

ANSWERING REVIEWERS

FEB 21, 2015

Dear Editor,



Thank you very much for your decision letter and advice on our manuscript. Please find enclosed the edited manuscript in Word format (file name: **16272-review.doc**).

Title: Incidence and treatment of brain metastasis in patients with esophageal carcinoma

Author: Wei Feng*, Peng Zhang, Xiao Zheng, Ming Chen, Weimin Mao

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16272

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Replies to Reviewer 1 :03087211

1)Country wise reports about tumor arising esophageal cancer is insufficient, need to mention some further reports. In addition, the authors need to debate about this carcinoma in countries other than Japan, China precisely.

Response:

a.Yes."the incidence of esophageal cancer has increased gradually "is not a good statement . I forgot to add the nation "in USA" or "adenocarcinoma".In China and other countries,the incidence of esophageal cancer is declining now.

b.I have discuss the data(I Modified the number ,including 2014) in the article :346 cases reports from 13 countries on BMEC, 321 cases reports from original articles (America 144, Japan 103 ,Chinese 31 ,Chinese and Japan 6 ,Germany and Austria 21, Germany 16) , 25 cases reports from case report (Japan 5 , American 8, Turkey 1, Italy 4, Ireland 1, Australia 1, Iran 1, India 1, UK 1, Canada 1, China 1).

2)There are some grammatical errors which need to be corrected.

Response:I have sent this manuscript to be edited by Jing-Yun Ma Editorial Office (English language editing companies), I hope grammatical errors could be corrected completely.

3)Besides, incidences I would suggest authors to include a brief summary of various causes of the reported incidents.

Response:

a brief summary of various causes "The literature talk about the incidence, clinic characteristics, survival and some unusual phenotypes about BMEC" have been added to the article.

4)The authors should include recent advances in the treatment of brain metastasis.**Response:**

I have wrote some recent advances of BMEC about targeted therapy (about HER-2) and gamma knife radiosurgery, but the recent advances are lack about BMEC . I can't find other advances that been used to treat BMEC, although those advances have been used to treat brain metastasis of other carcinomas.

(2) Replies to Reviewer 2 : 03081710

1)In the introduction, the authors stated "We searched the literature from PubMed and found 257 reports from 12 countries on BMEC". It is not clear how many of these reports were included in this analysis and the author should present these numbers. There are not many cases of BMEC and therefore it should not be difficult to include all recent studies done in US, Japan and China. If the author had not included all the studies, the selection criteria should be clearly discussed in the text.

Response:

a. I have modified the data(including 2014) in the article :346 cases reports from 13 countries on BMEC, 321 cases reports from original articles (America 144, Japan 103 ,Chinese 31 ,Chinese and Japan 6 ,Germany and Austria 21, Germany 16) , 25 cases reports from case report (Japan 5 , American 8, Turkey 1, Italy 4, Ireland 1, Australia 1, Iran 1, India 1, UK 1, Canada 1, China 1).

b. Because the incidence of BMEC is relatively rare. we have read the every article(full text) in english found from the pubmed and extracted the main idea about BMEC. This article is a review ,not a meta analysis. so we did not make the selection criteria. We only chose the best evidence in support of the view. We won't use the articles that repeat the old idea and have no new ideas and have incomplete information about the patients.

c. There are 298 cases of BMEC are in US, Japan and China(about 86.1%) ,with other articles ,we have cited about more than 95% articles.

2)Following up on the point above, how many studies in each country are included in the analysis of table 1? References are missed in the table**Response:**

a. Only one study in each country are included in the analysis of table 1.

b. I have provided the references in the table.

c. In this manuscript, I have commented : "Ogawa and colleagues believed that, excluding the 36 cases they had reported, there were only 61 cases of BMEC in Japan prior to 2002, of which 35 were published in 13 English journals and the remaining 26 cases published in 14 Japanese journals. If this is the case, it can cause great difficulties in retrospective studies on the diagnosis and treatment of brain metastasis from esophageal carcinoma based on the previous literature." This phenomenon is very common in Japan. So we chose one study of every country to show the own characters of the BMEC .

d. Except the USA, Japan and China, other countries may be have the small sample to be published.

