Patterns of Distant Failure and Second Primary Cancers in Patients with Oropharyngeal Squamous Cell Carcinoma: Implications for Surveillance Methodology

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Abstract: Background: We analyzed the pattern of distant metastasis (DM) and secondary primary cancers (SPC) in patients with oropharyngeal squamous cell carcinoma (OPSCC) to develop surveillance guidelines.

Methods: A retrospective review of 177 patients with OPSCC treated with intensity modulated radiation therapy ± chemotherapy between 2002 and 2012 was performed to characterize the rate, pattern, and timing of DM and SPC.

Results: Sixteen patients (9.0%) developed DM and 9 patients (5.1%) developed a SPC. Overall, 24/177 patients (13.6%) developed a DM and/or SPC for a total of 27 events. 92.6% (25/27) of events were detectable on physical exam and/or chest CT. p16+ patients developed DM later than p16- tumors (23.4 months versus 8.7 months).

Conclusions: Chest CT with physical examination detects the majority of DM and SPC in patients with OPSCC and would provide effective surveillance in these patients. A risk adapted surveillance strategy is proposed.

Keywords: Oropharynx cancer, surveillance, survivorship care, distant metastasis, second primary cancer.

INTRODUCTION

Distant metastasis (DM) remains a problem in the treatment of patients with oropharyngeal squamous cell carcinoma (OPSCC) and the most appropriate surveillance strategy for patients with this disease has not been identified. In two recent single institution series, the 3-year DM rates in patients with OPSCC treated with definitive intensity modulated radiation therapy (IMRT) were 8% [1, 2]. While the growing population of patients with HPV-related OPSCC has improved local-regional control (LRC) and overall survival (OS) [3, 4], the 3-year DM rate is reported to be 10% [3]. HPV-associated OPSCC demonstrates a unique DM pattern with patients developing DM over a longer period of time compared to HPV-negative patients [5]. Additionally, approximately 10% of patients with OPSCC will develop a metachronous second primary cancer (SPC) [3, 6]. Thus, monitoring patients for DM and SPC after treatment for OPSCC is important in optimal management of this disease.

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Due to the improved outcomes achieved with the use of concurrent chemoradiotherapy [7, 8] and due to the increased incidence of HPV-associated cancers, which are associated with favorable treatment outcomes, an increasing population of term survivors of OPSCC should be expected. Given this and the current focus on high quality survivorship care, there is a need for appropriate and cost-effective post-treatment surveillance. Such a strategy should include effective screening for DM and for SPCs, particularly in patients with a smoking history. In order to clarify reasonable screening elements, we analyzed the patterns of DM and the development of SPC in a cohort of patients with OPSCC treated with definitive IMRT. The goal of the analysis was to characterize the distribution and timing of DM and SPC in these patients such that an effective surveillance strategy could be proposed that would adequately detect these events.

MATERIALS AND METHODS

Patient Data

Patient data were retrospectively collected with approval of the University of Virginia Institutional Review Board for Health Science Research.

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Demographic data collected included age, sex, race, history of tobacco use, and history of alcohol use. Prior to treatment, all patients were discussed in a multidisciplinary head and neck cancer tumor board. Patients included in this analysis were treated for histologically confirmed OPSCC with definitive IMRT with or without chemotherapy at the University of Virginia between 1/1/02 and 5/31/12. When an adequate specimen was available for analysis, p16 status was determined with immunohistochemical (IHC) staining as per Reimers *et al*. [9]. Increased expression of the p16 protein (p16+) is associated with HPV-DNA in tumor cells [9]. Patients with HPV-associated OPSCC have improved treatment outcomes compared to HPV-negative OPSCC [3]. P16+ status is also prognostic in OPSCC, with p16+ patients faring better than patients without increased p16 expression (p16-) [3]. It is our institutional policy to perform IHC for p16 as a biomarker for HPV-associated OPSCC.

Radiation Therapy

Most patients were treated with a sequential boost technique at a dose of 1.8 – 2.0 Gy per day. The primary tumor was treated to 66 – 70 Gy and the pathologic lymph nodes were treated to 50 – 70 Gy depending on the extent of nodal disease and whether a post-radiation therapy neck dissection was planned. 50 Gy was delivered to the clinically uninvolved nodal regions. IMRT was utilized for the initial 50 – 56 Gy. A boost to the primary disease and involved lymph nodes was delivered with either a 3D conformal or IMRT technique for an additional 10 – 20 Gy to achieve total dose of 66 – 70 Gy to the gross disease. A small proportion of patients with early stage disease were treated with an accelerated hypofractionated technique with 66 Gy in 30 fractions to the gross disease and 54 Gy / 30 fractions to the clinically uninvolved nodal regions based on the Radiation Therapy Oncology Group (RTOG 0022) treatment protocol. IMRT treatment plans were optimized so at least 95% of the planning target volume was covered by the prescribed dose.

Treatment Outcomes

Retrospective review of treatment outcomes was performed to collect data on the development of DM and/or SPCs as identified with diagnostic imaging and/or physical exam. Intra-thoracic disease was defined as involving the lung parenchyma, pleura, mediastinum, thoracic spine, sternum, or ribs. DM or SPC at these sites were classified as detectable on standard chest CT.

