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

Matthew E. Spector, MD, **Steven B. Chinn, MD MPH**, **Andrew J. Rosko, BS**, **Francis Worden, MD**, **Vasu Divi, MD**, **Scott McLean, MD PhD**, **Jeffrey S Moyer, MD**, **Mark E. P. Prince, MD**, **Gregory T. Wolf, MD**, **Douglas B. Chepeha, MD MSPH**, and **Carol R. Bradford, MD**
Departments of Otolaryngology – Head and Neck Surgery and Medical Oncology, University of Michigan Health System, Ann Arbor, MI, USA

Abstract

Objectives—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—170 patients (mean age 59.1; M:F 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, 1 nasopharynx, 8 unknown primary. 16.5% (28/170) of patients 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 PET scan were more likely to have multiple DM sites(p=0.0001), there were no differences in life expectancy in patients who were diagnosed with or without PET scan(median 185 vs 165 days,p=0.833). 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=0.001).

Conclusions—Although PET scan is more likely to diagnose multiple DM sites, there was no difference in life expectancy. Patients that 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.

Keywords

Distant metastasis; survival; head and neck cancer; positron emission tomography (PET) scan

Corresponding Author: Matthew E. Spector MD, 1904 Taubman Center, 1500 E Medical Center Drive, Ann Arbor, MI 48109, Phone: (734) 936-8029, Fax: (734) 647-9691, mspector@med.umich.edu.

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Introduction

Distant metastasis from squamous cell carcinoma of the head and neck (HNSCC) affords an extremely poor prognosis (1)(2), with the detection of distant metastasis being an integral part of determining treatment options and appropriate patient counseling. The choice of diagnostic modality, which historically included chest x-ray or computed tomography (CT) in the detection of distant metastasis has been variable across specialties and treating physicians. This has been due partly to the advances in technology over the past ten years, specifically with the development positron emission tomography (PET). PET has seen broad adoption across HNSCC subsites for its use in screening and surveillance. There are reports that now suggest PET imaging is more sensitive at identifying occult metastatic disease than other radiographic modalities, such as CT or MRI (3). However, it is unclear whether detection of distant metastasis by this method has influenced the detection of the number or site of metastasis or influenced life expectancy in patients with HNSCC.

At the University of Michigan, our Specialized Program of Research Excellence (SPORE) has been prospectively identifying and following patients to better understand the molecular biology and develop novel clinical studies to improve outcomes in HNSCC. This database optimally allows for the study of a large group of patients with distant metastasis, and across a large time range that includes trends of change in imaging modalities in our patients. The purpose of this study is 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 squamous cell carcinoma of the head and neck who were 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 SPORE database and confirmed through the electronic medical record. 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 that were identified as having distant metastasis during the course of head and neck cancer treatment and baseline characteristics are shown in Table 1. 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, 1 (1%) nasopharynx, and 8 (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 163 (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 greater than 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 a more than one imaging modality identifying multiple distant metastatic sites, the first imaging modality was considered to have obtained the diagnosis and all sites of distant metastasis were considered to be present at the date of distant metastatic diagnosis. (i.e. if a patient had a chest x-ray showing metastatic disease, then 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 diagnosis of their head and neck cancer 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 multivariate Cox Regression models were used to test the association of clinical parameters with decreased survival time independent of other tested variables. The chi-square and fischer's exact tests were used to determine the relationship between the type of imaging modality and the site (single versus multiple) of distant metastases. A p-value of <0.05 was considered statistically significant. All statistics were analyzed on SPSS for Windows version 19.0 (SPSS Inc., Chicago, IL) 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=0.754). Patients who underwent 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=0.0001). There were no differences in life expectancy in patients who were diagnosed with distant metastasis by PET scan versus another imaging modality (Figure 1; median 185 vs 165 days; p=0.835).

The development of single versus multiple distant metastatic sites were not predictive of an increased life expectancy (Figure 2; median 194 vs 111 days; p=0.148). There were 130 patients with single metastatic sites and 40 patients with multiple metastatic sites. The most frequent sites in order of decreasing prevalence of distant metastasis were lung (137), bone

(41), liver (22), dermis (8), brain (7), and other (8). Patients with less common metastatic sites (bone, dermis, brain, other) were more likely to be symptomatic (p=0.0001).

