Tumori HPV correlati e radiosensibilità:

dobbiamo de-intensificare la radioterapia?

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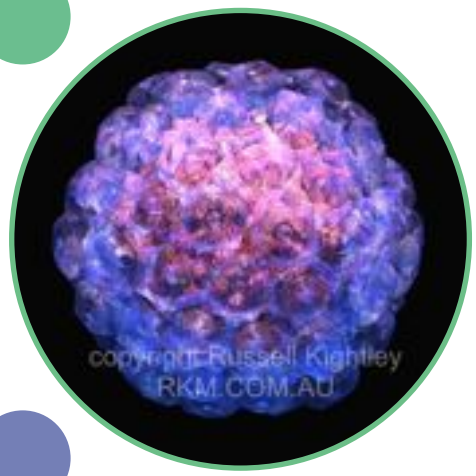
XXIX Congresso AIRB - 13 giugno 2014

Tumori HPV correlati: squamocellulari radiosensibili

Orofaringe

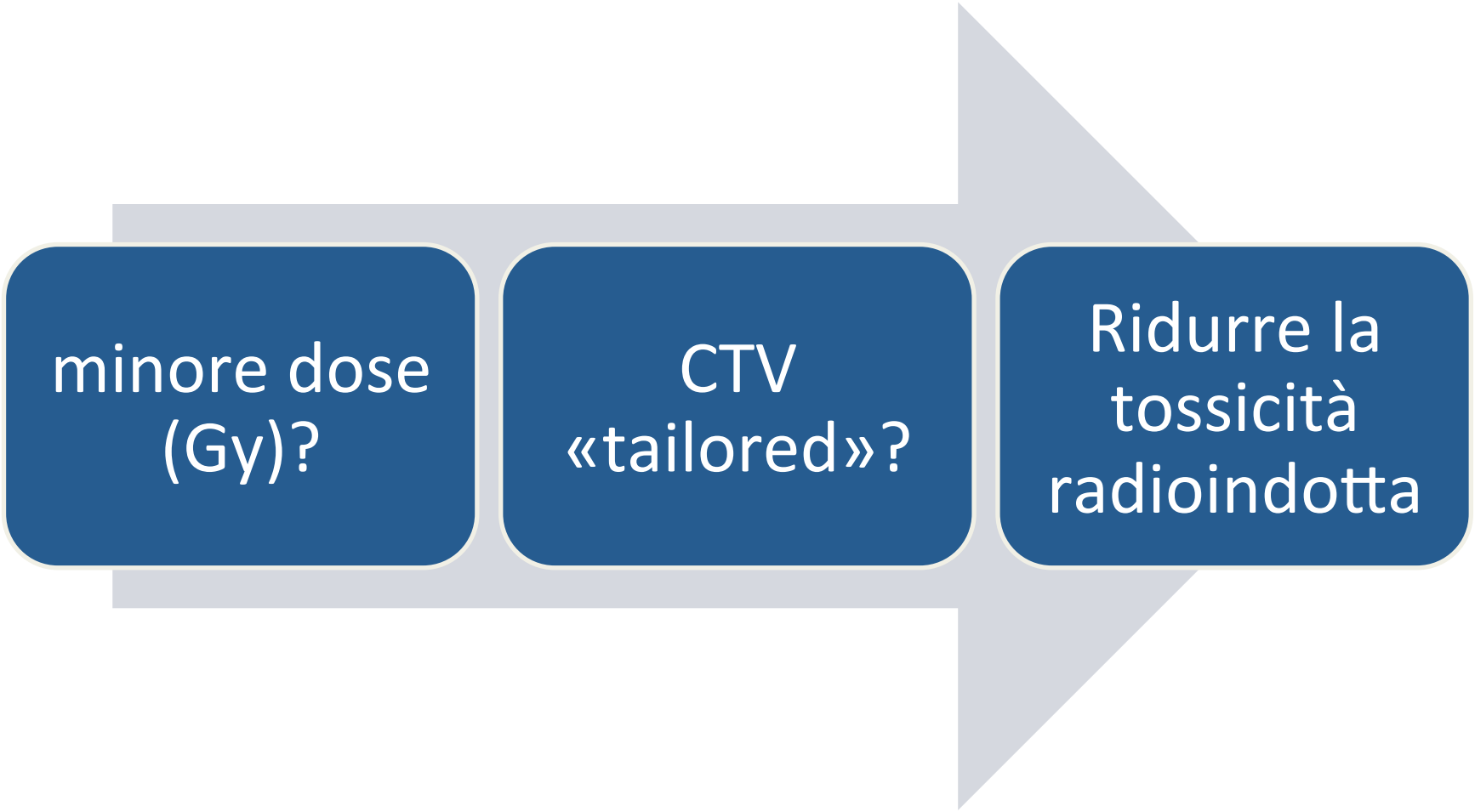
Cervice uterina

Carcinoma anale

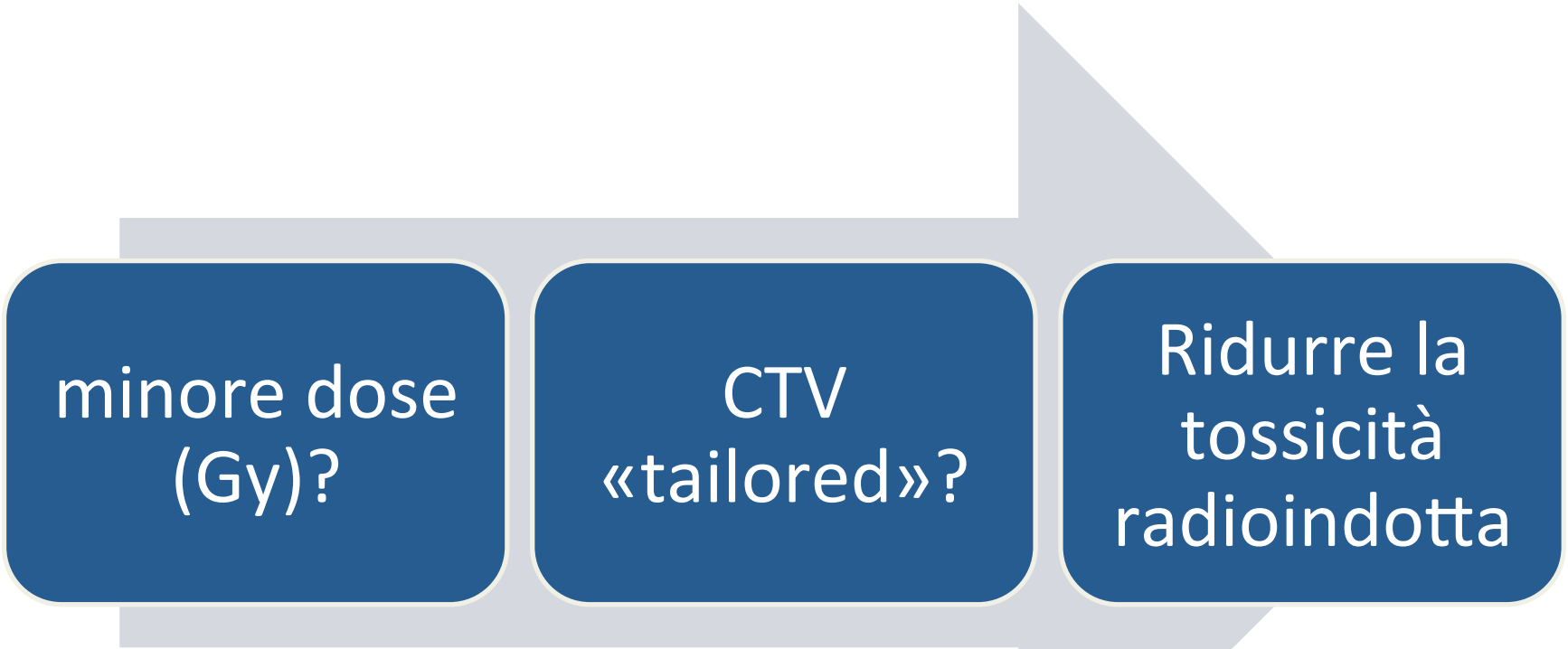


e Carcinoma penieno, vaginale e vulvare in minore entità

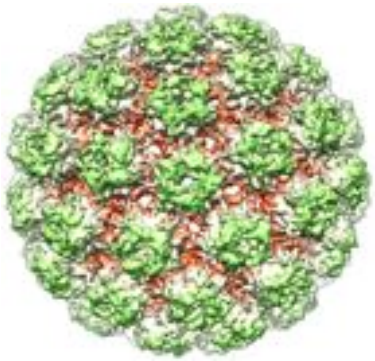
Quesito:
de-intensificare la radioterapia?

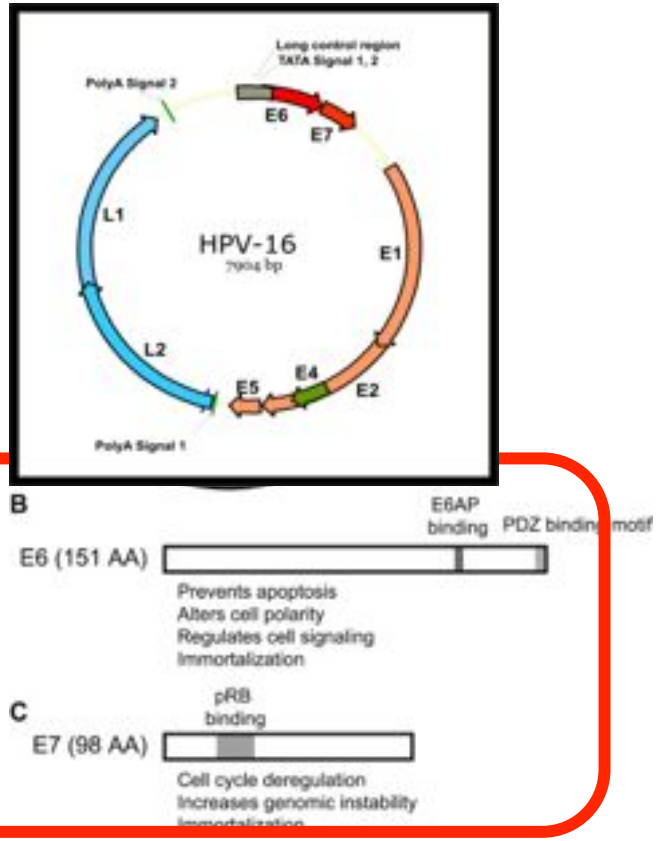


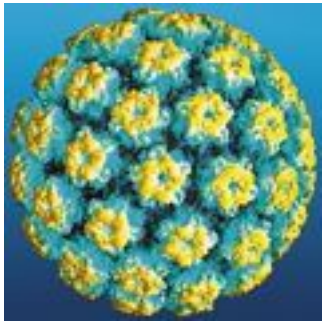
De-intensificare la radioterapia?



O …EVITARE L'ASSOCIAZIONE CON LA CHEMIOTERAPIA O….. ASSOCIARE TARGETED–THERAPY ALLA RADIOTERAPIA?







