# TOSSICITÀ EMERGENTI CON LE NUOVE TECNOLOGIE





The use of multibeam circumferential IMRT dose arrangement introduces higher integral dose to normal tissues compared with conventional techniques







#### L INVESTIGATION

## BEAM PATH TOXICITIES TO NON-TARGET STRUCTURES DURING INTENSITY-MODULATED RADIATION THERAPY FOR HEAD AND NECK CANCER

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"Decrements in specific toxicities (e.g., xerostomia) have lead some to assume that IMRT leads to a global reduction in toxicity as compared with 3D-CRT techniques." Table 3. Rates (%) of toxicities by treatment group: IMRT with or without concurrent cisplatin (100 mg/m<sup>2</sup>)

Incidence of toxicities by treatment group (%)

	IMRT alone	Concurrent cisplatin
Nausea	76	98
Vomiting	38	68
Headache	10	30
Occipital scalp epilation	40	25
Moist skin desquamation	28	35
Anterior oral mucositis	9	22

*Abbreviation:* IMRT = intensity-modulated radiation therapy.

Rosenthal DI, Int J Radiat Oncol Biol Phys. 72 (3): 747-755, 2008



 quantification of observed toxicity to noncontoured structures of interest;

- 2) dosimetric evaluation of the delivered dose to those structures;
- ③ determination of potential dose differentials of those structures in IMRT vs. 3D-CRT plans;
- ④ generation of dose/toxicity threshold values through exploratory recursive partitioning-based analysis to generate hypotheses for future testing.



## NAUSEA AND VOMITING

		Tokienty grade				
	0	1	2	3	4	
Nausea*						
IMRT alone	24	33	38	5	0	
Concurrent cisplatin	2	22	58	18	0	
Vomiting**				K		
IMRT alone	63	16	18	3	0	
Concurrent cisplatin	32	18	38	12	0	

Abbreviation: IMRT = intensity-modulated radiation therapy. \* p < 0.004 based on Pearson Chi-Square test. \*\* p < 0.04 based on Pearson Chi-Square test. In RPA, nausea and emesis were associated with reconstructed mean dose to the brainstem of >36 Gy



9 pts mean brainstem dose >36 Gy: 6 (66%) had clinically evident nausea, and all 9 (100%) emesis.

in 24 ore

50 pts mean brainstem dose < 36 Gy: 26 (52%) had nausea and 41 (82%) emesis

	Table 4. Percentage vomiting in the IMR	T ornd C	Oncology	76 (2005)	227–233	}	
		grou	groups mmendations for the use Toxicity ghaten				
a adric		0	1	2	3		i <sup>a</sup> .
	Nausea*	24	22	20	5	2(	004
	Concurrent cisplatin	24	33 22	58	18	0	
In the	IMRT alone Concurrent cisplatin	63 32	16 18	18 38	3 12	0 0 5	)
passe	mi three (mg-	intensity	-modulat	ed radiatio	on therap	" <sub>y.</sub> 1	L,
mode	rate, low and mini	mai),	hi-Squar Squar	e test. e test.			
the ris	sk possibility to de	velop	nause	a $a$ $a$ $a$ $a$ $a$ $a$ $a$ $a$ $a$		miting	g
and le	re than 90%, betwees than 30% of pa	tients	0 and , respe	90, 30 ectively	and :	<u>59%</u> ,	

## Risk Stratification in RINV

a prophylaxis or a rescue therapy with a 5-HT3 receptor antagonist is recommended



Feyer PC et al., 'Radiotherapy-induced Nausea and Vomiting (RINV): MASCC/ESMO Guideline for Antiemetics in Radiotherapy: Update 2009', *Supportive Care in Cancer*, 19 (2010), 5-14



The area postrema (AP), a chemoreceptor trigger zone for vomiting (emesis), is located on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle.

The role of the AP in radiation-induced vomiting remains controversial. Electrophysiological studies have reported that neurons in the AP increase their firing in response to emetic drugs.

Miller AD, Leslie RA. Front Neuroendocrinol 1994;15:301–320.



