The International Federation of Head and Neck Oncologic Societies

Current Concepts in Head and Neck Surgery and Oncology 2017

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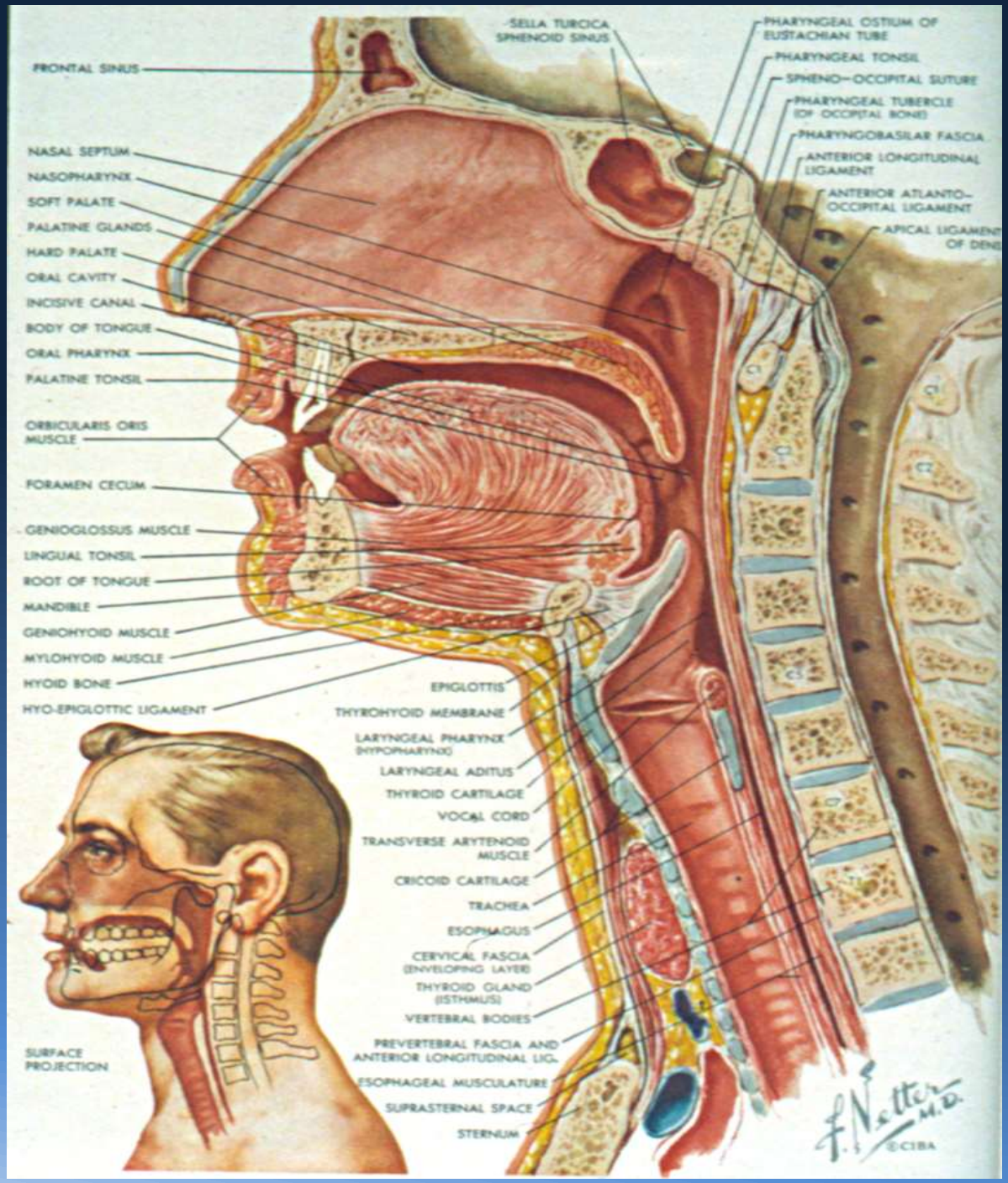
Oropharynx

Louis B. Harrison



2017
International Federation of Head and Neck Oncologic Societies

Oropharynx Cancer Management Options

- Primary Radiation Therapy
- When to add Concomitant chemotherapy to RT?
- Primary Surgery
- When to add RT and CT to S?
- Minimize therapeutic modalities
- Minimize toxicity and cost

Oropharynx Cancer Management Options

- RT alone or Surgery alone for early stage disease
- Surgery can help avoid RT or chemotherapy in some cases
- RT can help avoid surgery in some case
- Chemotherapy may not always be needed with RT
- Current focus is de-intensification and personalization of care

TABLE 17.7 Oncologic and Functional Outcomes of OPC, Tonsil, and Base of Tongue, Treated by Primary RT

Study	Number of Patients	Site	RT[b]	Median Follow-up (m)	Stage III–IV (%)	Oncologic Outcome	OS%	PEG
Mourad (2012)[127]	79	Tonsil	Daily (37%, 70 Gy), 14% CRT, 49% CRT + ND	56	92	5-yr LRC: 95% 5-yr LRC for stages I/II, III/IVA, and IVB: 100%, 95%, 100% 5-yr DM for stages I/II, III/IVA, and IVB: 0%, 7%, 33%	80%	4%
Setton (2012)[126]	442	Tonsil, 50% BOT, 46% PPW, 3% Soft palate, 2%	IMRT, 70, 59.4, 54 Gy	37	94	3-yr LC: 95%; RC: 94%	85%	4%
Eisbruch (2010)[280]	69	Tonsil 49% BOT 39% Soft palate 12%	IMRT 66/2.2, 54/1.8 Gy	34	0	2-yr LRC: 91%	DFS 82% OS 95.5%	0
Mendenhall (2006)[121]	503	Tonsil	Daily (25%, 70 Gy) or BID (75%, 76.8 Gy or DCB 72 Gy) N + CRT 18%	24	47	5-yr LC: T1, 88%; T2, 84%; T3, 78%; T4, 61% RC: N0, 95%; N1, 93%; N2a, 89%; N2b, 84%; N2c, 77%; N3, 66% RC: 97% contralateral neck post URT	DSS: Stage I, 100% Stage II, 86% Stage III, 84% Stage IVA, 73% Stage IVB, 46%	3.6%
Mendenhall (2006)[281]	333	BOT	Daily (25%, 70 Gy) or BID (75%, 76.8 Gy or DCB 72 Gy) N + CRT 18%	79	50	5-yr LC: T1, 98%; T2, 92%; T3, 82%; and T4, 53% LRC: Stages I–II, 100%; III, 82%; IVA, 87%; and IVB, 58%	5-yr OS and DSS: Stages I–II, 67%, 91% Stage III, 66%, 77% Stage IVA, 67%, 84% Stage IVB, 33%, 45%	6.3%
Garden (2004)[78]	299	Tonsil, 47% BOT, 40% Soft palate, 7% PP wall, 6%	Daily RT, 51%, 70 Gy DCB, 40%, 72 Gy XHF, 9%, 81.4 Gy	82	100	5-yr LRC: 85%, DFS: 71%, DM: 19%	2-, 5-, 10-yr OS: 80%, 64%, 50%	NR
Rusthoven (2009)[124]	20	Tonsil	URT, 70 Gy primary CRT, 60–66 for PORT	19	100	2-yr LRC: 100% 2-yr DMFS and DFS: 87% and 80%	80%	0%
Chronowski (2011)[125]	102	Tonsil	URT	39	65	5-yr ipsilateral LRC: 100%, 2% contralateral metastasis	95%	0%
O'Sullivan (2001)[116]	228	Tonsil	URT	68	0%	3-yr actuarial LC: 77%, 3.5% contralateral metastasis	3-yr DSS: 76%	0%

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Mourad, WF et al. "Cancer of the Oropharynx"; Head and Neck Cancer: A Multidisciplinary Approach, 4th Edition, eds. Harrison LB, Sessions RB, Kies MS. Lippincott Williams & Wilkins, Philadelphia, 2013

Jackson (1999)[115]	178	Tonsil	URT	NR	63%	5-yr LRC: Stage I: 91% Stage II: 74% and after salvage 81% Stage III: 51% and after salvage 71% Stage IV: 53% and after salvage 70%	5-yr DSS: 69% OS: 56%	0%
Kagei (2000)[119]	30	Tonsil	URT, 65 Gy/26 fx, ±5–15 Gy boost	44	NR	5-yr LC: 74% RC: 81% No contralateral neck failure	5-yr OS: 64% DSS: 79%	NR
Hu (2011)[117]	22	Tonsil	URT IMRT, 70, 63, 54 Gy	16	100	1.5-yr LC 100%, ipsilateral RC 93%, 0% contralateral metastasis	88	0%
Chao (2004)[282]	74	OPC	IMRT, 70 Gy	33	93	4-yr LRC: 87%	87	NR
Selek (2004)[283]	175	Tonsil, 34% Soft palate, 31% BOT, 24% PPW, 11%	Median, 66 Gy; CF: 49%; DCB: 42%, 10% XHF or BT boost	76	0	5-yr LRC: 81% DFS: 77% 5-yr ultimate LRC: 87%	5- and 10-yr actuarial OS: 70% and 43% 5- and 10-yr actuarial DSS: 85% and 79%	0%
de Arruda (2006)[185]	50	OPC	IMRT, 70, 59.4, 54 Gy	18	92	2-yr LC: 98% RC: 88%	98	12%
Yao (2006)[284]	66	OPC, 11% Tonsil, 47% BOT, 39% Soft palate, 1% PPW, 2%	IMRT 70–74, 60, and 54 Gy	27	92	3-yr LRC: 99%	OS: 78%, DFS: 64%	15%
Cmelak (2007)[122]	69	OPC	aIC-CCRT, IMRT 70 Gy	37	100	2-yr LRC: 84%	83	3%
Garden (2007)[285]	51	Tonsil, 65% BOT, 31% OPC, 4%	IMRT 66 and 54 Gy	45	84	2-yr LRC: 94%	94	8%
Lawson (2008)[157]	34	BOT	CCRT-IMRT 70 (2.13/fx) 63(1.9/fx), 57 (1.75 Gy/fx)	20	94	2-yr LC: 92% RC: 97%	90	9%
Sanguineti (2009)[286]	50	Tonsil, 68% BOT, 16% PPW, 4% Soft palate, 12%	IMRT: CH, hypofx, AHF	33	88	3-yr LC: 94% RC: 85%	NR	NR

