CANCER EDUCATION DAY

Epidemiology & Risk Factors Locally Advanced HNSCC: Published Data from WRH

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Epidemiology & Risk Factors

- Global incidence: Around 890,000 new cases annually, the 7th most common cancer.
- Mortality: Approximately 450,000 deaths per year.
- Geographic Disparity: About 70% of cases and deaths occur in low- and middle-income countries.
- Trends: Incidence is rising globally, particularly in East Asia, while mortality rates are declining in some areas due to better management.

Epidemiology & Risk Factors

- In 2022, approximately 7500 Canadians were diagnosed with head and neck cancer, and 2100 Canadians died from this disease.

- In 2025, 8,100 people in Canada will be diagnosed and 2,200 will die from it.
- 5,800 men will be diagnosed with head and neck cancer and 1,600 will die from it.
- 2,300 women will be diagnosed with head and neck cancer and 620 will die from it.

Major Risk Factors

- Tobacco & Alcohol: Major drivers
- Poor Oral Hygiene & Diet
- Genetic Factors
- Human Papillomavirus (HPV): A significant cause of oropharyngeal cancers in developed countries, with higher prevalence in certain US demographics.

Epidemiology & Risk Factors

- The most common head and neck malignancy (up to 90%) is head and neck squamous cell carcinoma (HNSCC), which develops from the mucosal epithelium in the oral cavity, pharynx, and larynx.
- Some risk factors for HNSCC include tobacco and alcohol consumption, exposure to environmental pollutants, and infection with viral agents.
- Specifically, persistent infection with human papillomavirus (HPV) and Epstein-Barr virus (EBV) are known etiological risk factors for HNSCC arising from the oropharynx and nasopharynx, respectively.

Treatment of HNC

- Multidisciplinary!
- Multidisciplinary!
- Multidisciplinary!

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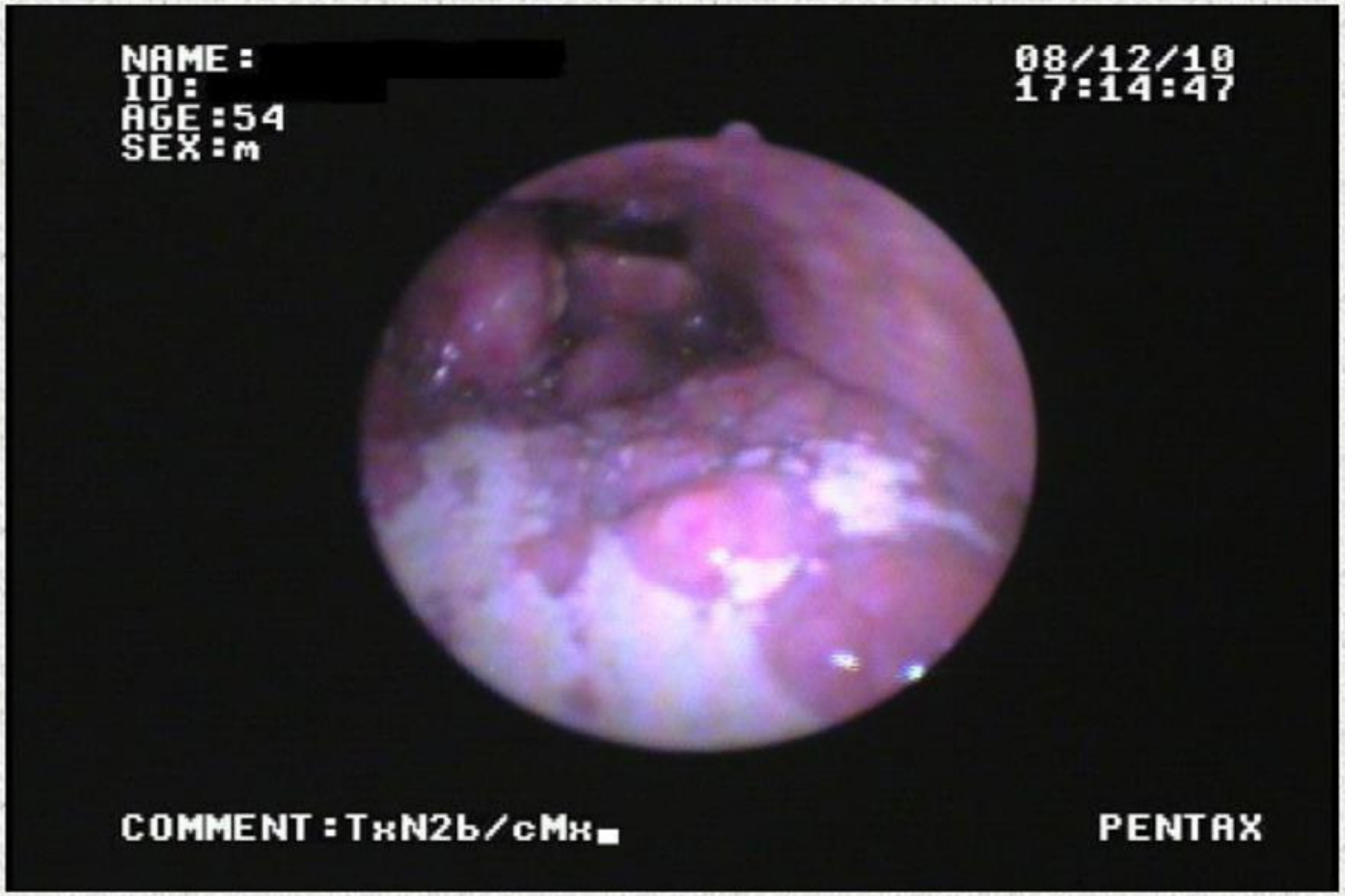

