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Tossicità ed efficacia del trattamento radiante con tecnica VMAT e boost simultaneo integrato in pazienti affetti da tumore del distretto testa-collo localmente avanzato : risultati preliminari.

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BACKGROUND

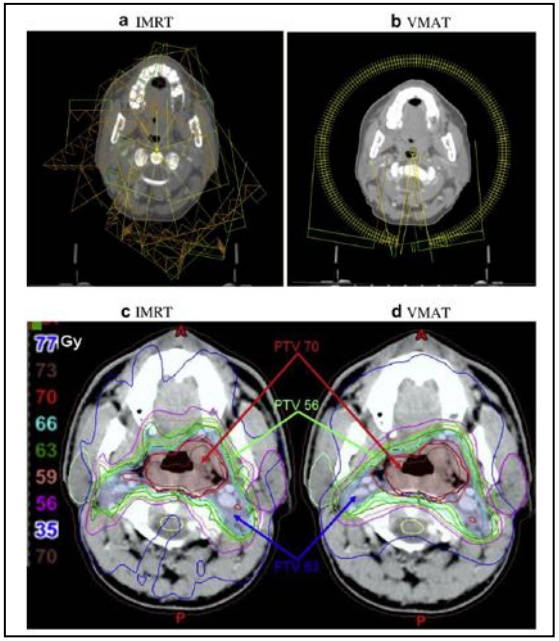
• The choice of the fractionation scheme in HNC patients is a delicate problem.

• The key point would be to shorten overall treatment time without increasing acute reactions.

• With the advances in linear accelerator technologies and the advent of intensity modulation, the treatment deliveries know today a significant improvement.

•An option available with the new technologies is the Simultaneous Integrated Boost (SIB) approach.

• Many dosimetric studies proved that volumetric modulated arc therapy (VMAT) could deliver very conformal treatments highly sparing most of the surrounding critical structures



In the current literature, very few reports about HNC patients treated with VMAT technology and SIB fractionation are published. Until now, only two studies explored the correlation between dosimetric data and acute toxicity, all with a few number of patients.

Scorsetti M, Fogliata A, Castiglioni S, et al. **Early clinical experience with volumetric modulated arc therapy in head and neck cancer patients**. *Radiat Oncol.* 2010; **5**:93.
Doornaert P, Verbakel WF, Bieker M, et al. **RapidArc planning and delivery in patients with locally advanced head-and-neck cancer undergoing chemoradiotherapy**. *Int J Radiat Oncol Biol Phys.* 2011; **79**:429-435.

Aim of the present study was to analyse the outcome data for a group of 102 patients presenting stage III and IV HNC and treated with VMAT based SIB with a common fractionation scheme. In detail, the study focused on the assessment of possible correlation between the planned dose distributions to the main dose limiting structures and the observed levels of toxicity like mucositis, xerostomia and dysphagia at both acute and late levels.

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PATIENT CHARACTERISTICS

Number of patients		102
Age [y.o.]	Median [range]	63 [31, 95]
Gender	Male	72 (71%)
	Female	30 (29%)
Tumour site	Larynx	11 (11%)
	Hypopharynx	13 (13%)
	Oral Cavity	4 (4%)
	Oropharynx	48 (47%)
	Nasopharynx	22 (22%)
	Nasal/paranasal sinus	4 (4%)
T stage	1	11 (11%)
	2	27 (26%)
	3	25 (25%)
	4	29 (28%)
	4a	9 (9%)
	4b	1 (%)
N stage	0	15 (15%)
	1	13 (13%)
	2	14 (14%)
	2a	4 (4%)
	2b	32 (31%)
	2c	18 (18%)
	3	5 (5%)
	3b	1 (1%)
TNM stage	Stage 3	20 (20%)
	Stage 4a	56 (55%)
	Stage 4b	26 (25%)
Induction Chemotherapy	No	47 (46%)
	TPF	47 (46%)
	CBCDA+5FU	2 (2%)
	CBCDA+adriamicin	1 (1%)
	CDDP+5FU	4 (4%)
	CDDP+adriamicin	1 (1%)
Concomitant Chemotherapy	No	9 (9%)
	Cetuximab	19 (19%)
	Weekly Cisplatinum	64 (63%)
	Three-weekly Cisplatinum	10 (10%)