## EFFECT OF BRAIN STEM AND DORSAL VAGUS COMPLEX DOSIMETRY ON NAUSEA AND VOMITING IN HEAD AND NECK INTENSITY-MODULATED RADIATION THERAPY

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Ciura K et al. Medical Dosimetry, Vol. 36, No. 1, pp. 41-45, 2011

Brain stem doses well below traditionally accepted tolerance levels are associated with nausea and vomiting (NV).

The area postrema (AP) in the medulla oblongata and the dorsal vagus nucleus have been linked to radiation-induced NV.





✓ 100 pts with IMRT. 51 **Concom**itant **CITE** NV developed around week 2 of treatment, indicating a possible 15–25 Gy dose correlation to toxicity.

 Limited sample size for RT/chemoRT groups makes difficult to make conclusions.

Mean brainstem dose emerges as a key parameter of interest

✓ No one dose parameter (mean/median/ EUD) best correlated with NV

# Alopecia of t ALOPECIA

when maximum occipital scalp doses was

> **30 Gy** (48%; 21 of 43 cases) vs.

< 30 Gy (19%; 3 of 13 cases)



Rosenthal DI, Int J Radiat Oncol Biol Phys. 72 (3): 747-755, 2008

## ACUTE MUCOSITIS <sup>n</sup> lance



structure, the anterior oral volume often receives 35–40 Gy, and additional focal "hot spots" may exacerbate mucositis.



Anterior oral cavity mucositis (Grade >1) was found to be more prevalent when anterior or lateral mandible maximum voxel doses were > 33.5 Gy,

7 of 26 (26%) patients receiving that dose experiencing detectable anterior mucositis 1 of 31 patients (3%) receiving < 33.5 Gy.

Rosenthal DI, Int J Radiat Oncol Biol Phys. 72 (3): 747-755, 2008

## **122** Dosimetric Correlation of Oral Cavity Dose with Acute Mucositis in Patients Treated with Intensity Modulated Radiation Therapy (IMRT) and Chemotherapy

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Correlation Analysis of Percent Volume of Oral Cavity Receiving More Than 15,30,40,45,50 Gy with Grade of Acute Oral Mucositis

Variable	Correlation Coefficient (Spearman Rho)	p value
V15	0.349	0.005
V30	0.301	0.016
V40	0.316	0.012
V45	0.328	0.009
V50	0.240	0.060

There was a statistically significant correlation between acute mucositis grade (p<0.05) and the V15, 30,40,45

Shogan G et al. Int J Radiat Oncol Biol Phys 2005;63:S73–S74.

#### INICAL INVESTIGATION

### PROSPECTIVE EVALUATION TO ESTABLISH A DOSE RESPONSE FOR CLINICAL ORAL MUCOSITIS IN PATIENTS UNDERGOING HEAD-AND-NECK CONFORMAL RADIOTHERAPY

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Prospective. 12 patients, 4 sites in oral cavity, MOSFET dosimeters and Eclipse dose distributions.

Outcome: Point dose >39.1 Gy resulted in mucositis 3+ weeks. Point dose <32 Gy resulted in mild (<= G1) mucositis for <=1 week

Conclusion: Dose **<32 Gy** minimal acute mucositis, dose **>39** Gy longer duration of mucositis

Narayan S Int. J. Radiat. Oncol. Biol. Phys., Vol. 72, No. 3, pp. 756–762, 2008

## **2303** Is it Feasible to Spare Part of the Mucosa with IMRT and Does It Matter

G. Sanguineti,<sup>1</sup> M. Sosa,<sup>1</sup> L. Culp,<sup>1</sup> E. Endres,<sup>2</sup> J. Bayouth<sup>2</sup>

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Reducing the dose to part of the 'mucosa' volume for early stage oropharyngeal cancer is dosimetrically feasible while meeting the other dose objectives.

Such a **dosimetric improvement** in such a critical location translates into a **clinically detectable benfit** (IMRT-YM was able to keep mucositis in the anterior part of the oral cavity within grade 1 or enanthema in 18/19 patients).

Sanguineti G, et al. Int J Radiat Oncol Biol Phys 2004;60:S517–S518.

