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^{99m}Tc bone scintigraphy does not affect preoperative workup for patients with potentially resectable esophageal squamous cell carcinoma

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Abstract

Background: ^{99m}Tc bone scintigraphy (BS) is the mainstay and most widely used technique in evaluation of bone metastasis (BM) in China. This study aimed to investigate the value of ^{99m}Tc BS in preoperative workup for patients with potentially resectable ($cT_{1-4a}N_{0-3}$) esophageal squamous cell carcinoma (ESCC).

Methods: This prospective cross-section clinical trial (ChiCTR1800020304) enrolled a total of 385 patients with ESCC diagnosed at thoracic surgery clinic from October 2018 to September 2020. All patients were diagnosed with stage $cT_{1-4a}N_{0-3}$ and were potential candidates for surgical resection. BS was performed preoperatively and the treatment strategy was changed after confirmation of BM. The primary endpoint was the rate of change of the treatment regimen because of BM, while the secondary endpoint was the rate of positive BS findings.

Results: Out of the 385 patients, only two (0.5%) changed their treatment regimen because of BM. The rate of positive BS findings was 1%, while two patients (0.5%) had false-positive or false-negative results. The BS diagnostic performance for BM was sensitivity 50%, specificity 99.5%, positive predictive value 50%, negative predictive value 99.5%, and accuracy 99.0%. There was no significant difference in BM in relation to age, sex, tumor location or clinical stage.

Conclusion: Our data demonstrated that ^{99m}Tc bone scintigraphy does not significantly affect the preoperative workup in patients with potentially resectable ESCC, especially in early clinical stage patients.

KEYWORDS
bone scintigraphy, esophageal cancer, metastasis, preoperative workup, squamous cell carcinoma

INTRODUCTION

Bone is one of the most common metastatic sites for many malignancies, such as prostate cancer, breast cancer, kidney cancer, and lung cancer.[1] Once bone metastasis (BM) is diagnosed, patients not only have to change the treatment strategy, but also may experience skeletal pain, hypercalcemia, pathologic fracture, and spinal cord or nerve root compression, often resulting in poor quality of life and worse survival rate.[2,3] it is therefore important to select the appropriate target population and tools for screening before surgery. Although positron emission tomography (PET)-CT is a widely used clinical tool for diagnosis of suspicious distant metastases,[4,5] it is associated with high costs and is undersupplied in rural or economically

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unattractive regions.[6,7] ^{99m}Tc bone scintigraphy (BS) is the mainstay method for the detection and evaluation of BM in various cancers at a relatively affordable cost. In addition, BS is still the most popular approach for detection of BM in preoperative staging in China.[8,9]

Esophageal cancer (EC), the sixth leading cause of cancer mortality in the world, is caused by complex factors as characterized by histology, population, and region.[10,11] Esophageal squamous cell carcinoma (ESCC) is one of the two most common histopathological types and prone to lymph node metastasis and distant metastasis. Accurate determination of tumor stage before commencement of therapy is vital in ensuring optimal outcomes for patients who undergo surgical resection for esophageal cancer.[12] A full-series preoperation workup for patients with newly diagnosed EC includes physical examination, pulmonary function test, echocardiography, endoscopy (ultrasound endoscopy) and biopsy, chest contrast-enhanced computed tomography (CT), ^{99m}Tc BS, enhanced magnetic resonance imaging (MRI) or CT of the brain, as well as abdominal ultrasonography or contrast-enhanced CT. Previous studies showed that there were few bone metastases cases in the preoperative staging processes involving potential resectable ESCC.[13] Routine performance of BS in EC patients remains controversial. Preoperative BS is not a recommended routine practice in patients with EC, as described in several international clinical guidelines, including the NCCN Guidelines (Version 5.2020), the Society of Thoracic Surgeons (STS) Guidelines, and the ESMO Clinical Practice Guidelines. Diverse opinions are also expressed in the literature. For instance, Allum et al. did not mention bone scan as an initial staging analysis,[12] while Quint et al. suggested that routine preoperative BS detects metastases only in patients with signs and/or symptoms of metastases.[14] However, Jennings et al. and Li et al. reported that BS should be used to detect metastasis before radical surgery.[13,15] Moreover, differences in metastatic pattern, geographic patterns, time trends, and primary risk factors were observed between ESCC and esophageal adenocarcinoma (AC).[11,15,16] Whereas ACs are more prevalent in some Western countries, ESCC is the predominant type of EC in Asia, especially in China.[14] Previous studies that evaluated the value of BS mainly focused on esophageal adenocarcinoma (EAC), but not ESCC. Thus, their conclusions may not provide appropriate guidance on BS for ESCC. Correct detection of BM in patients with ESCC is vital for prognosis and application of appropriate therapeutic strategies.

