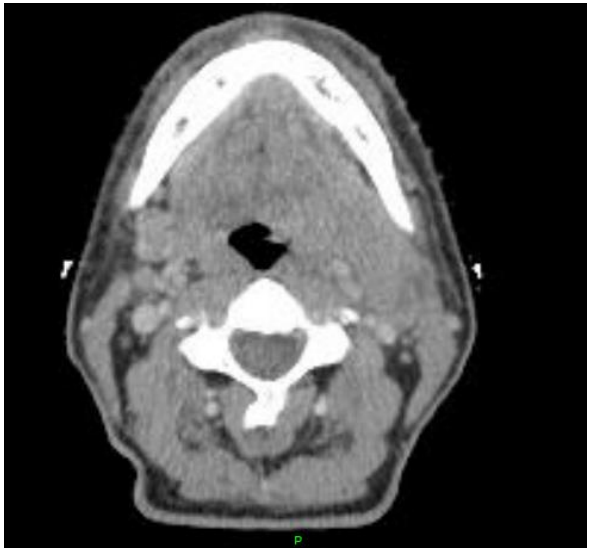
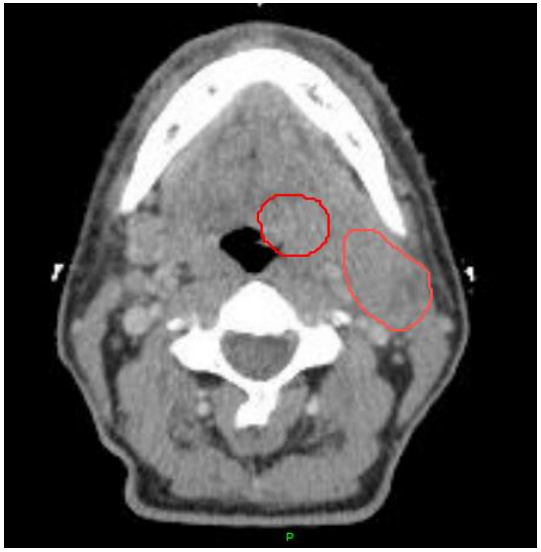
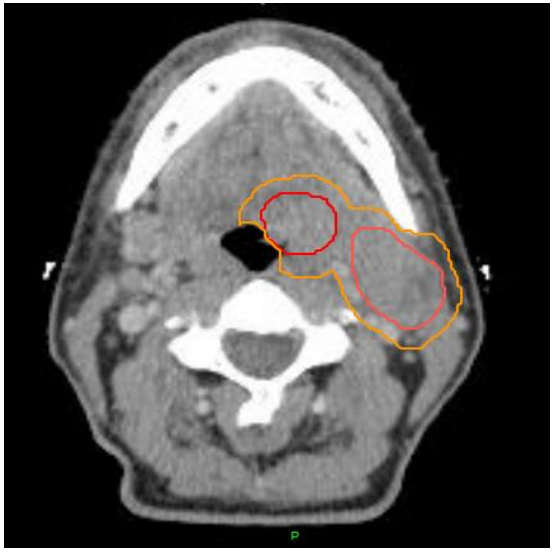
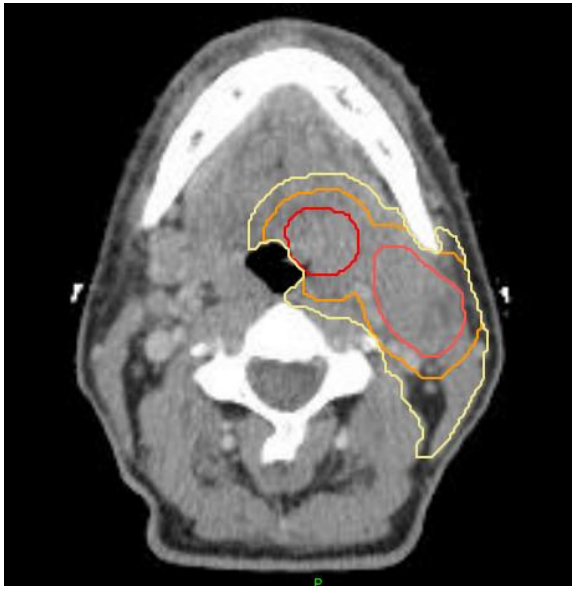
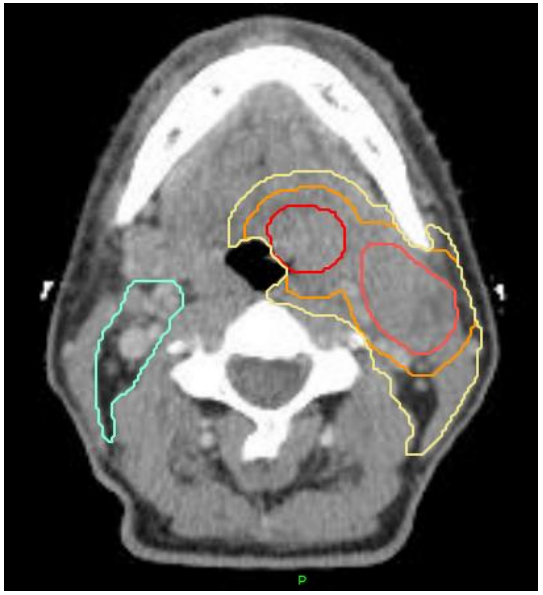
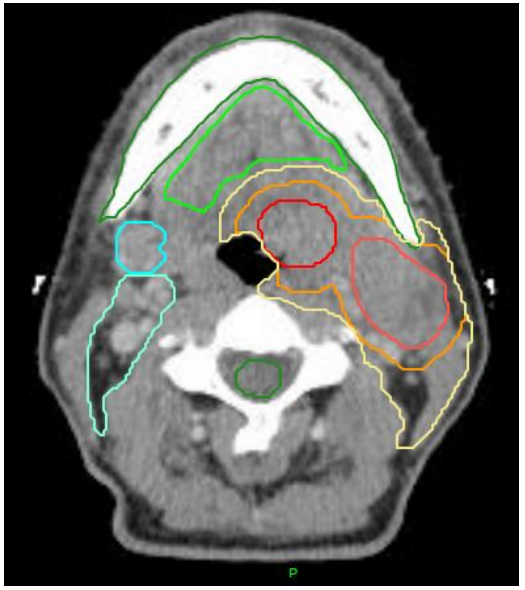
Avances de la Oncología radioterápica en Tumores de cabeza y cuello

Jon Cacicedo
Hospital Universitario de Cruces

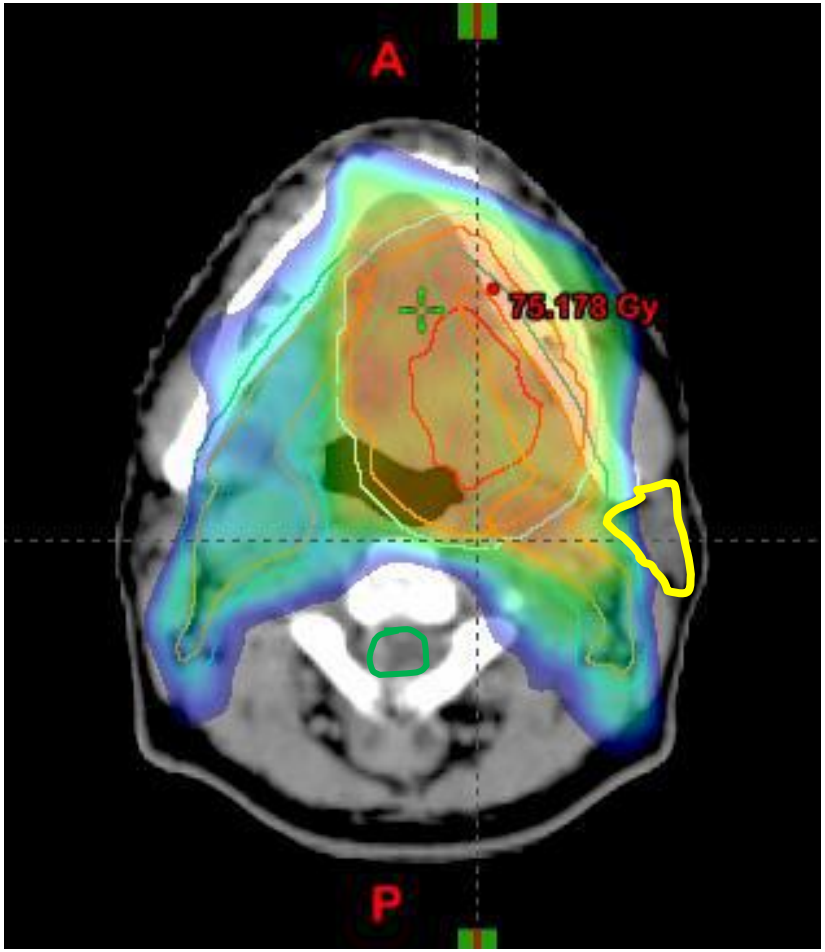
INTRODUCCION

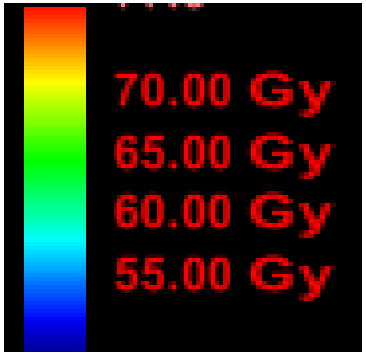
- Evolución técnica….¨menor toxicidad/control ¨
- **Delimitación …importancia de la formación**
  – Contorneo: protocolos educacionales/Guías

- Radioterapia adaptativa anatómica/biológica
- Carcinoma recurrente: Re-irradiación IMRT/SBRT
- Interés/modificaciones en relación a la **práctica** clínica diaria

IMPORTANCIA DE LA DELINEACION





- Lo que se va a irradiar con intención terapéutica depende de lo que se considere enfermedad en la delimitación

- Lo que se va a proteger depende de lo que se haya delimitado como órgano de riesgo

VOLUME 32 · NUMBER 34 · DECEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial to Test Accelerated Versus Standard Fractionation in Combination With Concurrent Cisplatin for Head and Neck Carcinomas in the Radiation Therapy Oncology Group 0129 Trial: Long-Term Report of Efficacy and Toxicity

VOLUME 33 · NUMBER 2 · JANUARY 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Institutional Clinical Trial Accrual Volume and Survival of Patients With Head and Neck Cancer

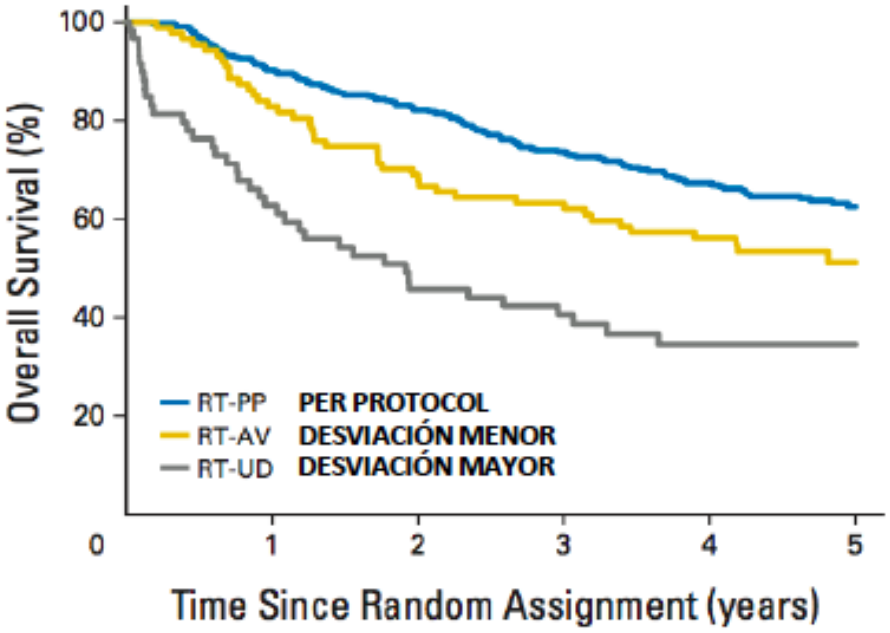
CRITERIO DE CALIDAD

	Per protocol PP	Desviación Menor AV	Desviación Mayor UV
Dosis Total	≤ 4%	> 4% y ≤ 9%	> 9%
Tiempo			
• RT estándar	46 – 52 días	53 – 60 días	> 60 días
• RT acelerada	39 – 43 días	50 – 57 días	> 57 días
Dias perdidos	≤ 2 días	3 – 5 días	> 5 días
Dosis en Médula	< 47 Gy	47 – 50 Gy	> 50 Gy