Statistical Analysis

All survival statistics were based on the date of diagnosis of the index OPSCC. Local and regional control was defined as the interval to diagnosis of local or regional failure. Overall survival was defined as the time to death from any cause. Freedom from distant metastasis (FFDM) was defined as interval to diagnosis of DM. Distant metastasis free survival (DMFS) was defined as the time to development of DM or death from any cause. Patients who were alive and without evidence of DM at the time of analysis were censored at the date of last follow up. SPSS software (Version 20; IBM, Armonk, NY) was used for statistical calculations. The log-rank test was used to compare Kaplan-Meier survival curves. The chi-square test, Yates' chi-square test, and Student t test were performed to assess differences between patient characteristics. A p value of < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics and Treatment

One hundred seventy seven consecutively treated patients were included in this analysis. The median follow up was 36.0 months for the entire cohort, 41.1 months for p16+ patients, and 27.5 months for p16- patients. P16 status was positive, negative, and unknown in 93 (52.5%), 43 (24.3%), and 41 (23.2%) patients, respectively. Of the 136 patients with known p16 status, 68.4% were p16+ and 31.6% were p16-. Patient demographics are summarized in Table **1**. P16+ patients were more likely to be Caucasian and to have no history of tobacco use or alcohol abuse. Clinical staging at time of diagnosis of primary disease is summarized in Table **2**. There was no significant difference between the T classification of p16+ versus p16- tumors, but patients with p16+ disease were more likely to have N2 or N3 disease and stage III or IVA/B disease compared to p16- patients.

The median radiation dose delivered was 70 Gy in 35 fractions. The range of dose delivered was 58 Gy – 73.5 Gy, however, all but four patients received 66 – 70 Gy. Table **3** summarizes the chemotherapy delivered to the cohort. 66.1% of patients received systemic therapy in addition to radiation therapy, which included cytotoxic agents and cetuximab. Only 3/177 patients received cetuximab, which was delivered concurrently with radiotherapy and in the absence of induction therapy. The cytotoxic agents utilized were cisplatin,

Table 1: Pre-Treatment Baseline Patient Demographics. Statistical Comparisons are between p16+ and p16- Patients

Factor	All patients (N = 177)		p16 unknown (N = 41)		p16 positive (N = 93)		p16 negative (N = 43)		p value
Age (mean, years)	57.5		56.1		57.2		59.5		0.24
	n	%	n	%	n	%	n	%	
Age > 70 years	19	10.7	3	7.3	11	11.8	5	11.6	0.97
Race									
Caucasian	154	87	35	85.4	90	96.8	29	67.4	< 0.001
African American	21	12	5	12.2	2	2.1	14	32.6	
Hispanic	1	0.5	1	2.4	0	0	0	0	
Asian	0	0	0	0	0	0	0	0	
Other	1	0.5	0	0	1	1.1	0	0	
Sex									
Male	145	81.9	34	82.9	79	84.9	32	74.4	0.141
Female	32	18.1	7	17	14	15.1	11	25.6	
History of Tobacco Use	132	74.5	31	75.6	59	63.4	42	97.7	< 0.001
History of Alcohol Use	100	56.5	22	53.7	47	50.5	31	72.1	0.018

Table 2: Pre-Treatment Staging Information. Statistical Comparisons are between p16+ and p16- Patients

Factor	All patients (N = 177)		p16 unknown (N = 41)		p16 positive (N = 93)		p16 negative (N = 43)		p value
	n	%	n	%	n	%	n	%	
T stage									
T1	48	27.1	8	19.5	28	30.1	12	27.9	0.91
T2	75	42.4	14	34.1	42	45.2	19	44.2	
T3	25	14.1	10	24.4	11	11.8	4	9.3	
T4a	26	14.7	8	19.5	11	11.8	7	16.3	
T4b	3	1.7	1	2.4	1	1.1	1	2.3	
N stage									
N0	29	16.4	10	24.4	9	9.7	10	23.3	0.09
N1	27	15.3	6	14.6	13	14.0	8	18.6	
N2a	15	8.5	4	9.8	10	10.8	1	2.3	
N2b	66	37.3	13	31.7	35	37.6	18	41.9	
N2c	33	18.6	7	17.1	21	22.6	5	11.6	
N3	7	4.0	1	2.4	5	5.4	1	2.3	
N stage									
N0 - 1	56	31.6	16	39.0	22	23.7	18	41.9	0.03
N2 - N3	121	68.4	25	61.0	71	76.3	25	58.1	
Cervical nodal level IV and/or V involvement	28	20.0	6	20.0	16	20.0	6	10.0	0.632

(Table 2). Continued.

