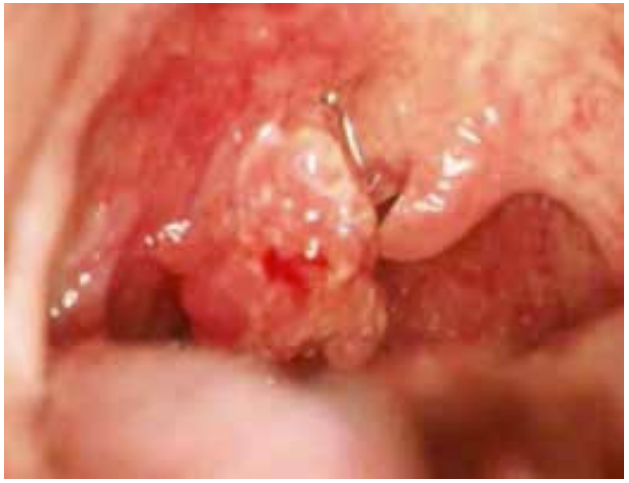
¿Desescalamiento en el tratamiento del cáncer de orofaringe VPH+?

A Favor

Miren Taberna Sanz

Oncología Médica
Unidad Funcional de Cáncer de Cabeza y Cuello
Unidad de Epidemiología Molecular y Genética en Infecciones y Cáncer
Institut Català d'Oncologia-IDIBELL

¿Por qué plantearnos una de-escalada de tratamiento?

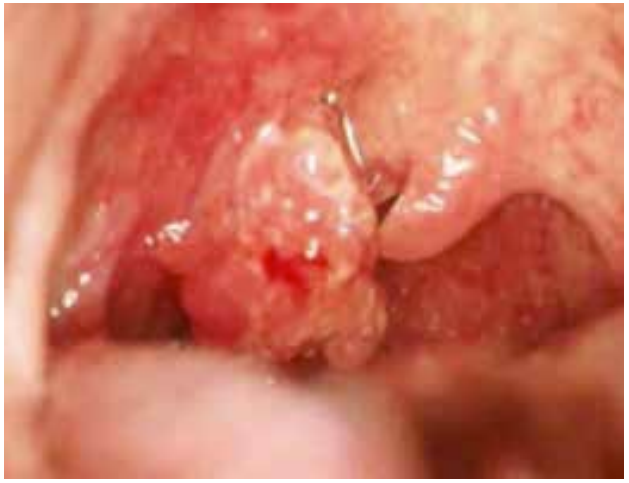


Epidemiológicas
Moleculares
Clínicas

Elevada toxicidad tratamientos actuales

Evidencia que soporta la des-intensificación

¿Por qué plantearnnos una de-escalada de tratamiento?



Diferencias

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Nivel epidemiológico

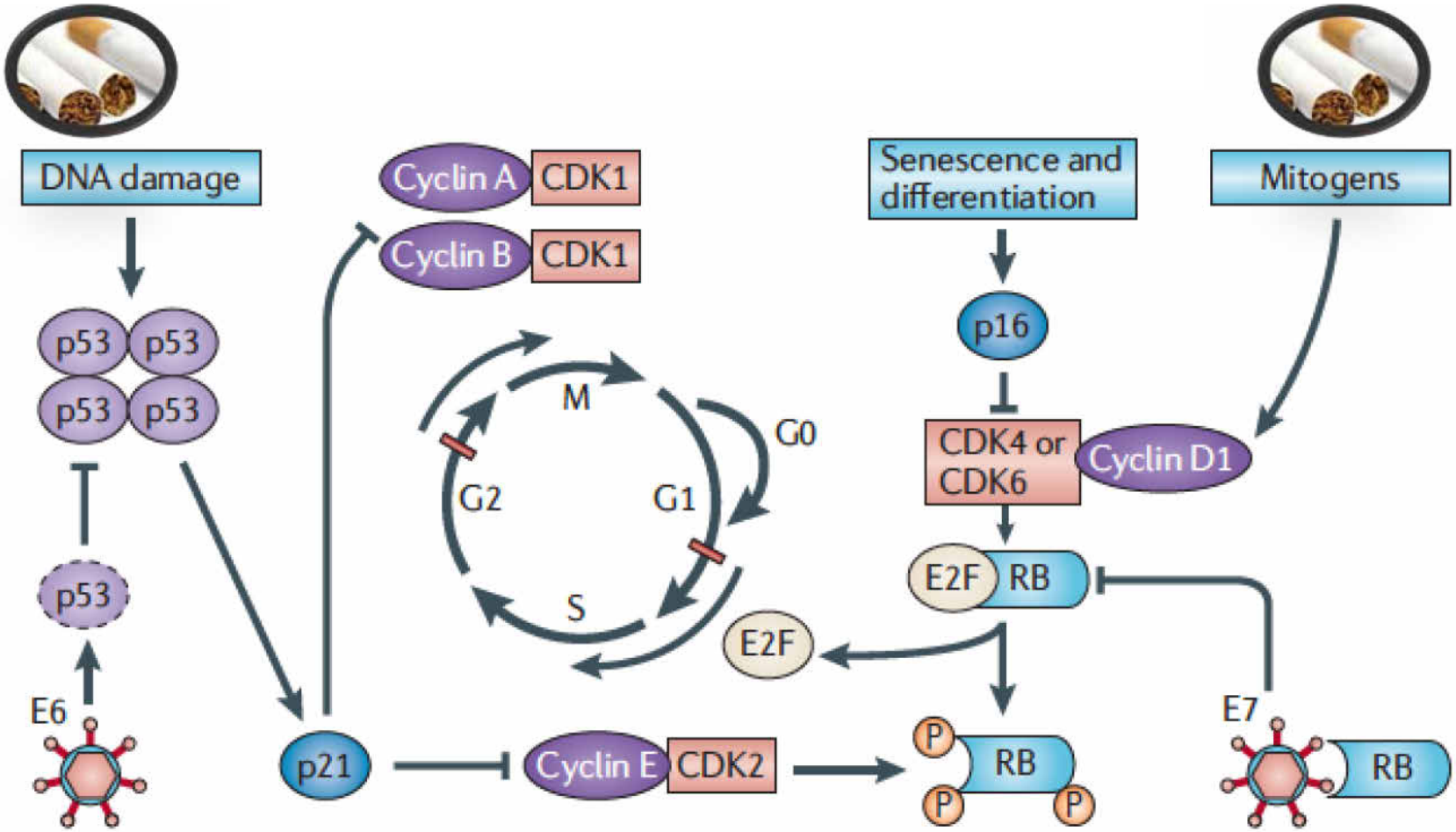
- Varón
- Edad avanzada
- Fumador
- Enol

