Diagnosis, staging and treatment of anal cancer

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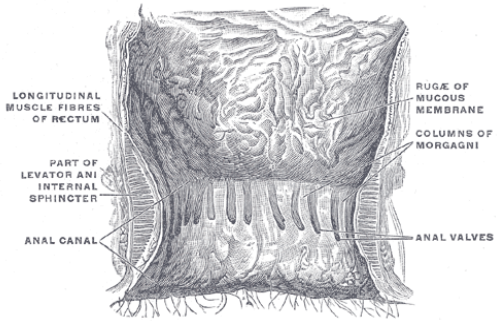
Barcelona, 2017

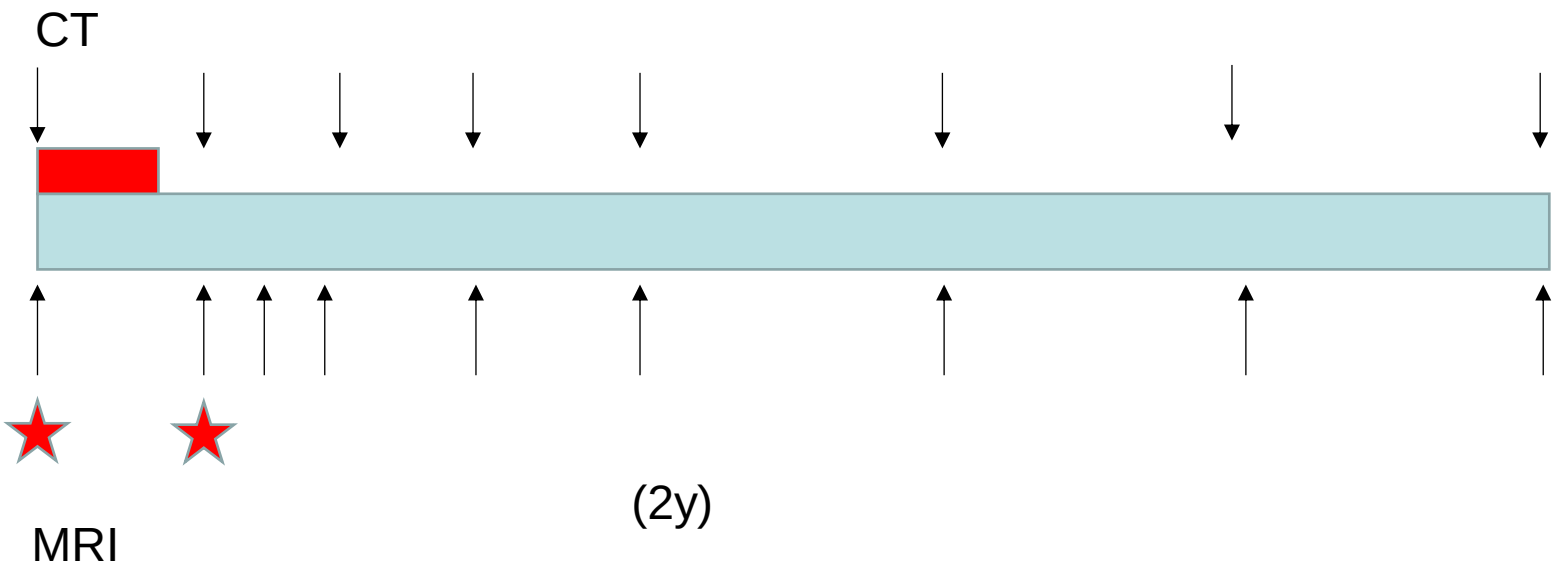
staging

Body CT
ECOG PS, comorbidities, HIV, CD4, viral load
Biopsy (HPV/p16)
Pelvic MRI



cTN	definition	stage
T1	<2cm	I, T1N0
T2	2-5 cm	II, T2,3 N0
T3	>5 cm	III, T4N0 or TxN1,2,3
T4	Organ infiltration	IV, M1
N1	Mesorectum lymph node infilitration	
N2	Internal iliac or inguinal (unilateral)	
N3	Internal iliac or inguinal (bilateral)	