3)The authors had done a relatively good job in summarizing the treatment options for BMEC, but the discussion on incidence was very short. The authors did not discuss whether there is any difference in incidence of BMEC between the three countries. It will also be worthwhile to discuss whether the incidence of BMEC correlates with that of esophageal carcinoma. Moreover, is there any genetic or environmental factor that may increase the risk of BMEC?

Response:

a.Chinese study was based on more than 10,000 patients of esophageal carcinoma from1953 to 2003 in zhejiang cancer hospital.Only 31 patients(about 0.3%)of BMEC could be found. Japanese study records of 36 patients(1.4%) with BMEC who were treated between 1986 and 2000 were reviewed. 2554 patients with esophageal carcinoma were treated at the three different Hospitals .American study of The University of Texas M. D. Anderson Cancer Center identified 1588 patients of primary esophageal carcinoma between June 1, 1993,and July 31, 2001.Of which, 27(1.7%) had diagnoses of BMEC.We have discussed in the front paragraph, autopsy ,historical and technical factors is the keys for the different incidence of three countries. Because the sum of esophageal carcinoma from zhejiang cancer hospital was not so accurate,we won't talk about incidence of BMEC of three studies.

b.Perhaps my title of this review may be modified to"Brain metastasis in patients with esophageal carcinoma from different countries".

c.very sorry,there no report that was about any genetic or environmental factor that may increase the risk of BMEC.The several case reports had reported HER2 maybe are the factors that influence the incidence of BMEC. (the reference [40,41,42])

4)A timeline diagram illustrating the milestones and new discoveries of BMEC (e.g. first case reported, new therapies introduced, etc) can be added.

Response:

I have gotten a paper of 1932,that may be the first case reported.

Dunlap, J. F. Metastatic malignant tumors of the brain. *Ann. Intern. Med.* 1932;5:1274-1288.

(3) Replies to Reviewer 3 : 03087223

1)The first part of the abstract: "The incidence....in the three countries" is re-used as it is in the core tip of the manuscript. Although the global description remains unchanged, authors might have to write this paragraph with a different lexical approach (rewrite the sentences).

Response:

I have re-write the paragraph.

Brain metastasis from esophageal carcinoma (BMEC) is very rare, but has increased in the United States, Japan,China and other counties. The reports tend to revolve around views such as whether Adjuvant therapy of esophageal cancer can influence survival time of BMEC, and imaging characteristics determined by the new medical equipment. The difference of different pathological types of esophageal cancer, especially adenocarcinoma and squamous cell carcinoma is one of the important factors that decide the influence of BMEC. Adjuvant therapy including radiotherapy and

chemotherapy for esophageal cancer with different principle in different countries may affect the treatment results of BMEC. The degree of popularization of advanced medical equipments is a major concern related to the prevalence of BMEC. Furthermore, the target treatment of BMEC is being developed in the developed countries. In this article, we reviewed the debates of BMEC, and compared BMEC studies from different perspective.

2)The description of reports on BMEC is well written and referenced in the introduction. However, the authors should show in a figure/diagram, the progression of esophageal tumor pathology, or at least the classification, as described in the text.

Response:

I have found that most of articles only told us the number of BMEC, no other information. The follows are figure/diagram of those articles. would I need to do this kind of figure/diagram?

1932:

Dunlap J. F. Metastatic malignant tumors of the brain. *Ann. Intern. Med* 1932;5:1274-1288.

Metastatic Malignant Tumors of the Brain 1279

TABLE 2
Situation of the Primary Malignant Tumors in all Cases Studied.

