Initial Experience with Oropharynx-targeted Radiation Therapy for Metastatic Squamous Cell Carcinoma of Unknown Primary of the Head and Neck

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Abstract. *Aim: Metastasis of unknown primary (MUP) is commonly treated with radiation therapy (RT) to the entire mucosal surfaces and bilateral neck nodes (LN). We report outcomes of oropharynx-targeted RT, retropharyngeal nodes (RPN) and bilateral LN in this context. Patients and Methods: Single-Institution retrospective study of 68 patients. Forty percent were treated with intensity-modulated radiation therapy (IMRT). Fifty-six percent received concurrent chemo-radiotherapy (CCRT). The median age was 58 years, 82% were Caucasian, and 75% males. Stage III disease was present in 9%, stage IVA in 75% and IVB in 16%. Results: At a median follow-up of 3.5 years, the actuarial locoregional control was 95.5%. The emergence of primary developed in 1patient (1.5%) and 2patients (3%) failed in the neck. The median time-to-locoregional failure (LRF) was 18 months. Actuarial long-term RT toxicity was grade 1 xerostomia (68%), dysphagia (35%), neck stiffness (15%) and trismus (6%). Conclusion: RT to the oropharynx, RPN, and bilateral neck provides excellent oncological and functional outcomes in MUP in non-Asian patients. Sparing the mucosal surfaces of the nasopharynx, hypopharynx, and larynx seems reasonable without impacting on survival and locoregional control.*

Presented at the Multidisciplinary Head and Neck Cancer Symposium, sponsored by AHNS, ASCO, ASTRO and SNM. January 2012. Phoenix, AZ, USA.

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Key Words: Metastatic unknown primary cancer squamous cell carcinoma, oropharynx-targeted radiation therapy concurrent chemoradiotherapy.

Metastatic squamous cell carcinoma of unknown primary (MUP) represents approximately 1-5% of all head and neck malignancies (1, 2). The use of advanced diagnostic tools, such as positron emission tomography (PET), has led to an increase in detection of primary tumor site of head and neck cancer (3). While such types of cancer with known primary site have an established treatment guideline, management of MUP continues to pose a dilemma in the planning of therapeutic strategy. Radiation therapy (RT) constitutes an important component in the management of this disease, where RT fields would typically cover bilateral neck nodes and all putative sites of cancer origin, including the nasopharynx, oropharynx, hypopharynx and larynx (4). However, data addressing the efficacy of elective irradiation of these potential primary mucosal sites remains controversial. For example, no statistically significant difference was found between targeted *vs*. comprehensive RT encompassing the bilateral neck and mucosal surfaces in primary emergence, for relapse-free or overall survival (5), suggesting that the comprehensive RT approach adds significant toxicity without a clear advantage over targeted RT. On the other hand, decreased rates of failure with a more comprehensive RT field continue to be reported (2, 6-8), rendering the management of MUP a therapeutic challenge for the clinician in balancing the efficacy of treatment and potential toxicities. The objective of our study was to report our single-Institution experience in long-term outcomes of patients with MUP treated with conservative mucosal-sparing RT targeted only to the oropharynx and bilateral neck.

Patients and Methods

Patient population and eligibility. This study represents a single-Institution retrospective investigation and was fully-approved by our Institutional Review Board. Between January 1998 and December 2010, 68 patients who had pathologically-proven squamous cell carcinoma (SCC) of MUP in the head and neck were treated. In

Table I. *Treatment modality, pattern of failure and toxicities. Treatment modality and pattern of failure based on AJCC 6th edition staging.*

AJCC 6th edition Stage	Patients		Treatment modality				Outcome	Pattern of failure #			Toxicity (grade) #	
	#	%	RT+ND	CCRT+ND	CCRT	RT	NED	LF	RF	DM	≤2	>2
III	6	9	04	00	00	02	5	1	0	0	2	1*
IVA	51	75	02	17	10	22	51	0	0	0	35	0
IVB	11	16	00	11	00	00	09	0	2	0	9	0
Total (%)	68	100	06	28	10	24	65	1	2	0	46	1
			9%	41%	15%	35%	95.5%	1.5%	3%	0%	68%	1.5%

Number (#), percentage (%), radiotherapy (RT), neck dissection surgery (ND), concurrent chemoradiation therapy (CCRT), no evidence of disease (NED), local failure (LF), regional failure (RF), and distant metastases (DM), unilateral neck dissection (ND). Grade 1 toxicities included: xerostomia, 24 pts (35%) with dysphagia, 19 patients (28%) with altered taste, 10 patients (15%) with neck stiffness, 8 patients (12%) with skin toxicity, 6 patients (9%) with dysphonia and 4 patients (6%) with trismus; grade 4 toxicity is dysphagia.*Patient with HIV.

general, all patients underwent bilateral tonsillectomy and targeted biopsies under anesthesia. All patients received RT *via* intensity modulated radiation therapy (IMRT) 40% and three dimensional conformal radiation therapy (3DcRT) 60%.