E6 → p53

E7 →pRB

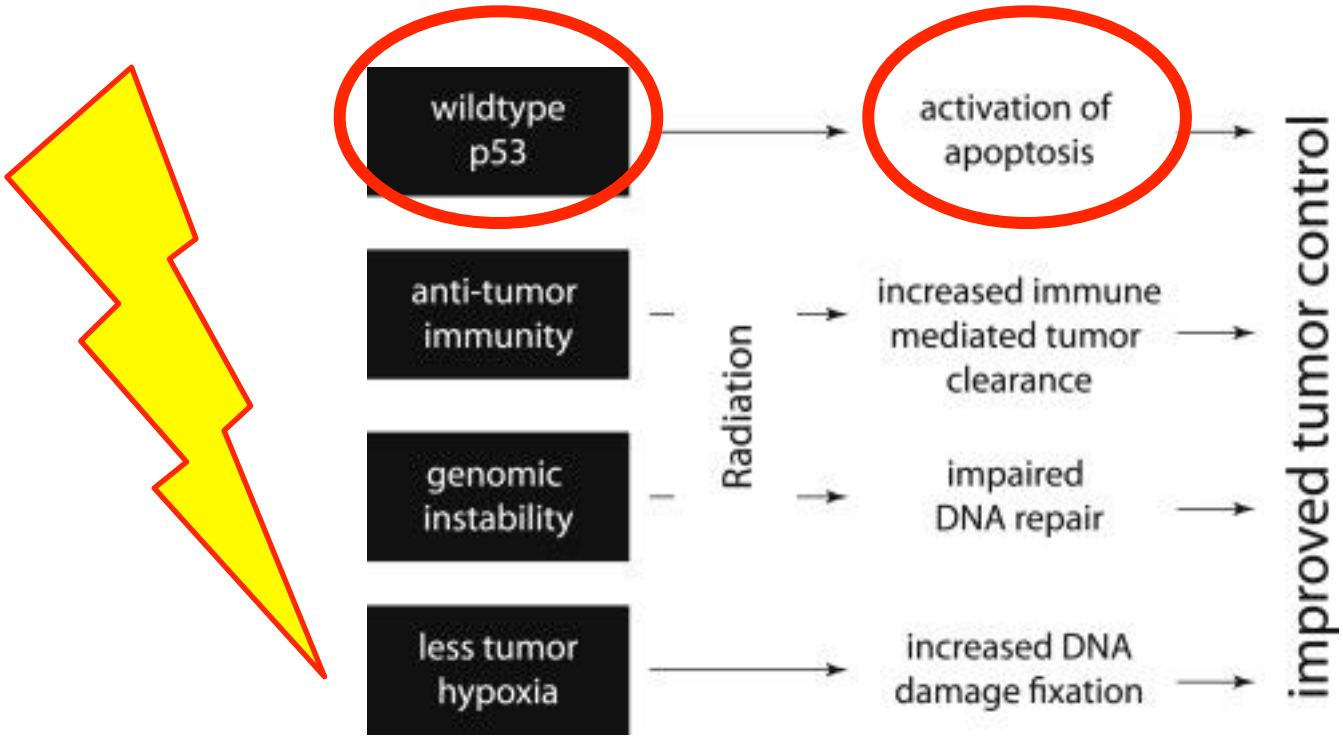
The human papillomavirus (HPV) genome is a double-stranded circular DNA containing approximately 8000 base pairs and encoding 8 proteins (A).
E6 (B) and E7 (C) are the predominant human papillomavirus oncogenes

Review of the Clinical and Biologic Aspects of Human Papillomavirus-Positive Squamous Cell Carcinomas of the Head and Neck

Grace C. et al

International Journal of Radiation Oncology*Biology*Physics, Volume 88, Issue 4, 2014, 761 - 770

http://dx.doi.org/10.1016/j.ijrobp.2013.08.029



Potential factors contributing to improved outcomes in patients with human papillomavirus-positive squamous cell carcinoma of the head and neck .

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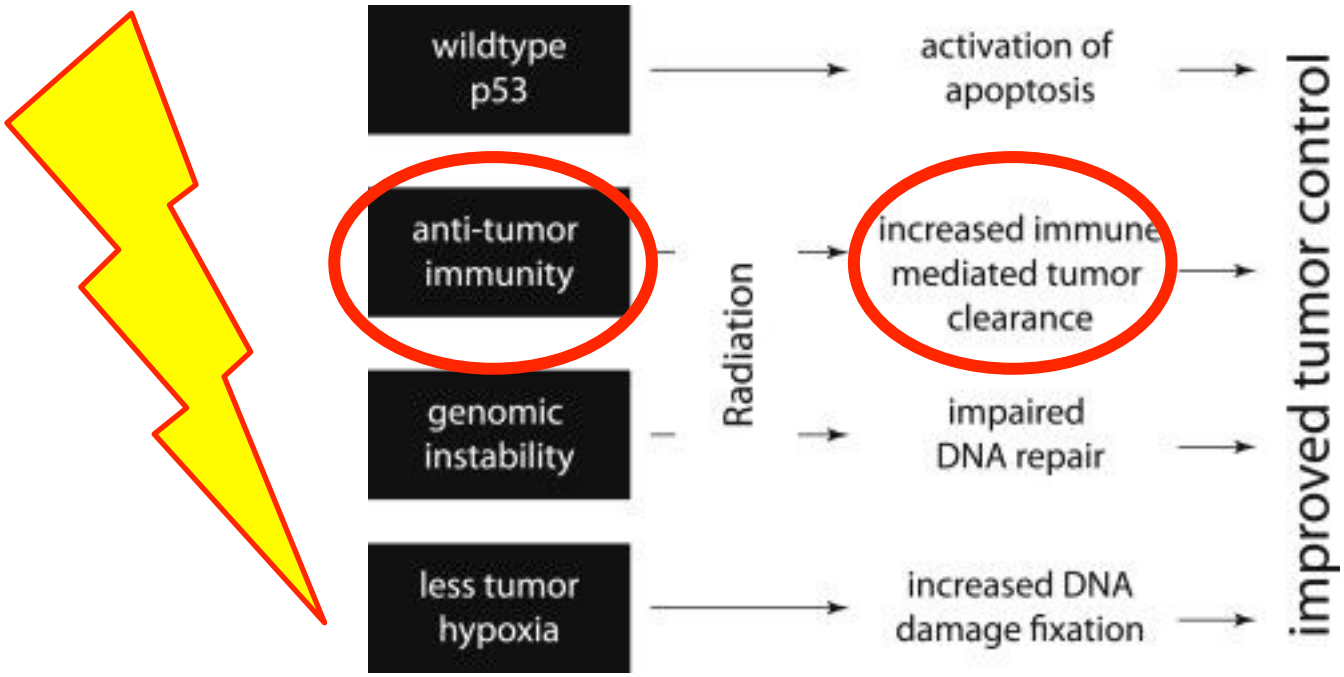

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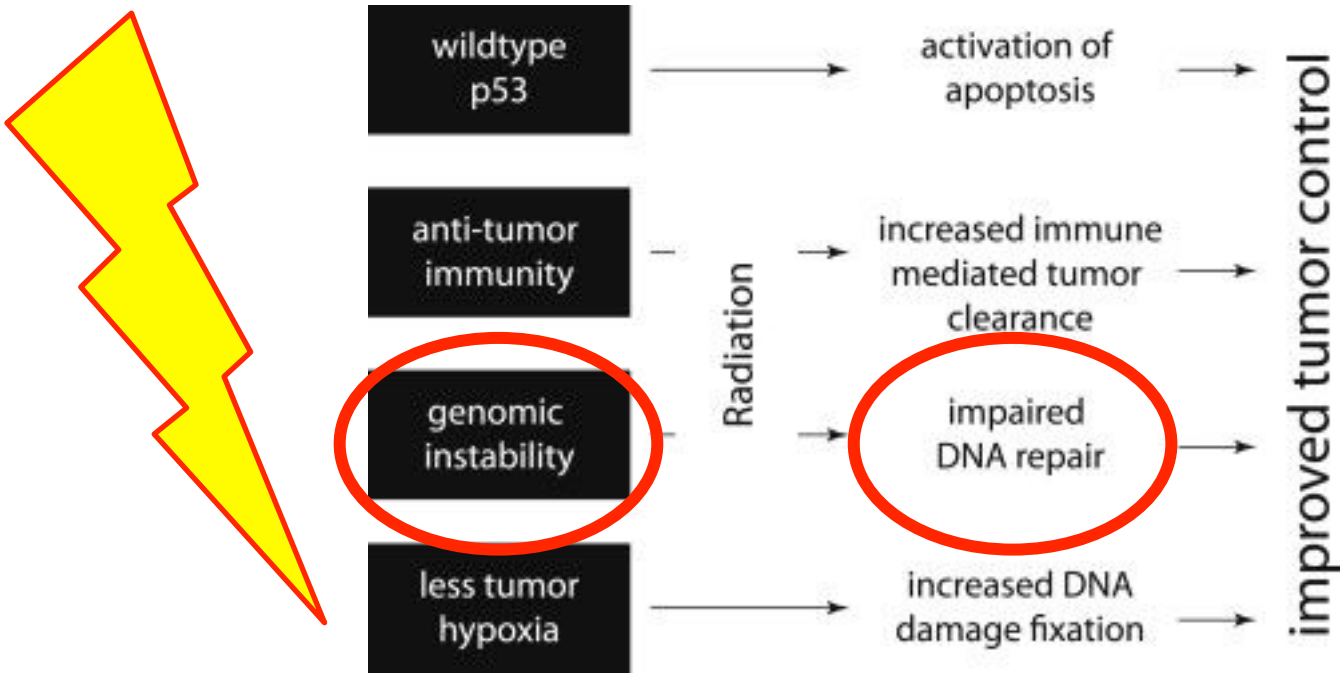

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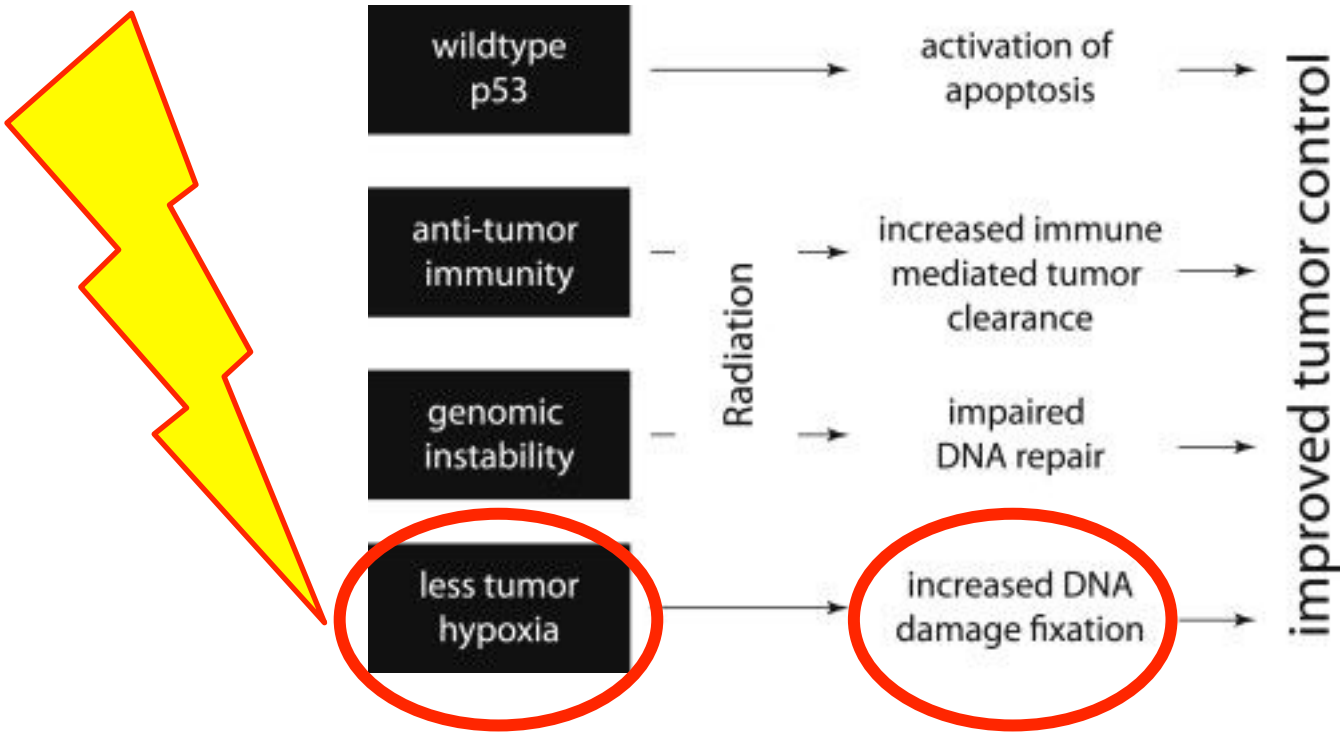

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	Detection	Remarks
	p16 expression (IHC) surrogate marker	Commonly performed in clinical laboratories, high correlation with outcome, but may be elevated in HPV-negative cases
DNA	in situ Hybridization (ISH)	Highly specific and can be performed on paraffin-embedded samples, but low sensitivity for tumors with low numbers of copies of the HPV genome
DNA	Polymerase Chain Reaction (PCR)	Highly specific and fast turn-around time, but environmental contamination can lead to false-positive results
DNA	RT-PCR	Sensitive and specific because it detects active HPV infection, but requires intact RNA so better results from fresh or frozen tissue than from paraffin-embedded tissue
	Serology	Easy to perform, but no direct relationship to viral-associated cancers

