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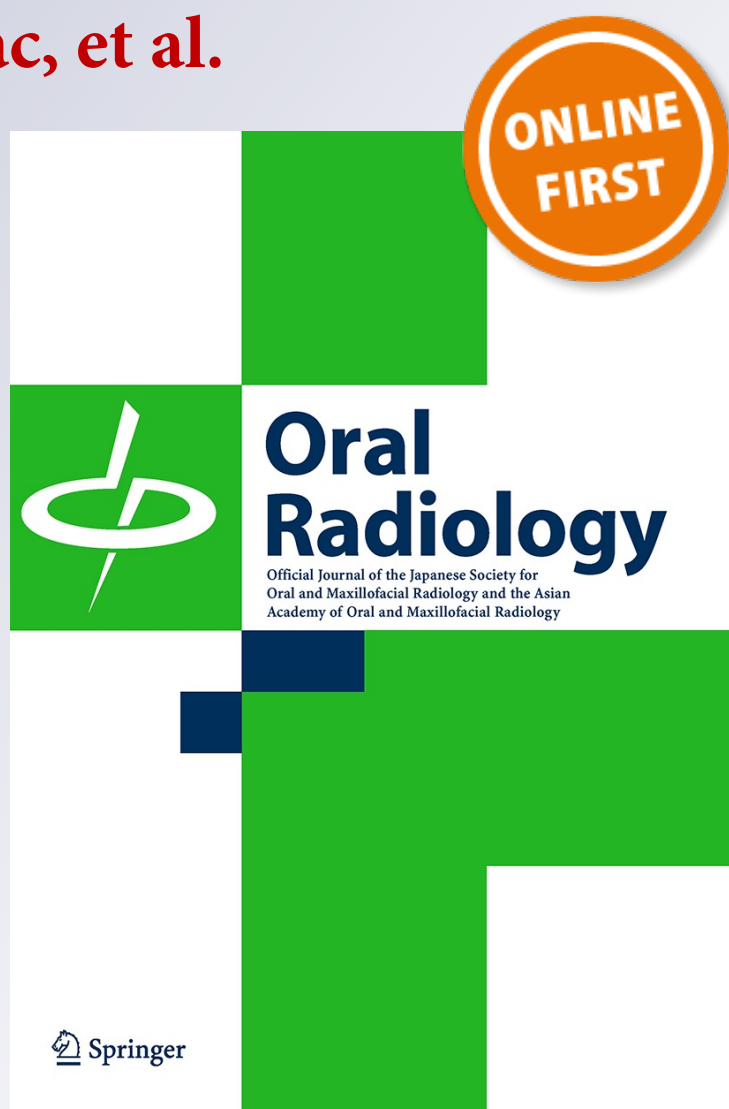
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CASE REPORT

Bilateral numb chin syndrome as a symptom of breast cancer metastasis in the mandible: a case report and discussion on the usefulness of cone-beam computed tomography to assess bone involvement in oral cancer

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Abstract Although extremely rare, cancer metastases in the oral cavity are significant because they represent a sign of relapse of the primary malignancy and are difficult to diagnose because of their uncharacteristic clinical appearance. Numb chin syndrome is considered an important symptom and a harbinger of malignancy, especially in patients with a history of malignant disease. A 60-year-old female patient with a history of breast cancer complained of a 6-month history of bilateral numb chin syndrome. Cone-beam computed tomography scans revealed malignant characteristics in a bone lesion, comprising a bilateral ill-defined osteolytic process in the mandibular body. A malignancy arising from the breast tissue was confirmed by biopsy results. When numb chin syndrome is present, a proper step-by-step clinical algorithm must include a detailed patient history, clinical examination, three-dimensional imaging of the maxillofacial area, and biopsy. Cone-beam computed tomography may be a useful diagnostic tool for evaluating jaw bone invasion by tumors.

Keywords Numb chin syndrome · Oral metastasis · Breast cancer · Cone-beam CT

Introduction

Cancer metastases in the oral cavity are extremely rare and comprise less than 1 % of all malignancies [1–3]. The most common primary tumors giving rise to metastases in the oral cavity include breast, lung, kidney, bone, colon, and prostate cancers [1–3]. The jaw bones, especially the mandible, are the most common locations of such metastases, while the soft tissues are rarely affected [1–3]. Metastases in the oral cavity are significant because they represent a sign of relapse of the primary malignancy and are difficult to diagnose because of their rarity and uncharacteristic clinical appearance [1–3].