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 (Figure 3; median 241 vs 73 days; p=0.001). 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 to have 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 (Figure 4a; median 249 vs 210 vs 333 days; p= 0.591). In the 55 patients who were identified to have distant metastasis discovered on imaging due to concerning symptoms, 10 (18%) were identified by PET scan, 24 (44%) by CT scan, 6 (11%) by chest x-ray and 15 (27%) by other imaging modalities (MR, bone scan). There were no differences in life expectancy in the patients who were identified to have distant metastasis discovered on imaging due to concerning symptoms when stratified by imaging modality (Figure 4b; median 49 vs 102 vs 43 vs 73 days; p=0.362).

Palliative chemotherapy was offered to patients who were considered healthy enough to tolerate treatment at the discretion of the medical onocologist and patient preference. There were 85 (63%) patients who received palliative chemotherapy, 50 patients did not receive palliative chemotherapy, and 35 patients whose palliative therapy was unknown. These patients typically received care closer to home and did not return for follow- up. There was a significant difference in life expectancy in patients who received palliative chemotherapy compare with those who did not receive palliative chemotherapy (Figure 5; median 285 vs 70; p=0.0001). There was no correlation between type of imaging and which patients received palliative chemotherapy (p=0.287).

Discussion

This study suggests that while PET scan is more likely to detect multiple metastatic sites, there is not a significant difference in life expectancy based on imaging modality or even the number of metastatic sites. As expected patients that 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.

Positron emission tomography (PET) was first introduced in the 1970s, and while initially its use was limited by poor resolution and high cost, improvements in technology and affordability have allowed for rapid expansion of its indications. PET scan is widely used today in head and neck cancer with studies reporting efficacy in pretreatment staging and the detection of occult primary tumors (4–8). PET scanning 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 scan has an important role in monitoring local and regional treatment response (9)(10), radiation treatment planning and, as examined by our study, surveillance

for distant metastasis. (11)(12) While PET has been shown to be able to accurately detect distant metastasis, the role in surveillance remains unclear. As health costs increase, providers need to vigilantly justify its use as a valuable tool to improve patient's 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. Similarly, the most common site for asymptomatic metastases were the lungs, while patients who developed bone, liver, brain or other sites of distant metastases were typically identified by imaging initiated by symptoms. This would suggest 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 not an increased life expectancy seen when stratifying by imaging modality (chest xray, CT, PET). Although stratification by subsite was not performed and this only represented a subpopulation of patients, screening 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 is to provide both palliation of symptoms, as well as 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 finding, although there is a selection bias in our study as typically patients must be healthy enough to receive chemotherapy, therefore lengthening this groups survival. Several factors have been identified as positive prognostic factors for survival in patients with metastatic head and neck cancer receiving chemotherapy. These include ambulatory performance status (ECOG 0 or 1), poorly differentiated histology, and response to chemotherapy. In contrast, weight loss, poor performance status, prior radiation therapy and active smoking have been associated with a poor prognosis. (14–18)

The retrospective nature of the study imparts non-randomization bias, selection bias and recall bias. Additionally, given the type of analysis, lead-time bias may play a significant role in the analysis of surveillance versus symptomatic patients and confound the finding of increased life expectancy in the surveillance cohort. It is possible that the difference in life expectancy based on identification of a distant metastasis by surveillance imaging compared to symptomatic imaging may purely be a result of screening patient having distant metastasis identified earlier, but intervention may not play a role. The finding that palliative chemotherapy improves life expectancy regardless of presentation type supports the role of screening imaging to direct care as needed.

Conclusions

In summary, the identification of distant metastasis in HNSCC in our patients is a devastating event. Our study demonstrates PET does not have the added benefit for prolonging life expectancy in patients with distant metastasis. As technology advances, we must constantly analyze both clinical and cost effectiveness. The indications for the use of PET for surveillance or symptomatic imaging may need to be re-evaluated. Further study into cost-effectiveness of PET for distant metastasis is necessary to understand its role in surveillance and diagnosis in HNSCC.