Treatment. All patients were treated with curative intent using a continuous course of once-daily RT with 1.8-2 Gy per fraction to a total dose of 70 Gy (median=70 Gy; range=54-70 Gy). Definitive RT of 70, 63 (green isodose line), 60 (green isodose line), and 54 (blue isodose line) Gy was given to gross disease, high risk ipsilateral involved neck, oropharynx, and low risk neck (uninvolved neck, lateral retropharyngeal nodes and bilateral low neck), respectively (Figure 1A-C). Those patients with more advanced disease and with lymph nodes that demonstrated partial response [*e.g.* bulky N2 (4-6 cm in size) and or N3] were planned to undergo neck dissection 2-3 months after completion of RT. Fifty-six percent of the patients underwent concurrent chemoradiotherapy (CCRT) with cisplatin (90%), carboplatin (5%), or cetuximab (5%). Carboplatin or cetuximab were prescribed as a replacement for cisplatin in patients with poor performance status or renal impairment. All patients who were treated with single-modality definitive RT had low-nodal involvement (*e.g.* N1 and or non-bulky N2; 3-4 cm in size).

Follow-up. Each patient had follow-up appointments every three months during the first year, four months in the second year, and every six months in years 3-5, then annually after five years. Each follow-up included a complete history and comprehensive physical examination, as well as a direct and indirect laryngoscope examination. No patients were lost to follow-up. Fluorodeoxyglucose (FDG) PET or computed tomography (CT) scan was performed three months after completion of RT and every six months afterwards during the first three years, then once yearly. Thyroid-stimulating hormone (TSH) level was considered for all patients. Dental prophylaxis, rehabilitation and speech/swallowing evaluations were performed as needed. Complications were defined as per Radiation Therapy Oncology Group (RTOG) toxicity scale (23). Patients who were unable to swallow to the extent that a percutaneous endoscopic gastrostomy tube (PEG) was necessary were coded as having grade 3 toxicity, while permanent PEG tube dependency was coded as grade 4 toxicity.

Statistics. The actuarial rates of local control (LC), regional control (RC), locoregional control (LRC), distant control (DC), distant metastasis (DM), overall survival (OS) and distant metastasis-free survival (DMFS) were calculated. Disease in patients who were successfully treated with salvage therapy after a local or regional recurrence was considered as controlled in the analysis of LRC. Salvage treatment was considered to be successful if the patient survived after the procedure and remained disease-free at least two years at that particular site.

Results

In the whole cohort, 55 (82%) patients were Caucasians, 10% Hispanic and 8% African American. Seventy-five percent (n=51) of the patients were male. The median age was 58 years (range=21-87 years). Definitive RT was the preferred treatment for all groups of patients with MUP treated at our institution during the time of this study; therefore, all 68 (100%) patients received RT. For all the groups, RT was in the form of 3DcRT (60%) or IMRT (40%); 38 (56%) patients received CCRT.

Treatment was administered as follows: Stage III: of the 6 patients, 2 received definitive RT and 4 underwent RT with surgery. Surgery was in the form of initial diagnostic excision biopsy of the solitary LN. For stage IVA: out of the 51 patients, 22 patients underwent definitive RT alone, 2 underwent RT with surgery, 10 underwent CCRT and 17 underwent CCRT with surgery. For stage IVB, all 11 patients underwent CCRT followed by surgery as part of their treatment (Table I). The surgical procedure for stage IV disease was in the form of planned ipsilateral neck dissection in all patients; 10 of these patients had bulky N2 and 11 patients had N3 neck disease.