Mental nerve neuropathy, or numb chin syndrome (NCS), is characterized by hypoesthesia, anesthesia, or paresthesia confined to the chin and lower lip arising as a consequence of disturbed function of the mental nerve, comprising the terminal sensory branch of the mandibular nerve [4]. NCS caused by either diagnosed or undiagnosed malignancy represents a sign of extensive metastatic disease and indicates an unfavorable prognosis for the patient [4]. Thus, when NCS is present, it should always be considered a malignant manifestation until proven otherwise.

Cone-beam computed tomography (CBCT) could be a useful diagnostic tool for evaluating jaw bone invasion by tumors. Previous studies found that CBCT had similar or even greater sensitivity and specificity for detecting bone pathologies in the orofacial region compared with conventional imaging techniques, namely panoramic radiography (PR), computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy [5–7]. CBCT provides high-resolution images together with reduced metal-induced artifacts, lower radiation dose, and lower costs than CT or MRI [5–7].

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In this report, we present a rare case of bilateral NCS caused by breast cancer metastasis and discuss the diagnostic algorithm that needs to be undertaken when NCS is present.

Case report

Chief complaint and history of present illness

A 60-year-old female patient was referred to the Clinic for Maxillofacial Surgery of the Military Medical Academy in Belgrade with the chief complaint of a 6-month history of bilateral numbness of the lower lip. The patient described that the symptom first appeared in May 2014 on the left side. In September 2014, the patient was assessed in a general dental practice for numbness of the lower lip, which was thought to be associated with an odontogenic infection. The attending dentist endodontically treated the first left lower premolar and prescribed antibiotic therapy. However, the symptoms remained, and the patient was referred to our clinic in October 2014.

Medical history

The patient's past medical history revealed a left breast adenocarcinoma 8 years previously, and osteoporosis. In 2006, the patient was diagnosed with postmenopausal stage II invasive adenocarcinoma of the left breast. She underwent cytoreductive systemic chemotherapy with radical left mastectomy, dissection of sentinel lymph nodes, and local radiotherapy at a different hospital. Reconstruction of the left breast was performed with a rectus abdominis muscle flap in 2007. In December 2007, metastatic disease was recovered from some axial lymph nodes, and treated with radiation and chemotherapy. After a 5-year course of chemotherapy with tamoxifen and bimonthly check-ups, the patient was pronounced tumor-free and discontinued chemotherapy in March 2012.

Physical examination

On physical examination, there were no facial swellings, asymmetry, or palpable or painful lymph nodes. There were no signs of cranial nerve lesions, except for paresthesia and anesthesia of both mandibular (V3) nerves. The intraoral status was normal, with no signs of infection, trauma, or mucosal lesions. The patient was partially edentulous with a fixed prosthesis in the lower dental arch. The remaining dentition was in good condition with generalized periodontal disease (Fig. 1a–c).

Radiological examination

PR showed a bilateral ill-defined radiolucency in the mandibular body (Fig. 1d). Based on the patient's history and our suspicion of bone metastasis, we conducted CBCT imaging with an Orthophos XG 3D System (Sirona, Bensheim, Germany). Imaging was performed in the high-contrast mode using 85-kV scans, according to the patient's characteristics in an upright position. The technical parameters were: field of view, 8×8 cm; X-ray generator, 85 kV with 5 mA; exposure time, 5 s; scan time, 14.1 s. Two hundred single images were constructed with a voxel resolution that amounted to $0.3 \times 0.3 \times 0.3$ mm (voxel size, 0.027 mm^3). The images were reconstructed using GalaxisTM software (Sirona) in a resolution mode, with an isotropic cubic voxel size of up to $125 \mu\text{m}$.

CBCT scans revealed an extensive bilateral osteolytic process in the mandibular body and ramus, with ill-defined margins. The mandible had a “moth-eaten” appearance, and the lesion affected the mandibular and mental nerve channels. The lesion became thinner and penetrated the buccal and lingual cortex of the mandible (Fig. 2).