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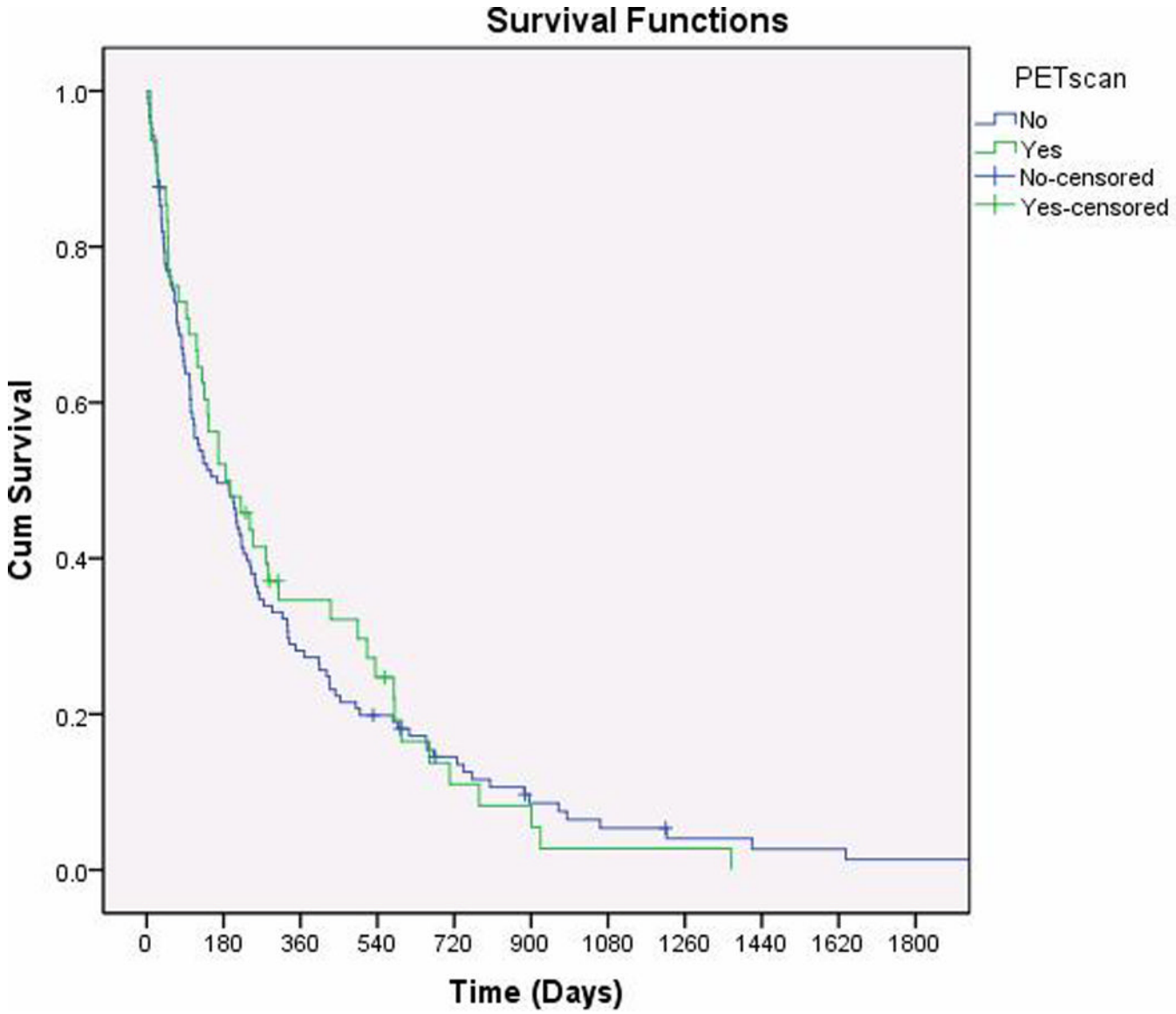


Figure 1. Kaplan-Meier Survival Curves of the Entire Cohort Stratified by Type of Imaging Modality

Figure 1 shows the Kaplan-Meier 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=0.835).

