Supplementary Information

Supplementary Figure Legends

Supplementary Figure 1 Epithelial-mesenchymal transition (EMT) occurs in tumors with missense *Trp53* mutation. The H&E-stained sections of a cecum tumor and representative metastases in the liver and diaphragm arising in a AKP^{270/fl} mouse 5 months post TAM injection are shown (top panels). Immunohistochemical stains show strong nuclear expression of β -catenin, loss of E-cadherin expression and strong expression of vimentin in both primary tumor and liver and diaphragm metastases, indicating that EMT has occurred in all the lesions shown here (bottom three panels). Black arrows indicate examples of areas with a loss of E-cadherin expression. The representative photomicrographs of H&E-stained sections were shown with low power magnification for orientation; the serial sections were subjected to immunohistochemical staining and the boxed area with stains for β -catenin, E-cadherin and vimentin were shown as high power magnification. Scale bars: 20 µm for all the images.

Supplementary Figure 2 CDX2 expression in mouse colon tumors with missense

Trp53 mutation. Immunohistochemical staining of CDX2 in primary and metastatic lesions arising in two representative AKP^{270/fl} mice after TAM induction. Strong CDX2 expression is found in moderately differentiated lung and lymph node metastases in one mouse (panel A, lymph node 1 and lung 1), while the primary and metastatic lesions that have undergone EMT in the second mouse show reduced CDX2 expression (in cecum, and lung, liver, diaphragm metastases, panel B) or very weak CDX2 expression (in lymph node metastasis, panel B). Scale bars: 20 μm.

Supplementary Figure 3 The primary and metastatic lesions arising in a AKP^{fl/fl} mouse after TAM injection. H&E stains (left panels) and immunohistochemical stains for β -catenin (right panels) are shown for the primary tumors (A, proximal colon and cecum) and the metastatic lesions (B, lymph node and liver) arising in AKP^{fl/fl} mouse after TAM injection. (C) Immunohistochemical staining of E-cadherin for the tumors described in (A and B) showed that both the primary and the metastatic lesions found in this mouse still maintain the epithelial profile. The dashed lines indicate the boundary of the muscularis propria. Scale bars: 100 µm for panels A and B; 20 µm for panel C.

Supplementary Figure 4 CDX2 expression in mouse colon tumors with null *Trp53* **mutation.** Immunohistochemical staining of CDX2 in primary and metastatic lesions arising in three AKP^{fl/fl} mice after TAM injection. (A) Weak CDX2 expression is found in moderately differentiated lymph node metastasis from the mouse described in Fig. 4a. (B) and (C) Strong CDX2 expression is found in primary and metastatic lesions in mice that have been described in Fig. 4b and Supplementary Figure 3B, respectively. Scale bars: 20 μm.

Supplementary Figure 5 Principal component (PC) analyses of gene expression and the distances between pairs of samples in the full space for mouse colon tumors with mutant *Trp53*. Total RNA was extracted from laser capture microdissected (LCM) colon tumor samples generated in AKP^{270/fl} mice (n=6) or AKP^{fl/fl} (n=6) mice 3 months post TAM injection. Microdissected wild-type colon cells were used as controls (WT cont, n=3). The first 5 principal components (PC) for log2-transformed mRNA array data using all 24562 probe-sets are shown. Supplementary Figure 6 Principal component (PC) analyses of gene expression and the distances between pairs of samples in the full space for organoids derived from the mouse colon tumors with mutant *Trp53*. Total RNA was extracted from organoids derived from colon tumors generated in $AKP^{270/fl}$ mice (n=3) or $AKP^{fl/fl}$ mice (n=2) 3 months post TAM injection. The organoids derived from the adenomas in the *Apc*^{fl/fl} mice (Cont 1, after 15 days post TAM injection, n=3) and wild-type colon epithelium (Cont 2, n=4) were used as controls. The first 5 principal components (PC) for log2-transformed mRNA array data, and the distances between pairs of samples for all 24562 probe-sets are shown.

Supplementary Figure 7 Principal component (PC) analyses of gene expression in human colorectal tumors from TCGA database. We compared 9 tumors with TP53 codon 273 mutations to 36 tumors with null mutations (caused by frame shift, splice site, and nonsense mutations, see Supplementary Table 3 for details) by analyzing log2-transformed normalized counts (after adding 1 to each value) for colorectal data from TCGA. The first 5 PCs are shown.



