the presence/absence of TAF in 34 of 258 cases (14%). Of the 34 cases with disagreement on the presence versus absence of TAF, 16 were ultimately resolved as present; 10 as unifocal, 4 as multifocal, and 2 as widespread. For the cases with TAF identified by both pathologists on initial review (n=104), there was initial agreement on TAF extension in 65 (63%) cases. For cases with initial disagreement on TAF extension, the cases scored as unifocal by one of the pathologists but not the other (n=29) were typically “upgraded” to either multifocal (n=17) or widespread (n=11) after joint review, with only 1 case retaining the unifocal designation. For cases initially scored as multifocal TAF by a single pathologist (n=27), 17 were resolved as multifocal and 10 were resolved as widespread, with none assigned to the unifocal group. For cases initially scored as widespread TAF by only one pathologist (n=22), most (n=21) were resolved as widespread after alignment, with only 1 case resolving as unifocal. In summary, these data demonstrate substantial agreement for widespread TAF and the most common need for resolution corresponded to the distinction between unifocal and multifocal TAF.

eTable 2. Expanded Multivariable Analysis for Association With Clinical Outcome

Variable	Level	All-cause mortality (no. observed: 121/258, 47%)		Disease-specific mortality (no. observed: 36/258, 14%)	
		HR [95% CI]	p-value	HR [95% CI]	p-value
Age	N/A	**1.07 [1.05-1.09]**	**<0.005**	1.01 [0.98-1.04]	0.68
Sex	Female	1.0 (reference)			
	Male	0.93 [0.64-1.36]	0.72	0.86 [0.44-1.68]	0.66
Stage	II	1.0 (reference)			
	III	**1.60 [1.03-2.51]**	**0.04**	**3.57 [1.39-9.18]**	**0.008**
Grade	Low	1.0 (reference)			
	High	0.75 [0.48-1.17]	0.20	0.56 [0.25-1.23]	0.15
Tumor Loc.	Left	1.0 (reference)			
	Right	1.08 [0.72-1.61]	0.72	0.82 [0.40-1.65]	0.57
Hist. Type	Adeno	1.0 (reference)			
	Mucinous	0.78 [0.40-1.52]	0.46	0.94 [0.32-2.78]	0.91
LVI	Absent / NOS	1.0 (reference)			
	Present	1.15 [0.72-1.84]	0.55	1.13 [0.45-2.85]	0.80
TAF (categorical)	Absent	1.0 (reference)			
	Unifocal	1.30 [0.64-2.65]	0.46	0.58 [0.13-2.62]	0.48
	Multifocal	0.85 [0.46-1.56]	0.59	0.79 [0.23-2.76]	0.72
	Widespread	**1.79 [1.14-2.81]**	**0.01**	**2.19 [1.01-4.75]**	**0.05**

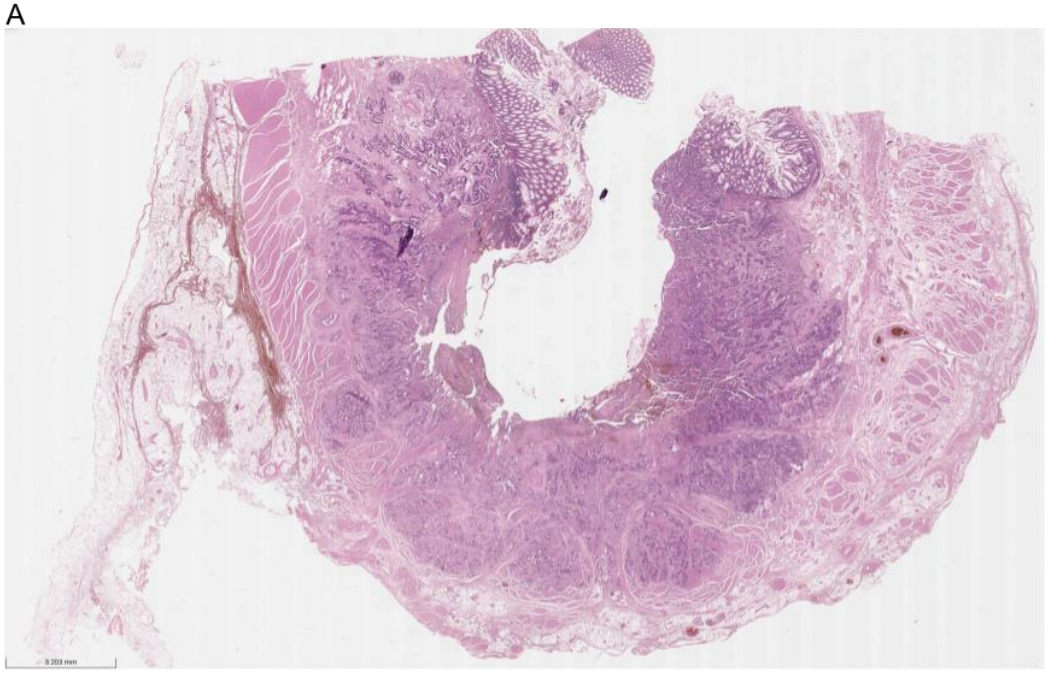
eTable 3. Expanded Univariable Analysis for Association With Clinical Outcome