Treatment follow-up in anal cancer



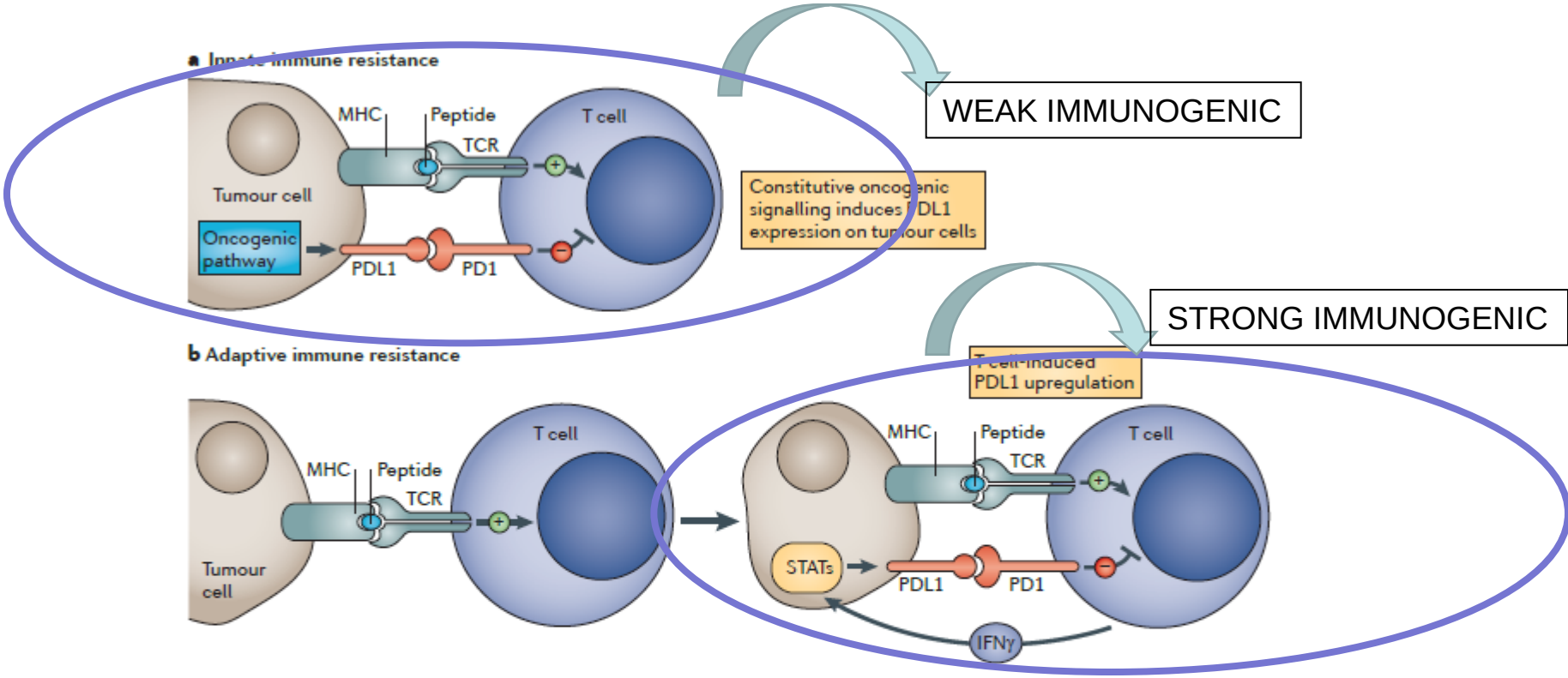
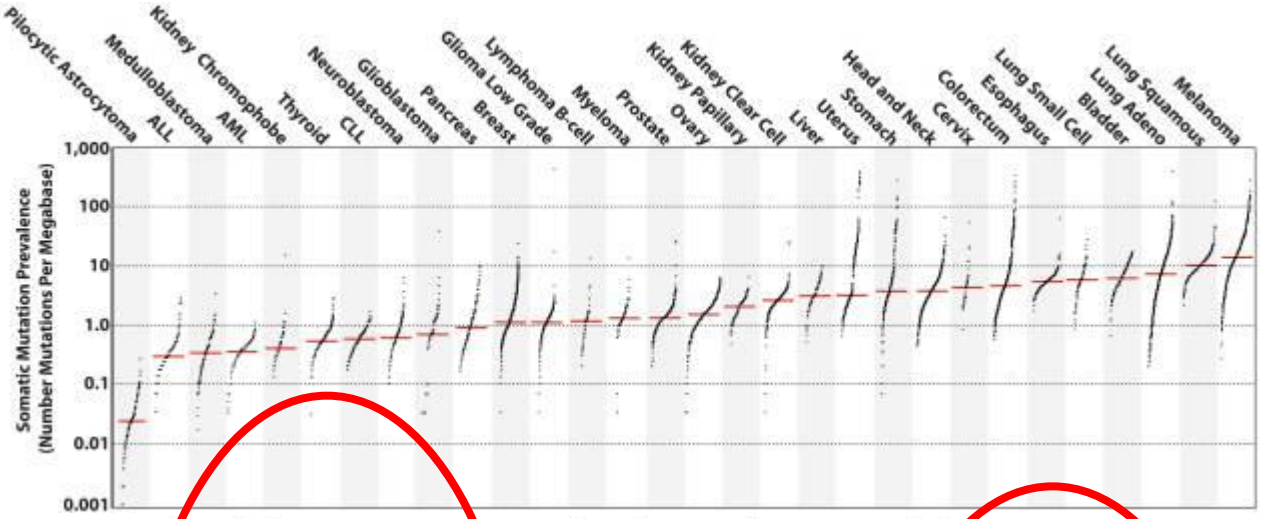
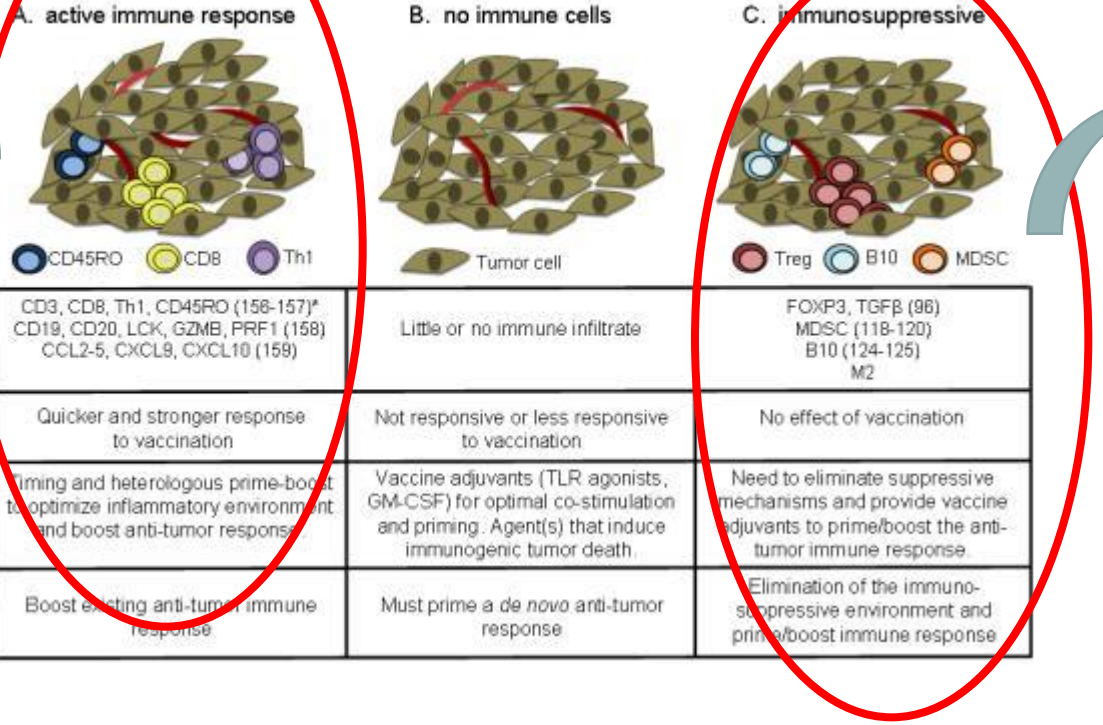


