Management and Outcomes of Head and Neck Cancer of Unknown Primary: Our Institutional Experience

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Introduction

- Head and neck squamous cell carcinoma of unknown primary (HNSCCUP) remains a diagnostic and therapeutic challenge due to the inability to identify a primary tumor site for which to direct treatment.[1,2]
- The primary tumor is suspected to arise from mucosal sites within the oropharynx and often is identified following a comprehensive workup.[2]
- Less commonly, the primary site is never found.[2]
- The purpose of this study was to describe the management of HNSCCUP at our institution when the primary site was never identified, and to compare outcomes based on treatment modalities delivered.

Methods

- Patients who presented initially with cervical lymphadenopathy, confirmed to be biopsy-proven squamous cell carcinoma, and who failed to have a primary tumor site identified after comprehensive workup including:
  - Physical examination.
  - Nasopharyngolaryngoscopy.
  - Diagnostic imaging (CT, PET/CT).
  - Direct laryngoscopy or panendoscopy.
- All patients were treated with definitive surgery, radiation, and/or chemotherapy with curative intent.
- Patients were excluded if:
  - The primary tumor site was identified prior to completion of definitive therapy.
  - Patient had a history of prior or synchronous malignancies.

Table 1. Baseline patient characteristics and treatment modalities delivered.

Age (Mean ± SD)	60.8 ± 9.4
Male Gender, n (%)	26 (78.8%)
p16+, n (%)	23 (69.7%)
Surgical Management of Any Oropharyngeal Subsite, n (%)	21 (63.6%)
Ipsilateral Tonsillectomy Performed, n (%)	15 (45.5%)
Contralateral Tonsillectomy Performed, n (%)	8 (24.2%)
Ipsilateral Base of Tongue Resection Performed, n (%)	18 (54.5%)
Contralateral Base of Tongue Resection Performed, n (%)	5 (15.2%)
Neck Dissection Performed, n (%)	16 (48.5%)
Radiation Therapy, n (%)	27 (81.8%)
Ipsilateral Tonsil Radiation Dose (Gy)	60.6 ± 5.5
Contralateral Tonsil Radiation Dose (Gy)	56.3 ± 4.9
Ipsilateral Base of Tongue Radiation Dose (Gy)	56.9 ± 4.7
Contralateral Base of Tongue Radiation Dose (Gy)	56.3 ± 4.9
Ipsilateral Neck Radiation Dose (Gy)	66.4 ± 5.5
Contralateral Neck Radiation Dose (Gy)	59.2 ± 6.0
Average Number of Fractions Completed (Mean ± SD)	31.5 ± 2.2
Systemic Chemotherapy, n %)	18 (54.5%)
Average Number of Cycles Completed (Mean ± SD)	5.1 ± 1.3

References

1. Larsen MHH, Channir HI, von Buchwald C. Human Papillomavirus and Squamous Cell Carcinoma of Unknown Primary in the Head and Neck Region: A Comprehensive Review on Clinical Implications. *Viruses*. 2021;13(7):1297. Published 2021 Jul 2. doi:10.3390/v13071297
2. Moy J, Li R. Approach to the Patient with Unknown Primary Squamous Cell Carcinoma of the Head and Neck. *Curr Treat Options Oncol*. 2020;21(12):93. Published 2020 Oct 6. doi:10.1007/s11864-020-00791-3

Table 2. Treatment modalities delivered, radiation dose, and oncologic outcomes stratified by surgical interventions provided.