Supplementary Figure 2





Supplementary Figure 3



Supplementary Figure 4

	Distan	Distances between samples													
	AKP ^{fl/fl}	AKP ^{fl/fl}	AKP ^{fl/fl}	AKP ^{fl/fl}	AKP ^{fl/fl}	AKP ^{fl/fl}	AKP ^{270/fl}	WT cont	WT cont	WT cont					
AKP ^{fl/fl}	0	88	82	95	98	97	95	82	96	98	94	97	157	157	158
AKP ^{fl/fl}	88	0	75	85	87	89	94	90	94	95	91	91	153	154	156
AKP ^{fl/fl}	82	75	0	81	81	81	92	84	90	91	87	89	153	152	156
AKP ^{fl/fl}	95	85	81	0	90	96	99	95	100	103	93	94	155	155	157
AKP ^{fl/fl}	98	87	81	90	0	89	98	95	91	95	92	90	151	151	154
AKP ^{fl/fl}	97	89	81	96	89	0	100	96	99	97	96	97	146	144	148
AKP ^{270/fl}	95	94	92	99	98	100	0	95	96	98	96	100	153	153	154
AKP ^{270/fl}	82	90	84	95	95	96	95	0	94	99	95	93	152	153	155
AKP ^{270/fl}	96	94	90	100	91	99	96	94	0	95	89	98	155	155	158
AKP ^{270/fl}	98	95	91	103	95	97	98	99	95	0	97	102	159	158	161
AKP ^{270/fl}	94	91	87	93	92	96	96	95	89	97	0	94	156	156	158
AKP ^{270/fl}	97	91	89	94	90	97	100	93	98	102	94	0	153	154	155
WT cont	157	153	153	155	151	146	153	152	155	159	156	153	0	79	83
WT cont	157	154	152	155	151	144	153	153	155	158	156	154	79	0	79
WT cont	158	156	156	157	154	148	154	155	158	161	158	155	83	79	0

	Distanc	Distances between samples													
	AKP ^{fl/fl}	AKP ^{fl/fl}	AKP ^{270/fl}	AKP ^{270/fl}	AKP ^{270/fl}	Cont 1	Cont 1	Cont 1	Cont 2	Cont 2	Cont 2	Cont 2			
AKP ^{fl/fl}	0	73	74	69	73	114	102	96	127	132	131	121			
AKP ^{fl/fl}	73	0	66	73	58	115	100	94	119	123	122	113			
AKP ^{270/fl}	74	66	0	70	63	113	95	91	121	121	121	113			
AKP ^{270/fl}	69	73	70	0	67	107	103	98	131	131	132	123			
AKP ^{270/fl}	73	58	63	67	0	114	97	91	122	122	120	111			
Cont 1	114	115	113	107	114	0	102	99	137	128	135	120			
Cont 1	102	100	95	103	97	102	0	46	102	108	108	84			
Cont 1	96	94	91	98	91	99	46	0	100	104	104	83			
Cont 2	127	119	121	131	122	137	102	100	0	102	80	75			
Cont 2	132	123	121	131	122	128	108	104	102	0	80	85			
Cont 2	131	122	121	132	120	135	108	104	80	80	0	79			
Cont 2	121	113	113	123	111	120	84	83	75	85	79	0			

#Mice		10	10	13	14
Rates per mouse	s per mouse SM or worse		2.2	7.3	8.9
All lesions		AK	AKP ^{270/+}	AKP ^{fi/fi}	AKP ^{270/fl}
13.1	AK		0.016	1.4E-15	2.2E-16
18.5	AKP ^{270/+}	0.0028		2.1E-08	3.5E-12
28.0	AKP ^{fl/fl}	5.1E-15	3.1E-06		0.16
24.2	AKP ^{270/fl}	6.8E-10	0.0034	0.054	

Supplementary Table 1. *P*-values of Exact Poisson Tests

P-values below the diagonal test differences in the total number of lesions, while those above the diagonal test "SM or worse". AKP^{fl/fl} has slightly more lesions than AKP^{270/fl} (28.0 vs 24.2 per mouse, *P* = .054), but slightly less "SM or worse" lesions (7.3 vs 8.9 per mouse, *P* = .16).