Variable	Level	All-cause mortality (no. observed: 121/258, 47%)		Disease-specific mortality (no. observed: 36/258, 14%)	
		HR [95% CI]	p-value	HR [95% CI]	p-value
Age	N/A	**1.06 [1.04-1.09]**	**<0.005**	1.00 [0.98-1.03]	0.85
Sex	Female	1.0 (reference)			
	Male	0.95 [0.66-1.35]	0.77	0.94 [0.49-1.82]	0.86
Stage	II	1.0 (reference)			
	III	**1.62 [1.12-2.34]**	**0.01**	**3.94 [1.72-9.00]**	**<0.005**
Grade	Low	1.0 (reference)			
	High	0.91 [0.60-1.36]	0.63	0.89 [0.42-1.89]	0.76
Tumor Loc.	Left	1.0 (reference)			
	Right	1.37 [0.94-2.00]	0.10	0.77 [0.40-1.48]	0.43
Hist. Type	Adeno	1.0 (reference)			
	Mucinous	0.87 [0.46-1.67]	0.68	1.19 [0.42-3.36]	0.74
LVI	Absent / NOS	1.0 (reference)			
	Present	1.45 [0.97-2.14]	0.07	2.03 [0.92-4.45]	0.08
TAF (categorical)	Absent	1.0 (reference)			
	Unifocal	0.95 [0.49-1.86]	0.88	0.72 [0.16-3.14]	0.66
	Multifocal	1.05 [0.58-1.92]	0.87	0.91 [0.26-3.15]	0.88
	Widespread	**2.09 [1.40-3.14]**	**<0.005**	**3.17 [1.56-6.42]**	**<0.005**

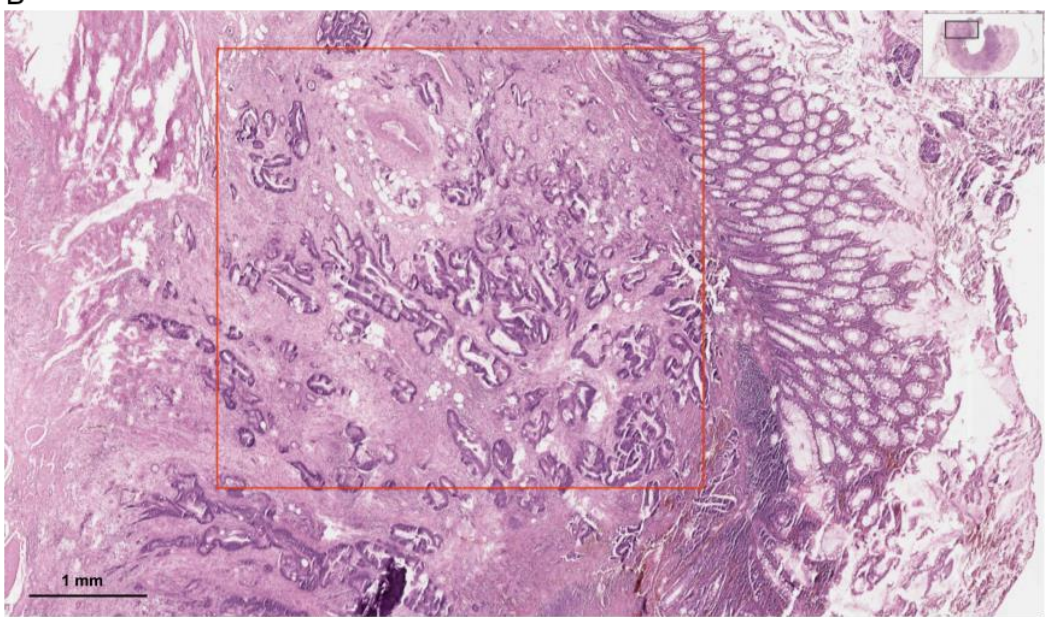
eFigure 1. Example 1 Used for Illustrating the Tumor Adipose Feature (TAF) in the Context of a Slide, (A) the Full Slide and (B-D) Zoomed in Panels. In the zoomed-in panels, the top right “minimap” shows the location of the crop as a black box. Note, the zoomed in panels represent regions enriched for TAF according to the published computational model, these regions do not correspond to the specific TAF “patches” themselves or to pathologist-identified TAF. Width of full portion of image pictured in B is 9mm.