Wuthrick et al. JCO 2015

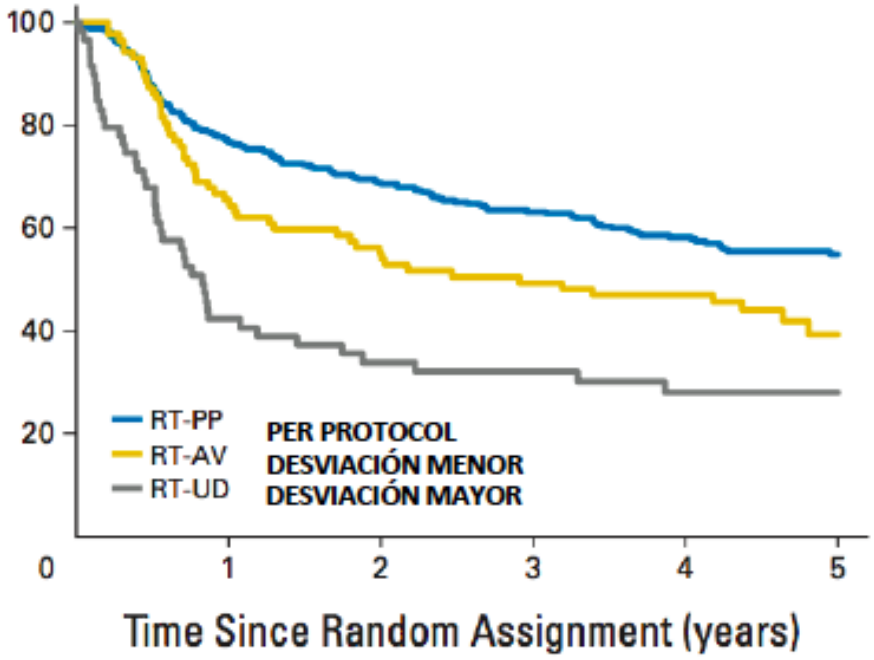
Supervivencia en función de la calidad de RT

Supervivencia



No. at risk						
RT-PP	325	293	263	231	189	92
RT-AV	87	72	59	54	46	17
RT-UD	59	37	27	23	16	6

Supervivencia libre de progresión



	325	249	220	199	162	80
	87	57	48	42	38	11
	59	25	20	18	13	6

Wuthrick et al. JCO 2015

Homogeneizar el contorneo del tumor y órganos de riesgo en cabeza y cuello

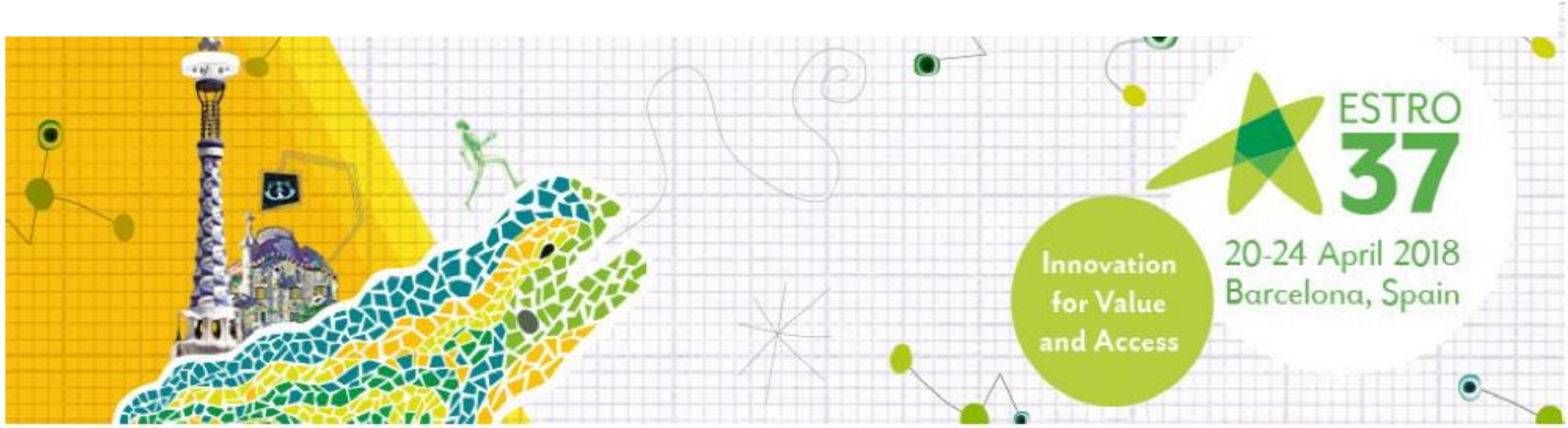
Long-term impact on contouring skills achieved by online learning

Rivera S[1], Petit C[1], Navarro-Martin A[2], Cacicedo J[3], Leaman O[4], Atencio Rosselot MC[5], Lazaryan A[6], Akbarov K[7], Sinaika V[8], Umaña RM[9], Fröbe A[10], Kevlishvili G[11], Stojkovski I[12], Magsar B[13], Corovic M[14], Mahmood H[15], Alauddin Z[16], Barriga O[17], Lucas M[18], Palmu M[19], Zubizarreta E[20], Hopkins KI[20], Eriksen JG[21]

[1]Dept of Radiation Oncology, Gustave Roussy, Villejuif, France, [2]Dept of Radiation Oncology, Instituto Catalan de Oncología, Barcelona, Spain, [3]Dept of Radiation Oncology, Cruces University Hospital, Bilbao, Spain, [4]Microenvironment and Metastasis Group, Spanish National Cancer Research Centre, Madrid, Spain, [5]Fundación Escuela de Medicina Nuclear, Mendoza, Argentina, [6]National Center of Oncology, Dept of Radiation Oncology, Yerevan, Armenia, [7]National Centre of Oncology, Baku, Azerbaijan, [8]N.N. Alexandrov National Cancer Centre of Belarus, Minsk, Belarus, [9]Caja Costarricense del Seguro Social, San José, Costa Rica, [10]University Hospital Center, Sestre Milosrdnice, Zagreb, Croatia, [11]High Technology Medical Center, University Clinic, Tbilisi, Gerorgia, [12]University Clinic of Radiotherapy, Skopje, F.Y.R. of Macedonia, [13]National Cancer Centre, Ulaanbaatar, Mongolia, [14]Radiotherapy Dept, Clinical Centre of Montenegro, Podgorica, Montenegro, [15]Nuclear Medicine, Oncology and Radiotherapy Institute, Islamabad, Pakistan, [16]Institute of Nuclear Medicine and Oncology, Lahore, Pakistan, [17]Centro de Radioterapia de Lima, Lima, Peru, [18]ONCOSUR, Florida, Uruguay, [19]ESTRO Office, Brussels, Belgium, [20]Applied Radiation Biology and Radiotherapy Section, Division of Human Health, IAEA, Vienna, Austria, [21]Dept of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

ASTRO
TARGETING CANCER CARE

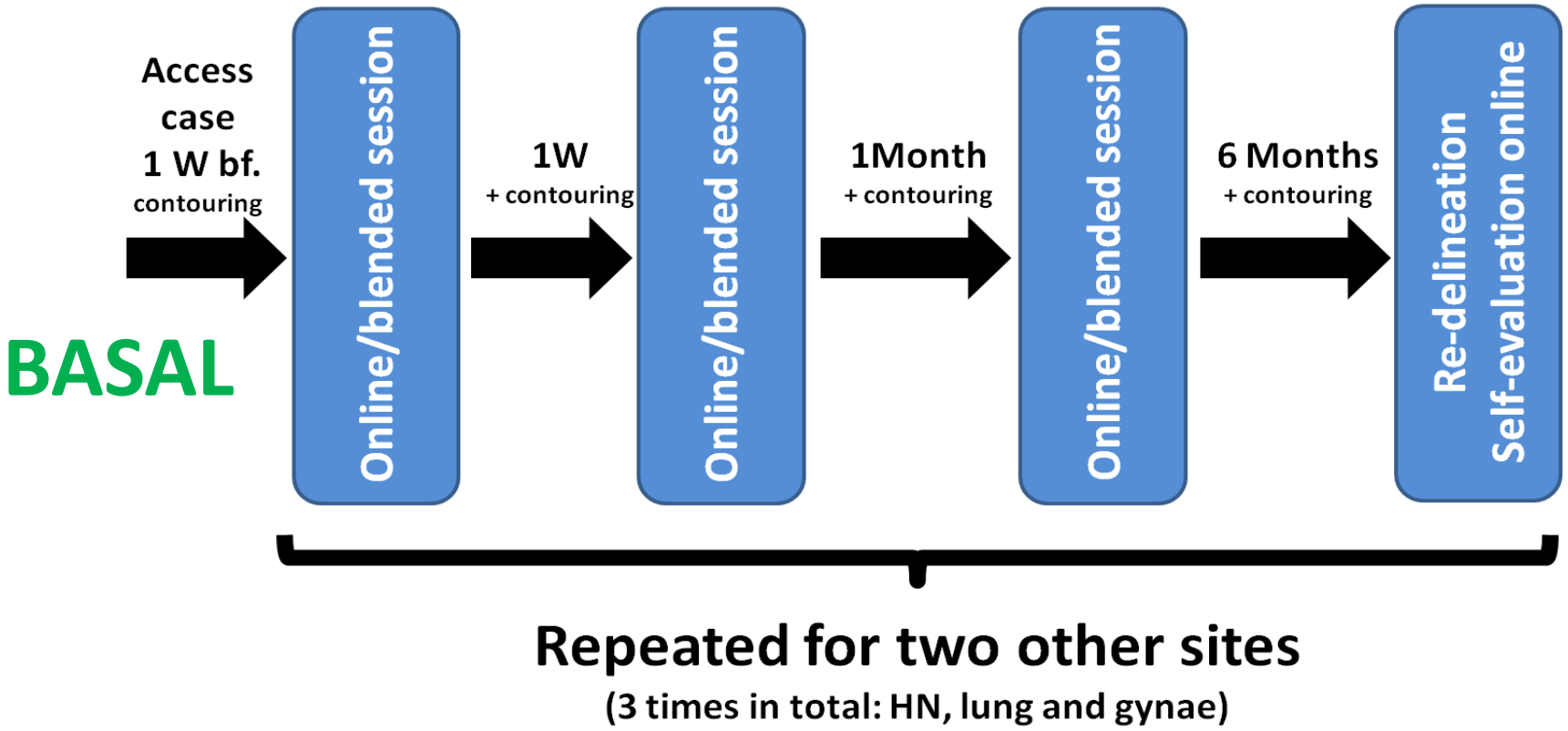
Long-term impact on contouring skills can be achieved by online learning. An ESTRO-FALCON-IAEA study

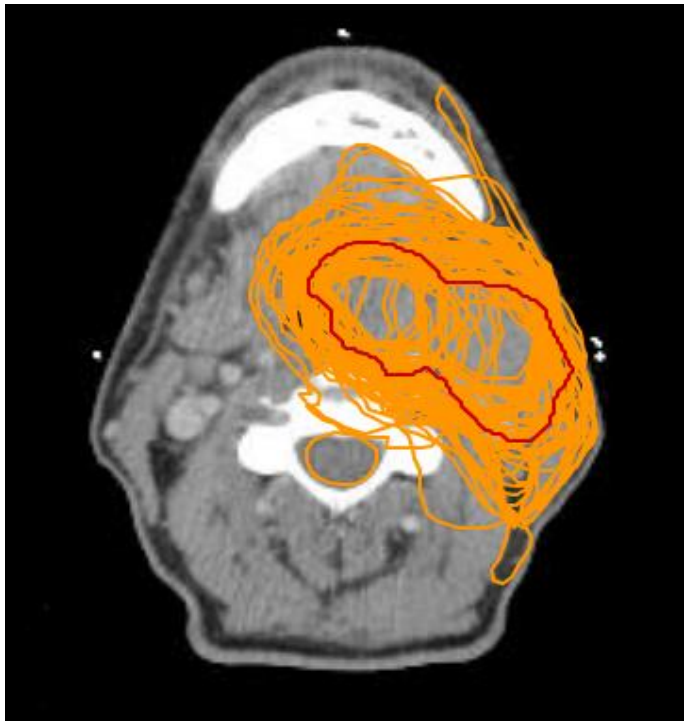


- En la **primera sesión educacional** en línea, los contornos de referencia de los participantes se muestran de forma anónima en superposición para ilustrar la heterogeneidad en el contorneado entre los participantes. Se discuten los contornos y finalmente se muestran y discuten las pautas y / o recomendaciones.