Supplementary table 2. Top 10 gene sets for list of genes up- or down-regulated in both $AKP^{270/fl}$ and $AKP^{fl/fl}$ tumor cells compared to wild-type cells for both tissues and organoids (*P* <.05, FC >1.3)

	N o		Number of	<i>P</i> -value,	Number of	Estimated False	Observed
			those	one-sided	gene sets	discovery rate,	/
		in gene	genes we	Fisher	that good in	based on 100	/ Expected
Regulation	Gene set title	set	selected	Exact Test	our data	permuted data-sets	Expected
Up	G2M_CHECKPOINT	186	24	1.89E-09	1	0	4.29
Up	E2F_TARGETS	195	20	1.82E-06	2	0	3.41
Up	ΗΥΡΟΧΙΑ	188	19	4.09E-06	3	0	3.36
Up	MITOTIC_SPINDLE	193	17	7.64E-05	4	0	2.93
Up	UNFOLDED_PROTEIN_RESPONSE	108	11	0.00041	5	0.002	3.38
Up	GLYCOLYSIS	192	15	0.00072	6	0.0033	2.6
Up	TNFA_SIGNALING_VIA_NFKB	189	14	0.0018	7	0.0043	2.46
Up	MTORC1_SIGNALING	191	14	0.002	8	0.0038	2.44
Up	EPITHELIAL_MESENCHYMAL_TRANSITION	184	13	0.0038	9	0.0089	2.35
Up	IL2_STAT5_SIGNALING	192	12	0.014	10	0.048	2.08
Down	PEROXISOME	101	15	2.84E-06	1	0	4.16
Down	INTERFERON_GAMMA_RESPONSE	177	20	5.38E-06	2	0	3.16
Down	XENOBIOTIC_METABOLISM	192	20	1.82E-05	3	0	2.92
Down	FATTY_ACID_METABOLISM	145	16	6.18E-05	4	0	3.09
Down	BILE_ACID_METABOLISM	109	13	0.00014	5	0	3.34
Down	ESTROGEN_RESPONSE_EARLY	190	18	0.00016	6	0	2.65
Down	REACTIVE_OXIGEN_SPECIES_PATHWAY	46	8	0.0002	7	0	4.87
Down	APOPTOSIS	153	15	0.00039	8	0	2.75
Down	ADIPOGENESIS	191	16	0.0014	9	0.0044	2.35
Down	ANDROGEN_RESPONSE	94	10	0.0019	10	0.006	2.98

Methods: We mapped mouse genes to human homologs using only 1-to-1 best homologs from NCBI Homologene build 68, giving 15850 distinct genes. We asked that comparisons of $AKP^{270/fl}$ and $AKP^{fl/fl}$ tumor cells give P < .05 and fold-changes of at least 1.3 fold compared to wild-type cells for both the tissue and organoid analyses (the intersection of 4 comparisons) and obtained 477 up and 566 down genes. We used one-sided Fisher Exact Tests to ask if the intersection of our up and down gene lists with 50 Hallmark gene sets from the Molecular Signatures Database (MSigDB v6.1, http://www.broadinstitute.org/gsea/msigdb/index.jsp) were larger than expected by chance. We estimated false discover rates (FDRs) based on similar tests of 100 data sets in which the identities of our 15850 genes were randomly permuted, and estimated the FDR as the average number of gene sets giving *P*-values smaller than *P* in the permuted data sets, divided by the number of gene sets with *P*-values that small in the actual data. The last column is the number of genes in the intersections divided by the number expected by chance given the size of our list and the size of the gene set.

Supplementary Table 3. TCGA samples used for comparison of *TP53* null mutations with mutations at amino acid 273.