- Varón (mujer según área geográfica)
- Jovén
- Elevado número de parejas sexuales
- No fumador/no enol (según área geográfica)
- Nivel cultural alto

A simple vista en la consulta…

Gillison et. al, JCO 2016

Nivel molecular



Nivel clínico

Diferencias en supervivencia VPH+ vs VPH-

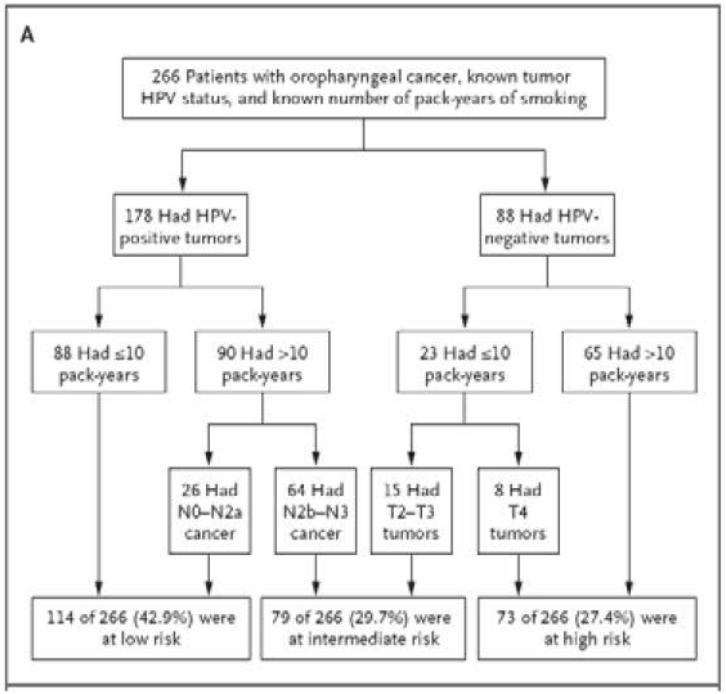
Study	Design	Site (n)	Treatment	HR HPV+ vs HPV- (Follow-up time)
Fakhry C, 2008	Phase II	Oropx, Lx (96)	**CT**	**0.36 [0.15-0.85] (2y)**
Lassen P, 2009	Phase III	Px, Lx (156)	**RDT**	**0.44 [0.28-0.68] (5y)**
Ang K, 2010	Phase III	Oropx (323)	**CT**	**0.42 [0.27-0.66] (3y)**
Rischin D, 2010	Phase III	Oropx (172)	**CT**	**0.45 [0.21-0.96] (2y)**
Lassen P, 2011	Phase III	OC, Px, Lx (794)	**RDT**	**0.54 [0.42-0.68] (5y)**
Posner MR, 2011	Phase III	Oropx (111)	**CT**	**0.20 [0.10-0.38] (5y)**

