Multiple Regression Analysis of Predictors of Bone Scintigraphy Positivity in Patients with Head and Neck Cancers

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Abstract

Purpose The value of bone scintigraphy (BS) in patients with head and neck cancers (HNCs) has been questioned, with conflicting findings regarding positivity yield with some reports recommending BS be omitted from work-up of HNC patients since it rarely yields positive results. This study aims to determine the positivity yield of BS in HNCs and to determine predictors for BS positivity to help tailor appropriate BS utilization. **Methods** BS studies of HNC patients were reviewed, the positivity yield was determined. Clinical predictors for BS positivity including age, sex, site of cancer, staging, histological grading were analyzed using univariable and multivariable logistic regression.

Results Among the 259 BS studies included, 35 (13.5%), 194 (74.9%), and 30 (11.6%) were positive, negative, and equivocal for bone metastasis, respectively. After exclusion of equivocal cases, 229 were analyzed in the regression models.

Independent predictors of BS positivity include site of tumor at the nasopharynx (OR 4.37, 95% C.I. 1.04–18.41, $p = 0.044$), age less than 45 years (OR 3.01, 95% C.I. 1.24–7.33, $p = 0.015$), and presence of distant metastasis to other organs (OR 3.84, 95% C.I. 1.19–12.43, $p = 0.025$).

Conclusions In contrast to several studies, bone metastasis as detected by BS was found in a relatively high proportion of patients with HNCs. Independent predictors of BS positivity include the age of less than 45 years, tumor site at the nasopharynx, and the presence of extraskelatal distant metastasis. BS could be useful in patients with these characteristics which enhance the pretest probability of bone metastasis.

Keywords Bone scintigraphy · Radionuclide imaging · Head and neck cancers · Bone metastasis

Introduction

Head and neck cancers (HNCs) refer to a group of malignant tumors occurring at anatomical sites of the upper aerodigestive tract. The disease burden varies among geographical regions with incidences ranging from 2–15 per 100,000 in males and 0.7–4 per 100,000 in females [1]. The majority of HNCs are squamous cell carcinomas (SCC) which can be further graded into well differentiated, moderately differentiated, poorly differentiated, and undifferentiated subtypes [2]. Nasopharyngeal carcinomas are particularly prevalent in regions including China and Southeast Asia [3] and can be classified into squamous cell carcinoma (SCC), non-keratinizing carcinoma, and undifferentiated carcinoma according to the WHO classification [4]. Management of HNCs mainly involves surgical resection, chemotherapy, and radiation therapy. Early stage cancers can be treated with resection alone while more advanced stages need multimodal

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therapy [5]. A crucial feature of disease staging is the determination of metastasis to distant organs. The overall prevalence of distant metastasis from HNCs at initial diagnosis was reported to range from 1.5% to 16.8% [6]. Nasopharyngeal carcinoma, in particular has been found to be associated with distant metastasis of more than a quarter of cases [7]. The common sites of distant metastasis from HNCs include the lung, the bones, and the liver [6–8]. Bone scintigraphy (BS) has long been used to evaluate for distant metastasis from various cancers. The test has been found to offer a good balance between its reasonable accuracy and relatively low cost and radiation dose compared with other imaging modalities such as FDG PET/CT and, thus, is commonly used as the initial screening test for bone metastasis [9, 10]. BS has been found to have sensitivity and specificity ranging from 55% to 88% and 50% to 98%, respectively for diagnosis of bone metastasis and local bone invasion from HNCs [9, 11–14]. Previous studies have examined positivity yield of BS in patients with HNCs and reported conflicting results. Several studies found that BS examinations were positive in only a small fraction of cases ranging from 0.8% to 2.2% [15–19]. While another study found that BS was positive in 23% of patients with nasopharyngeal carcinoma [20]. These discrepant results could be due to varying characteristics of patients among different studies. Several studies have examined several predictors for bone metastasis and BS positivity mostly focusing on tumor staging. Most studies found a positive link between lymph node involvement and the development of bone metastasis [18, 21–23]. The T-stage was found to be predictive of bone metastasis in some studies [7, 21] but not others [22, 23]. One study found that bone metastasis was not correlated with age, sex, tumor histology, or the presence of metastasis to other organs [23]. Another study found that HNC patients less than 45 years of age had increased odds of developing distant metastasis mainly to the lung and bone [8]. The objective of this study is to determine the positivity yield of BS in patients with various HNCs as well as to determine clinical factors predictive of BS positivity.