Figure 4 | **Two general mechanisms of expression of immune-checkpoint ligands on tumour cells.** The examples in this figure use the programmed cell death protein 1 (PD1) ligand, PDL1 (also known as B7-H1), for illustrative purposes, although the concept probably applies to multiple immune-checkpoint ligands, including PDL2 (also known as B7-DC). **a** | Innate immune resistance. In some tumours, constitutive oncogenic signalling can upregulate PDL1 expression on all tumour cells, independently of inflammatory signals in the tumour microenvironment. Activation of the AKT and signal transducer and activator of transcription 3 (STAT3) pathways has been reported to drive PDL1 expression. **b** | Adaptive immune resistance. In some tumours, PDL1 is not constitutively expressed, but rather it is induced in response to inflammatory signals that are produced by an active antitumour immune response. The non-uniform expression of PDL1, which is commonly restricted to regions of the tumour that have tumour-infiltrating lymphocytes, suggests that PDL1 is adaptively induced as a consequence of immune responses within the tumour microenvironment. Adaptive induction may be a common mechanism for the expression of multiple immune-checkpoint molecules in tumours. IFNγ, interferon-γ; MHC, major histocompatibility complex; TCR, T cell receptor.



Immune-gene signature



Dominant immune signature	CD3, CD8, Th1, CD45RO (156-157)* CD19, CD20, LCK, GZMB, PRF1 (158) CCL2-5, CXCL9, CXCL10 (159)	Little or no immune infiltrate	FOXP3, TGFβ (96) MDSC (118-120) B10 (124-125) M2
Response to vaccination	Quicker and stronger response to vaccination	Not responsive or less responsive to vaccination	No effect of vaccination
Potential treatment	Timing and heterologous prime-boost to optimize inflammatory environment and boost anti-tumor response	Vaccine adjuvants (TLR agonists, GM-CSF) for optimal co-stimulation and priming. Agent(s) that induce immunogenic tumor death	Need to eliminate suppressive mechanisms and provide vaccine adjuvants to prime/boost the anti-tumor immune response
Result of targeted vaccination	Boost existing anti-tumor immune response	Must prime a *de novo* anti-tumor response	Elimination of the immuno-suppressive environment and prime/boost immune response