Biopsy

An intraoral incisional biopsy was performed to obtain tissue samples and bone specimens for pathohistological analysis. The pathohistological analysis revealed high-grade infiltrative metastatic cancer. Thinned osseous trabeculae with medullary spaces were occupied by nests of neoplastic cells. The neoplastic cells exhibited a pleomorphic and hyperchromatic nucleus along with a reduced eosinophilic cytoplasm. Immunohistochemically, the tumor cells were positive for epithelial membrane antigen, cytokeratin 7, and estrogen receptor, and negative for cytokeratin 20, tumor protein p63, vimentin, and thyroid transcription factor 1 (Fig. 3).

Given the findings for the patient's history, CBCT imaging, and immunochemical profile of the malignancy, it was concluded that the patient had metastatic breast cancer in the mandible.

Oncological work-up

Based on the final pathology results, an oncology work-up was initiated. Radiological examination revealed multiple bone metastases in the humerus, sternum, and iliac bones. MRI of the brain, CT imaging of the chest and abdomen, and mammography results were unremarkable. Laboratory data showed elevated levels of carcinoembryonic antigen and breast cancer antigen 15-3.

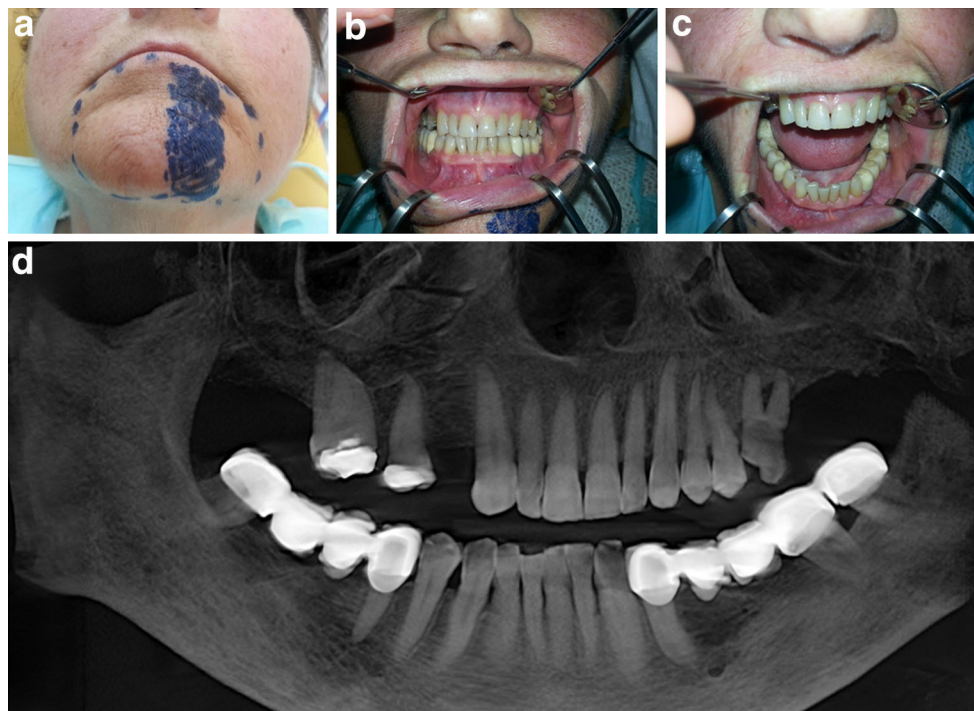


Fig. 1 Clinical examination. **a** The discontinuous line marks the area of numbness of the lower lip. The painted field marks the area of complete anesthesia. **b, c** Normal intraoral appearance of the lower

dental arch, oral mucosa, and alveolar process. **d** A panoramic radiograph shows a bilateral ill-defined radiolucency in the mandibular body

Therapy

Given the extent of the disease, the hospital's tumor board decided on palliative radiation therapy of the metastases. The patient also received chemotherapy with capecitabine and hormonal therapy with tamoxifen and megestrol. The therapy halted the tumor progression and the numbness of the lower lip disappeared after 3 weeks of therapy.

Discussion

This report provides clinical, radiographic, and pathological descriptions of a case of NCS of malignant origin, and shows the usefulness of CBCT imaging for detecting malignant invasion of the jaw bones. This report also shows that, if NCS is present, a red flag alert should be raised for possible malignancy.