HPV DETECTION

HPV DNA +/p16 +

HPV DNA -/p16+

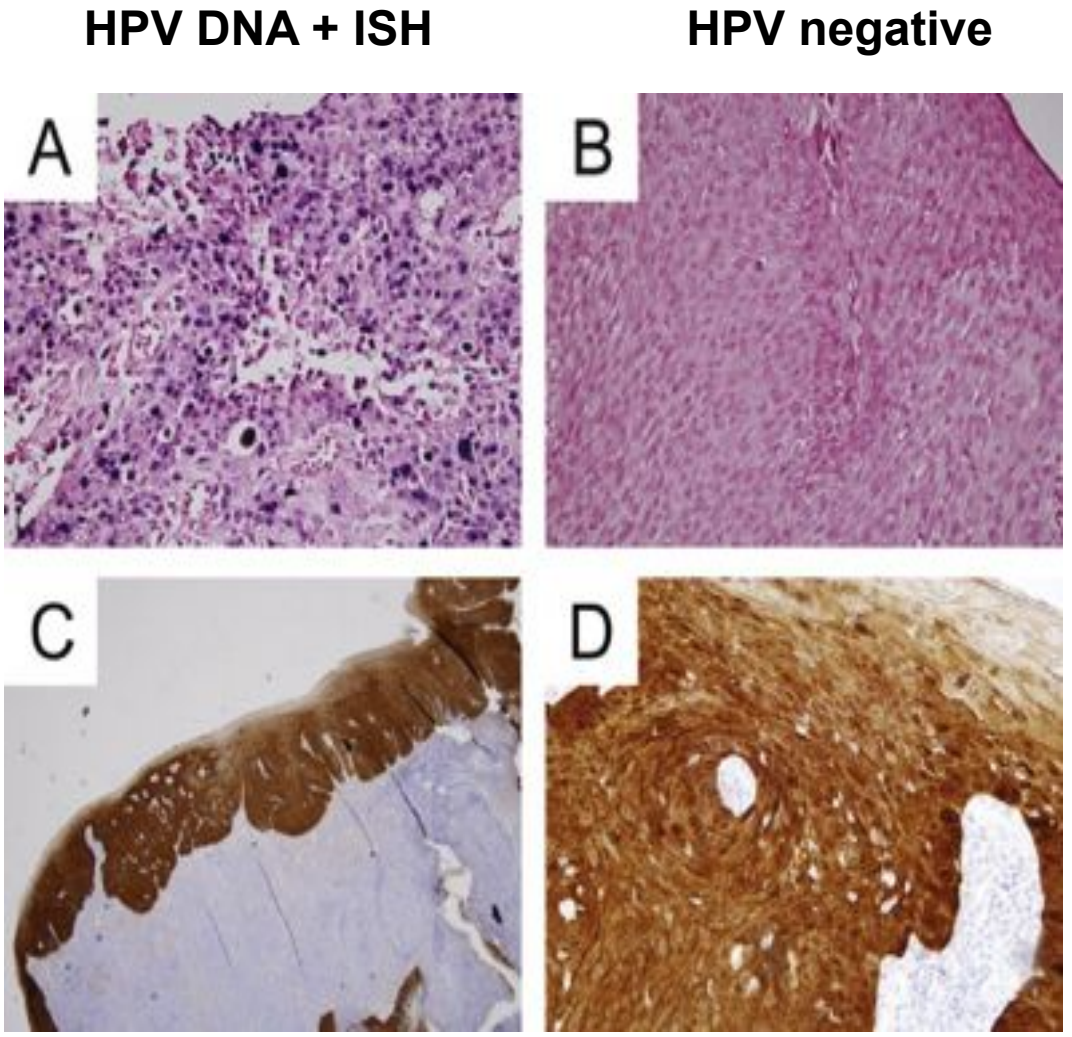
vs

HPV DNA -/p16 –

Sono positivi per HPV:

p16 con cut-off > 70% e

HPV PCR o ISH +



HPV + p16 overexpression

HPV status:
prognostico o predittivo di risposta?

Fattore prognostico

- è legato alla biologia del tumore indipendentemente dalla terapia adottata

Fattore predittivo di risposta

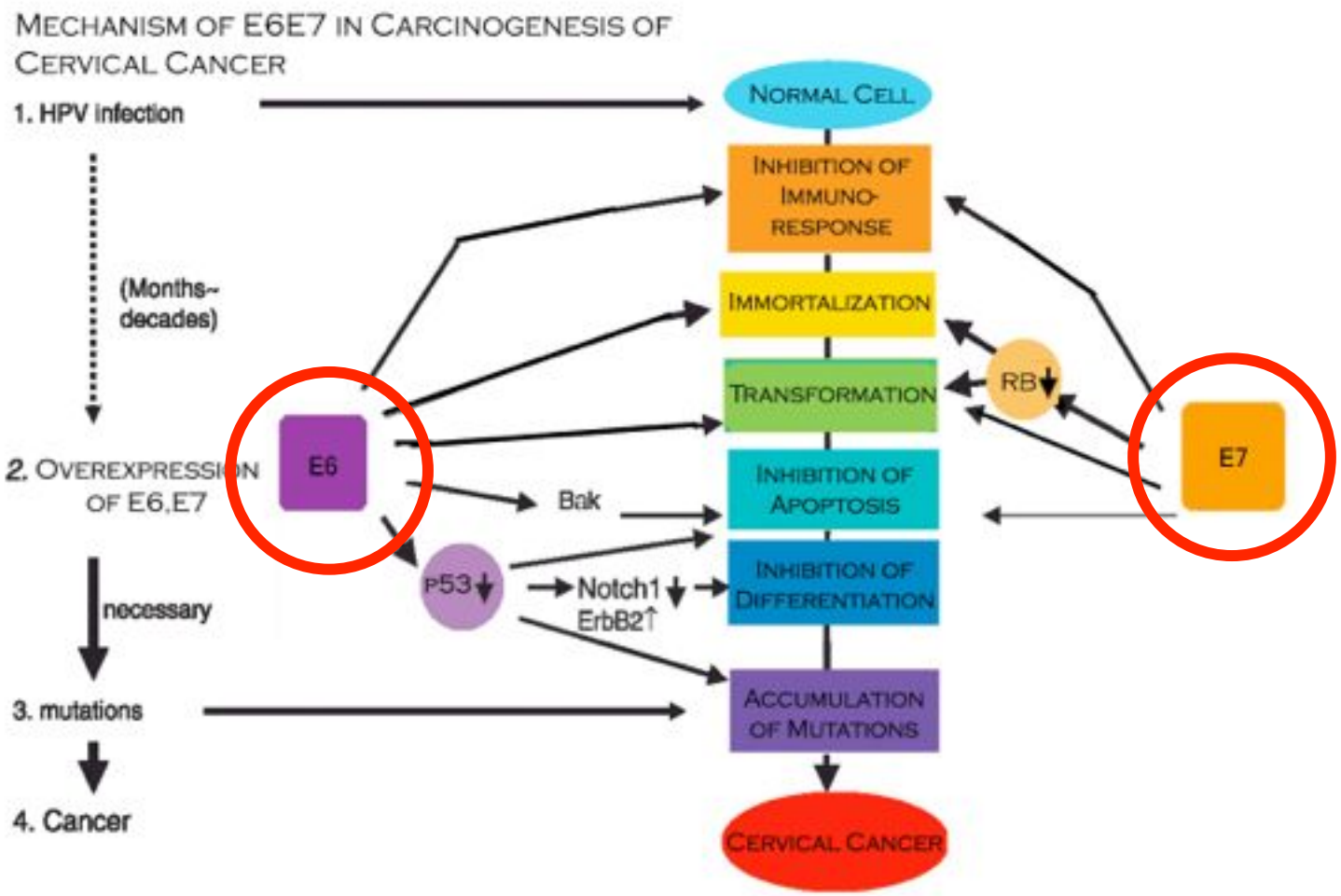
- può permettere di de-intensificare (no chemioterapia) o intensificare la terapia

HPV e SCC della Cervice Uterina

Premio Nobel 2008

a Harald zur Hausen

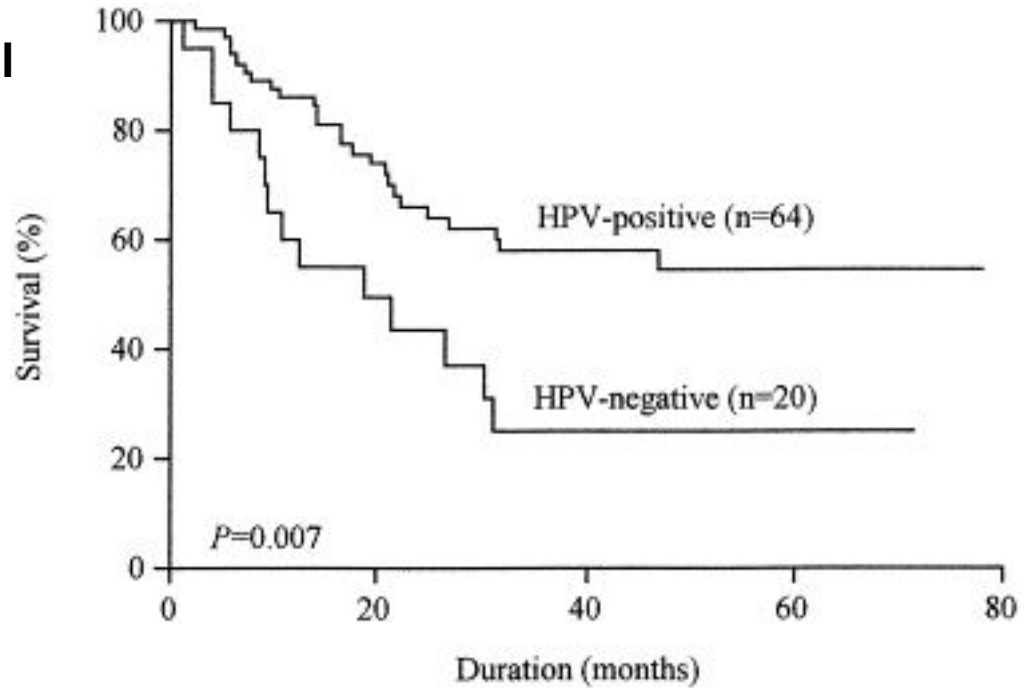
HPV e Cervice uterina: implicazioni per la radioterapia



Overall survival

84 women

1995-2000 yrs



The 64 HPV-positive patients survived significantly longer than the 20 HPV-negative patients (p = 0.007).

Yoko Harima , Satoshi Sawada , Kenji Nagata , Mitsuharu Sougawa , Takeo Ohnishi

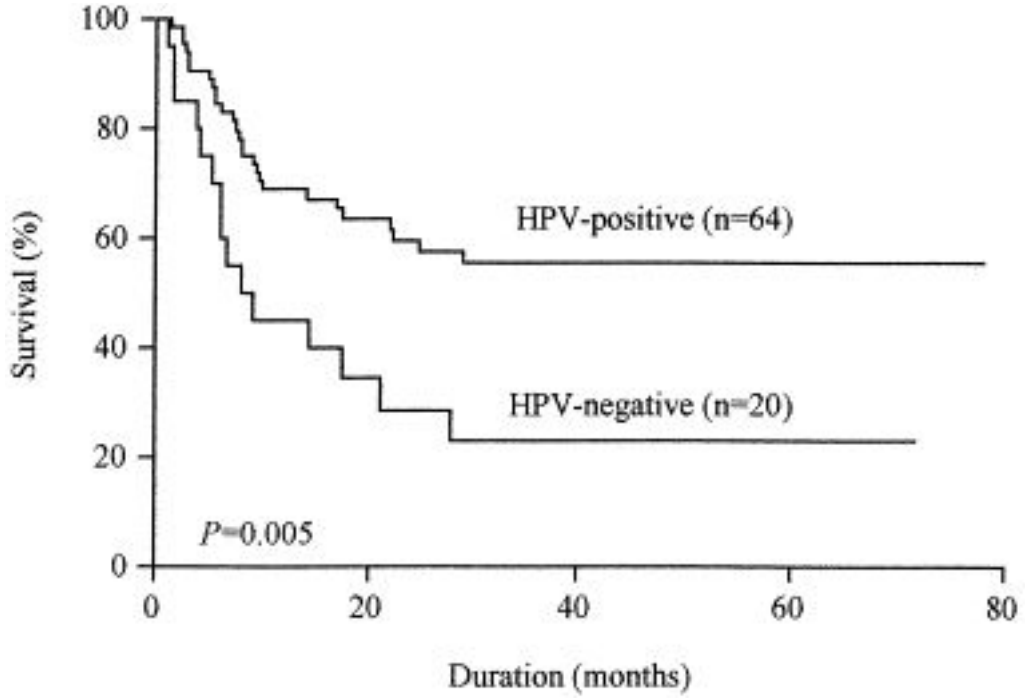
Human papilloma virus (HPV) DNA associated with prognosis of cervical cancer after radiotherapy

International Journal of Radiation Oncology*Biology*Physics, Volume 52, Issue 5, 2002, 1345 - 1351

http://dx.doi.org/10.1016/S0360-3016(01)02796-1

Disease-free survival

HPV 18 + worse prognosis than HPV 16 +



The 64 HPV-positive patients survived significantly longer than the 20 HPV-negative patients (p = 0.005)

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International Journal of Radiation Oncology*Biology*Physics, Volume 52, Issue 5, 2002, 1345 - 1351