Factor	All patients (N = 177)		p16 unknown (N = 41)		p16 positive (N = 93)		p16 negative (N = 43)		p value
	n	%	n	%	n	%	n	%	
Stage									
I	7	4.0	5	12.2	0	0.0	2	4.7	0.45
II	14	7.9	3	7.3	5	5.4	6	14.0	
III	29	16.4	5	12.2	17	18.3	7	16.3	
IVA	120	67.8	26	63.4	67	72.0	27	62.8	
IVB	7	4.0	2	4.9	4	4.3	1	2.3	
Stage									
I/II	21	11.9	8	19.5	5	5.4	8	18.6	0.015
III/IV	156	88.1	33	80.5	88	94.6	35	81.4	

carboplatin, 5-flurouracil, paclitaxel, and capecitabine. Multiple combinations of these drugs were delivered in the induction and/or concurrent setting. Six of one hundred seventy seven patients (3%) received induction chemotherapy alone without concurrent chemotherapy. Only 2/21 patients with stage I/II disease were treated with chemotherapy.

Loco-Regional Control

The 3-year actuarial local and regional control rates for the patient cohort were 89.5% and 94.1%, respectively. The 3-year actuarial local control was 97.7% for p16+ patients and 76.0% for p16- patients ($p < 0.001$). The 3-year actuarial regional control was 95.9% for p16+ patients and 84.2% for p16- patients ($p = 0.032$).

Distant Control

Sixteen patients (9.0%) developed DM (Table **4**). Sites of initial involvement with DM included the lungs (75%), intra-thoracic lymph nodes (43.8%), pleura (18.8%), intra-thoracic bone (12.5%), liver (12.5%), extra-thoracic non-regional lymph nodes (12.5%), brain (6.3%), and skin/sub-cutaneous tissue (12.5%). Of the 16 patients classified as developing DM, 10 were confirmed histologically. In all 6 cases where biopsy confirmation was not obtained, patients presented with numerous pulmonary or pleural nodules ± mediastinal adenopathy and were classified as having DM by the treating physician. In 5/6, pulmonary disease was discovered between 2.2 and 8.3 months from the time of diagnosis of OPSCC, and 4/5 of these patients chose to enter hospice with all dying of disease within

Table 3: Chemotherapy Delivered before and/or Concurrent with Radiation Therapy. Statistical Comparisons are between p16+ and p16- Patients

	All Patients (N=177)		Stage III/IV Patients (N = 156)		Stage III/IV and known p16 status (N = 123)				
					p16+ (n = 88)		p16- (n = 35)		
	n	%	n	%	n	%	n	%	p value
Any chemotherapy	117	66.1	115	73.7	67	76.1	20	57.1	0.037
Any Induction Chemotherapy	74	41.8	72	46.2	36	40.9	12	34.3	0.497
Induction + Concurrent Chemotherapy	68	38.4	66	42.3	35	39.8	9	25.7	0.142
Induction Chemotherapy Alone	6	3.4	6	3.8	1	1.1	3	8.6	0.124
Any Concurrent Chemotherapy	111	62.7	109	69.9	66	75.0	17	48.6	0.005
Concurrent Chemotherapy Alone	43	24.3	43	27.6	31	35.2	8	22.9	0.183
Radiation Therapy Alone	60	33.9	41	26.3	21	23.9	15	42.9	0.037

Table 4: Sites of Distant Metastasis (DM) Identified at Time of Diagnosis of Metastatic Disease. Time to DM is defined as duration of time between diagnosis oropharyngeal squamous cell carcinoma and diagnosis of DM. LRR = local and/or regional recurrence at any time after completion of definitive radiation therapy. TNM classification per the American Joint Committee on Cancer Staging Manual, 7th edition

Patient	p16 status	TNM Classification	Cervical nodal level IV and/or V involvement	LRR	Time to DM (months)	Sites of DM at presentation
1	Negative	T3N2bM0	No	No	2.2	Lung
						Intra-thoracic lymph nodes
2	Negative	T1N1M0	No	No	8.1	Pleura
3	Negative	T4aN2cM0	No	Yes	8.1	Lung
						Intra-thoracic lymph nodes
						Intra-thoracic bone (rib)
						Liver
4	Negative	T2N0M0	No	Yes	8.3	Lung
						Intra-thoracic lymph nodes
5	Negative	T4aN1M0	No	Yes	8.7	Cutaneous
6	Negative	T1N2bM0	No	Yes	11.9	Lung
						Intra-thoracic lymph nodes
7	Negative	T3N2bM0	Yes	No	12.1	Lung
						Pleura
8	Negative	T1N2bM0	Yes	No	15.1	Lung
						Intra-thoracic lymph nodes
						Intra-thoracic bone (spine)
						Liver
						Extra-thoracic distant lymph nodes
9	Negative	T2N2bM0	Yes	Yes	20.9	Lung
10	Positive	T1N2bM0	Yes	No	6.5	Lung
						Intra-thoracic lymph nodes
						Brain
						Extra-thoracic distant lymph nodes
11	Positive	T2N2bM0	No	No	15.8	Pleura
12	Positive	T2N2cM0	Yes	No	30.9	Lung
13	Positive	T2N2bM0	No	Yes	62.1	Lung
14	Unknown	T2N0M0	No	No	7	Lung
15	Unknown	T3N2cM0	No	No	11.6	Lung
						Intra-thoracic lymph nodes
16	Unknown	T3N2bM0	No	Yes	65.8	Cutaneous