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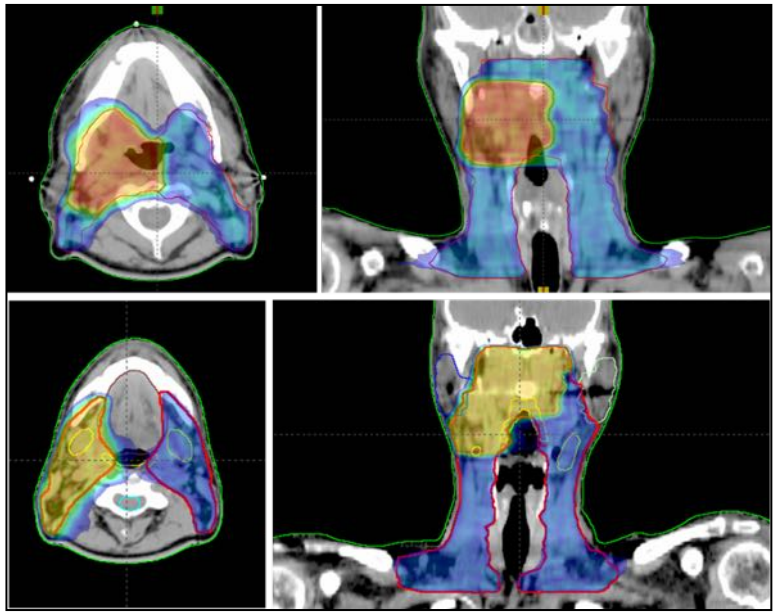
Overall dosimetric parameters (Mean±StandardDeviation

Structure	Parameter	All cases	Larynx Hypopharynx	Oropharynx Oral cavity	Nasopharynx
PTV_69.96Gy	Volume [cm^3]	263±147	233±168	273±141	273±131
	Mean [Gy]	69.96	69.96	69.96	69.96
	$D_{2\%}$ [Gy]	72.5±0.8	72.4±0.7	72.5±0.8	72.8±0.9
	$D_{98\%}$ [Gy]	65.3±1.3	65.7±1.0	65.3±1.4	65.2±1.0
	Std.Dev. [Gy]	1.7±0.4	1.6±0.3	1.7±0.4	1.9±0.5
PTV_54.45Gy*	Volume [cm^3]	442±198	459±195	413±181	477±222
	Mean [Gy]	56.2±2.0	56.2±1.6	56.3±2.1	56.2±2.1
	$D_{98\%}$ [Gy]	50.9±1.2	50.9±1.1	51.0±1.0	50.9±1.6
	Std.Dev. [Gy]	2.8±1.0	2.9±0.9	2.8±0.9	2.8±1.0
Spinal Cord	$D_{2\%}$ [Gy]	36.2±8.1	36.5±5.4	34.6±6.4	38.9±11.5
Brain Stem	$D_{2\%}$ [Gy]	34.3±15.9	27.4±12.9	29.1±14.6	47.7±11.3
Constrictor inf.	Mean [Gy]	48.6±13.8	66.6±4.9	44.3±9.4	39.5±10.6
Constrictor mid.	Mean [Gy]	59.2±11.0	67.5±5.1	58.8±9.5	52.4±12.3
Constrictor sup.	Mean [Gy]	62.9±8.8	57.0±9.1	66.1±4.5	62.4±11.1
Oral Cavity	Mean [Gy]	44.9±8.2	37.4±6.5	49.9±6.2	43.0±6.4
	V_{50Gy} [%]	40.5±18.7	23.7±12.5	52.6±15.5	34.6±12.8
Parotids	Mean [Gy]	26.0±7.2	22.5±3.8	27.4±8.0	26.6±7.0
Submandibulars	Mean [Gy]	61.1±10.0	59.2±8.0	63.2±8.1	59.3±13.3
Larynx	Mean [Gy]	38.7±9.0	51.6±13.6**	36.9±7.5	38.1±5.8
Eyes	Mean [Gy]		1.3±0.2	1.2±0.4	6.1±6.8
Thyroid	Mean [Gy]	43.9±8.2	47.4±9.4	43.0±7.8	42.5±6.7