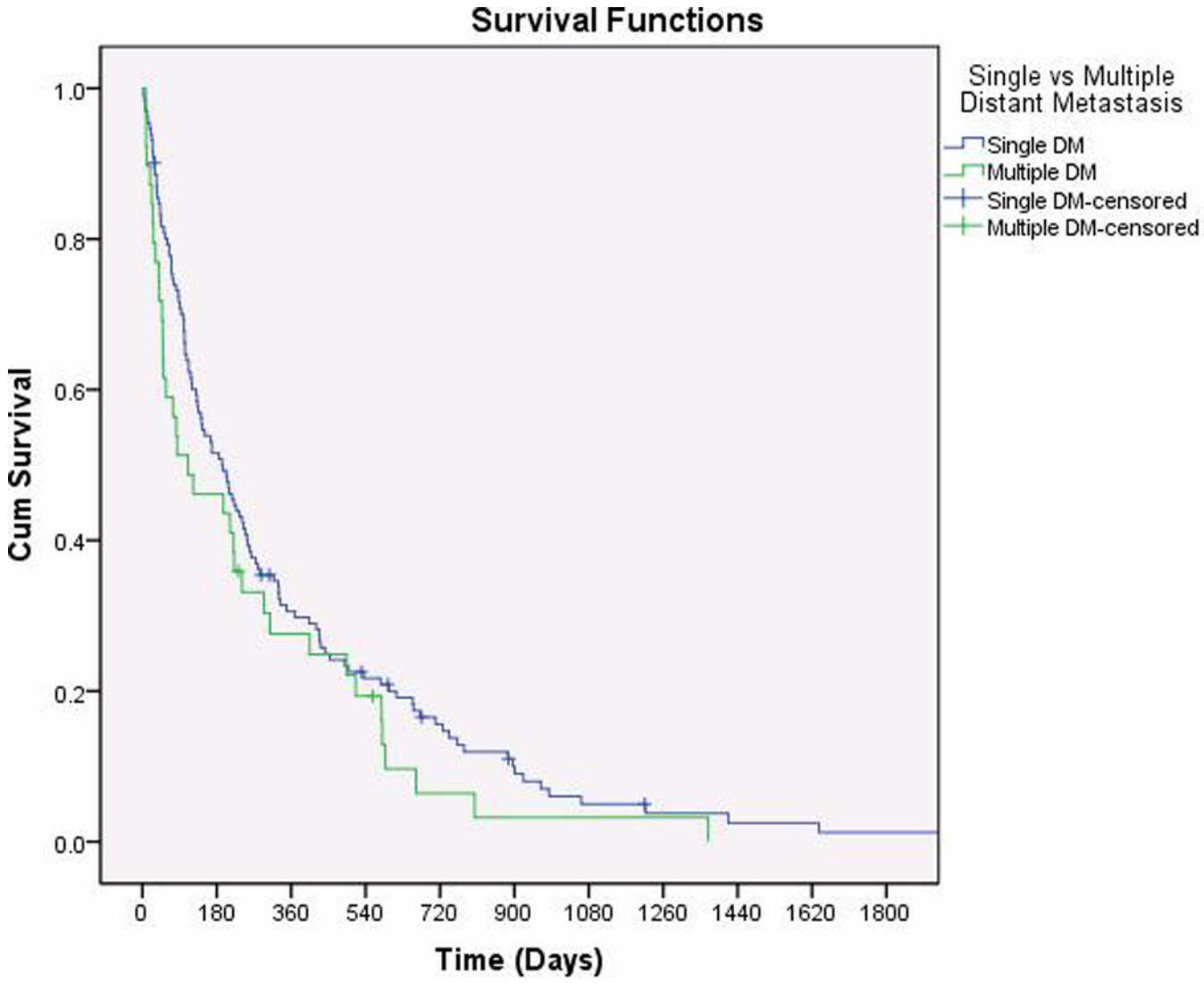


Figure 2. Kaplan-Meier Survival Curves of the Entire Cohort Stratified by the Presence of Single versus Multiple Metastasis

Figure 2 shows the Kaplan-Meier Survival Curves of the entire cohort stratified by the presence of single versus multiple metastasis. The median life expectancy of patients who were diagnosed with single site metastasis was 194 days and for patients who were diagnosed with multiple site metastasis was 111 days (p=0.148).

