The Laryngoscope

Diagnostic Modalities for Distant Metastasis in Head and Neck Squamous Cell Carcinoma: Are We Changing Life Expectancy?

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Objectives/Hypothesis: To determine if the various imaging modalities for distant metastasis (DM) diagnosis alters life expectancy in head and neck squamous cell carcinoma (HNSCC).

Study Design: Retrospective.

Methods: One hundred seventy patients (mean age, 59.1 years; male:female, 135:35) with HNSCC who developed DM were reviewed. The main outcome measures were the method of DM diagnosis and time from DM diagnosis to death while controlling for clinical parameters (age, gender, tobacco status, primary tumor site, initial TNM classification, number and site of DM, administration of palliative chemotherapy).

Results: Tumor subsites were: 40 oral cavity, 75 oropharynx, 36 larynx, 10 hypopharynx, one nasopharynx, and eight unknown primary. Of the patients, 16.5% (28/170) had distant metastasis at presentation; the remaining 142 patients were diagnosed with DM at a median of 324 days from diagnosis. Although patients diagnosed with DM by positron-emission tomography (PET) scan were more likely to have multiple DM sites ($P = .0001$), there were no differences in life expectancy in patients who were diagnosed with or without PET scan (median, 185 vs. 165 days, $P = .833$). There were no differences in life expectancy based on age, gender, site of primary tumor, or number/site of DM. The use of palliative chemotherapy resulted in a significantly longer life expectancy (median, 285 vs. 70 days; $P = .001$).

Conclusions: Although a PET scan is more likely to diagnose multiple DM sites, there was no difference in life expectancy based on imaging modality. Patients who are symptomatic from their distant metastasis have a worse life expectancy, and palliative chemotherapy was able to increase life expectancy, even in patients who were symptomatic from the distant metastasis.

Key Words: Distant metastasis, survival, head and neck cancer, positron emission tomography scan.

Level of Evidence: 2b.

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INTRODUCTION

Distant metastasis from squamous cell carcinoma of the head and neck (HNSCC) affords an extremely poor prognosis.[1,2] The detection of distant metastasis is an integral part of determining treatment options and appropriate patient counseling. The choice of diagnostic modality for the detection of distant metastasis, has historically included chest x-ray (CXR) or computed tomography (CT). Over the past 10 years, positron-emission tomography (PET) has seen broad adoption across HNSCC subsites for its use in screening and surveillance. There are recent reports that suggest PET imaging is more sensitive at identifying occult metastatic disease than other radiographic modalities, such as CT or magnetic resonance imaging (MRI).[3] However, it is unclear whether detection of distant metastasis by this method has influenced the number or site of metastasis or influenced life expectancy in patients with HNSCC.

The purpose of this study was to determine if the various imaging modalities used to diagnose distant metastasis alters life expectancy in HNSCC and to identify factors, if any, that improve life expectancy.

MATERIALS AND METHODS

Study Population

This study was a retrospective review of patients who had pathologically confirmed HNSCC diagnosed between 1997 and 2010 and developed distant metastasis either at presentation or during the course of their care. Patient identification and data collection were conducted through our University of Michigan Specialized Program of Research Excellence (SPORE) database

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and confirmed through the electronic medical records. All patients were staged based on the 2002 American Joint Committee on Cancer staging system and provided written informed consent to participate in the University of Michigan SPORE program, which was approved by the institutional review board.

Population Characteristics

There were 170 patients who were identified as having distant metastasis during the course of head and neck cancer treatment; baseline clinical characteristics are shown in Table I. There were 135 (79%) male patients and the average age at initial diagnosis was 59.1 years. Stratification by subsites revealed 40 (24%) oral cavity, 75 (44%) oropharynx, 36 (21%) larynx, 10 (6%) hypopharynx, one (1%) nasopharynx, and eight (5%) unknown primary tumors. There were 28 (16%) patients who presented with distant metastasis; the remaining 142 (84%) patients were diagnosed with distant metastasis during the course of their care at a median of 381 days from head and neck cancer diagnosis. There were 164 (96%) patients with stage III or IV disease at the time of their initial diagnosis. Chemotherapy was used in 110 (65%) patients for either primary concurrent therapy with radiation or for adjuvant treatment after surgical extirpation. Tobacco status was defined categorically as never, prior (quit >6 months ago), or current use of cigarettes, cigars, pipe, chewing tobacco, snuff, or snus. There were 20 (12%) never tobacco users, 57 (34%) prior tobacco users, and 93 (55%) current tobacco users at initial diagnosis.

