

Incidence of brain metastasis in patients with esophageal carcinoma

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Received: June 4, 2010 Revised: November 25, 2010

Accepted: December 2, 2010

Published online: May 21, 2011

Abstract

AIM: To determine the incidence of brain metastasis in a contemporary group of patients with carcinoma of the esophagus.

METHODS: Retrospective analysis of 53 patients with esophageal carcinoma who received radiotherapy as a component of treatment between 1998 and 2007, including patient and tumor characteristics, and subsequent diagnosis of brain metastasis. The association between the histological type of esophageal cancer and the incidence of brain metastasis was assessed using Fisher's exact test.

RESULTS: Forty-four of the fifty-three patients in this study had adenocarcinoma and nine had squamous cell carcinoma, ranging from stage II A-IV B. Primary treatment was surgery with neoadjuvant chemoradiotherapy (trimodality therapy) in 19% of patients; chemoradiotherapy in 42%; and surgery and adjuvant radiotherapy in 7%. Twenty-five percent of patients in

this study received palliative radiotherapy. The overall incidence of brain metastasis in this cohort was 13%. Adenocarcinoma was the primary tumor histology in all of the patients who developed brain metastasis, representing an incidence of 16% in this subgroup. No patients with squamous cell carcinoma received trimodality therapy. The association between histology and brain metastasis was not statistically significant.

CONCLUSION: The incidence of brain metastasis in this contemporary cohort of patients with esophageal carcinoma is higher than previously reported and was confined to those with adenocarcinoma.

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Key words: Brain metastasis; Esophageal carcinoma

Peer reviewers: Nadia Peparini, MD, PhD, Department of General Surgery "Francesco Durante", La Sapienza University, Viale del Policlinico, 155, Rome, 00161, Italy; Luis Grande, Professor, Department of Surgery, Hospital del Mar, Passeig Marítim 25-29, Barcelona 08003, Spain

Smith RS, Miller RC. Incidence of brain metastasis in patients with esophageal carcinoma. *World J Gastroenterol* 2011; 17(19): 2407-2410 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v17/i19/2407.htm> DOI: <http://dx.doi.org/10.3748/wjg.v17.i19.2407>

INTRODUCTION

The incidence of esophageal cancer has been increasing in the United States over the past thirty years^[1], with an expected 16 470 cases and 14 530 deaths in 2009^[2,3]. Underlying this increase is a steady rise in the incidence of adenocarcinoma histology, surpassing squamous cell between 1990 and the early 2000s as the most common histology in the United States^[1,4-6].

Brain metastasis secondary to esophageal carcinoma

is considered to be a rare event, with a reported incidence of between 0.5% and 4.8%^[4,7-13]. However, many of these studies included patients from the 1980s and 1990s when squamous cell was the predominant histology. In patients with non-small cell carcinoma of lung, the risk of brain metastasis is correlated with histological type, ranging from 40% to 50% in those with adenocarcinoma, vs 10% to 20% among those with squamous cell carcinomas^[14-18]. Whether the incidence of brain metastasis in patients with esophageal carcinoma will increase as the predominant histology shifts from squamous cell to adenocarcinoma is unknown. Our recent clinical experience suggests that the incidence of brain metastasis in patients with esophageal carcinoma is higher than what has been reported. Therefore, a review of our database of patients with esophageal carcinoma at this community-based cancer center was undertaken to determine the incidence of brain metastasis in a contemporary group of patients with this disease. All of the patients received radiotherapy as a component of their treatment, but none had a diagnosis or suspicion of brain metastasis at the time of initial consultation.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, the medical records of all patients with a primary diagnosis of esophageal carcinoma between 1998 and 2007 treated in the Department of Radiotherapy at our center (Mayo Health System practice) were reviewed. Patient demographics, clinical characteristics, treatment modality, diagnosis of brain metastasis, and survival data were collected. All cases of brain metastases were diagnosed by radiographic imaging (CT or MRI scan). The association between the histology of esophageal cancer and the incidence of brain metastasis was assessed using the Fisher's exact test, with *P*-value of less than 0.05 considered to be statistically significant.