Situation	Groups			Total
	1	2	3	
Breast	5	20	3	12
Kidney	3	4	5	12
Lung	5	1	3	9
Skin	2	3		5
Suprarenal gland	2		3	5
Colon	2	1	1	4
Thyroid gland	1	1	2	4
Stomach	1	1	1	3
Testis		2	1	3
Bone		2	1	3
Esophagus			1	1
Pancreas	1			1
Gallbladder		1		1
Prostate gland			1	1
Uterus		1		1
Tonsil		1		1
Parotid gland		1		1
Carotid body		1		1
Eye		1		1
Undetermined	1	3	4	8

proper was not invaded. Of the two remaining cases, one was a case of sarcoma which had metastasized throughout the body in the fat-bearing tissues, and the other was a case of melanopitheliomatosis.

In the cases of group 1, in which metastasis occurred to the tissue of the brain, secondary nodules were found to be scattered irregularly throughout the gray and the white matter; just as in clinical examination, so in this examination, no site of predilection for the development of metastasis was noted. The tumors were usually rather sharply demarcated from the adjacent brain tissue and often were the site of rather marked necrosis and hemor-

1979 Bosch A, Frias Z, Caldwell WL, Jaeschke WH. Autopsy findings in carcinoma of the esophagus. *Acta Radiol Oncol Radiat Phys Biol* 1979; **18**: 103–112. PMID: 495189

Frequency of metastases from esophageal carcinoma in reported autopsy series

Metastatic site	Author(s) and year of publication					
	Dormanns (1939)	Raven (1948)	Attah & Hajdu (1968)	Ming (1973)	Cedermark et coll. (1977)	Present series
Lymph nodes						
Cervical	45 (5)*	2 (2)	17 (15)	22 (46)	24 (21)	5 (6)
Supradiaphragmatic	625 (76)	5 (5)	72 (64)	43 (90)	47 (40)	28 (34)
Infradiaphragmatic	236 (29)	7 (6)	33 (29)	20 (42)	18 (16)	17 (21)
Site unspecified	—	33 (31)	—	—	—	—
Organs						
Liver	264 (32)	26 (24)	37 (33)	12 (25)	21 (18)	22 (27)
Lung	176 (21)**	16 (15)	32 (28)	15 (31)**	32 (28)	19 (23)
Bone	68 (8)	12 (11)	8 (7)	3 (7)	17 (15)	3 (4)
Kidney	59 (7)	7 (6)	10 (9)	3 (6)	16 (14)	9 (11)
Peritoneum	44 (5)	8 (7)	—	5 (10)	10 (9)	4 (5)
Adrenal gland	35 (4)	12 (11)	8 (7)	3 (6)	12 (10)	10 (12)
Stomach	34 (4)	—	6 (5)	3 (6)	—	2 (2)
Heart and pericardium	33 (4)	5 (5)	—	1 (2)	—	2 (2)
Intestines	17 (2)	—	—	1 (2)	—	—
Thyroid gland	15 (2)	2 (2)	8 (7)	4 (8)	—	3 (4)
Pancreas	15 (2)	7 (6)	—	4 (8)	—	4 (5)
Spleen	14 (2)	—	—	—	—	—
Larynx, trachea, bronchus	13 (2)	3 (3)	6 (5)	—	—	—
Diaphragm	5 (1)	3 (3)	6 (5)	4 (8)	—	1 (1)
Brain	7 (1)	2 (2)	—	2 (4)	11 (9)	1 (1)
Pleura	**	2 (2)	7 (6)	**	10 (9)	2 (2)
Gallbladder	—	1 (1)	—	—	—	1 (1)
Skin	—	—	—	—	—	1 (1)
Total no. of cases	824	108	113	48	116	82

* Supraclavicular and infraclavicular both.

** Lung and pleura both.

Per cent expressed in parentheses.

3) In the chapter “Incidence of BMEC”, the authors claimed: “Until recently, a large number of BM has been detected by MRI, of which only a small proportion has been pathologically confirmed”. The authors should argue in terms of percentage.