### IS THERE A "MUCOSA-SPARING" BENEFIT OF IMRT FOR HEAD-AND-NECK CANCER?

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## ) no dose objective

- 2) a 30-Gy maximum dose objective on the portion of the mucosa outside any PTV.
- 3) expanding PTV54 concentrically by 8, 15, 20, and 30 mm. On the portion of the mucosa volume overlapping with any of these rings, a maximum dose objective of 40 Gy, 26 Gy, 16 Gy, and 6 Gy was placed for the 8-mm, 15-mm, 20-mm, and 30-mm expansion, respectively. This approach allows us to minimize the dose in the mucosa volume outside any PTV by forcing the high-dose region within the PTVs.

Sanguineti G et al. Int. J. Radiat Oncol Biol. Phys., Vol. 66, No. 3, pp. 931–938, 2006



✓ NM-IMRT results in a significantly larger amount of mucosa exposed to clinically relevant doses over CF.

✓ Improvement of mucositis rate over 3FT is strictly correlated with the amount of mucosa that does not overlap with any PTV. Therefore, primary tumor size are expected to have a role in this.



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"IMRT could lead to significantly higher rates of dysphagia and prolonged feeding tube requirement than seen with the 3D-CRT technique if appropriate dose constraints for the cervical esophagus, for example, are not used."

FuaTF et al., Int J Radiat Oncol Biol Phys., 67 (2007), 976-981



✓ The mean pharyngo-esophageal axis dose was 55.2 Gy in the WF-IMRT group and 27.2 Gy in the j-IMRT group. (p = 0.001).

✓ **G3 dysphagia** was 95% (19/20) in the WF-IMRT group and 63% (5/8) in the j-IMRT group. (p = 0.058).

✓ The median duration of a feeding tube was significantly shorter for the j-IMRT group compared with the WF-IMRT group, 6 days (range, 0 –119 days) compared with 38 days (range, 0 –341 days) respectively (p = 0.037).

### **INICAL INVESTIGATION**

## CHEMO-IMRT OF OROPHARYNGEAL CANCER AIMING TO REDUCE DYSPHAGIA: SWALLOWING ORGANS LATE COMPLICATION PROBABILITIES AND DOSIMETRIC CORRELATES

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✓ Difference in the dose–effect relationships between the objective VFbased assessments of dysphagia and patient-reported worsening of dysphagia, the former having substantially lower TD50 compared with the latter.

✓ What is the reason for the different dose-effect relationships of patient-reported and objective, VF-based dysphagia?

• Silent aspirations

• Shifting over time of patient-reported outcomes representing either a true improvement or an accommodation to their new functional status, termed "response shift".

✓ Which dosimetric measure should be used as a constraint or an objective for IMRT plans in efforts to reduce dysphagia?
High correlations between the mean doses and the VDs, making the VDs redundant.

 ✓ What are the mean doses which should guide IMRT planning? The mean PC doses above which the risk of dysphagia increases significantly range in various studies between 45–60 Gy (Gluck I Int J Radiat Oncol Biol Phys. 2010 July 1; 77(3): 727–733)

The doses we have found in the current study (73 pts) regarding VFassessed swallow dysfunction were TD50 and TD25 of 63 Gy and 56 Gy, respectively, for the PCs, and 56 Gy and 39 Gy, respectively, for the GSL, whereas the corresponding TDs for significant patientreported worsening of swallow were substantially higher.

VF-based TD25 as goals for optimization would be reasonable

✓ Which are the reasons for the differences in the dose – effect relationships between the different published series?

•inclusion of patients receiving RT alone

•different assessments of dysphagia in different series: aspiration and objective imaging, feeding tube dependency, patient-reported dysphagia, strictures, or observer-reported such as RTOG, CTCAE, or PS Scale

retrospective analysis

•exclusion of pretreatment data on dysphagia

•different methods to delineate the organs (for example, drawing the PCs anatomically, results in different mean doses compared with drawing only the posterior pharyngeal wall, without differences in the IMRT plans and dose distributions).