Sample	TP53 mutation	Variant classification	TP53 group
TCGA-AA-3949-01	p.R273H	Missense_Mutation	273
TCGA-AA-3556-01	p.R273H	Missense_Mutation	273
TCGA-AA-3561-01	p.R273C	Missense_Mutation	273
TCGA-AA-3844-01	p.R273C	Missense Mutation	273
TCGA-AA-A01D-01	p.R273H	Missense_Mutation	273
TCGA-AY-4070-01	p.R273C	Missense_Mutation	273
TCGA-AG-3578-01	p.R273H	Missense_Mutation	273
TCGA-AG-3581-01	p.R273H	Missense_Mutation	273
TCGA-AG-3587-01	p.R273H	Missense_Mutation	273
TCGA-AA-3811-01	p.H179fs	Frame_Shift_Del	null
TCGA-AG-A02N-01	p.T125M	Splice_Site	null
TCGA-AA-3517-01	p.Q331H	Splice Site	null
TCGA-AA-3866-01	p.C176*	Nonsense_Mutation	null
TCGA-AA-3930-01	p.R306*	Nonsense_Mutation	null
TCGA-AA-3972-01	p.R342*	Nonsense Mutation	null
TCGA-AA-A00O-01	p.PS98fs	Frame Shift Del	null
TCGA-AA-A02W-01	p.R196*	Nonsense Mutation	null
TCGA-AG-4001-01	p.V122fs	Frame Shift Del	null
TCGA-A6-2678-01	p.R196*	Nonsense Mutation	null
TCGA-A6-3807-01	p.Y236*	Nonsense Mutation	null
TCGA-AA-3524-01	p.R306*	Nonsense Mutation	null
TCGA-AA-3560-01	p.F212fs	Frame Shift Del	null
TCGA-AA-3673-01	p.T125T	Splice Site	null
TCGA-AA-3842-01	p.R335fs	Frame Shift Del	null
TCGA-AA-3848-01	, p.I195fs	Frame Shift Ins	null
TCGA-AA-3856-01	p.P322fs	Frame Shift Del	null
TCGA-AA-3858-01	p.L35fs	Frame Shift Ins	null
TCGA-AA-3860-01	p.P60fs	Frame Shift Del	null
TCGA-AA-3867-01	p.P27fs	Frame Shift Del	null
TCGA-AA-3955-01	p.LRK289fs	Frame Shift Del	null
TCGA-AA-3977-01	p.R213*	Nonsense Mutation	null
TCGA-AA-A00D-01	p.R196*	Nonsense Mutation	null
TCGA-AA-A01Z-01	p.Q331fs	Frame Shift Ins	null
TCGA-AG-3890-01	p.R335fs	Frame Shift Ins	null
TCGA-AG-3898-01	p.PK318fs	Frame Shift Ins	null
TCGA-AG-4005-01	p.R306*	Nonsense Mutation	null
TCGA-AG-4015-01	p.Q331*	Nonsense Mutation	null
TCGA-AG-A01Y-01	p.R306*	Nonsense Mutation	null
TCGA-AG-A026-01	p.S33fs	Splice Site	null
TCGA-AG-A02X-01	p.E285*	Nonsense Mutation	null
TCGA-AA-3553-01	p.R213*	Nonsense Mutation	null
TCGA-A6-2674-01	p.R213*	Nonsense Mutation	null
TCGA-AA-3980-01	p.R213*	Nonsense Mutation	null
TCGA-AG-3594-01	p.R213*	Nonsense Mutation	null
TCGA-AG-3999-01	p.R213*	Nonsense_Mutation	null

Supplementary Table 4. Genes in the two-way intersections between 3 studies for weak selection (P < .05, FC >1.3)

	Organoids AKPfl/fl vs	. AKP ^{270/fl}	Tissues AKP ^{fl/fl} vs.	AKP ^{270/fl}	Humans TP53	null vs 273
Symbol	P FC		P FC)	P	FC
Trp53	7.9E-09	0.048	3.6E-05	0.37	2.0E-10	0.22
Cadps	0.019	0.10	0.043	0.27	0.618	1.27
Aspa	0.033	0.28	0.042	0.42	0.965	1.01
Prom2	0.014	0.45	0.003	0.61	0.060	0.41
Grasp	0.046	0.66	0.002	0.66	0.641	1.10
Gabrr1	0.021	0.72	0.043	0.73	0.179	2.35
Olfr45	0.048	0.76	0.016	0.71	#N/A	#N/A
Pced1b	0.023	0.77	0.038	0.68	0.957	1.01
1700016P04Rik	0.028	1.30	0.003	1.35	#N/A	#N/A
Wfdc17	0.026	1.31	0.042	1.68	#N/A	#N/A
Slc35a3	0.004	1.43	0.036	1.43	0.331	0.83
4930523C07Rik	0.037	1.45	0.007	1.63	0.568	0.91
Gm6548	0.019	1.58	0.015	1.78	#N/A	#N/A
Mir3070b	0.004	1.99	0.037	1.35	#N/A	#N/A
Mir669c	0.048	2.17	0.004	1.46	#N/A	#N/A
Ngef	0.674	0.88	0.000	1.49	0.010	1.70
ll6ra	0.535	0.80	0.020	0.51	0.012	0.63
Evx2	0.922	1.01	0.002	0.74	0.012	0.62
Srd5a3	0.264	1.11	0.003	0.67	0.024	0.61
Smarcd3	0.773	0.94	0.038	0.72	0.025	0.65
Fzd2	0.997	1.00	0.020	0.74	0.036	0.50
Sgsm1	0.878	0.98	0.017	0.70	0.036	0.49
Gnai1	0.832	0.88	0.018	0.49	0.047	0.58
Etv5	0.799	0.94	0.050	0.56	0.048	0.55