* subtracting the PTV_69.96Gy volume
** only hypopharyngeal tumours

Treatment plans fulfilled the dosimetric criteria of target coverage and OAR sparing in almost all the cases.



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Toxicity profile

	Acute toxicity		Late toxicity	
	Grade	Nb. patients (%)	Grade	Nb. patients (%)
Mucosal Toxicity	0	15 (15%)	0	99 (97%)
	1	33 (32%)	1	2 (2%)
	2	43 (42%)	2	1 (1%)
	3	11 (11%)	3	-
Salivary Toxicity	0	74 (73%)	0	64 (63%)
	1	24 (23%)	1	19 (19%)
	2	4 (4%)	2	18 (18%)
	3	-	3	1 (1%)
Taste Toxicity	0	65 (64%)	0	82 (80%)
	1	29 (28%)	1	13 (13%)
	2	8 (8%)	2	7 (7%)
Swallowing Toxicity	0	49 (48%)	0	99 (97%)
	1	21 (20%)	1	2 (2%)
	2	26 (25%)	2	1 (1%)
	3	6 (6%)	3	-
Skin Toxicity	0	26 (25%)	0	102 (100%)
	1	39 (38%)	1	-
	2	33 (31%)	2	-
	3	4 (4%)	3	-

Acute mucosal and swallowing toxicities higher than grade 3 were reported by only 11% and 6% of the patients, respectively; late morbidities (G1 and G2, no G3) were present only in 3% of the cases. Conversely, late salivary toxicity profile was worse than acute toxicity, with 19% of persisting late grade equal or higher than 2.

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Dosimetric parameters (Mean ± Std. Error of Mean) stratified to the toxicity grading

MUCOSAL TOXICITY		G0	G1	G2	G3
Oral Cavity	V_{30Gy} [%] *	73.3±4.4	73.4±2.8	83.2±1.7	84.3±6.9
	V_{40Gy} [%] *	53.6±5.2	53.0±3.5	62.3±2.5	70.5±7.8
	V_{70Gy} [%] *	6.9±2.8	8.8±1.6	14.9±2.1	17.4±6.6
	Mean [Gy]	42.5±2.7	43.9±1.4	47.7±1.1	49.6±4.4
SALIVARY TOXICITY		G0	G1	G2	G3
Parotid Ipsilateral	Mean [Gy]	30.0±1.2	27.0±1.1	34.9±7.5	
Parotid Contralateral	Mean [Gy]	22.4±0.7	22.9±0.6	23.8±0.3	
Parotids	Mean [Gy]	25.9±0.7	25.1±0.7	29.4±3.7	
Submandibulary Right	Mean [Gy]	61.0±1.3	60.8±1.5	60.5±3.4	
Submandibulary Left	Mean [Gy]	60.9±1.3	62.2±1.2	60.8±3.7	
SWALLOWING TOXICITY		G0	G1	G2	G3
Inferior Constrictor	$D_{1/3V}$ [Gy] *	45.9±2.1	55.3±2.6	54.5±2.3	58.8±6.1
	$D_{1/2V}$ [Gy] *	43.0±2.1	53.6±2.8	52.0±2.4	56.9±6.4
	$D_{2/3V}$ [Gy] *	40.1±2.1	51.4±2.8	49.2±2.5	55.5±6.7
	V_{30Gy} [%]*	84.0±3.9	98.9±0.6	98.0±1.1	100.0±0.1
	V_{40Gy} [%]*	55.6±5.4	84.4±6.1	78.2±5.3	84.4±13.9
	V_{50Gy} [%]*	28.4±5.0	54.8±9.0	52.0±8.1	62.3±18.5
	Mean [Gy]*	43.4±2.0	53.5±2.6	51.9±2.3	57.5±6.1
Middle Constrictor	Mean [Gy]	56.8±1.8	59.9±1.9	62.5±1.5	63.1±3.9
Superior Constrictor	Mean [Gy]	62.4±1.5	62.7±1.5	63.6±1.6	60.6±3.1