Mourad, WF et al. "Cancer of the Oropharynx"; Head and Neck Cancer: A Multidisciplinary Approach, 4th Edition, eds. Harrison LB, Sessions RB, Kies MS. Lippincott Williams & Wilkins, Philadelphia, 2013

TABLE 17.7 Oncologic and Functional Outcomes of OPC, Tonsil, and Base of Tongue, Treated by Primary RT (Continued)

Study	Number of Patients	Site	RT[b]	Median Follow-up (m)	Stage III–IV (%)	Oncologic Outcome	OS%	PEG
Huang (2008)[269]	71	OPC	IMRT-CCRT 70 at 2.12 Gy/fx 59.4 at 1.8 54 at 1.64	33	100	3-yr LRC: 94%	83	NR
Fakhry (2008)[123]	62	OPC	[a]IC-CCRT, IMRT 70 Gy	39	100	2-yr LRC: 95% HPV positive 2-yr LRC: 67% HPV negative 2-yr LRC: 81% whole cohort	95 HPV +ve 62 HPV –ve 79 All patients	NR
Ang (2010)[61]	433	OPC		58	100	3-yr LRC: 86% HPV positive 3-yr LRC: 65% HPV negative 3-yr LRC: 76% whole cohort	82 HPV +ve 57 HPV –ve 70 All patients	NR
Daly (2010)[287]	107 21% S + RT	Tonsil, 44% BOT, 50% PPW, 4% Soft palate, 3%	IMRT 66 at 2.2 Gy/fx	27	96	3-yr LRC: 92%	83	3%
Garden (2011)[128]	777	OPC	IMRT	54	89	5-yr LRC: 90%	84	NR
Palta (2011)[288]	204	OPC	CCRT, HF (64%), CF (29%), r AXF (2%)	56	100	10- and 15-yr LRC: 80%, 70%	DFS: 72%, 63% DMFS: 84%, 84% OS: 47%, 26%	<10%
Koyfman (2011)[138]	82	BOT, 51% Tonsil, 46% OPC, 3% 75% HPV +ve	3DCRT 70–74 Gy –CCRT	26	100	NR	2-yr OS 97%	13%
Greskovich (2011)[289]	30	OPC	IMRT-CCRT	21	100	LRC: 97%, 100% after salvage	100%	NR
Chan (2011)[66]	132	OPC 92% HPV +ve	42% IMRT	48	100	3-yr DMFS: 82%, LRC 95%	DSS: 90% PFS: 81% OS: 84%	NR
McBride (2011)[290]								

DFS, disease-free survival; OS, overall survival; URT, unilateral radiotherapy; OPC, oropharyngeal cancer; LC, local control; RC, regional control; LRC, loco-regional control; HPV, human papilloma virus.
[a]2 cycles of paclitaxel 175 mg/m^2 followed by CCRT paclitaxel 30 mg/m^2 IV, IMRT 70 Gy/35 fx/7 weeks, 2 Gy/fx.
[b]Doses are stated as either PTV or as a dose per fraction.

Mourad, WF et al. "Cancer of the Oropharynx"; Head and Neck Cancer: A Multidisciplinary Approach, 4th Edition, eds. Harrison LB, Sessions RB, Kies MS. Lippincott Williams & Wilkins, Philadelphia, 2013

TABLE 17.9 Outcomes of a Sampling of Prospective Randomized Studies Comparing RT Alone to Chemo-RT Using Platinum-based Chemotherapy

Study	Patients	Chemotherapy	RT		≥3 yr OS Chemo-RT vs. RT	*p*-Value
Jeremic (1997)[295]	159	Cisplatin daily: 6 mg/m^2	Standard	70 Gy@2 Gy/Fx	32% vs. 15%	0.011
		Carboplatin daily 25 mg/m^2	Standard		29% vs. 15%	0.0019
Calais (1999)[140]	226	Carboplatin + 5-FU × 3	Standard	70@2 Gy/Fx	22% vs. 16%	0.05
		70 mg/m^2/d + 5-FU 600 mg/m^2 × 3 CI				
Adelstein (2003)[83]	295	Cisplatin × 3 D1, 22,43 = 100 mg/m^2	Standard	70@2 Gy/Fx	37% vs. 23%	0.014
		Cisplatin 75 mg/m^2 + 5-FU × 3 = 4-d 1 gm/m^2/d = Ci/4 wk	Split course	30 Gy 1st, 30–40 Gy 3rd cycle	27% vs. 23%	
Fountzilas (2004)[296]	124	Cisplatin × 3 D1, 22, 43 = 100 mg/m^2	Standard	70@2 Gy/Fx	52% vs. 17.5%	0.0002
		Carboplatin × 3= 7 AUC on D 2, 22, 42	Standard		42% vs. 17.5%	0.001
Ruo Redda (2010)[297]	164	Carboplatin daily every other week 45 mg/m^2 D1-5, weeks 1, 3, 5,7	Standard	70@2 Gy/Fx	28.9% vs. 11.1%	0.02
Brizel (1998)[298]	116	Cisplatin 12 mg/m^2 D1-5 + 5-FU 600 mg/m^2 × 2 D1-5 weeks 1 and 6 of RT	HF	75 Gy@1.25 Gy BID 70 Gy@1.25 Gy BID + chemo	55% vs. 34%	0.07
Jeremic (2000)[299]	130	Cisplatin daily: 6 mg/m^2	HF	77 Gy/70Fx 35 d 7 wk	46% vs. 25%	0.0075
Staar (2001)[141]	240	Carboplatin 70 mg/m^2 D1-5 and D29—33 + 5-FU × 2,600 mg/m^2 D	HF	69.9 Gy/38D; weeks 1–3: 1.8 Gy/D, weeks 4 and 5: BID 1.8 Gy/1.5 Gy)	25.6% vs. 15.8%	0.0016
Huguenin (2004)[300]	224	Cisplatin 20 mg/m^2 D1-5, weeks 1 and 5	HF	BID 1.2 Gy/d, 5 d/wk, = 74.4 Gy	59% vs. 49%	0.147
Bensadoun (2006)[301]	171	Cisplatin 100 mg/m^2 (D1, D22, D43) + 5-FU × 3	HF	BID 1.2 Gy/d, 5 d/wk, = 80.4 Gy (OPC) 75.6 Gy (HPX)	37.8% vs. 20%	0.038

5-FU, 5-fluorouracil; HF, hyperfractionated; NS, nonsignificant.

Mourad, WF et al. "Cancer of the Oropharynx"; Head and Neck Cancer: A Multidisciplinary Approach, 4th Edition, eds. Harrison LB, Sessions RB, Kies MS. Lippincott Williams & Wilkins, Philadelphia, 2013

Rischin et: Prognostic significance of HPV and p16 – oropharynx cancer JCO 27:15s, 2009 (ASCO) abstract

	2 Year OS		2 Year FFS	
HPV (+ve)	94%	P=.007	86%	P=.035
HPV (–ve)	77%		75%	
P16 (+ve)	92%	P=.004	87%	P=.003
P16 (–ve)	75%		72%	

Radio-curability of HPV+ H&N Ca

- HPV+ outcomes among prospective H&N trials:[7]

Author & Cooperative Grp	N	XRT	Induction	Concurrent	Median F/U	HPV+	Outcome Time	HPV+	HPV-	p-value	Hazard Ratio HPV+ vs. HPV-
Fakhry ECOG	96	70 Gy	2 cycles paclitaxel 175mg/m2 + carbo AUC 6	weekly paclitaxel 30mg/m2 x 7	39 mo	40%	2-year	95%	62%	0.005	0.36
Rischin TROG	195	70 Gy	none	cisplatin +/- tirapazamine	27 mo	28%	2-year	94%	77%	0.007	0.29
Gillison RTOG 0129	323	70-72 Gy	none	cisplatin 100mg/m2 x2-3	4.8 yrs	64%	3-year	79%	46%	0.002	0.44
Settle TAX324	119	70-74 Gy	3 cycles taxotere 75mg/m2 +cisplatin 100mg/m2 + 5FU 1000mg/m2/day x 4	weekly carboplatin AUC 1.5 x 7	67 mo	50%	5-year	93%	35%	<0.001	0.2
Lassen DHA NCA5	156	62-68 Gy	none	nimorazole 1200mg/m2/day x 30	>60 mo	22%	5-year	62%	26%	0.003	0.44

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Trotti et al. RTOG 1016 Protocol. www.rtog.org

Refining American Joint Committee on Cancer/Union for International Cancer Control TNM stage and prognostic groups for human papillomavirus-related oropharyngeal carcinomas.

Huang SH, et al. J Clin Oncol. 2015 Mar 10;33(8):836-45. doi: 10.1200/JCO.2014.58.6412. Epub 2015 Feb 9.