The oral cavity is not a common site for tumor metastases, and such metastases usually represent cases of advanced malignant disease. Early detection of metastases in the oral cavity is of prime importance because of their poor prognosis and 4-year survival rate of <10 % after diagnosis [3]. Diagnosis of tumor metastases in the oral cavity is difficult because of their rarity and atypical clinical appearance, which may include pain, swelling, tooth mobility, hemorrhage, ulcerations, cervical lymphadenopathy, and peripheral

nerve neuropathy [1–3]. Previous papers have described that breast cancer metastases in the oral cavity were misdiagnosed as gingivitis [8], periapical lesions [9], periimplantitis [10], periodontal abscess [11], parotitis [12], or alveolitis [13].

NCS may be an important symptom and a harbinger of metastatic disease, especially in patients with a history of malignant disease. In approximately 25 % of cases, NCS is the first sign of tumor recurrence, while in one-third of cases, it may precede the diagnosis of the primary tumor [4]. The mechanisms underlying NCS include compression of the inferior alveolar nerve or mental nerve arising from tumor growth, perineural spread, leptomeningeal spread, paraneoplastic syndrome, or invasion of the skull base with trigeminal nerve involvement [4]. However, NCS may be a common symptom caused by various iatrogenic, infectious, or traumatizing factors, and is seen with more generalized diseases such as sickle cell anemia, diabetes mellitus, or viral infections [4]. In addition, special consideration should be given to bisphosphonate-related osteonecrosis of the jaws, which can be manifested as NCS and mimic bone metastases [14]. Bearing in mind that metastatic disease in the oral cavity can mimic inflammatory and benign processes in bones and soft tissues, radiographic imaging and biopsy performance are needed for a differential diagnosis.

Bone metastases are diagnosed in 65–75 % of patients with breast cancer [15]. The expression of nuclear estrogen