Figure 1: Scope image showing the primary lesion of T3N2c oropharyngeal SCC occupying vallecula in a 54 year old male smoker

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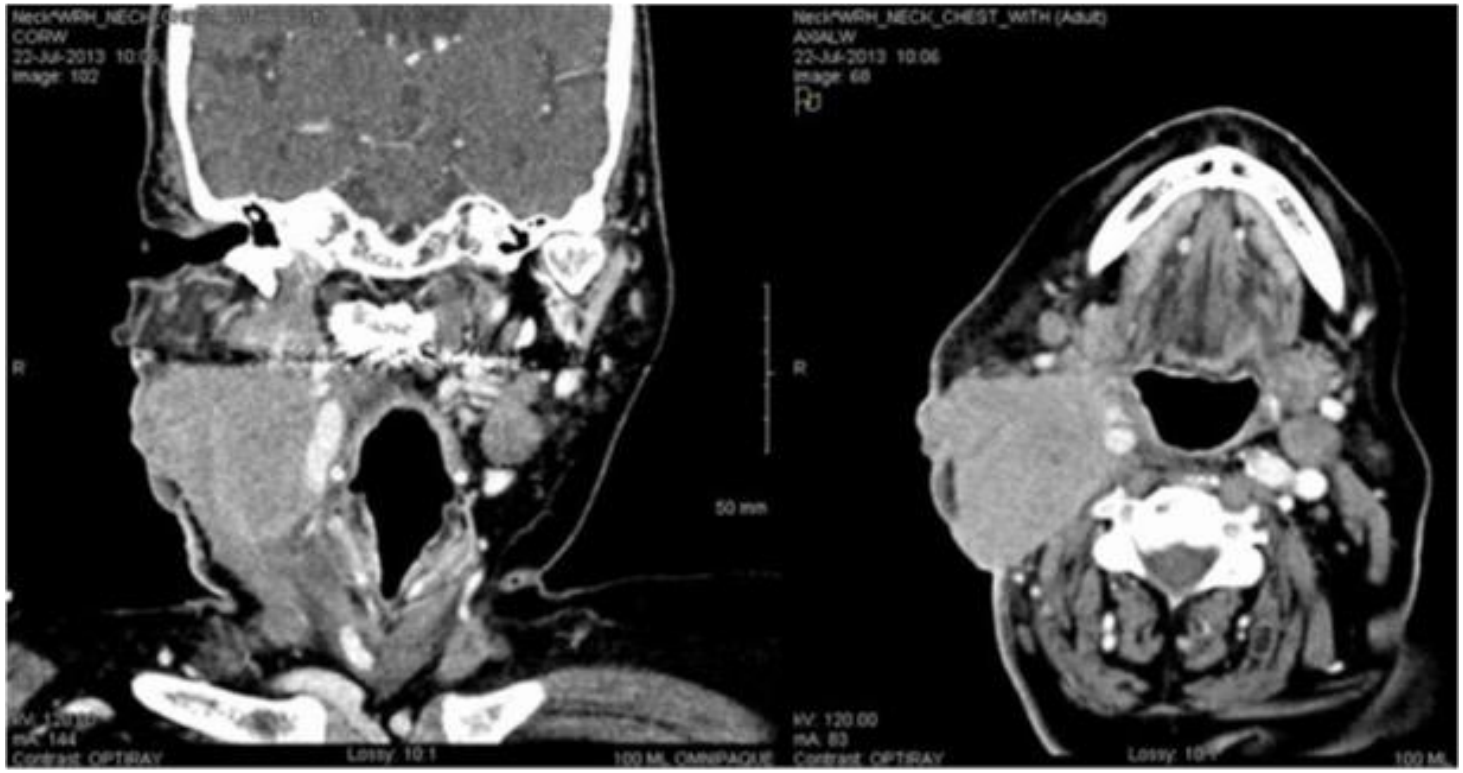
Nonsmoker 72-yr female T4N3 right tonsil SCC positive for p16 invading skin and the carotid artery



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Improvement in Radiation Treatment for HNC

- Radiation therapy for advanced HNC has shifted from three-dimensional conformal radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT).
- IMRT has reduced toxicities, specifically the sparing of the parotid gland, resulting in the decrease of xerostomia for patients treated with IMRT compared with 3D-CRT.
- Volumetric modulated arc therapy (VMAT) is a newer technique of IMRT that delivers radiation dose using a rotating gantry with varying speed and dose rate in contrast to conventional IMRT (cIMRT), which uses fixed gantry beams.
- Although several studies have demonstrated shorter planning and treatment time, improved dose homogeneity, and normal tissue sparing when comparing VMAT to cIMRT, few studies have explored its long-term clinical outcomes.