Disease control. After a median follow-up of 42 months (range=2-163 months), the actuarial 3-year rate of LC for the whole cohort was 98.5%; one patient with a significant smoking history developed a sub-glottic SCC two-year after

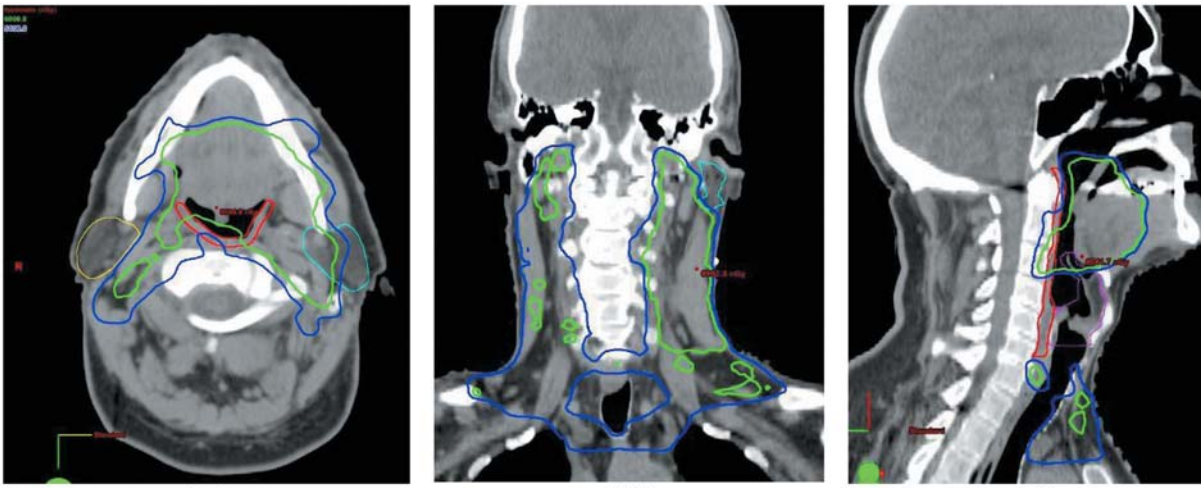

Figure 1. *A, B and C: Axial, coronal , and sagittal CT views, respectively of the oropharynx targeted by radiotherapy. The 60 Gy (green isodose line), and 54 Gy (blue isodose line) were prescribed to high risk ipsilateral involved neck, oropharynx, and low risk neck (uninvolved neck, lateral retropharyngeal nodes and bilateral low neck), respectively.*

RT. The actuarial 3-year rate of RC was 95.5%. Two patients who had level II/III nodal status of N3 (stage IVB) were initially planned to undergo CCRT followed by surgery in cases of persistent mass in the neck. After completion of therapy, during the annual follow-up PET/CT scan (1 and 5 years post-RT for each patient), it was found that these patients developed regional failure within the same neck levels (level II/III) as the initial lymph node. The 3-year rate of LRC after salvage surgery was 100% despite the aforementioned local and regional failures, since all three failures were successfully salvaged with surgery. All of these local and regional failures were observed within the first 6 years of treatment, with a median time of 24 months (range=12-63 months). No patient developed distant metastases (DM), making the actuarial 3-year OS and DMFS both 100%. All patients who were treated with single-modality definitive RT had low-nodal involvement (*e.g.* N1 and or non-bulky N2 disease; 3-4 cm in size).

Treatment-related toxicity. Late grade 1 toxicities included: 46 patients (67%) with xerostomia, 24 (35%) with dysphagia, 19 (28%) with altered taste, 10 (15%) with neck stiffness, eight (12%) with skin toxicity, six (9%) with dysphonia and four (6%) with trismus. Severe late complication (grade 3 or higher) was found in one patient with HIV (1.5%) with grade 4 dysphagia (*i.e.* PEG tube-dependent).

Discussion

With conflicting data and recommendations surrounding the extent of radiation volume necessary for the treatment of patients with MUP, examination of therapeutic options that balance the efficacy of treatment with potential toxicities is critical. Traditionally, MUP has been managed by comprehensive RT fields that covered bilateral neck nodes and mucosal sites of putative origin (4). In recent years, modified mucosal volume coverage RT that only covers the nasopharynx and oropharynx has been applied based on the premise that primaries of the hypopharynx and larynx are rare (9). In a retrospective study, Barker *et al*. reviewed treatment results from 17 patients who underwent larynx-sparing RT with and without neck dissection (10). Analysis from this study revealed the 5-year cause-specific rate was 88% and OS rate was 82%, where no patient developed SCC in the mucosal site or distant metastasis after RT. Good LRC was also reported, where only one patient (6%) experienced persistent nodal disease and another patient (6%) had recurrent nodal disease one year after completing RT. The authors concluded that LRC and survival of patients undergoing larynx-sparing RT was comparable to that of comprehensive RT, with the benefit of reduced irradiation and toxicities of the spared mucosal sites.

