

Primary tumor prevalence has an impact on the constituent ratio of metastases to the jaw but not on metastatic sites

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This article provides an overview of metastases to jaws (MJ), mainly concerning the differences between American and Chinese patients, and exploring the relationship between the primary tumors' prevalence (PTP) and constituent ratio of MJ. Information concerning of 399 MJ cases in 215 papers, including one new case in our hospital, was subjected to statistic analysis. The main clinical features of MJ, such as constituent ratio of PTP and that of MJ, metastatic sites, treatments, and prognosis were summarized. Breast, lung, kidney, prostate and thyroid (in descending order) were the leading primary sites of MJ. Furthermore, the constituent ratio of MJ was found to be correlated with that of PTP in all subjects including American and Chinese subjects in our study. As to metastatic sites in the mandible, a specific "M" shaped pattern appeared regardless of the tumor type or constituent ratios of MJ were in all subjects. Almost all subjects received traditionally palliative treatments, and the prognosis was quite poor. The PTP had a significant impact on the constituent ratio of MJ. However, it was the properties of the microenvironment rather than characteristics or constituent ratios of tumor cells, that decided the metastatic sites in various tumor subjects.

Keywords: tumor; metastases; jaws

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Introduction

Metastatic tumors from distant primary foci to the oral and maxillofacial (OMF) region are rare, accounting for only 1% of all malignancies in the OMF region. The jaw bones, especially the mandible, are the most frequently involved colonizing sites [1-3]. Though most metastases to the OMF region (OMF metastases) are noted after the diagnosis and treatment of the primary malignancy else-

where, about one-third of them are the initial sign of a cancer. The diagnosis usually involves searching for the primary disease, and the follow-up treatment is quite a challenge, often with unsatisfactory curative results to OMF surgeons and related clinicians [4-5].

Although a few anatomic routines were suspected as the metastatic pathways [6-7], the precise mechanism of OMF metastasis is still unclear.

In one of our previous papers [8], the incidence of OMF metastases was found to be influenced by the PTP. However, there was no linear correlation between the two. Theoretically, the lack of a relationship could be due to the interaction between the unequal metastasizing opportunity of different tumors and the diverse microen-

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vironment in different tissues. The similar tissue environment of jaw bones provides an opportunity for further study to exclude the influence of different host environment on the progress of the metastases.

Based on the above presumptions, we conducted a systematic analysis of 387 MJ reported in the literatures together with 12 cases in our hospital, then assessed the relationship between the PTP and constituent ratio of MJ.

Patients and Methods

Case report

This study was ratified by the Committee for the Use of Human Subjects in Research, Sichuan University. One new case added was a mandible metastasis from the left lung of a 78-year-old man who initially complained of numbness of the lower lip, and was then referred to our hospital in July 2008. A chest CT scan showed an irregular soft tissue mass in the left lung and a panographic X-ray showed pathological fracture in his left mandible. Biopsy of both foci demonstrated adenocarcinoma from the lung (Figure 1). Treatment was declined by the patient, and follow-up was available only for one month.

Search strategy

We systematically searched MEDLINE (Medical Literature Analysis and Retrieval System online) and CBMDisc (China BioMedical literature on disc) for English and Chinese papers (January 1950-August 2008) by entering 'jaw neoplasms'/sc (secondary) and 'maxillary sinus neoplasms'/sc as the medical subject heading terms, together with "metastasis" or "metastases" or "metastasize" or "metastasizing", with "maxilla", "maxillary", "maxillary sinus", "maxillary antrum", "mandible", "mandibular", "condyl*", "ramus", "jaw*", or "jaw bone", and with "mouth", "oral", "oral cavity", "maxillofacial", "craniofacial" or "head and neck region" as the text words. A total of 411 papers were retrieved and checked carefully, and their reference lists were explored to find other potentially relevant papers. Furthermore, 9 427 cases of hospitalized patients with OMF malignancies treated in the West China Hospital of Stomatology, from January 1954 to August 2008, were analyzed to find cases of MJ. Clausen-Meyer criteria were employed as inclusion criteria [9-10], as follows: 1) a proved primary tumor with histologic confirmation and possible roentgenographic supportive evidence; 2) maxillary and mandibular metastasis with histologic confirmation and possible roentgenographic evidence; 3)