STAGE	WHY?
Stage I	-No difference
• T_{1-3}, N_0-N_{2b}	
Stage II	-Bilateral Neck
• T_{1-3}, $N2_C$	nodes is worse
Stage III	T_{4a}=T_{4b}
• T_4 or N_3	N_3 worse
Stage IV	
• M_1	

NRG HN002: A Randomized Phase II Trial for Patients with p16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer

Eligibility

- OP SCCA
- ≤10 pack-year
- T1-T2 N1-N2b
- T3 N0-N2b

REGISTER

Central review
p16+ IHC

STRATIFY

Declare Intent
Unilat vs Bilat Neck XRT

RANDOMIZE

60 Gy XRT (2Gy/fx) in 6 weeks + cisplatin 40 mg/m2 weekly x 6 cycles

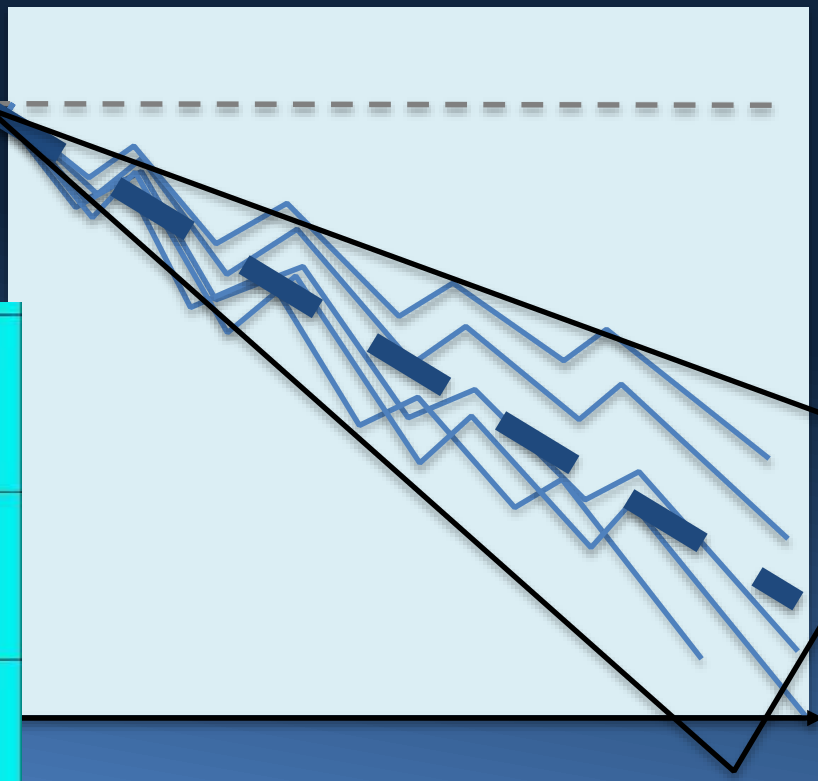
60 Gy XRT (2 Gy/fx) at 6 fractions/week for 5 weeks

44% of RTOG 1016 population eligible

New Ideas To Personalize and Optimize Radiation Therapy

- Mathematical Modeling
- Adaptive Therapy
- Genomics and Dose personalization
- Radiomics and Cancer Specific Imaging

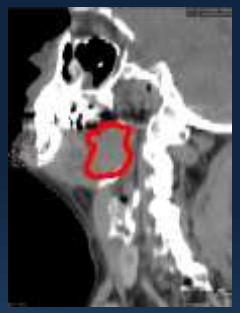
Mathematical models of treatment response



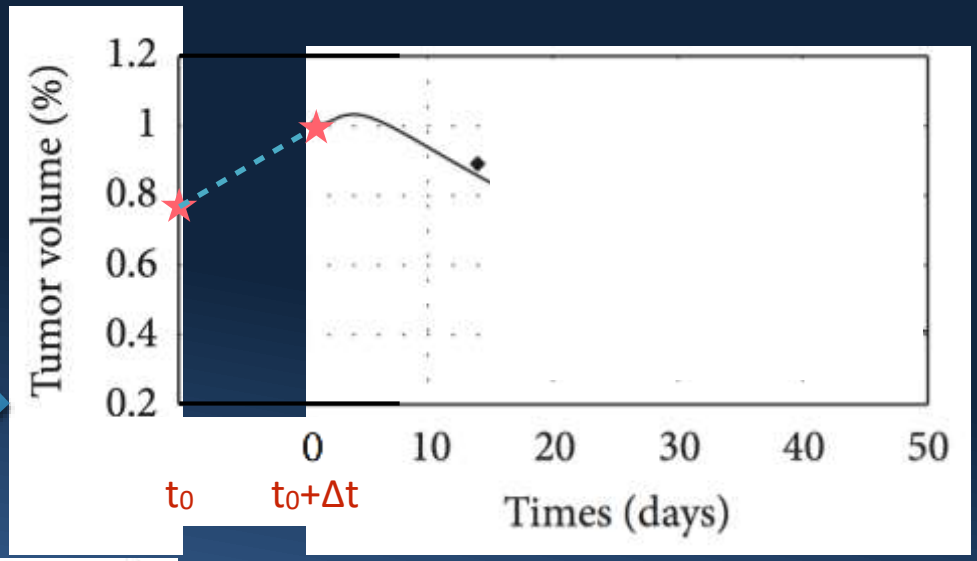
forecasting cancer

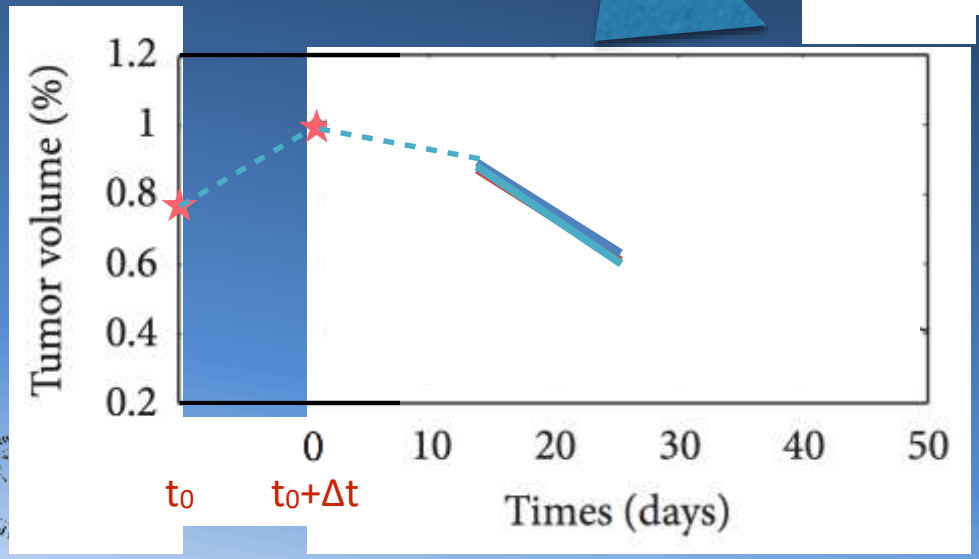
Framework for patient-specific adaptive radiation fractionation

Diagnosis



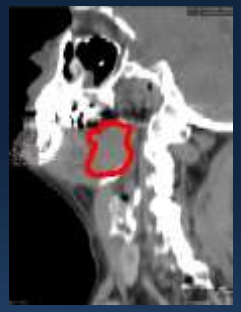
Treatment simulation



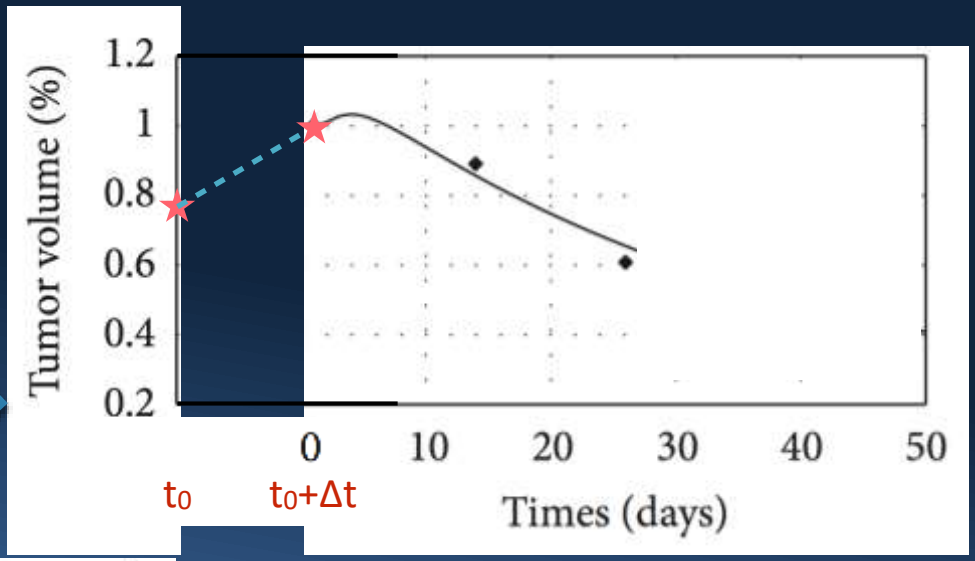


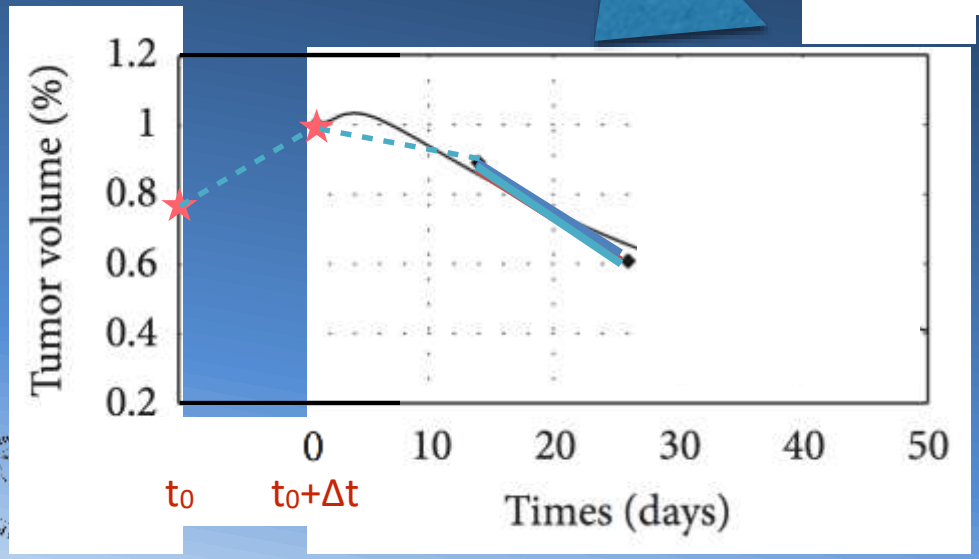
Framework for patient-specific adaptive radiation fractionation