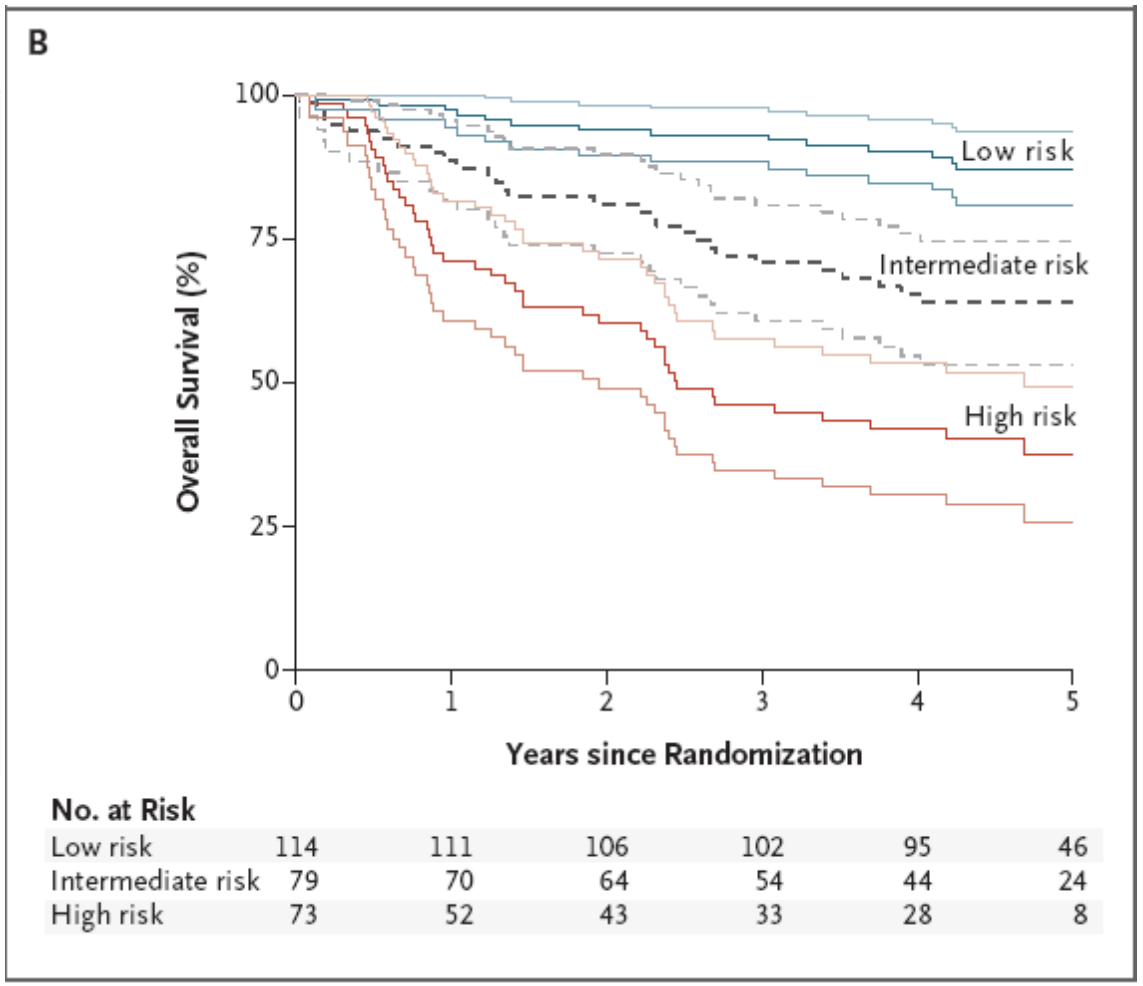
"CT": Chemotherapy, "RDT": Radiotherapy.

Hazard ratio - adjusted by different information such as age, stage, …;

Gillison ML et al. Vaccine. 2012.

Diferencias en supervivencia VPH+ vs VPH-





Ang et al. NEJM 2010

	OPSCC HPV-non related	OPSCC HPV-related
Risk factor	Alcohol, tobacco	Number of oral sex partners
Age	Older	Younger
Incident trends	Mostly decreasing	Increasing
Head and neck tumor location	Anyone	Base of the tongue , tonsil
Stage	Anyone	Small T , large N involvement
Radiological image	Anyone	Cystic nodal involvement
Histopathological features	keratinizating	Basaloid Non-keratinizating
Tumor differentiation	Anyone	Undifferentiated
Biology and genetic alterations:		
CDKN2A	Common	Rare
p16^{INK4a} overexpression	Rare	Common
EGFR	Common (amplification)	Rare
p53	Common	Rare (p53 degradation by E6)
pRb	Rare	Rare (pRb degradation by E7)
PI3KCA	Common	Common (APOBEC)
TRAF3	Rare	Common
Outcomes	Worse OS and PFS	Better OS and PFS
Metastatic dissemination	Yes	Rarely
Comorbidity	Yes	No
Second primary tumors	Yes	No
Prevention strategies	Quitting smoking and drinking	Vaccination (in developmet)

Taberna M. et al, manuscript in preparation

OPSCC: oropharyngeal squamous cell carcinoma;
OS: overall survival, PFS: progression free survival

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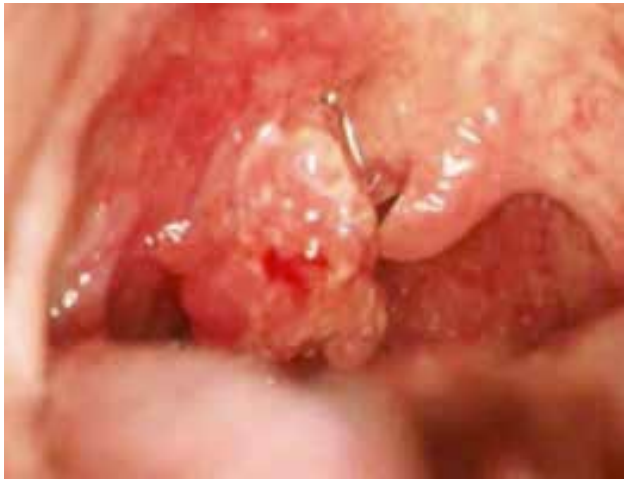

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Cancer of the Oropharynx

NCCN Guidelines Inde
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Base of tongue/tonsil/posterior pharyngeal wall/soft palate

WORKUP

- H&P[a,b] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Biopsy of primary site or FNA of the neck
- Tumor human papillomavirus (HPV) testing recommended[c]
- Chest imaging as clinically indicated
- CT with contrast and/or MRI with contrast of primary and neck
- Consider FDG-PET/CT for stage III-IV disease
- Dental evaluation,[d] including panorex as clinically indicated
- Nutrition, speech and swallowing evaluation/ therapy, and audiogram as clinically indicated[e]
- EUA with endoscopy as clinically indicated
- Pre-anesthesia studies

Multidisciplinary consultation as clinically indica d

CLINICAL STAGING

T1-2

T

A

T
o
U
o
U

M
a

-P16 expression is highly correlated with HPV status and is widely available.
-HPV in situ hybridization or PCR-based assay is also available.
Although not used to guide treatment, HPV testing is valuable prognostically.