Material and Methods

Patients

This retrospective cross-sectional study was approved by the Khon Kaen University institutional review board (Ref. HE601105). Patients with histopathologically confirmed HNCs who underwent BS at the Division of Nuclear Medicine, Department of Radiology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University were included. Patients with incomplete pathological diagnosis regarding type and grade of tumors as well as patients with another coexisting malignancy other than HNCs were excluded.

Clinical data were obtained from the patient database of Srinagarind Hospital. Collected data included sex, age, site of cancer, cancer stage according to the 7th edition of the American Joint Committee on Cancer AJCC Cancer Staging Manual, and cancer histology and grading.

Bone Scintigraphy

Patients were intravenously injected with 15–18 mCi of Tc-99 m methylene diphosphonate, then anterior and posterior static whole body planar images were acquired approximately 3 h later using either Vertex V60 EPIC HP dual headed gamma camera (ADAC, CA, USA), Genesys single headed gamma camera (ADAC, CA, USA), or Discovery NM/CT 670 (GE Healthcare, IL, USA) equipped with low energy general purpose collimator with a 1024 x 1024 x 16 imaging matrix with an energy peak set at 140 keV $\pm$ 10% using continuous acquisition mode with detector speed of 15 cm per minute. Single photon emission computed tomography/computed tomography (SPECT/CT) was obtained in selected cases where the attending nuclear medicine physician deemed that the information from planar scanning was not sufficient for diagnosis. BS images were interpreted by an experienced nuclear medicine physician. BS results were categorized into three groups: positive for bone metastasis, negative for bone metastasis, and equivocal. Positive scans were further described regarding locality of bone metastasis, i.e., single or multiple, and sites of abnormality.

Statistical Analysis

Patient, tumor, and BS characteristics were summarized as mean, standard deviation, and percentage. Univariable and multivariable logistic regression analyses were used to test the relationship between clinical predictors and BS positivity. Only BS examinations that were unequivocally positive or negative were included in the regression model. Statistical analysis was carried out using Stata version 10 (StataCorp LLC, TX, USA). A *P*-value of <0.05 indicates statistical significance. Accompanying 95% confidence interval (95% C.I.) was reported where appropriate.

Results

Patients

From November 2013 to February 2017, a total of 352 patients with HNCs underwent BS. A total of 82 patients had incomplete pathology reports for HNCs mostly because they were sent for bone scintigraphy from other hospitals, while 11 patients had other coexisting malignancies. Therefore, those 93 patients were excluded, which leaves a total of 259 included patients. Table 1 details baseline characteristics of included

Table 1 Patient characteristics

Characteristics	Value	
Age (years)		
Mean $\pm$ SD	54.1	$\pm$ 13.5
Range	8–84	
Sex		
Male	184	71.0%
Female	75	29.0%
Tumor site		
Nasopharynx	144	55.6%
Oral cavity	44	17.0%
Oropharynx	25	9.7%
Hypopharynx	16	6.1%
Larynx	25	9.7%
Nasal cavity/paranasal sinuses	5	1.9%
T stage		
T1	35	13.5%
T2	60	23.2%
T3	42	16.2%
T4	122	47.1%
N stage		
N0	48	18.5%
N1	39	15.1%
N2	114	44.0%
N3	58	22.4%
Other distant metastasis		
None	232	89.6%
Lung	18	6.9%
Liver	7	2.7%
Lung and liver	1	0.4%
Pleura	1	0.4%
Histological grading		
Nasopharyngeal carcinoma	144	
WHO type 1	11	7.6%
WHO type 2	97	67.4%
WHO type 3	34	23.6%
Other histology	2	1.4%
Other sites	115	
Well differentiated SCC*	57	49.6%
Moderately differentiated SCC	33	28.7%
Poorly differentiated SCC	18	15.6%
Other histology	7	5.1%

*SCC; squamous cell carcinoma

patients as well as tumor characteristics. The cohort had an average age of 54 years and was comprised mostly of males. The most common tumor site was the nasopharynx which accounted for over half of included cases. As shown in Table 2 which details the T and N stage of included patients, most patients had advanced local disease with predominantly

Table 2 Tumor and lymph node staging according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition

Tumor (T) stage	Lymph node (N) stage				
	N0	N1	N2	N3	Total
T1	6	7	9	13	35
T2	6	7	31	16	60
T3	9	7	18	8	42
T4	27	18	56	21	122
Total	48	39	114	58	259