HNC in Windsor Ontario

- WRCC serves a population base of approximately 650,000.
- Higher smoking rates and alcohol consumption than the provincial average and the low HPV vaccination rates could ultimately be contributing factors to higher incidence and poorer prognosis of HNSCC in our region.
- We started cIMRT in 2009 and VMAT in 2012 as the standard radiation modality for the definitive treatment of locally advanced HNSCC.
- We published a study to review our experience with stage III, IVA, and IVB HNSCC treated with VMAT versus cIMRT by comparing outcomes and the toxicity of these two modalities over a decade.

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Methods

- A 10-year retrospective review of electronic medical records (EMR) included 296 patients with stage III, IVA, and IVB HNSCC (American Joint Committee on Cancer, 7th edition).
- Survival outcomes were compared between VMAT and cIMRT using Kaplan-Meier survival curves and adjusted for relevant demographic factors using Cox's proportional hazards model.
- Analysis was performed using R software (R Foundation, Vienna, Austria).

Study approval and patient selection

- This retrospective study received approval from the Windsor Regional Hospital's Research Ethics Board (REB) (WRH REB #21-396).
- We reviewed the electronic medical records (EMR) of patients presenting with head and neck malignancies over a decade.

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Patient selection

- Inclusion criteria encompassed 296 consecutive patients with locally advanced head and neck squamous cell carcinoma (HNSCC) - specifically stages III, IVA, and IVB, as classified per the American Joint Committee on Cancer, Seventh Edition (AJCC-7) guidelines.
- Lymphomas, thyroid cancers, melanoma & non-complicated cancers were excluded.

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Data collection

- Patients were typically treated with 70Gy over 33 to 35 fractions or 66Gy/33, vs post-operative adjuvant courses of 60Gy/30.
- Palliative treatments varied in dosage, primarily 30Gy/10 or 20Gy/5.
- The therapeutic modalities evolved during the study period, beginning with cIMRT in August 2009 and progressing to VMAT starting in 2012.
- For patients in the palliative care category, three-dimensional conformal radiation therapy (3D-CRT) was predominantly utilized.

Follow-up and outcome measures

- We documented recurrence patterns, distinguishing between locoregional and distant metastatic progression.
- Locoregional control (LC) was stringently defined to capture the absence of tumor reemergence within the initial tumor site or regional lymphatics.
- Overall survival (OS) was another critical endpoint, calculated from the date of treatment completion to ensure consistency with the clinical endpoint of radiation effectiveness.

Statistical analysis

- Subgroup analysis: palliative cases and early 3D-CRT treatments were excluded to focus on the comparative effectiveness of VMAT and cIMRT in a curative setting.
- A total of 264 patients, 198 treated with VMAT and 66 with cIMRT, were included in the model-based analysis.
- Survival analyses, incorporating Kaplan-Meier curves, provided unadjusted survival probabilities.

Statistical analysis

- Multivariate analysis using Cox's proportional hazards models enabled us to adjust for various demographic and clinical factors, potentially confounding the relationship between treatment modality and survival outcomes.
- All statistical computations were performed using the R statistical software (R Foundation, Vienna, Austria), ensuring rigorous and reproducible analysis.

Table 1: Baseline Patient Demographics & Clinical Characteristics

Age (years)	26-96	63 (median)
Sex	n	%
Male	237	80%
Female	59	20%
Smoking History	n	%
Smoker	114	39%
Non-smoker or Unknown History	182	61%
P16 Status Available	124	42%
P16 Positive	96	32%
Comorbidities	n	%
With at least 1 major comorbidities	229	77%
With at 2 or more major comorbidities	156	53%
Primary Tumor Site	n	%
Nasopharynx	3	1.00%
Oropharynx	153	51.70%
Hypopharynx	19	6.40%
Larynx	43	14.50%
Nasal Cavity & Sinuses	4	1.40%
Parotid	8	2.70%
Skin	3	1.00%
Primary Unknown	5	1.70%
Other	58	19.60%
Received EBRT	287	97%
50Gy or higher	264	89%
IMRT	66	22%
VMAT	198	67%
Underwent planned surgery (primary & neck dissection)	89	30%
2nd salvage surgery	17	6%
Received Chemotherapy	182	61%