Diagnosis of Distant Metastasis

The diagnosis of distant metastasis was defined by a radiologic or clinical finding that was considered by the treating physician to be metastatic disease. Histologic confirmation was not always necessary at the discretion of the treating physician. The imaging modality first identifying distant metastasis was recorded along with the date and site(s) of disease. The reason for the treating physician to order any imaging modality was recorded and for analysis purposes was divided into two categories: surveillance imaging or symptomatic imaging. If patients had more than one imaging modality identifying distant metastatic sites, the first imaging modality was considered to have obtained the diagnosis. All sites of distant metastasis were considered to be present at the initial date of distant metastatic diagnosis (i.e., if a patient had a chest x-ray showing metastatic disease, followed by a chest CT showing chest and liver metastasis, the modality that obtained the diagnosis would be chest x-ray, and metastasis to the lung and liver were recorded). Patients with distant metastasis found within 30 days of initial head and neck cancer diagnosis were considered to have distant metastasis at presentation.

Statistical Analysis

The main outcome measures were the method of distant metastasis diagnosis and time from distant metastasis diagnosis to death (life expectancy) while examining clinical parameters (age, gender, tobacco status, primary tumor site, initial TNM classification, number and site of distant metastasis, presence of symptoms attributed to distant metastasis, and administration of palliative chemotherapy). Patients who were alive with disease were censored on the date of their last clinical visit in any department. Patients with no evidence of disease were censored on the last date of their clinical visit in otolaryngology, radiation oncology, or medical oncology.

Survival estimates were computed using the Kaplan-Meier method and were defined from the date of distant metastasis diagnosis to date of censorship (death, last follow-up). Univariate and bivariate Cox regression models were used to test the association of clinical parameters with decreased survival time independent of other tested variables. The χ^2 and Fischer exact tests were used to determine the relationship between the type of imaging modality and the site (single versus multiple) of

TABLE I.
Baseline Characteristics of Patients Who Developed Distant Metastasis in Head and Neck Squamous Cell Carcinoma.

Characteristics	Patients Who Developed Distant Metastasis, N = 170
Age, mean (SD), yr	59.1 (10.6)
Subsite, % (no.)	
Oral Cavity	23.5 (40)
Oropharnyx	44.1 (75)
Larynx	21.2 (36)
Hypopharynx	5.9 (10)
Nasopharnyx	0.6 (1)
Unknown Primary	4.7 (8)
Overall stage, % (no.)	
I	1.2 (2)
II	2.4 (4)
III	9.4 (16)
IV	87.1 (148)
T classification, % (no.)	
TX	4.7 (8)
T1	5.9 (10)
T2	15.9 (27)
T3	18.8 (32)
T4	54.7 (93)
N classification, % (no.)	
N0	18.8 (32)
N1	11.8 (20)
N2	47.7 (81)
N3	21.8 (37)
Diagnostic method, % (no.)	
PET	28.2 (48)
CT	47.6 (81)
Chest x-ray	15.3 (26)
Other	8.8 (15)
Reason for imaging modality, % (no.)	
Surveillance	67.6 (115)
Symptomatic	32.4 (55)
Tobacco status, % (no.)	
Never	11.8 (20)
Prior	33.5 (57)
Current	54.7 (93)
Palliative chemotherapy, % (no.)	
Yes	50 (85)
No	29.4 (50)
Missing data	20.6 (35)

The majority of patients initially presented with advanced T and N classification, and roughly two-thirds of distant metastasis were detected on surveillance imaging in patients without symptoms.