T3-T4 and N2-N3 disease. Approximately 10% of patients had metastasis to organs other than the bone, with the most common being pulmonary metastasis. Patients with nasopharyngeal carcinoma mostly had a WHO type 2 histology, i.e., nonkeratinizing carcinoma. Almost all patients with HNCs of other sites had SCC, most of which were well-differentiated. Nine patients from the entire cohort had other tumor pathologies—three patients had adenoid cystic carcinoma of the nasopharynx, gum, and soft palate, respectively. Two patients had myoepithelial cell tumors of the soft palate and floor of mouth, respectively. The remaining four patients had poorly differentiated adenocarcinoma of the tongue, polymorphous low-grade adenocarcinoma of the right maxillary sinus, papillary Schneiderian carcinoma of the nasopharynx, and minor salivary gland oncocytoma of the base of tongue, respectively.

Bone Scintigraphy

Among the 259 BS examinations, 183 were for staging while 86 were for disease surveillance. As shown in Table 3, 13.5% (35/259) of BS examinations were positive, 74.9% (194/259) were negative, and 11.6% (30/259) were equivocal. Unequivocally positive bone scans mostly showed multiple bone metastases while the remaining 20% presented single bone metastasis. The most common metastatic sites were the spine and rib which were involved in almost two-thirds of positive cases. As detailed in Table 4, among the 30 patients whose BS results were equivocal, 11 went on to receive further investigation with either plain film radiograph, computed tomography (CT), magnetic resonance imaging (MRI), or follow-up BS, which resulted in exclusion of bone metastasis in nine, whereas two remained equivocal, while no patient went on to have confirmed metastasis. The skeletal site most commonly associated with equivocal findings were the rib followed by the spine. Additional imaging with SPECT/CT as an adjunct to routine planar BS was done in 26 patients (10%). As shown in Table 5, add-on SPECT/CT resulted in definite BS readings in 22 cases (84.6%) which would have otherwise been equivocal on planar imaging alone.

Table 3 Bone scintigraphy findings

Characteristics	Number	Percent
Indication		
All	259	100.0
Staging	183	70.7
Surveillance	76	29.3
Positivity		
All	259	100.0
Positive	35	13.5
Negative	194	74.9
Equivocal	30	11.6
Focality		
Positive BS	35	100.0
Single	7	20.0
Multiple	28	80.0
Metastatic sites		
Positive BS	35	100.0
Spine	20	57.1
Rib	20	57.1
Pelvis	18	51.4
Femur	13	37.1
Scapula	9	25.7
Humerus	8	22.9
Skull	7	20.0
Sternum	7	20.0
Clavicle	4	11.4
Forearm	2	5.7
Tibia/fibula	0	0.0

Predicting Bone Scintigraphy Positivity

After exclusion of 30 patients with equivocal bone scintigraphy results, 229 patients were included in the regression model. Of these 229 patients, 162 were for staging and 67 were for surveillance. There was no significant difference in the positivity fractions between staging BS and surveillance BS which were 13.0% (21/162) and 21.0% (14/67), respectively (P -value = 0.132). As detailed in Table 6, clinical predictors including sex, age, cancer site, tumor staging, and histological grading were scrutinized in the univariable regression, and since all of these factors are clinically relevant factors, they were included in the multivariable regression model regardless of the P -values obtained in the univariable analysis. Based on previous findings which suggested that patients younger than 45 years old were more likely to have distant metastasis from HNCs [8], patients in this study were divided into those younger than 45 years of age, and those at or older, to be used as a categorical predictor in the regression analysis. Since nasopharyngeal carcinoma dominated other types of cancers in this cohort, cancer site was grouped into two categories, i.e.,

Table 4 Details of equivocal bone scintigraphy studies

Details	Number	Percent
Equivocal BS	30	100.0
No further evaluation	19	63.3
Further evaluation	11	36.7
Follow-up BS	4	13.3
Plain film	2	6.7
CT	4	13.3
MRI	1	3.3
Site of suspected abnormality		
Equivocal scans	30	100.0
Skull	2	6.7
Spine	7	23.3
Pelvis	4	13.3
Rib	12	40.0
Sternum	1	3.3
Scapula	2	6.7
Humerus	2	6.7
Femur/hip	4	13.4
Results of further evaluation		
Further evaluation	11	100.0
Metastasis excluded	9	81.8
Metastasis confirmed	0	0.0
Remained equivocal	2	18.2

nasopharyngeal carcinoma and cancers at other sites of the head and neck. Because histological grading of head and neck cancers was rather detailed and the pattern of pathological reporting was quite variable, for simplification, tumors in this study were therefore grouped into one of two categories, i.e.,