Combined modality radiation therapy has been shown to yield outcomes superior to RT-alone in head and neck cancer (11-14). While these studies specifically excluded patients with MUP, the positive outcome of these studies led to the wide use of CCRT for the treatment of MUP, which turned out to have an excellent locoregional control and survival (15, 16). Recently, Chen *et al*. examined whether the addition of concurrent chemotherapy to RT influences outcome and found that CCRT is associated with significant toxicity without a clear advantage for OS, LRC and PFS in the treatment of MUP (17). Since radiation

Table II. *Comparison of recent studies of metastases of unknown primary treatment modality, pattern of failure and toxicities.*

Study	Frank *et al*. 2010 (17)	Chen *et al*. 2011 (16)		Klem *et al*. 2008 (18)	Mourad *et al*. 2013
Patients (n)	52	60		60	68
Mean age, years (range)	56 (range not reported)	60 (31-78)		57 (39-80)	58 (21-87)
Gender (% male)	89%	89%		81%	75%
Nodal stage (%)	Nx: 16%				
	N1: 10%	N1: 14%	N1: 3%	N1: 43%	N1: 9 %
	N2a:19%	N2a:46%	N2a:41%	N2a:0%	N2a:24%
	N2b: 35%	N2b: 29%	N2b: 38%	N2b: 38%	N2b: 41 %
	N2c: 12%	N2c:0%	N2c: 0%	N2c :5%	N2c: 10%
	N3: 8%	N3: 11%	N3: 19%	N3: 14%	N3: 16 %
Treatment modality (%)	RT: 100% IMRT	RT - 100% (58% IMRT)		RT - 100% IMRT	RT - 100% (40% IMRT)
	CCRT: 27% (cisplatin)	CCRT: 53% (cisplatin)		CCRT: 67% (cisplatin[b])	CCRT: 56% (cisplatin[c])
	ND: 26%	ND: 60%	ND: 62%	ND:50%	
RT target volume: Neck and mucosal sites	Dependent on nodal involvement[a]	Bilateral (100%)		Bilateral (100%)	Bilateral (100%)
	Nasopharynx (100%)	Nasopharynx (100%)		Nasopharynx (90%)	Nasopharynx (0%)
	Larynx and hypopharynx (67%)	Oropharynx (100%)		Oropharynx (100%)	Oropharynx (100%)
	-omitted in non-smoker or patients with level II cystic nodule)	Larynx (100%)		Larynx (100%)	Larynx (0%)
		Hypopharynx (100%)		Hypopharynx (100%)	Hypopharynx (0%)
Median Fup (months)	44 (Range not reported)	30 (32 for RT and 28 for CCRT)		20 (5-21)	42 (2-163)
Outcome	All	RT	CCRT	All	All
OS	81% 5 years	90% 2 years	89% 2 years	85% 2 years	100% 3 years
LRC	94% 5 years	92% 2 years	89% 2 years	90% 2 years	96% 3 years
DM	8.3% 5 years	14% 2 years	18% 2 years	10% 2 years	0% 3 years
Complications of treatment (Late toxic events)	Grade 1: 12% (xerostomia)	RT	CCRT	Grade 1: 24% (neuropathy)	Grade 1: 67% (xerostomia);
	Grade 2: 8% (hypothyroidism and xerostomia)			Grade 1: 5% (Tinnitis)	35% (dysphagia),
		Grade≥3 dysphagia 11%	Grade3+ dysphagia 41%	Grade 1 &2: 19% & 5% (hearing loss)	28% (altered taste);
	Grade 3: 4% (esophageal stricture)	Grade≥3 esophageal stricture 7%	Grade3+ esophageal stricture 34%	Grade 3:14% (esophageal stricture)	15% (neck stiffness),
	No grade 4.				12% (skin toxicity),
					9% dysphonia),
					6% (trismus).
					Grade ≥2=0%
					Grade 4 dysphagia: 1.5% (HIV +ve pt)
Other	All patients with regional failure (6%) presented with Stage T0N2b disease; all patients died of their disease within 3 years after salvage surgery. 10% of the patients developed secondary primary tumors.	4% and 0% of the patients were dependent on gastrostomy tube 6 months and 12 months after treatment, respectively.	28% and 16% of the patients were dependent on gastrostomy tube 6 months and 12 months after treatment, respectively.	62% of the patients required PEG tube before (29%) or during (33%) treatment. 43% and 72% of patients treated with RT alone and CCRT after treatment required a PEG tube, respectively.	Patient with grade 4 dysphagia required feeding tube. All three patients (4%) with failure were successfully treated with salvage surgery.