1.2 months. A single patient in the non-biopsied group developed clinical evidence for DM concurrently with a biopsy proven loco-regional recurrence 20.9 months after diagnosis of OPSCC. This patient was treated with palliative chemotherapy and subsequently developed progressive disease and died 14 months later. The 3-year actuarial FFDM was 90.9% for the entire cohort, 95.7% for p16+ tumors, and 77.7% for p16- tumors ($p = 0.002$) (Figure **1**). Predictors for FFDM are presented in Table **5**. In addition to p16 status, loco-regional failure and involvement of cervical nodal level IV and/or V were predictive for FFDM. The

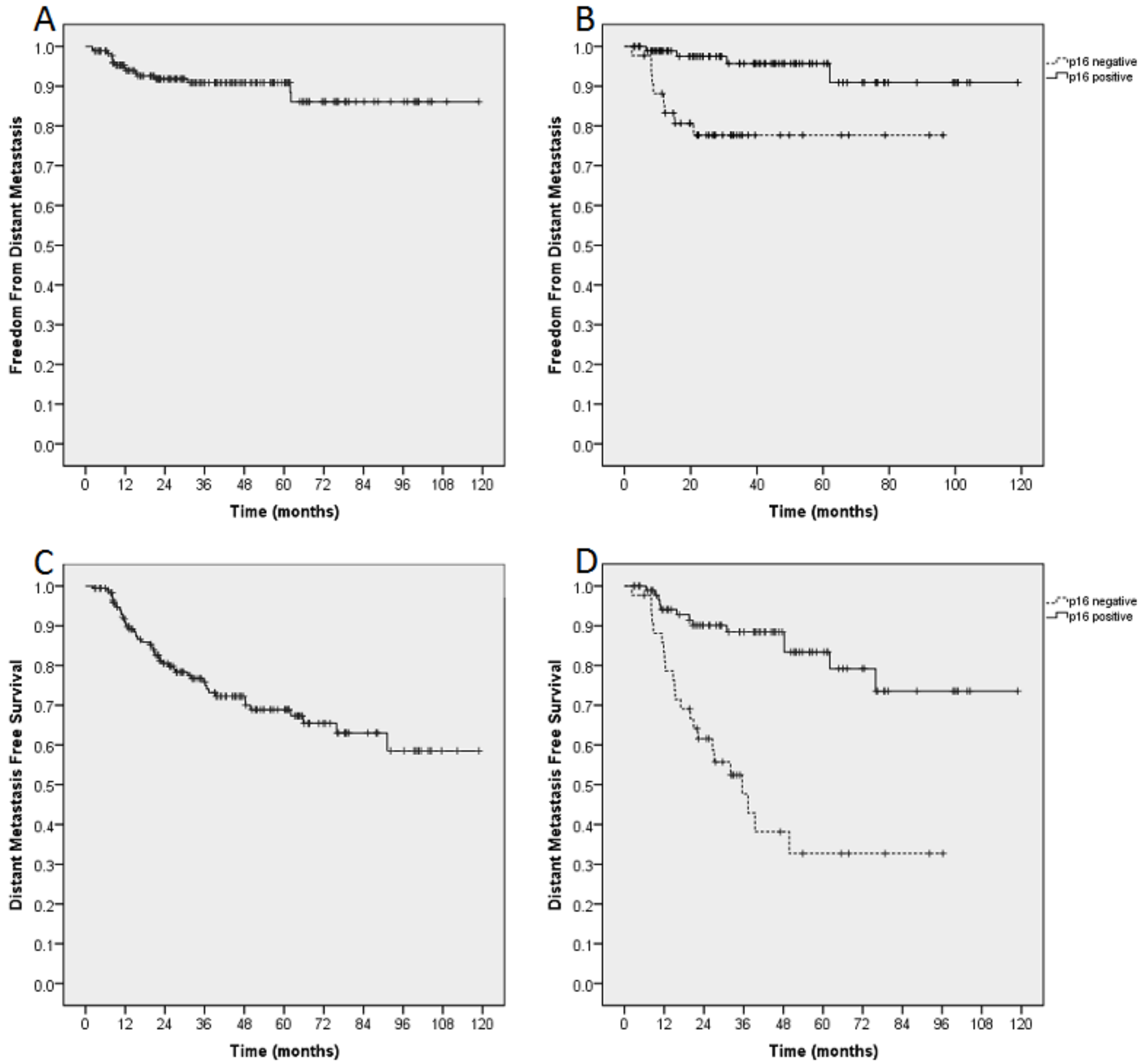

Figure 1: Kaplan-Meier estimates of freedom from distant metastasis for the entire patient cohort (**1a**), freedom from distant metastasis stratified by p16 status (**1b**), distant metastasis free survival for the entire patient cohort (**1c**), and distant metastasis free survival stratified by p16 status (**1d**).

use of induction chemotherapy was borderline significant. When stratified by p16 status, involvement of cervical nodal level IV/V was associated with decreased FFDM in p16+ patients, and loco-regional recurrence was associated with decreased FFDM in p16- patients. Loco-regional recurrence was of borderline significance in p16+ patients.

The 3-year actuarial DMFS was 75.8% for the entire cohort, 88.4% for p16+ tumors, and 47.7% for p16- tumors ($p < 0.001$) (Figure **1**). The 3-year actuarial overall survival was 79.9% for the entire cohort, 92.1% for p16+ tumors, and 55.7% for p16- tumors ($p < 0.001$).