Results

- 296 patients, median follow-up 42 months (6 - 107 m)
- Median age at diagnosis was 63 y (26-89 y)
- 237 (80%) patients were male
- 96 (32%) had a positive P16 histology
- 156 (53%) had at least two significant comorbidities
- Most common primary tumor sites were the oropharynx (51.7%), larynx (14.5%), and hypopharynx (6.4%).
- AJCC 7th edition: stage III (19.9%), IVA (74.4%), and IVB (5.6%).
- 97% received radiotherapy, 89% received 50Gy or higher, including 66 (22%) cIMRT and 198 (67%) VMAT
- 30% had surgery & 61% had systemic therapy (platinum-based chemo or cetuximab)

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Results

- Using Kaplan-Meier Curves, the LC and OS of the entire cohort were 79.5% and 56.7% at 5 y, respectively (Figure 1).
- Treatment modality only significantly impacted 5-year OS (VMAT 63.4% vs. cIMRT 43.8%, p=0.0023)
- No significant difference was shown in the 5-year LC (VMAT 81% vs. cIMRT 74.5%, p=0.17) (Figure 2).

Figure 1: Overall survival (A) and Local Regional Control (B)

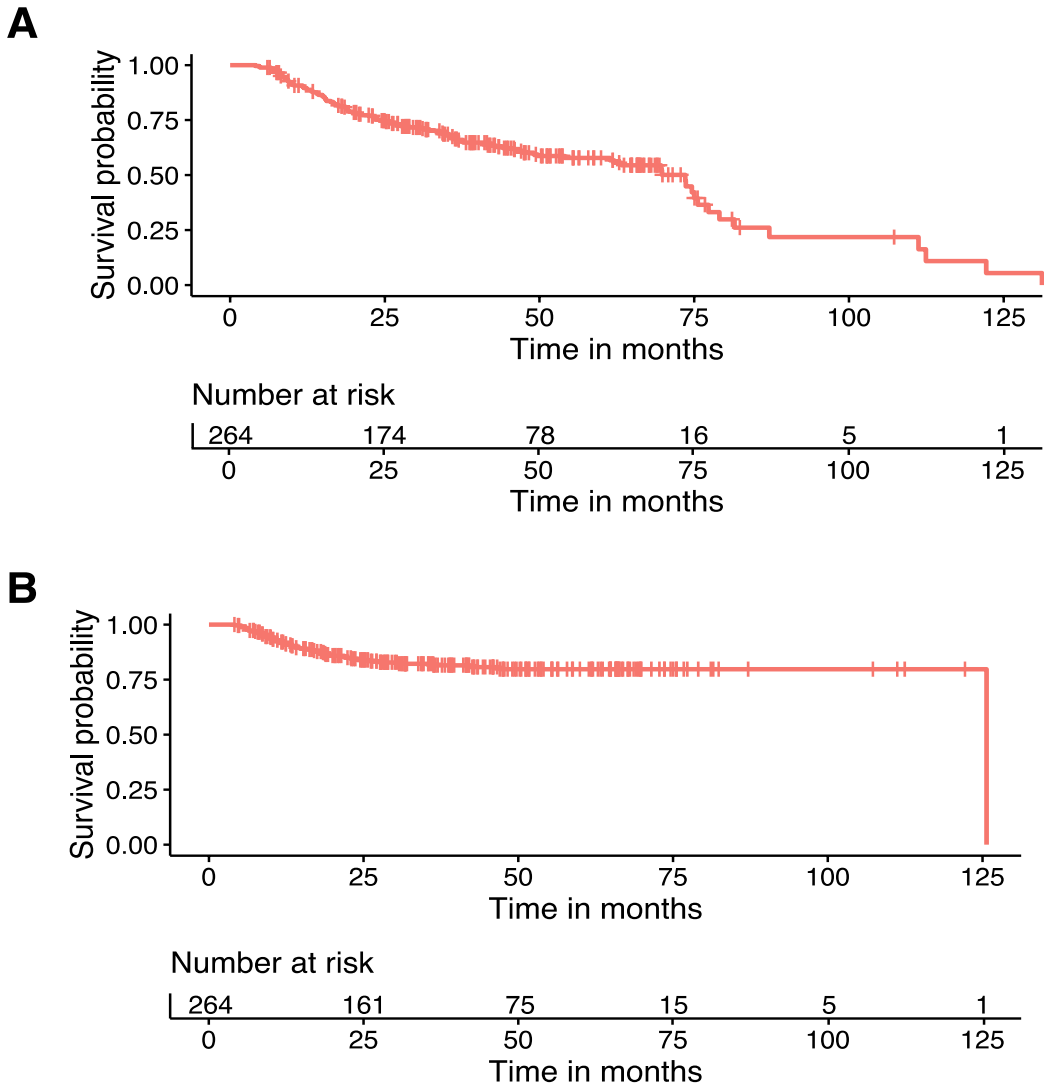