Additional training details: Pathologists reviewed both previously published TAF patches and the TAF regions highlighted by the bounding boxes in Supplementary Figures 1-4. These examples provided contextual examples of TAF (as identified based on the previously described computational feature clustering). The overall TAF training and review process was established via discussion amongst pathologists and researchers involved in the initial TAF study and consisted of approximately 4 hours of image review and discussion followed by independent scoring and discussion of discordant cases across approximately one hundred archived cases.

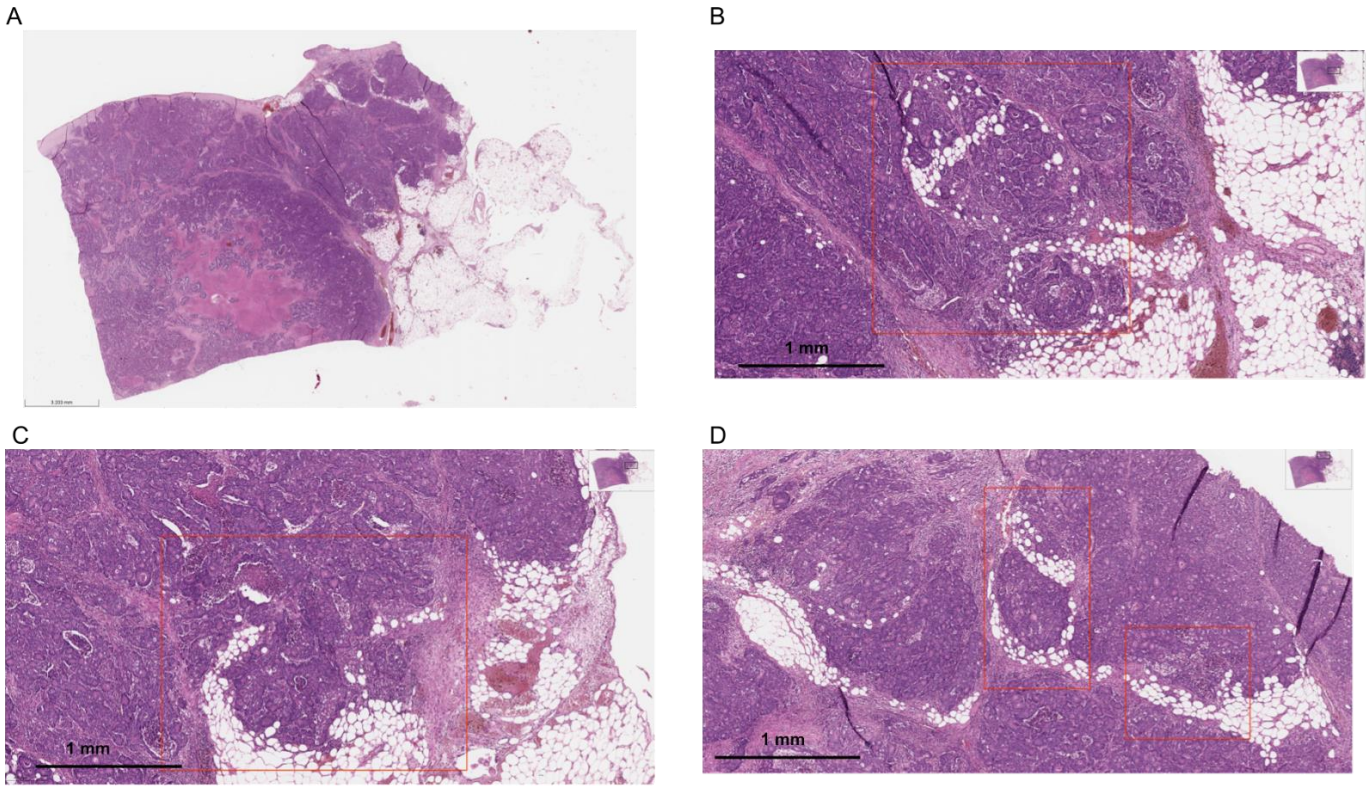
A



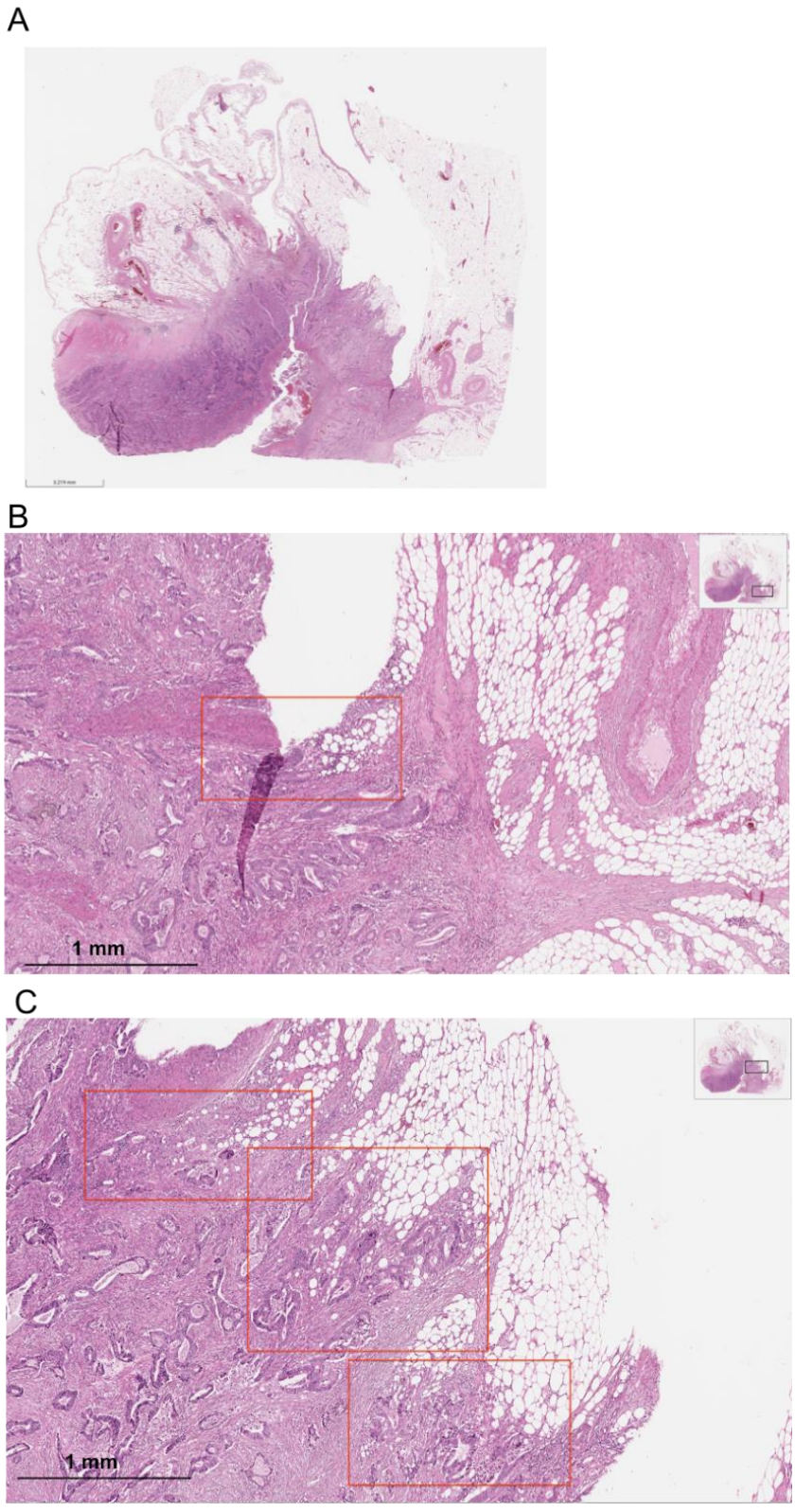
B



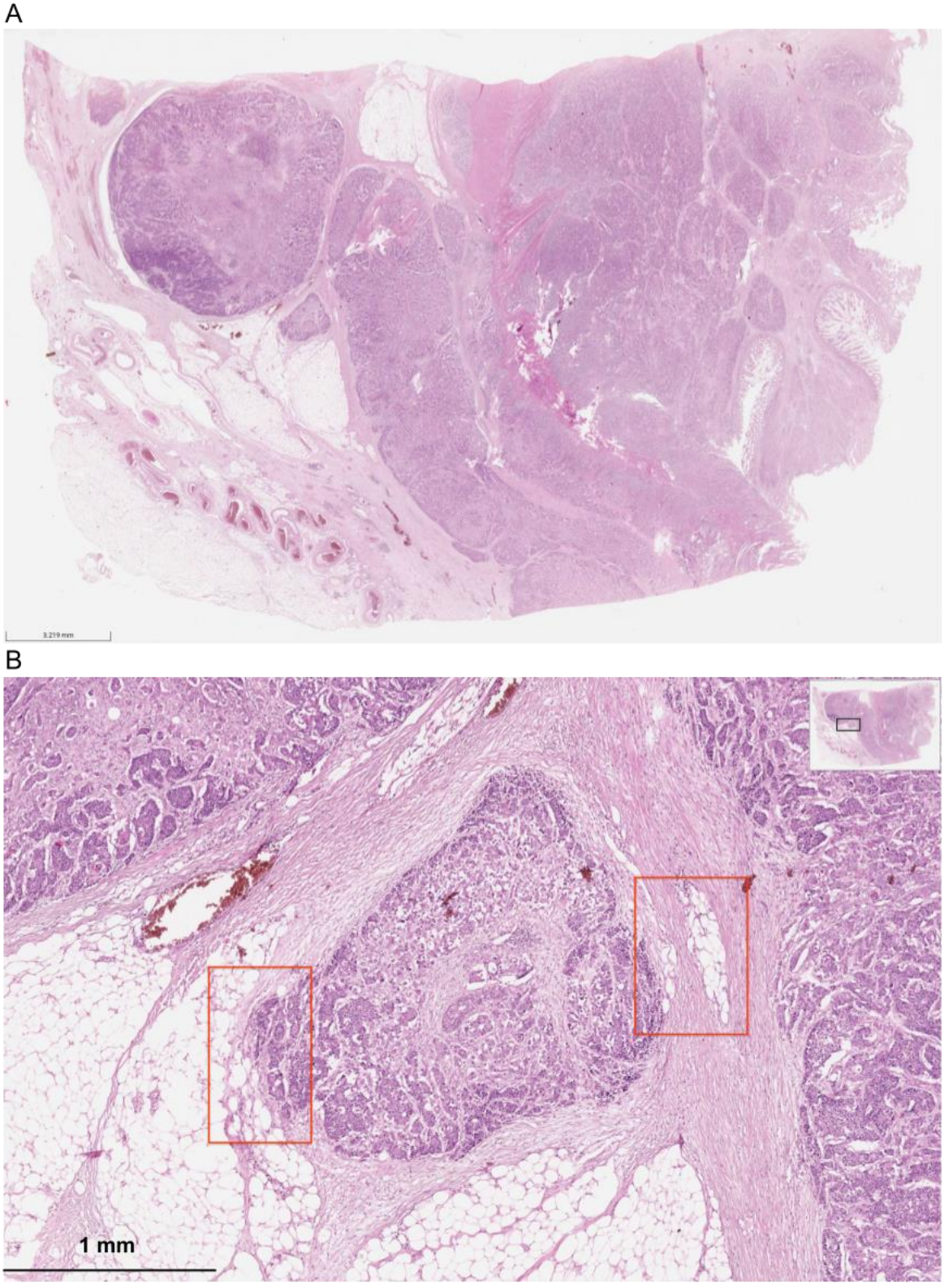
eFigure 2. Example 2 Used for Illustrating the Tumor Adipose Feature (TAF) in the Context of a Slide. (A) the full slide and (B-D) zoomed in panels. In the zoomed-in panels, the top right “minimap” shows the location of the crop as a black box. Note, the zoomed in panels represent regions enriched for TAF based on the previously published computational model, these regions do not correspond to the specific TAF “patches” themselves. Width of full portion of image pictured in B-D is 4.5mm.