Mesenchymal signature

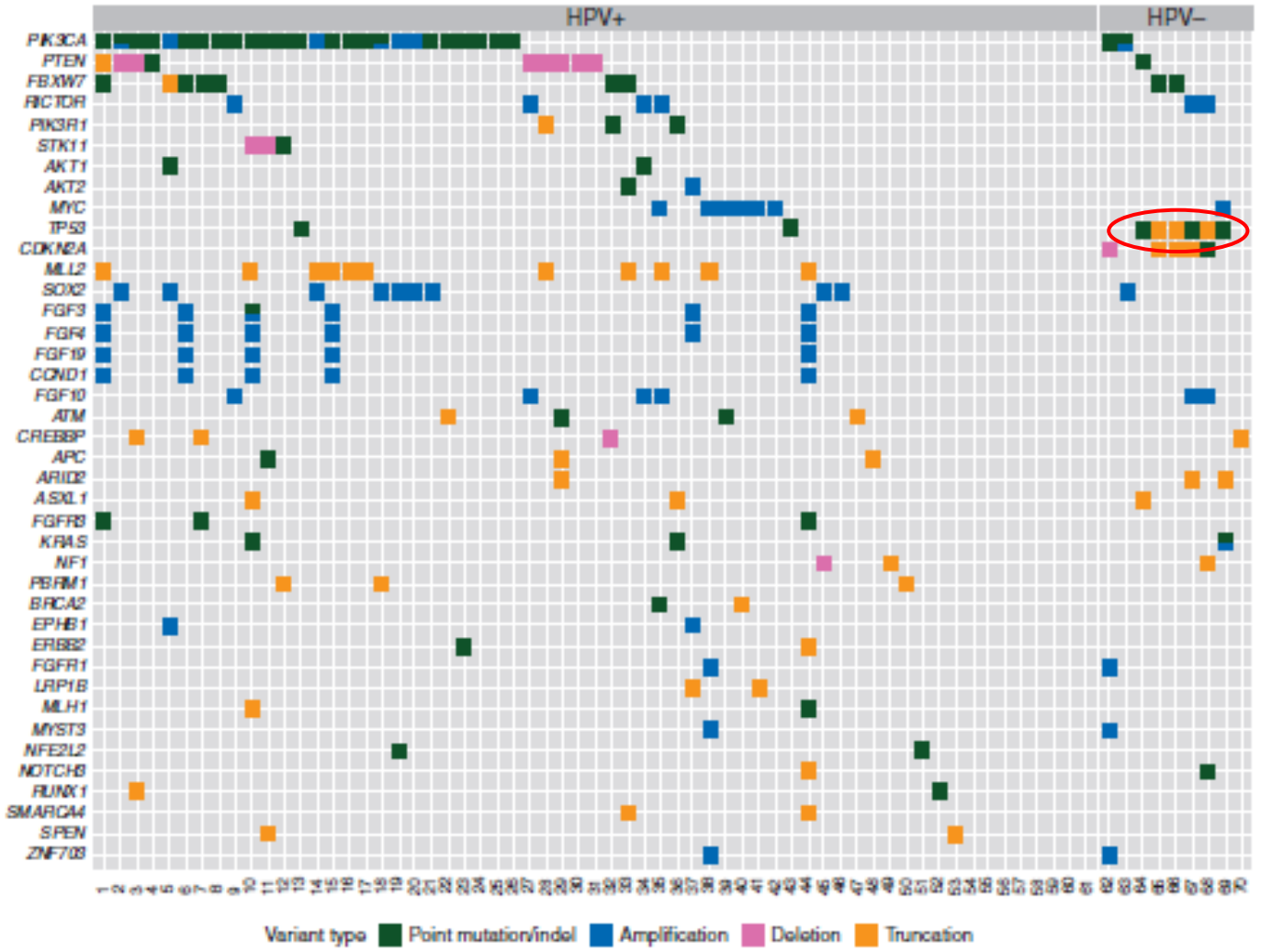
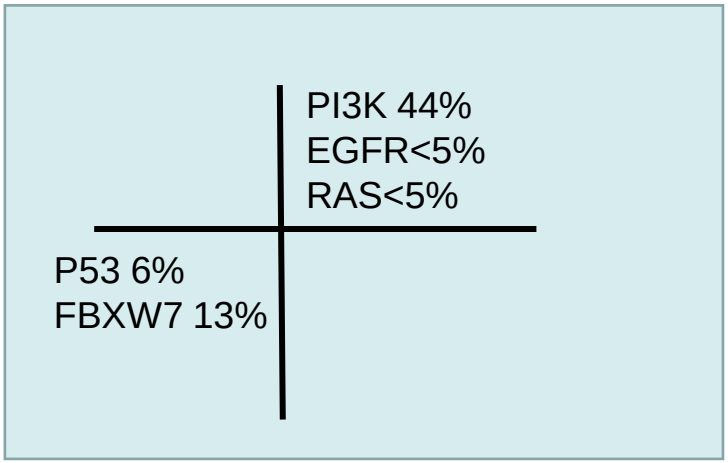


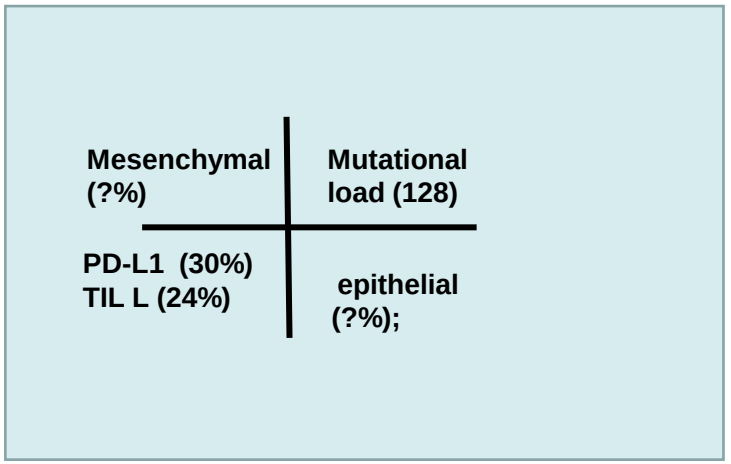
Figure 2. Tile plot demonstrating recurrent genomic alterations ($n \geq 2$) and differences between HPV(+) and HPV(–) cases of ASCC.