SD = standard deviation; PET = positron-emission tomography; CT = computed tomography.

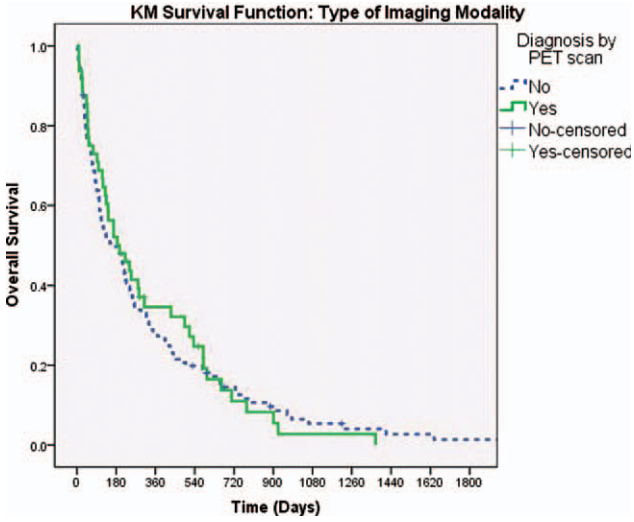

Fig. 1. Kaplan-Meier (KM) survival curves of the entire cohort stratified by type of imaging modality. The median life expectancy of patients who were diagnosed by positron-emission tomography (PET) scan was 185 days, and for patients who were diagnosed by other modalities was 165 days ($P = .835$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

distant metastases. A P value of $<.05$ was considered statistically significant. All statistics were analyzed on SPSS for Windows version 19.0 (IBM, Armonk, NY) with consultation from the University of Michigan Center for Statistical Consultation and Research.

RESULTS

The median life expectancy for the entire cohort after diagnosis of distant metastasis was 185 days. Patients who were found on presentation of their head and neck cancer to have distant metastasis had no difference in life expectancy compared to those who developed distant metastasis during follow-up (median, 196 vs. 168 days; $P = .754$). Patients who underwent a PET scan as the imaging modality for the diagnosis of distant metastasis were more likely to be diagnosed with multiple metastases compared with other imaging modalities (50% vs. 13%; $P = .0001$). There were no differences in life expectancy in patients who were diagnosed with distant metastasis by PET scan versus another imaging modality (Fig. 1; median 185 vs. 165 days; $P = .835$).

The development of a single versus multiple sites of distant metastasis were not predictive of an increased life expectancy (Fig. 2; median 194 vs. 111 days; $P = .148$). There were 130 patients with a single metastatic site and 40 patients with multiple metastatic sites. The most frequent site in order of decreasing prevalence of distant metastasis were lung (137), bone (41), liver (22), dermis (eight), brain (seven), and other (eight). Patients with less common metastatic sites (bone, dermis, brain, other) were more likely to be symptomatic ($P = .0001$).

There was a significant difference in life expectancy in patients who were discovered to have distant metastasis on routine surveillance imaging compared with patients who were symptomatic at time of diagnosis (Fig. 3; median 241 vs. 73 days; $P = .001$). There were 115 patients who were identified to have distant metastasis by surveillance imaging and 55 patients who had distant metastasis discovered on imaging due to concerning symptoms. Pulmonary symptoms were the most common presenting symptom of distant metastasis (31), followed by skeletal (23).