		Patients, n	Site	Dysphagia endpoint	Dosimetric factors correlated with dysphagia	
Feng	(2007) <sup>67</sup>	36	OP/NP	Videofluoroscopy	Pharyngeal constrictor muscles (mean dose, V50, V60, V65) and larynx (mean dose, V	50)
Leven	dag (2007) <sup>68</sup>	56	OP	HNSW	Superior and middle phanungeal constrictor muscles (mean dose)	
Jense Tegul Tegul	th	e be	est a	approa	ch consists of keeping	
Cagla	th	e ra	dia	tion do	ose to these structures	e,
Caude			2	as low	as nossible	
Dirix			L			an
OP=oro HNSW= subsite	-coropean org s. D60=minim	um dose receiv	ed by 60% c	f a structure. V70=volume	nar <del>y 55 swanowing symptom score. Fees – intreoptic endoscopic evaluation of swanowing. A</del> of a structure receiving ≥70 Gy.	Gy. I=all

Table 3: Overview of studies assessing crucial structures for late dysphagia

Both the mean dose to the pharyngeal constrictor muscles and the larynx, as well as the volume of structures receiving 50–60 Gy, have been shown to be significantly correlated with the occurrence of late dysphagia.

However, no clear dose or volume constraints can yet be proposed.

Dirix P. Evidence-based organ-sparing radiotherapy in head and neck cancer Lancet Oncol 2010; 11: 85–91

✓ Which are most important: the dose to the SPC, IPC, or larynx in determining dysphagia?

it depends on where the primary tumor is!!

In oropharyngeal cancer SCP has the highest p value In larynx cancer, doses to the IPC or the larynx are most significantly correlated with dysphagia



any effort should be made to spare all the swallowing structures, **when possible.** 

Inferior constrictor

	C
	-
Esophagus —	

Inferior constrictor (Cricopharyngeus)

## CAL INVESTIGATION

Upper C3

constrictor

Upper C4

Inferior

C5

Mid C6

Middle C6 -

Middle

Head and Neck

### TREATMENT TECHNIQUES AND SITE CONSIDERATIONS REGARDING DYSPHAGIA-RELATED QUALITY OF LIFE IN CANCER OF THE OROPHARYNX AND NASOPHARYNX

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Caudal Part Corpus Hyoid constrictor Hyoid bone - APRILITY CON Thyroid cartilage Caudal part Cricoid Cricopharyngeus ALC: NO. First ring trachea Cricoid cartilage DM: COUCH Esophagus 1cm Distant eter

ICCUPC IIIC IIIGIICOL UOOC because of the treatment techniques used, dysphagia is still less as opposed to patients with cancer of the BOT. The explanation of this phenomenon remains somewhat unclear; it is speculated that this might have to do with the infiltrative (muscles) nature of the BOT cancers.

Fig. 2. Schematic diagram of the delineated five muscular structures considered of paramount importance in swallowing.

Teguh DN et al. I Int J Radiat Oncol Biol Phys. 72(4): pp 1119-1127. 2008

FULL PAPER

# The BITTLE DE BRACHIAL PLEXUS PY for

A M Chen, MD', W H Hall, MD', B-Q Li, MD, PhD', M Guiou, MD, PhD', C Wright, CMD<sup>1</sup>, M Mathai, CMD<sup>1</sup>, A Dublin, MD<sup>2</sup> and J A Purdy, PhD<sup>1</sup>

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Dose to the brachial plexus is significantly increased among patients with IMRT compared to CRT for head and neck cancer.

Mean irradiated volumes of the brachial plexus using IMRT vs CRT:

V50 (18 $\pm$ 5 ml) vs (11 $\pm$ 6 ml), p = 0.01;

V60 (6 $\pm$ 4 ml) vs (3 $\pm$ 3 ml), p = 0.02;

V66 (3 $\pm$ 1 ml) vs (1 $\pm$ 1 ml), p = 0.04,

V70 (0 $\pm$ 1 ml) vs (0 $\pm$ 1 ml), p = 0.68.

The maximum point dose to the brachial plexus was 68.9 Gy and 66.1 Gy for the IMRT and CRT plans, respectively (p = 0.01).

Chen AM et al., British Journal of Radiology, 84 (2010), 58-63

#### EDUCATION EXHIBITS

TEACHING

See last page

POINTS

Brachial Plexus Contouring with CT and MR Imaging in Radiation Therapy Planning for Head and Neck Cancer<sup>1</sup>

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Truong MT et al., Radiographics, 30 (2010), 1095-1103

1095



Figure 4. Sagittal CT scan depicts the interspaces between the C4–5 (circled in green) and T1–2 (circled in blue) vertebral bodies, thereby helping identify the upper and lower limits of the brachial plexus for contouring. Red circle = treatment isocenter.