Diagnosis



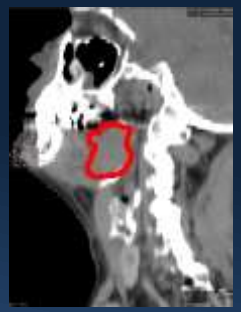
Treatment simulation



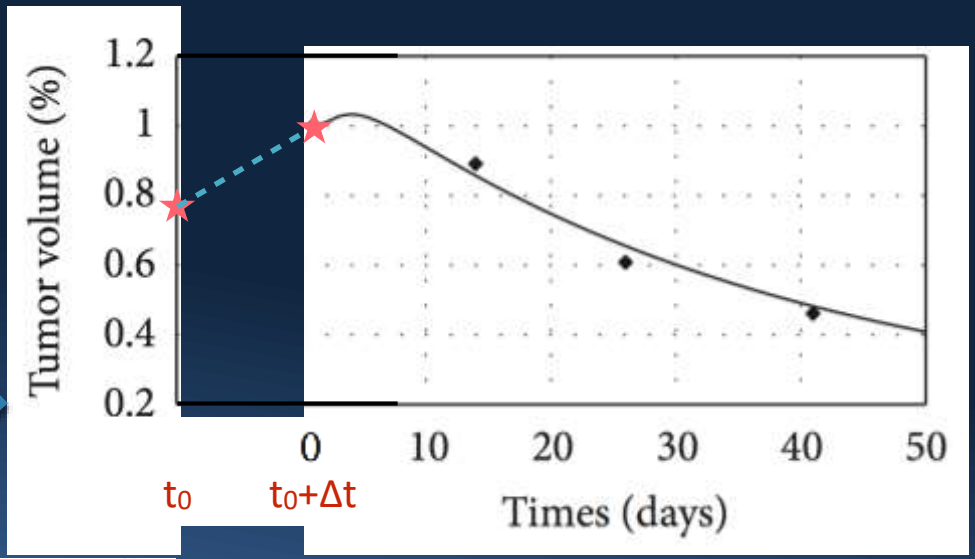


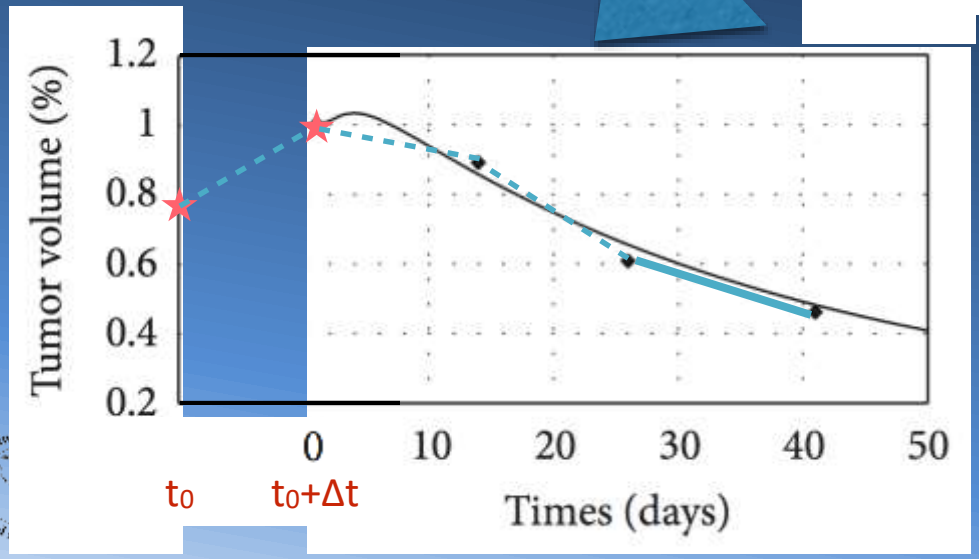
Framework for patient-specific adaptive radiation fractionation

Diagnosis



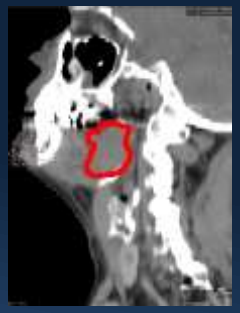
Treatment simulation



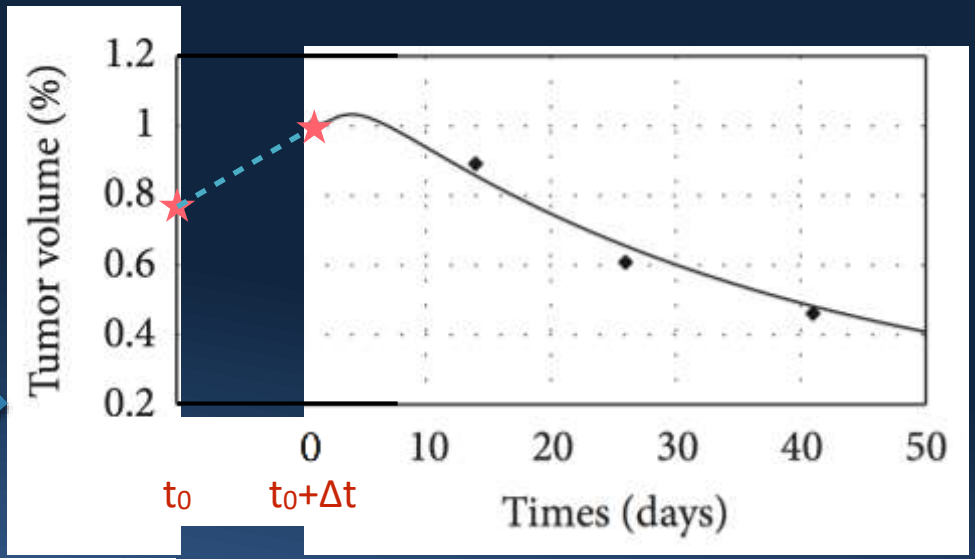


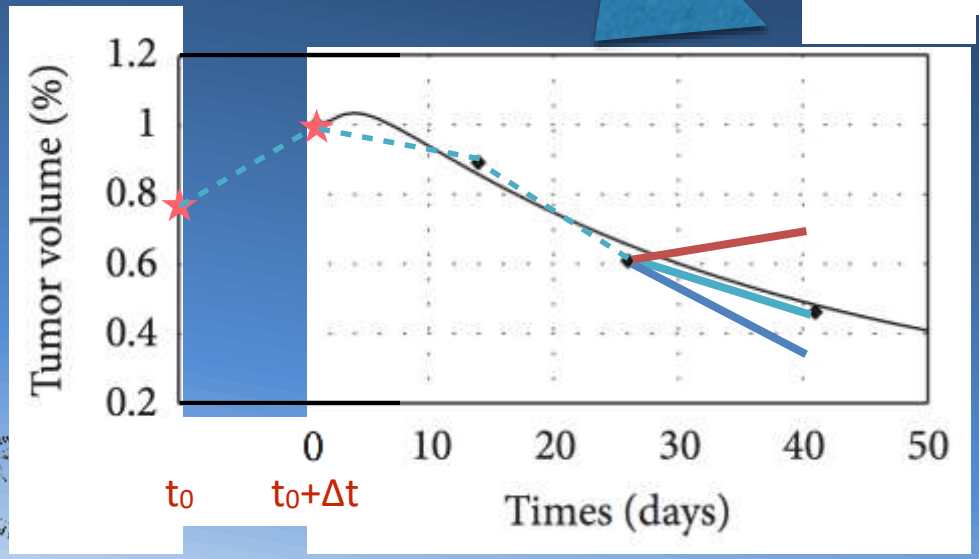
Framework for patient-specific adaptive radiation fractionation