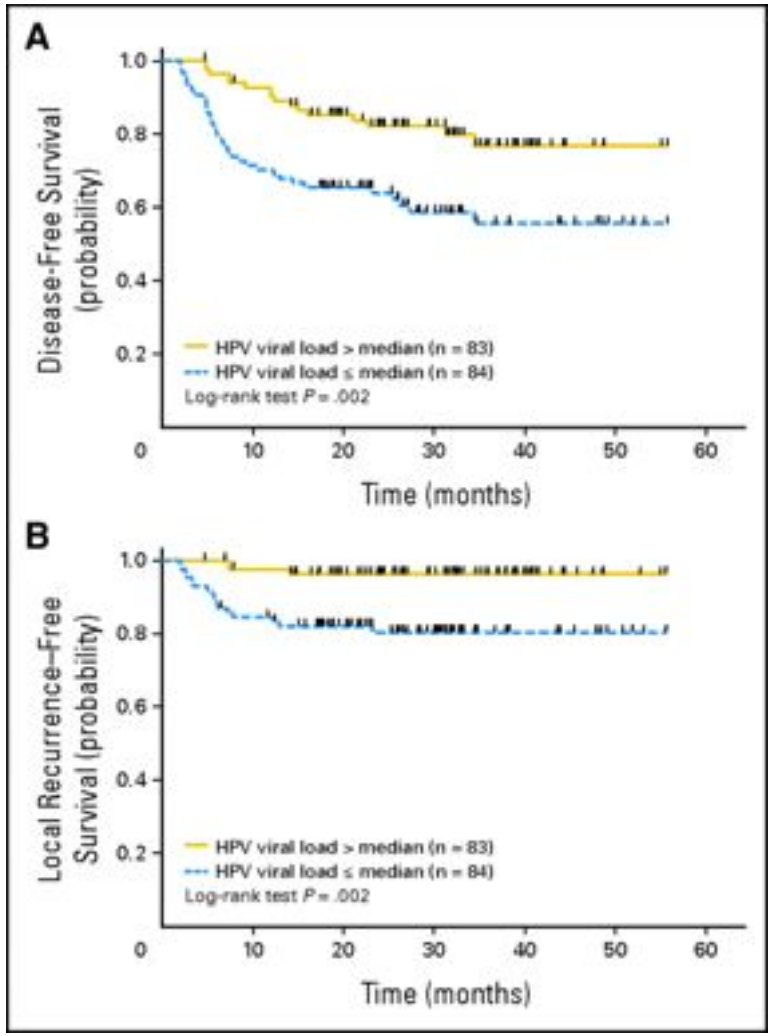
http://dx.doi.org/10.1016/S0360-3016(01)02796-1

(A) Disease-free survival and (B) local recurrence–free survival by human papillomavirus (HPV) viral load.

169 pts
cervical smear

HPV DNA Load
- **median:**

more radiosensitive



HPV > mediana

HPV < mediana

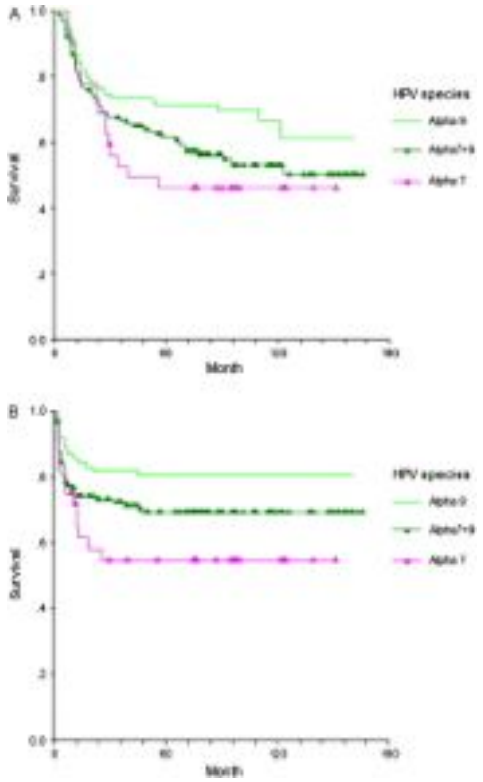
HPV > mediana
HPV < mediana

Kim J et al. JCO 2009;27:5088-5093

JOURNAL OF CLINICAL ONCOLOGY ASCO

DFS

Local control



HPV negative or alpha 9 risk group (HPV **16**, 18, 33, 52, 39, 31 e 45)

better than

alpha 7 risk group (HPV **18**, 39, 45)

RESPONSE ACCORDING TO DIFFERENT HPV STATUS OR GENOTYPES.

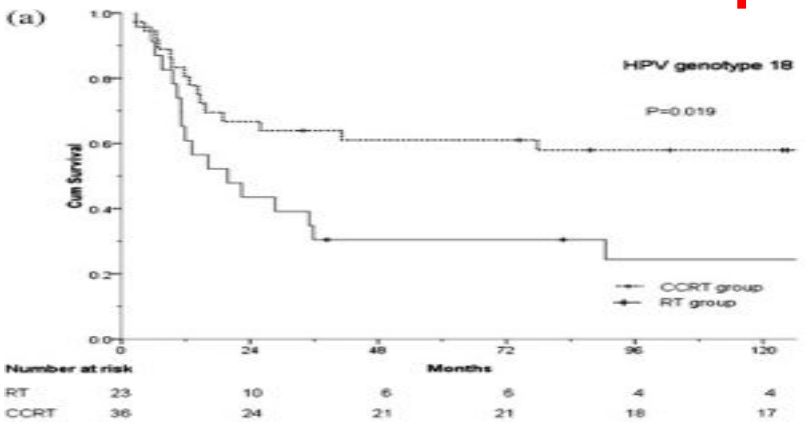
Chun-Chieh Wang , Chyong-Huey Lai , Huei-Jean Huang , Angel Chao , Chee-Jen Chang , Ting-Chang Chang , Hung-Hsueh ...

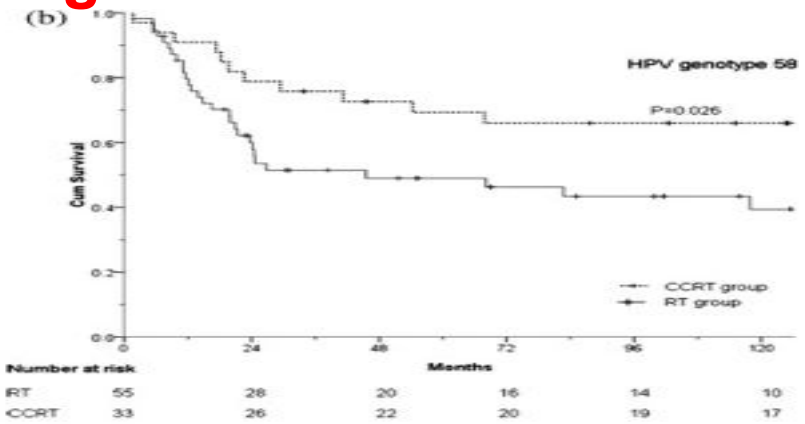
Clinical Effect of Human Papillomavirus Genotypes in Patients With Cervical Cancer Undergoing Primary Radiotherapy

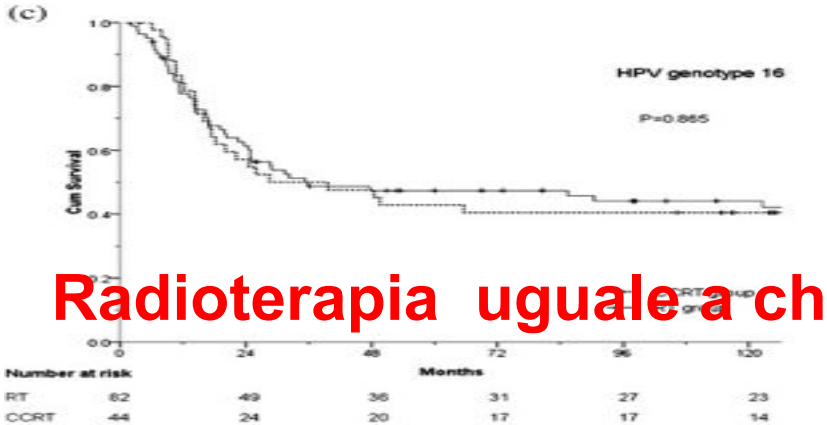
International Journal of Radiation Oncology*Biology*Physics, Volume 78, Issue 4, 2010, 1111 - 1120

http://dx.doi.org/10.1016/j.ijrobp.2009.09.021

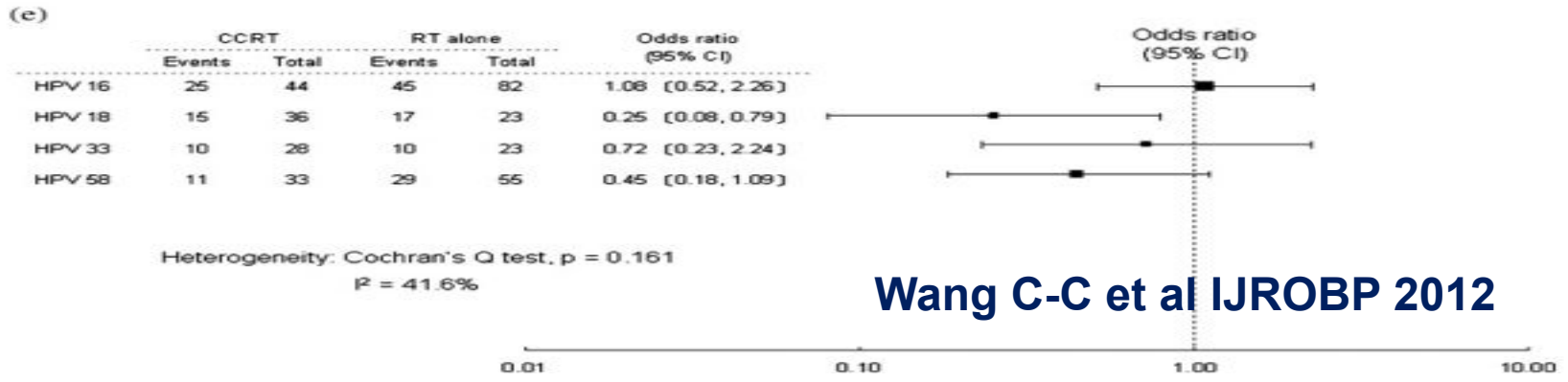
Chemio-radioterapia meglio nei HPV 18+







Radioterapia uguale a chemioradioterapia nei HPV 16+



Wang C-C et al IJROBP 2012

HPV e cervice uterina: conclusioni

- **Le pazienti HPV- (circa 30%) presentano un rischio maggiore di ricaduta locale e di metastasi a distanza**

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- **Prospettive: omettere chemioterapia in Low Risk Patients (HPV 16+)?**

HPV e SCC Anale

HPV + vs HPV –

Yhim HY et al, IJC 2011

Rodel F et al, IJC May 2014

The prognostic significance of tumor human papillomavirus status for patients with anal squamous cell carcinoma treated with combined chemoradiotherapy (IJC 2011)

47 pts

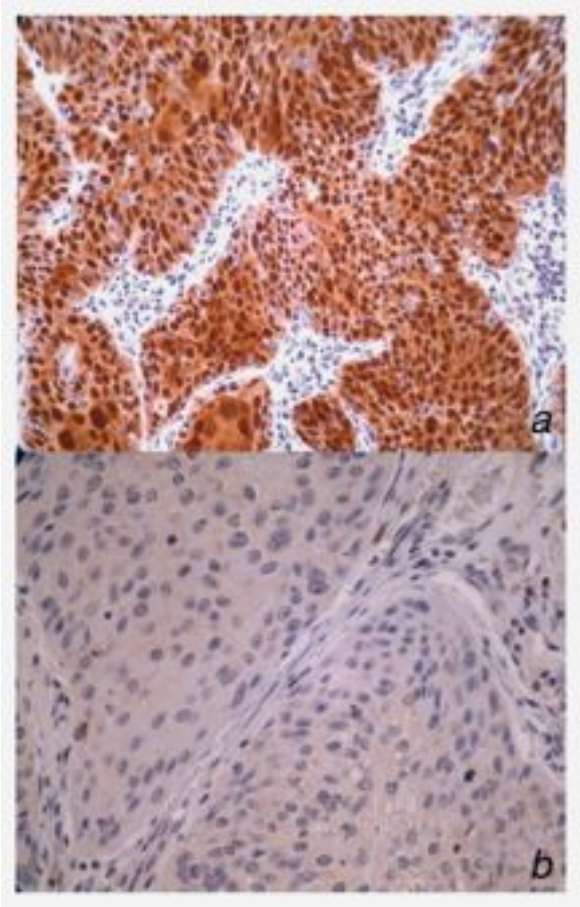
HPV status by p16

Negative Impact

of Nodal status

and HPV 16 negative

on PFS



International Journal of Cancer
Volume 129, Issue 7, pages 1752-1760, 26 FEB 2011 DOI: 10.1002/ijc.25825
http://onlinelibrary.wiley.com/doi/10.1002/ijc.25825/full#fig1