This prospective study aimed to investigate the effect of BS as a routine preoperative staging tool in patients with potentially resectable ($cT_{1-4a}N_{0-3}$) ESCC.

METHODS

Eligibility criteria

This prospective cross-section clinical trial evaluated a total of 385 patients with ESCC diagnosed at the thoracic surgery clinic at the Cancer Hospital, Chinese Academy of Medical Sciences from October 2018 to September 2020. Candidates were screened according to inclusion criteria and exclusion criteria. Inclusion criteria included (i) had been histologically confirmed as potentially resectable thoracic ESCC, clinically staged as $T_{1-4a}N_{0-3}$ before treatment; (ii) were aged between 18 and 75 years; (iii) had normal hematologic, renal and hepatic function; (iv) had a Karnofsky performance score of≥90; and (vi) had no bone-related symptoms. Patients with (i) a previous history of malignancy or any antitumor treatment and (ii) those with related bone disease which can cause osteogenesis or osteolysis were excluded from this study. A total of 385 eligible patients identified from the Department of Thoracic Surgery of National Cancer Center/Cancer Hospital were included (Figure 1). All patients gave their informed consent prior to their inclusion in the study. The design and implementation of the research conformed to the provisions of the Declaration of Helsinki (1995). This study was approved by the institutional review boards and the ethics committee of the National Cancer Center. This trial was registered in Chinese Clinical Trials (ChiCTR1800020304).

Follow-up and identification of bone metastases

All patients were seen at the outpatient clinic at 3-month intervals during the first 2 years. Follow-up extended until March 2021, ensuring a minimal potential follow-up of 6 months. The primary endpoint for this study was the rate of change of surgical plan because of positive BS results. It was defined as the number of patients whose treatment strategy was changed due to positive BS results divided by the total number of patients. The secondary endpoint was the rate of positive BS results.

The BS examination protocol was in accordance with the European Association of Nuclear Medicine guidelines. Two experienced nuclear medicine physicians independently determined whether a BS was positive or negative. If the two doctors disagreed, a consensus was reached after discussion with a senior physician. If a positive conclusion was drawn, an MRI of the lesion was performed to confirm the results.

Patients with abnormal findings after BS underwent further MRI if bone metastases could be excluded, as shown in Figure 2a,c. Based on previous literature research,[13,17] this study defined bone recurrence as BM detected as the first site of recurrence with or without R0 esophagectomy within 6 months. Therefore, a negative BS was identified as false negative (Figure 2b) if BM was confirmed by MRI in patients within 6 months after initial BS.