Diagnosis



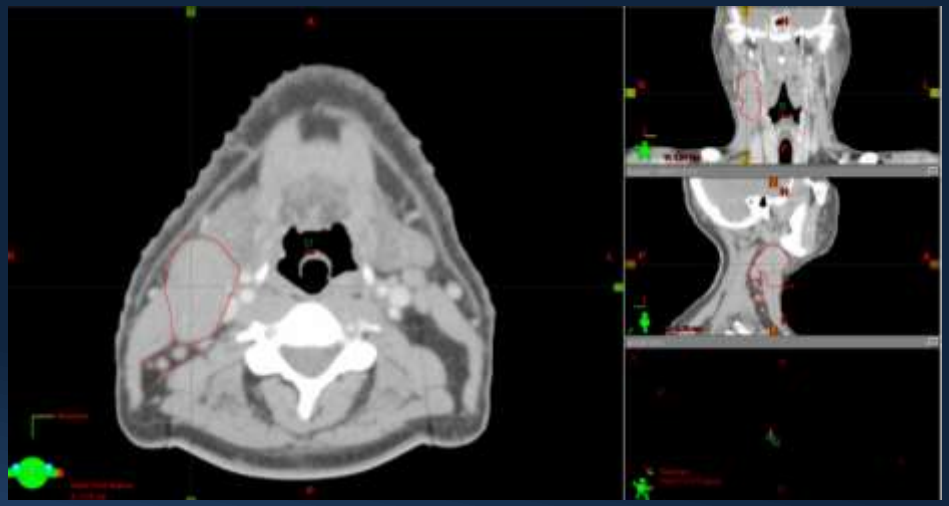
Treatment simulation



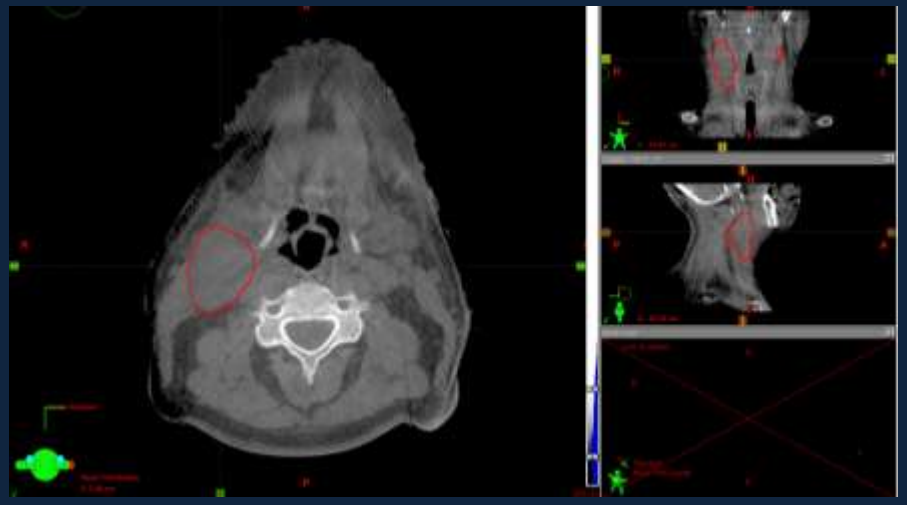


Prediction of response to fractionation adaptation.

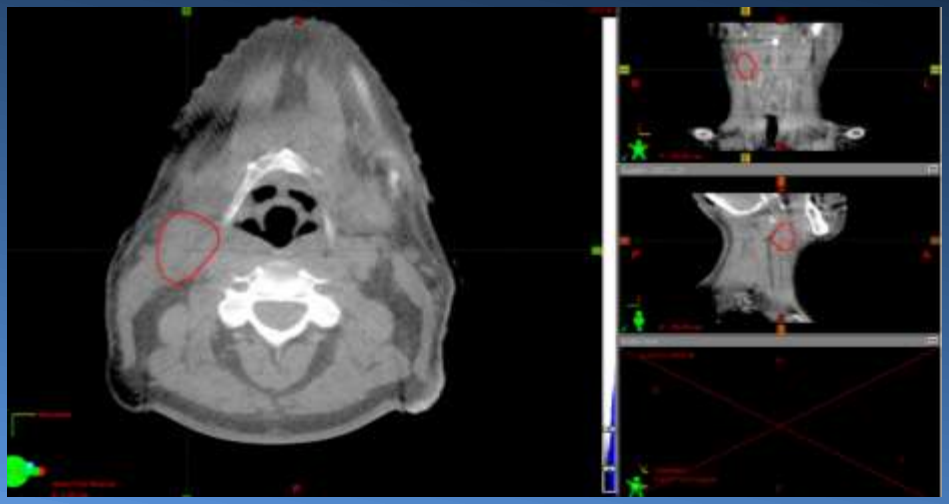
Patient-specific treatment recommendation.



Planning Scan



CBCT day 10



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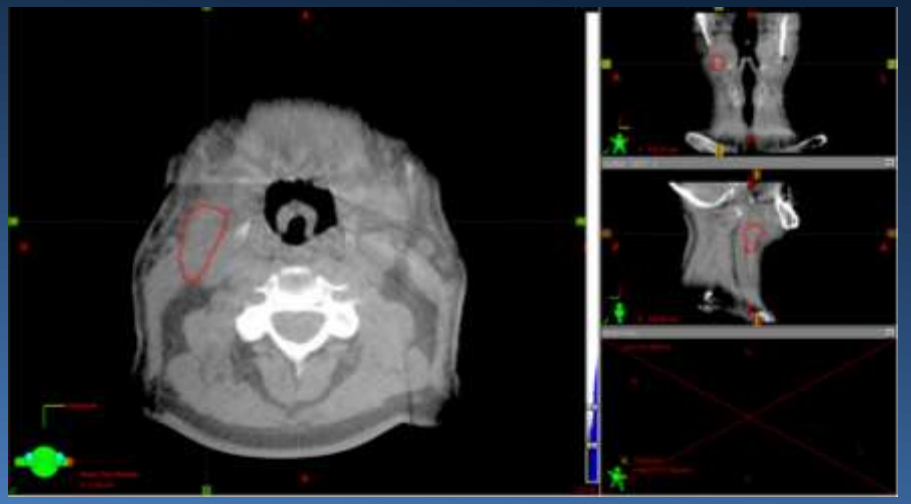

CBCT day 35

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Use of Cone Beam CT to Assess Mid Treatment Nodal Response to Chemoradiation Therapy in Oropharyngeal Squamous Cell Carcinomas: Implications for Adaptive Radiation Therapy

Stewart R et al ASTRO 2015

Nodal Decrease Day 20	> 40 %	< 40% and p value
Regional Control	100%	78.4% p=0.03
2 year DFS	95.5%	72.7% p=0.06
Local Control	100%	85% p=0.08
Overall Survival	100%	100% p=0.11

Use of Cone Beam CT to Assess Mid Treatment Nodal Response to Chemoradiation Therapy in Oropharyngeal Squamous Cell Carcinomas: Implications for Adaptive Radiation Therapy Stewart R et al ASTRO 2015

2 year Distant Metastasis Rate

>10 vs < 10 pack year smoking	**30% vs 0% p=0.01**
p16 (-) vs p16 (+)	29% vs 4 % p=0.01

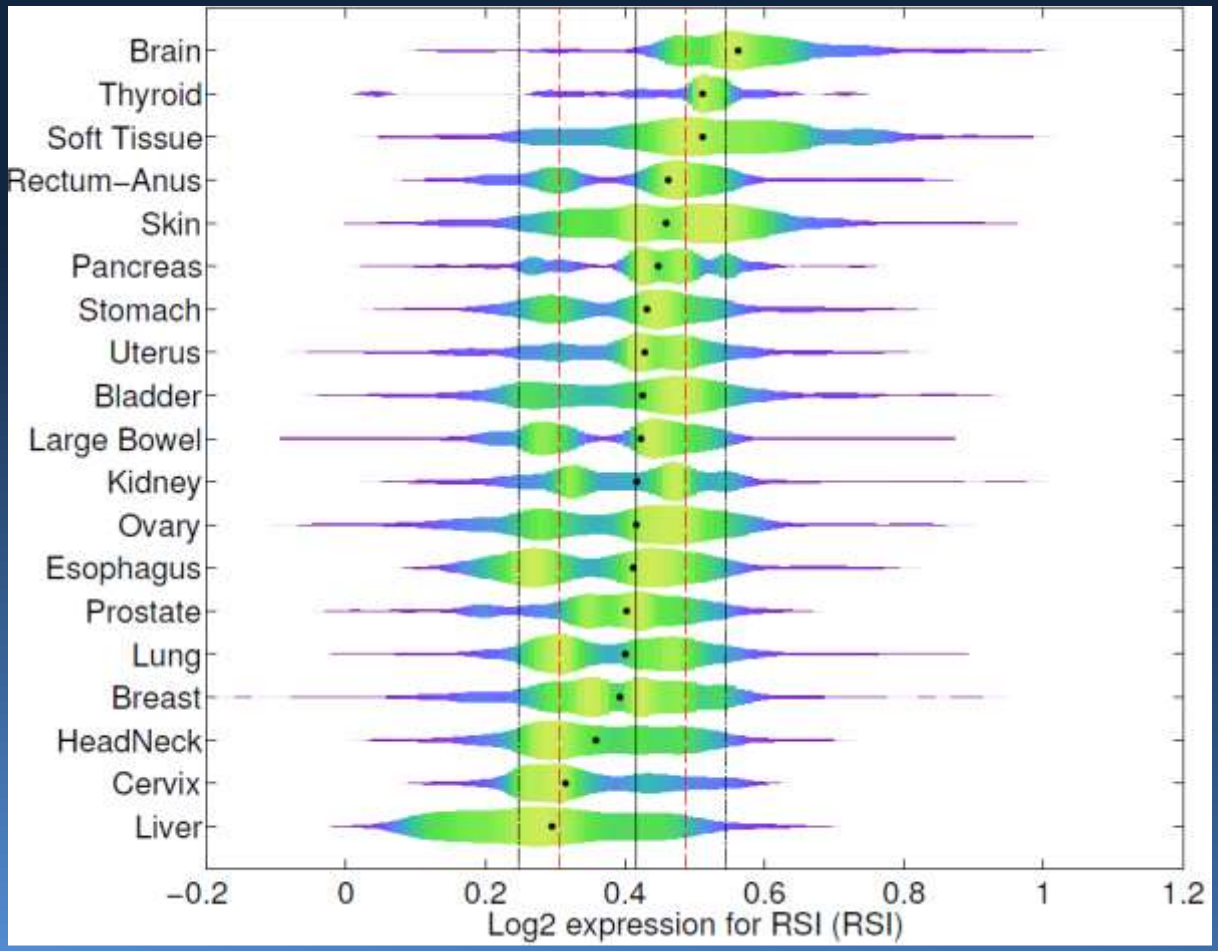
Use of Cone Beam CT to Assess Mid Treatment Nodal Response to Chemoradiation Therapy in Oropharyngeal Squamous Cell Carcinomas: Implications for Adaptive Radiation Therapy