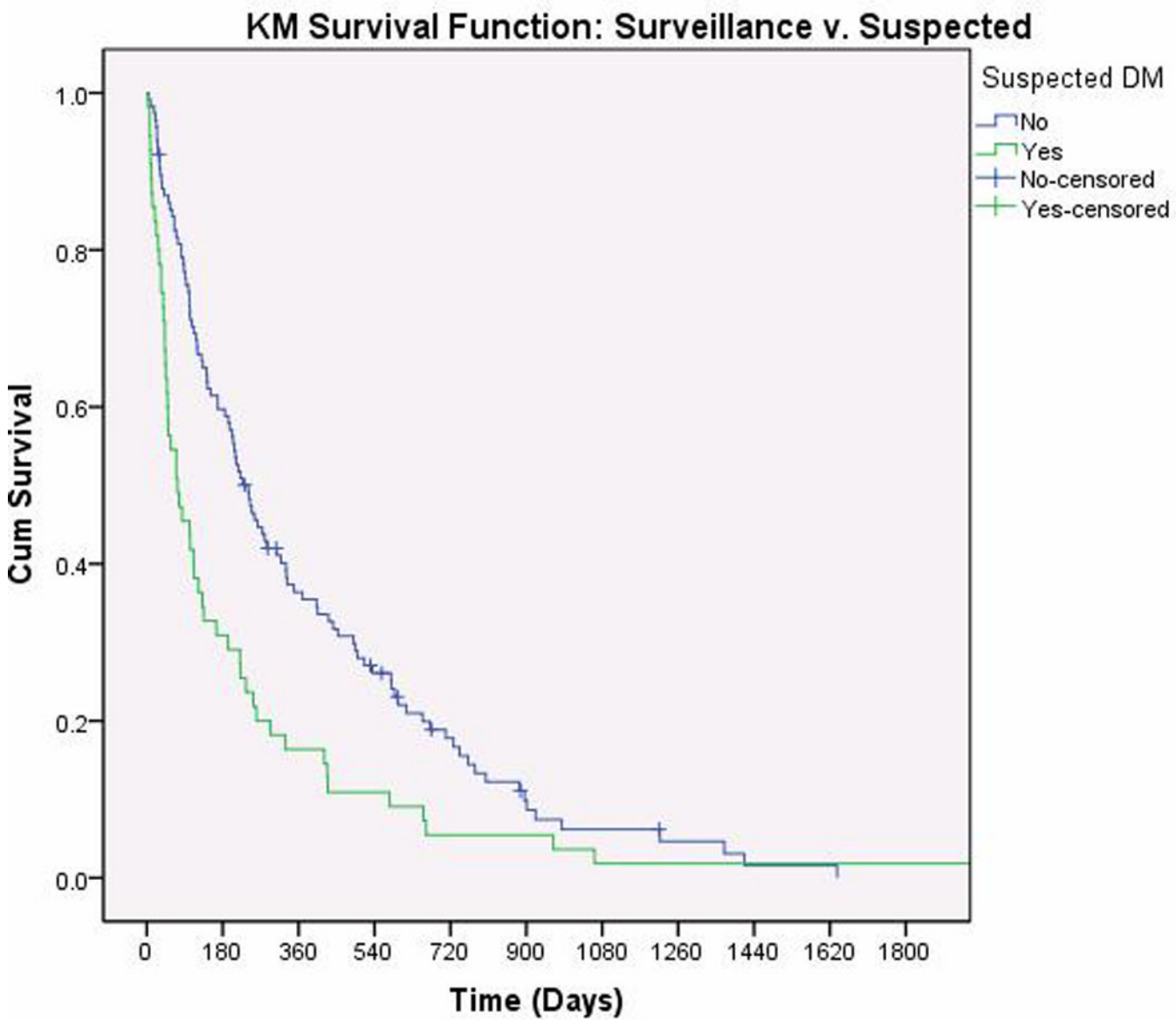