* significant with $p<0.05$

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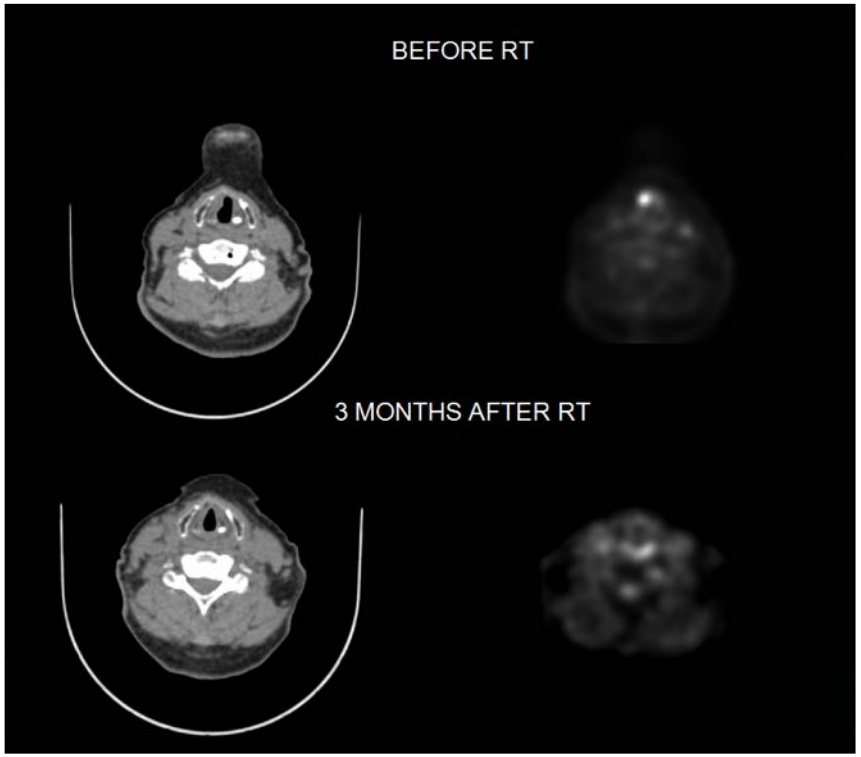
RESULTS



Sixty-seven patients had complete clinical and radiological response at the first post-treatment visit and imaging; of this group, three patients presented later a loco-regional relapse and are still alive at the moment of the analysis, and one patient died for appearance of distant metastases (lung). Fifteen cases presented a partial response to the treatment with persistence of disease in either primary or nodal sites.