	+Ipsilateral Tonsillectomy (n = 15)	No Ipsilateral Tonsillectomy (n = 18)	Sig. (p-value)
Need for Radiation Therapy, n (%)	12 (80.0%)	15 (83.3%)	1.000
Ipsilateral Tonsil Dose (Gy)	57.4 ± 1.9	63.6 ± 6.0	0.015
Contralateral Tonsil Dose (Gy)	53.9 ± 1.9	58.8 ± 5.9	0.044
Ipsilateral Base of Tongue Dose (Gy)	55.1 ± 2.2	58.8 ± 5.9	0.128
Contralateral Base of Tongue Dose (Gy)	53.9 ± 1.9	58.8 ± 5.9	0.044
Ipsilateral Neck Dose (Gy)	63.3 ± 5.5	68.8 ± 4.3	0.014
Contralateral Neck Dose (Gy)	57.3 ± 5.4	60.6 ± 6.3	0.246
Need for Systemic Chemotherapy, n (%)	7 (46.7%)	11 (61.1%)	0.494
Overall Survival, n (%)	14 (93.3%)	16 (88.9%)	1.000
Disease-free Survival, n (%)	13 (86.7%)	11 (61.1%)	0.134
	+Ipsilateral Base of Tongue Resection (n = 18)	**No Ipsilateral Base of Tongue Resection (n = 15)**	**Sig. (p-value)**
Need for Radiation Therapy, n (%)	13 (72.2%)	14 (93.3%)	0.186
Ipsilateral Tonsil Dose (Gy)	58.3 ± 4.9	62.8 ± 5.3	0.089
Contralateral Tonsil Dose (Gy)	55.0 ± 1.4	57.6 ± 6.8	0.303
Ipsilateral Base of Tongue Dose (Gy)	55.0 ± 1.4	58.9 ± 6.1	0.101
Contralateral Base of Tongue Dose (Gy)	55.0 ± 1.4	57.6 ± 6.8	0.303
Ipsilateral Neck Dose (Gy)	65.1 ± 6.5	67.4 ± 4.6	0.334
Contralateral Neck Dose (Gy)	58.3 ± 6.0	59.8 ± 6.2	0.587
Need for Systemic Chemotherapy, n (%)	7 (38.9%)	11 (73.3%)	0.080
Overall Survival, n (%)	17 (94.4%)	13 (86.7%)	0.579
Disease-free Survival, n (%)	17 (94.4%)	8 (53.3%)	0.004
	+Neck Dissection (n = 16)	**No Neck Dissection (n = 17)**	**Sig. (p-value)**
Need for Radiation Therapy, n (%)	11 (68.8%)	16 (94.1%)	0.085
Ipsilateral Tonsil Dose (Gy)	59.0 ± 4.8	62.1 ± 5.9	0.255
Contralateral Tonsil Dose (Gy)	53.4 ± 1.5	58.6 ± 5.6	0.034
Ipsilateral Base of Tongue Dose (Gy)	54.9 ± 2.27	58.6 ± 5.6	0.122
Contralateral Base of Tongue Dose (Gy)	53.4 ± 1.5	58.6 ± 5.6	0.034
Ipsilateral Neck Dose (Gy)	62.0 ± 4.3	69.8 ± 3.6	<0.001
Contralateral Neck Dose (Gy)	55.6 ± 2.5	62.4 ± 6.4	0.009
Need for Systemic Chemotherapy, n (%)	5 (31.3%)	13 (76.5%)	0.015
Overall Survival, n (%)	15 (93.8%)	15 (88.2%)	1.000
Disease-free Survival, n (%)	13 (81.3%)	11 (64.7%)	0.438

Results

- There were 33 patients included in the series (Table 1).
- The oropharynx was addressed with surgery for 21 patients (63.6%). Twenty-seven patients (81.8%) underwent radiation therapy. 18 patients (54.5%) received systemic chemotherapy with cisplatin.
- Overall survival was 90.9%, and disease-free survival was 72.7%.
- Need for radiation and chemotherapy, radiation dose delivered, overall survival, and disease-free survival for patients stratified by ablative operation performed are shown in Figure 1.
- Radiation dose delivered to the ipsilateral tonsil (57.4 ± 1.9 Gy versus 63.6 ± 6.0 Gy, p = 0.015), contralateral tonsil (53.9 ± 1.9 Gy versus 58.8 ± 5.9 Gy, p = 0.044), and contralateral base of tongue (53.9 ± 1.9 Gy versus 58.8 ± 5.9 Gy, p = 0.044) was significantly reduced if ipsilateral tonsillectomy was performed.
- Ipsilateral tonsillectomy was not associated with any overall survival (93.3% versus 88.9%, p = 1.000) or disease-free survival (86.7% versus 61.1%, p = 0.134) benefit.
- Disease-free survival was significantly higher in patients who underwent ipsilateral base of tongue resection (94.4% versus 53.3%, p = 0.004), but overall survival did not differ significantly (94.4% versus 86.7%, p = 0.579)
- Neck dissection was not associated with any overall survival (93.8% versus 88.2%, p = 1.000) or disease-free survival (81.3% versus 64.7%, p = 0.438) benefit.