Canal Anal

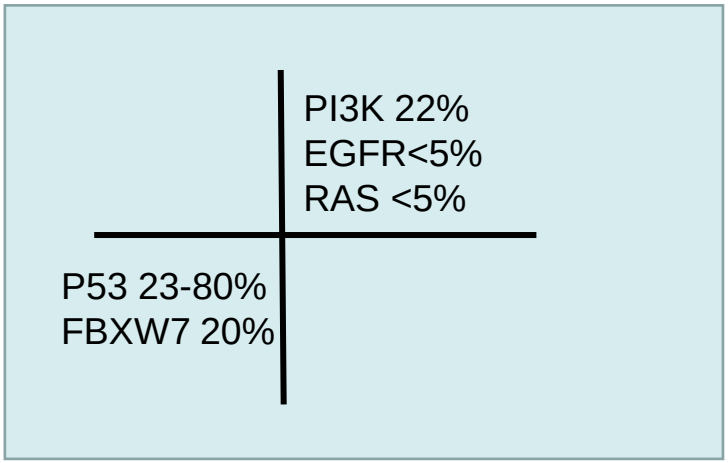
HPV+



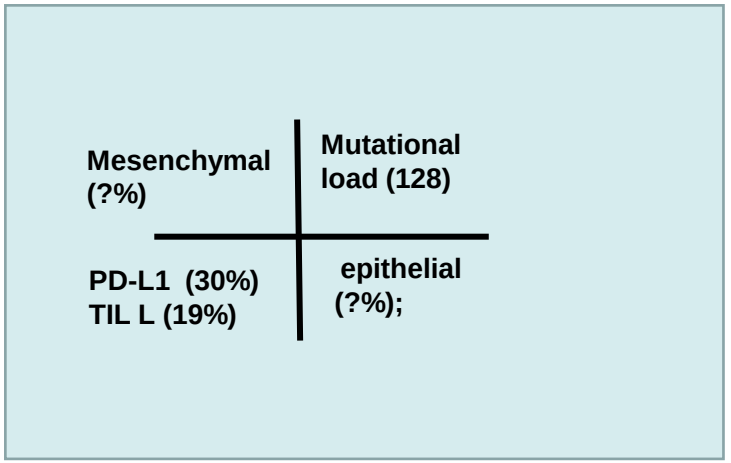
HPV+



HPV-



HPV-



Randomized studies

study	*No*	*Arms*	*Stage T4/N+*	*LR%*	*CFS%*	*DFS%*	*OS%*
ACT I	585	RT	15/23	59	20	24	27
		RT+FU/M		36	30	36	33
RTOG-98	644	RT+FU/P	8/26	26	65	58	70
		RT+FU/M		20	72	68	78
ACT II	940	RT+FU/P	14/32	-	65	72	-
		RT+FU/M		-	68	73	-