Stewart R et al ASTRO 2015

Importance of Response in Smokers and p16 (+) Patients- Power of Adaptive Therapy

Smoker >10pyh or p16 (+) status	Nodal Decrease Day 20 > 40 %	Nodal Decease Day 20 < 40% and p value
2 year Regional Control- >10pyh	100%	49% p=0.04
2 year Regional Control p16 (+)	100%	78% p=0.05

Calibrate Expected Success of RT: RSI Score Distribution



Torres-Roca JF et al (2014) ASTRO

Head and neck cancer 2

The future of personalised radiotherapy for head and neck cancer

Jimmy J Caudell, Javier F Torres-Roca, Robert J Gillies, Heiko Enderling, Sungjune Kim, Anupam Rishi, Eduardo G Moros, Louis B Harrison

Radiotherapy has long been the mainstay of treatment for patients with head and neck cancer and has traditionally involved a stage-dependent strategy whereby all patients with the same TNM stage receive the same therapy. We believe there is a substantial opportunity to improve radiotherapy delivery beyond just technological and anatomical precision. In this Series paper, we explore several new ideas that could improve understanding of the phenotypic and genotypic differences that exist between patients and their tumours. We discuss how exploiting these differences and taking advantage of precision medicine tools—such as genomics, radiomics, and mathematical modelling—could open new doors to personalised radiotherapy adaptation and treatment. We propose a new treatment shift that moves away from an era of empirical dosing and fractionation to an era focused on the development of evidence to guide personalisation and biological adaptation of radiotherapy. We believe these approaches offer the potential to improve outcomes and reduce toxicity.

Lancet Oncol 2017

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See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(17)30269-3

This is the second in a Series of four papers about head and neck cancer

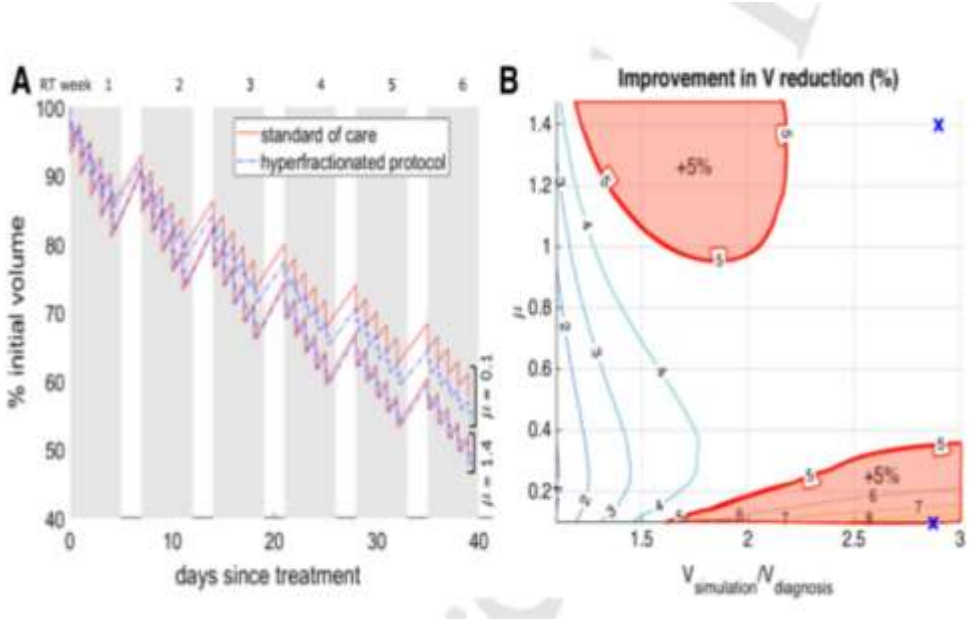
Department of Radiation

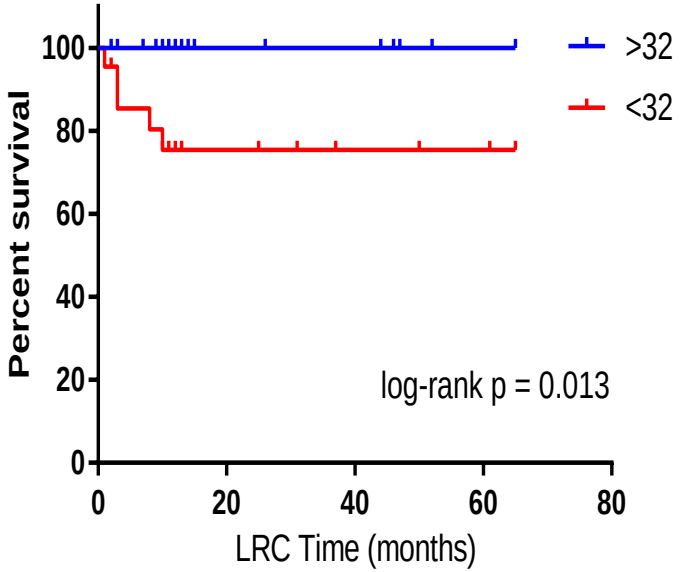
2017

Phase II Protocol to Test Proliferation Saturation Index to Personalize Radiation Therapy Fractionation for Patients with Squamous Cancer of the Head and Neck

Radiation Oncology
Jimmy Caudell, MD, PhD

Heiko Endegling, PhD





Hypothesis: By personalizing fractionation, we can improve the percentage of patients achieving a 32% or greater tumor reduction by week 4 from ~50% to ~70%

Personalized Radiotherapy for Head and Neck Cancer: Future Directions

Jimmy J. Caudell, M.D., Ph.D., Javier F. Torres-Roca, M.D., Robert J. Gillies, Ph.D., Heiko Enderling, Ph.D., Sungjune Kim, M.D., Ph.D., Anupam Rishi, M.B.B.S., Eduardo G. Moros, Ph.D., and Louis B. Harrison, M.D.

Departments of Radiation Oncology, Cancer Imaging and Metabolism, and Integrated Mathematical Oncology
Moffitt Cancer Center and Research Institute, Tampa FL

Lancet Oncology-In Press

Biologically Adaptive Radiation Therapy for Head and Neck Cancer – A Personalized Approach Based Upon Genomics and Response

Simulation

Eval MR @ 20 Tx

PRE-Tx

PET-CT
MRI
RSI-GARD → 60 Gy / 70 Gy

PRESCRIBE

CT

WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7
Daily CBCT	Daily CBCT	Daily CBCT	Daily CBCT	Daily CBCT	Daily CBCT	Daily CBCT
√	√	√	√	√	√	√

	GARD ≤ STD	GARD > STD
≥ 40 RR	Reduce dose to GARD Floor 54 or 60 Gy	STANDARD
< 40 RR	STANDARD ACCEL	Go to GARD up to 80 Gy ACCEL