Sample size estimation

Without knowledge of the incidence of BS in the potentially resectable thoracic ESCC clinically staged as $T_{1-4a}N_{0-3}$, we set the prevalence to be 0.5, the survey accuracy d was set as

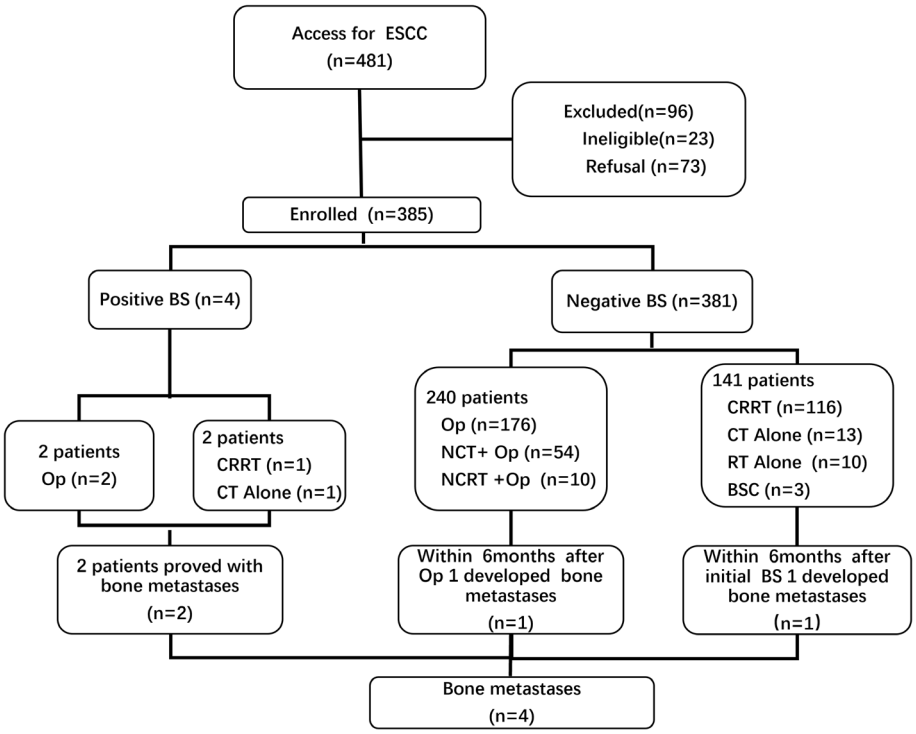

FIGURE 1 ESCC, esophageal squamous cell carcinoma; BS, bone scintigraphy; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; RT, radiotherapy; BSC, best supportive care; Op, operation; NCT + Op, neoadjuvant chemotherapy followed by operation; NCRT + Op, neoadjuvant chemoradiotherapy followed by operation