Notes: [a]In Frank *et al*., nodal levels II-V were irradiated on the involved side. If the primary was unlikely to be of nasopharyngeal origin, levels II-IV on contralateral sides were considered for irradiation. Level IB nodes were treated in the ipsilateral neck if patients presented with disease in levels II or III. [b]In Klem *et al*., most patients received cisplatin for concurrent chemoradiation therapy (CCRT) but some received carboplatin and 5-FU due to comorbidities and toxicity from cisplatin. Nine out of the 11 patients that developed chronic toxicity had received CCRT. [c]In our study, 90% of the patients received cisplatin for CCRT, 5% received carboplatin, and 5% cetuximab due to comorbidities and toxicity from cisplatin, as explained in the text.

fields for MUP have classically covered all potential mucosal disease sites, limiting the toxicity imposed by RT becomes even more crucial in the setting of added toxicity associated with CCRT.

Frank *et al*. reported the outcome of 52 patients with MUP treated with IMRT (100%) with or without concurrent chemotherapy and targeted RT (18). Only when the disease location or histological findings strongly suggested a primary nasopharyngeal tumor origin, the larynx and hypopharynx were excluded from RT coverage in 17 patients (33%). Grade 1 xerostomia was reported in five patients (12%) and grade 2 xerostomia in three patients (6%). Grade 3 esophageal toxicity was found in two patients (4%), where one patient required continuous use of PEG and another patient with an esophageal stricture required dilation. The authors concluded that IMRT for MUP produces excellent outcome and suggested that CCRT might not be necessary when RT is delivered to the pharyngeal axis.

Our treatment approach for MUP was similar to Frank *et al*.'s study in terms of utilizing targeted RT with chemotherapy and IMRT, except our studies mainly employed CCRT (56%), with less use of IMRT (40%) while Frank *et al*. mainly utilized IMRT (100%) and less CCRT (37%). Of note, the proportion of patients with grade 1 toxicity was higher in our patient population than that of Frank *et al*. However, grade 2 and higher complications were more prevalent in their patient population, while our patient population basically did not experience any toxicity above grade 1, except for one patient with HIV who experienced grade 4 dysphagia. While a direct comparison cannot be made, it is plausible that the differences in the incidence and severity of toxicities between the two studies are due to difference in RT coverage of mucosal site that leads to infrequent but more severe toxicity. As a result of ongoing controversy regarding the best treatment modality in treating MUP, we were interested in assessing our unique treatment strategies and their impact on outcomes in a relatively homogeneous population treated for MUP over the past 13 years. Table II compares recent studies (17-19), as well as our own experience. The studies selected were chosen to be representative of the various approaches taken towards treatment at present. Some caveats, in comparison, include differing end-points and inclusion criteria among different studies.

Additional consideration should be given to the fact that the etiology of head and neck cancer is changing. Studies have shown that SCC of the oropharynx is increasingly associated with human papilloma virus (HPV), more common in those with a history of smoking or alcohol abuse while its incidence is also increasing among non-smokers (20-22). There is, however, a higher incidence of *p53* gene mutation in smokers and drinkers compared to patients with no such habits (21, 22). In the present study, 12 (18%) of the patients were non-smokers. Furthermore, ethnicity becomes an important consideration in the management of MUP since non-Asian patients are more likely to develop SCC of the oropharynx associated with HPV, while Asian patients are more likely to develop SCC of the nasopharynx associated with Epstein–Barr virus (EBV). At the time our patients were treated, the role of HPV and EBV status in the prognosis was not clear; as such, it was not feasible for us to analyze all original tumor samples for HPV or EBV. This represents a limitation of our study. Hence, the pathological specimens of all patients in the present study will be analyzed for viral status in a future study to determine whether the improvement in outcomes was more closely linked to HPV- or EBV-positive disease.

Finally, the strengths of our study include: single-Institute experience and RT by two radiation oncologists (LBH and KSH). The caveats include: a non-randomized retrospective analysis, relatively small number of patients, dependent upon accuracy of documentation, vulnerability to selection bias, and unknown (HPV-P16 or EBV) tumoral status and poorly-documented smoking history.

Conclusion

Definitive RT targeted to the oropharynx and bilateral neck, sparing the nasopharynx, hypopharynx and larynx, provides excellent long-term tumor control, with acceptable late toxicity in treating metastatic SCC of unknown primary of the head and neck in non-Asian patients.

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Received November 6, 2013
Revised December 6, 2013
Accepted December 9, 2013