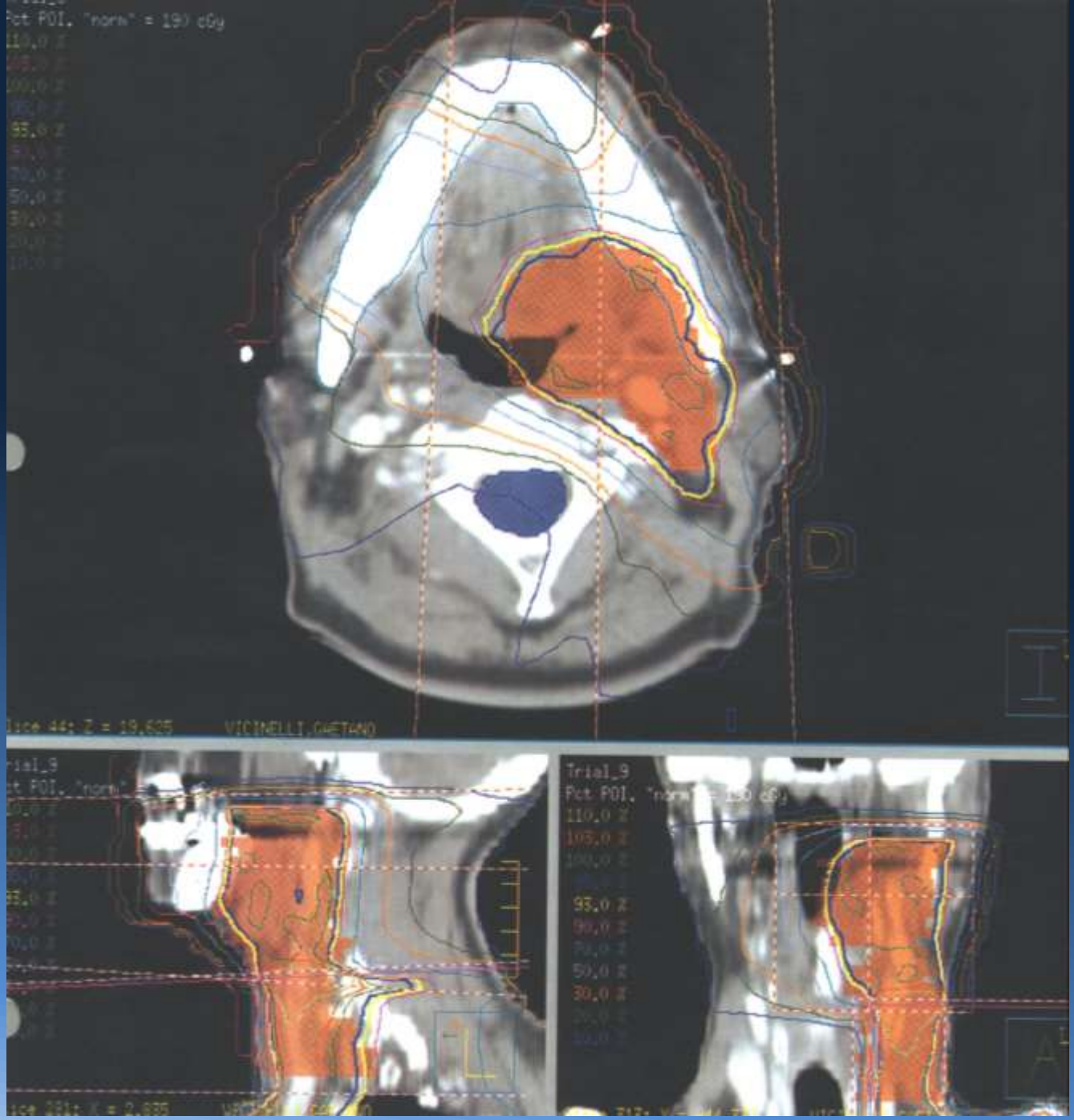
Data Collection
PSI Modeling
Radiomics

NON INFERIORITY

70%

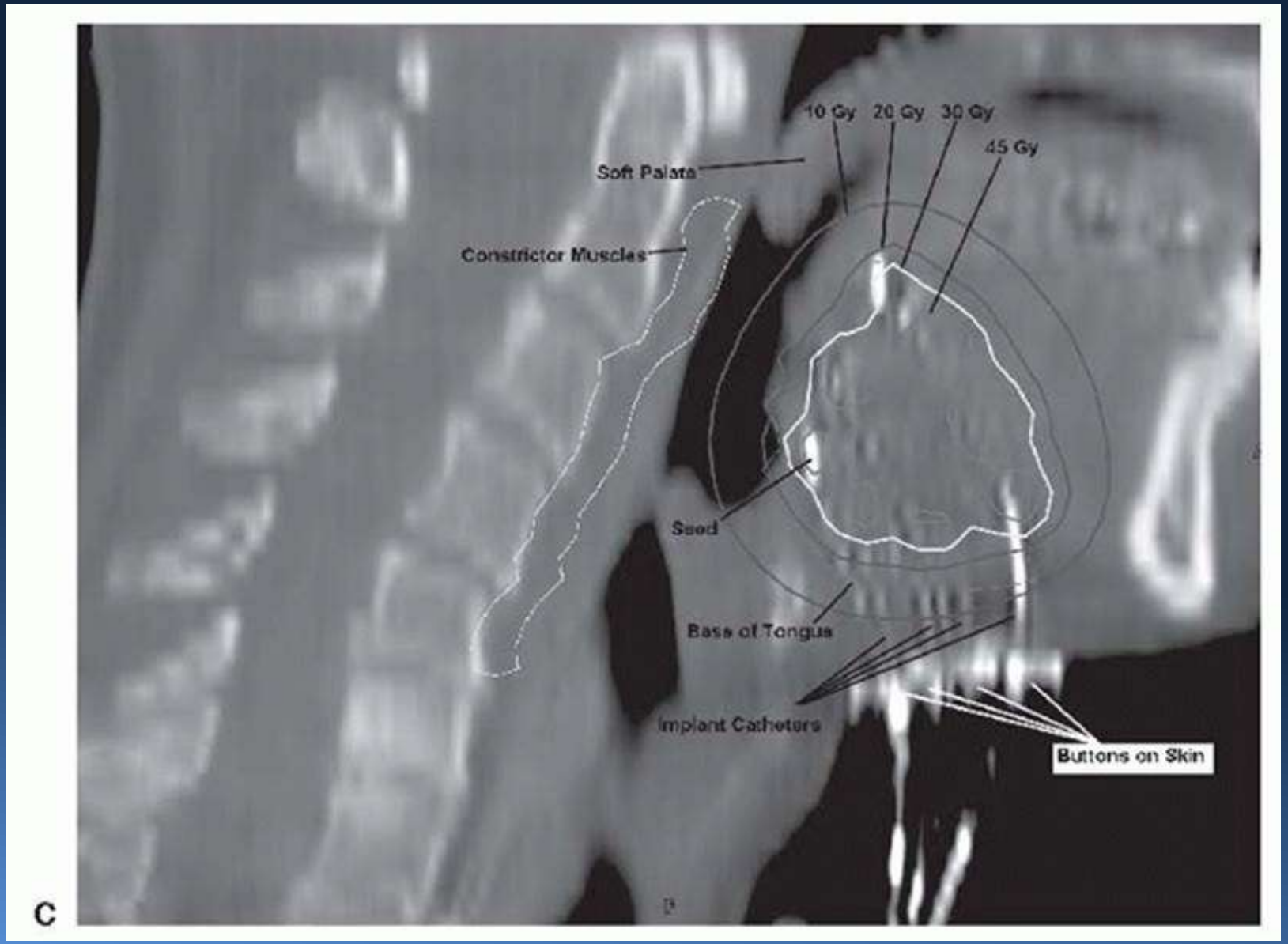
Case: Re-irradiation for recurrent disease/second primary cancer

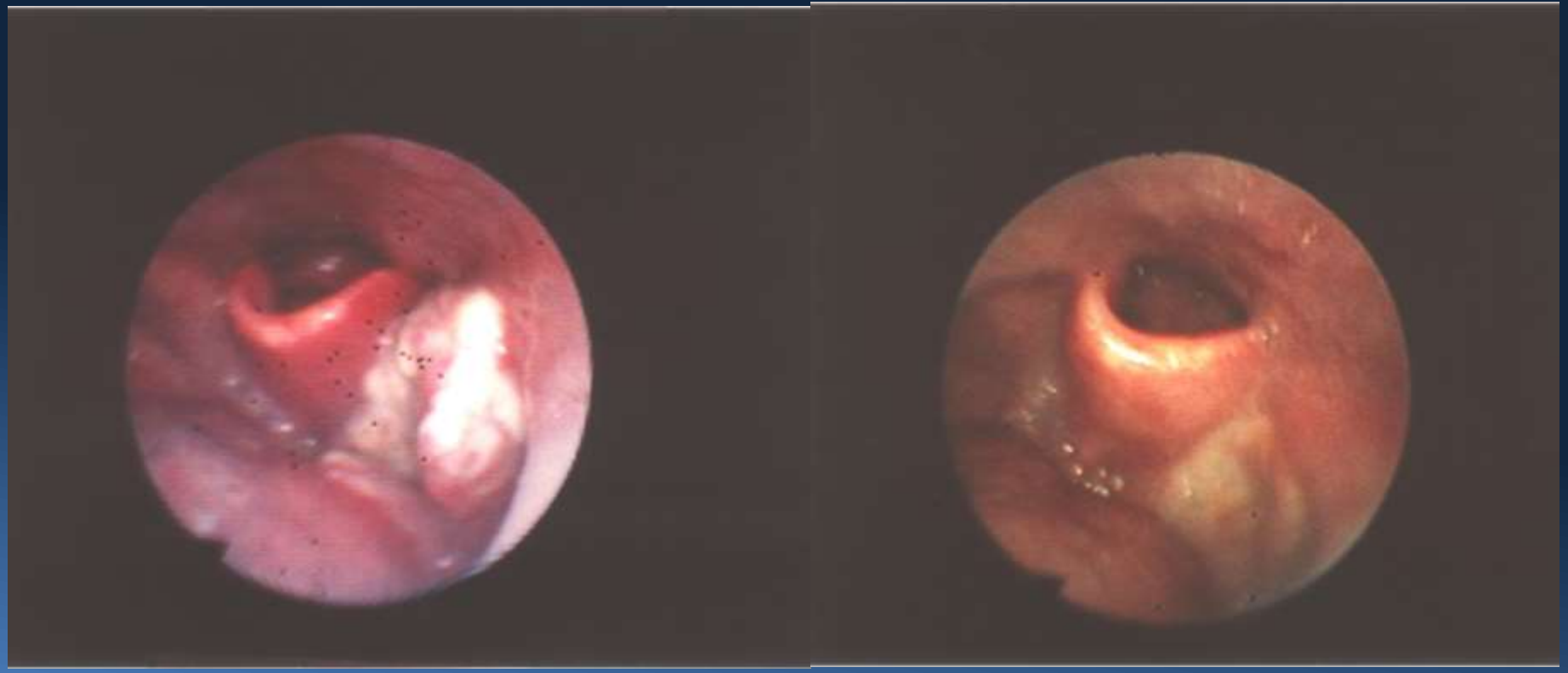
65 y/o man S/P S+RT for a R parotid cancer. In 2004 he presented with a L BOT/pharyngoepiglottic fold cancer.