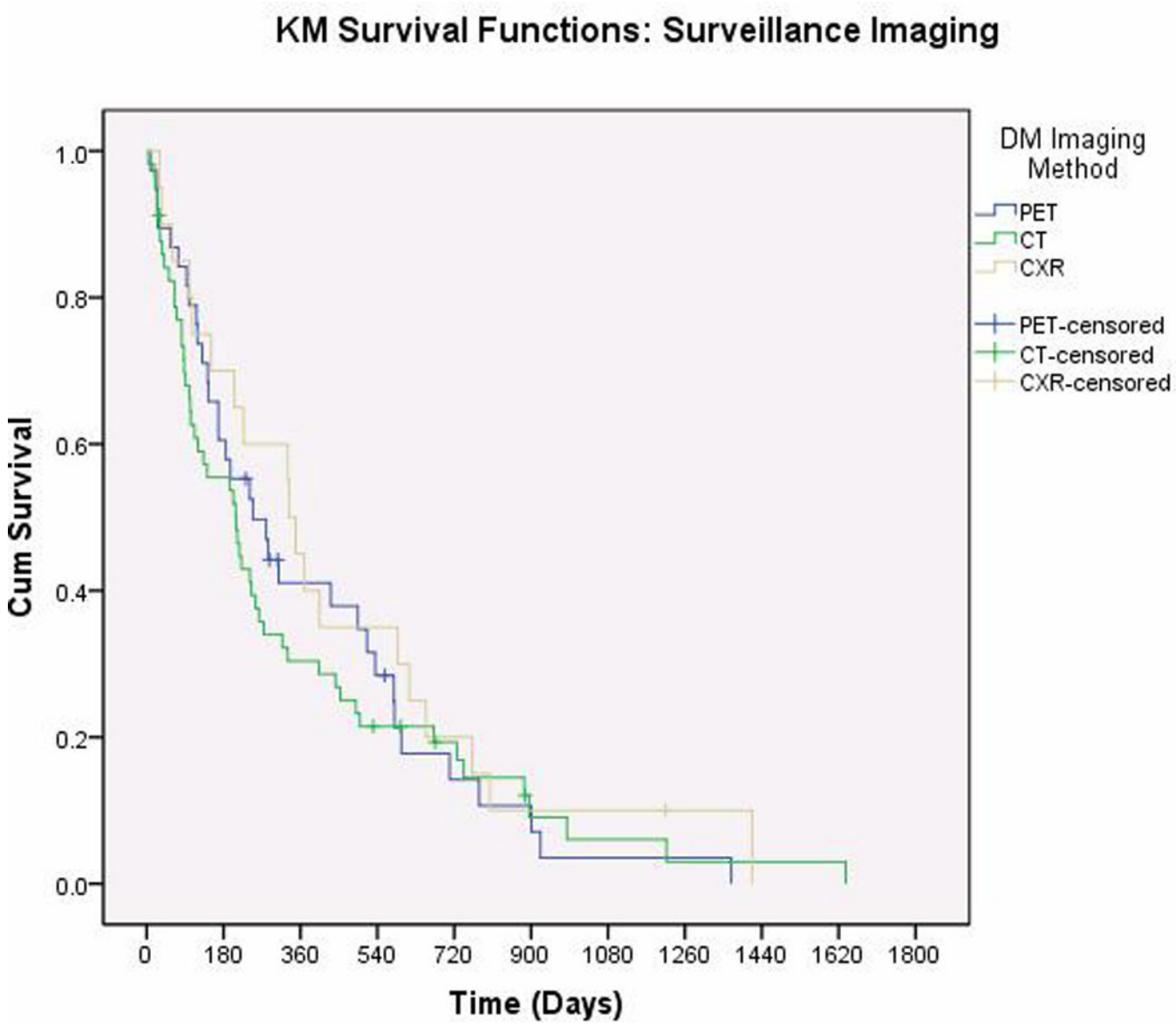