-<u>The results of HPV testing should not change management decisions except in the context of a clinical trial.</u>

[a]H&P should include docum tation and quantification (pack years smoked) of tobacco use history. Smoking cessation counseling as clinically indicated. All current smokers should be adv d to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support and resources, smokers can be ref d to the NCCN Guidelines for Smoking Cessation and www.smokefree.gov.
[b]Screen for depre on (See NCCN Guidelines for Distress Management).
[c]P16 expression is highly correlated with HPV status and is widely available. HPV in situ hybridization or PCR-based assay is also available. Although not used to guide treatment, HPV testing is valuable prognostically. The results of HPV testing should not change management decisions except in the context of a clinical trial.
[d]See Principles of Dental Evaluation and Management (DENT-A).
[e]See Principles of Nutrition: Management and Supportive Care (NUTR-A).

NCCN Guidelines Version 2.2016
Cancer of the Oropharynx

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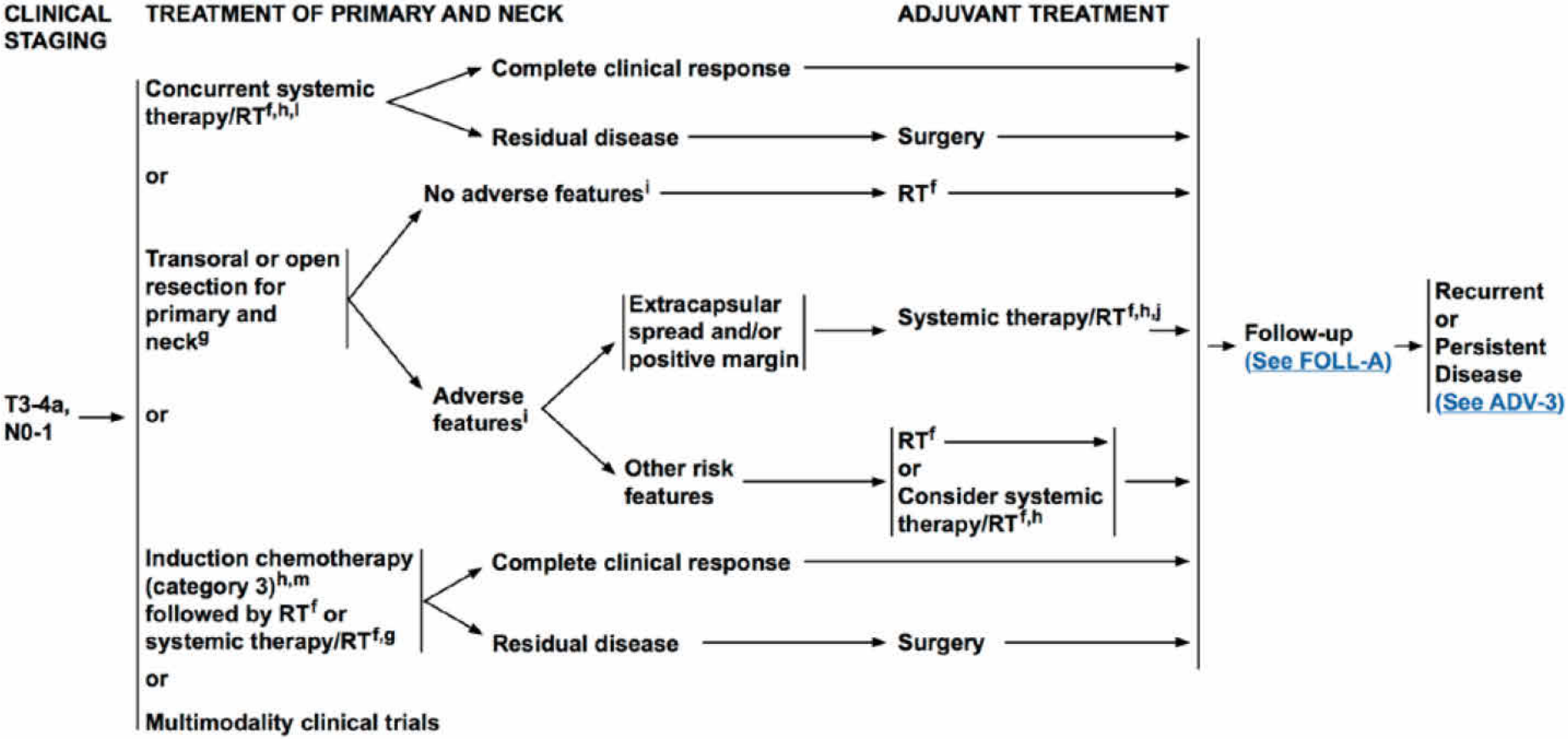

[f] See Principles of Radiation Therapy (ORPH-A).
[g] See Principles of Surgery (SURG-A).
[h] See Principles of Systemic Therapy (CHEM-A).
[i] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (lymphovascular invasion) (See Discussion).
[j] The recommendations for patients at high risk with extracapsular spread + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.
[l] When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[m] See Discussion on induction chemotherapy.