RESULTS

The clinical characteristics of fifty-three patients with a diagnosis of carcinoma of the esophagus are shown in Table 1. None of the patients had a diagnosis or suspicion of brain metastasis at the time of referral for radiotherapy evaluation. Forty-four patients had adenocarcinoma as the primary histology. Staging information was unavailable for three patients, and tumor grade was not available for twelve patients. Primary treatment modality is also shown in Table 1, with the majority (42%) receiving definitive chemoradiotherapy. No patients with squamous cell carcinoma underwent trimodality therapy. Thirteen patients with stage IVB disease received palliative radiation only. Forty-nine of the 53 patients have died. The median length of survival was 14 mo (range 3 to 56 mo) for squamous cell carcinoma patients and 13 mo (range 2 to 72 mo) for those with adenocarcinoma.

Seven (13%) of the fifty-three patients in this review

Table 1 Summary of patient characteristics

Characteristics	
No. of patients	53
Age (mean, yr)	68 (40-92)
Gender	44 male, 9 female
Length of follow-up (mean, mo)	16, (2-72)
Histology of primary tumor	
Adenocarcinoma	44
Squamous cell carcinoma	9
Grade of tumor	
1	2
2	13
3	19
4	7
Unknown	12
Stage	
II A	5
II B	2
III	18
IVA	8
IVB	17
Unknown	3
Treatment	
Chemo-radiation/surgery	10
Chemo-radiation	22
Surgery/chemo-radiation	4
Surgery/radiation	4
Radiation (palliative)	13
Sites of metastases	
Brain	7
Liver	14
Lung	1
Chest	1
Spine	3
Other	8

Table 2 Characteristics of patients with brain metastasis

Characteristics	
No. of patients	7
Age (mean, yr)	66 (57-75)
Gender	6 male, 1 female
Histology of primary tumor	
Adenocarcinoma	7
Squamous cell carcinoma	0
Grade of tumor	
2	1
3	3
4	2
Unknown	1
Stage	
II A	1
III	2
IVA	2
IVB	2
Treatment	
Chemo-radiation/surgery	3
Chemo-radiation	2
Surgery/chemo-radiation	1
Surgery/radiation	1
Radiation (palliative)	0
Time between original diagnosis and brain metastasis (mean, mo)	10, (2-25)

were subsequently diagnosed with brain metastases, all by radiographic imaging (CT or MRI scan). Characteristics of patients diagnosed with brain metastasis are shown in Table 2. Adenocarcinoma was the histology of the primary tumor in all seven patients, representing an incidence of 16% for the adenocarcinoma subgroup. The association between the histological type and brain metastasis was not statistically significant ($P = 0.24$). In six of these seven patients, the diagnosis of brain metastasis occurred within 11 mo of initial diagnosis of esophageal cancer.

DISCUSSION

This review identified a higher incidence of brain metastasis (13%) in a contemporary series of patients with carcinoma of the esophagus than has been previously reported^[4,7-13]. The incidence of brain metastasis in those studies ranged from 0.5% to 4.8%. Information on the incidence of brain metastases by histology type is limited. Three studies from Japan reported the incidence of brain metastasis in patients diagnosed with esophageal cancer in the 1980s to early 2000s as ranging from 1.4%-1.5%^[7,8,11]. Squamous cell carcinoma was the predominant histological type of esophageal cancer in Japan over that time period^[7,11,19]. One of the studies concluded that although squamous cell was the primary tumor histology in over 95% of patients in Japan, the patients with brain metastasis “frequently exhibited other histologic types”^[11].

Several studies in the United States also reported low incidence of brain metastasis in patients with esophageal cancer^[1,4,6,10,13]. In a large series of patients from The University of Texas M.D. Anderson Cancer Center diagnosed with primary carcinoma of the esophagus between 1993 and 2001, adenocarcinoma was the predominant histology (68% of cases versus 25% with squamous cell carcinoma). The overall incidence of brain metastasis was 1.7% and the authors concluded that histology did “not appear to be a risk factor for the development of brain metastasis”^[4]. However, Gabrielsen *et al.*^[13] reported a 3.6% incidence of brain metastasis in a review of 334 patients with esophageal carcinoma who underwent esophagectomy and concluded that there was a trend ($P = 0.16$) toward higher incidence of brain metastasis in those with adenocarcinoma. Although our results revealed the incidence of brain metastasis to be confined to those with adenocarcinoma, we could not demonstrate that histology was a significant risk factor for subsequent diagnosis of brain metastasis because of the small sample size, especially in the group with squamous cell carcinoma.