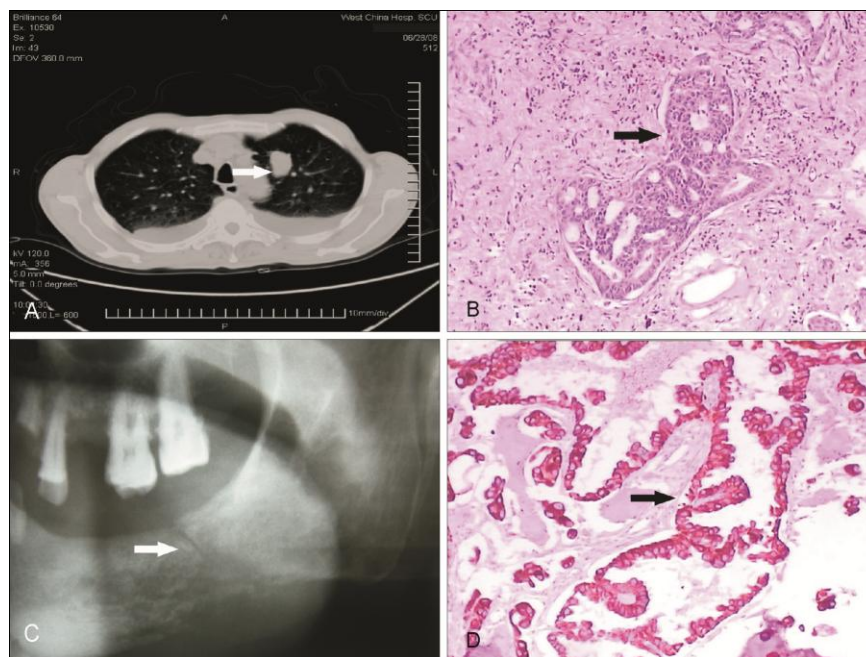


Figure 1 A rare case of MJ encountered in West China Hospital of Stomatology, who was admitted because of numbness of the lower lip and pathological fracture. (A) A chest CT scan shows an irregular soft tissue mass in the left lung and pleural fluid in both lungs. (B) A transthoracic needle aspiration biopsy identifies a mediate differentiated adenocarcinoma. HE stain, $\times 200$. (C) The arrowhead points to the fracture site of left mandible. (D) Biopsy of the mandible demonstrates adenocarcinoma from lung. LCK stain, $\times 200$.

histologic correlation of the metastatic jaws lesion with primary lesion; and, 4) when the primary lesion is anatomically near the metastasis, there should no tumor tissue be present between the two foci. Reports were excluded that had no clinical, radiographic and histologic evidences to confirm the diagnosis as primary sites. The main clinical features, such as constituent ratio of PTP and that of MJ, metastatic sites, treatment and prognosis were summarized. The five-year prevalence data of primary foci were obtained from GLOBOCAN 2002 [11]. And the International Classification of Diseases Edition 10 (ICD-10) is adopted in this article.

Data analysis

Rank correlation, Chi-square test and Kruskal-Wallis Test were used to compare the different characteristics of MJ. Survival analysis was also used to analyze the outcome and survival time. Data are expressed as mean \pm SEM. A probability of 0.05 or less was considered significant.

Results

General information

A total of 214 papers containing 387 searched MJ patients were analyzed [1-7, 9-10, 12-216]. In addition, twelve cases of MJ in our hospital were assessed including 11 reported cases [8] and one newly-reported case. Among 215 papers and 399 patients, 92 papers

from the English-language literature, with 143 MJ cases, while 37 papers were associated with 91 Chinese MJ patients. Genders was noted for 212 male patients and 179 female patients. The age of the 365 published cases ranged from 9 months to 90 years, with a mean of 51.48 ± 1.03 .