- 1. Identify the C4–5 and T1–2 neural foramina at sagittal planning CT to determine the upper and lower limits of the brachial plexus.
- 2. Contour the ventral rami of C5-T1 as they exit through the intervertebral neural foramina as seen at axial CT.
- 3. Contour the trunks of the brachial plexus between the anterior and middle scalene muscles.
- 4. Follow the insertion of the scalene muscles into the first rib.
- 5. Contour the brachial plexus divisions, cords, and terminal nerves by following the subclavian artery into the axilla.

Preliminary studies on brachial plexus-sparing IMRT are in progress.

The maximum dose to the brachial plexus should be limited to **60 Gy** for the diseased portion of the neck, and to **54 Gy** for the uninvolved portion.

If a lymph node is present at level IV and the supraclavicular area, it may be challenging to avoid limiting the radiation dose to the terminal branches of the brachial plexus to 60 Gy. In such case **avoiding hot spots** in BP is a priority.



Chen AM et al., British Journal of Radiology, 84 (2010), 58-63



60-year-old man with radiation plexopathy 5 years after chemoradiation for right tonsillar squamous cell carcinoma with nodal metastases. Patient had 6-month history of progressive arm weakness and numbness.

A, Coronal enhanced fat-saturated T1 image shows marked enhancement and thickening of multiple roots of right brachial plexus (arrows)

B, Coronal fat-saturated T2 image obtained as part of neurography examination shows markedly hyperintense and smoothly expanded nerve roots (arrows).

Glastonbury CM et al Am J Roentgenol.2010 Aug;195(2):164-71.

## Brachial Plexus RT Tolerance

- Three distinct syndromes
- 1) Transient neuropathy
- 2) Classic, delayed, progressive fibrosis (unlikely to occur <60 Gy)
- 3) Acute ischemic plexopathy
- Dose constraints
  - RTOG 0236 (SBRT): 24/3
  - RTOG 0412 (RT+chemo): 60/30
  - RTOG 0435 (RT+chemo): 60/30
  - RTOG 0522 (RT+chemo): 60/30
  - RTOG 0615 (RT+chemo): 66/33 RTOG 0617 (RT+chemo): 66/33



CAL INVESTIGATION

Head and Neck

[.D.

ACUTE SKIN TOXICITY

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✓ The average dose increase was about 18% owing to the bolus effect of the mask.

✓ Multiple tangential fields used in IMRT plans contributed to an increase in skin dose by about 19% and 27%, with and without the mask, respectively.

✓ If the skin of the neck was contoured as a sensitive structure for dose optimization, the volume of skin that received >45 Gy was further reduced by about 20%.

Lee N Int. J. Radiat. Oncol. Biol. Phys., Vol. 53, No. 3, pp. 630-637, 2002



 $\checkmark$  To reduce the skin toxicity, at simulation, the mask should be stretched firmly toward the patient's feet to thin the polystyrene in the targeted area to minimize the bolus effect the mask contributed to the skin.

 $\checkmark$  At the time of treatment planning, if the grossly enlarged neck nodes do not involve the skin, the neck skin has to be excluded from the target volume.

 $\checkmark$  The skin has to be identified as a "sensitive structure" in the planning system, keeping the **dose constraint at 55 Gy**.

#### **MYSICS CONTRIBUTION**

## CONE-BEAM CT ASSESSMENT OF INTERFRACTION AND INTRAFRACTION SETUP ERROR OF TWO HEAD-AND-NECK CANCER THERMOPLASTIC MASKS

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Randomized. 762 CBCT scans in 20 patients. Arm 1) standard mask (SM) vs Arm 2) skin-sparing mask (SSM) modified with low neck cutout





Velec M et al. Int. J. Radiat. Oncol. Biol. Phys., Vol. 76, No. 3, pp. 949–955, 2010

RTOG grade	SM [No. (%)]	SSM [No. (%)]			
0	0	0			
1	5 (45.5)	6 (66.7)			
2	4 (36.4)	3 (33.3)			
3	2 (18.2)	0			

Table 4. Highest-graded acute skin toxicity during and up to 3 months after radiotherapy

*Abbreviation:* RTOG = Radiation Therapy Oncology Group; SM = standard mask; SSM = skin-sparing mask.