P: *P*-values based on ANOVA models described in results. FC: fold-change. Human genes were mapped to mouse 1-to-1 best homologs using build 68 of NCBI's Homologene.

Supplementary Table 5. Clinicopathological features of TCGA samples used for comparison of TP53 null mutations with mutations at amino acid 273

Person	TP53	Age	Dead	Days	Tissue_site	Stage12	Stage	P_stage	T_sta	ge N_stage	M_stage	Gender	Year	Radiation _therapy	Histological_type	Residual _tumor
TCGA-AA-3949	R273	87	0	791	colon	s34	s3	stage_iiib	t3	n1	m0	female	2009	no	colon_mucinous_adenocarcinoma	rO
TCGA-AA-3556	R273	78	0	700	colon	s12	s1	stage_i	t2	n0	m0	male	2008	no	NA	r0
TCGA-AA-3561	R273	72	0	424	colon	s12	s2	stage_iia	t3	n0	m0	male	2009	no	colon_adenocarcinoma	r0
TCGA-AA-3844	R273	78	0	454	colon	s34	s3	stage_iiic	; t3	n2	m0	female	2009	yes	colon_adenocarcinoma	r0
TCGA-AA-A01D	R273	47	1	334	colon	s34	s3	stage_iiic	; t3	n2	m0	female	2009	no	colon_mucinous_adenocarcinoma	r0
TCGA-AY-4070	R273	50	1	496	colon	s34	s3	stage_iiic	; t3	n2	m0	female	2007	no	colon_adenocarcinoma	r1
TCGA-AG-3578	R273	76	0	974	rectum	s12	s2	stage_iia	t3	n0	m0	female	2007	no	rectal_mucinous_adenocarcinoma	r0
TCGA-AG-3581	R273	63	0	215	rectum	s12	s1	stage_i	t2	n0	m0	male	2007	no	rectal_adenocarcinoma	r0
TCGA-AG-3587	R273	65	0	1400	rectum	s12	s1	stage_i	t2	n0	m0	male	2007	yes	rectal_adenocarcinoma	r0
TCGA-AA-3811	null	84	1	306	colon	s34	s3	stage_iii	t3	n2	m0	female	2007	no	colon_adenocarcinoma	rO
TCGA-AG-A02N	null	67	0	1885	rectum	s12	s2	stage_ii	t3	n0	m0	male	2005	NA	rectal_adenocarcinoma	rO
TCGA-AA-3517	null	60	0	1186	colon	s12	s2	stage_iia	t3	n0	m0	male	2007	no	colon_adenocarcinoma	r0
TCGA-AA-3866	null	78	0	518	colon	s12	s1	stage_i	t2	n0	m0	female	2006	no	colon_adenocarcinoma	r0
TCGA-AA-3930	null	66	1	61	colon	s34	s4	stage_iv	t3	n2	m1	male	2008	no	colon_adenocarcinoma	r2
TCGA-AA-3972	null	72	0	1551	colon	s34	s4	stage_iv	t3	n1	m1	male	2008	no	colon_adenocarcinoma	r2
TCGA-AA-A00O	null	83	0	822	colon	s34	s3	stage_iiic	; t3	n2	m0	female	2008	no	colon_adenocarcinoma	r0
TCGA-AA-A02W	null	73	0	1247	colon	s12	s1	stage_i	t2	n0	m0	female	2006	no	colon_adenocarcinoma	r0
TCGA-AG-4001	null	74	0	1096	rectum	s12	s2	stage_iia	t3	n0	m0	female	2009	no	rectal_adenocarcinoma	r0
TCGA-A6-2678	null	43	0	1286	colon	s34	s3	stage_iiib	t3	n1	m0	female	2009	no	colon_adenocarcinoma	r0