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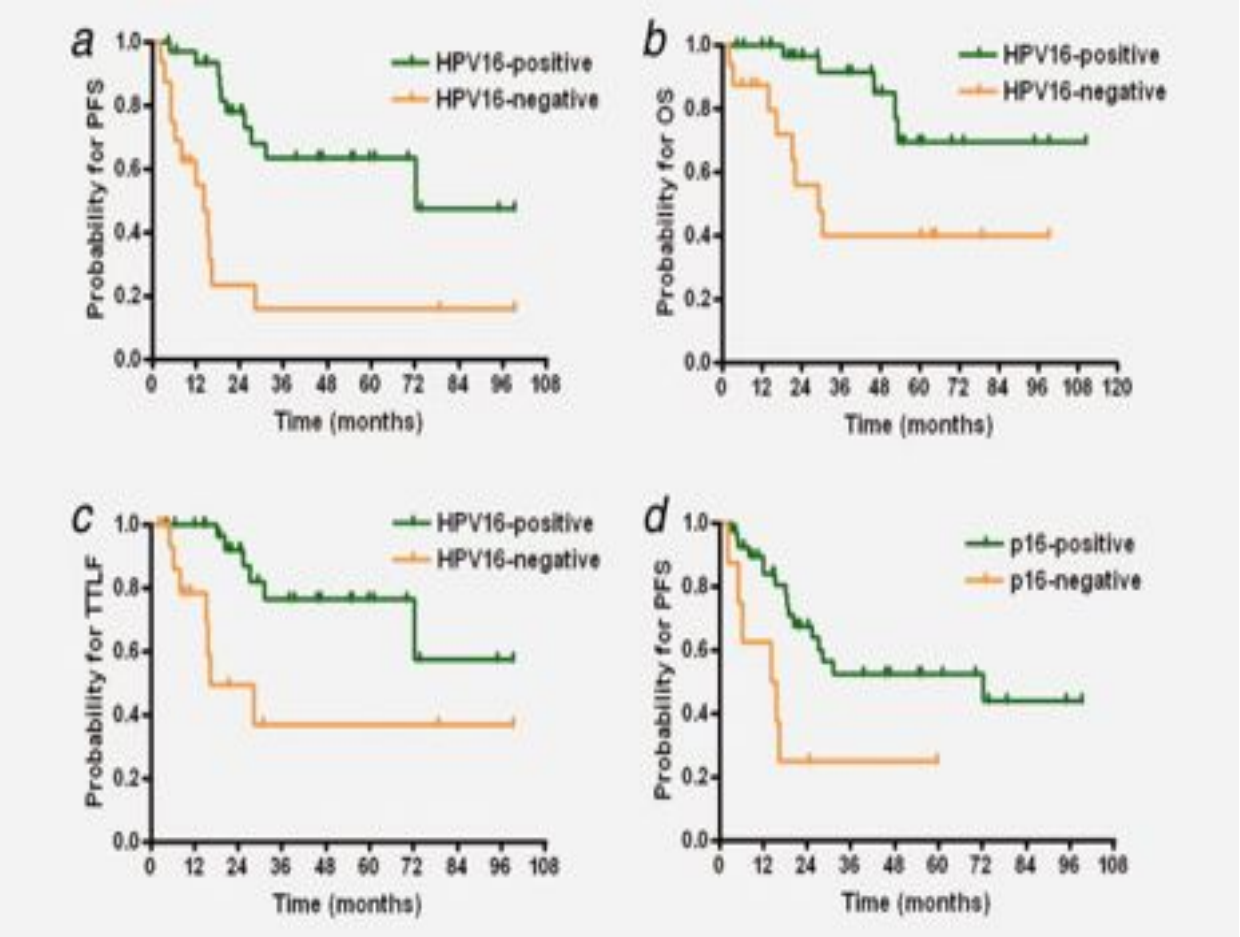

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http://onlinelibrary.wiley.com/doi/10.1002/ijc.25825/full#fig2

HPV e SCC anale : conclusioni

- **Pochi studi**
- **HPV+ nel 75-90% dei casi**

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HPV e SCC anale : conclusioni

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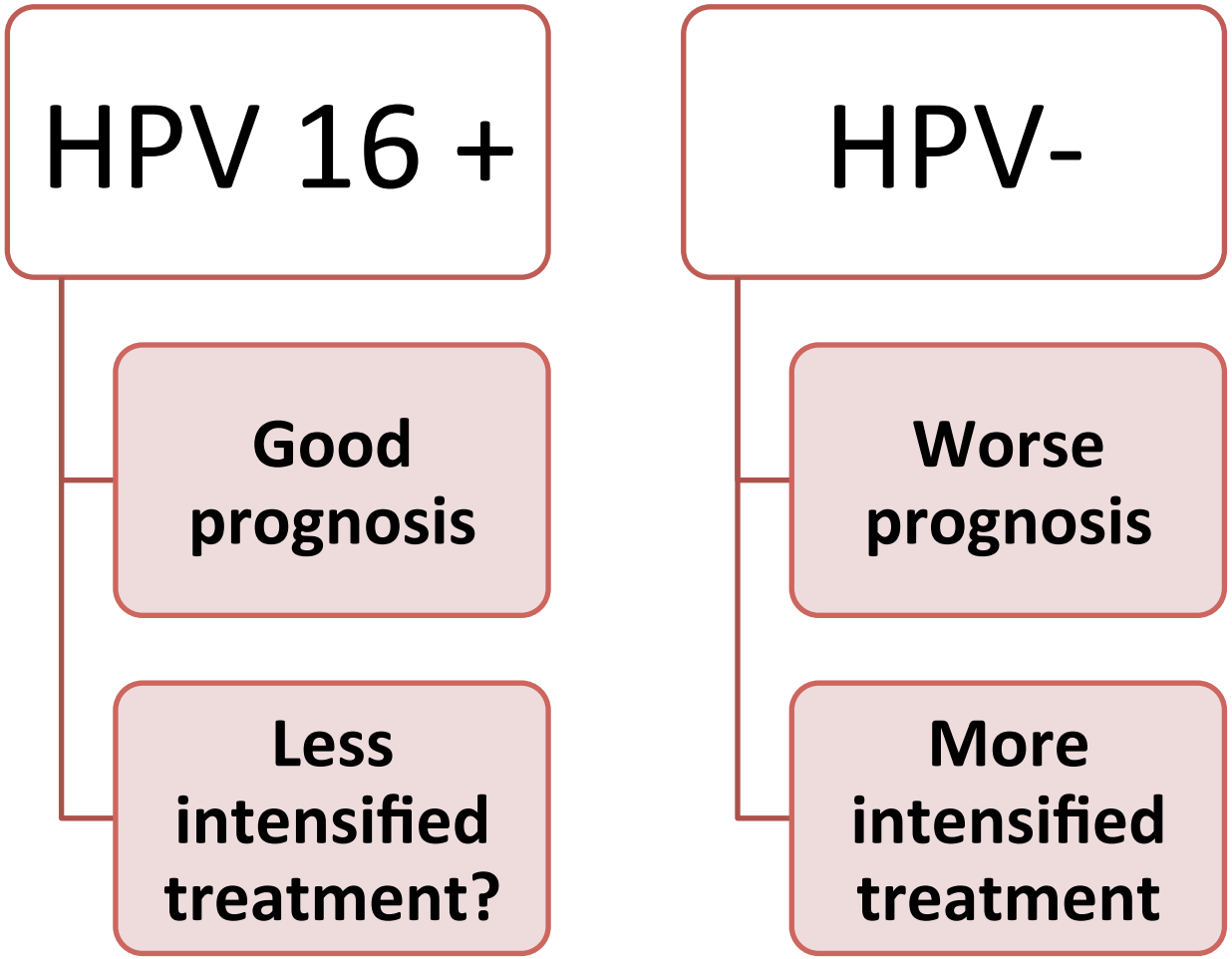
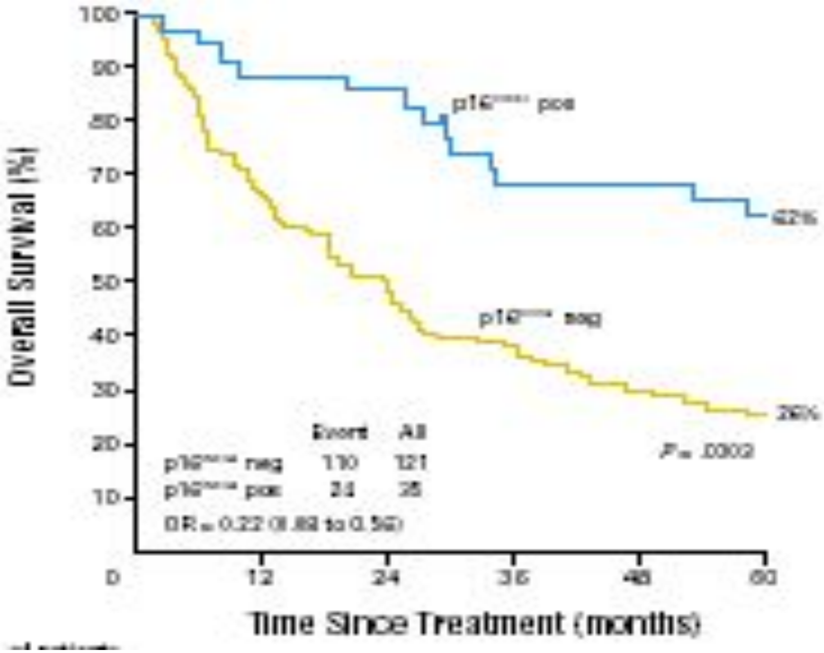
- **HPV 16 → prognosi favorevole**
- **Se HPV neg → intensificazione terapia?**
- **Se HPV 16 + → de-intensificare terapia?**

Oropharyngeal Cancer





VOLUME 27 · NUMBER 12 · APRIL 20 2009

JOURNAL OF CLINICAL ONCOLOGY — ORIGINAL REPORT

Effect of HPV-Associated p16[INK4A] Expression on Response to Radiotherapy and Survival in Squamous Cell Carcinoma of the Head and Neck

Picchi di età:

30-34 anni (no alcool/ fumo)

55-64 anni (anche fumatori)