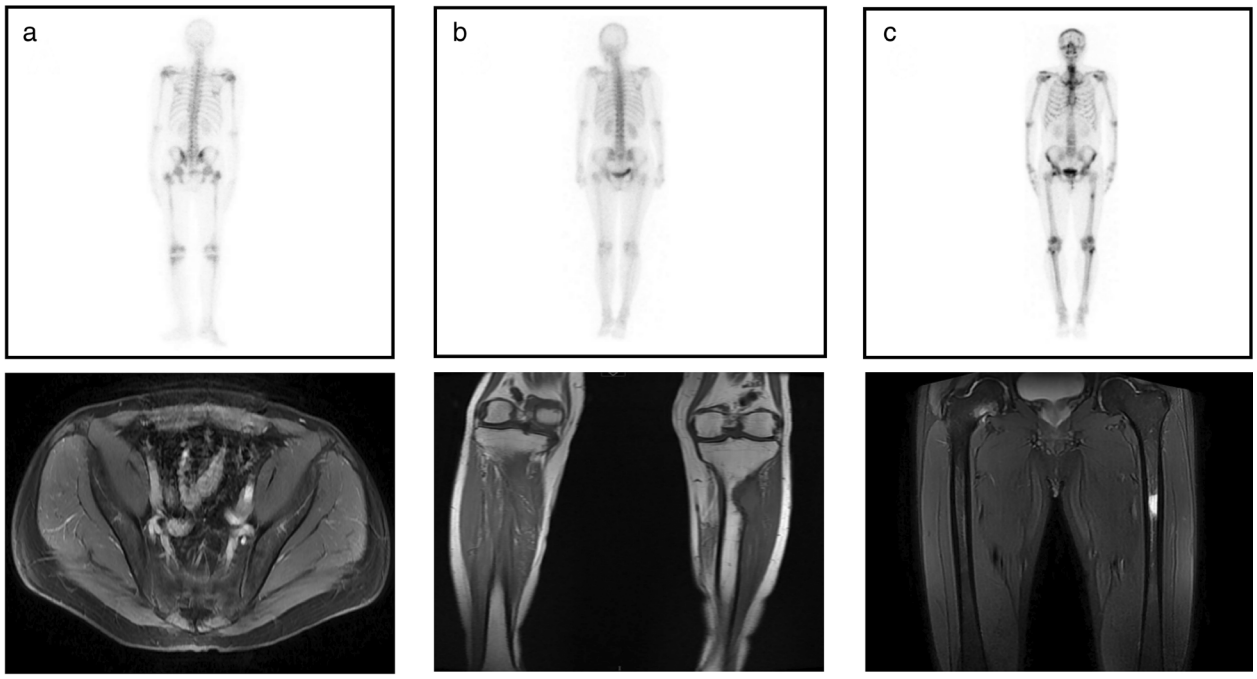

FIGURE 2 (a) False positive: Bone scintigraphy shows increased radioactivity uptake of the iliac bone, but enhanced magnetic resonance imaging shows no bone destruction. (b) False negative: No abnormalities were found on bone scintigraphy, enhanced magnetic resonance imaging results in destruction of the tibial bone. (c) True positive: Both bone scintigraphy and enhanced magnetic resonance imaging detected bone abnormality

0.05, and the confidence level was 0.95. We then calculated the conservative sample size to be 385 patients. We hypothesized that if (i) the incidence rate of patients with potentially resectable thoracic ESCC who had their surgical plan changed due to positive BS results was 0.5% (P0) and (ii) the rate of patients who had their surgical plan changed because of positive BS results was 2% (P1), then the preoperative BS examination would be regarded as a routine preoperative workup for the potentially resectable thoracic ESCC clinically staged as $T_{1-4a}N_{0-3}$. The null hypothesis was H0: $P \leq P0$, while the alternative hypothesis was HA: $P \geq P1$, $\alpha = 0.05$, $1 - \beta = 0.9$.

Statistical analyses

The Pearson X^2 test or Fisher exact tests were adopted to assess the correlation between clinic pathologic variables and the frequency of BM. The statistical analyses were performed using SPSS 26.0 for Windows (SPSS Inc.).

RESULTS

From October 2018 to September 2020, the thoracic surgery clinic diagnosed a total of 481 patients with ESCC. Ninety-six patients were excluded from the study: 73 were ineligible for advanced locoregional disease or other distant metastases, while the remaining 23 could not complete the BS for personal reasons. All the 385 patients enrolled in this study were followed up for more than a year or until death. The average age of the 385 patients was 62.0 ± 7.6 years (ranging from 38 to 75 years old). Thirty-nine patients had The Amercian Joint Committee on Cancer (AJCC) 8th stage I disease, 171 patients had AJCC 8th stage II disease, 149 patients had AJCC 8th stage III disease, while 149 patients had AJCC 8th stage IV disease (Table 1). Four patients (1%) were found with abnormal radiological uptake on preoperative BS. MRI was used for sites with abnormal uptake and revealed that there was no evidence of BM in two of the four patients, and only two patients (0.05%) changed their clinical treatment because of BM. No patients with a false-positive BS were proven to have BM within the first year after surgery.

Out of the 381 patients with negative bone scan, 240 patients received esophagectomy. Out of the 240 patients, one patient showed left tibia metastases at the fourth month and died within 6 months after surgery. On the other hand, out of the other 141 patients who did not receive surgery, one patient developed scapula metastasis on the third month and died within 8 months after initial negative bone scan.

The presence of positive BS as an indication of metastasis presented 40% sensitivity (2/4), 99.5% specificity (379/381), 50% positive predictive value (PPV), and 99.5% negative predictive value (NPV) (Table 1). According to the 8th AJCC stage, in 210 patients with stage I and stage II ESCC, there was no confirmation of final BM, while in patients with stage III and stage IV, there were two cases with BM (Table 1).