TCGA-A6-3807	null	53	0	1054	colon	s34	s3	stage_iiic	; t3	n2	m0	female	2009	no	colon_adenocarcinoma	r0
TCGA-AA-3524	null	85	0	1096	colon	s12	s2	stage_ii	t3	n0	m0	male	2007	no	colon_adenocarcinoma	r0
TCGA-AA-3560	null	72	0	608	colon	s34	s3	stage_iiic	; t3	n2	m0	female	2009	no	colon_adenocarcinoma	r0
TCGA-AA-3673	null	53	0	1522	colon	s12	s2	stage_ii	t3	n0	m0	female	2006	no	colon_adenocarcinoma	r0
TCGA-AA-3842	null	51	0	1126	colon	s34	s3	stage_iiia	t2	n1	m0	male	2009	no	colon_adenocarcinoma	r0
TCGA-AA-3848	null	82	1	306	colon	s34	s3	stage_iiic	; t3	n2	m0	female	2009	no	colon_adenocarcinoma	r0
TCGA-AA-3856	null	59	0	30	colon	s12	s2	stage_iia	t3	n0	m0	male	2009	NA	colon_adenocarcinoma	r0
TCGA-AA-3858	null	67	0	945	colon	s12	s1	stage_i	t2	n0	m0	male	2009	no	colon_adenocarcinoma	r0
TCGA-AA-3860	null	53	0	945	colon	s34	s3	stage_iiib	t3	n1	m0	female	2009	no	colon_adenocarcinoma	r0
TCGA-AA-3867	null	74	0	731	colon	s34	s4	stage_iv	t3	n2	m1	male	2007	no	colon_adenocarcinoma	r2
TCGA-AA-3955	null	38	0	638	colon	s34	s3	stage_iiib	t2	n2a	m0	male	2010	no	colon_adenocarcinoma	r0
TCGA-AA-3977	null	65	0	761	colon	NA	NA	NA	t2	n0	NA	male	2009	no	colon_adenocarcinoma	NA
TCGA-AA-A00D	null	70	0	578	colon	s12	s1	stage_i	t2	n0	m0	male	2007	no	colon_adenocarcinoma	r0
TCGA-AA-A01Z	null	68	0	1126	colon	s12	s2	stage_ii	t3	n0	m0	male	2004	no	colon_adenocarcinoma	r0
TCGA-AG-3890	null	62	0	518	rectum	s12	s1	stage_i	t2	n0	m0	male	2009	no	rectal_adenocarcinoma	r0
TCGA-AG-3898	null	61	0	1461	rectum	s12	s2	stage_iia	t3	n0	m0	male	2006	no	rectal_adenocarcinoma	r0
TCGA-AG-4005	null	64	0	427	rectum	s34	s4	stage_iv	t3	n2	m1	male	2007	no	rectal_adenocarcinoma	r0
TCGA-AG-A026	null	66	1	59	rectum	s12	s2	stage_ii	t4	n0	m0	male	2006	NA	rectal_adenocarcinoma	r1
TCGA-AG-A02X	null	77	0	1247	rectum	s12	s1	stage_i	t2	n0	m0	male	2007	NA	rectal_adenocarcinoma	rO
TCGA-AA-3553	null	61	0	730	colon	s12	s1	stage_i	t2	n0	m0	female	2008	no	colon_adenocarcinoma	rO
TCGA-A6-2674	null	71	0	1331	colon	s34	s4	stage_iv	t3	n2	m1	male	2009	no	colon_mucinous_adenocarcinoma	r0
TCGA-AA-3980	null	89	0	822	colon	s12	s1	stage_i	t2	n0	m0	female	2009	no	colon_adenocarcinoma	NA
TCGA-AG-3594	null	77	1	61	rectum	s12	s2	stage_iia	t3	n0	m0	male	2007	no	rectal_mucinous_adenocarcinoma	r0
TCGA-AG-3999	null	61	0	853	rectum	s34	s3	stage_iiic	; t3	n2	m0	female	2008	no	rectal_adenocarcinoma	r0