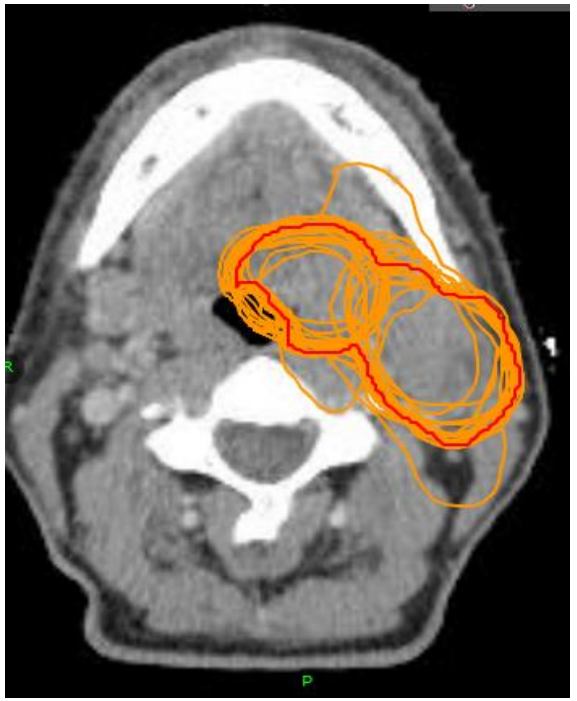
- Los participantes ahora tienen una semana para **volver a contornear** basándose en el conocimiento que han obtenido

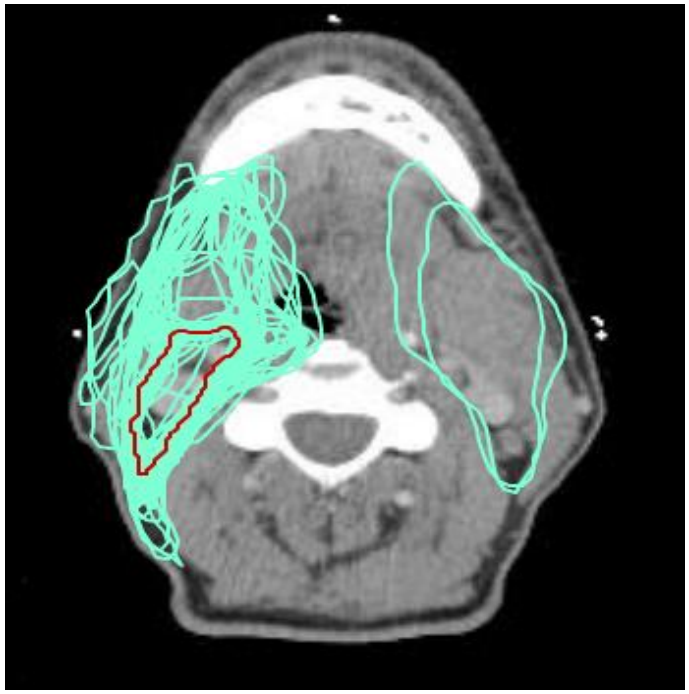
- EVALUACION **INMEDIATA** y **A LARGO PLAZO**





cambio





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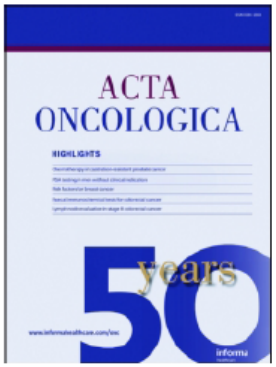

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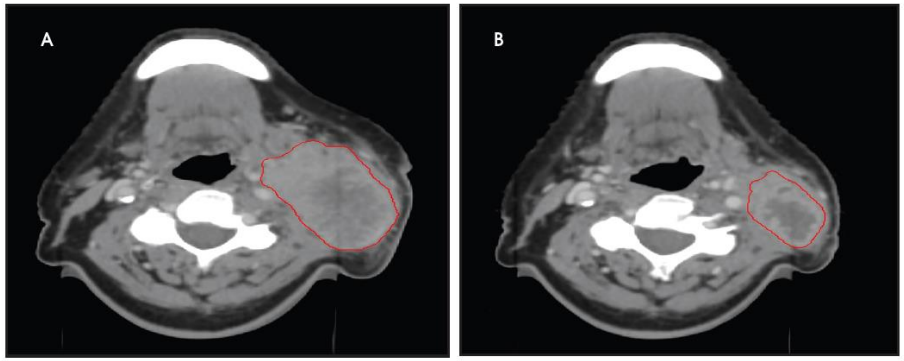
Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: http://www.tandfonline.com/loi/ionc20

Adaptive radiotherapy in head and neck cancer is required to avoid tumor underdose

J. Castelli, A. Simon, B. Rigaud, E. Chajon, J. Thariat, K. Benezery, E. Vauleon, F. Jegoux, O. Henry, C. Lafond & R. de Crevoisier

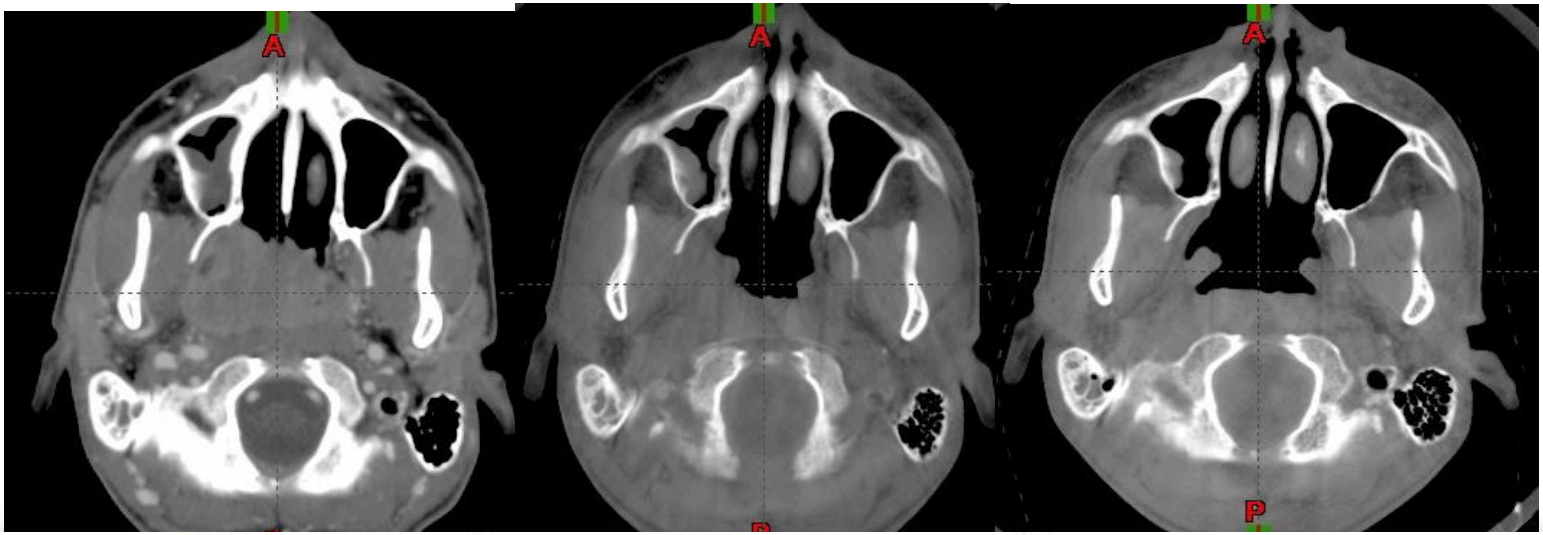
ACTA ONCOLOGICA 28 Apr 2018.

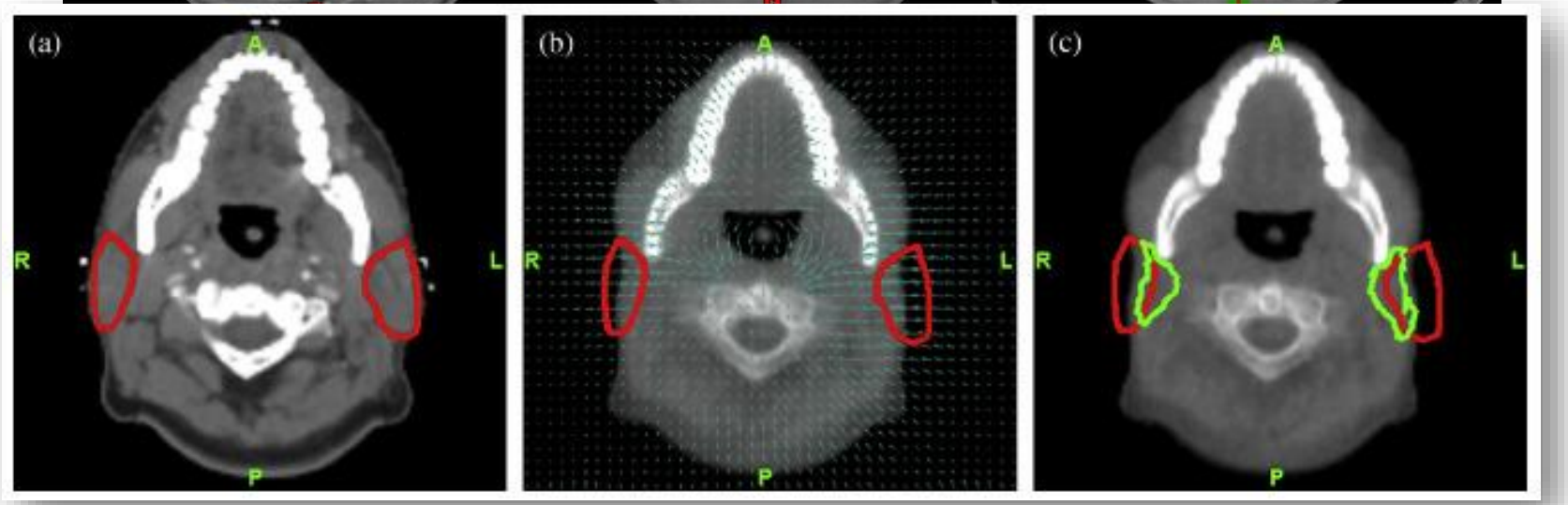


- **Múltiples factores**
  - Reducción del **tumor primario** y/o **masa ganglionar**
  - Resolución de **cambios postoperatorios**
  - Pérdida de **peso**

- A pesar de la máscara de inn para minimizar la variación de po dumbres subyacentes durante el trata

Cambios durante la radioterapia…

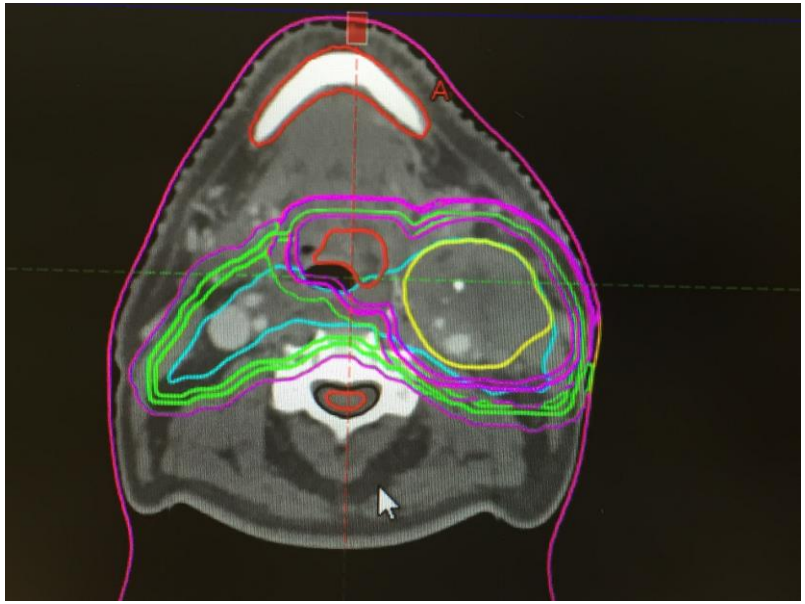




Cambios anatómicos y efectos-dosimétricos

La distribución de dosis calculada para el paciente puede **diferir** de forma significativa **respecto al plan original debido a cambios anatómicos que ocurren durante la radioterapia:**