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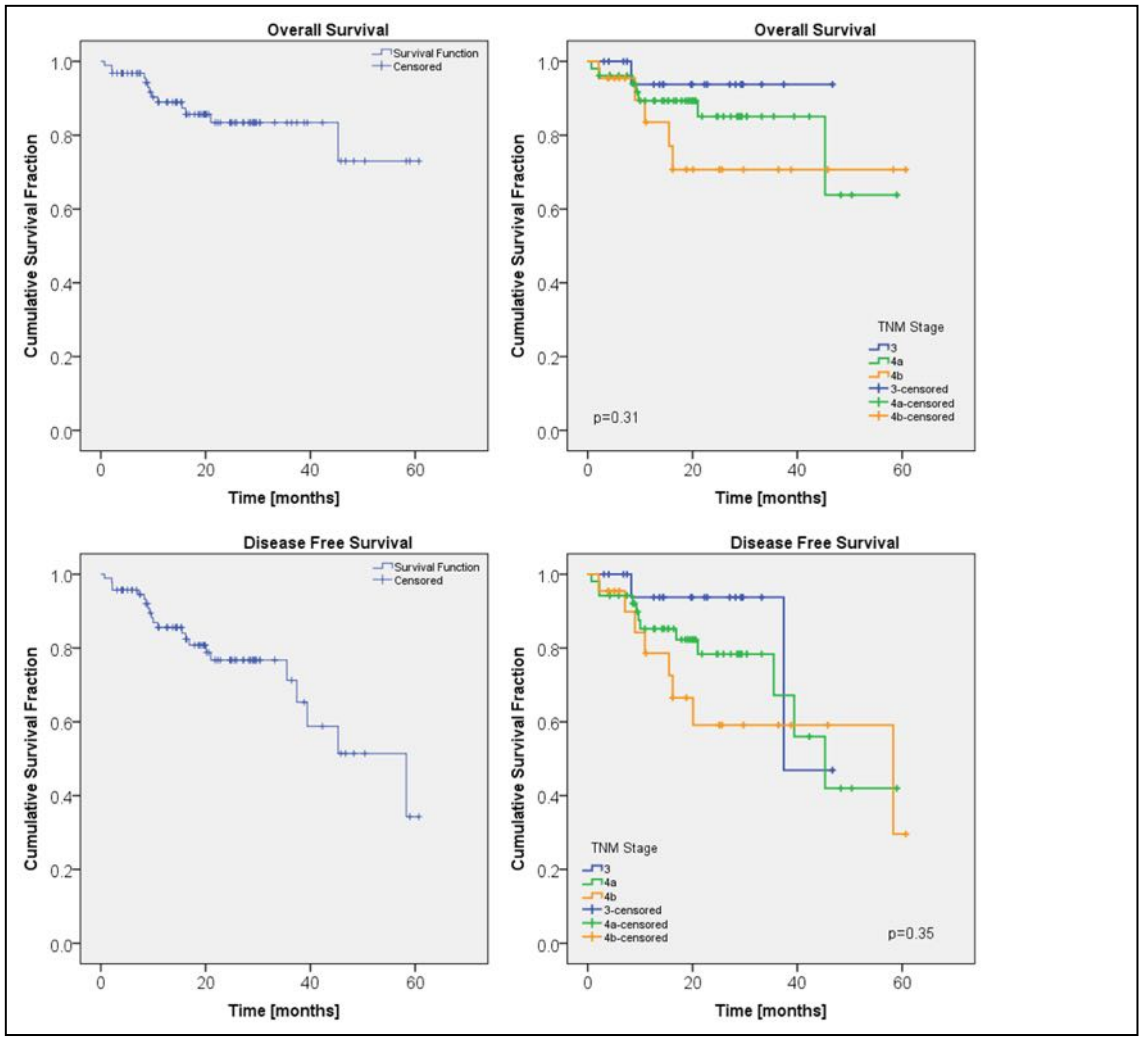
Kaplan-Meier for Overall and Disease Free Survivals



Overall Survival for the patient cohort are at 3 and 5 years: 83% ±4%, and 73%±10%.

Estimated mean Overall Survival is 51±3 months (46-56 months at 95% confidence level).

Disease Free survival at 2, 3, 4 and 5 years are: 77%±5%, 71%±7%, 51%±11% and 34%±16%, respectively.

Estimated mean Disease Free Survival is 43±3 months (38-49 months at 95% confidence level).