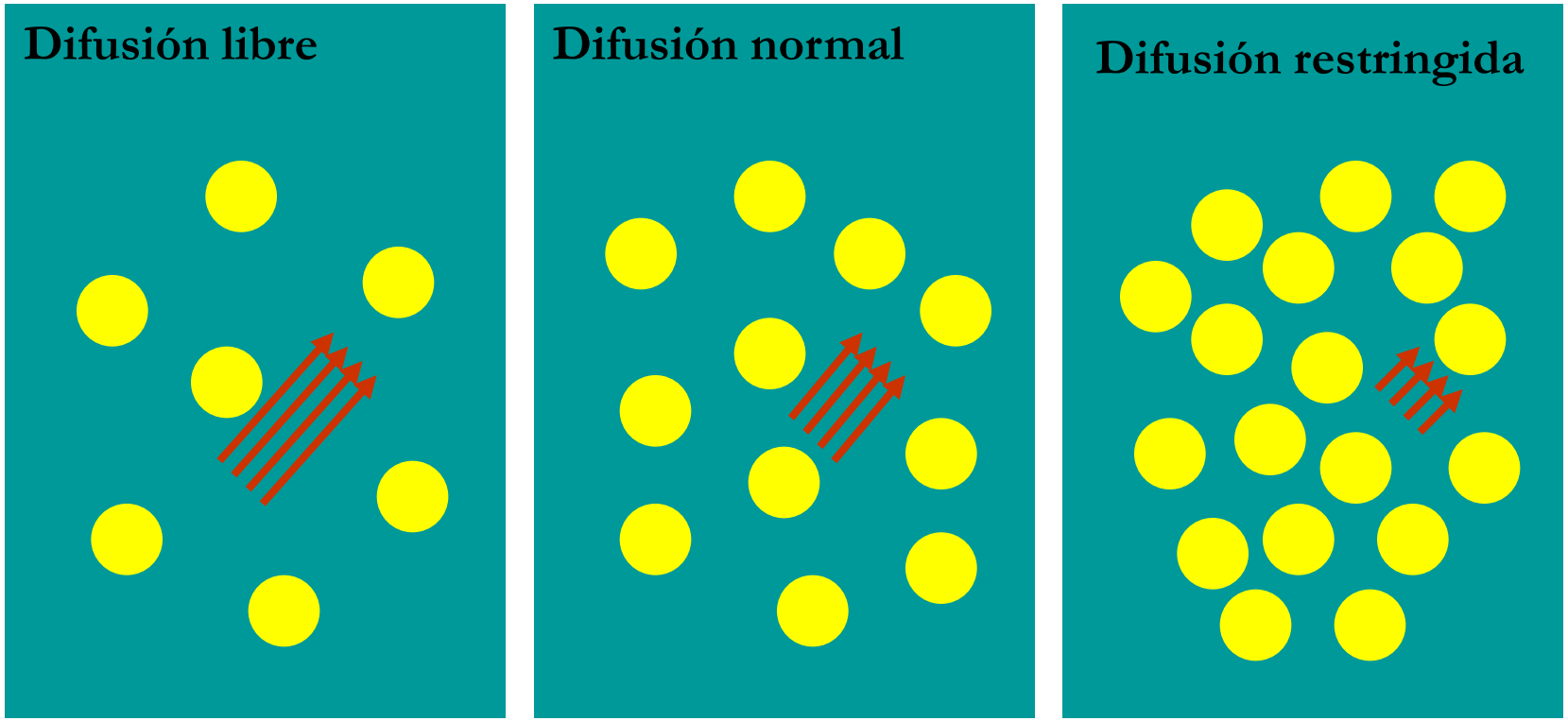
Efficacy in HPV patients

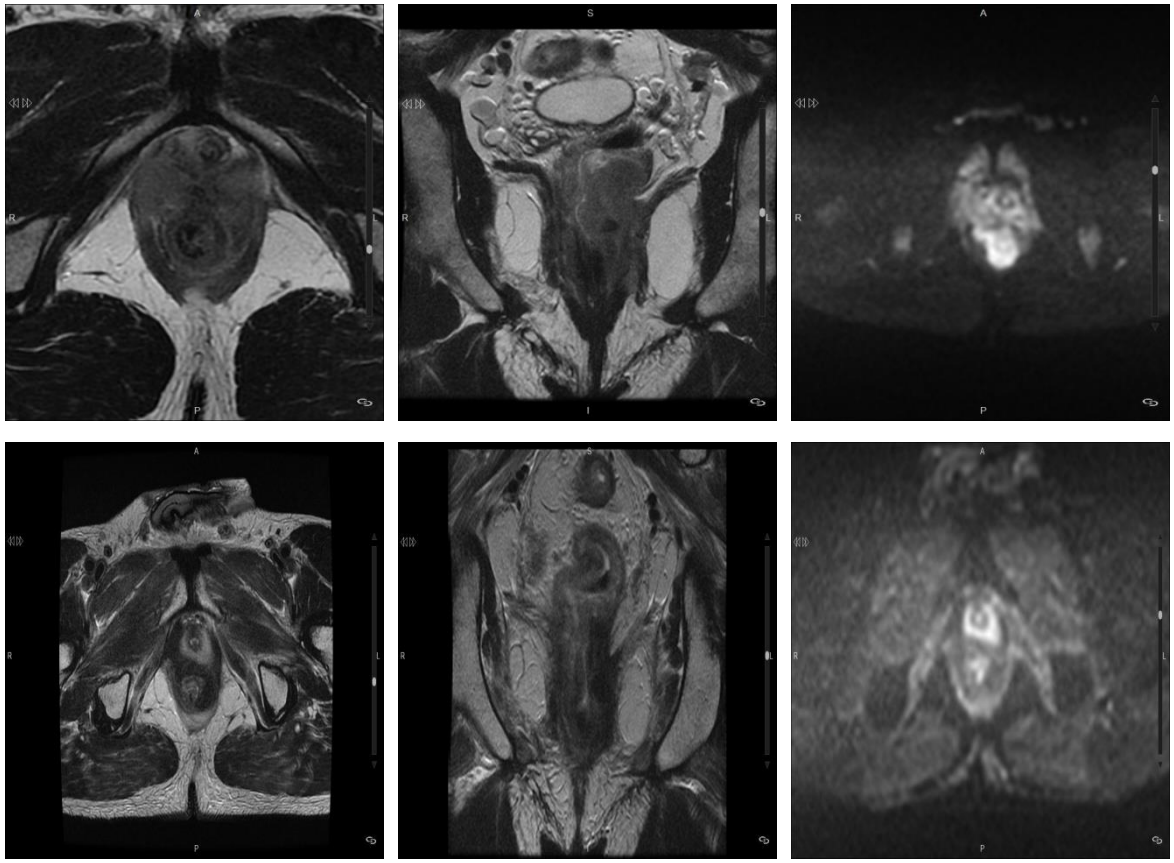
	No	***% HVP+***	***%p16+***	***DFS***
Serup-Hansen (2014)	143	89	92	84 vs 52 (HVP +vs -) 85 vs 30 (p16 + vs -)
Meulendijks (2015)	107	87	91	82 vs 15 (HVP/p16 +/+ vs -/-)
Mai (2015)	106	68	70	88 vs 56 (HVP/p16 +/+ vs -/-)
Gilbert (2016)	284 (153/131)	-	89/92	73 vs 37 78 vs 30 * p16+ (TIL high vs TIL low-absent) 92 vs 63

Efficacy in HIV patients

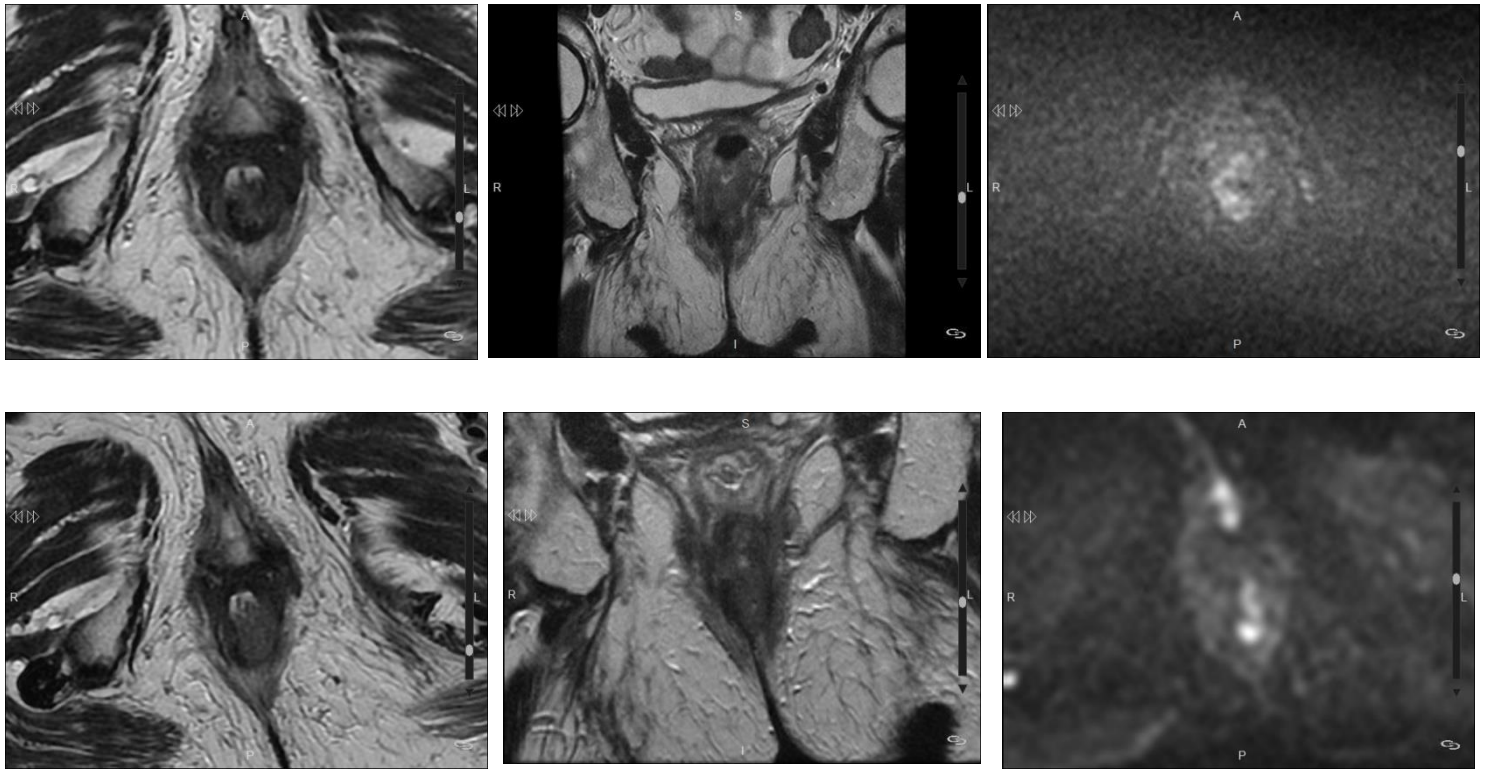
	No	***treatment***	***CR***	***DFS***
Efron (2001)				
HIV+	6	RT+M-FU	-	33
HIV-	13		-	70
Oelher (2008)				
HIV+	40	RT+/-M-FU	92	38
HIV-	81		96	87