Response:

The sentence have been re-written:

“Until recently, most of BM has been detected by MRI or CT, of which only treated surgically could be pathologically confirmed”.

4) In the chapter “Auxiliary treatment of esophageal cancer promotes BMEC”, it is written: “The risk for occurrence of BM between the two groups was compared. Years later, they found that 29 patients (six from the control group and 23 from the intervention group) developed BM, 20 of who developed BM within one year”. Could the authors specify how long after the patients developed BM?

Response:

At diagnosis of brain metastases, the lesion was solitary in 48% and unilateral in 60% . One patient had leptomeningeal metastases. In all cases, the esophageal tumor was adenocarcinoma. In most cases,

the esophageal tumor was considered to be locally controlled, but in 44% there was evidence of other sites of metastasis. Whole-brain radiation therapy, either alone or in combination with local therapy, was the most common treatment for brain metastases. Patients died rapidly after diagnosis of brain metastases. Median survival was 3.5 months.

Treatment of brain metastases	
WBRT alone	15 (54)
Surgery + WBRT	4 (14)
SRS + WBRT	2 (7.1)
Surgery alone	2 (7.1)
None	5 (18)
Unknown	1 (—)

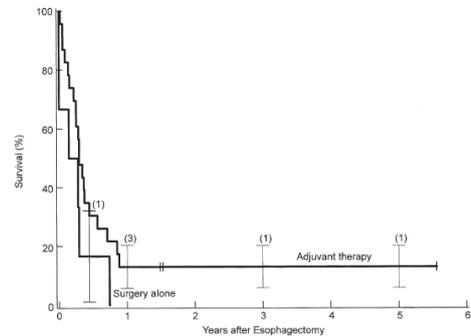


Fig 4. Survival after occurrence of brain metastases following surgery alone or adjuvant therapy ($p = 0.1$). Each step represents an occurrence, and short vertical lines are patients remaining alive (censored); vertical bars represent ± 1 standard error.

5)The following sentence should be re-written: “Moreover, some authors believe that not only the disease itself, but also adjuvant chemo-radiation that affects the development of distant metastasis and reduces survival.

Response:

The sentence have been re-written:

“Moreover, some authors proposed the hypothesis that not only the disease itself, but also adjuvant chemo-radiation that affects the development of BMEC . “

6)In the chapter #6, the authors reported the case of a patient with squamous cell carcinoma who has exhibited 14 years survival post brain surgery and chemotherapy for BMEC; and they mentioned the case as the one with the longest survival time among BMEC patients. Although the finding is interesting, the report should be published first in a peer-review journal before being described in the current review.

Response:

I have added the references to the case.

Feng W, Zhang P, Zheng X, Shan G, Chen M, Mao W. Neuroimaging and clinical characteristics of brain metastases from esophageal carcinoma in Chinese patients. *J Cancer Res Ther* 2014;10Suppl:296-303.PMID: 25693939.

7)The authors should add references to the following: “Recently, the difference in survival time of patients with adenocarcinoma BMEC and those with squamous cell carcinoma BMEC has been debated”.

Response:

I have added the references to the sentence.

Smith RS, Miller RC. Incidence of brain metastasis in patients with esophageal carcinoma. *World J Gastroenterol* 2011; **17**: 2407-2410. doi: 10.3748/wjg.v17.i19.2407 PMID: 21633640

8)In the chapter #7, the authors have emphasized on the correlation between a genetic disease and BMEC. The disease should be at least clearly named, described and discussed.

Response:

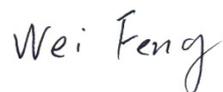
The disease's named is Williams Syndrome,I have described and discussed it.

Another study reported a young patient (33 years old) with Williams Syndrome and concomitant esophageal cancer who eventually developed BM. Williams syndrome is a multisystem neurodevelopmental disorder.The patient was diagnosed by hemizygous for 7q11.23 that assessed by FISH.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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