Rice and colleagues reported a correlation between adjuvant therapy and incidence of brain metastasis in a large series of patients with esophageal carcinoma from 1985 to 2002 who underwent esophagectomy with or without adjuvant therapy^[10]. The overall incidence of brain metastasis was 3.8%; however, the rate at five years post treatment was 2.5% with surgery alone, and as high as 18.4% in patients who underwent surgery with both preoperative and postoperative therapy. Interestingly, all cases of brain metastasis occurred in patients with adenocarcinoma, con-

sistent with the pattern seen in our study. The incidence for those receiving multi-modality therapy was similar to the 16% observed for the adenocarcinoma group in our study. This finding deserves more investigation, including whether treatment type influenced the subsequent development of brain metastasis or if multi-modality therapy may have been a surrogate for advanced stage (although this was not supported in a matched-pair analysis in the above study) and/or adenocarcinoma histology.

In a population based study from the Mayo Clinic, the median survival of patients with adenocarcinoma of the esophagus improved from 8.5 to 11.7 mo between 1971 and 2000; however, this was not deemed to be a significant change^[20] and is similar to the median length of survival of 13 mo in our study. Therefore, it is not clear that the higher rate of brain metastasis reported in this study can be explained by patients living significantly longer with modern therapy. The results observed in this study might reflect a difference in underlying tumor biology and metastatic potential for CNS involvement between the two primary histologies. This would be similar to the pattern seen in patients with non-small cell lung carcinoma, where the incidence of brain metastasis is at least two-fold higher in those with adenocarcinoma versus squamous cell carcinoma^[14-18].

The relatively short interval between diagnosis of the primary tumor and development of brain metastases noted in our study (median 7 mo) is similar to the 5.6 mo reported by Weinberg *et al.*^[4]. Furthermore, in the study by Rice *et al.*^[10], twenty of the twenty-nine patients who developed brain metastasis did so within one year following esophagectomy. Based on these findings, close attention to neurological signs and symptoms, with consideration of brain imaging as clinically indicated, should be a component of initial and follow-up evaluations in patients with esophageal cancer, especially in those with adenocarcinoma.

Limitations of this study include the retrospective nature and the relatively small sample size, precluding the ability to demonstrate statistical correlation with histology or treatment modality. In addition, this review was limited to patients who received radiotherapy as a component of their treatment; therefore, it may not be representative of all patients with esophageal cancer. However, none of the patients in our study had a diagnosis or suspicion of brain metastasis at the time of referral for radiotherapy evaluation.

In conclusion, this study revealed a higher incidence of brain metastasis than previously reported in patients with esophageal cancer, and occurred exclusively in those with adenocarcinoma, possibly identifying a trend that may increase as the incidence of this particular histology continues to rise. However, other factors, including gender, stage, and treatment type, could not be thoroughly assessed. Further research, to include a larger sample size in a contemporary group of patients with esophageal carcinoma, is required to confirm the findings in this study and to better understand the possible association between histology, patient characteristics, and/or treatment modality and the development of brain metastasis.

ACKNOWLEDGMENTS

We thank Qing Chen, PhD for assistance with the statistical analysis and Michael Haddock, MD for his thoughtful critique.

COMMENTS

Background

This is an original study analyzing the incidence of brain metastasis in patients with esophageal carcinoma. The study assessed whether the incidence is higher in a contemporary group of patients than previously reported.

Research frontiers

Previous studies have shown very low incidence of brain metastasis in patients with esophageal carcinoma when the primary histological type was squamous cell carcinoma. The predominant histology has shifted to adenocarcinoma; therefore, this study addressed the question of whether the incidence of brain metastasis is higher than when squamous cell was the predominant histology. This would be similar to the pattern seen in patients with non-small cell lung carcinoma, where the incidence of brain metastasis is two- to five-fold higher in patients with adenocarcinoma versus squamous cell carcinoma.

Innovation and breakthroughs

The authors reported a higher incidence of brain metastasis than previously reported and all patients with brain metastasis had adenocarcinoma. In addition, there was a relatively short interval between the diagnosis of the primary tumor and development of brain metastasis, similar to data reported by other studies.

Applications

The findings of this study highlight the need for attention to neurological signs and symptoms with consideration of brain imaging as clinically indicated, in patients with esophageal cancer, especially those with adenocarcinoma.

Peer review

This is an original study concerning the incidence of brain metastasis in patients with esophageal carcinoma. The topic is interesting, the number of cases is not negligible; the study is well described and provides indication for further researches. The references are updated.