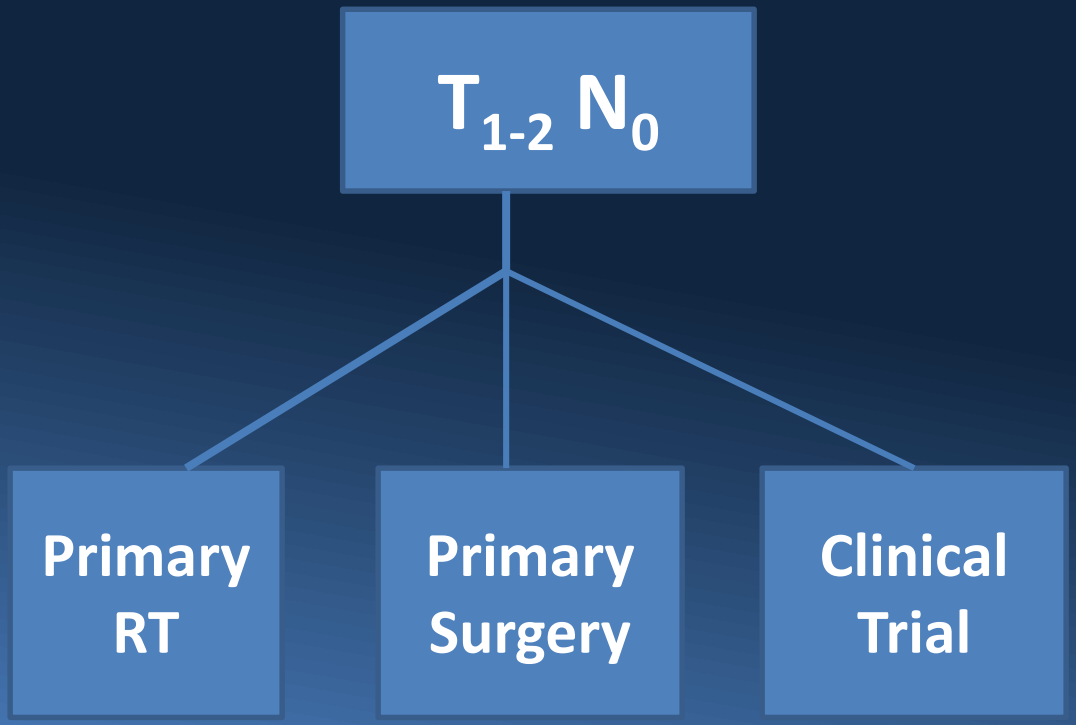
2017
International Federation of Head and Neck Oncologic Societies


LOADING

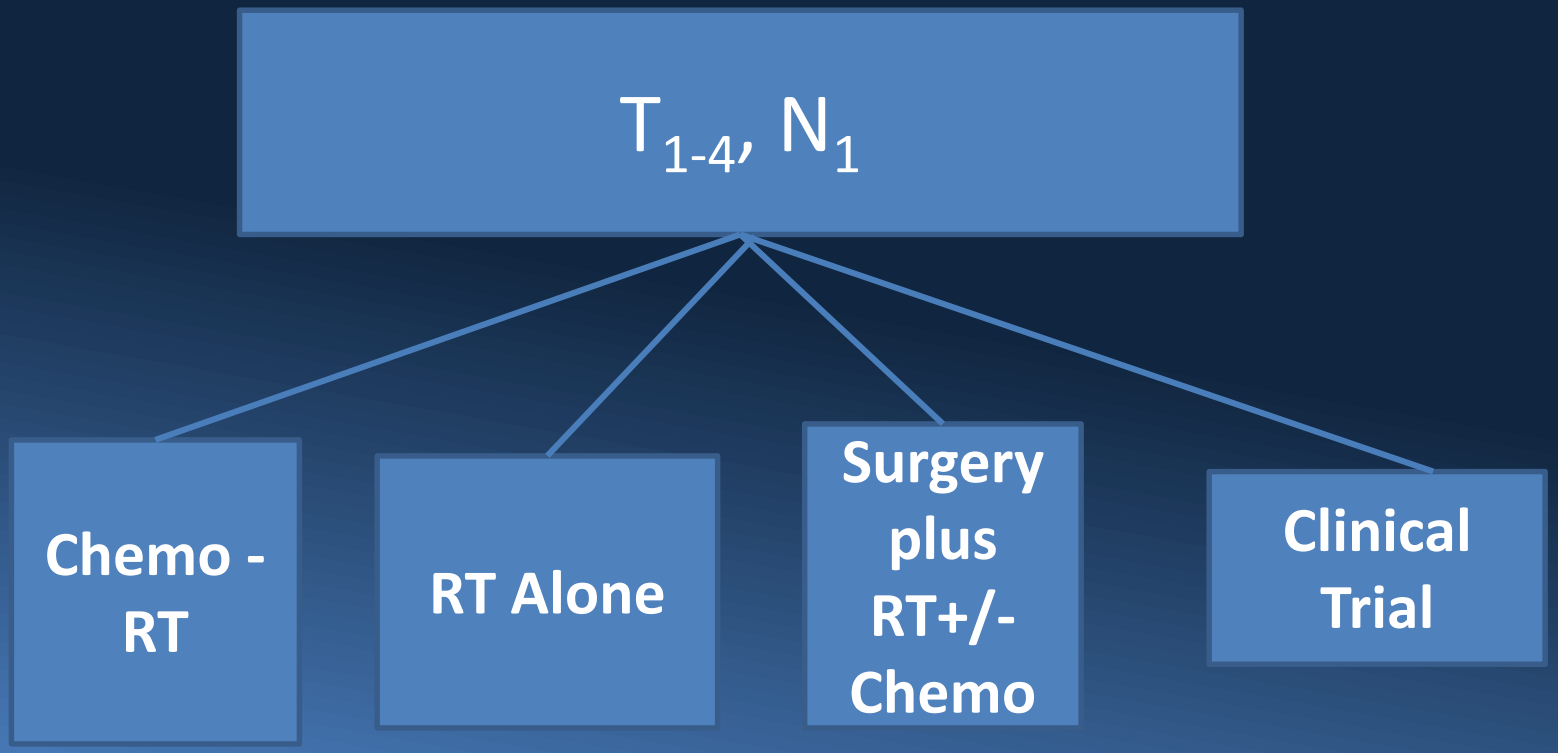

10 Gy
20 Gy
30 Gy
45 Gy
Soft Palate
Constrictor Muscles
Seed
Base of Tongue
Implant Catheters
Buttons on Skin
C



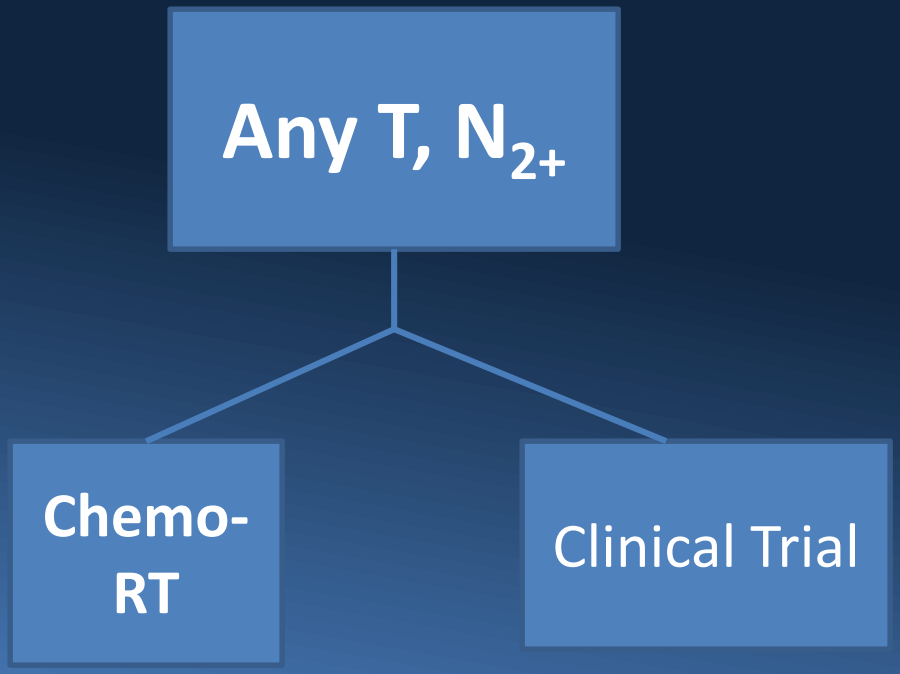
Oropharynx Cancer Schema



Oropharynx Cancer Schema



Oropharynx Cancer Schema



2017

Follow Up Care

Chemo-RT OR RT Alone → 3 MONTHS → **PET-CT FOR Re-Evaluation**

- Overwhelming percentage of events occur in the first 3-6 months and definitely by 12 months
- De-Intensify follow up beyond 12 months.

Frakes, J et al. Cancer Volume 122, Issue 4, pp 634-641 13 Nov 2015

Prognostic Implication of Pathologic Residual Disease on Neck Dissection after Chemoradiation

Author	# pts	% path residual disease	Survival (pLN+ vs pCR)	Distant metastasis (pLN+ vs pCR)	Regional Failure (pLN+ vs pCR)	Local Recurrence (pLN+ vs pCR)
Sewall [130]	107	28%			13% vs 1%	
Hu [145]	82	29%	DFS 47% vs 85% p=0.013	41% vs 11% p=0.011	14% vs 4%, p=0.376	
McHam [131]	76	33%			20% vs 0% p<0.001	
Stenson [132]	73	21%	3 yr OS: 36% vs 72% p=0.008			
Argiris [133]	61	31%	5yr PFS:62% vs 80% p=0.11			
Lavertu [136]	35	34%	50% vs 83% (p=0.03)			
Newkirk [120]	33 (39% CT)	45%				33% vs 0%

Oropharynx- Conclusions

- Oropharynx cancer treatment is evolving
- New principles beyond TNM are guiding the next generation of therapeutics
- Model for both multidisciplinary care as well as the development of personalized oncology

Thank You

H. Lee Moffitt Cancer Center and Research Institute; Tampa, Florida

2017