Fourteen of sixteen patients with metastatic disease presented with DM as the first evidence of recurrent disease. Initial sites of DM included lung, pleura, intra-thoracic lymph nodes, liver, bone, cutaneous, brain, and extra-thoracic distant lymph nodes (Table **4**). In 14/16 patients, initial presentation of metastatic disease included an intra-thoracic location, and all 14 intra-thoracic recurrences were easily detectable on chest CT. The remaining 2 patients had cutaneous metastases that were obvious on physical exam. One patient developed a focus of suprasternal cutaneous metastatic disease and the other developed cutaneous metastatic disease in the anterior chest and thigh. The median time to diagnosis of DM was 11.8 months for all

Table 5: Univariate Predictors for 3 Year Freedom from Distant Metastasis (FFDM)

		All patients		p16+ patients		p16- patients	
		3 year FFDM	p value	3 year FFDM	p value	3 year FFDM	p value
p16 status	p16+	95.7%	0.002	n/a		n/a	
	p16-	77.7%					
Overall stage	Stage I/II	95.0%	0.943	100.0%	0.591	85.7%	0.613
	Stage III/IV	90.3%		95.0%		75.9%	
T classification	T1-2	92.5%	0.271	94.7%	0.353	82.6%	0.148
	T3-4	87.5%		100.0%		65.6%	
N classification	N0-1	94.2%	0.525	100.0%	0.277	82.4%	0.655
	N2-3	89.2%		94.2%		74.3%	
Cervical nodal level IV and/or V involvement	Yes	73.0%	0.047	75.0%	0.026	44.4%	0.122
	No	93.5%		98.0%		83.3%	
Loco-regional recurrence	Yes	75.3%	<0.001	100.0%	0.091	38.9%	0.005
	No	94.3%		95.0%		87.4%	
Any chemotherapy	Yes	92.9%	0.153	95.8%	0.895	85.2%	0.229
	No	86.9%		95.2%		70.0%	
Induction chemotherapy	Yes	93.5%	0.065	96.3%	0.255	91.7%	0.156
	No	88.5%		95.4%		71.7%	
Concurrent chemotherapy	Yes	93.5%	0.166	95.6%	0.72	88.5%	0.162
	No	87.0%		95.8%		69.3%	

tumors [inter-quartile range (IQR): 8.1 – 19.6] overall, 23.4 months for p16+ tumors [IQR: 8.8 – 54.3], and 8.7 months for p16- tumors [IQR: 8.1 – 13.6].

Overall, 7 patients received treatment for their metastatic disease and 6 patients underwent supportive measures only due to poor functional status. Treatment after diagnosis of metastatic disease was unknown in 3 patients. Treatment of DM included chemotherapy in 6 patients, surgical resection of a lung metastasis in 1 patient, and palliative radiation therapy in 5 patients. The survival after diagnosis of DM was poor with a median of 3.6 months [IQR: 1.1 – 7.4 months]. One patient with p16+ disease was a long term survivor and was alive at last follow up with an interval of 66.9 months after treatment for oligometastatic disease to the lung with a lobectomy. Another patient with unknown p16 status survived 26.2 months after initial diagnosis of metastatic disease to the lungs and mediastinum which was treated with palliative radiation therapy and chemotherapy.

Second Primary Cancers

Nine patients (5.1%) developed a SPC (Table **6**). The incidence of SPC was 7.5% (3/40) for p16- patients, 4.5% (4/89) for p16+ patients, and 5.1% (2/39) for patients with unknown p16 status. The median time to develop SPC was 47.3 months [IQR: 17.4 – 66.7]. Of the 11 total SPCs, 4 were lung primaries and 5 were metachronous head and neck or cutaneous primaries that were detectable on surveillance head and neck physical exam. All 4 lung primaries were easily detectable on chest CT. Two of four patients classified as having a second primary lung cancer underwent biopsy, with one showing poorly differentiated non-small cell lung carcinoma and the other showing squamous cell carcinoma. One patient received definitive chemoradiation and the other underwent lobectomy with mediastinal lymph node dissection. The other two patients presented with synchronous lung and brain masses, and were classified by the treating physician as having stage IV lung cancer. Both had a poor performance status at presentation of SPC, declined biopsy, and underwent minimal treatment.

Detection of Distant Metastasis or Second Primary Cancer

Overall, 24/177 patients (13.6%) in this cohort developed either DM or a SPC, for a total of 27 events. 92.6% (25/27) of these events were detectable with standard chest CT and thorough physical exam.