Table 5 Usefulness of SPECT/CT as an add-on to planar bone scintigraphy

Details	Number	Percent
Additional SPECT/CT		
All	259	100.0
Yes	26	10.0
No	233	90.0
Site of SPECT/CT		
Additional SPECT/CT	26	100.0
Spine	18	69.2
Pelvis	3	11.5
Chest	3	11.5
Extremity	2	7.8
Impact of additional SPECT/CT		
Additional SPECT/CT	26	100.0
Excludes bone metastasis	18	69.2
Confirms bone metastasis	4	15.4
Study remained equivocal	4	15.4

Table 6 Predictors of bone scintigraphy positivity by univariable and multivariable logistic regression

Factors	Positive	Negative	Positivity fraction (%)	Univariable logistic regression		Multivariable logistic regression	
				OR (95% C.I.)*	P-value	OR (95% C.I.)*	P-value
Sex							
Male	27	133	16.9%	1.00		1.00	
Female	8	61	11.6%	0.65 (0.28–1.50)	0.311	0.61 (0.23–1.56)	0.300
Age group							
≥45 years	22	156	12.4%	1.00		1.00	
< 45 years	13	38	25.5%	2.43 (1.12–5.25)	0.024	3.01 (1.24–7.33)	0.015**
Cancer site							
Other sites	7	94	6.9%	1.00		1.00	
Nasopharyngeal	28	100	21.9%	3.76 (1.57–9.02)	0.003	4.37 (1.04–18.41)	0.044**
T stage							
T1	7	24	22.6%	1.00		1.00	
T2	12	40	23.1%	1.03 (0.36–2.97)	0.958	1.41 (0.44–4.50)	0.566
T3	9	29	23.7%	1.06 (0.34–3.28)	0.914	1.77 (0.50–6.22)	0.377
T4	7	101	6.5%	0.24 (0.08–0.74)	0.013	0.36 (0.11–1.23)	0.104
N stage							
N0	2	41	4.7%	1.00		1.00	
N1	4	29	12.1%	2.83 (0.49–16.48)	0.248	1.52 (0.23–10.11)	0.661
N2	15	90	14.3%	3.42 (0.75–15.64)	0.113	2.02 (0.41–10.03)	0.388
N3	14	34	29.2%	8.44 (1.79–39.76)	0.007	3.29 (0.62–17.34)	0.160
Other distant metastasis							
Absent	28	177	13.7%	1.00		1.00	
Present	7	17	29.2%	2.60 (0.99–6.84)	0.052	3.84 (1.19–12.43)	0.025**
Differentiation							
Well/moderately differentiated	8	86	8.5%	1.00		1.00	
Poorly/un- differentiated	27	108	20.0%	2.69 (1.16–6.21)	0.021	0.70 (0.17–2.82)	0.618

*Odds ratio and 95% confidence interval

** $P < 0.05$ which indicates statistical significance from multivariable logistic regression analysis

well/moderately differentiated tumors or poorly/un- differentiated tumors. The former group comprised WHO type 1 nasopharyngeal carcinomas, well differentiated-, and moderately differentiated SCC of other head and neck sites, as well as tumors with other atypical histology as detailed in Table 1 since most of these tumors were considered to be low grade tumors. The latter group comprised WHO type 2 and 3 nasopharyngeal carcinomas, poorly differentiated SCC, or undifferentiated carcinomas of other head and neck sites, as well as one case of poorly differentiated adenocarcinoma. As shown in Table 6, independent predictors of bone scintigraphy positivity were age less than 45 years (OR 3.01, 95% C.I. 1.24–7.33, P -value 0.015), tumor site at the nasopharynx (OR 4.37, 95% C.I. 1.04–18.41, P -value 0.044), and the presence of other distant metastasis (OR 3.84, 95% C.I. 1.19–12.43, P -value 0.025). Predictors that showed statistical significance only in univariable logistic regression were N3 lymph node stage and poorly/un-differentiated histology.