MRI: Diffusion

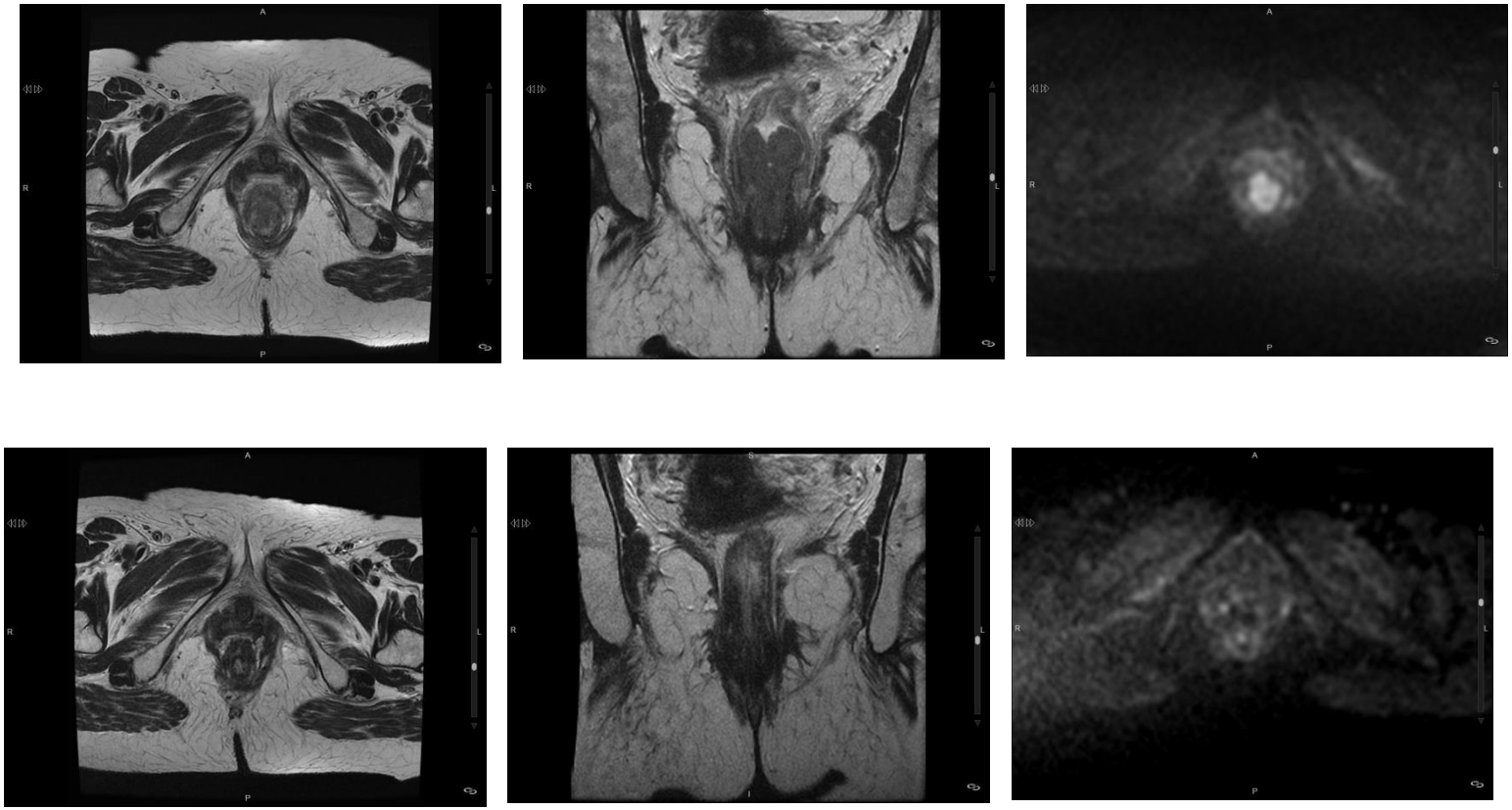




Male. 44 years. HIV+. cT4N2. MMC-FU-PAN/RT. RC (MRI). Biopsy-Local relapse at 12 months. Miles. NED 48m FU.



82-year. Female. HIV-. cT2N0. P-FU/RT. RP (MRI). Biopsy+. Miles. Local and distant M1.17 months. Death 29m.



78-year. Female. HIV-. cT2N1. MMC-FU-PAN/RT. RC (MRI). Biopsy-. NED 45 m FU.