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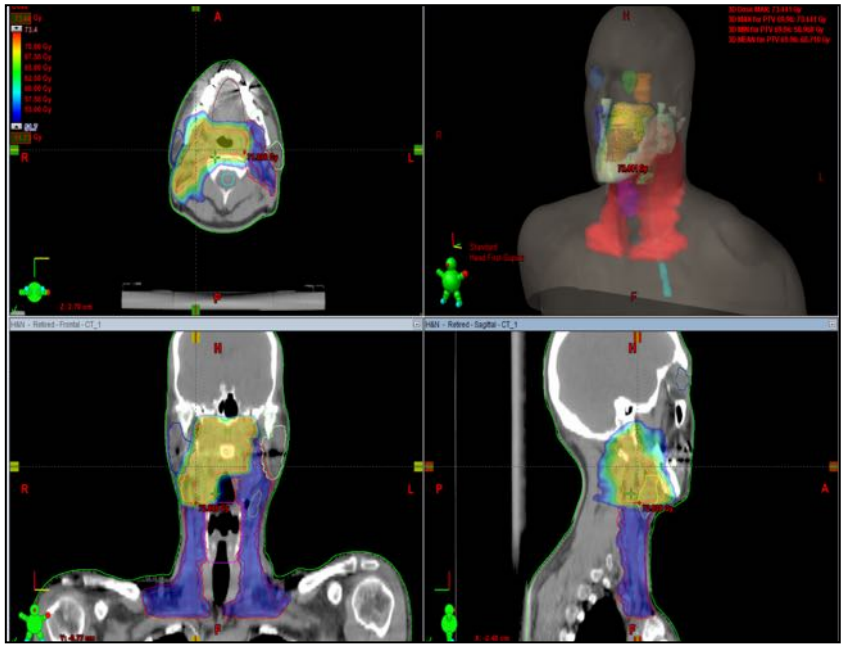
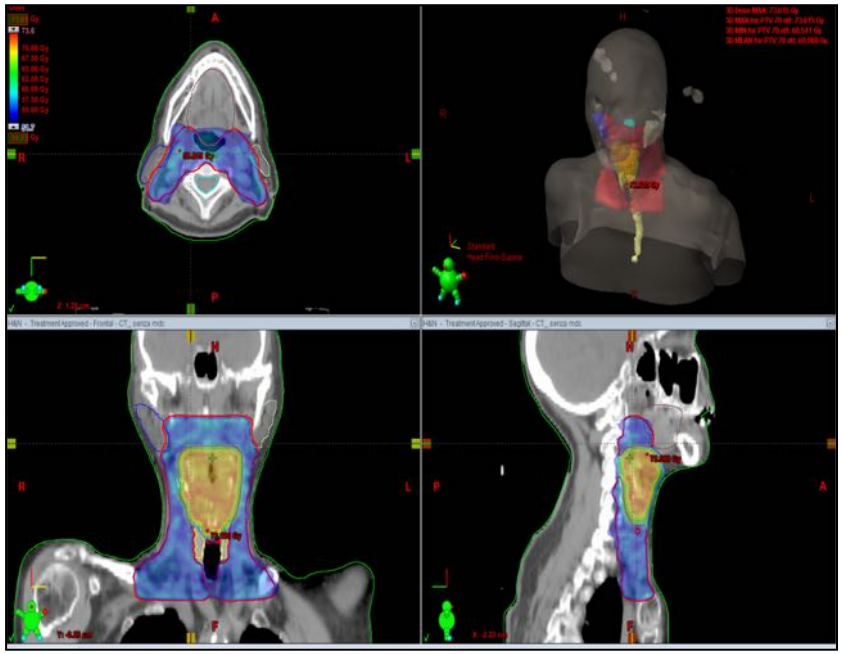
CONCLUSIONS

The use of RapidArc technology to improve the OAR sparing associated with a SIB of 1.65 and 2.12Gy/fraction in 33 fractions showed a good toxicity profile and an encouraging trend for overall survival and disease free survival for patients with advanced stage III-IV HNC.





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