- Aumento del **2.2 %** de dosis en parótidas por dia de tratamiento
- Aumento de **dosis media** de parótida de hasta 5 Gy
- Estudios dispares con detrimento en la dosis recibida a nivel de **volumen tumoral** profiláctico y/o terapéutico y se ha pensado que el impacto a este nivel era escaso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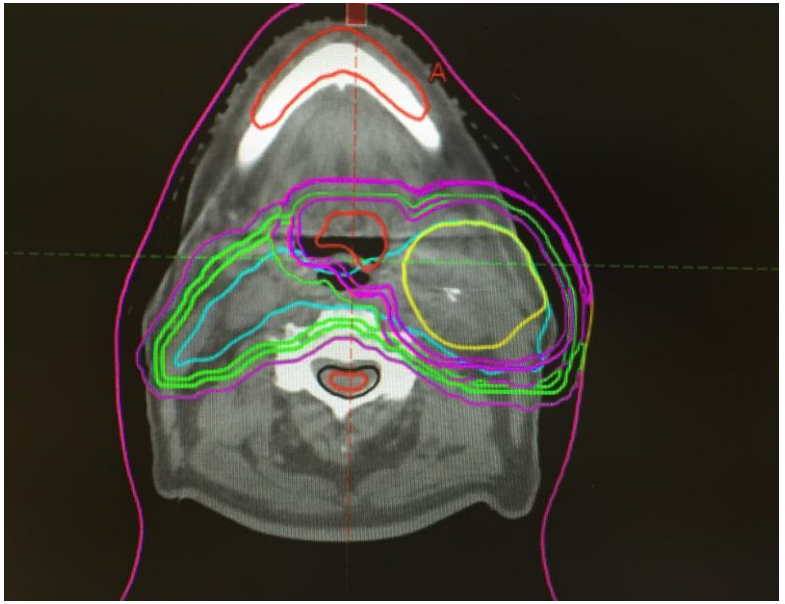
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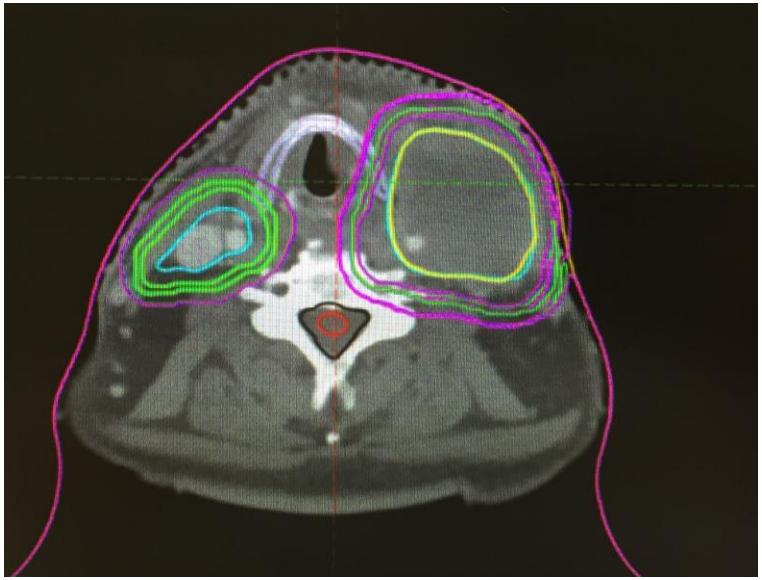
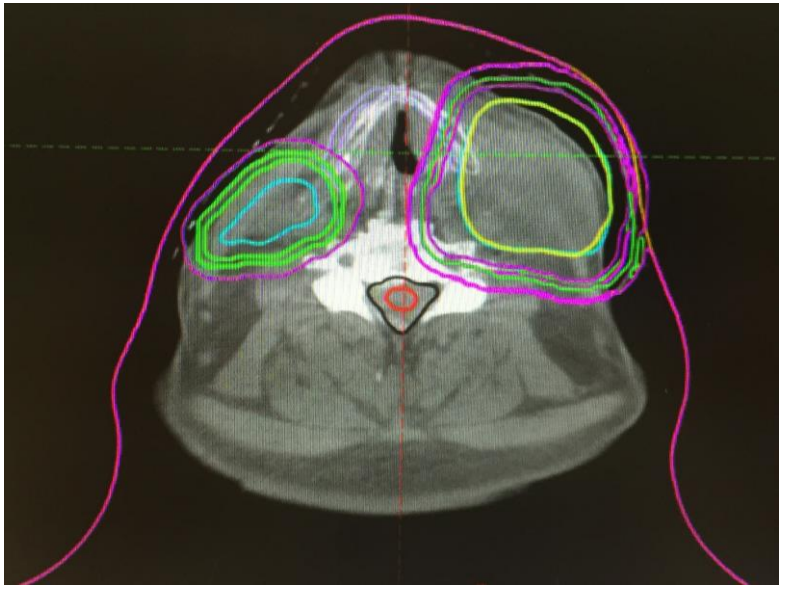
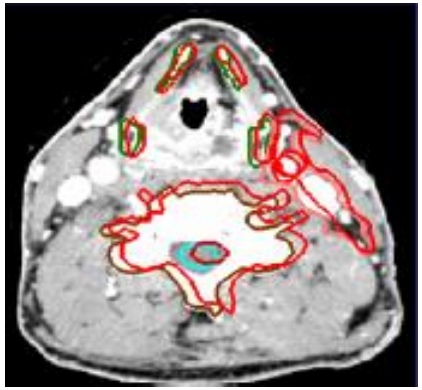
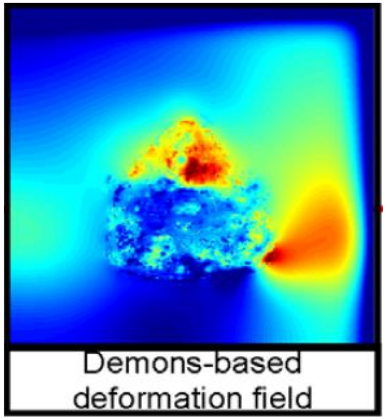
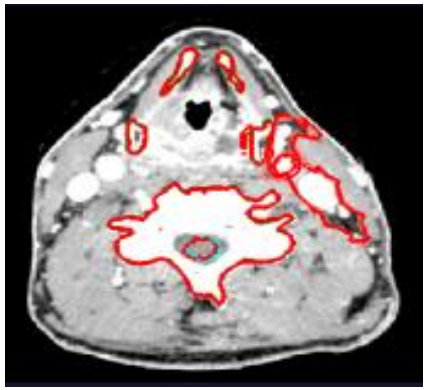