NCCN Guidelines Version 2.2016
Cancer of the Oropharynx

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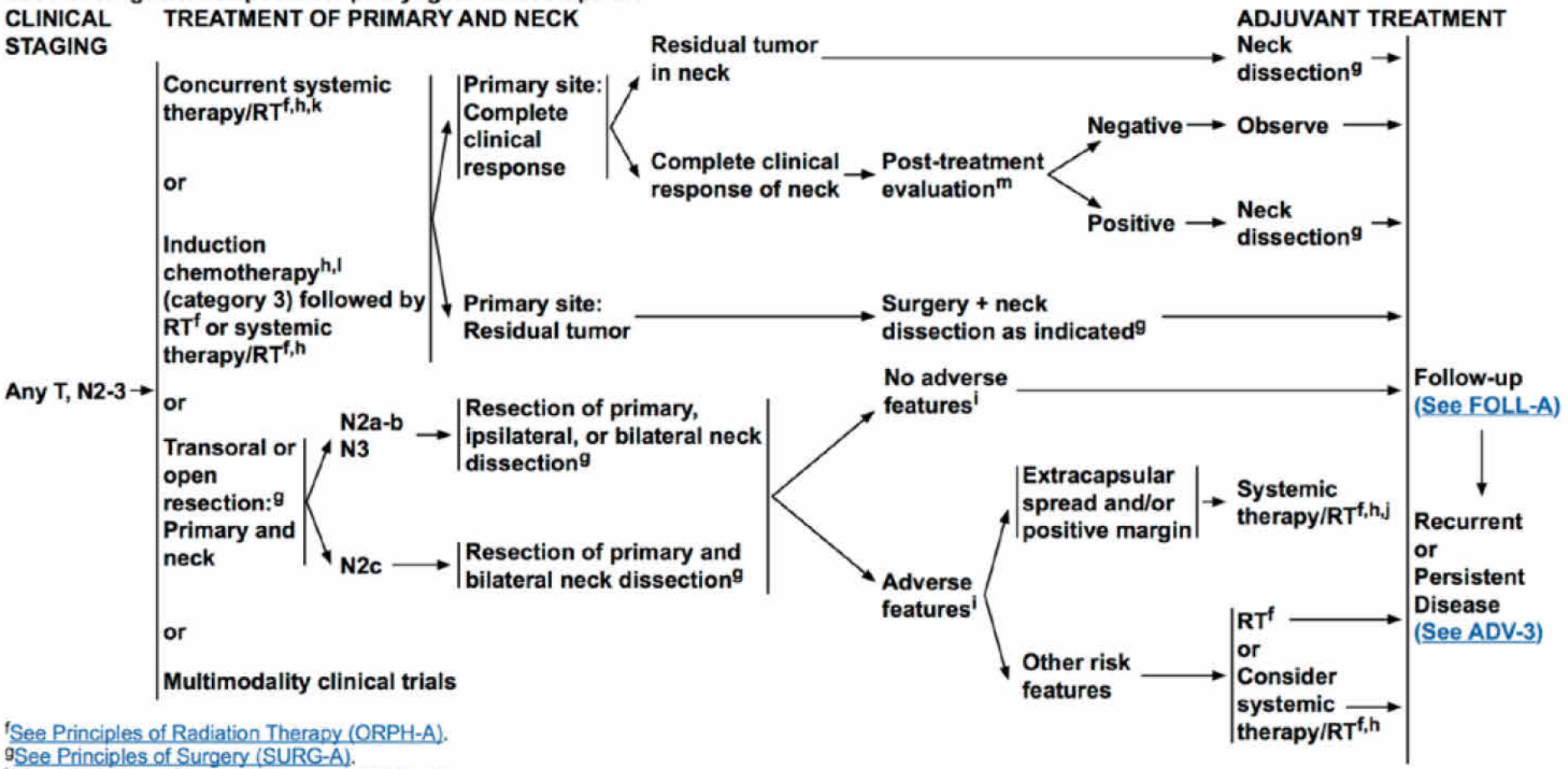

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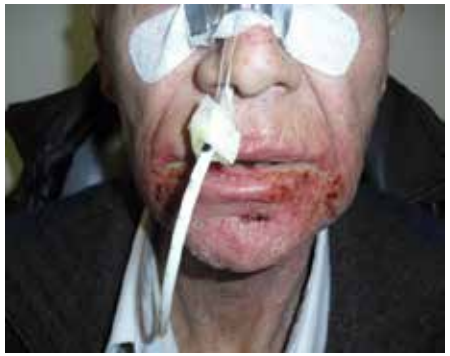
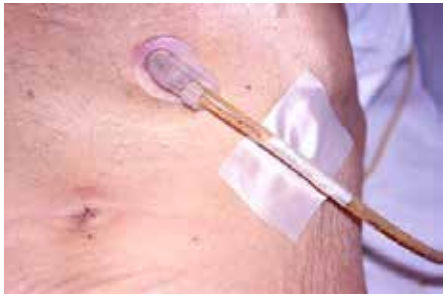
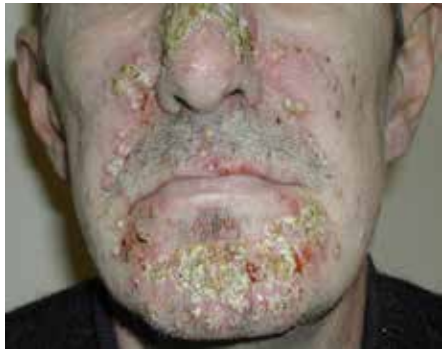
[m] See Discussion on induction chemotherapy.
[n] See Post Chemoradiation or RT Neck Evaluation (FOLL-A 2 of 2).