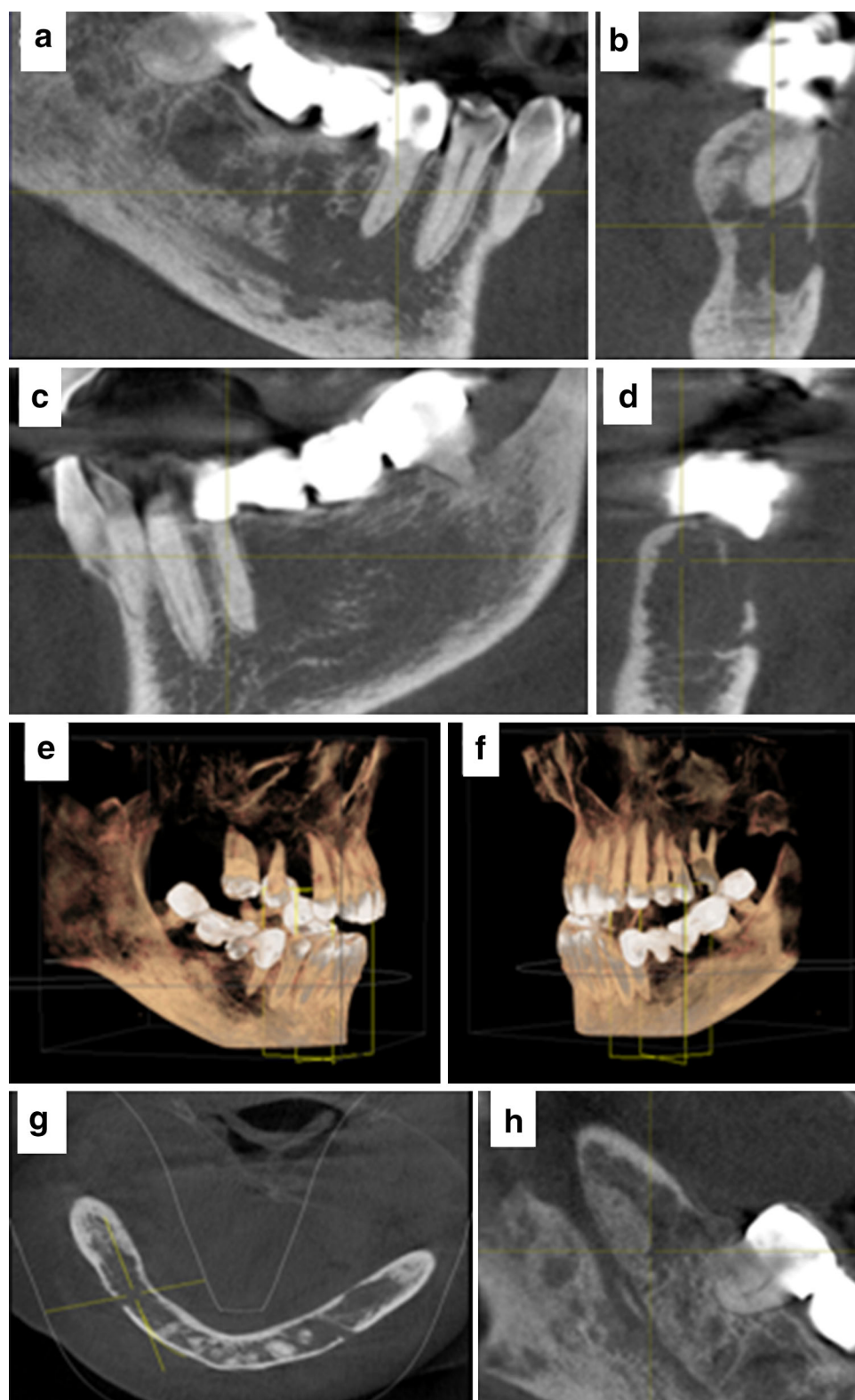


Fig. 2 Cone-beam computed tomography scan of the jaw bones. **a, b** Cross-sectional and sagittal views of the poorly defined osteolytic lesion on the *right side* of the mandibular body. **c, d** Cross-sectional and sagittal views of the poorly defined osteolytic lesion on the *left side* of the mandibular body. **e, f** Three-dimensional volume images of the *right* and *left* affected sites in the mandibular body show

irregular bone destruction. **g** An axial view shows a bilateral osteolytic process in the mandibular body with thinning of the cortical plate and perforation of the buccal and lingual lamina. **h** A cross-sectional view shows a poorly defined osteolytic lesion on the right mandibular ramus

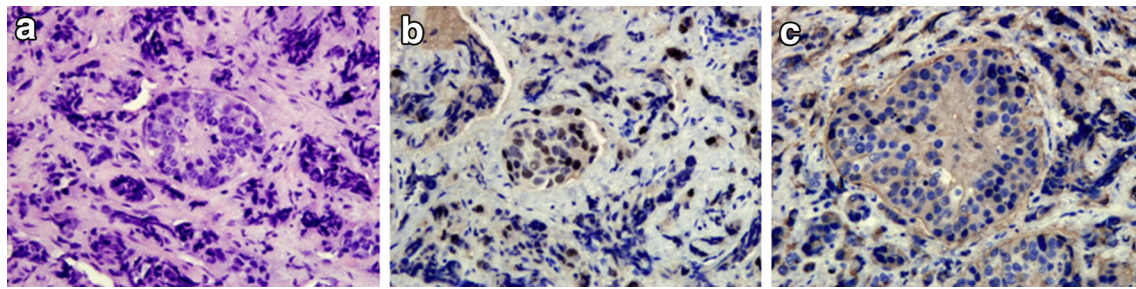


Fig. 3 Biopsy specimens taken from the intrabony lesion. **a** Neoplastic cells with a large, pleomorphic, and hyperchromatic nucleus and an abundant eosinophilic cytoplasm (hematoxylin–eosin staining; original magnification $\times 400$). **b** Positive estrogen receptor staining

confirms a breast cancer origin of the malignant cells (original magnification $\times 400$). **c** Positive cytokeratin 7 immunostaining demonstrates an epithelial origin of the tumor cells (original magnification $\times 400$)

Table 1 Published papers including CBCT for preoperative assessment of bone invasion in oral cancer