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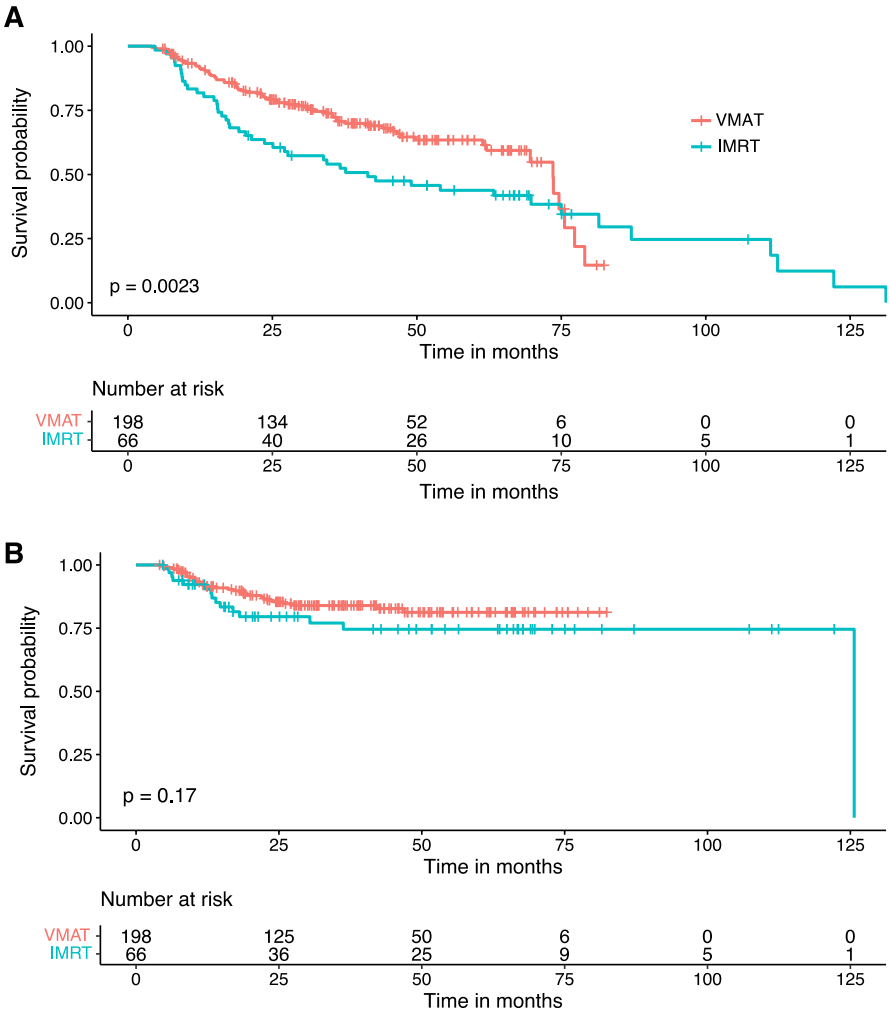
Figure 2: Overall survival (A) and Local Regional Control (B) Subdivided by treatment modality



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Results

- Cox's model showed VMAT, stage, and age at the time of diagnosis were the only factors that significantly impacted OS
- Hazard ratio (HR) 0.583 (95% CI 0.388-0.876, VMAT vs cIMRT)
- HR 0.38 (95% CI 0.155-0.933, stage III vs IVB)
- HR 1.526 for every 10-year increase in age (95% CI 1.269-1.836)
- Age was the only factor that significantly impacted LC, with HR 1.4 (95% CI 1.046-1.874) for every 10 years increase in age.

Toxicities

- There was no treatment-related death
- 22.5% of the patients had grade 3-4 acute toxicity (RTOG Acute Radiation Morbidity Scoring Criteria)
- No significant difference between VMAT and cIMRT subgroups in grade 3-4 acute toxicity and the eventual need for a feeding tube.

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Table 2: Analysis of baseline patient demographic data