Tratamiento habitual para los Carcinomas de Orofaringe localmente avanzados

IQ (+/- QMT-RDT) vs QMT-RDT o BioRDT (+/- QMT Inducción (TPF))



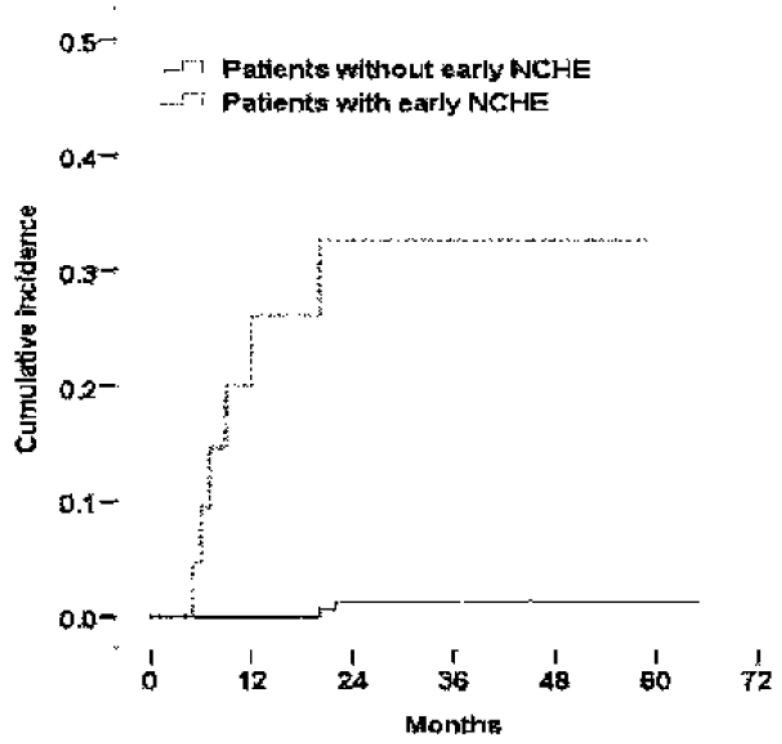




- Fibrosis
- Xerostomía/ Alt. dentarias
- Problemas respiratorios
- Disfagia
- Disfonía
- Alteraciones auditivas

Bentzen and Trotti. JCO 2007.

Aumento del número de muertes debido a eventos no-relacionados con cancer (Cardiovasculares, cerebrales…)



No. at risk							
Without NCHE	168	164	136	85	43	9	0
With NCHE	22	16	10	7	3	0	0

NCHE: non-cancer health event

Kang et al. Medicine, 2016.

Toxicidad aguda

+

Toxicidad tardía

+

Comorbilidad

+

Pacientes jóvenes

Impacto social y económico

Gillison et al. JCO 2012

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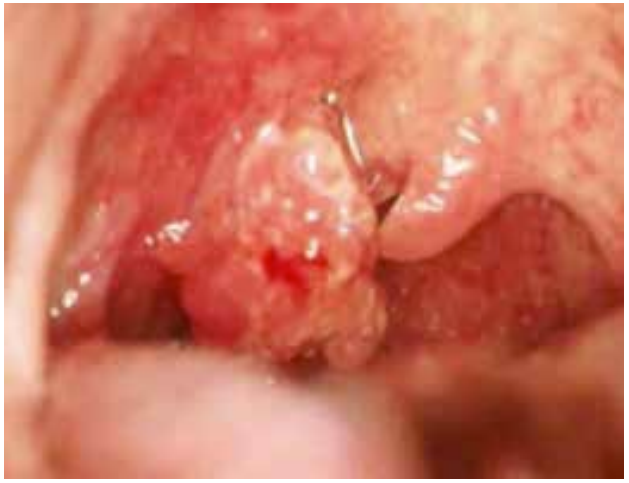

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International Journal of Radiation Oncology*Biology*Physics
Volume 93, Issue 5, 1 December 2015, Pages 976–985

114003||

Clinical Investigation

Phase 2 Trial of De-intensified Chemoradiation Therapy for Favorable-Risk Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

Bhishamjit S. Chera, MD*, †, , , Robert J. Amdur, MD‡, §, Joel Tepper, MD
Bahjat Qaqish, PhD†, ||, Rebecca Green, MSW*, Shannon L. Aumer, MA#, Neil [illegible]s,
MD, MPH†, ¶, Jared Weiss, MD†, ¶, Juneko Grilley-Olson, MD†, ¶, Adam Zanation [illegible]#,
Trevor Hackman, MD#, William Funkhouser, MD**, Nathan Sheets, MD††, Mark
Weissler, MD#, William Mendenhall, MD‡, §

- Phase II study
- N=43 low volumen HPV-OPSCC
- Cisplatin 30 mg/m2/week + 60 Gy IMRT à **16% reduction in RT and a 60% reduction in cisplatin dose**

-Excellent **pCR rate of 86%** (98% for the primary site and 84% for the cervical neck nodes)
-Comparatively lower acute toxicities with a de-intensified CRT regimen in favorable-risk HPV-associated OPSCC.
- Our observed pCR rate is similar to the 87% local–regional control rate after standard-dose CRT

Existen precedentes desde el año 2001 para el tto de pacientes con cáncer de orofaringe HPV+ con dosis reducidas de RDT a 60 Gy / 5 semanas

-449 OPSCC were treated with RT alone. Variety of schedules (60-70 Gy over 4-7 weeks).
-148 patients with p16-positive OPSCC, 41% had T3-T4 tumors and 87% were stage III-IVB.
-**Patients with p16-positive OPSCC who had ≤10 pack-years (n = 37) had 3-year OS, cause-specific survival, local control, and regional control rates of 86%, 92%, 95% and 97%, with distant control rates of 92%**
- Additional analyses indicated high volume disease (T4 or N3) to have a high-risk of disease progression, even if tobacco exposure is <10 pack-years

Estrategias principales para la des-intensificación del tratamiento:

- Utilización de **terapias anti-EGFR** (Cetuximab) como una alternativa al tratamiento con Cisplatino en la concomitancia con Radioterapia.

- **Reducción de la dosis de Radioterapia** en el tratamiento concomitante radical tras haber obtenido una buena respuesta a la quimioterapia de inducción.