Reference	N	Tumor localization	Imaging methods	Values of diagnostic accuracy (%)								
				TP	TN	FP	FN	Sensitivity	Specificity	Accuracy	PPV	NPV
Momin et al. [19]	50	Mandible	CBCT	78 ^a	10 ^a	6 ^a	8 ^a	89 ^a	60 ^a	92 ^a	/	/
				34 ^b	64 ^b	2 ^b	0 ^b	99 ^b	93 ^b	98 ^b	/	/
			PR	64 ^a	6 ^a	2 ^a	24 ^a	73 ^a	80 ^a	79 ^a	/	/
				18 ^b	63 ^b	2 ^b	14 ^b	56 ^b	96 ^b	87 ^b	/	/
Hendriks et al. [5]	23	Mandible	CBCT	43	52	0	4	91	100	96	100	92
			PR	26	48	4	21	55	92	74	86	69
			MRI	39	35	17	8	82	67	74	69	80
Dreisedler et al. [20]	77	Mandible 58	CBCT	/	/	/	/	92	97	93	98	88
		Maxilla 19	CT	/	/	/	/	80	100	89	100	75
			SPECT	/	/	/	/	91	40	72	70	75
Hakim et al. [7]	48	Mandible	CT	/	/	17	9	63	84	72	76	73
			CBCT	/	/	3	19	94	59	77	73	89
			SPECT/BSCI	/	/	2	26	97	50	72	64	94
				/	/	18	41	59	82	74	62	80
Linz et al. [6]	197	Lip 5, maxilla 20, soft palate 8, mandible 58, tongue 43, cheek 12, floor of mouth 50, salivary gland 1	PR (197)	/	/	17	12	88	83	85	72	93
			CBCT (197)	/	/	8	33	67	92	83	80	85
			CT/MRI (197)	/	/	14	36	64	86	77	76	78
			CT (108)	/	/	3	25	75	97	92	90	92
			MRI (99)	/	/	14	5	96	86	89	78	97
			BSCI (197)	/	/	14	5	96	86	89	78	97

N number of patients, CBCT cone-beam computed tomography, PR panoramic radiography, MRI magnetic resonance imaging, CT computed tomography, BSCI bone scintigraphy, SPECT single-photon emission computed tomography, TP true positive, TN true negative, FP false positive, FN false negative, PPV positive predictive value, NPV negative predictive value

^a Alveolar bone involvement

^b Mandibular canal involvement

receptors plays an important role in the prognosis of breast cancer, and estrogen receptor positivity is generally thought to be associated with bone metastasis [15]. Breast cancers have a proclivity for metastasis to the jaw bones, especially the mandible [3]. Since the jaw bones do not contain lymphatic vessels, such metastases occur via the bloodstream. Most metastases occur in the mandibular premolar and molar region owing to its anatomy, presence of bone marrow, and slowing-down of the circulation that

favors the entrapment of cancer cells [3]. In the majority of cases, breast cancer cells stimulate osteoclast activity via parathyroid hormone-related protein, interleukin-8, and interleukin-11, and produce osteolytic destructive lesions in the bone [16]. A previous study reported a median time of 4 years between breast cancer diagnosis and the onset of NCS [3].

Precise radiologic evaluation of pathological lesions affecting bones has a significant impact on diagnosis and

Table 2 Advantages of CBCT over conventional CT in 3D examination of the maxillofacial area described in previous studies

Properties	CBCT vs. CT
Radiation dose	Effective dose of radiation of CBCT for imaging in the maxillofacial area ranges from 39.6 to 50 μ Sv, which is significantly reduced by up to 100 % compared with CT [22, 23]
Limitation of area of interest	CBCT technology allows limitation of the X-ray beam and a reduction in size of the irradiated area relative to the area of interest [22, 23]
Scanning time	Scanning time and motion artifacts are reduced with CBCT [17, 18]
Scanning position	Scanning position for CBCT imaging is the upright position, which enables distortion of the maxillofacial soft tissues by gravity [24]
3D resolution	CBCT allows higher 3D resolution through isotropic voxel resolutions, while CT resolutions are anisotropic [22]
2D images	CBCT has the potential to generate dental 2D images (retroalveolar, panoramic, lateral cephalogram, and TMJ images) [25]
Image artifacts	CBCT images are less disturbed by metal artifacts than CT images [25]
Viewing software	Reconstruction of CBCT images can be performed on a personal computer [22, 25]
Economic benefit	CBCT imaging has lower costs than CT technology [25]
Energy saving	CBCT imaging is energy saving compared with CT imaging [25]