Covariate	Statistics	Level	VMAT (N= 198)	IMRT (N= 66)	Parametric P-value*
Gender	N (Col %)	Male	162 (81.82)	55 (83.33)	0.781
	N (Col %)	Female	36 (18.18)	11 (16.67)	
Age at diagnosis	N		198	66	0.494
	Mean		63.08	62.02	
	Median		63	59.5	
Stage (AJCC 7)	N (Col %)	III	40 (20.3)	12 (18.18)	0.928
	N (Col %)	IVA	146 (74.11)	50 (75.76)	
	N (Col %)	IVB	11 (5.58)	4 (6.06)	
Sites	N (Col %)	Nasopharynx	3 (1.52)	0 (0)	0.185
	N (Col %)	Oropharynx	110 (55.56)	33 (50)	
	N (Col %)	Hypopharynx	8 (4.04)	8 (12.12)	
	N (Col %)	Larynx	30 (15.15)	8 (12.12)	
	N (Col %)	Nasal Cavity & Sinuses	2 (1.01)	1 (1.52)	
	N (Col %)	Parotid	7 (3.54)	0 (0)	
	N (Col %)	Skin	2 (1.01)	0 (0)	
	N (Col %)	Primary Unknown	4 (2.02)	1 (1.52)	
	N (Col %)	Other	32 (16.16)	15 (22.73)	
Smoking	N (Col %)	yes	60 (30.3)	40 (60.61)	**<.001**
	N (Col %)	no	138 (69.7)	26 (39.39)	
Comorbidities	N (Col %)	No comorbidities	47 (23.74)	17 (25.76)	0.136
	N (Col %)	Multiple	105 (53.03)	27 (40.91)	
Grade 3-4 toxicities	N (Col %)	yes	40 (20.73)	18 (27.69)	0.245
	N (Col %)	no	153 (79.27)	47 (72.31)	
Permanent Xerostomia	N (Col %)	yes	27 (15.7)	3 (4.62)	0.022
	N (Col %)	no	145 (84.3)	62 (95.38)	
Feeding tube	N (Col %)	yes	47 (24.23)	22 (33.85)	0.129
	N (Col %)	no	147 (75.77)	43 (66.15)	

Discussions

- Our study is one of the first to evaluate the outcome of VMAT versus cIMRT for treating locally advanced HNSCC (stage III-IVB) between 2009 and 2019.
- Several previous studies have reported on the role of cIMRT and VMAT for HNSCC.
- Few studies have focused on locally advanced HNSCC, which are associated with poorer outcomes.
- In our analysis, the 3-year LC and OS were 80% and 70%, and the 5-year LC and OS were 79.5% and 56.7%, respectively, which is consistent with the values reported in the literature for IMRT treatment of locally advanced HNSCC.