Linfoadenopatie specifiche

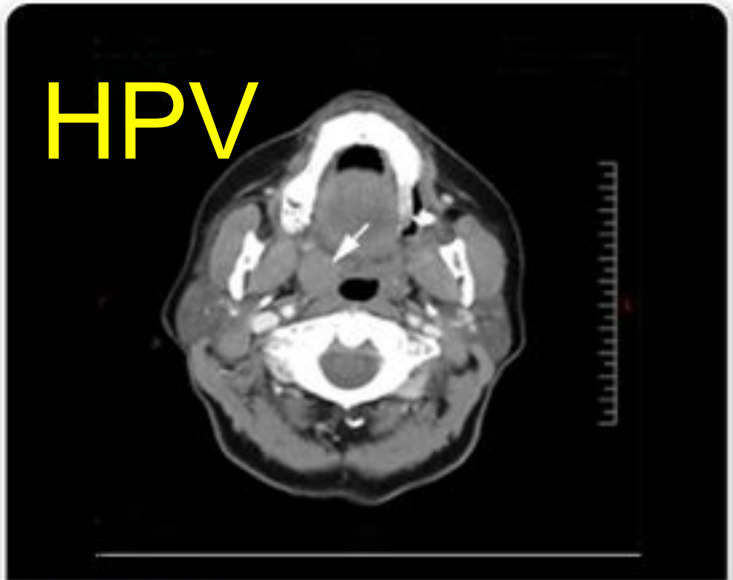


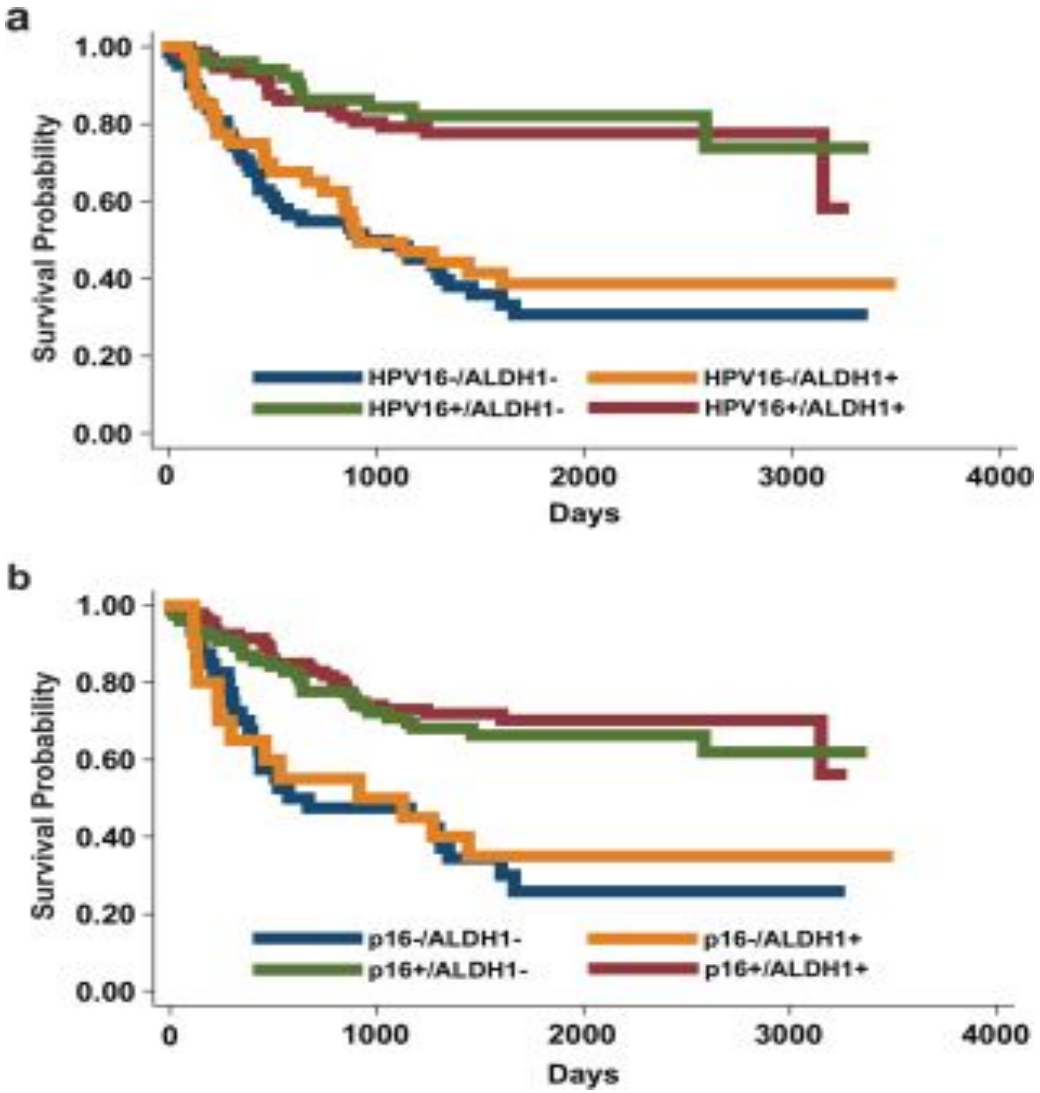
FIGURE 1. CT scan of a 2 cm mass in the right tonsil region (arrow) subsequently identified on needle aspiration biopsy as a P16-positive squamous cell cancer.

Elevated intrinsic cancer stem cell population in human papillomavirus-associated head and neck squamous cell carcinoma

HPV 16 +

CORRELATED

WITH OUTCOME



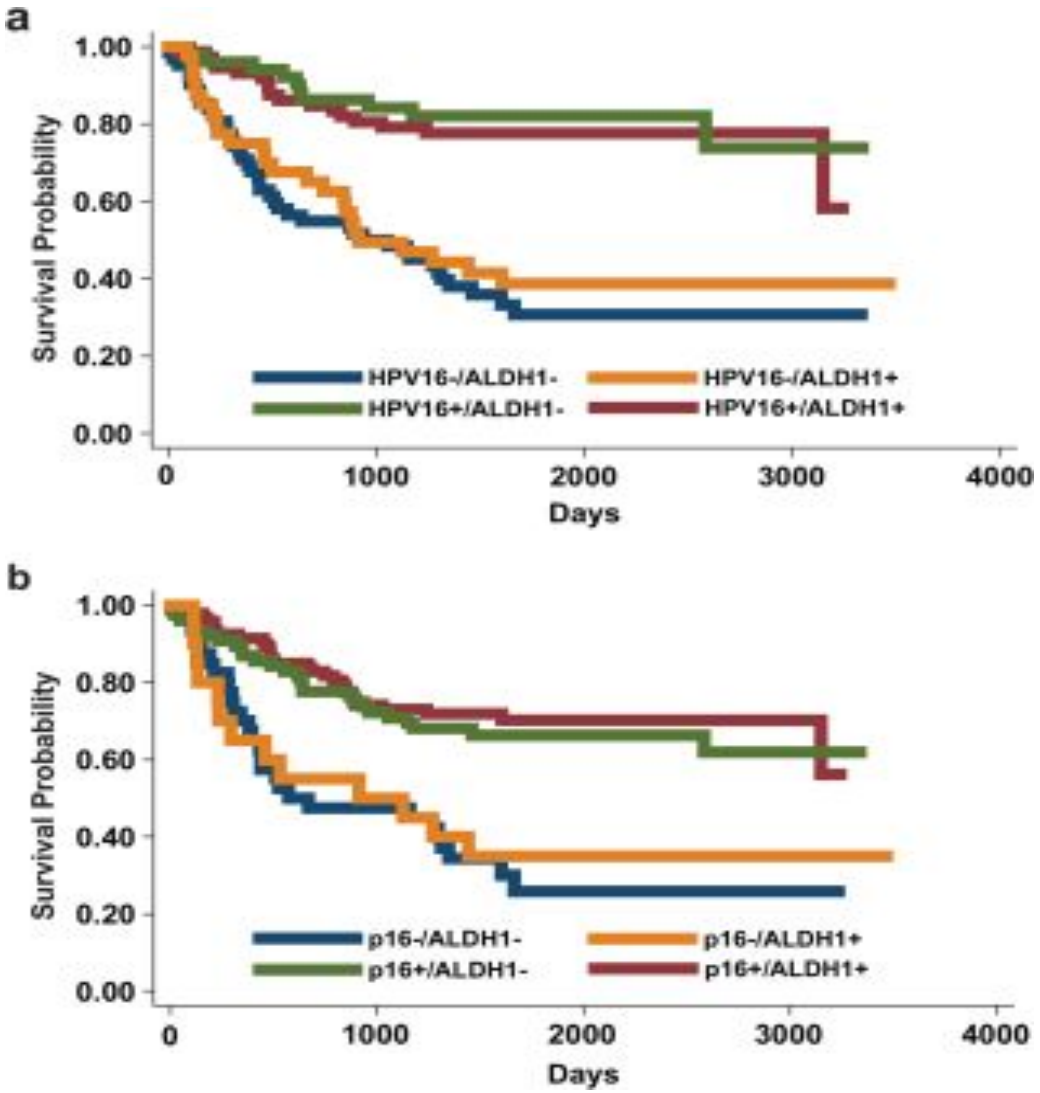
Cancer
Volume 120, Issue 7, pages 992-1001, 30 DEC 2013 DOI: 10.1002/cncr.28538
http://onlinelibrary.wiley.com/doi/10.1002/cncr.28538/full#cncr28538-fig-0004

Elevated intrinsic cancer stem cell population in human papillomavirus-associated head and neck squamous cell carcinoma

ALDH1 LEVEL OF CANCER STEM CELLS

NOT

CORRELATED WITH OUTCOME



Cancer
Volume 120, Issue 7, pages 992-1001, 30 DEC 2013 DOI: 10.1002/cncr.28538
http://onlinelibrary.wiley.com/doi/10.1002/cncr.28538/full#cncr28538-fig-0004

Human HPV and survival in oropharynx patients
Ang KK et al,
N Engl J Med July 2010

Oropharynx SCC

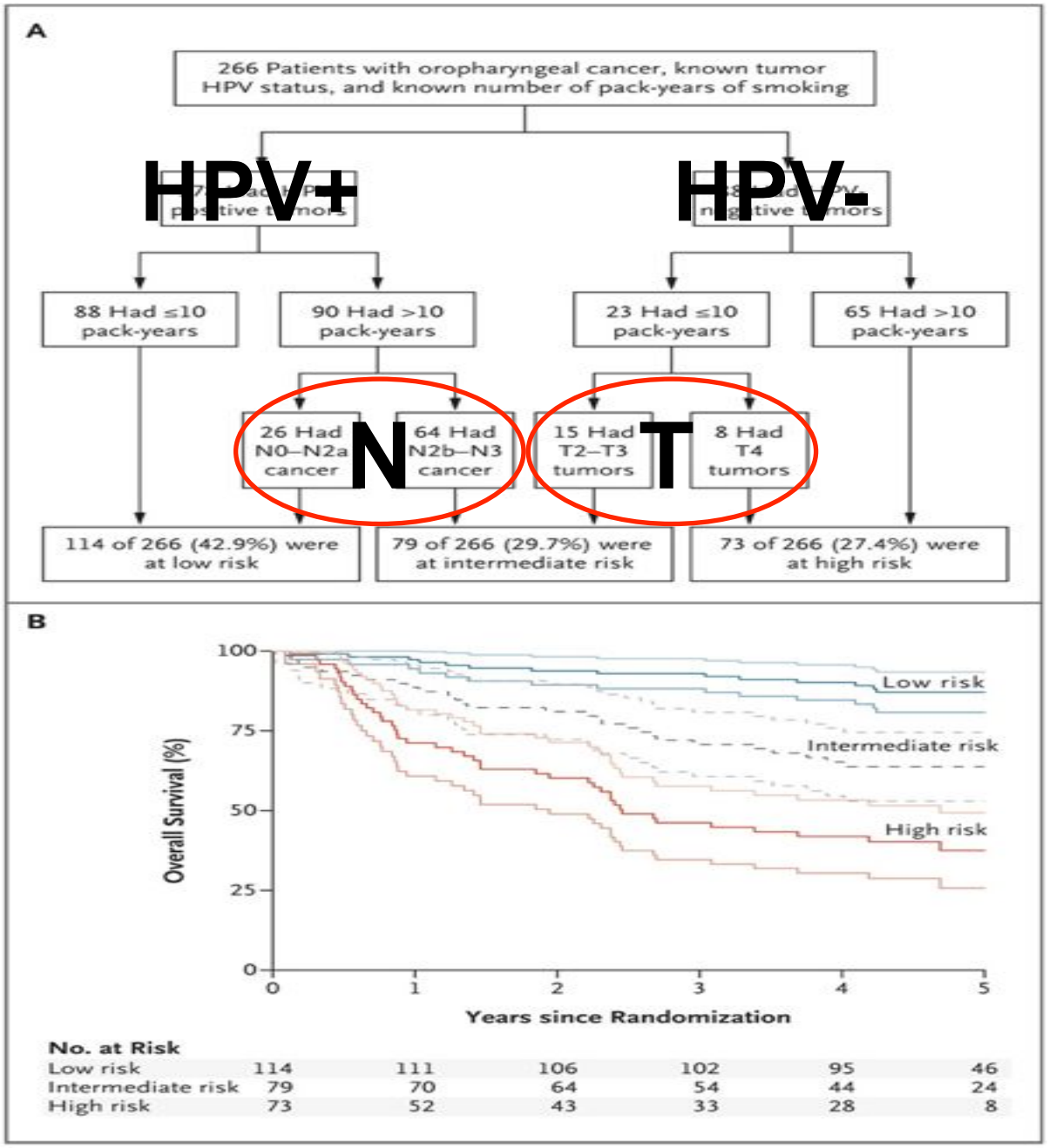
Prognosis based on:

HPV status

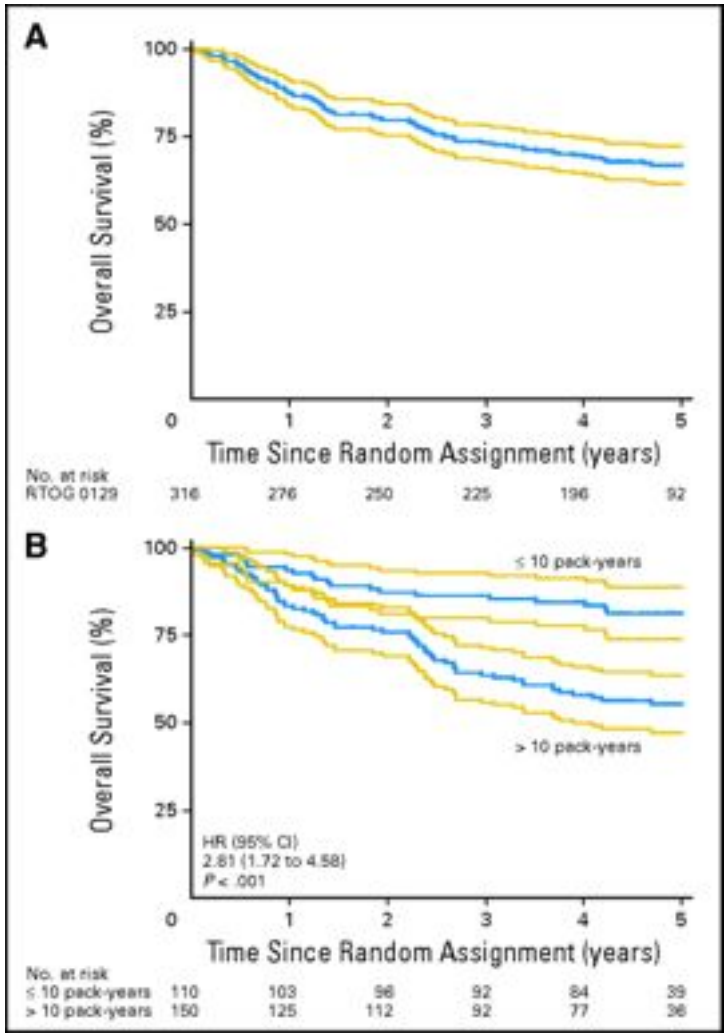
Tobacco smoke

Nodal stage

Tumor stage



Survival outcomes for patients with oropharyngeal carcinoma with known p16 status in Radiation Therapy Oncology Group (RTOG) 0129.