Table 6: Second Primary Cancers (SPC) Developed after Completion of Radiation Therapy. Time to SPC is defined as the duration of time between diagnosis of oropharyngeal squamous cell carcinoma and diagnosis of a SPC. TNM classification per the American Joint Committee on Cancer Staging Manual, 7th edition

Patient	p16 status	TNM Classification	SPC	Time to SPC (months)
1	Negative	T2N2bM0	Lung cancer	16.8
2	Negative	T2N2bM0	Metachronous head and neck cancer	35.3
3	Negative	T3N1M0	Lung cancer	9.7
4	Positive	T2N2cM0	Metachronous head and neck cancer	100.9
5	Positive	T2N2cM0	Metachronous head and neck cancer	82.6
6	Positive	T2N0M0	Lung cancer	66.7
7	Positive	T2N0M0	Pancreatic cancer	47.3
8	Unknown	T1N0M0	Metachronous head and neck cancer	30.6
			Cutaneous Melanoma	52.3
			Chronic lymphocytic leukemia	55.3
9	Unknown	T1N0M0	Lung cancer	17.4

DISCUSSION

Our analysis demonstrates a pattern of DM and SPC in patients with OPSCC treated with definitive IMRT that is informative to our goal of proposing an appropriate surveillance strategy. In 14/16 patients who developed metastatic disease, the initial site was intra-thoracic and easily detectable on chest CT. This is consistent with a prior study examining pre-treatment staging in a group of high risk head and neck cancer patients where 16 of 17 patients with DM had intra-thoracic disease and only one patient had involvement of the liver in the absence of disease in the lungs or mediastinum [10]. In the present study, the two DM not initially detectable with chest CT were cutaneous recurrences that were easily discernable by physical examination. Three patients had metastases outside the chest, including liver, extra-thoracic (non-cervical) lymph nodes, and brain, but all of these patients also had simultaneous intra-thoracic metastatic disease detectable on chest CT. The incidence of SPCs was lower than in prior studies, and we did not find a difference in the rate of SPC's between patients with p16+ and p16- disease as has been previously reported [6]. However, the predominance of SPCs occurring in the head and neck and lungs is consistent with prior reports. When DM and SPC events are combined in the present analysis, 92.6% were detectable with chest CT and thorough physical exam. Only two SPCs would not have been detectable with this follow-up strategy (1 pancreatic cancer, 1 leukemia).

Patients with OPSCC have an approximately 10-15% risk of developing DM after definitive treatment; after DM is detected, the prognosis is poor with few long term survivors. However, the use of surveillance imaging for metastatic disease results in earlier detection of DM, and patients found to have metastatic disease based on surveillance imaging have improved survival compared to those in whom imaging was obtained when symptomatic (241 days versus 73 days), though this could be the result of lead-time bias [11]. It is possible that earlier detection of DM with a surveillance approach, particularly in patients with good baseline functioning, could allow for more aggressive treatment such as metastatectomy, stereotactic body radiation therapy and/or systemic chemotherapy. Additionally, 5-10% of patients develop a SPC after definitive treatment for OPSCC with a high percentage in the lungs. This is not surprising given the high rates of tobacco use in the study population and the risk this poses for the development of lung cancer. A recent randomized trial demonstrated an increased sensitivity for the detection of lung cancers, as well as improved survival, with the use of screening CT chest compared to chest X-ray [12]. Based on these findings and the data presented in our study, we propose that chest CT would be an ideal surveillance modality for patients with OPSCC since it will effectively detect nearly all DMs and non-head and neck SPCs, and it is likely that earlier detection of intra-thoracic disease, particularly in patients with good baseline functioning, will allow for more aggressive treatment and thus prolonged survival.

For such a surveillance approach to be most cost-effective, it is necessary to identify patients at high risk for DM or SPC and perform chest CT in this subgroup. In the present series, p16 negative status, loco-regional failure, and cervical nodal involvement of levels IV and/or V predicted for DM on univariate analysis (Table **5**, Figures **1b** and **1d**). When stratified by p16 status, cervical nodal level IV and/or V involvement was predictive for p16+ tumors, and loco-regional recurrence was predictive for p16- tumors. Advanced overall stage, T classification, and N classification did not predict for DM on univariate analysis for the whole patient cohort or for the subgroups with known p16 status, nor did the use of any chemotherapy, induction chemotherapy or concurrent chemotherapy with radiation. Multivariate analysis was not performed due to an insufficient number of events.

In the present study, the lack of a statistically significant influence of advanced T and N classification on the DM rate is likely due to the low overall number of DM events and lack of power to detect a difference. Larger series with more than 400 patients each [13, 14] have both clearly demonstrated that advanced T and N classification are predictive for DM in patients with OPSCC. In the recursive partitioning analysis classification presented by O'Sullivan *et al*. [13], patients with HPV+ T1-3 and N0-N2c disease were classified as low risk, and those with T4 and/or N3 disease were classified as high risk. The 3-year DM rates were 7% and 24% ($p < 0.001$) and the 3-year LRF rates were 5% and 18% for the low and high risk groups, respectively. Patients with HPV- T1-2 and N0-N2c disease were classified as low risk, and those with T3-4 and/or N3 disease were classified as high risk. The 3-year rates of DM were 7% and 28%, and the 3-year rates of LRF were 24% and 38%, respectively ($p = 0.006$). It is clear from these findings from a large group of patients with OPSCC that loco-regionally advanced disease predicts for DM, and these stratifications appear to be a simple and useful method to identify high risk patients.