Bivariate analysis was performed in patients who had distant metastasis found on surveillance imaging and who were symptomatic to identify factors within each group that may increase life expectancy. In the 115 patients who were identified as having distant metastasis by surveillance imaging, 38 (33%) were identified by PET scan, 57 (50%) by CT scan, and 20 (17%) by chest x-ray. There were no differences in life expectancy in the patients who were identified to have distant metastasis by surveillance imaging when stratified by imaging modality (Fig. 4a; median 249 vs. 210 vs. 333 days; $P = .591$). In the 55 patients who were identified as having distant metastasis discovered on imaging initiated by concerning symptoms, 10 (18%) were identified by PET scan, 24 (44%) by CT scan, six (11%) by chest x-ray, and 15 (27%) by other imaging modalities (MRI, bone scan). There were no differences in life expectancy in the patients who were identified as having distant metastasis discovered on imaging due to concerning symptoms when stratified by imaging modality (Fig. 4b; median 49 vs. 102 vs. 43 vs. 73 days; $P = .362$).

Palliative chemotherapy was offered to patients who were considered healthy enough to tolerate treatment at the discretion of the medical oncologist and patient preference. There were 85 (63%) patients who received palliative chemotherapy, 50 patients who did not receive palliative chemotherapy, and 35 patients whose palliative therapy was unknown. These 35 patients typically received care closer to home and did

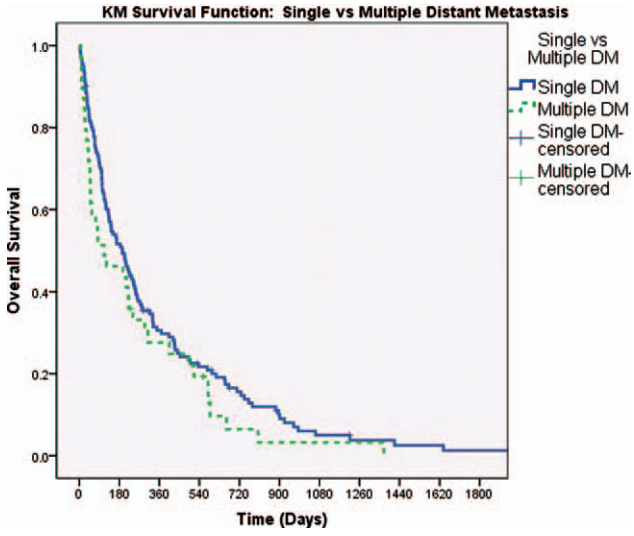

Fig. 2. Kaplan-Meier (KM) survival curves of the entire cohort stratified by the presence of a single versus multiple metastasis. The median life expectancy of patients who were diagnosed with a single-site metastasis was 194 days, and for patients who were diagnosed with multiple site metastasis was 111 days ($P = .148$). DM = distant metastasis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

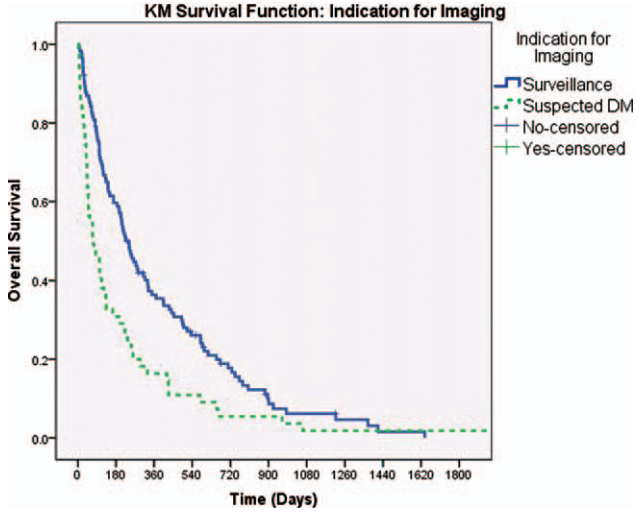

Fig. 3. Kaplan-Meier (KM) survival curves of the entire cohort stratified by the rationale for obtaining an imaging study. The median life expectancy of patients who were discovered to have distant metastasis (DM) on routine surveillance imaging was 241 days, and for patients who were symptomatic at time of diagnosis was 73 days ($P = .001$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

not return for follow-up. There was a significant difference in life expectancy in patients who received palliative chemotherapy compared with those who did not receive palliative chemotherapy (Fig. 5; median 285 vs. 70; $P = .0001$). There was no correlation between type of imaging modality and which patients received palliative chemotherapy ($P = .287$).