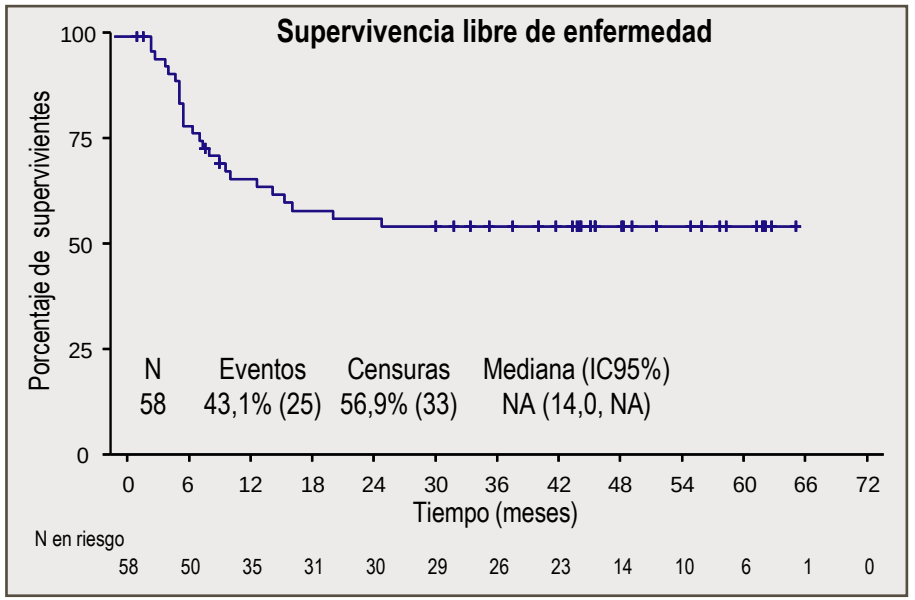
Studies with anti-EGFR

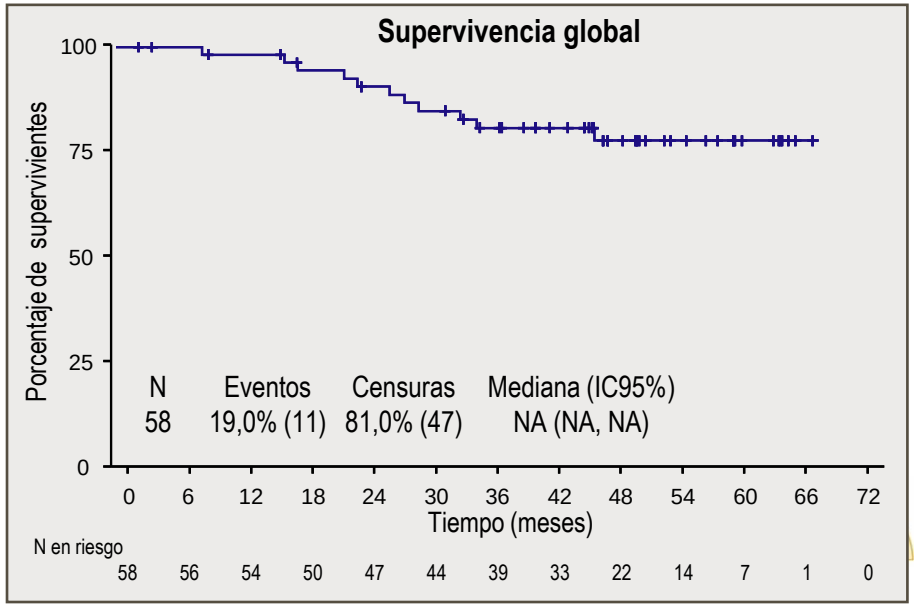
study	***No***	***Arms***	***Stage T4/N+***	***CR%***	***DFS% 5y***	***OS% 5y***
Unicancer 2013	16*	RT+FU-P CET	NA	55	-	-
Olivatto 2013	26*	RT+FU-P CET	96*	43	64 (3y)	-
E3205 2017	63	RT+FU-P CET	16/54	35-59	46	75
AMC 045 2017*(HIV+)	45	RT+FU-P CET	0/35	62	72	77
VITAL GEMCAD 09-02	58	RT+FU-M PAN	68*	68	52	75

VITAL (GEMCAD 09-02)

SLE (3 años)*, % (IC 95%)	55 (40–67)
SG (3 años)*, % (IC 95%)	81 (67–89)
Tasa de fracaso loco-regional, n (%)	20 (34)
Tasa de colostomía (2 años)†, n (%)	13 (31)
Respuesta por RMN (6 meses)§, n (%)	
RC	27 (68)
RP	4 (10)
EE	3 (8)
EP	4 (10)
No evaluable	2 (5)

*Estimación Kaplan-Meier
†N de pacientes que alcanza RC tras dos años = 42
§N de pacientes con RMN disponible en la visita a los 6 meses = 40
SLE: supervivencia libre de enfermedad; SG: supervivencia global; RNM: resonancia magnética nuclear; RC: respuesta completa; RP: respuesta parcial; EE: enfermedad estable; EP: enfermedad progresiva





Studies with PD-L1

study	***No***	***Arms***	***PD-L1***	***RR***	***PFS (median)***
Morris (Lancet Oncology 2017)	39	nivolumab	NA	24%	4.1 months
Ott (Annals of Oncology 2017)	24	pembrolizumab	74%	17%	3 months

Conclusions

- MMC/FU-RT o P/FU-RT is an active treatment in HPV+/HIV-
- MRI with diffusion optimally evaluate treatment efficacy
- Anti-EGFR treatment shows promising activity in HIV+ patients.
- PD-1 and PD-L1 therapy would be specially active in HPV with high TIL infiltration.