Discussion

In this study, the authors evaluated the positivity fraction and clinical factors which could potentially predict positive BS in patients with HNCs. The patient cohort consisted of mostly middle-aged to elderly patients with a male predilection which was typical for HNCs. Nasopharyngeal carcinoma accounted for over half of the patients which was expected in a study cohort comprising patients of Asian ethnicity and concurred with published reports [24–26]. Overall, patients had rather advanced locoregional disease as demonstrated by the majority of patients having T3 and T4 disease. Similarly, most patients had regional lymph node metastasis. This is most likely due to the observational nature of this study and reflects practice patterns at the authors' institute where BS is more likely to be requested in HNCs that are locally advanced. The histological profiles of tumors fit with previously published reports with the majority of nasopharyngeal carcinoma of non-

keratinizing type [27] while tumors at other head and neck sites were mostly of the keratinizing type [28]. The proportion of positive bone scintigraphy studies for nasopharyngeal carcinoma and tumors of other sites was approximately 22% and 7% which was higher than that reported in previous studies [15–19] which could be because the majority of our patients had advanced stage disease. The higher prevalence of bone metastasis from nasopharyngeal carcinoma was also likely because the majority of our patients had non-keratinizing tumors which have a greater propensity for distant metastasis compared with keratinizing tumors [29]. Bone metastasis was most commonly found in the spine, rib, and pelvis which were the typical sites of metastatic involvement. The use of SPECT/CT proved to be valuable in patients with equivocal planar BS; additional information from SPECT/CT helped solve approximately 85% of equivocal cases by confirming that abnormalities in the planar BS were mostly due to degenerative changes and inflammatory processes.

Several clinical factors were found to be predictive of BS positivity. N3 disease was found to be predictive of BS positivity in the univariable analysis but not the multivariable analysis. This finding is not in line with previously reported studies which determined that N stage was an independent predictor of distant metastasis [18, 21] which could be because of the smaller sample size in this present study. Interestingly, patients with T4 tumors were less likely to have positive BS in the univariable analysis which could be because of the 108 patients with T4 disease, only 16 had N3 disease. This apparent relationship was lost in the multivariable analysis. Tumor site at the nasopharynx was found to be an independent predictor of BS positivity in this study as compared with tumors at other sites. This concurred with a previous study which demonstrated a high prevalence of bone metastasis in studies with nasopharyngeal carcinoma [20]. Approximately one-fifth of patients in this study were less than 45 years of age. Most of these younger patients had nasopharyngeal carcinoma which was in contrast to a previous study which found that most head and neck cancer patients younger than 40 years of age had oral and oropharyngeal cancers [30]. This likely represents differences of cancer epidemiology among Caucasian and Asian patients. Age of less than 45 years was found to be an independent predictor of BS positivity which is in concordance with a previous study which found increased odds of distant metastasis in HNC patients less than 45 years of age [8]. A possible explanation of this finding is the fact that in this study, patients less than 45 years of age had a higher proportion of nasopharyngeal carcinoma than patients 45 years of age or older. The presence of other distant metastasis was also found to independently predict BS positivity. This finding correlated with the previous study by Garavello et al. [8] which found that almost one-third of patients with HNCs with distant metastasis had metastasis in more than one organ. However, to the authors' knowledge, there has not been a

previous investigation that determined the presence of other distant metastasis to be an independent risk factor for bone metastasis. Poorly and undifferentiated tumors were more likely to have positive BS than well or moderately differentiated tumors in the univariable analysis, but this correlation did not hold true in the multivariable analysis. This is most likely because most poorly differentiated tumors were nasopharyngeal carcinomas thus resulting in multicollinearity which was negated in the multivariable analysis. The main limitation of this study lies within its retrospective nature; thus, introducing selection bias—patients in the cohort tended to have more advanced disease. Another major limitation of this study is the fact that metastatic bone lesions were not confirmed by histopathology since it is neither possible nor practical to obtain tissue diagnosis of all metastatic bone lesions demonstrated in BS. The pathology report among patients with HNCs had considerable heterogeneity and molecular markers were not routinely done, thus detailed categorization was not feasible.

Conclusion

The current study demonstrates that in contrast to most previous studies, bone metastasis as detected by bone scintigraphy may be found in a relatively high proportion of patients with head and neck cancers. Independent predictors of bone scan positivity include age of less than 45 years, tumor site at the nasopharynx, and the presence of distant metastasis to other organs. These findings indicate that bone scintigraphy is useful in patients with selected characteristics that enhance the pretest probability of bone metastasis.

Compliance with Ethical Standards

Conflict of Interest Daris Theerakulpisut, Nantapom Wongsurawat, Narudom Supakalin, and Charoonsak Somboonporn, declare that they have no conflict of interest. No funding was received for conduction of this study.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The institutional review board of our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

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