Constituent ratio of MJ (proportion of different primary sites within MJ)

The most common primary foci of MJ (classified by ICD-10), were breast, followed in descending order by lung, kidney, liver and intrahepatic bile duct (liver & IBD), prostate and thyroid, taking up 19.30%, 13.03%, 11.28%, 8.52%, 8.02% and 8.02%, respectively (Table 1). The most common primary sites in China were liver and intrahepatic bile duct (liver & IBD, 18.68%) and lung (18.68%), followed by thyroid (14.29%), breast (12.09%), and kidney (7.69%), while the most popular primary foci in the USA were breast (24.48%), prior to kidney (13.29%), lung (11.19%), prostate (9.09%), and intestine (6.29%). We found there was a significant difference in constituent ratio of MJ between the USA and China by Chi-square test ($P < 0.01$, Figure 2).

Correlation between constituent ratio of PTP and that of MJ

The five-year prevalence data of primary tumors were converted into constituent ratios of PTP (Table 1), and a rank correlation test was performed between the cons-

Table 1 The constituent ratio comparison between 5-year prevalence and no. of MJ of primary sites

Primary sites	MJ		5-year Prevalence		ICD-10
	Cases	Constituent ratio /%	Cases	Constituent ratio /%	
Oesophagus	12	3.01	424 470	1.73	C15
Stomach	11	2.76	1 473 559	6.00	C16
Colon and rectum	23	5.76	2 830 416	11.52	C17-20
Liver & IBD	34	8.52	385 985	1.57	C22
Pancreas	4	1.00	142 837	0.58	C25
Lung	52	13.03	1 362 226	5.54	C33-34
Melanoma of skin	5	1.25	642 643	2.62	C43
Breast	77	19.30	4 406 080	17.93	C50
Uterus	13	3.26	2 184 807	8.89	C53-54
Prostate	32	8.02	2 368 659	9.64	C61
Testis	4	1.00	192 239	0.78	C62
Kidney etc.	45	11.28	585 639	2.38	C64-65
Bladder	7	1.75	1 110 265	4.52	C66-67
Brain, nervous system	4	1.00	276 546	1.13	C70-72
Thyroid	32	8.02	531 369	2.16	C73
Others	44	11.03	5 652 375	23.01	
All sites but skin	399	100.00	24 570 115	100.00	

tituent ratio of PTP and that of MJ. Interestingly, there was a significant linear correlation between them (Spearman's correlation coefficient=0.621, $P=0.010$). For example, carcinomas of breast, lung and prostate had a high incidence of MJ in our study. Thus, they had likewise a

high prevalence in the GLOBOCAN 2002. It is interesting to note that there also exists a linear correlation between them in the USA (correlation coefficient=0.567, $P=0.027$), as well as in China (correlation coefficient=0.523, $P=0.046$, Figure 2).