MODELO DOSIS ACUMULATIVA







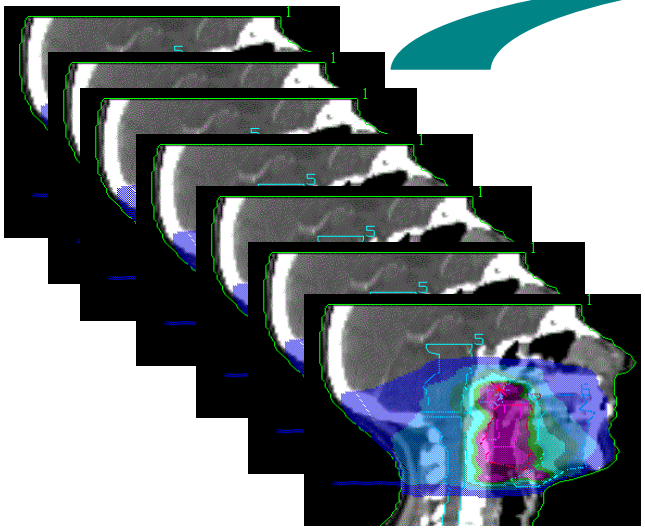
CBCT diario

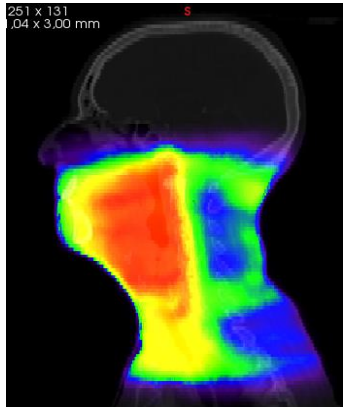
ANATOMIA

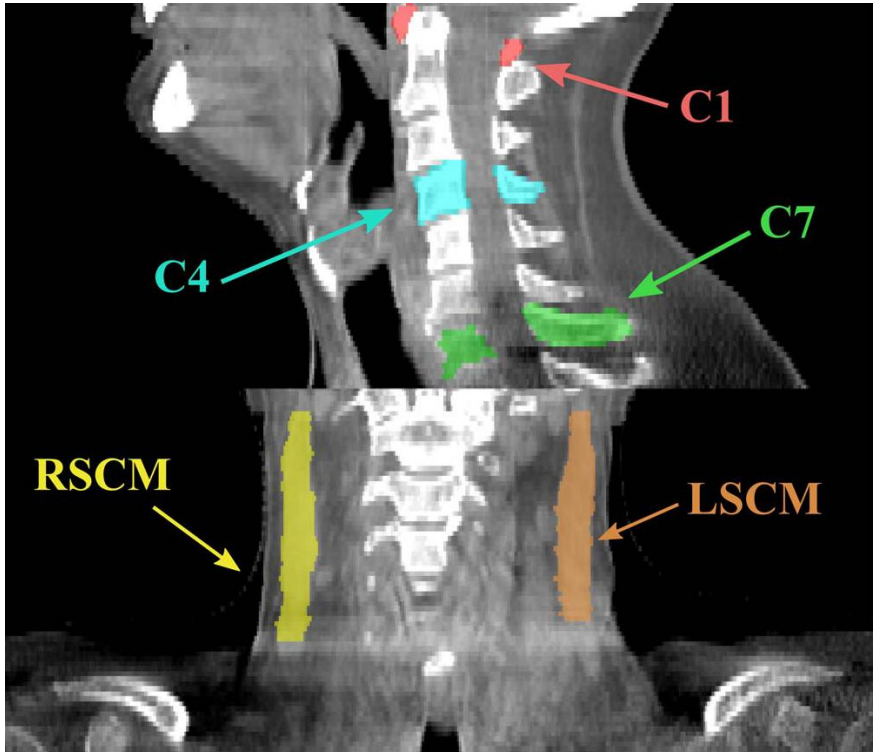
Planning CT

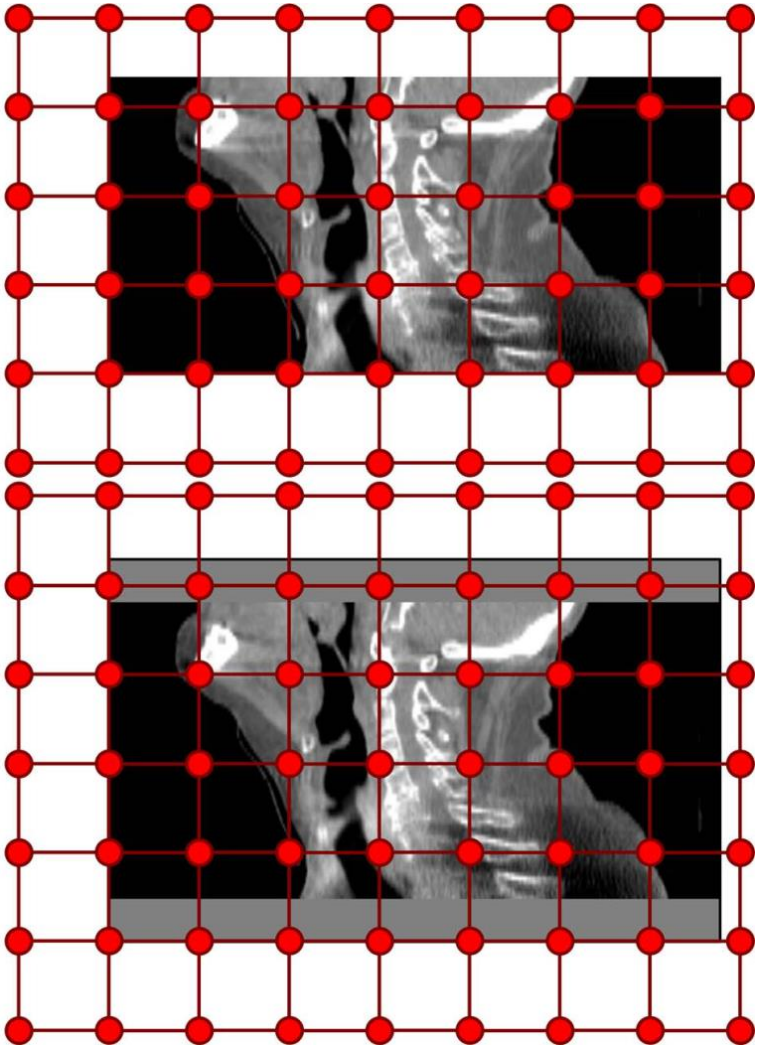
FUSION DEFORMABLE

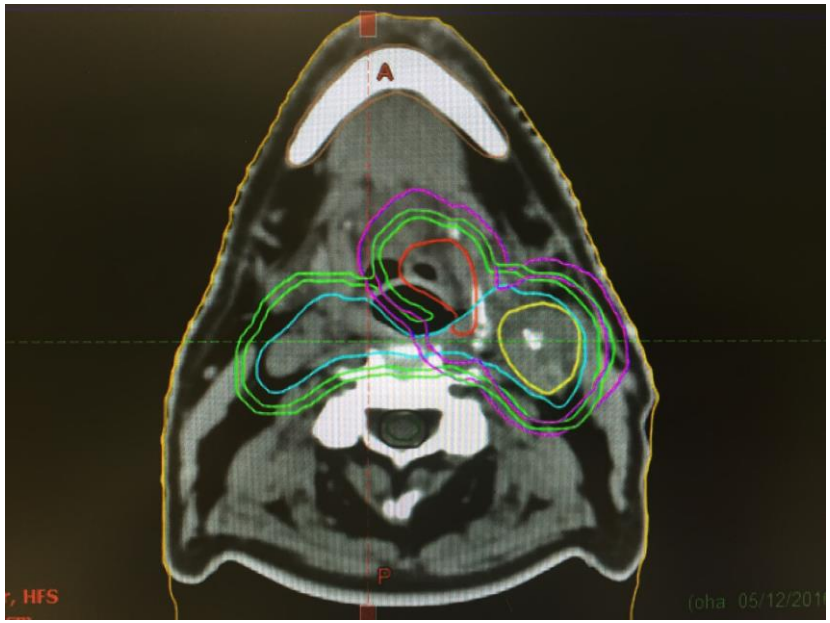
DOSE






C1
C7
C4
RSCM
LSCM

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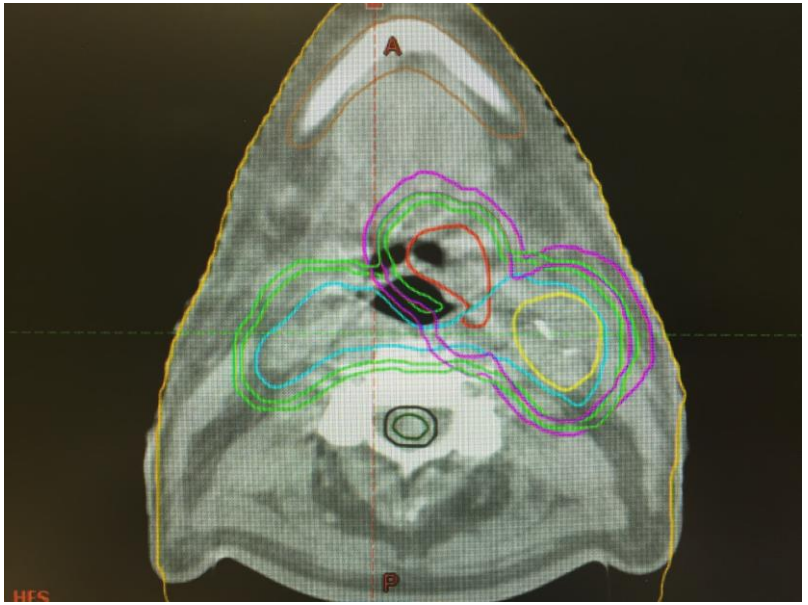
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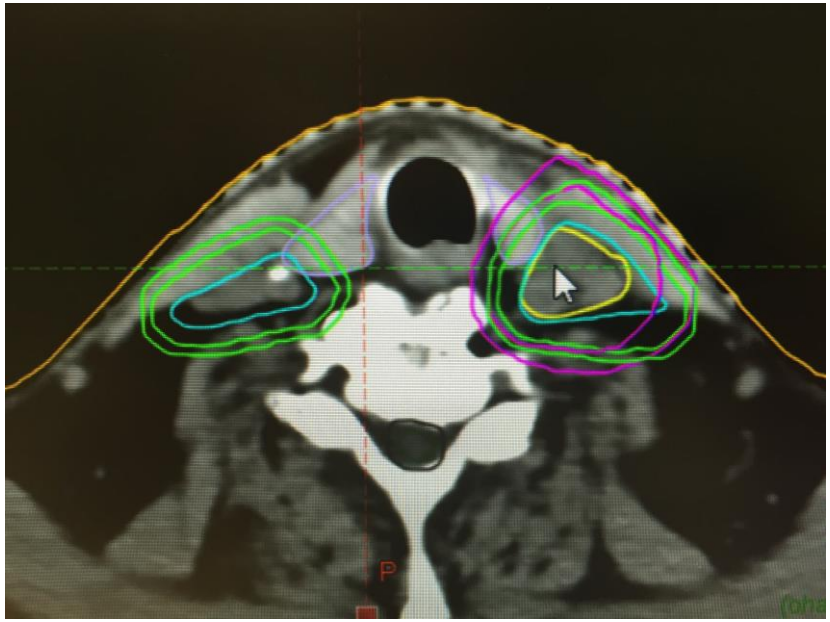
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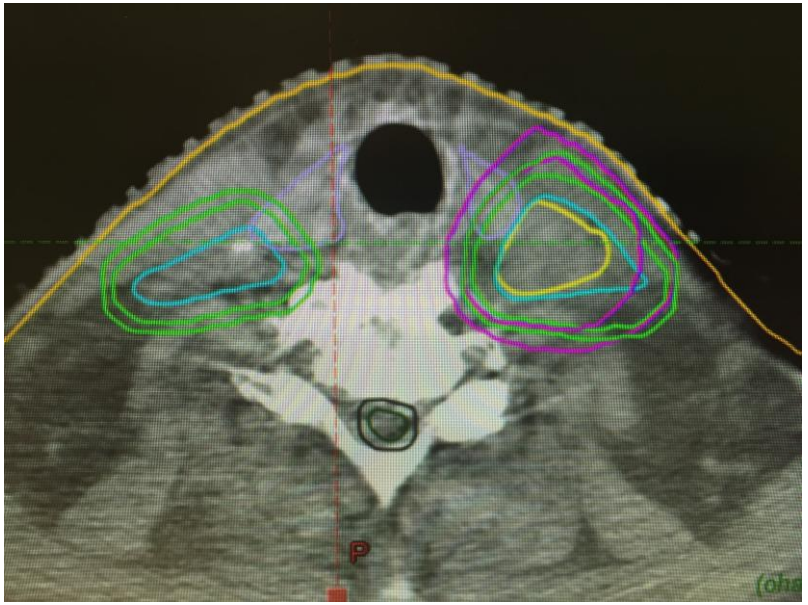
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- Es importante **monitorizar** los cambios anatómicos producidos durante la RT de los tumores de cabeza y cuello por su repercusión dosimétrica.

- IMRT
  - **Alto gradiente** de dosis
  - **Mayor riesgo** de cambios dosimétricos

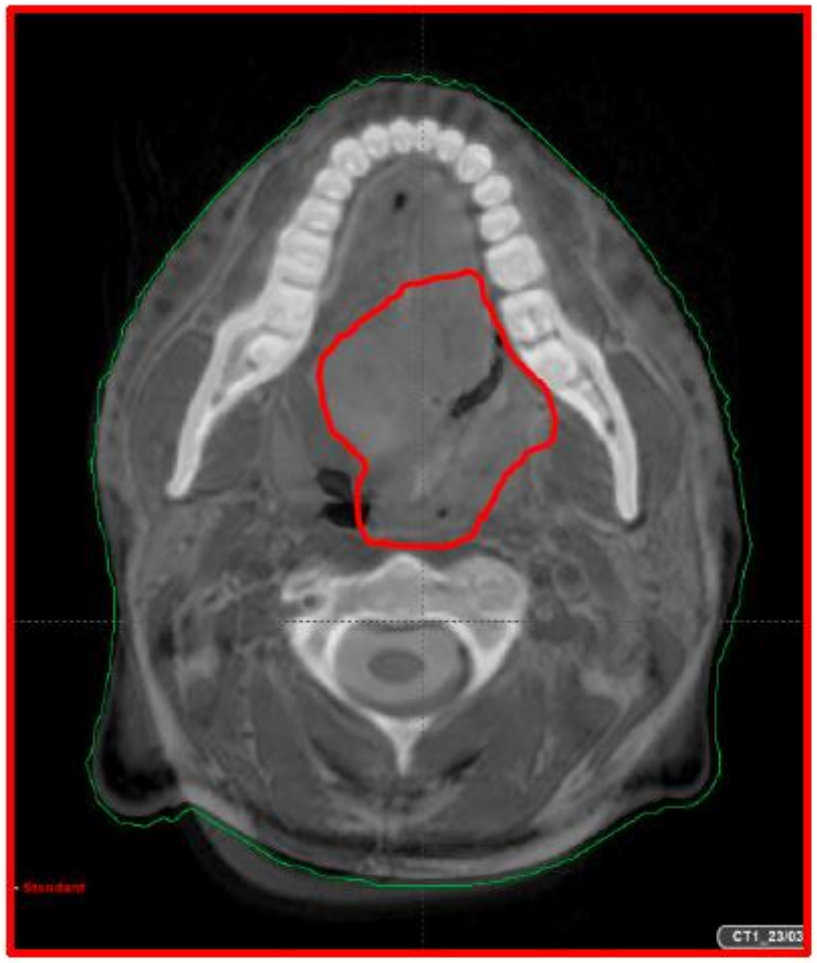
El impacto de los cambios anatómicos en la dosimetría se ha demostrado……. y que se puede compensar con la re-planificación del tratamiento

SI NO HACEMOS UNA IMAGEN… no veremos los cambios anatómicos… si no ¨propagamos¨ los contornos…no veremos su impacto