Riaz *et al*. [14] reported a 3-year DM rate of 35% for patients with T2-4 N2-3 OPSCC with pathologic nodes in the low neck (defined as level IV and Vb), but the analysis did not evaluate p16 status. In our study, the statistically significant effect of low cervical nodal involvement was demonstrated when analyzing the entire patient cohort and the p16+ stratum, but not the p16- stratum. This is despite a nearly 40% difference in 3 year FFDM in the p16- patients, and is likely due to the low number of p16- patients with low cervical nodal disease in our series. Therefore, cervical nodal level IV and/or V involvement, in addition to advanced N classification, appears to be a good predictor for high risk of DM.

After completion of definitive treatment for OPSCC, the National Comprehensive Cancer Network (NCCN) recommend post-treatment baseline imaging of the primary and neck, and a structured regimen of evaluations using history and physical exam [15]. Despite the substantial risk of DM and SPC in this patient population, the guidelines are not specific regarding surveillance imaging. Neck and/or chest imaging is recommended as clinically indicated (not explicitly defined), and surveillance imaging of the chest is suggested in patients at high risk for lung cancer which includes patients (1) age 55-74 years and ≥ 30 pack year history of smoking and duration of smoking cessation < 15 years, or (2) age ≥ 50 and ≥ 20 pack year history of smoking and one additional risk factor (radon exposure, occupational exposure, cancer history, family history of lung cancer, or pulmonary disease history) [16]. While patients with HPV- OPSCC are more likely to have a substantial smoking history and fall within the lung cancer screening guidelines, the majority of HPV positive patients do not [3]. In the absence of clinical suspicion, the majority of HPV positive patients would not receive surveillance imaging for DM or SPC based on these guidelines. Thus, we propose a surveillance imaging methodology (Table **7**) for patients with OPSCC that combines the concerns for DM and SPC, including lung cancer. This proposal is adapted for HPV+ and HPV- patients based on (1) clinical features predictive for high risk for DM, (2) patterns of DM, (3) patterns of SPCs, and (4) timing of DM.

Since lung cancer screening with chest CT is more sensitive than chest X-ray [12], we propose that chest CT be used for surveillance after treatment for OPSCC because the vast majority of DM and non-head and neck SPC are intra-thoracic. As discussed previously, advanced T/N classification is a high risk feature for DM in both HPV+ and HPV- OPSCC [13, 14], and can identify patients with a 3-year risk of DM of 24% (HPV+) and 28% (HPV-). Low cervical nodal involvement was demonstrated as a high risk feature in this analysis as well as another large series [14]. In our analysis, the 3-year FFDM was 73% when low neck involvement was present and 93.5% when it was absent (Table **5**). The timing and duration of DM differs between p16+ and p16- patients. Most p16- patients are found to have DM in the first year after diagnosis,

Table 7: Proposed surveillance imaging methodology for DM and SPC in patients with oropharyngeal squamous cell carcinoma (OPSCC). T and N classification per the American Joint Committee on Cancer Staging System, 7th edition

HPV+ OPSCC

Indications:

- T4 and/or N3
- Pathologic involvement of cervical level IV and/or V lymph nodes
- Performance status permissive for salvage therapy
- High risk for lung cancer
    - age 55-74 and ≥ 30 pack years and duration of smoking cessation < 15 years, or
    - age ≥ 50 and ≥ 20 pack years and one additional risk factor (radon exposure, occupational exposure, cancer history, family history of lung cancer, or pulmonary disease history)

Intervention & Frequency:

- Chest CT every 6 months for years 1-5

HPV- OPSCC

Indications:

- T3-4 and/or N3
- Pathologic involvement of cervical level IV and/or V lymph nodes
- Performance status permissive for salvage therapy
- High risk for lung cancer (as above)

Intervention & Frequency:

- Chest CT every 4-6 months for years 1-2
- Chest CT every 12 months for years 3-5

and all patients in this series manifested DM within 2 years. More frequent surveillance early in the course of follow up for high risk p16- patients appears warranted, and we propose chest CT every 4-6 months for years 1-2, followed by yearly chest CT during years 3-5. This latter time period would essentially be a screening period for pulmonary SPCs. Chest CT beyond 5 years is not likely to be beneficial since no DM occurred after that time period in p16 negative patients, and only 1/4 SPCs in the entire patient series developed beyond 5 years. For p16+ patients, the duration of time at risk is more prolonged. Chest CT surveillance should be considered in high risk patients every 6 months for 5 years.

Intensive imaging surveillance should be limited to high risk patients considered healthy enough to tolerate salvage therapy. Table **4** details the characteristics of the patients in our analysis that developed DM. Overall, 17/41 (41%) of p16- patients met high risk criteria for DM based on advanced T/N classification and/or low cervical nodal involvement, and 6/17 developed DM (35%). Of the three p16- patients with DM that did not meet the high risk criteria, two developed loco-regional recurrence, which was associated with DM in this analysis. In the p16+ patient group, 24/93 (26%) met high risk criteria for DM based on advanced T/N classification and/or low cervical nodal involvement, and 2/24 (8%) developed DM. In our analysis, p16+ patients had a low incidence of DM, but tended to develop DM over a longer period of time. It is possible that with longer follow up, the proportion of patients in the high risk group that manifest DM will increase. Of the two p16+ patients with DM that did not meet the high risk criteria, one developed a regional recurrence nearly four years after completion of definitive therapy which preceded manifestation of DM.