- **Reducción de la quimioterapia adyuvante** o de la **dosis de radioterapia** tras un primer tratamiento quirúrgico.

- Utilización de **inmunoterapia** como una alternativa al tratamiento con Cisplatino en la concomitancia con Radioterapia.

Estrategias principales para la des-intensificación del tratamiento

Strategy	Country	Trial	Phase	N	Comments
Cetuximab with IMRT radiation **(in comparison with IMRT-cisplatin)**	US	RTOG 1016 NCT01302834	Phase III	706	
	US	NCT01663259	Phase III	36	Smoking history <10 pack-year
	Australia	TROG 1201 NCT01855451	Phase III	200	
	UK	De-ESCALaTE NCT01874171	Phase III	304	
Reduction dose of IMRT when given in combination with CT, after iCT	US	ECOG 1308 NCT01084083	Phase II	90	2-years PFS of 80% reported for patients with cCR
	US	NCT01133678	Phase II	80	Everolimus in combination with iCT
	US	Quarterback trail NCT01706939	Phase III	365	Non-smokers
	US	OPTIMA NCT02258659	Phase II	61	iCT with Nab-paclitaxel and carboplatin
Reduced-dose of IMRT with or without CT	US	NRG-HN002 NCT02254278	Phase II	296	Low risk HPV-related OPSCC*
	US	NCT01932697	Phase II	80	Hyperfractionated IMRT and Docetaxel Smoking history <10 pack-year
Surgery followed by reduction of adjuvant CT or low dose of IMRT	US	ADEPT NCT01687413	Phase III	496	No margins affected but extracapsular spread in lymph nodes
	US	ECOG 3311 NCT01898494	Phase II	377	Transoral surgey
	UK	PATHOS NCT02215265	Phase II	88	Transoral surgey Stage T1-T3, N0-N2b
	US	SIRS TRIAL NCT02072148	Phase II	200	Robotic surgery
	US	NCT02159703	Phase II	60	Transoral robotic surgery

Taberna M. et al, manuscript in preparation

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CT: chemotherapy; IMRT: intensity modulated radiation therapy,
iCT: induction chemotherapy, cCR: clinical Complete Response.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx— ECOG-ACRIN Cancer Research Group

Shanthi Marur, Shuli Li, Anthony J. Cmelak, Maura L. Gillison, Weiqiang J. Zhao, Robert L. Ferris, William H. Westra, Jill Gilbert, Julie E. Bauman, Lynne I. Wagner, David R. Trevarthen, Jahagirdar Balkrishna, Barbara A. Murphy, Nishant Agrawal, A. Dimitrios Colevas, Christine H. Chung, and Barbara Burtness

Purpose

Human papillomavirus (HPV)–associated oropharyngeal squamous cell carcinoma (OPSCC) is treatment-responsive. Definitive chemoradiation results in high cure rates but causes long-term toxicity and may represent overtreatment of some patients. This phase II trial evaluated whether complete clinical response (cCR) to induction chemotherapy (IC) could select patients with HPV-associated OPSCC for reduced radiation dose as a means of sparing late sequelae.

Methods

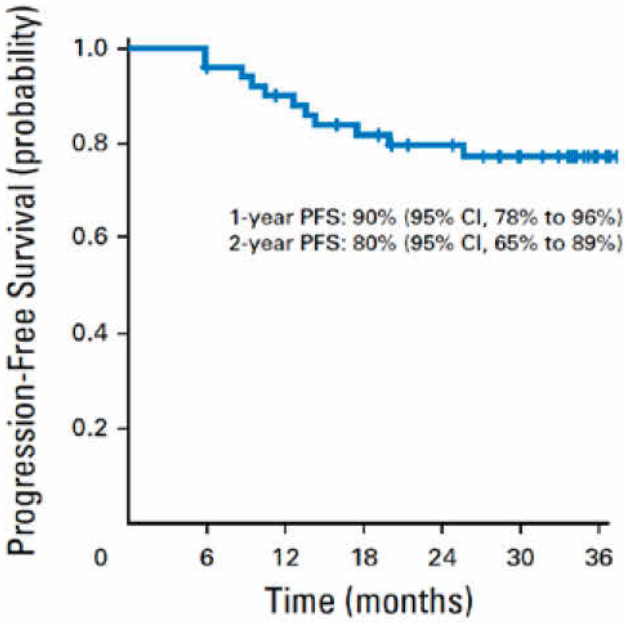
Patients with HPV16 and/or p16-positive, stage III-IV OPSCC received three cycles of IC with cisplatin, paclitaxel, and cetuximab. Patients with primary-site cCR to IC received intensity-modulated radiation therapy (IMRT) 54 Gy with weekly cetuximab; those with less than cCR to IC at the primary site or nodes received 69.3 Gy and cetuximab to those regions. The primary end point was 2-year progression-free survival.