DISCUSSION

This study suggests that even though PET scan is more likely to detect multiple metastatic sites, there is no significant difference in life expectancy based on imaging modality or the number of metastatic sites. As expected, patients who are symptomatic from their distant metastasis had a worse life expectancy, and palliative chemotherapy was able to increase life expectancy, even in patients who were symptomatic from the distant metastasis.

PET was first introduced in the 1970s, and although initially its use was limited by poor resolution and high cost, improvements in technology and affordability have allowed for rapid expansion of its indications. Currently, PET scans are widely used in head and neck cancer management, with studies reporting efficacy in pretreatment staging and the detection of occult primary tumors.[4–8] PET has a higher sensitivity than CT or ultrasound-guided fine-needle aspiration and a better specificity than MRI in patients with borderline enlarged cervical lymph nodes, demonstrating an important prognostic role in patients who may not have histopathologic confirmation of their tumors.[4]

In addition, PET imaging has played an important role in monitoring local and regional treatment response,[9,10] radiation and surgical treatment planning, and as examined by our study, surveillance for distant metastasis.[11,12] Although PET has been shown to accurately detect distant metastasis, the role in surveillance remains unclear. As healthcare costs increase, providers need to vigilantly justify its use as a tool to improve patients' outcomes or change treatment strategies. In this study, we demonstrated that PET had a greater ability to identify multiple distant metastasis compared to other imaging modalities, although this did not translate to a survival benefit. The most common site for asymptomatic metastases were the lungs, whereas patients who developed bone, liver, brain, or other sites of distant metastases were typically identified by imaging initiated by symptoms. This would suggest

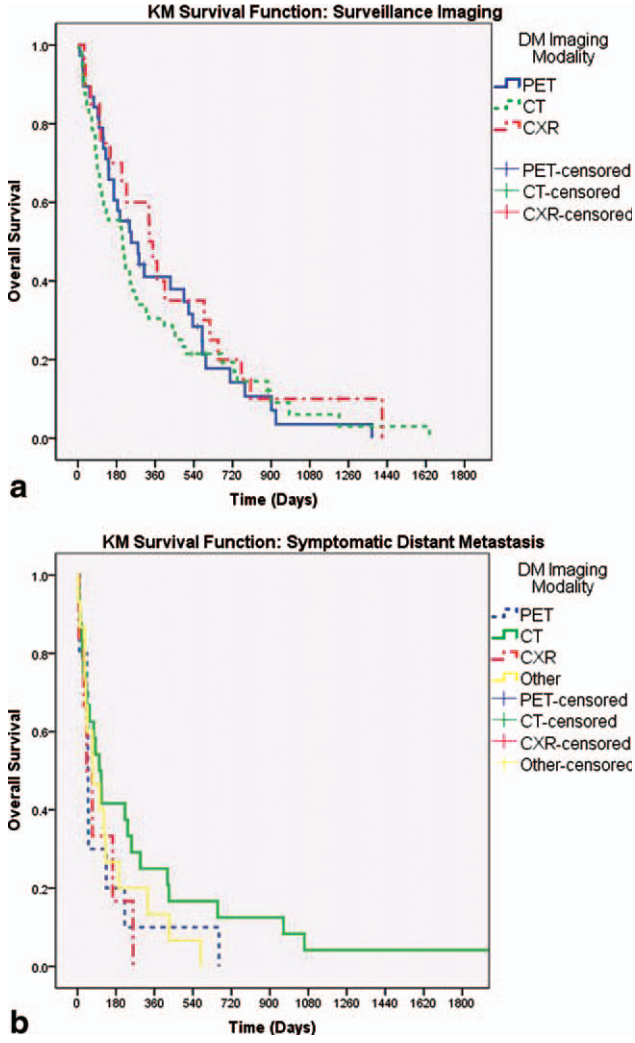

Fig. 4. (a) Kaplan-Meier (KM) survival curves of patients who had surveillance imaging stratified by diagnostic imaging modality. There were no differences in life expectancy in the patients who were identified as having distant metastasis (DM) by surveillance imaging when stratified by imaging modality. (b) Kaplan-Meier survival curves of patients who had symptomatic imaging stratified by diagnostic imaging modality. There were no differences in life expectancy in the patients who were identified as having distant metastasis discovered on imaging initiated by concerning symptoms when stratified by imaging modality. PET = positron-emission tomography; CT = computed tomography; CXR = chest x-ray. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