Results (continued)

- Patients were stratified by adjuvant therapy received: observation alone (15.2%), radiation therapy (30.3%) and chemoradiation (51.5%).
- All patients in the observation group underwent neck dissection (p = 0.015) and prophylactic ipsilateral tongue base resection (p = 0.032). There were no other significant differences between the observation only group and others.
- OS did not differ significantly (p = 0.722) between observation (100.0%), radiation (90.0%), or chemoradiation (94.1%) adjuvant therapy groups.
- Disease-free survival did not differ significantly (p = 0.366) between observation (100.0%), radiation (70.0%), or chemoradiation (70.6%) adjuvant therapy groups.
- There seven (21.2%) recurrences in this series. One local recurrence at the tongue base (3.0%), three regional (9.1%), and three distant recurrences (9.1%).
- Average time to recurrence was 16.2 ± 22.5 months (7.3 ± 4.3 months for locoregional recurrence, 25 ± 31.8 months for distant recurrence).
- The four patients with locoregional recurrence were treated with definitive intent, and all re-recurred within an average of 5.4 ± 3.4 months (range = 2.4-9.3 months).

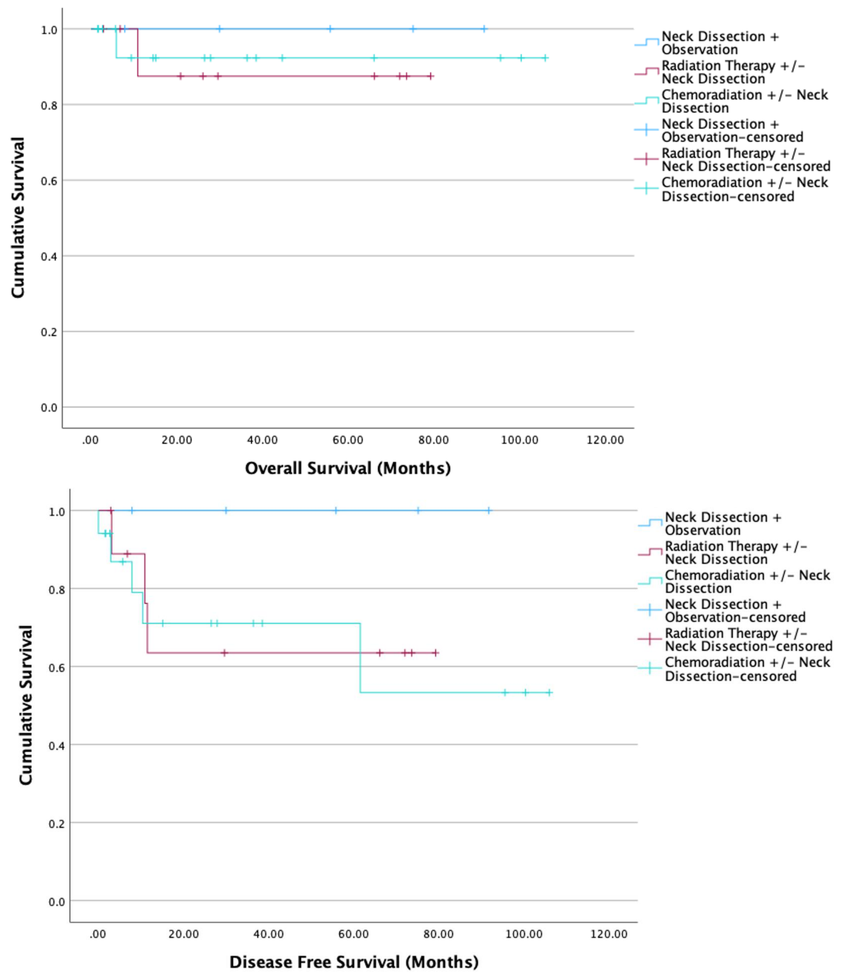

Figure 1. Kaplan Meier Survival Curves. Overall survival (top) and disease-free survival (bottom) for patients stratified by adjuvant therapy received.

Discussion

- Surgical intervention including resection of oropharyngeal subsites may be beneficial in HNSCCUP management even without prior confirmation of a primary tumor site, as these sites may harbor occult malignancy.
- Base of tongue resection was associated with improved disease-free survival.
- Neck dissection was associated with a reduction in radiation dose delivered and obviated the need for systemic chemotherapy unless extranodal extension was identified.
- The rate of local recurrence was 3.0% despite having not identified any primary tumor site.
- Overall survival and disease-free survival were 100% in patients who did not undergo any adjuvant therapy after surgery, despite lack of confirmation of primary tumor resection.