REFERENCES

- 1 Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005; **97**: 142-146
- 2 Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlander N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK (eds). *SEER Cancer Statistics Review, 1975-2005*. Bethesda, MD: National Cancer Institute; 2008. Available from: URL: <http://seer.cancer.gov/csr/1975-2005>
- 3 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59**: 225-249
- 4 Weinberg JS, Suki D, Hanbali F, Cohen ZR, Lenzi R, Sawaya R. Metastasis of esophageal carcinoma to the brain. *Cancer* 2003; **98**: 1925-1933
- 5 Trivers KF, Sabatino SA, Stewart SL. Trends in esophageal cancer incidence by histology, United States, 1998-2003. *Int J Cancer* 2008; **123**: 1422-1428
- 6 Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst* 2008; **100**: 1184-1187
- 7 Ogawa K, Toita T, Sueyama H, Fuwa N, Kakinohana Y, Kamata M, Adachi G, Saito A, Yoshii Y, Murayama S. Brain metastases from esophageal carcinoma: natural history, prognostic factors, and outcome. *Cancer* 2002; **94**: 759-764
- 8 Yoshida S. Brain metastasis in patients with esophageal carcinoma. *Surg Neurol* 2007; **67**: 288-290
- 9 Kaneko T, Hirao M, Shimada M, Takayama T, Iwazawa T, Murata K, Inoue M, Terashima T, Mizunoya S, Okagawa K. [Postoperative brain metastasis from esophageal carcinomas: report of 4 cases]. *Kyobu Geka* 1991; **44**: 1013-1017
- 10 Rice TW, Khuntia D, Rybicki LA, Adelstein DJ, Vogelbaum MA, Mason DP, Murthy SC, Blackstone EH. Brain metastases from esophageal cancer: a phenomenon of adjuvant therapy? *Ann Thorac Surg* 2006; **82**: 2042-2049, 2049.e1-e2
- 11 Kawabata R, Doki Y, Ishikawa O, Nakagawa H, Takachi K, Miyashiro I, Tsukamoto Y, Ohigashi H, Sasaki Y, Murata K, Ishiguro S, Imaoka S. Frequent brain metastasis after chemotherapy and surgery for advanced esophageal cancers. *Hepatogastroenterology* 2007; **54**: 1043-1048
- 12 Quint LE, Hepburn LM, Francis IR, Whyte RI, Orringer MB. Incidence and distribution of distant metastases from newly diagnosed esophageal carcinoma. *Cancer* 1995; **76**: 1120-1125
- 13 Gabrielsen TO, Eldevik OP, Orringer MB, Marshall BL. Esophageal carcinoma metastatic to the brain: clinical value and cost-effectiveness of routine enhanced head CT before esophagectomy. *AJNR Am J Neuroradiol* 1995; **16**: 1915-1921
- 14 Mujoomdar A, Austin JH, Malhotra R, Powell CA, Pearson GD, Shiao MC, Raftopoulos H. Clinical predictors of metastatic disease to the brain from non-small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases. *Radiology* 2007; **242**: 882-888
- 15 Bajard A, Westeel V, Dubiez A, Jacoulet P, Pernet D, Dalphin JC, Depierre A. Multivariate analysis of factors predictive of brain metastases in localised non-small cell lung carcinoma. *Lung Cancer* 2004; **45**: 317-323
- 16 Figlin RA, Piantadosi S, Feld R. Intracranial recurrence of carcinoma after complete surgical resection of stage I, II, and III non-small-cell lung cancer. *N Engl J Med* 1988; **318**: 1300-1305
- 17 Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain. *Cancer* 2007; **109**: 1668-1675
- 18 Shi AA, Digumarthy SR, Temel JS, Halpern EF, Kuester LB, Aquino SL. Does initial staging or tumor histology better identify asymptomatic brain metastases in patients with non-small cell lung cancer? *J Thorac Oncol* 2006; **1**: 205-210
- 19 Shibata A, Matsuda T, Ajiki W, Sobue T. Trend in incidence of adenocarcinoma of the esophagus in Japan, 1993-2001. *Jpn J Clin Oncol* 2008; **38**: 464-468
- 20 Crane SJ, Locke GR 3rd, Harmsen WS, Zinsmeister AR, Romero Y, Talley NJ. Survival trends in patients with gastric and esophageal adenocarcinomas: a population-based study. *Mayo Clin Proc* 2008; **83**: 1087-1094

S- Editor Tian L L- Editor Stewart GJ E- Editor Ma WH