5-year OS:
67%

but ….different survivals according to tobacco exposure
***p* < 0.001**

Gillison M L et al. JCO 2012;30:2102-2111

JOURNAL OF CLINICAL ONCOLOGY

HPV status and smoke

HPV+	**HPV+**	**HPV-**
• Never smoker • Excellent prognosis	• Ever smoker • Intermediate prognosis	• Worse prognosis

HPV status and smoke

HPV+	**HPV+**	**HPV-**
• Never smoker • Excellent prognosis	• Ever smoker • Intermediate prognosis	• Worse prognosis

However, no impact of HPV 16 + on distant metastases risk

HN-SCC: ongoing trials on HPV+

		n.	trial
Phase 2	ECOG	83	Neoadiuvant CT → response-adapted RT (54 Gy vs 66-70 Gy) plus cetuximab

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Phase 3	Mount Sinai University	365	Weekly carboplatin/cetuximab + 56 Gy RT vs weekly carboplatin + 70 Gy RT

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Phase 3	Washington University	496	Post-operative 60 Gy RT plus/minus weekly cisplatin

HPV e SCC Orofaringe: conclusioni

- HPV DNA detection è superiore a HPV p16 status

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- Gli studi attuali non autorizzano una de-intensificazione (meno Gy, CTV limitati, omissione della chemioterapia, utilizzo del cetuximab) del trattamento standard

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- Nei pazienti HPV+ con stadio avanzato il rischio di metastasi a distanza rimane immutato

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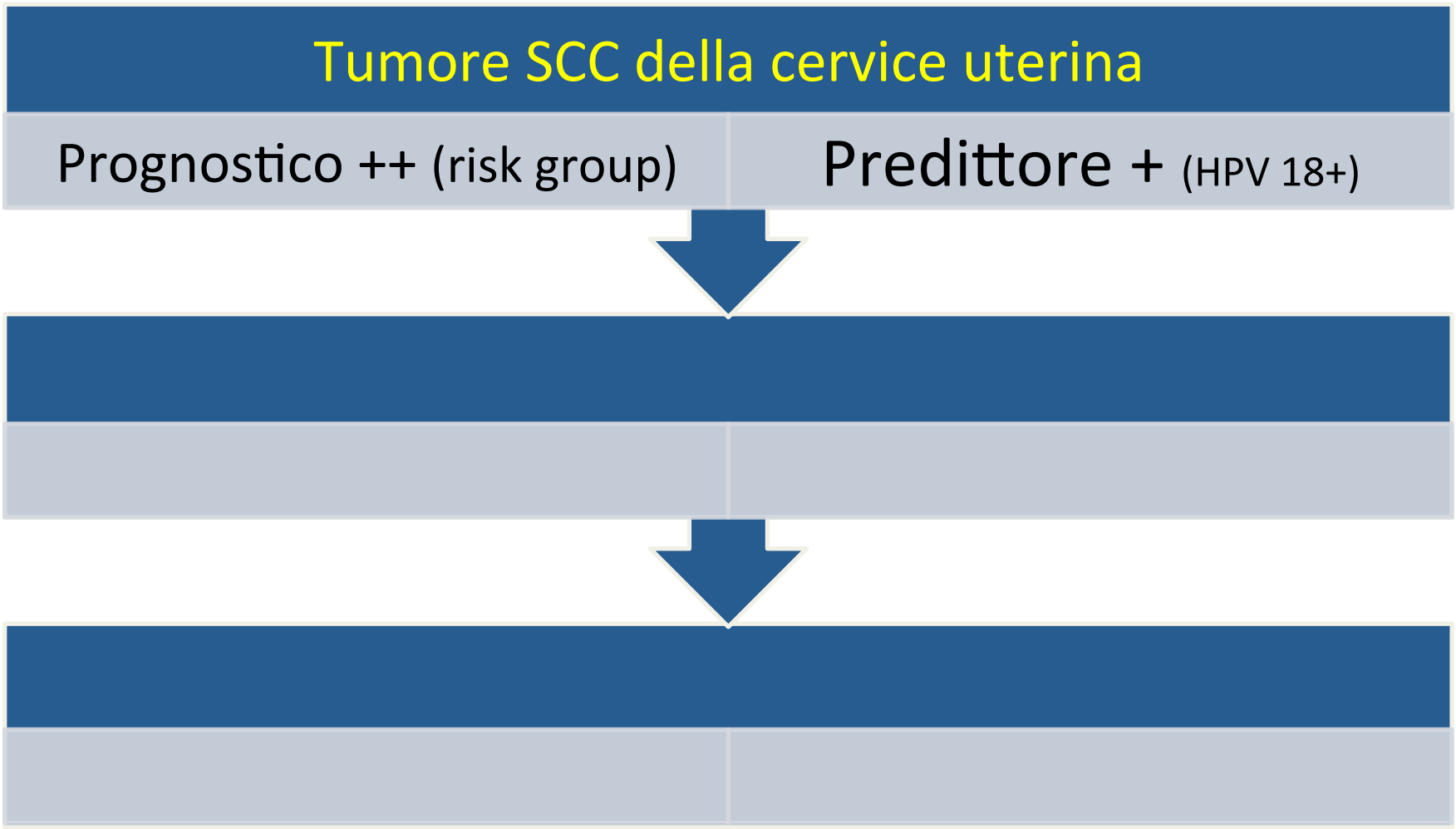
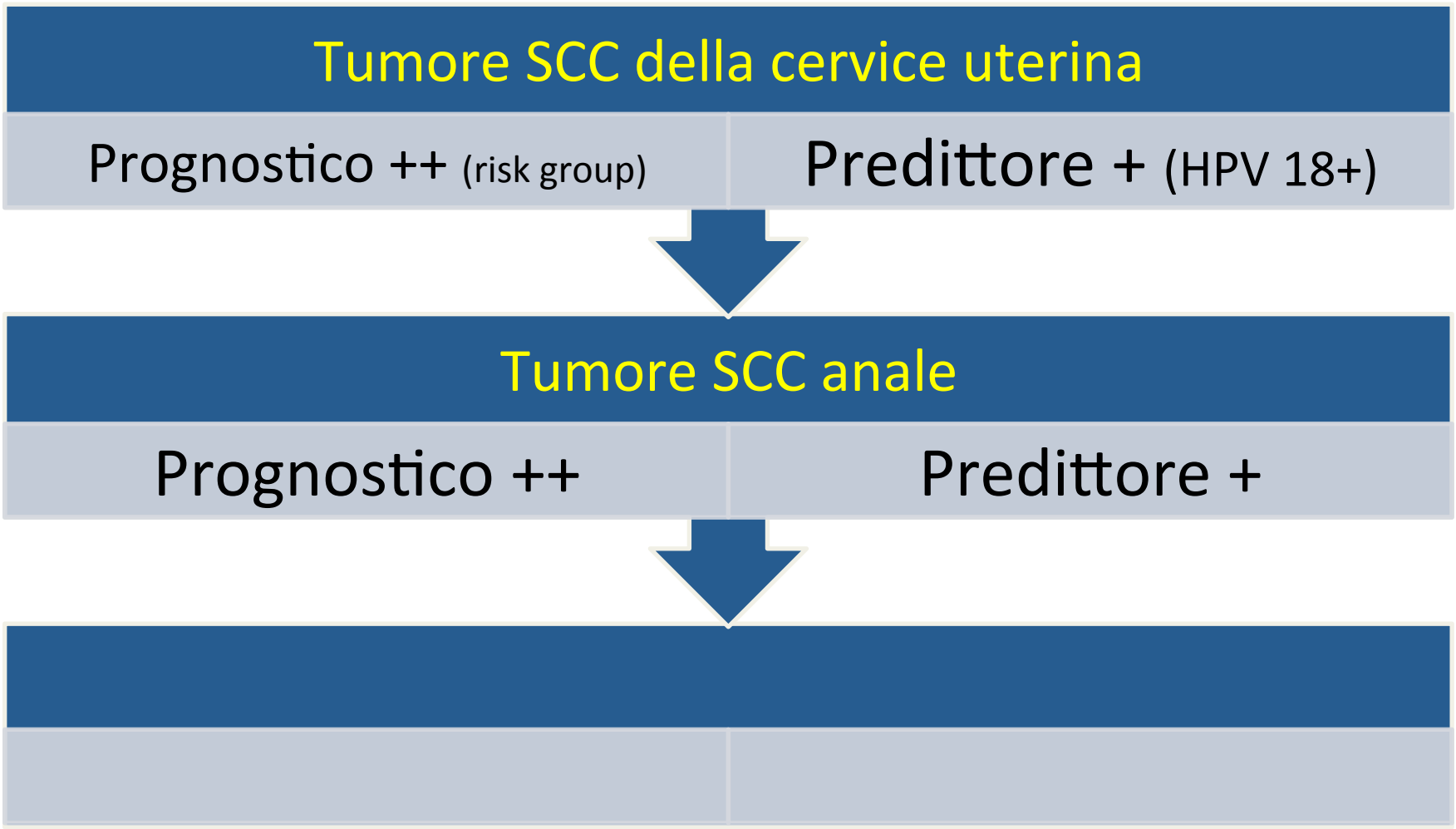
- Gli studi attuali non autorizzano una de-intensificazione (meno Gy, CTV limitati, omissione della chemioterapia, utilizzo del cetuximab) del trattamento standard
- Nei pazienti HPV+ con stadio avanzato il rischio di metastasi a distanza rimane immutato
- Prospettive per un vaccino anti HPV 16?