Close follow up with history and physical examination is also important in these patients to evaluate for loco-regional recurrence, which was predictive for DM in this analysis, and other DM not detected by chest CT. The NCCN provides post-treatment recommendations for history and physical which included examination every 1-3 months for year 1, every 2-6 months for year 2, every 4-8 months for years 3-5, and every 12 months after year 5 [15]. In this series, thorough physical exam and chest CT would have detected 92.6% of DM and SPC.

This study is limited by its retrospective nature and due to the small numbers of events. While we propose a surveillance imaging strategy, it was not evaluated in the study or compared to other surveillance approaches. Additionally, the data presented herein do not indicate that aggressive surveillance in high risk patients will result in improved outcomes and survival. However, based on our observations and other published series regarding the risk, distribution, and timing of DM and SPC in patients with OPSCC, the proposed methodology provides a useful and easily implementable preliminary guideline for post-treatment surveillance in patients with high risk OPSCC who have a predicted 25-35% risk of developing DM within 3 years and remain at high risk for lung cancer.

CONCLUSIONS

Surveillance chest CT with thorough physical examination appears adequate to detect nearly all DM and SPC after definitive IMRT for OPSCC. We propose a risk adapted surveillance imaging approach that identifies and monitors patients at high risk for DM, which frequently involves the thorax in this patient population. Further study is warranted to address the high DM rates in these patients and to evaluate the efficacy and cost effectiveness of personalized risk adapted surveillance imaging approaches.

REFERENCES

[1] Daly ME, Le QT, Maxim PG, *et al*. Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: Clinical outcomes and patterns of failure. Int J Radiat Oncol Biol Phys 2010; 76: 1339-46. http://dx.doi.org/10.1016/j.ijrobp.2009.04.006

[2] Setton J, Caria N, Romanyshyn J, *et al*. Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: An update of the memorial sloan-kettering cancer center experience. Int J Radiat Oncol Biol Phys 2012; 82: 291-8. http://dx.doi.org/10.1016/j.ijrobp.2010.10.041

[3] Ang KK, Harris J, Wheeler R, *et al*. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010; 363: 24-35. http://dx.doi.org/10.1056/NEJMoa0912217

[4] Shonka DC Jr, Shoushtari AN, Thomas CY, *et al*. Predicting residual neck disease in patients with oropharyngeal squamous cell carcinoma treated with radiation therapy: Utility of p16 status. Arch Otolaryngol Head Neck Surg 2009; 135: 1126-32. http://dx.doi.org/10.1001/archoto.2009.153

[5] Huang SH, Perez-Ordonez B, Weinreb I, *et al*. Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. Oral Oncol 2013; 49: 79-85. http://dx.doi.org/10.1016/j.oraloncology.2012.07.015

[6] Huang SH, Perez-Ordonez B, Liu FF, *et al*. Atypical clinical behavior of p16-confirmed HPV-related oropharyngeal squamous cell carcinoma treated with radical radiotherapy. Int J Radiat Oncol Biol Phys 2012; 82: 276-83. http://dx.doi.org/10.1016/j.ijrobp.2010.08.031

[7] Blanchard P, Baujat B, Holostenco V, *et al*. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): A comprehensive analysis by tumour site. Radiother Oncol 2011; 100: 33-40. http://dx.doi.org/10.1016/j.radonc.2011.05.036

[8] Denis F, Garaud P, Bardet E, *et al*. Final results of the 94-01 french head and neck oncology and radiotherapy group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004; 22: 69-76. http://dx.doi.org/10.1200/JCO.2004.08.021

[9] Reimers N, Kasper HU, Weissenborn SJ, *et al*. Combined analysis of HPV-DNA, p16 and EGFR expression to predict prognosis in oropharyngeal cancer. Int J Cancer 2007; 120: 1731-8. http://dx.doi.org/10.1002/ijc.22355

[10] de Bree R, Deurloo EE, Snow GB, Leemans CR. Screening for distant metastases in patients with head and neck cancer. Laryngoscope 2000; 110(Pt 1): 397-401. http://dx.doi.org/10.1097/00005537-200003000-00012

[11] Spector ME, Chinn SB, Rosko AJ, *et al*. Diagnostic modalities for distant metastasis in head and neck squamous cell carcinoma: Are we changing life expectancy? Laryngoscope 2012; 122: 1507-11. http://dx.doi.org/10.1002/lary.23264

[12] National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, *et al*. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395-409. http://dx.doi.org/10.1056/NEJMoa1102873

[13] O'Sullivan B, Huang SH, Siu LL, *et al*. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol 2013; 31: 543-50. http://dx.doi.org/10.1200/JCO.2012.44.0164

[14] Riaz N, Setton J, Tam M, *et al*. Recursive partition analysis identifies oropharyngeal cancer patients at high risk for distant metastasis. Int J Radiat Oncol Biol Phys 2012; 84: S482.

[15] Head and neck cancer clinical practice guidelines version 2.2013 [Internet]. National Comprehensive Cancer Network; cited November 15, 2013]. Available from: NCCN.org.

[16] Lung cancer screening clinical practice guidelines version 1.2014 [Internet]. National Comprehensive Cancer Network; cited November 15, 2013]. Available from: NCCN.org.

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