Figure 3. Kaplan-Meier Survival Curves of the Entire Cohort Stratified by the Rationale for Obtaining an Imaging Study

Figure 3 shows Kaplan-Meier 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 on routine surveillance imaging was 241 days and for patients who were symptomatic at time of diagnosis was 73 days (p=0.001).



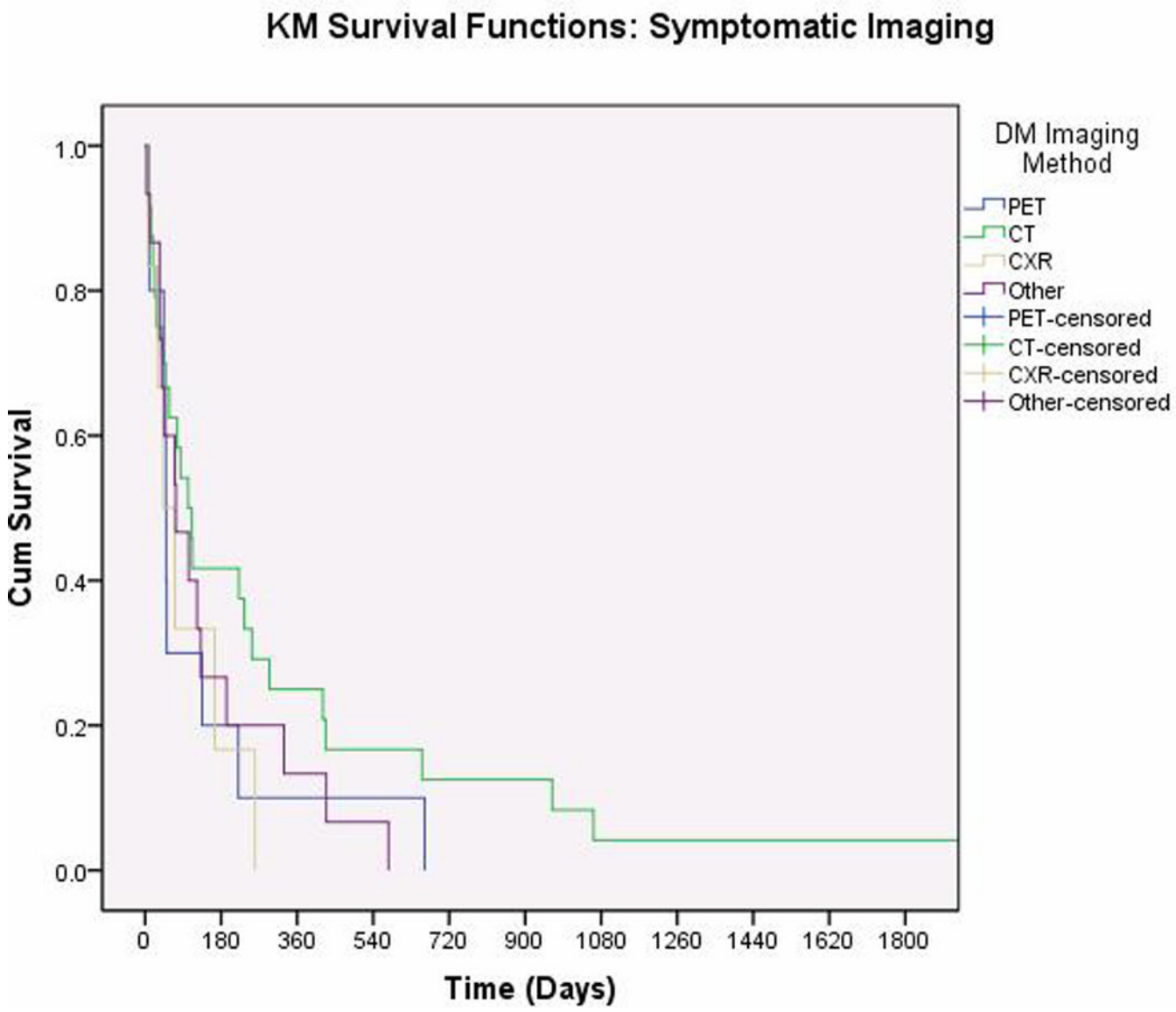


Figure 4. Kaplan-Meier Survival Curves of patients who had Surveillance Imaging and Symptomatic Imaging Stratified by the Diagnostic Imaging Modality

Figure 4a shows Kaplan-Meier Survival Curves of patients who had surveillance imaging stratified by the diagnostic imaging modality. 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. Figure 4b shows Kaplan-Meier Survival Curves of patients who had symptomatic imaging stratified by the diagnostic imaging modality. There were no differences in life expectancy in the patients who were identified to have distant metastasis discovered on imaging due to concerning symptoms when stratified by imaging modality.