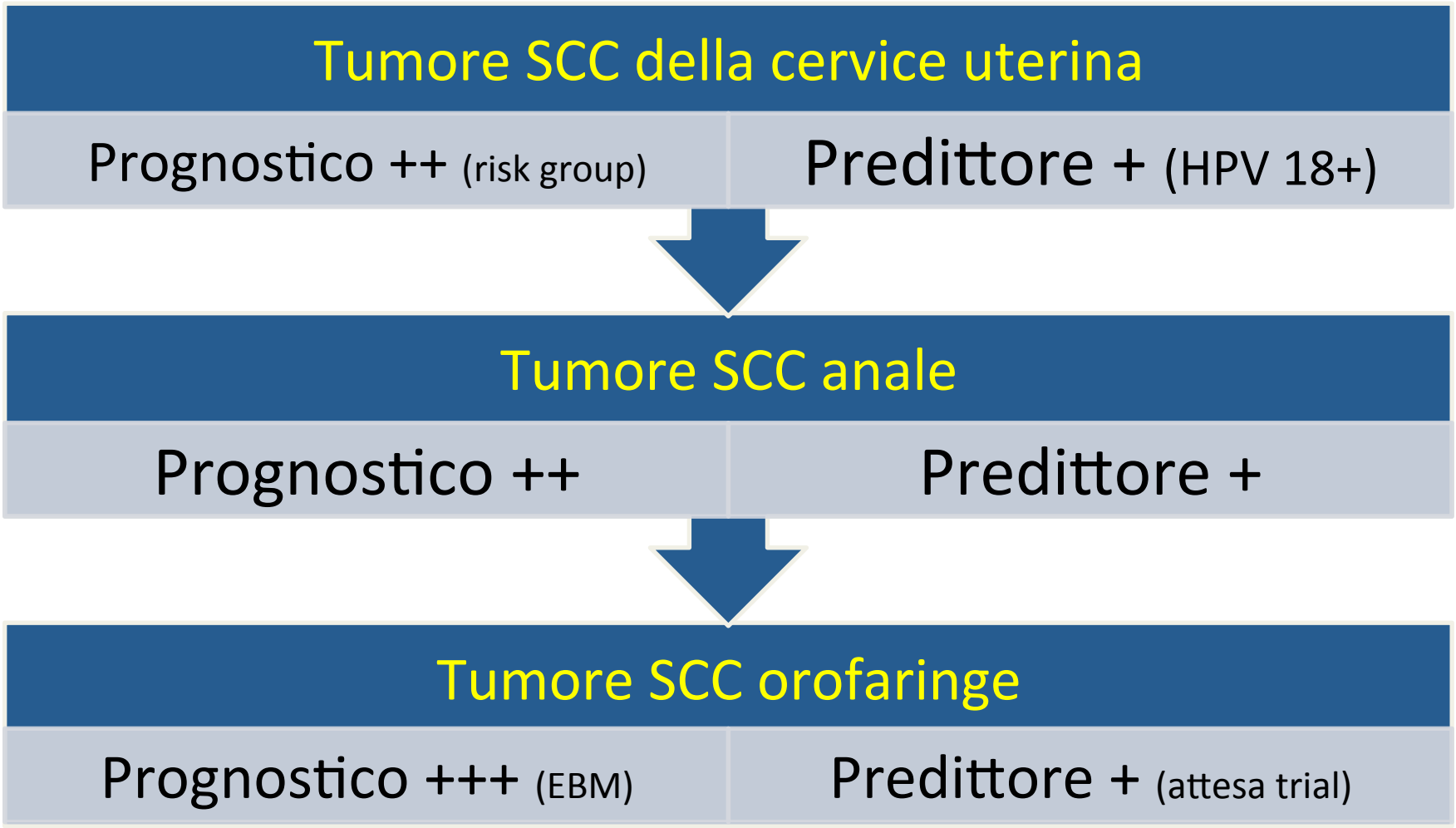
HPV status: fattore prognostico o predittore di risposta alla (chemio)radioterapia?



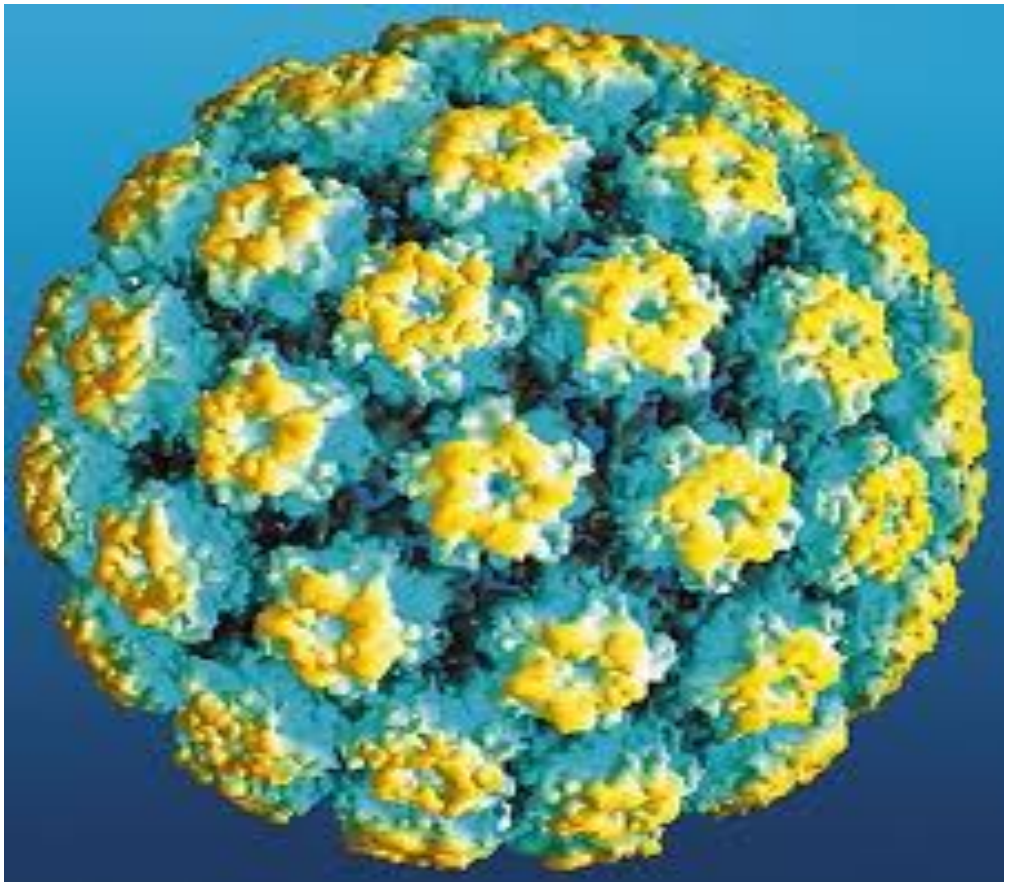
HPV status: fattore prognostico o predittore di Risposta alla (chemio)radioterapia?

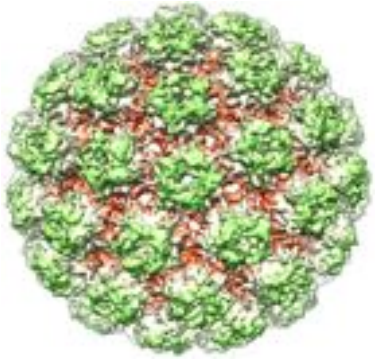


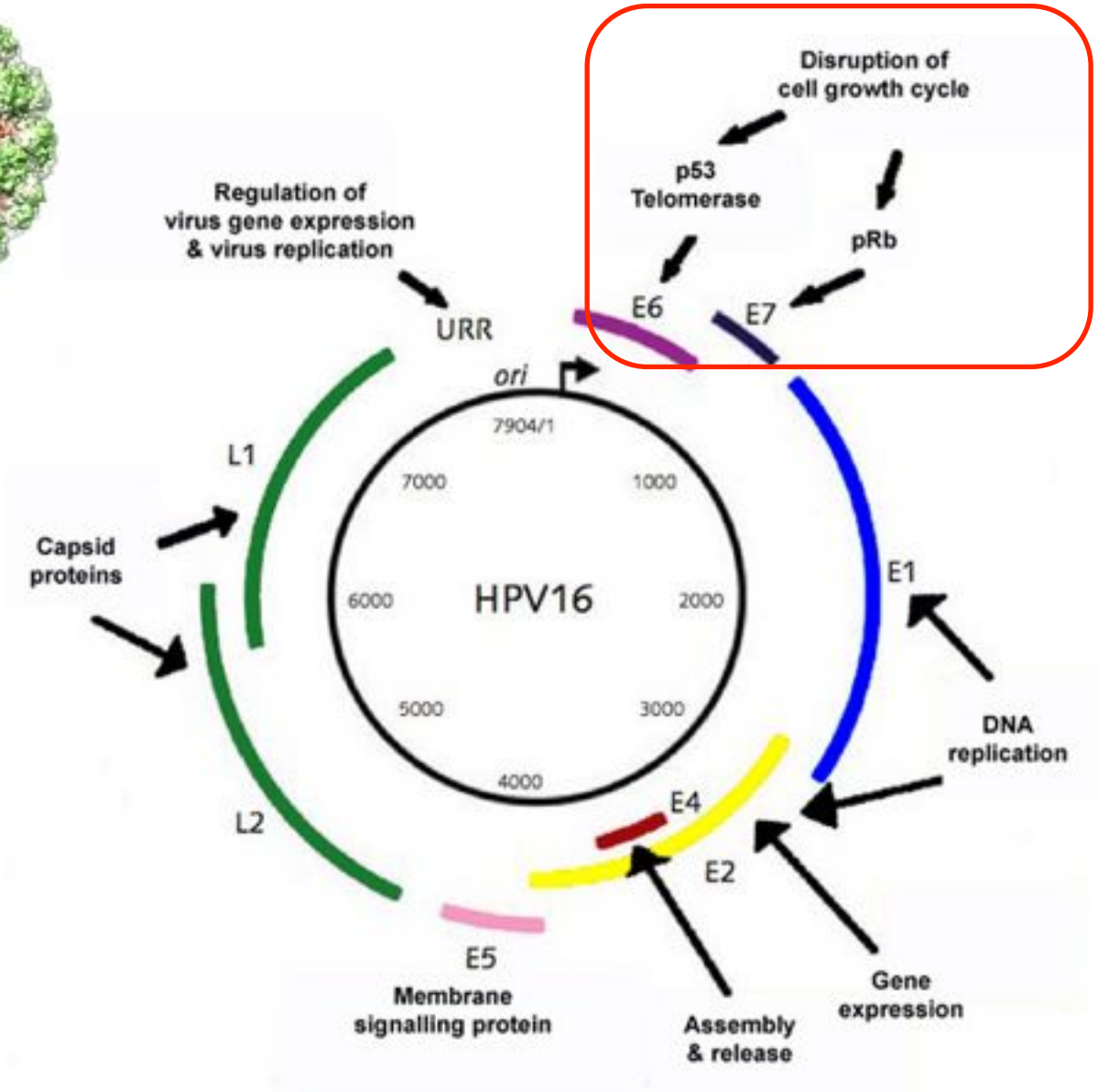
HPV status: fattore prognostico o predittore di Risposta alla (chemio)radioterapia?



Domande? Commenti?
Grazie!






Disruption of
cell growth cycle
p53
Telomerase
pRb
E6
E7
Regulation of
virus gene expression
& virus replication
URR
ori
7904/1
1000
2000
3000
4000
5000
6000
7000
HPV16
L1
L2
Capsid
proteins
E1
DNA
replication
E4
E2
E5
Membrane
signalling protein
Assembly
& release
Gene
expression

Advantages and limitations of randomized controlled trials and observational studies

Randomized controlled trial		Observational study	
Advantages	**Limitations**	**Advantages**	**Limitations**
Measures treatment efficacy	Poor generalizability of results	Measures treatment effectiveness	Subject to selection bias and confounding
Lack of selection bias by virtue of randomization	Relative short follow-up time	Good generalizability of results	Methodologically complex
Well-defined study populations	Costly	Cheaper; less time-consuming	Heterogeneous patient populations
Homogeneous patient populations	Time-consuming; long timelines to conclude	Provides resource utilization and cost data	Less detailed clinical information
High patient adherence to treatment protocols	Not enough power to compare rare events	Long follow-up times; well-powered to detect rare events	Data often not collected for research purposes
Research-oriented, high-quality data collection protocols	Not enough power to study rare diseases	Large sample sizes; well-powered to study rare diseases	Variable patient adherence; does not capture new treatments
Detailed clinical information	Control groups often do not reflect current practice	Control groups reflect current practices	Quality of reporting highly variable

Methods of evidence generation

1.1. Randomized clinical trials

- **Head to head trials: randomization at the subject level**

- **Cluster randomized trials: randomization at group levels (eg hospitals)**

- **Adaptive designs: eg Bayesian adaptive randomization**

- **Pragmatic trials: control arms defined as “usual practice,” broad inclusion criteria; evaluates new interventions in realistic healthcare settings**

Methods of evidence generation

1.2. Observational study designs

- **Prospective and retrospective cohort: subjects are identified by the exposure variable (eg treatment) and followed over time for the occurrence of outcome events (eg death)**

- **Case–control: subjects are identified by the outcome and retrospectively evaluated for the exposure of interest**

- **Cross-sectional: evaluates exposure and outcomes simultaneously at a single point or period of time; cannot distinguish whether exposure precedes the outcome**

- **Ecological: studies of aggregated data (eg by country)**

- **Other: registry studies, administrative health claims databases; patterns-of-care studies**

Methods of evidence generation

2. Methods of evidence synthesis

2.1. Meta-analysis: quantitative methods to synthesize evidence (eg fixed-effects)

2.2. Systematic reviews: descriptive methods to synthesize evidence

2.3. Mathematical models: decision analytic models (often used in cost-effectiveness analyses)

Dose de-escalation to the elective nodal sites in HNSCCs

- **D.Nevens et al, Leuven, ESTRO 2014**

200 pts randomized to :

50 Gy/2 Gy fx **vs 40 Gy**/2 Gy fx to explore reduced dose to swallowing apparatus.

- Less dysphagia (**p=0.017**) at 6 months with 40 Gy/2 Gy fx
- No differences at 12 and 18 months