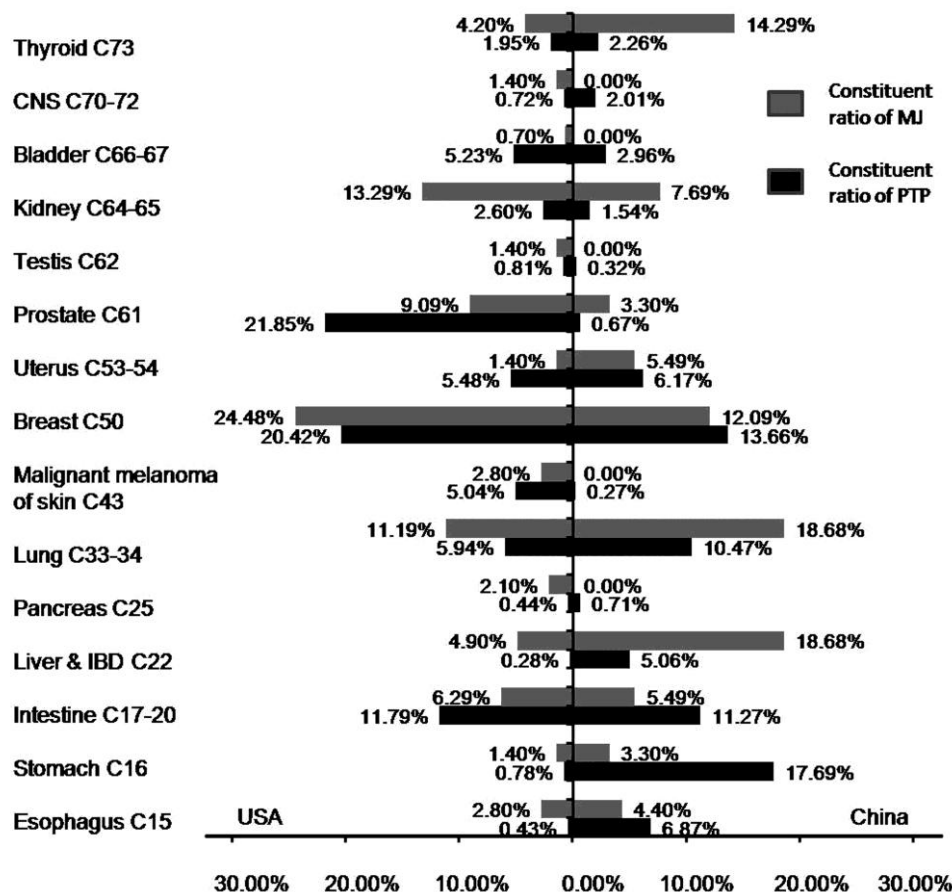


Figure 2 The major constituent ratio of PTP in all cancers (not including non-melanoma skin cancers) and their constituent ratio in MJ.

Metastatic sites

Most MJ involved one oral site (383 cases), and only a few involved two or three sites (14 cases and 2 cases, respectively). Among them, eight metastases invaded both jaw bones. The mandible was more commonly involved than maxilla (337 cases: 70 cases). Most tumors metastasized to the unilateral mandible, whereas only three cases to bilateral mandibles. A total of 337 MJ cases involved 474 specific sites of the mandible including 111 undefined sites (*i.e.*, 72 cases of "mandible" and 39 cases of "body"). Interestingly, these sites were distributed in an "M" curve pattern, with ramus (92 sites)

and molar area (91 sites) the most frequently encountered specific sites, followed by angle (57 sites), premolar area (48 sites), condyle (43 sites), and anterior area (28 sites, Figure 3).

It was also found that each primary tumor metastasized to specific sites of the same pattern, *i.e.*, there were no significant statistical differences between primary tumors and specific sites ($P>0.05$). It is interesting that the "M" curves existed for all cases we studied and the same was true for both American and Chinese cases. There was no significant differences in specific metastatic sites between the American and Chinese cases by Chi-square test ($P>0.05$).

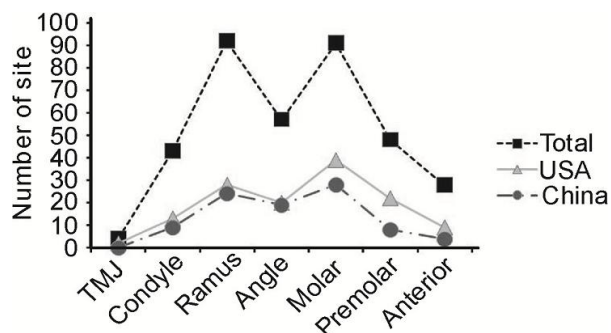


Figure 3 An interesting universal “M” curve with ramus and molar area standing out as peak point of metastatic sites.

Treatments and prognosis

Treatment and prognosis were documented in 230 cases. Among them, radiotherapy was the most commonly adopted monotherapy (115 cases), followed by chemotherapy (93 cases), surgery (87 cases), symptomatic treatment (5 cases), embolization (3 cases) and supportive care (2 cases). A total of 72 subjects accepted two or three of the above mentioned therapies (*i.e.*, multitherapy). The mean survival times of surgical, radiotherapeutic and chemotherapeutic subjects were 15.84 ± 4.46 , 6.24 ± 1.27 , and 7.30 ± 1.87 months, respectively. And the mean survival times of non-therapeutic, multitherapeutic, and mono-therapeutic groups were 9.11 ± 2.25 , 11.79 ± 2.23 , and 9.51 ± 1.61 months, respectively. However, there were no significant differences among them by Kruskal-Wallis Test ($P > 0.05$). The mean survival time of all subjects was 9.90 ± 1.14 month. Fifty percent of cases died 5.30 ± 0.39 months after diagnosis of MJ; 75% cases died in 13.97 ± 2.17 months, and the five-year survival rate was only 2.58% (Figure 4).