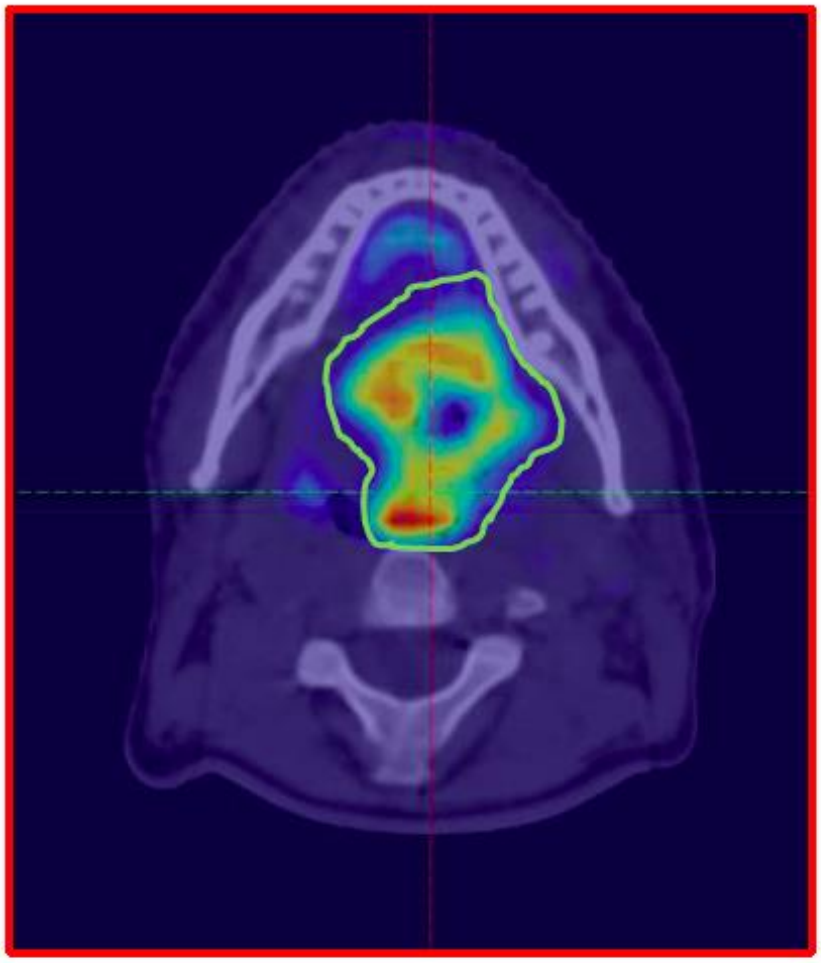
ADAPTATIVA BIOLOGICA

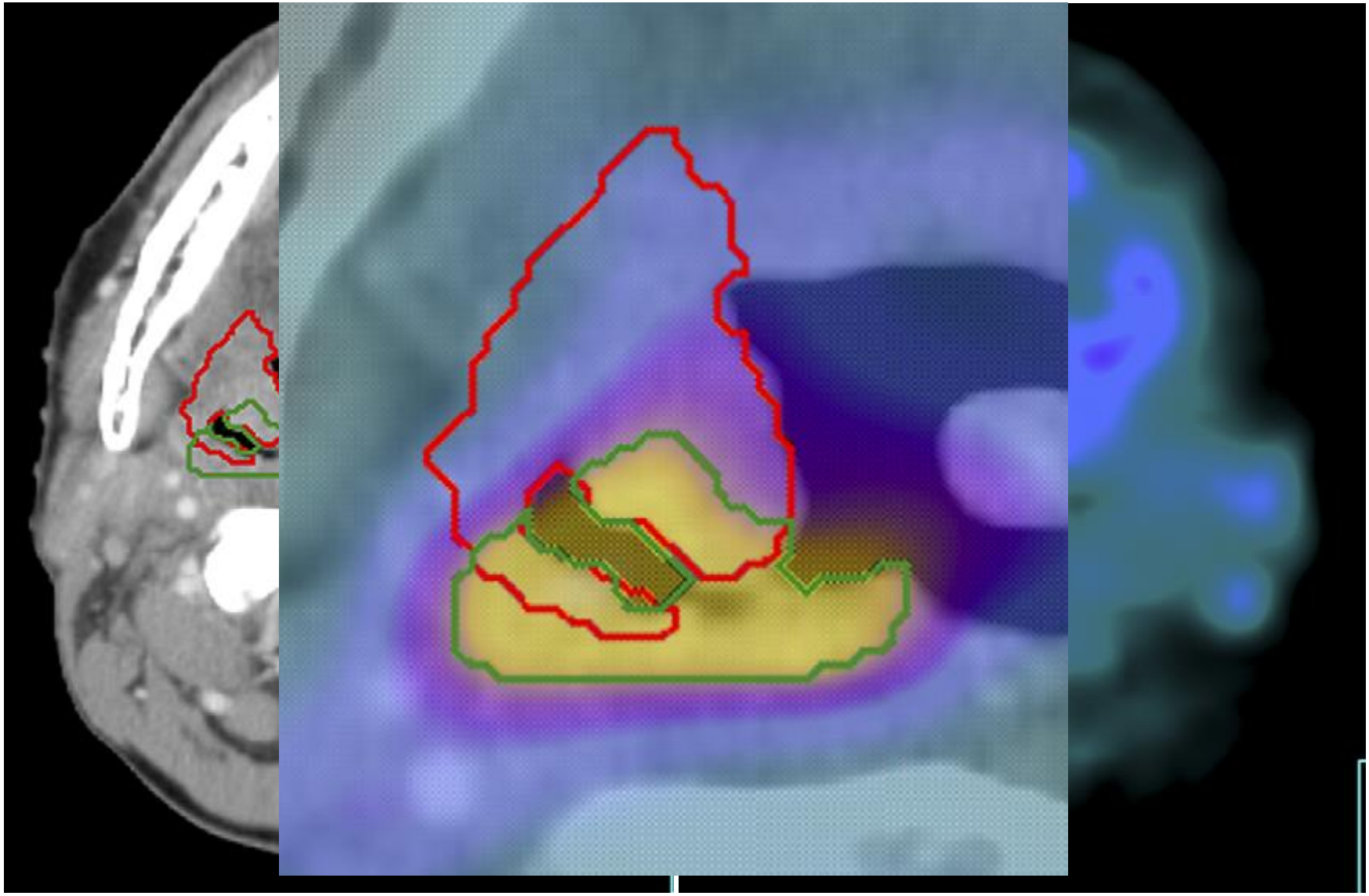
PLANIFICACION MULTIMODAL IMAGEN

CT / RM



CT / PET





T3 N2c orofaringe

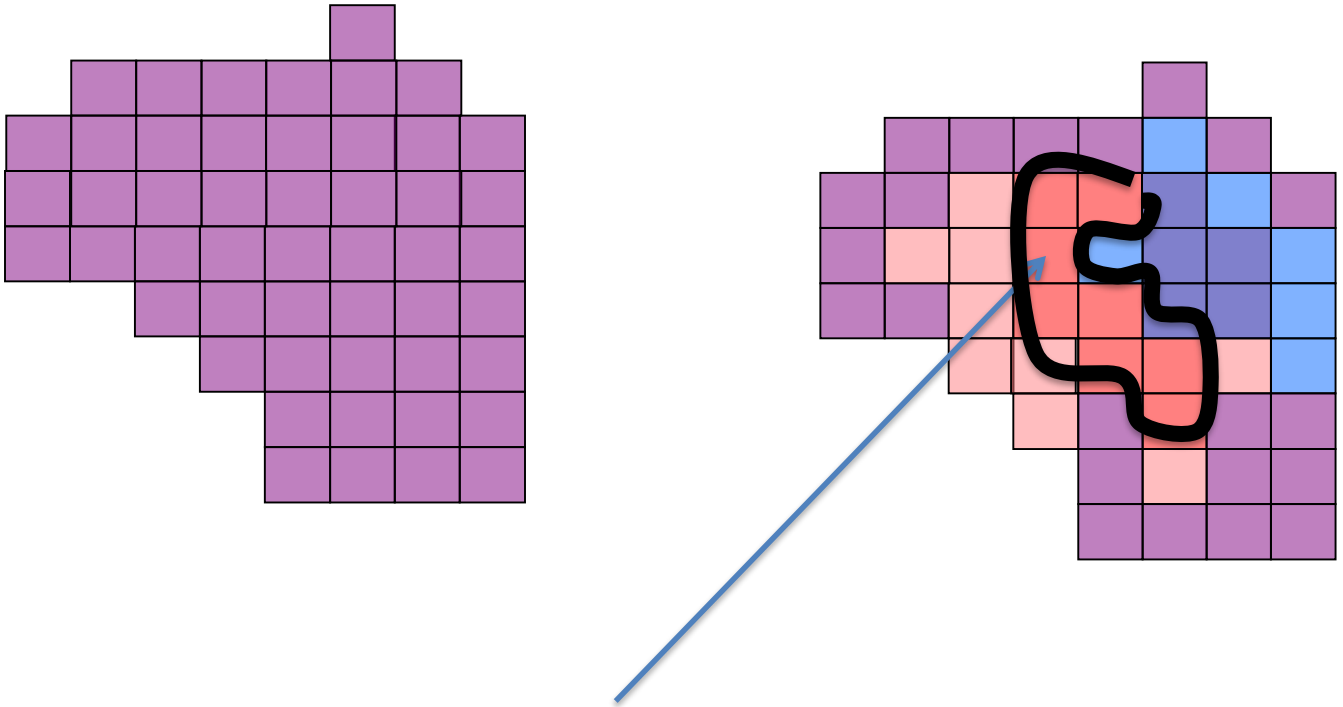
OTROS MARCADORES UNCIONALES (HIPOXIA)

- Metaanalisis ha demostrado que la **hipoxia reduce el control local y supervivencia**

- Las **recurrencias locales** tienden a ser ¨ in-field¨

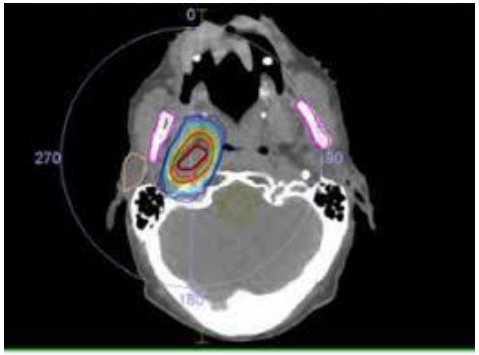
- Estrategia emergente: detección de hipoxia gracias a imagen funcional y escalada de dosis en subvolúmenes del GTV

Overgaard Radiother Oncol 2011



USO MAS EFICIENTE DE LA DOSIS

REIRRADIACION (radioterapia externa)
INDICACIONES, VENTAJAS y PROBLEMAS



Partimos de…

- Los trabajos pioneros de los estudios **RTOG 9610** (1.5**bid** + 5FU + Hidroxiurea x 5 días) y **RTOG 9911** (**RDT 3D**, 1.5**bid** + CDDP + paclitaxel x 5 días). **Total: 4ciclos (15 Gy cada uno)** cambiaron el paradigma de la **factibilidad** de la reirradiación mediante radioterapia hiperfraccionada + tratamiento sistémico

- Supervivencia a 2 años del 15-26%...a expensas de una toxicidad aguda y tardía ≥ grado 3 del 63-78% y 22-37%, respectivamente…resultados discretos…. (supervivencia media **8.5meses** →RTOG **9610** y **14.1 meses** en el estudio RTOG 9911). Especialmente considerando que la supervivencia media excedía marginalmente al tratamiento administrado con quimioterapia…y **muertes tóxicas del 7.6% y 11%**

- Con la nueva tecnología la IMRT y SBRT se han publicado series que sugieren una mejoría del control local, del perfil de toxicidad y ….calidad de vida??

Sulman et al Int J Radiat Oncol Biol Phys 2009;73:399-409
Lee et al, Int J Radiat Oncol Biol Phys 2007;68: 731-740.
Chen et al, Laryngoscope 2014;124:1807-1812.

Cancer Treatment Reviews 40 (2014) 178–189

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Controversy

The role of re-irradiation of secondary and recurrent head and neck carcinomas. Is it a potentially curative treatment? A practical approach

Jon Cacicedo [a,*], Arturo Navarro [b,1], Filippo Alongi [c,2], Alfonso Gómez de Iturriaga [a,3], Olga del Hoyo [a,3], Elsira Boveda [a,3], Francisco Casquero [a,3], Jose Fernando Perez [d,3], Pedro Bilbao [a,3]

Table 1
Selected chemotherapy (and targeted therapies) trials for locally recurrent and metastatic head and neck cancer.

Author	Type of study	Year	Number of patients		Regimen	Response rate (%)	Median survival (months)
Forastiere et al. [14]	Randomized	1992	277	87	Cisplatin + fluorouracil	32	6.6 NS
				86	Carboplatin + fluorouracil	21	5.0
				88	Methotrexate	10	5.6
Jacobs et al. [16]	Randomized	1992			Cisplatin + fluorouracil	32	5.7 NS
			249		Cisplatin	17	
					Fluorouracil	13	
Schrijvers et al. [17]	Randomized	1998	244	122	Cisplatin + fluorouracil + IFNα-2b	47	6.0 NS
				122	Cisplatin + fluorouracil	38	6.3
Forastiere et al. [13]	Randomized	2001	199	101	Cisplatin + paclitaxel (high dose)	35	7.6 NS
				98	Cisplatin + paclitaxel (low dose)	36	6.8
Soulieres et al. [18]	Phase II	2004	115		Erlotinib	4	6.0
Gibson et al. [15]	Randomized	2005	204	104	Cisplatin + fluorouracil	27	8.7 NS
				100	Cisplatin + paclitaxel	26	8.1
Burtness et al. [12]	Randomized	2005	117	57	Cisplatin + cetuximab	26	9.2*
				60	Cisplatin + placebo	10	8.0
Bourhis et al. [11]	Phase I/II	2006		53	Platinum + fluorouracil + cetuximab	36	9.8
Vermorken et al. [19]	Randomized	2008	442	220	Platin + fluorouracil	20	7.4
				222	Platin + fluorouracil + cetuximab	36	10.1**
Argiris et al. [10]	Randomized	2013	270	136	Docetaxel + placebo	6.2	6.0
				134	Docetaxel + gefitinib	12.5	7.3 NS

J Cacicedo et al Cancer Treatment Reviews 40 (2014) 178–189

ESCASO INDICE TERAPEUTICO

- Con la nueva tecnología la IMRT y SBRT se han publicado series que sugieren una mejoría del control local, del perfil de toxicidad y ….calidad de vida??

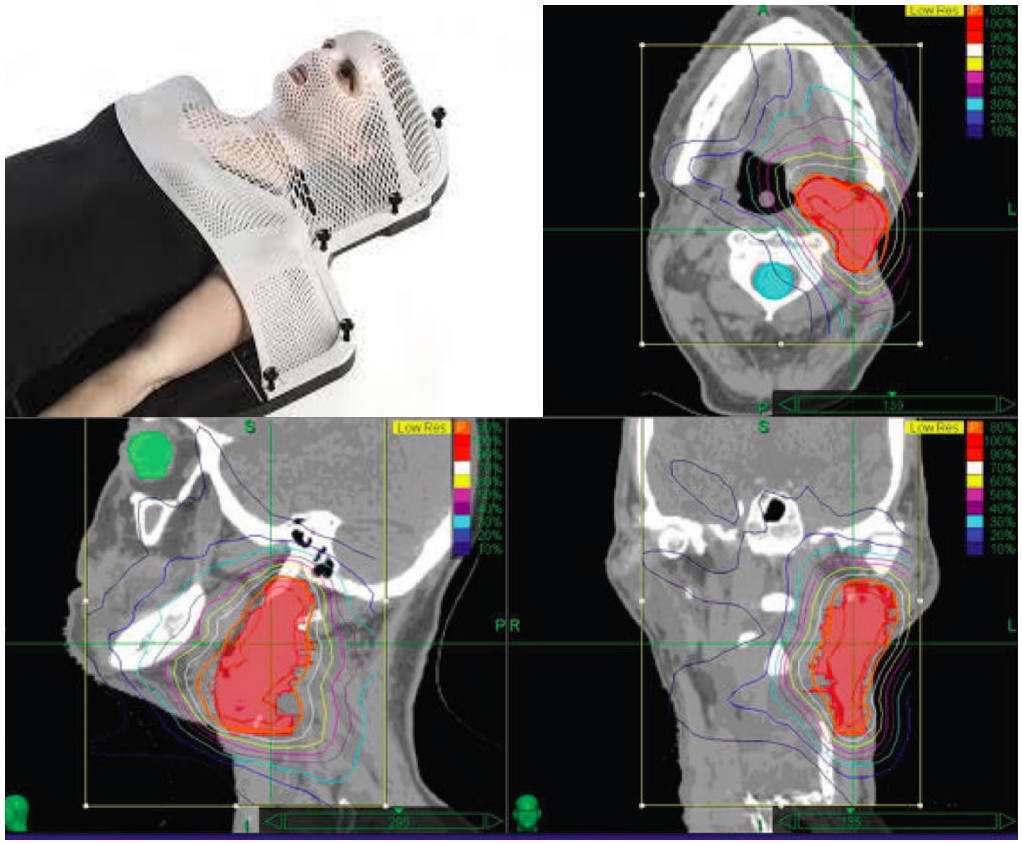
Sulman et al Int J Radiat Oncol Biol Phys 2009;73:399-409
Lee et al, Int J Radiat Oncol Biol Phys 2007;68: 731-740.
Chen et al, Laryngoscope 2014;124:1807-1812.