Analysis of the relationship between BM and clinical variables showed that the frequency of BM had no association with age, sex, tumor location or pathologic subtype (Table 2).

DISCUSSION

Routine performance of BS in ESCC patients remains controversial. In this prospective cross-sectional study, we analyzed the value of ^{99m}Tc bone scintigraphy in the staging of potentially resectable ($cT_{1-4a}N_{0-3}$) ESCC. The results showed that the incidence of BM seemed to be low (1%) in patients who were diagnosed with potentially resectable ESCC. Furthermore, there was a total of four patients (1%) with positive BS, but only two patients (0.5%) changed their surgical strategies because of BM, while the other two did not have BM but received radical surgery. Among the 381 patients with negative BS results, two had BM at the fourth month after surgery and the third month after antitumor treatment. The data showed that BS has a high false-positive rate (50%, 2/4). In our analyses, BM was not found in 39 stage I and 171 stage II patients, while in stage III and stage IV patients, the incidence of BM was only 2.2%, indicating that the value of BS may be limited for ESCC, at least in clinical stage I and II patients.

Previous studies reported that the most common site of distant metastases in EC was liver, followed by lymph nodes, lung, bone, and then brain,[18] therefore BM in the patients with EC is uncommon, with incidence rates ranging from 5.2% to 7.7% in all-stage patients with EC and from 15.3% to 23.6% in patients with metastases.[19] Adenocarcinoma (AC) and squamous cell carcinoma (SCC) are two major histological subtypes of EC. In a large study involving 25 955 patients with esophageal cancer, Zhang et al.[20] reported that there was more occurrence of BM in AC than SCC. In addition, they showed that patients with T4 stage grade III and N1-3 were the main risk factors in BM, consistent with findings in our study.

To date, there is no clear clinical screening guideline on BM in EC. The BM diagnosis is mainly based on radiographic imaging strategies, such as CT, ^{99m}Tc bone scintigraphy, MRI, and fluorodeoxyglucose positron emission tomography integrated with computed tomography (FDG-PET)/CT.[21] There are limited data on the value of BS in esophageal cancer staging. For instance, Jennings et al.[13] demonstrated that BS has a high false-positive rate (11/22,50%) and a third of patients (5/16, 31%) did not have BM before surgery. Another

TABLE 1 Sensitivity, specificity, PPV, NPV, and accuracy of bone scan in 385 patients with esophageal squamous cell carcinoma

8th AJCC stage	Bone metastasis	Abnormal bone scan finding	Sensitivity	Specitivity	PPV	NPV	Accuracy
All ($N = 385$)	4	4	50% (2/4)	99.5% (379/381)	50% (2/4)	99.5% (379/381)	99.0% (381/385)
I ($N = 39$)	0	0	-(0/0)	100% (39/39)	-(0/0)	100% (39/39)	100% (39/39)
II ($N = 171$)	0	2	-(0/0)	98.8% (169/171)	0% (0/2)	100% (169/169)	98.8% (169/171)
III ($N = 149$)	2	0	0% (0/2)	100% (147/147)	-(0/0)	98.7% (147/149)	98.7% (147/149)
IV ($N = 26$)	2	2	100% (2/2)	100% (24/24)	100% (2/2)	100% (24/24)	100% (26/26)

Abbreviations: AJCC,; NPV, negative predictive value; PPV, positive predictive value.

TABLE 2 Clinicopathologic features of 385 esophageal squamous cell carcinoma patients with ^{99m}Tc bone scintigraphy

Factors	Overall number (%)	Without bone metastasis (%)	Bone metastasis (%)	*p* value
Age (years)				
≥63	198 (51.4%)	197 (99.5%)	1 (0.05%)	0.575
<63	187 (48.6%)	184 (98.4%)	3 (1.6%)	
Sex				1.000
Male	331 (86.0%)	327 (98.8%)	4 (1.2%)	
Female	54 (14.0%)	54 (100%)	0 (0%)	
Tumor location				0.708
Upper	53 (13.8%)	53 (100%)	0 (0%)	
Middle	182 (47.3%)	180 (98.9%)	2 (1.1%)	
Lower	150 (38.9%)	148 (98.7%)	2 (1.3%)	
T stage				0.423
T1 + T2	119 (30.9%)	119 (100%)	0 (0%)	
T3 + T4a	266 (69.1%)	262 (98.5%)	4 (1.5%)	
N stage				0.133
Negative	192 (49.9%)	192 (100%)	0 (%)	
Positive	193 (50.1%)	189 (97.9%)	4 (2.1%)	
8thAJCC stage				0.090
I + II	210 (54.5%)	210 (100%)	0 (0%)	
III + IV	175 (45.5%)	171 (97.7%)	4 (2.3%)	

χ^2 test, Fisher's exact test, or t test was used for statistically analyzed.

retrospective study by Li et al.[15] showed that BS has a high false-positive rate in early-stage (I and II) patients (8/12, 66%), and all the positive results were confirmed by further examinations. Certainly, BS is a cheaper, clinically established, and widespread screening method for detection of BM. However, our data showed that the detection efficiency of BM by bone scanning alone is not high. In some studies, whole-body MRI and PET-CT showed higher accuracy compared with BS.[22–24] Kato et al. compared PET-CT with BS in esophageal carcinoma patients, and showed that PET-CT had 92% sensitivity, 94% specificity, and 93% accuracy, compared with 77%, 84%, and 82%, respectively, for BS.[25] Without consideration of the investigation costs and medical insurance reimbursement, MRI or PET-CT may be recommended for detection of BMs. However, even BS or PET-CT was performed as routine preoperative examination, both methods were more invasive than the other preoperative workup and were associated with safety issues due to radiation exposure.

Although our study highlights important findings, it was limited by the narrow population coverage and thus there is a need for larger prospective multicenter studies to confirm our results. This study is also a cross-sectional survey and the results were not further verified by PET-CT due to the refusal by the China's medical insurance payment system to pay for these procedures.

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DISCLOSURE

The authors report no conflicts of interest in this work.

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REFERENCES

1. Coleman RE, Croucher PI, Padhani AR, Clézardin P, Chow E, Fallon M, et al. Bone metastases. Nat Rev Dis Primers. 2020;6(1):83.
2. Decroisette C, Monnet I, Berard H, Quere G, le Caer H, Bota S, et al. Epidemiology and treatment costs of bone metastases from lung cancer: a French prospective, observational, multicenter study (GFPC 0601). J Thorac Oncol. 2011;6(3):576–82.
3. Fornetti J, Welm AL, Stewart SA. Understanding the bone in cancer metastasis. J Bone Miner Res. 2018;33(12):2099–113.
4. Chen H, Pang Y, Wu J, Zhao L, Hao B, Wu J, et al. Comparison of [(68)Ga]Ga-DOTA-FAPI-04 and [(18)F] FDG PET/CT for the diagnosis of primary and metastatic lesions in patients with various types of cancer. Eur J Nucl Med Mol Imaging. 2020;47(8):1820–32.
5. Vaarwerk B, Breunis WB, Haveman LM, et al. Fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) for the detection of bone, lung, and lymph node metastases in rhabdomyosarcoma. Cochrane Database Syst Rev. 2021;11:CD012325.
6. Dreger M, Langhoff H, Henschke C. Adoption of large-scale medical equipment: the impact of competition in the German inpatient sector. Eur J Health Econ. 2021;23:791–805.
7. Matsumoto M, Koike S, Kashima S, Awai K. Geographic distribution of CT, MRI and PET devices in Japan: a longitudinal analysis based on National Census Data. PLoS One. 2015;10(5):e0126036.
8. Davila D, Antoniou A, Chaudhry MA. Evaluation of osseous metastasis in bone scintigraphy. Semin Nucl Med. 2015;45(1):3–15.
9. Li H, Ye T, Li N, Xia G, Li B, Zhang Y, et al. Is (99m) Tc bone scintigraphy necessary in the preoperative workup for patients with cT1N0

subsolid lung cancer? A prospective multicenter cohort study. Thorac Cancer. 2021;12(4):415–9.
10. Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, et al. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): a phase III multicenter, randomized, open-label clinical trial. J Clin Oncol. 2018;36(27):2796–803.
11. Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. Gastroenterology. 2018;154(2):360–73.
12. Hayes T, Smyth E, Riddell A, Allum W. Staging in esophageal and gastric cancers. Hematol Oncol Clin North Am. 2017;31(3):427–40.
13. Jennings NA, Griffin SM, Lamb PJ, Preston S, Richardson D, Karat D, et al. Prospective study of bone scintigraphy as a staging investigation for oesophageal carcinoma. Br J Surg. 2008;95(7):840–4.
14. Quint LE, Hepburn LM, Francis IR, Whyte RI, Orringer MB. Incidence and distribution of distant metastases from newly diagnosed esophageal carcinoma. Cancer. 1995;76(7):1120–5.
15. Li SH, Huang YC, Huang WT, Lin WC, Liu CT, Tien WY, et al. Is there a role of whole-body bone scan in patients with esophageal squamous cell carcinoma. BMC Cancer. 2012;12:328.
16. Gockel I, Kneist W, Junginger T. Incurable esophageal cancer: patterns of tumor spread and therapeutic consequences. World J Surg. 2006;30(2):183–90.
17. Lee SJ, Lee KS, Yim YJ, Kim TS, Shim YM, Kim K. Recurrence of squamous cell carcinoma of the oesophagus after curative surgery: rates and patterns on imaging studies correlated with tumour location and pathological stage. Clin Radiol. 2005;60(5):547–54.
18. Wu SG, Zhang WW, He ZY, Sun JY, Chen YX, Guo L. Sites of metastasis and overall survival in esophageal cancer: a population-based study. Cancer Manage Res. 2017;9:781–8.
19. Imura Y, Yamamoto S, Wakamatsu T, Tanaka T, Tamiya H, Sugimura K, et al. Clinical features and prognostic factors in patients with esophageal cancer with bone metastasis. Oncol Lett. 2020;19(1):717–24.
20. Zhang J, Ma W, Wu H, Wang J, Lin Y, Wang X, et al. Analysis of homogeneous and heterogeneous factors for bone metastasis in esophageal cancer. Med Sci Monit. 2019;25:9416–25.
21. Cook GJR, Goh V. Molecular imaging of bone metastases and their response to therapy. J Nucl Med. 2020;61(6):799–806.
22. Fujimoto R, Higashi T, Nakamoto Y, Hara T, Lyshchik A, Ishizu K, et al. Diagnostic accuracy of bone metastases detection in cancer patients: comparison between bone scintigraphy and whole-body FDG-PET. Ann Nucl Med. 2006;20(6):399–408.
23. Ghanem N, Uhl M, Brink I, Schäfer O, Kelly T, Moser E, et al. Diagnostic value of MRI in comparison to scintigraphy, PET, MS-CT and PET/CT for the detection of metastases of bone. Eur J Radiol. 2005;55(1):41–55.
24. Kruger S, Buck AK, Mottaghy FM, et al. Detection of bone metastases in patients with lung cancer: 99mTc-MDP planar bone scintigraphy, 18F-fluoride PET or 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging. 2009;36(11):1807–12.
25. Kato H, Miyazaki T, Nakajima M, Takita J, Kimura H, Faried A, et al. Comparison between whole-body positron emission tomography and bone scintigraphy in evaluating bony metastases of esophageal carcinomas. Anticancer Res. 2005;25(6C):4439–44.

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