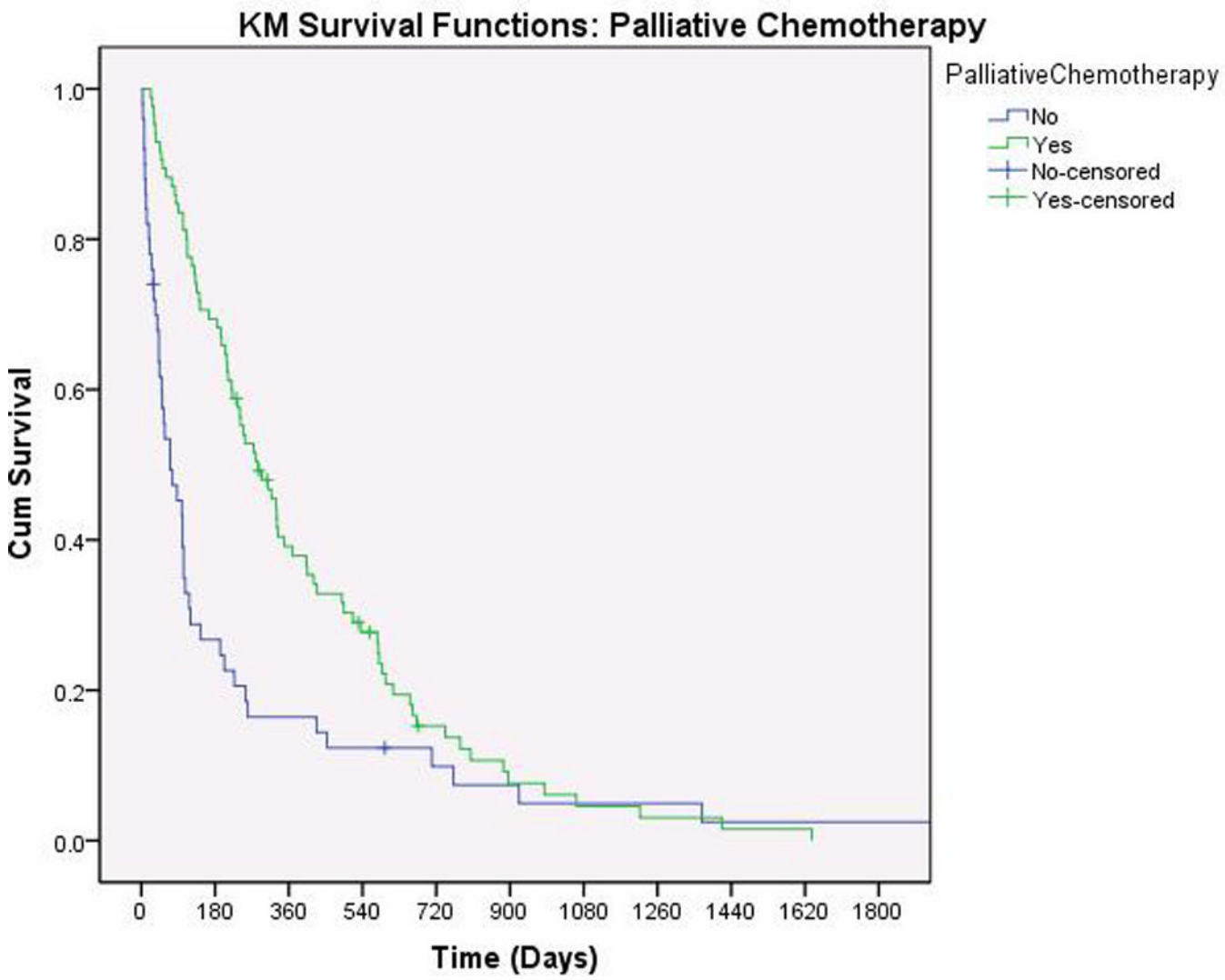


Figure 5. Kaplan-Meier Survival Curves of the Entire Cohort Stratified by the Administration of Palliative Chemotherapy

Figure 5 shows Kaplan-Meier 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=0.0001).

Table 1

Baseline Characteristics of Patients who Develop Distant Metastasis in Head and Neck Squamous Cell Carcinoma

Table 1 shows baseline characteristics of patients who develop distant metastasis in head and neck squamous cell carcinoma. The majority of patients initially presented with advanced T and N classification, and roughly 2/3 of distant metastasis were detected on surveillance imaging in patients without symptoms.

Characteristics		**Patients who develop distant metastasis n=170**
Age	mean (sd)	59.1 (10.6)
Sub-Site	Oral Cavity Oropharnyx Larynx Hypopharynx Nasopharnyx Unknown Primary	23.5% (40) 44.1% (75) 21.2% (36) 5.9% (10) 0.6% (1) 4.7% (8)
Overall Stage	I II III IV	1.2% (2) 2.4% (4) 9.4% (16) 87.1% (148)
T classification	TX T1 T2 T3 T4	4.7% (8) 5.9% (10) 15.9% (27) 18.8% (32) 54.7% (93)
Nclassification	N0 N1 N2 N3	18.8% (32) 11.8% (20) 47.7% (81) 21.8% (37)
Diagnostic Method	PET CT Chest x-ray Other	28.2% (48) 47.6% (81) 15.3% (26) 8.8% (15)
Reason for Imaging Modality	Surveillance Symptomatic	67.6% (115) 32.4% (55)
Tobacco Status	Never Prior Current	11.8% (20) 33.5% (57) 54.7% (93)
Palliative Chemotherapy	Yes No Missing Data	50% (85) 29.4% (50) 20.6 (35)