EVOLUCION TECNICA

- 2D/3D convencional

- IMRT/VMAT y SBRT
- Mejora la definición del volumen y disminuye irradiación adyacente de tejidos sanos. Posibilidad de dar la misma o mayor dosis con menor perfil de efectos secundarios

EVOLUCION TECNICA… SBRT

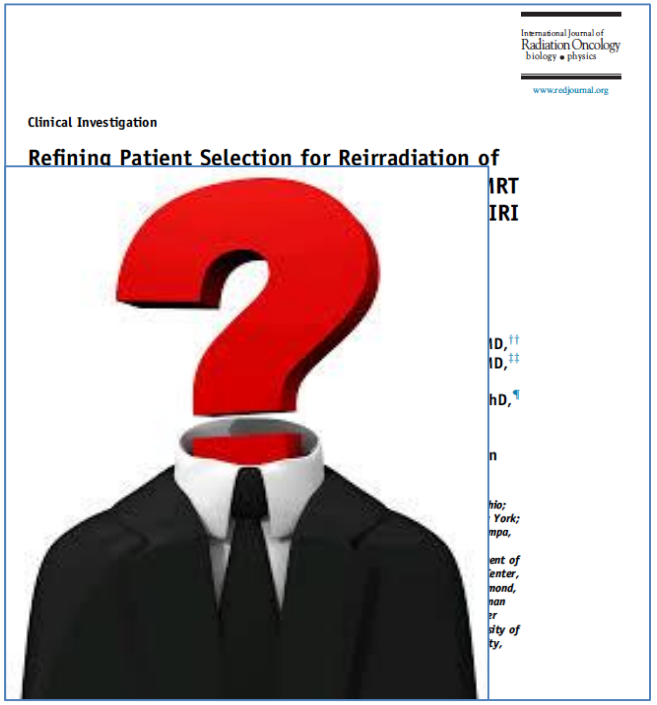


- Técnica de alta conformabilidad
- **Hipofraccionado** (5-30Gy)
- Control guiado por la imagen

Multi-Institution Analysis of IMRT-based Re-Irradiation for Head and Neck Cancer: *Prognostic Factors and Recursive Partitioning Analysis for Overall Survival*

Matthew C. Ward, MD; Nadeem Riaz, MD MS; Jimmy J Caudell, MD PhD; Neal E Dunlap, MD; Derek Isrow, MD PhD; Sara J Zakem, MD; Joshua Dault, MD; Musaddiq J Awan, MD; John A Vargo, MD; Dwight E Heron, MD MBA FACRO FACR; Kristin A Higgins, MD; Jonathan J Beitler, MD MBA FACR FASTRO; Min Yao, MD PhD; Mitchell Machtay, MD; Farzan Siddiqui, MD PhD; Andy M Trotti, MD; Nancy Y Lee, MD; Shlomo A Koyfman, MD

on behalf of the **Multi-Institution Re-Irradiation (MIRI) Collaborative**



LA CLAVE DEL ÉXITO ES LA SELECCION

Ward et al.Int J Radiat Oncol Biol Phys 2018;100:586-594.

Results (N=412)

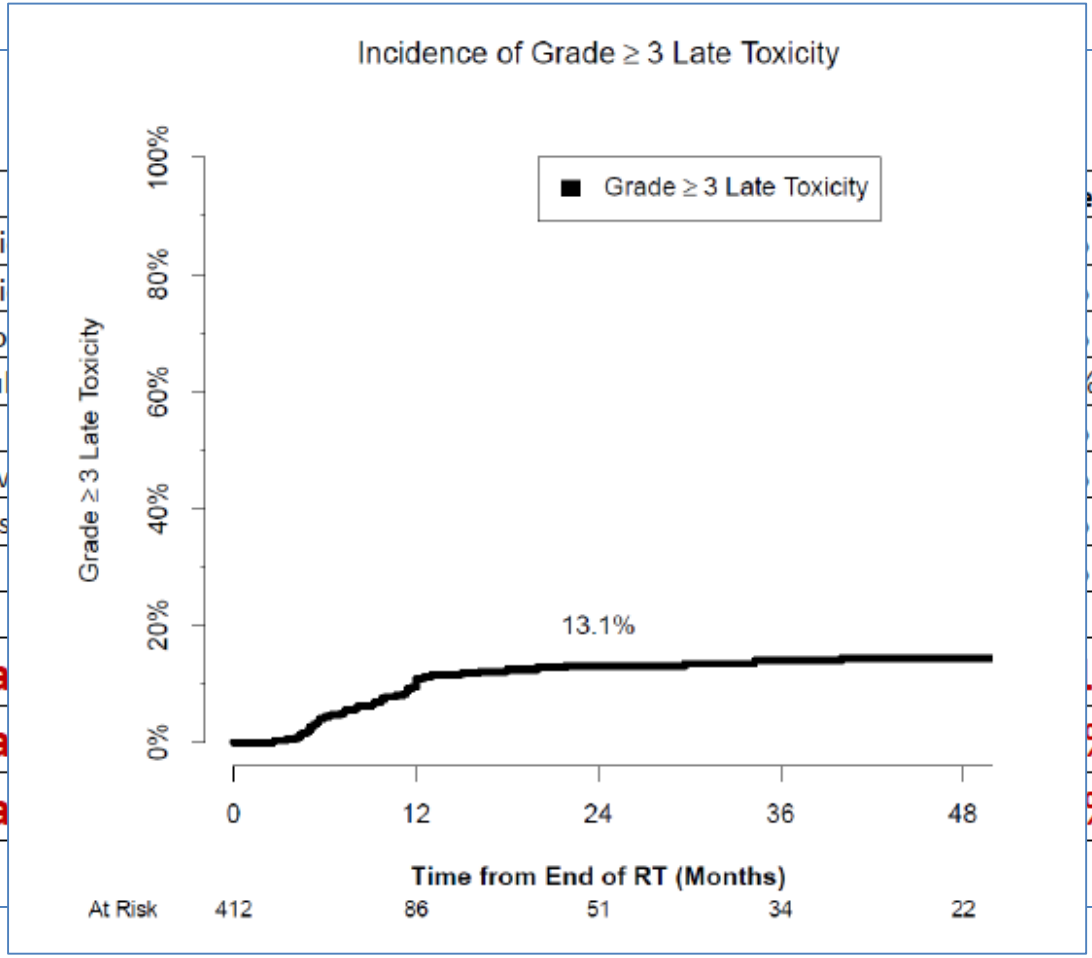
Age at Time of Re-Irradiation	Median (Range)	62 (21-92)
Gender	Male (%)	301 (73.1%)
Comorbidity Score	No comorbidity (N, %)	244 (59.2%)
Dose of RT During First Course	Median, Gy (Range)	**66 (40-80)**
Tumor Site	Oropharynx	112 (27.2%)
	Neck Only (No Primary Site)	88 (21.4%)
	Larynx/Hypopharynx	68 (16.5%)
	Oral Cavity	66 (16.0%)
	Nasopharynx/Base of Skull	42 (10.2%)
	Others	36 (8.7%)
Recurrent or Second Primary	Recurrent	305 (74.0%)
	Second Primary	107 (26.0%)
Pre-existing Organ Dysfunction	Yes	161 (39.1%)

Results: Second Course

Treatment Approach	Post-operative	195 (47.3%)
	Definitive	217 (52.6%)
Chemotherapy	Yes (%)	166 (40.2%)
Time Between Courses of RT	Median, Years (Range)	2.4 (0.2-34)
Completed Re-Irradiation as Prescribed	Yes (%)	391 (94.9%)
Re-Irradiation Dose	Median, Gy (Range)	60 (39.2-79.2)
Fractionation	Daily	330 (80.1%)
	Hyperfractionated	81 (19.7%)

Grade 2 Aspirati
Grade 3 Aspirati
New Tracheosto
New Feeding Tu
Stricture
Neutropenic Fev
Wound/Soft Tiss
Other Grade ≥3

Overall Gra
Overall Gra
Overall Gra



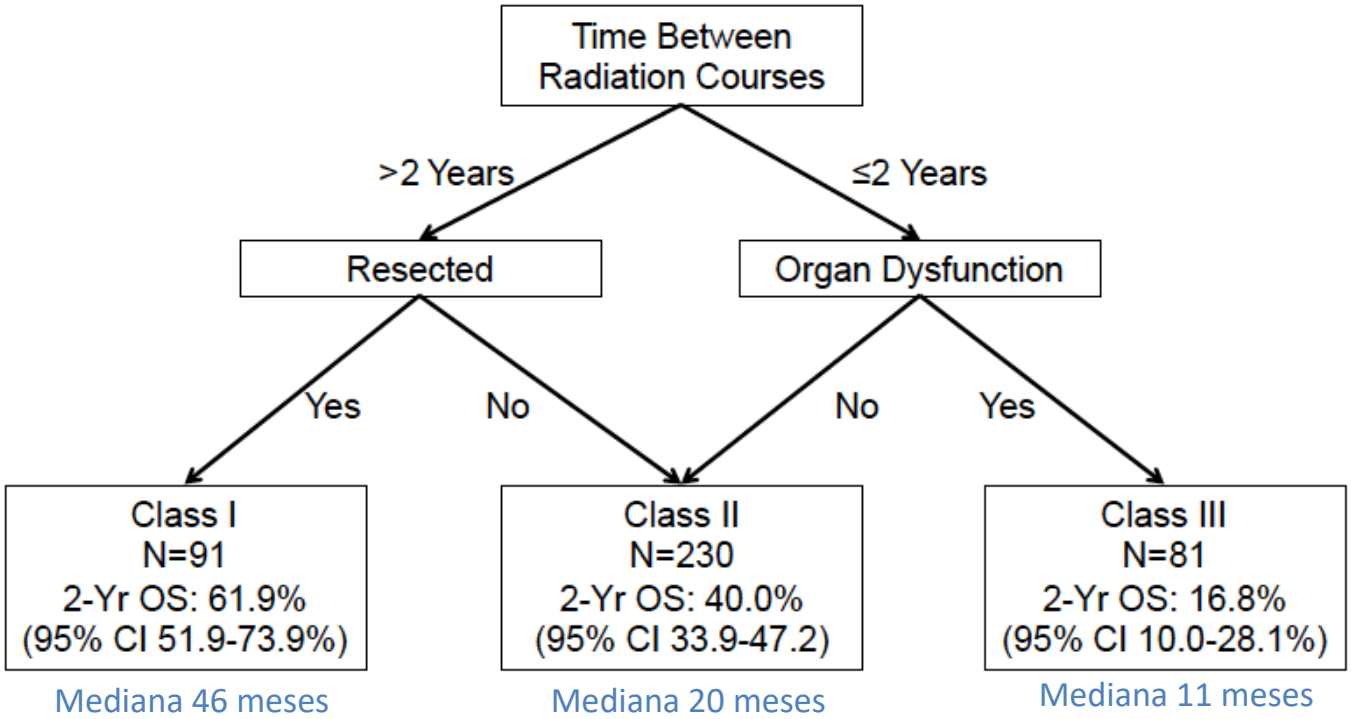
Ruptura carotídea en 9 pacientes (5 sin progresión=1.2%)

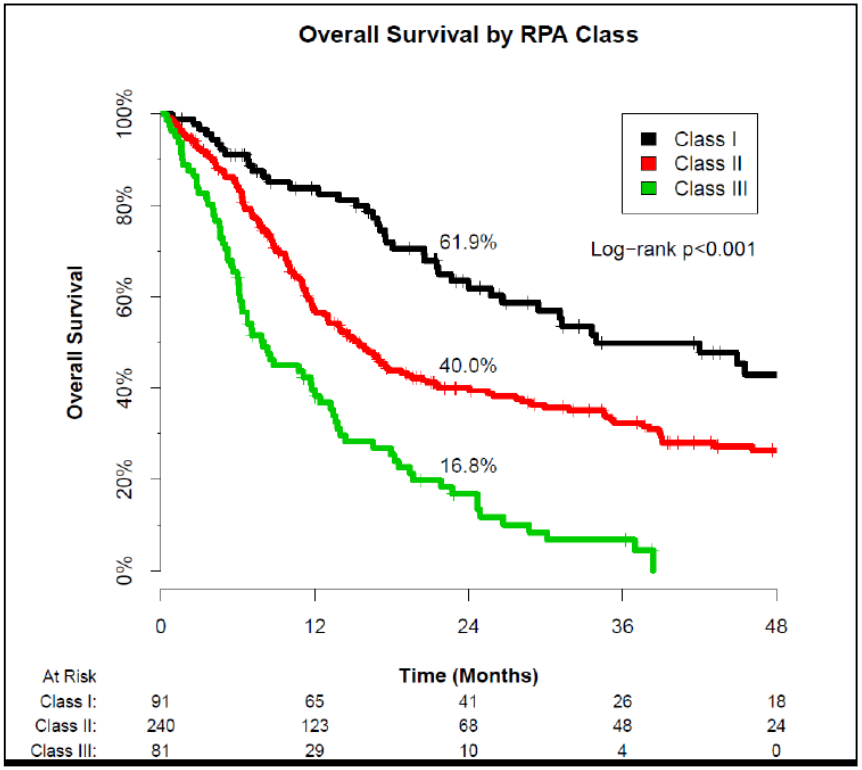
RTOG 9911 TOXICIDAD GRADO 3 EN EL 78%

Results: Multivariable Cox Model for OS

		HR	p	95% CI
Age	Continuous	1.011	0.056	0.999-1.023
Gender	Male vs. Female	0.847	0.250	0.641-1.091
KPS	>70 vs. ≤70	0.652	**0.025**	0.448-0.948
Rec. or 2nd Primary	Recurrent vs. 2nd Primary	1.235	0.250	0.860-1.774
rT Stage	Tis-T2 vs. T0	0.950	0.850	0.568-1.589
	T3-4/Unknown vs. Tis-T2	1.283	0.120	0.936-1.758
Organ Dysfunction	Yes vs. No	1.631	**0.0003**	1.251-2.170
Time Between RT	Continuous – Linear	0.976	0.076	---
	Continuous – Non-linear	---	**0.028**	---
Surgery	Non-Operative vs. Operative	1.862	**<0.0001**	1.399-2.596
Systemic Therapy	Yes vs. No	1.236	0.200	0.892-1.661