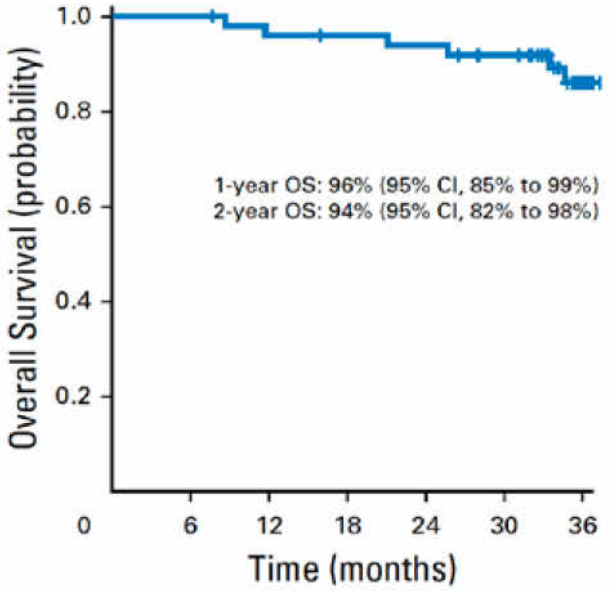
Results

Of the 90 patients enrolled, 80 were evaluable. Their median age was 57 years (range, 35 to 73 years), with the majority having stage T1-3N0-N2b OPSCC and a history of < 10 pack-years of cigarette smoking. Three cycles of IC were delivered to 77 of the 80 patients. Fifty-six patients (70%) achieved a primary-site cCR to IC and 51 patients continued to cetuximab with IMRT 54 Gy. After median follow-up of 35.4 months, 2-year progression-free survival and overall survival rates were 80% and 94%, respectively, for patients with primary-site cCR treated with 54 Gy of radiation (n = 51); 96% and 96%, respectively, for patients with < T4, < N2c, and < 10 pack-year smoking history who were treated with ≤ 54 Gy of radiation (n = 27). At 12 months, significantly fewer patients treated with a radiation dose ≤ 54 Gy had difficulty swallowing solids (40% *v* 89%; $P = .011$) or had impaired nutrition (10% *v* 44%; $P = .025$).

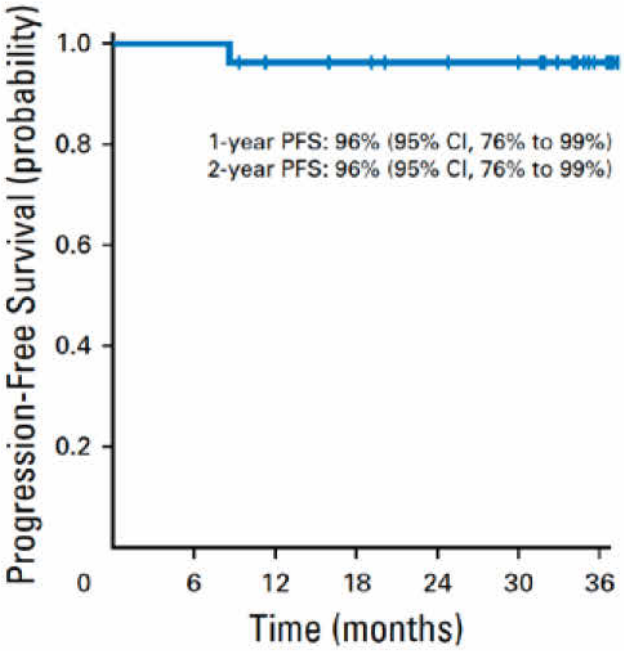
Conclusion

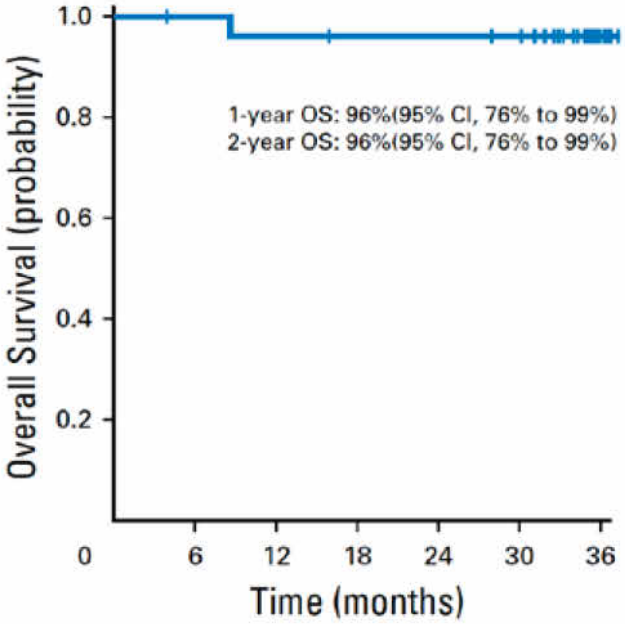
For IC responders, reduced-dose IMRT with concurrent cetuximab is worthy of further study in favorable-risk patients with HPV-associated OPSCC. Radiation dose reduction resulted in significantly improved swallowing and nutritional status.





General population





PFS and OS in favorable cohort (non-T4, non-N2c, 10 pack-year smokers) with clinical complete response to induction chemotherapy treated with low-dose radiation of 54 Gy (n = 27).

Conclusiones

Si, a favor de las terápias de des-intensificación

- Técnica diagnóstica de un carcinoma orofaringe HPV-positivo
- HPV-alto riesgo: T4/N3 , fumadores> 10 paquetes/año

Muchas gracias

Generalitat de Catalunya
Departament de Salut

ICO 10 MÉS 10
Institut Català d'Oncologia

Bellvitge
Hospital Universitari
Institut Català de la Salut

mtaberna@iconcologia.net

http://ico.gencat.cat

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Institut Català d'Oncologia

ICO l'Hospitalet
Hospital Duran i Reynals
Av. Granvia de L'Hospitalet, 199-203
08908 L'Hospitalet de Llobregat

ICO Badalona
Hospital Germans Trias i Pujol
Ctra. del Canyet s/n
08916 Badalona

ICO Girona
Hospital Doctor Trueta
Av. França s/n
17007 Girona

ICO Camp de Tarragona i Terres de l'Ebre
Hospital Joan XXIII
C. Dr. Mallafrè Guasch, 4 43005 Tarragona
Hospital Verge de la Cinta
C. de les Esplanetes, 14 43500 Tortosa