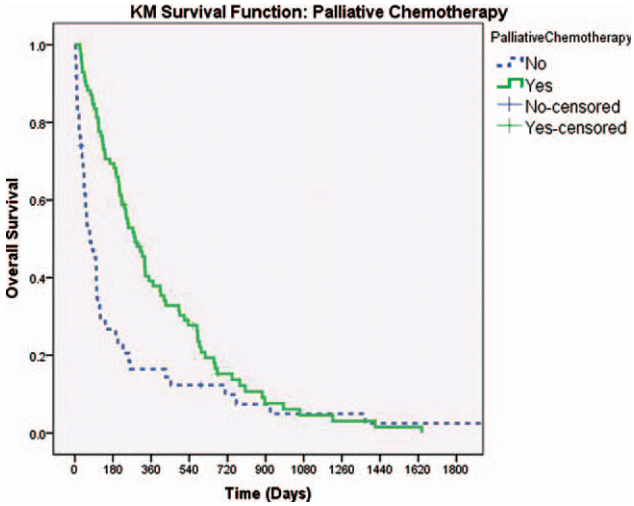

Fig. 5. Kaplan-Meier (KM) survival curves of the entire cohort stratified by the administration of palliative chemotherapy. The median life expectancy in patients who received palliative chemotherapy was 285 days, and for patients who did not receive palliative chemotherapy was 70 days ($P = .0001$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

that in patients who present with symptoms, imaging modalities that focus on site specific symptoms would be more efficient than PET. For patients who are asymptomatic, there was no increased life expectancy seen when stratifying by imaging modality (chest x-ray, CT, PET). Although stratification by subsite was not performed, and this only represented a subpopulation of patients, chest x-ray or CT may provide the most cost-effective screening modality for HNSCC surveillance. However, cost effectiveness is out of the realm of this study and warrants further examination.

Chemotherapy is an option for the treatment of metastatic head and neck cancer, with the objective of systemic therapy to provide both palliation of symptoms and lengthen life expectancy. Previous studies have shown the effectiveness of chemotherapy, with the majority showing lengthening of the median survival from 6 to 15 months.[13,14] Our results confirm these findings, although there is a selection bias in our study, as patients must be healthy enough at the time of distant metastasis diagnosis to receive chemotherapy. Patients with high ambulatory performance status (Eastern Cooperative Oncology Group 0 or 1), poorly differentiated histology, and previous response to chemotherapy typically have a better response to palliative chemotherapy. In contrast, weight loss, poor performance status, prior radiation therapy, and active smoking have been associated with a poor prognosis.[14–17]

The retrospective nature of this study imparts nonrandomization bias, selection bias, and recall bias. Additionally, it is possible that the difference in life expectancy based on identification of a distant metastasis by surveillance imaging compared to symptomatic imaging may be a result of screening patients having distant metastasis identified earlier (lead time bias). This lead time bias may confound the results and should be further explored.

CONCLUSION

In summary, the identification of distant metastasis in patients with HNSCC is a devastating event. Although PET has been shown useful in other clinical settings, our study demonstrates that PET does not have the added benefit for prolonging life expectancy in patients with distant metastasis. Although PET has been shown useful in other clinical settings, our. The indications for the use of PET for surveillance or symptomatic imaging of distant metastasis may need to be reevaluated. Further study into the cost effectiveness of PET for distant metastasis is necessary to understand its role in HNSCC.

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