There were no significant changes in interfraction and intrafraction setup errors in head-and-neck cancer patients randomized to treatment with thermoplastic SSMs (slin-sparing masks) vs. SMs (standard masks), as evaluated with daily CBCT.



On the basis of the results of this study, cutout masks are being recommended for all of our head-and-neck cancer patients treated with IMRT and daily CBCT IGRT.

and 35% with 70 Gy

TH

HYPOTHYROIDISM

BENEDETTA FRANCHI, M.D., \* ALBERTO D'ONOFRIO, SC.D., \* VALERIA PIAZZI, M.SC., \* ELENA RONDI, M.Sc., \* MARIO CIOCCA, M.SC., \* BIANCA GIBELLI, M.D., <sup>||</sup> ENRICA GROSSO, M.D., <sup>||</sup> NICOLETTA TRADATI, M.D., <sup>||</sup> LUIGI MARIANI, M.D., PH.D., <sup>¶</sup> GENOVEVA IONELA BOBOC, M.D., \* AND ROBERTO ORECCHIA, M.D.\*<sup>†</sup>

Studies evaluting dose–volume relationship to thyroid injury are scattered and controversial. There seems to be a role for sex and **volume** of thyroid irradiated as risk factor fo hypothyroidism.

EMAMI 1991: if the entire thyroid volume is irradiated, the 5-year risk of clinical hypothyroidism is estimated to be 8% with 45 Gy; 13% with 60 Gy;

Head and

Alterio D et al Int. J. Radiat Oncol Biol. Phys., Vol. 67, No.1, pp.144-150, 2007

## HYPOTHYROIDISM AS A CONSEQUENCE OF INTENSITY-MODULATED RADIOTHERAPY WITH CONCURRENT TAXANE-BASED CHEMOTHERAPY FOR LOCALLY ADVANCED HEAD-AND-NECK CANCER

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Sixty-one of 128 evaluable patients (47.7%) developed hypothyroidism after a median of 1.08 years after IMRT (range, 2.4 months to 3.9 years), suggesting a **shorter latency** with IMRT when compared with a median of 1.4–1.8 years (range, 0.3–7.2 years) in two of the largest studies of patients treated with conventional radiotherapy.

Age and **volume** of irradiated thyroid were associated with hypothyroidism development after IMRT

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Compared with 3D-RT, **IMRT with no thyroid dose constraints** resulted in significantly **higher minimum, maximum, and median dose** (p < 0.0001) and percentage thyroid volume receiving 10, 20, and 60 Gy (p < 0.05).

Compared with 3D-RT, **IMRT with thyroid dose constraints** resulted in **lower median dose** and percentage thyroid volume receiving 30, 40, and 50 Gy (p < 0.005) **but higher minimum and maximum dose** (p < 0.005).



**Fig. 3**—35-year-old woman with supraglottic laryngeal squamous cell carcinoma and radiation-induced atrophy of thyroid gland.

**A**, Coronal reformation enhanced CT image shows irregular, necrotic left level 3 nodal mass (*arrow*) and normal contour and enhancement of thyroid gland (*asterisks*).

**B**, Coronal reformation enhanced CT image obtained 2 years after chemoradiation shows resolution of adenopathy but diffuse atrophy of thyroid gland (*asterisks*), which remains homogeneously enhancing. Patient had normal thyroid function test results.



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Our results suggest that the **development of hypothyroidism by IMRT is not a deterministic effect**, because we could not detect a specific dose of radiation or volume of thyroid irradiated after which hypothyroidism would irrevocably manifest.

Prospective studies should be conducted to test the **hypothesis that this is a stochastic effect**, in which decreasing the dose and/or volume of radiation to the thyroid would decrease the all-or-none probability of developing hypothyroidism.



## What is not contoured cannot be given a dose constraint and an appropriate hierarchical dose-goal rank.

ASTRO report 2011 on IMRT safety: the report touches up on elements of a "culture of safety" (mutual trust, defined roles and responsibilities, event tracking); technical considerations (training, IMRT system commissioning, QA program); and includes a list of recommendations to safeguard against catastrophic failures in IMRT.

The report suggests use of a "forced time out" to assure adequate time to perform reviews and quality assurance at key points in the process.