*All tumor sites except sinonasal were associated with inferior outcomes compared to nasopharynx, HR 1.734-2.924, p all <0.05


Time Between Radiation Courses
>2 Years
≤2 Years
Resected
Organ Dysfunction
Yes
No
No
Yes
Class I
N=91
2-Yr OS: 61.9%
(95% CI 51.9-73.9%)
Class II
N=230
2-Yr OS: 40.0%
(95% CI 33.9-47.2)
Class III
N=81
2-Yr OS: 16.8%
(95% CI 10.0-28.1%)
Mediana 46 meses
Mediana 20 meses
Mediana 11 meses
Organ dysfunction: pre-existing tracheostomy or feeding tube dependence



- **SELECCIÓN de los pacientes es fundamental**
- **NUEVA ERA CON TECNICAS DE MAYOR CONFORMABILIDAD**
- **Mejor ratio terapéutico con menor tasa de efectos ¨fatales¨ que en las series tradicionales**
- **RPA: puede utilizarse en la decisión terapéutica multidisciplinar**
  - **GUIA para la selección de tratamiento**
  - **GUIA para diseño de ensayos clínicos**

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Clinical Investigation

A Multi-institutional Comparison of SBRT and IMRT for Definitive Reirradiation of Recurrent or Second Primary Head and Neck Cancer

John A. Vargo, MD,[*] Matthew C. Ward, MD,[†]
Jimmy J. Caudell, MD, PhD,[‡] Nadeem Riaz, MD, MS,[§]
Neal E. Dunlap, MD,[‖] Derek Isrow, MD, PhD,[¶] Sara J. Zakem, BS,[#]
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Drexell H. Boggs, MD,[¶¶] James A. Bonner, MD,[¶¶] Min Yao, MD, PhD,[††]
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UPMC CancerCenter

Partner with University of Pittsburgh Cancer Institute

A Multi-Institutional Comparison of SBRT and IMRT for Definitive Re-Irradiation of Recurrent or Second Primary Head and Neck Cancer

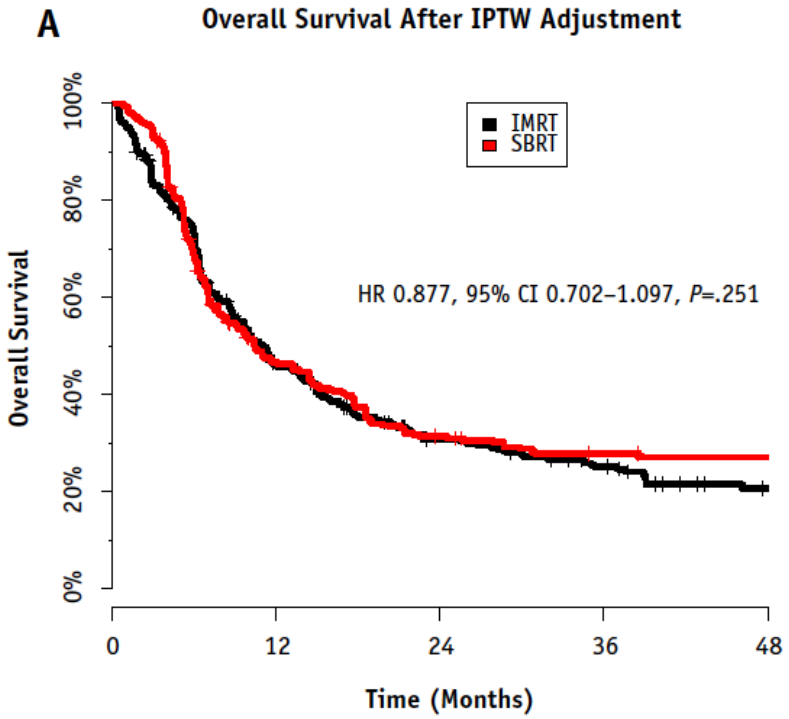
John Austin Vargo MD
University of Pittsburgh Cancer Institute
Department of Radiation Oncology

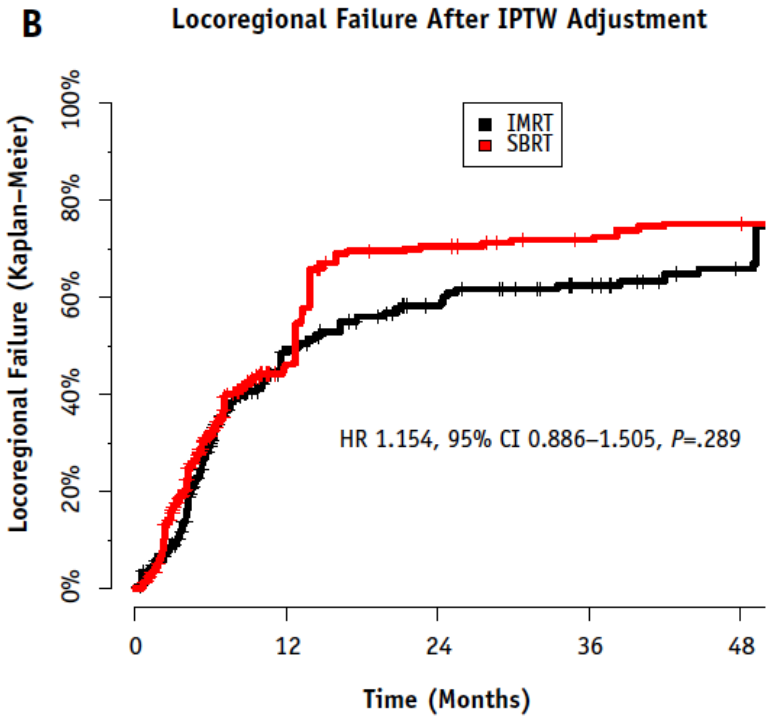
- Las diferencias entre IMRT y SBRT desde el punto de vista radiobiológico, dosis por fracción, duración del tratamiento y definición del volumen de tratamiento **hacen difícil la elección entre una técnica y otra**…

- Las distintas series (generalmente retrospectivas y unicéntricas) presentan **datos similares** entre las 2 técnicas

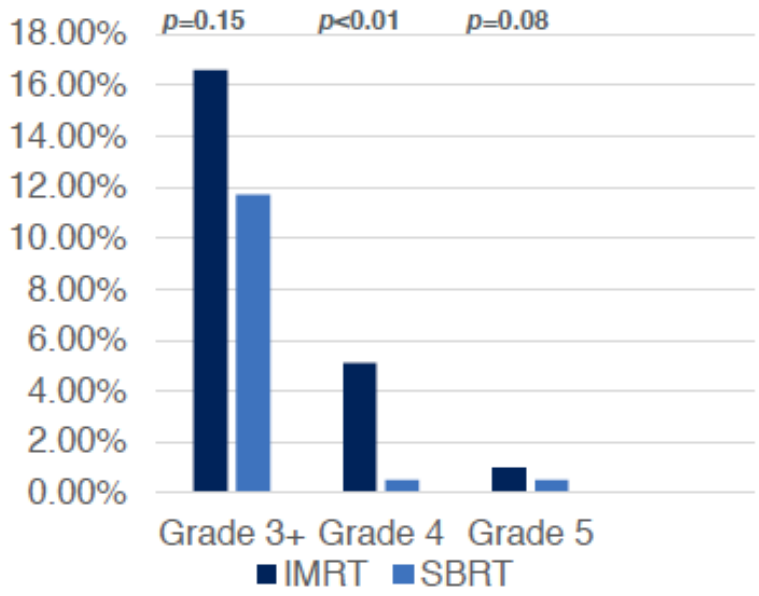
- HIPOTESIS
  - La IMRT y SBRT tienen la misma supervivencia y toxicidad
  - La Clasificación RPA también puede ser *útil para los pacientes con SBRT* y asi poder seleccionar entre SBRT e IMRT

RESULTADOS IMRT vs SBRT

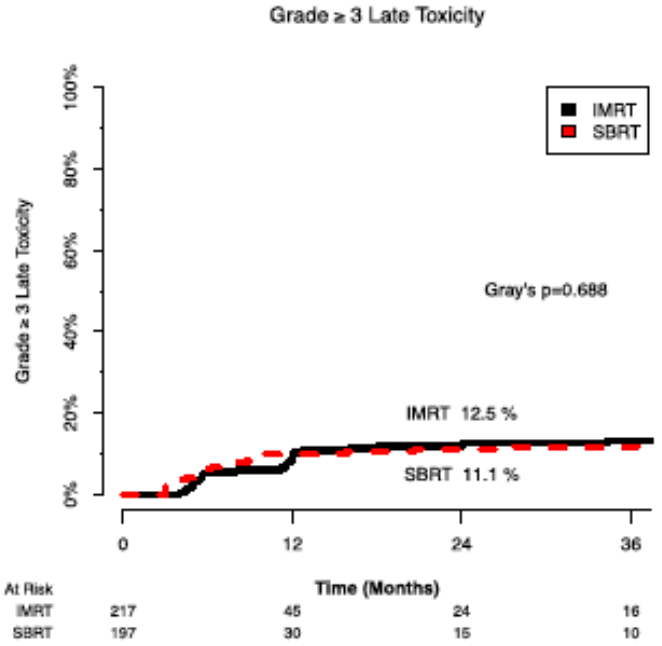


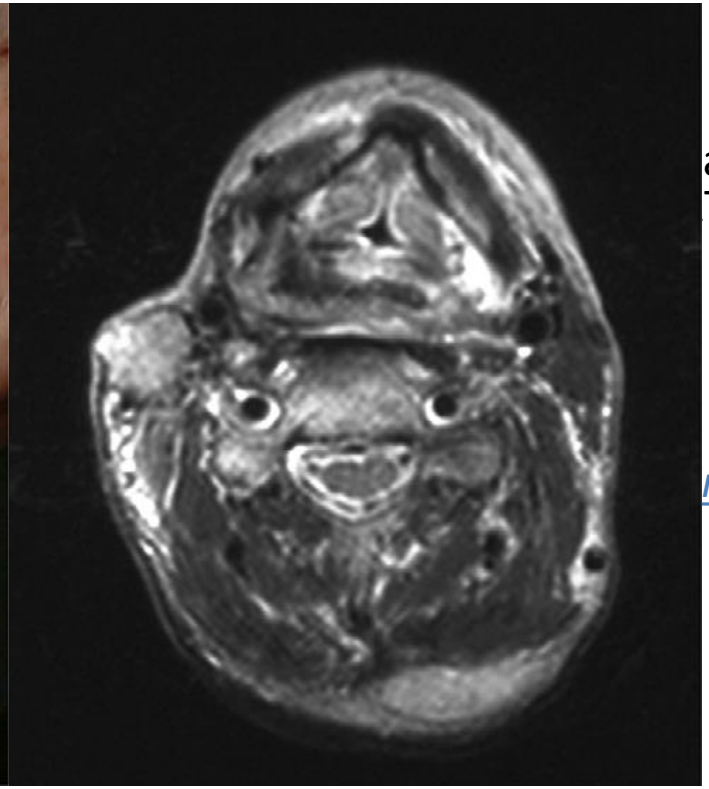


Acute Toxicity Higher with IMRT



No Significant Difference in Late Toxicity





a reportado una
T (0-3%) o RT 3D

nfática

- Tratamiento a días alternos, **no consecutivos** **(constraints no bien definidos en SBRT)**

Yamazaki et al,Radiotherapy and Oncology 115 (2015) 67–71; Yazici et al. Radiation Oncology 2013, 8:242

MUCHAS GRACIAS