CBCT cone-beam computed tomography, CT computed tomography, 3D three-dimensional, 2D two-dimensional

treatment. About 90 % of jaw bone metastases appear as osteolytic lesions [1–4]. Rarely, such metastases, including prostate cancer metastases, may occur as osteoblastic lesions [3]. Importantly, 5 % of all metastatic bone lesions lack radiological changes on two-dimensional radiograms [3]. CBCT is used routinely in dental implantology, planning of orthognathic surgery, and evaluation of impacted teeth and paranasal sinuses as well as in traumatology of the face [17]. CBCT allows easy identification of bone pathologies by reproducing anatomical details with sub-millimeter accuracy, thus enabling clinicians to obtain precise three-dimensional visualization of the pathologic entity [17, 18]. To date, the role of CBCT in the assessment of jaw bone invasion by cancer has been evaluated in a small number of clinical trials (Table 1). The results of these trials showed better performance of CBCT over PR and similar diagnostic parameters to CT, bone scintigraphy, and MRI. These results proved that CBCT has the potential to become a standard diagnostic tool in the evaluation of jaw bone involvement in malignant diseases because of its high sensitivity and specificity.

Panoramic tomography is still widely used in clinical practice, but its use is limited by the lack of accuracy, inherent magnification, and overlapping anatomy [21]. For detection of osteolytic lesions on PR, bone mineral loss of more than 30 % is required, thus leading to low sensitivity and high false-negative rates, especially in the early stages of bone invasion [6]. CT/MRI is the preferred combination for the assessment of bone invasion in oral carcinoma, because of the simultaneous assessment of bone, soft tissue, and cervical lymph nodes, which are of major importance in the planning of a surgical resection [5–7]. Although CT demonstrates high sensitivity and specificity for detecting bone invasion in oral carcinoma, CBCT

imaging could be a useful alternative for three-dimensional examination of the maxillofacial area with several advantages, including reduction of radiation, easy handling, reduced costs, and upright position of the patient during imaging (Table 2). However, CBCT has some important limitations. CBCT provides very limited inner soft tissue information, has a limited field of view, and cannot be used for estimation of Hounsfield units [25]. Similar to CT, CBCT has relatively high false-negative rates and tends to underestimate the extent of bone invasion by a tumor [5–7, 19, 20]. The sensitivity of CBCT is influenced by the presence of periodontal disease, which can result in local bone erosion similar to bone invasion [6, 19]. In this report using CBCT, we were able to observe mandibular invasion by a metastatic tumor manifested as an ill-defined osteolytic process and a moth-eaten appearance of the bone that, along with the patient's history and clinical signs, enabled us to suspect malignancy and perform a biopsy. For preoperative planning, assessment of inner soft tissue invasion and facial and cervical lymph nodes is mandatory. Despite its limitations, CBCT could replace CT for imaging in the maxillofacial area if combined with another imaging modality to analyze the inner soft tissues. Thus, the combination of CBCT/MRI may be a promising strategy for diagnosis and preoperative planning of tumors involving the maxillofacial area [6].

In conclusion, bilateral NCS is an important symptom of malignancies involving the jaw bones, and clinical, radiological, and pathological diagnostic tests are required when NCS is present. Because of the various etiological factors that can lead to NCS, clinicians often overlook this symptom for the presence of malignant disease and lose valuable time for the patient. The poor prognosis of oral metastases emphasizes the need for their early detection.

Although a definite diagnosis of bone pathologies is not possible without a biopsy, precise radiological imaging is essential for the differential diagnosis, thereby providing a guide toward a definitive diagnosis.

Although this is a report of a single case, we can conclude that CBCT is an effective tool for assessment of jaw bone involvement by tumors. Therefore, we propose that CBCT could be included in the clinical algorithm for the assessment of patients with suspected malignancies involving the jaw bones, along with preferred imaging modalities.

Compliance with ethical standards

Conflict of interest Slobodan Loncarevic, Denis Brajkovic, Biserka Vukomanovic-Djurdjevic, Tatjana Kanjevac, and Miroslav Vasovic declare that they have no conflict of interest.

Human rights statements and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from the patient for being included in the study.

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