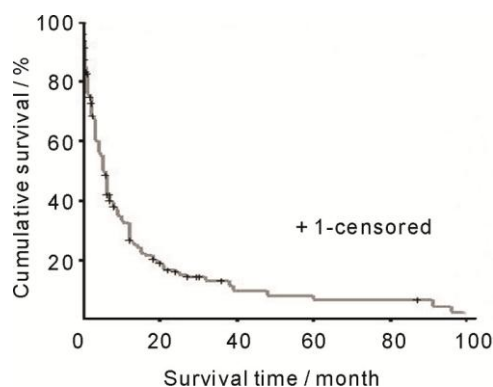


Figure 4 Survival curve of MJ patients.

Discussions

The authors conducted a systematic analysis of 399 cases and evaluated the relationship between the PTP and constituent ratio of MJ. The most common primary foci of MJ were breast, followed by lung, kidney, prostate and thyroid. Interestingly, there was a significant linear correlation between the constituent ratio of PTP and that of MJ. The metastatic sites were distributed specifically in an “M” curve pattern, and the prognosis of these patients was quite poor when treated by a traditional “seeds-oriented” therapeutic strategy.

From the perspective of anatomy, bone and soft tissues of the OMF region share a common blood-supply, but provide absolutely different tissue environments. A valid premise may be that metastatic tumor cells select a favorable environment to anchor and proliferate, this being the tissue/organ specificity of cancer metastasis [217]. And the “seed-soil” theory proposed by Paget is accepted as the basic mechanism for cancer metastasis [218-220]. The results of these studies have enriched the Paget’s hypothesis: the potential of a tumor cell to metastasize depends on its interactions with the homeostatic factors that promote tumor cell growth, survival, angiogenesis, invasion and metastasis [221].

According to the results of rank correlation analysis in our previous work, there was no significant linear relationship between the constituent ratio of PTP and that of OMF metastases [8]. However, when it was narrowed down to MJ, a linear relationship was established between constituent ratio of PTP and that of MJ. The results suggest that different tissue environments could cause bias in the relationship between PTP and constituent ratio of MJ.

With respect to favorable metastatic sites of MJ, it was interesting to see the appearance of an “M” curve in all cases including American and Chinese cases. Successful metastatic cells depend largely on the virtue of intrinsic features of the cells and the ability of the tumor cells to engage and interact successfully with the micro-environment [222]. However, according to our result, there was no significant difference between primary tumors and specific sites ($P > 0.05$). Thus, it seems that regardless of tumor type or constituent ratios of MJ, metastases formed preferentially in the mandible. In other words, the characteristics of the microenvironment rather than properties or constituent ratios of tumor cells decided the metastatic site.

According to our study results, the prognosis of MJ was not different among non-therapeutic, multitherapeutic, and monotherapeutic groups, which reflects the shortcomings of the current “seeds-oriented” therapeutic

strategy. Perhaps, reformation of the “soil” might inhibit the formation and development of the metastases, if the growth and dissemination of the primary tumors cells (*i.e.*, “seeds”) can be impeded. In the past decades, this strategy was experimented in several new anti-cancer therapeutic regimens, such as anti-tumor angiogenesis, organ growth factors, *etc.*, one of which got dramatic effect in treating metastases: the clinic use of bisphosphonates to inhibit bone metastases by changing bone metabolism. Bisphosphonates are potent inhibitors of bone osteolysis and could interrupt the tumor cell adhering to bone marrow, thereby impeding both the development of bone metastases and preventing the tumor cells and dormant cells in the bone marrow microenvironment from subsequent dissemination to extra-osseous sites [223–224]. Furthermore, it could be better still if we could find methods to change the metabolism of soft tissues.

Conclusion

The PTP had a significant impact on constituent ratio of MJ. Our findings may have significant value for clinicians to evaluate the risks of MJ occurrence in various tumor patients. However, it was the properties of microenvironment rather than properties or constituent ratios of tumor cells that decided the metastatic sites. Therefore, interference with the “microenvironment” may be was an efficient therapeutic strategy for inhibiting metastatic tumor growth in jawbones.

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