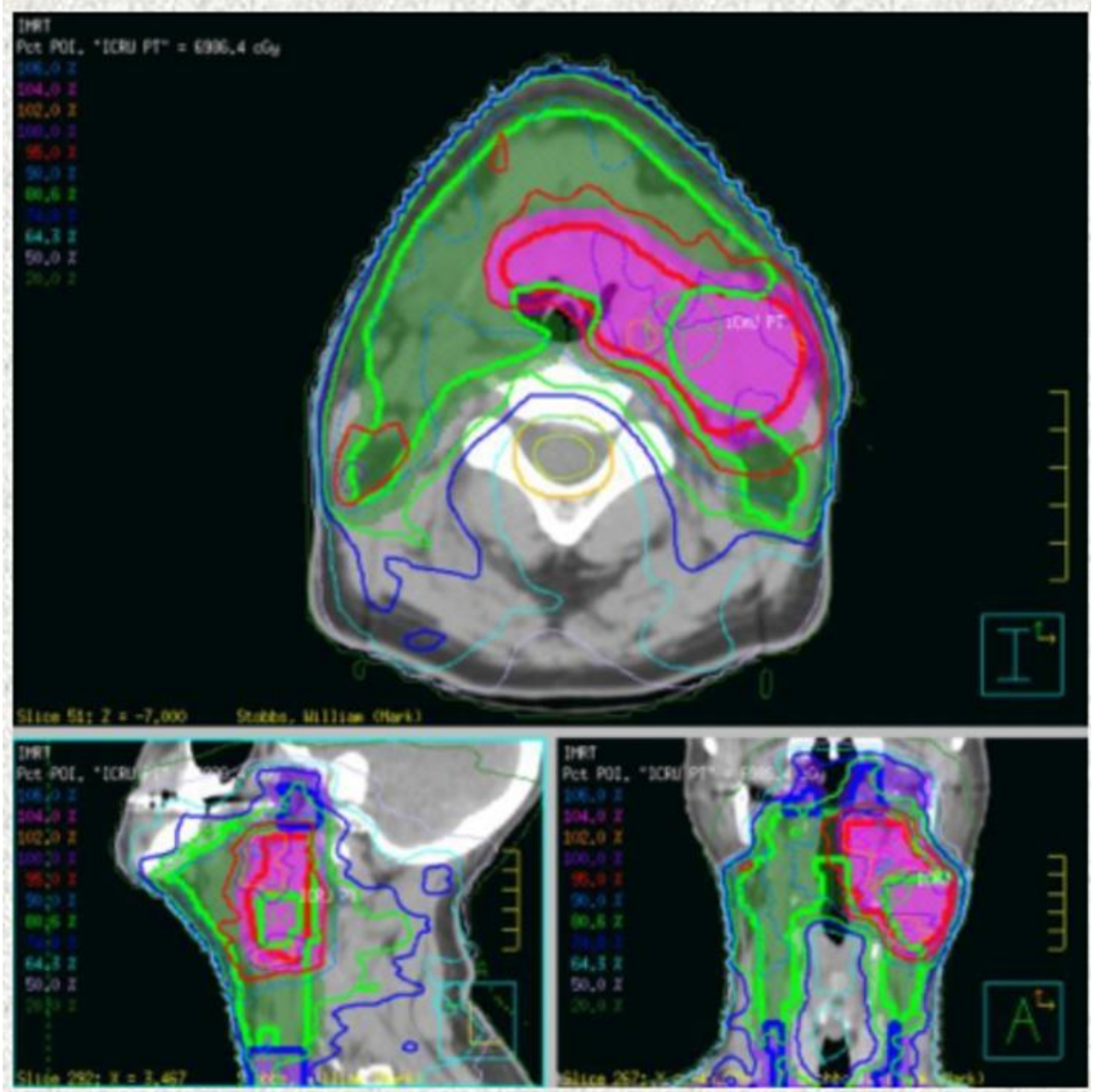

Figure 3: IMRT plan

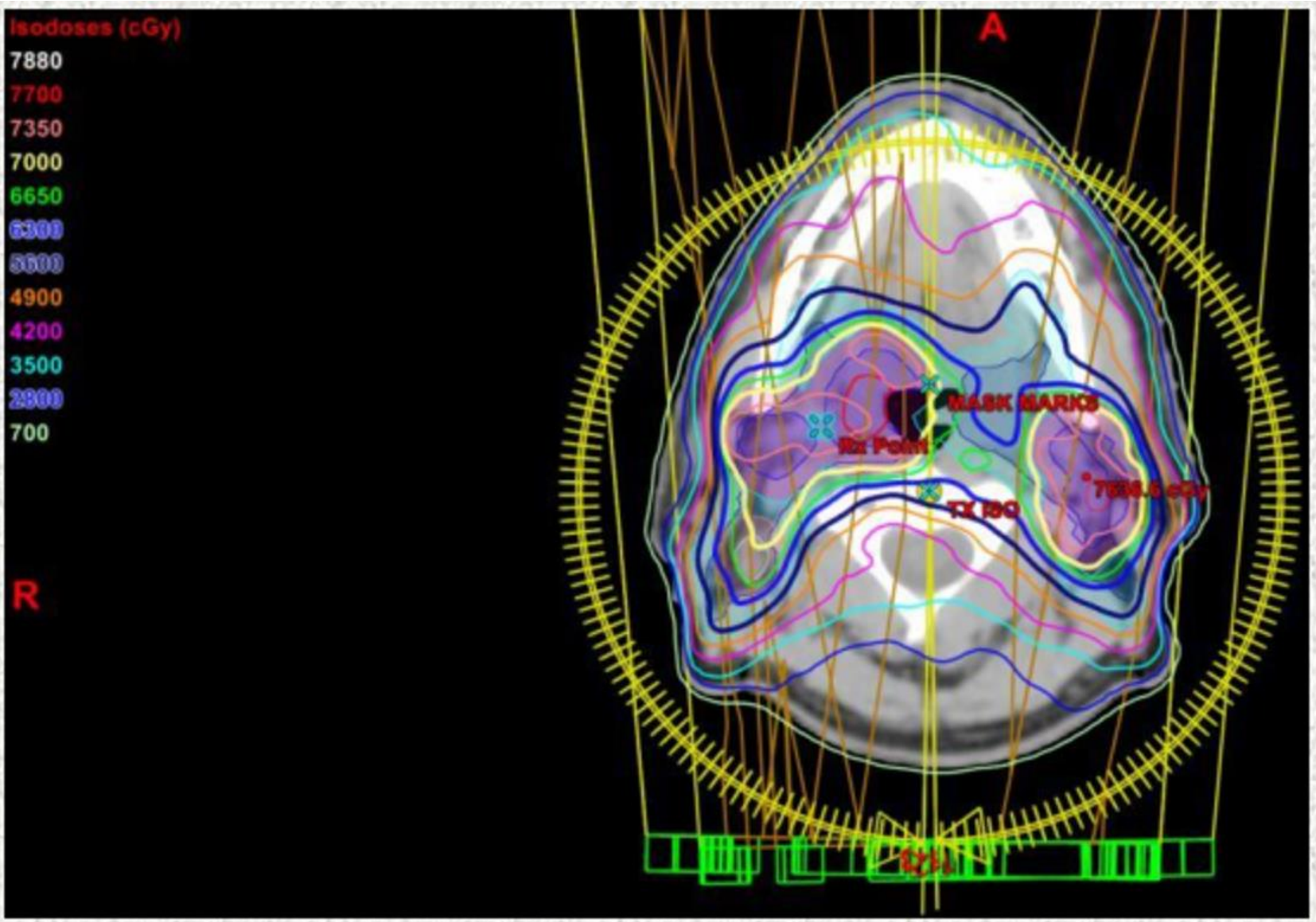

Figure 4: VMAT plan

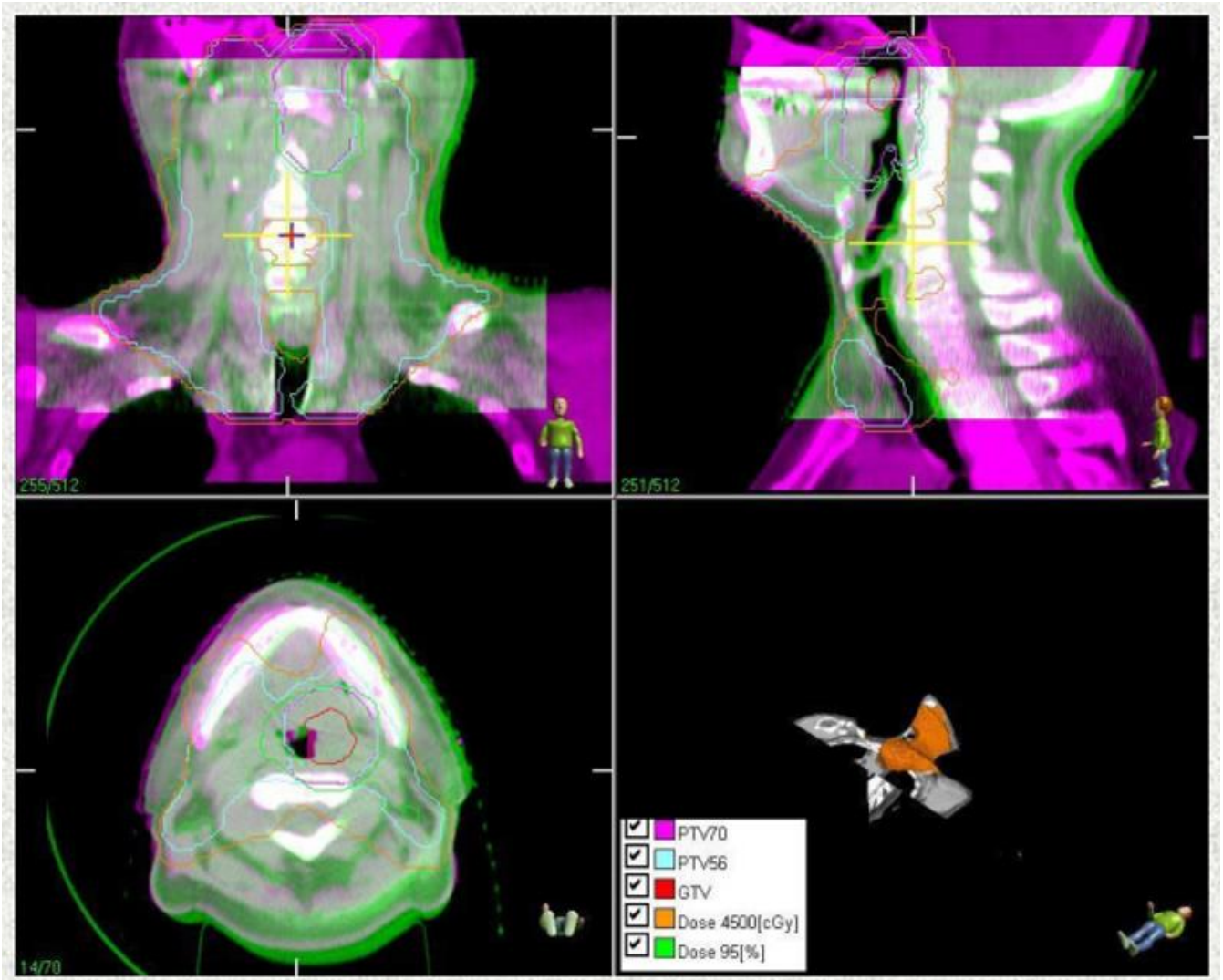

Figure 5: IGRT showing Day 1 CBCT in green with planning CT in purple

Conclusions

- Our study presents evidence of VMAT's efficacy over cIMRT in enhancing overall survival for patients with locally advanced HNSCC.
- The results suggest that VMAT may improve long-term survival outcomes.

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Conclusions

- The limitations of retrospective analyses, such as potential selection bias and evolving treatment protocols, were acknowledged.
- Nonetheless, the observed trend towards improved survival with VMAT supports its consideration in future clinical decision-making.
- However, larger randomized controlled trials and dosimetric studies are needed to confirm these findings.

References

- *Comparison of Volumetric Modulated Arc Therapy (VMAT) and Conventional Intensity-Modulated Radiotherapy (IMRT) for Locally Advanced Head and Neck Squamous Cell Carcinoma: A Retrospective Cohort Study*. Algouneh A, Schneider K, Huang K, Hussein A, Pan M. Cureus. 2024 May 24;16(5):e61022. doi: 10.7759/cureus.61022. PMID: 38910701; PMCID: PMC11194100.
- https://pmc.ncbi.nlm.nih.gov/articles/PMC11194100/

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Thank you!

Question & Answer