eFigure 3. Example 3 Used for Illustrating the Tumor Adipose Feature (TAF) in the Context of a Slide, (A) the Full Slide and (B-C) Zoomed in Panels. In the zoomed-in panels, the top right “minimap” shows the location of the crop as a black box. Note, the zoomed in panels represent regions enriched for TAF based on the previously published computational model, these regions do not correspond to the specific TAF “patches” themselves. Width of full portion of image pictured in B-C is 4.5mm.

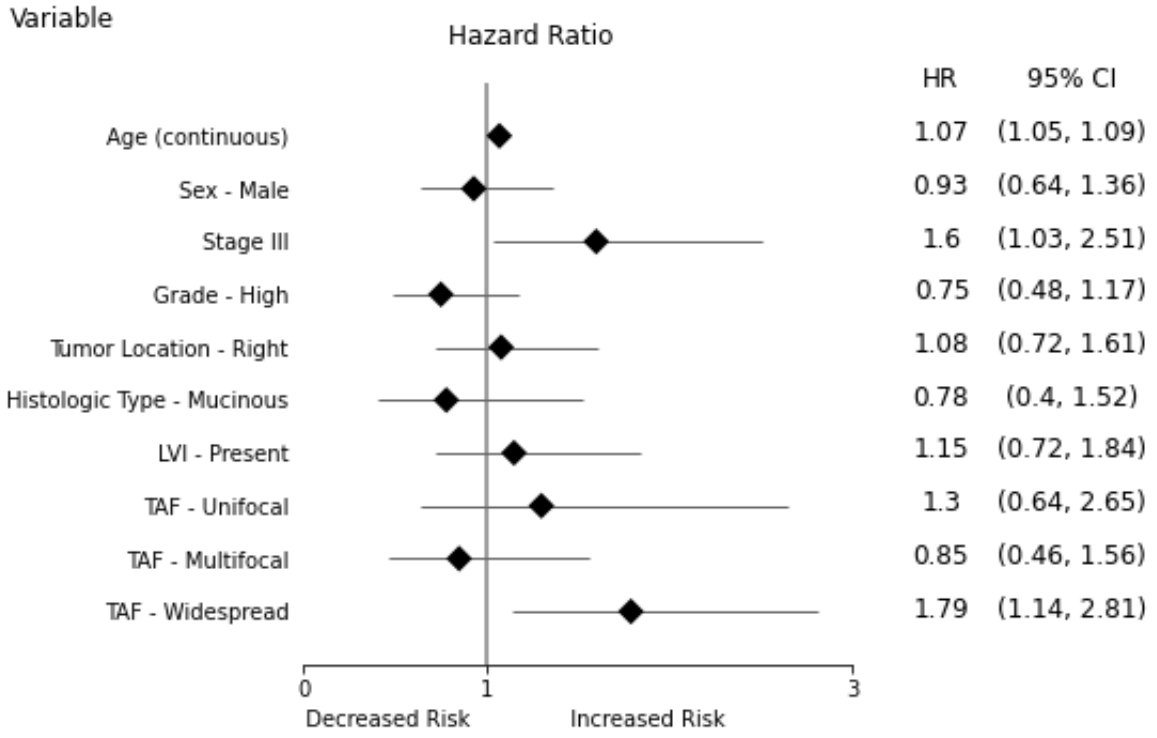


eFigure 4. Example 4 Used for Illustrating the Tumor Adipose Feature (TAF) in the Context of a Slide, (A) the Full Slide and (B) as a Zoomed in Panel. In the zoomed-in panel, the top right “minimap” shows the location of the crop as a black box. Note, the zoomed in panels represent regions enriched for TAF based on the previously published computational model, these regions do not correspond to the specific TAF “patches” themselves. Width of full portion of image pictured in B is 4.5mm.



eFigure 5. Forest Plots for Expanded Multivariable Analysis Corresponding to eTable 2

Overall Survival:



Disease Specific Survival: