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Patterns of bone metastases from head and neck squamous cell carcinoma

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ABSTRACT

Objective: To report clinical features of bone metastases (BM) from head and neck squamous cell carcinoma (HNSCC).

Methods: Among 772 patients with HNSCC diagnosed at our hospital over 9 years, 30 patients (3.9%) had clinical evidence of BM (24 men and 6 women; mean age: 63 years). We assessed the time interval from the primary diagnosis to BM development, symptoms attributable to BM, presence of distant metastases to other organs, number of BM, sites of BM, morphologic changes on computed tomography (CT) images, treatment for BM, and overall survival (OS).

Results: BM at the initial stage were found in 9 patients with HNSCC (30%), and in 21 patients (70%) with HNSCC during the course of the disease. In the later patients, the median time interval from the primary diagnosis was 11.5 months. Nineteen patients (63%) did not have BM-related symptoms, 6 (20%) had pain, 3 (10%) had neurologic symptoms resulting from vertebral or skull metastases, and 2 (7%) had hypercalcemia. Seventeen patients (57%) showed bone-exclusive metastases, and 13 (43%) had distant metastases in other organs. Eleven patients (37%) had monostotic metastases (solitary BM), and 19 patients (63%) had polyostotic metastases (multiple BM). When combined, 9 patients (30%) showed bone-exclusive and monostotic metastases. The most commonly affected site was the thoracolumbar spine, accounting for 34% of total BM, followed by the pelvis (24%), shoulder and thorax (21%), and the extremities (17%). Notably, metastases to bones above the clavicle (craniofacial bones and cervical spine) accounted for only 3% of all bone lesions. CT images showed variable morphologic patterns with osteolytic type in 17 patients (57%), intertrabecular in 7 (23%), osteoblastic in 4 (13%), and mixed in 2 (7%). Systematic chemotherapy for BM was performed in 19 patients and radiotherapy in 18. The median survival time for patients with bone-exclusive and monostotic metastases was significantly longer

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than that for patients with multi-organ metastases or polyostotic metastases at 18.2 months vs. 5.7 months (p = 0.02). Neither chemotherapy nor radiotherapy extended OS.
Conclusion: Thirty percent of BM cases from HNSCC showed bone-exclusive and monostotic metastases. These patients tended to show a more favorable prognosis than patients with multi-organ metastases or polyostotic metastases.

1. Introduction

The incidence of distant metastases in head and neck squamous cell carcinoma (HNSCC) is 1.2–2.8% at presentation [1–3], and 8.9–13.8% [1,3,4] over the course of the disease. Following the lungs, bone is the second-most frequent site of metastases, accounting for 15–39% of distant metastases cases [1–5]. In addition to denoting a dismal prognosis, skeletal-related events due to bone metastases (BM) cause significant alterations in performance status and quality of life [6]. Nevertheless, descriptions of BM from HNSCC have remained limited [7–11]. The purpose of this study is to report patterns of BM from HNSCC encountered during a 10-year period in our institution.

2. Material and methods

This retrospective study was approved by our institutional review board, and the need to obtain informed consent was waived. Among a total of 917 patients with HNSCC registered at our institution between January 2009 and December 2017, we identified 30 cases that developed BM by searching an electronic database for the time period from January 2009 to December 2018. The diagnoses of BM were made by histopathological examination of biopsied or surgically resected specimens in 5 patients. In the remaining 25 patients, diagnoses were made by imaging. BM were diagnosed by magnetic resonance (MR) examinations, which were performed for skeletal-related events in 6 patients, by the detection of bone lesions by follow-up computed tomography (CT) in 2 patients, and by a combination of the detection of bone lesions by ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) for staging and the presence of corresponding abnormalities on CT or MR images in 17 patients.

The age, gender, primary site, initial T- and N-classification distributions of these 30 patients are shown in Table 1. Patients were 24 men and 6 women with a mean age of 63 years (range: 38–87 years). The primary tumor site was the nasopharynx in 7 (23%) patients, the oropharynx in 8 (27%), the oral cavity in 8 (27%), the hypopharynx in 5 (17%), and the sinonasal cavity in 2 (7%). T-classifications were T1 in 3 patients (10%), T2 in 9 (30%), T3 in 6 (20%), and T4 in 12 (40%). N-classifications were N0 in 6 patients (20%), N1 in 2 (7%), N2 in 16 (53%), and N3 in 6 (20%). We assessed the time interval from the initial primary diagnosis to the development of BM, symptoms attributable to BM, presence of distant metastases to other organs, number of BM, sites of BM, morphologic changes on CT images, treatment for BM, and overall survival (OS). Anatomical sites were divided into the following 5 areas: above the clavicle (craniofacial bones and cervical spine), shoulder and thorax (clavicle, scapula, sternum, and ribs), the thoracolumbar spine, the pelvis (ilium, ischium, pubis, hip, and sacrum-coccyx), and the extremities. Morphologic changes on CT images were evaluated independently by two radiologists and classified into osteolytic, intertrabecular, osteoblastic, and mixed types. Discrepancies between the two radiologists were resolved by consensus decisions.

OS was defined from the date of diagnosis of BM to the date of death from any cause or the end of data collection (March 2019), and the mean follow-up period was 17.5 months (range: 1–101 months). The Kaplan–Meier method was used to estimate cumulative survival and to depict survival curves. Statistical differences in survival curves were evaluated using the log-rank test. Univariate analyses using a Cox proportional hazards model were performed to identify relationships between the extent of distant metastases or treatment modalities with OS.

JMP software version 12.2.0 (SAS Institute; Cary, NC, USA) was used for all statistical analyses. GraphPad Prism version 6.0b (GraphPad Software, Inc.; San Diego, CA, USA) was used to generate a Kaplan–Meier curve. A p-value <0.05 was used to assess statistical significance.

3. Results

Clinical features of BM are summarized in Tables 2 and 3, and representative cases and a Kaplan–Meier curve of OS are shown in Figs. 1–3. BM were found at the initial tumor stage in 9 patients (30%) and during follow-up in 21 patients (70%). The median time interval from the initial diagnosis to subsequent development of BM was 11.5 months (average: 11.3 months; range: 1–32 months). Nineteen patients (63%) had BM without relevant skeletal-related symptoms, and 11 patients (37%) had skeletal-related symptoms. According to the skeletal-related symptoms, pain was the most common symptom that was seen in 6 patients, followed by neurological symptoms in 3 patients, and hypercalcemia in 2 patients.

Seventeen patients (57%) presented with bone-exclusive metastases, and 13 (43%) had distant metastases to other organs. Of these 13 patients, metastases to extra-regional lymph nodes were found in 8 patients, lung metastases were found in 8, liver metastases in 5, adrenal metastases in 1. Eleven patients (37%) had monostotic metastases, and 19 patients (63%) had polyostotic metastases, and resulting in 9 patients (30.0%) showing bone-exclusive and monostotic metastases.

Table 1
Patient characteristics.

Patients distributions (N = 30)	
Gender	
Male	24 (80%)
Female	6 (20%)
Age (mean, range)	63 years (38-87 years)
Tumor location	
Nasopharynx	7 (23%)
Oropharynx	8 (27%)
Oral cavity	8 (27%)
Hypopharynx	5 (17%)
Sinonasal Cavity	2 (7%)
T classification	
T1	3 (10%)
T2	9 (30%)
T3	6 (20%)
T4	12 (40%)
N classification	
N0	6 (20%)
N1	2 (7%)
N2	16 (53%)
N3	6 (20%)

Table 2
Characteristics of bone metastases.

Clinical features (N = 30)	
Time to developing BM	
Initial tumor staging	9 (30%)
During disease course	21 (70%)
<Median time interval from the primary diagnosis>	11.5 months (range 1–32)
Symptom attributable to BM	
None	19 (63%)
Pain	6 (20%)
Neurological symptom	3 (10%)
Hypercalcemia	2 (7%)
Metastases to other organs	
None	17 (57%)
Present	13 (43%)
Number of BM	
Monostotic metastases	11 (37%)
Polyostotic metastases	19 (63%)
Sites of BM	
Thoracicolumbar spine	34%
Pelvis	24%
Shoulder and thorax	21%
Extremities	17%
Above the clavicle	3%
CT morphology	
Osteolytic type	17 (57%)
Intertrabecular type	7 (23%)
Osteoblastic type	4 (13%)
Mixed type	2 (7%)
Treatment for BM	
Surgery with adjuvant chemo-radiotherapy	1 (3%)
Systematic chemotherapy	18 (60%)
Palliative radiotherapy	17 (57%)
Bone modifying agent	7 (23%)
None	4 (13%)

N: number of patients, BM: bone metastases.

The most commonly affected site was the thoracolumbar spine, accounting for 34% of total BM, followed by the pelvis (24%), shoulder and thorax (21%), and the extremities (17%). Notably, metastases to bones above the clavicle (craniofacial bones and cervical spine) accounted for only 3% of all BM.

Morphologic changes on CT images were variable: osteolytic types in 17 patients (57%), intertrabecular types in 7 patients (23%), osteoblastic types in 4 patients (13%), and mixed types in 2 patients (7%).

Eighteen patients underwent systematic chemotherapy for BM, and one patient underwent surgical resection followed by adjuvant radiotherapy (RT) and systematic chemotherapy. To alleviate or prevent skeletal-related events, palliative RT was performed in 17 patients, and bone modifying agents were administered in 7 patients. In 4 patients, no treatment for BM was performed to enable the best supportive care.

With regard to prognosis, median survival time, 1-year OS rate, and 3-year OS rate for all patients were 6.6 months, 35%, and 14%. Those for patients with bone-exclusive and monostotic metastasis was 18.2 months, 56% and 33%, and those for patients with multi-organ or polyostotic metastases was 5.7 months, 25% and 5%, showing the former group had a significantly longer OS ($p = 0.02$). In contrast, any treatment for BM did not influence OS: MST, 1-year OS rate, and 3-year OS rate for patients who underwent chemotherapy were 9.0 months, 33% and 17%, respectively, and for those who did not undergo chemotherapy, they were 4.9 months, 36% and 9%, respectively ($p = 0.30$). For patients who underwent RT: MST, 1-year OS rate, and 3-year OS rate were 14.1 months, 55% and 18%, respectively, and for those who did not undergo RT, they were 5.7 months, 22% and 11%, respectively ($p = 0.26$).

4. Discussion

More than a decade ago, BM from HNSCC were thought to be late events that occur in a setting of other widespread metastases, and the reported incidences were 1.3–2.4% [11–13]. The recent wide availability of FDG-PET examination for HNSCC staging revealed occult metastases, resulting in an increase of incidences ranging from 1.9% to 8.4% [3,7–9]. The observed incidences in our study (3.9%) were in accord with these new ranges, and in half of our cases, BM without skeletal-related symptoms were found by FDG-PET examinations for staging. According to skeletal-related symptoms, pain and neurologic dysfunctions were the usual presenting symptoms, which is in accordance with previous reports [11,14,15].

The reported ratios of BM found at initial presentation and those found during the overall disease course showed an extremely broad range from 0% to 72.2% [3,7–11]. This variety seems to be due to deviations of primary sites and T- and N-classifications resulting from the small patient population size. In our cases, 30% of cases with BM were found at initial staging, and most of the remaining cases were found within two years after initial primary presentation, which is in accordance with data of overall distant metastases from HNSCC collected in larger cohorts [1,3,4]. Therefore, we presume that the incidence of BM from HNSCC shows a similar time course than that of lung metastases from HNSCC, which is the most frequent site of distant metastases.

Table 3
Univariate analyses for overall survival.

Overall survival					
	N (%)	MST (months)	1-year OS (%)	3-year OS (%)	P-Value
All patients	30 (100)	6.6	35	14	
Extent of BM					
Bone-exclusive and monostotic	9 (30)	18.2	56	33	**0.02**
Multi-organ or polyostotic	21 (70)	5.7	25	5	
Chemotherapy					
Yes	19 (63)	9.0	33	17	0.30
No	11 (37)	4.9	36	9	
Radiotherapy					
Yes	18 (60)	14.1	55	18	0.26
No	12 (40)	5.7	22	11	

Statistically significant P value is given in bold.
N: number of patients, MST: median survival time, OS: overall survival, BM: bone metastases.

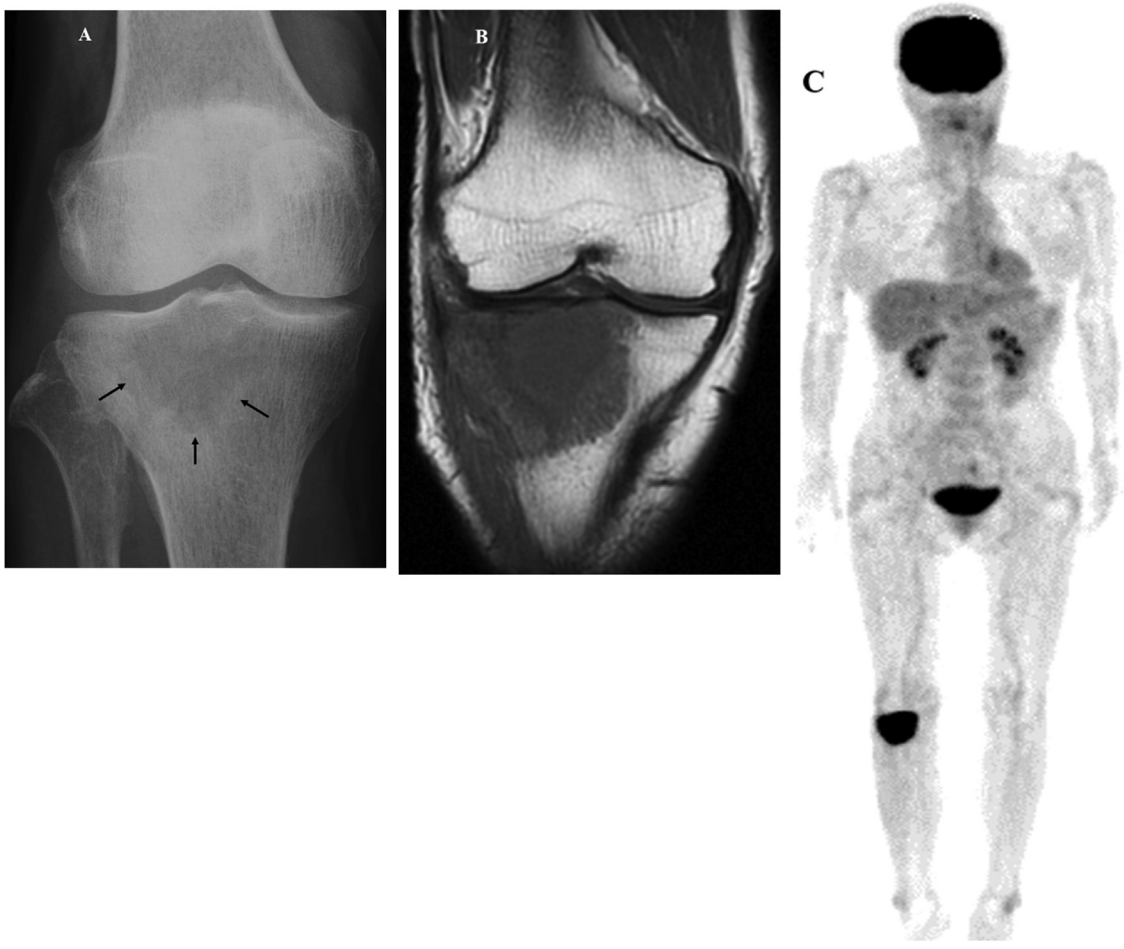

Fig. 1. Bone-exclusive and monostotic metastasis from nasopharyngeal squamous cell carcinoma.
A 69-year old woman with nasopharyngeal carcinoma (T4 T2b M0) was treated with chemoradiotherapy, resulting in complete remission. 15 months after the initial tumor presentation, she complained of gonalgia. Plain radiography and MR imaging suggested osteolytic metastasis to the tibia (A and B), and subsequent FDG-PET examination (C) did not show any other metastases. The patient was treated with local palliative radiotherapy and systematic chemotherapy and is alive without tumor recurrence for 15 months.

Recent studies have shown that neither metastases exclusive to the bone nor monostotic metastases are rare, with the former having a prevalence of 24–46% and the latter of 24–50% [7–9]. In accordance with these data, 57% of current cases showed bone-exclusive metastases, and 37% showed monostotic metastases. In addition, 30% of current cases presented with bone-exclusive and monostotic metastasis, which is in line with the previous data. In other words, the presence of BM from HNSCC does not always mean a widely disseminated stage of the disease.

It has been observed that BM from common malignant tumors preferentially occur in bones anatomically adjacent to

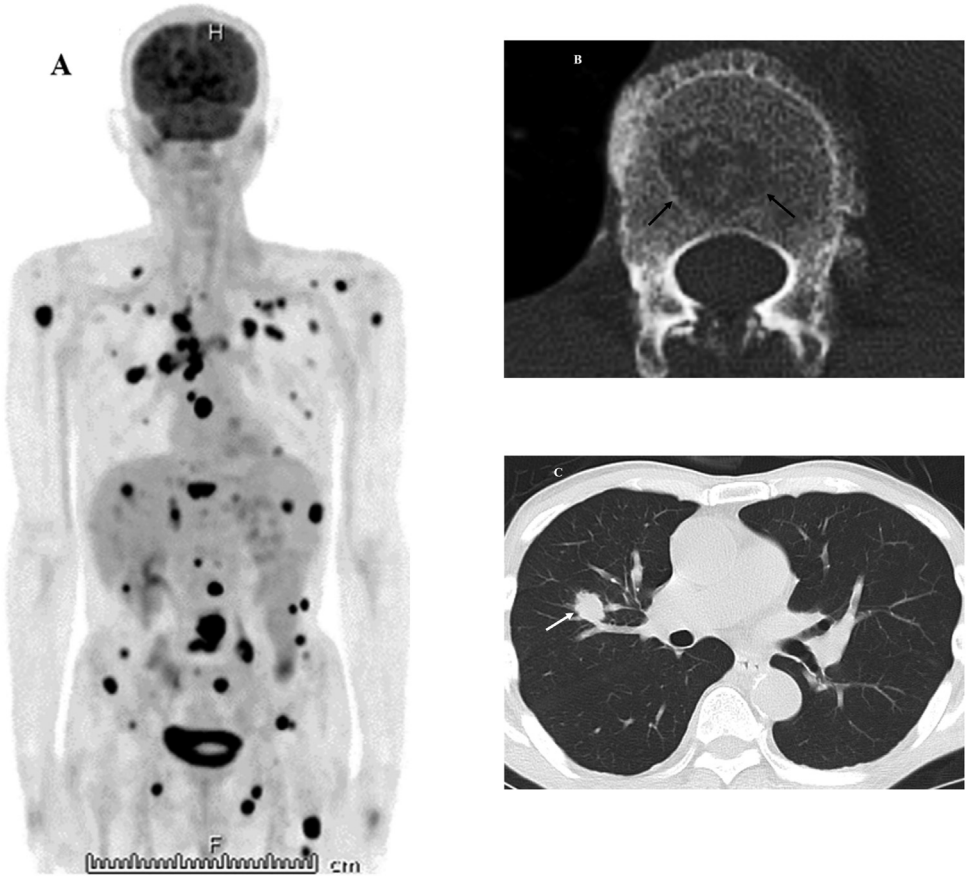

Fig. 2. Multi-organ and polyostotic metastases from oral squamous cell carcinoma.
Curative surgical resection was performed in a 72-year old man with oral cancer (T2 N2a M0). Follow-up FDG-PET/CT examination, which was performed 15 months after the initial tumor presentation, suggested multi-organ and polyostotic metastases (A). CT confirmed osteolytic bone metastases and multiple lung metastases (B and C). In spite of systematic chemotherapy, the patient died two months after the development of metastases.

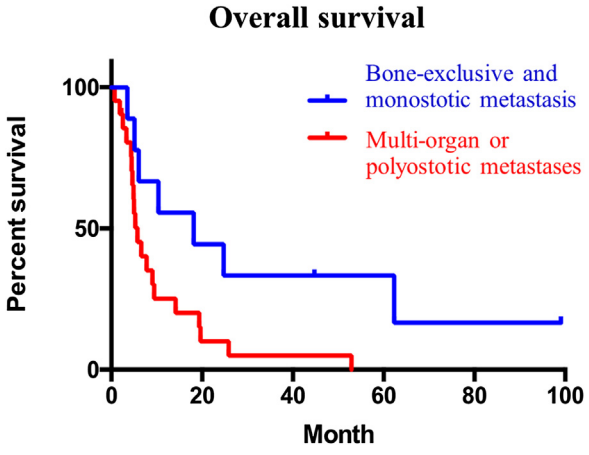

Fig. 3. Kaplan-Meier curve of overall survival (OS) after development of bone metastasis.
Patients with bone-exclusive and monostotic metastasis had significantly longer median survival time than those with multi-organ metastases or polyostotic metastases (18.2 months VS 5.7 months, Long Rank test p = 0.02).

the primary site, especially in the early stage; for example, prostate and rectal cancers preferentially form metastases in the pelvic bone and lumbar spine, and breast cancer preferentially forms metastases in the ribs and sternum [16–18]. This behavior was explained by the fact that metastatic deposits were primarily a mechanical phenomenon; in other words, cancer cells were primarily directed to a specific site based on the anatomy of the venous blood flow or lymph flow.

In contrast, the site distribution in the current cases was more general. Commonly involved bones were the thoracolumbar spine and pelvic bones. Conversely, only 3% of all BM were located in craniofacial bones above the clavicle, which is less than in the extremities. In accordance with previous reports of BM from HNSCC, this distribution approximately matches the red marrow distribution in the general skeletal system [7,8,11]. Therefore, BM from HNSCC is thought to be the result of a systematic spread of cancer cells.

According to our results, the morphologic CT changes of BM from HNSCC did not reveal any tendencies, which may be attributable to the diverse characteristics of HNSCC. Similarly, the reported morphologic CT changes of BM from HNSCC were variable, depending on the series. Basu et al. and Al-Bulushi et al. reported that over 80% of cases showed an osteolytic type [7,9], while Kim et al. and Nakanishi et al. reported osteoblastic and intertrabecular types in over 60% of cases [8,10]. Further work with larger cohorts may allow the characterization of the morphologic changes of BM from HNSCC in the head and neck region, the degree of differentiation of the squamous cell carcinoma, and the status of viral infection.

Although data on the prognoses limited to patients with BM from HNSCC have not been reported, patients with overall distant metastases from HNSCC reportedly show dismal prognoses, with a median survival time from development of BM ranging from 2 to 9 months [2–4]. Similarly, patients in the current study have shown poor prognoses with a median survival time of 6.6 months, and neither chemotherapy nor radiotherapy extended OS. However, we found favorable prognoses in patients with bone-exclusive and metastases, with a median survival time of 18.2 months. An oligometastatic state, representing a limited number of metastases in one organ, was thought to be an intermediate state between the localized state and the widely metastatic state [19]. Clinically, this concept implies a situation potentially amenable to local therapy. In fact, curative surgical resection of liver metastases from colon cancer, lung metastases from soft-tissue sarcoma, and adrenal metastases from lung cancer have resulted in remission for some patients [19]. With regard to HNSCC, only a few retrospective analyses with relatively small patient numbers have suggested that pulmonary or mediastinal oligometastases from HPV-positive oropharyngeal SCC portend a better prognosis [20,21]. So, further prospective analyses with larger numbers of cases are needed to clarify whether the concept of an oligometastatic status can be applied to HNSCC.

Our retrospective study has several limitations. First, only 5 cases were directly confirmed to be BM from HNSCC by histopathological examinations. Although histopathological confirmation is the gold standard, biopsy and/or resection of bone lesions may be impractical or unethical in some patients, especially in those with poor overall health associated with widely disseminated disease. Second, the relatively small size of the patient population, due to the fact that this study was carried out at a single institution, does not allow us to investigate various predictive factors of prognoses by multivariate analyses. Therefore, we mainly focused on the presence of bone-excusive and monostotic metastasis in patients with BM from HNSCC. Our data warrants further studies to determine predictive factors for prognoses by multivariate analyses with a larger patient population.

5. Conclusion

BM from HNSCC showed a general site distribution and variable morphologic types on CT images. It is noteworthy that 30% of current cases showed bone-exclusive and monostotic metastasis, and that these patients showed favorable prognoses compared with patients with multi-organ or polyostotic metastases.

Disclosure

The authors declare no conflict of interest.

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