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Survival in esophageal cancer patients with hematogenous distant organ metastases

Objective: Esophageal cancer is a rapidly progressive cancer. In the majority of patients local invasion or distant metastasis may be present at the time of diagnosis. The present study reviewed the records of esophageal cancer patients with hematogenous distant organ metastases with the aim of reporting primary tumor location, histological type, location of metastases, and survival rates, according to treatment administered.

Method: Distant organ metastasis was detected in 50 of 316 consecutive patients that presented to the Thoracic Surgery Department of Atatürk University between 2002 and 2007. Patient age and gender, tumor location, history of esophagectomy, metastasis organ, treatment type, and survival outcome were retrospectively reviewed.

Results: The liver was the most common organ of distant metastasis and was observed in 24 (38.7%) patients, followed by lung metastasis, which was observed in 21 (33.9%) patients. Bone metastases were detected in 5 patients, pancreatic metastases in 4, pleural metastases in 2, and metastasis in the spleen, peritoneum, kidney, adrenal gland, brain, and diaphragm were each observed in 1 patient. Nine patients had metastases in more than 1 organ. Overall, 6-month survival was 58%, 1-year survival was 28%, and 2-year survival was only 2%. Mean survival was 7.8 months in patients with isolated liver metastases (range: 1-18 months) versus 7.1 months (range: 2-14 months) in patients with isolated lung metastases. Mean survival was 6.2 months (range: 1-32 months) in patients with multiple organ metastases, versus 7.6 months (range: 1-18 months) in those with metastasis in 1 organ. Mean survival was 7.7 months (range: 1-18 months) in patients that received chemotherapy, as compared to 7.1 months (range: 1-32 months) in those that did not. Overall, mean survival was 7.3 months in patients with hematogenous distant organ metastases.

Conclusion: Our results show that survival rates in esophageal cancer patients with distant organ metastases were similar in those that received and did not receive chemotherapy. Thus, we consider that new therapeutic protocols are required for metastases of esophagus carcinoma.

Key Words: Esophageal cancer, metastasis, survey

Hematojen uzak organ metastazlı özofagus kanserinde sağkalım

Amaç: Özofagus kanseri en hızlı progresyon gösteren kanserlerden biridir. Birçok hasta tanı aldığında lokal yayılım veya uzak metastaz bulunabilmektedir. Bu çalışmada hematojen yolla uzak organ metastazı saptadığımız özofagus kanserli hastaları yeniden gözden geçirerek primer tümör lokalizasyonu ve histolojik tiplere göre metastazların dağılımı ile metastaz lokalizasyonu ve uygulanan tedaviye göre survey sonuçları hakkında bilgi elde etmeyi amaçladık.

Metod: 2002 ve 2007 yılları arasında Atatürk Üniversitesi Tıp Fakültesi Göğüs Cerrahisi Kliniği'ne başvuran özofagus kanserli 50 hastada uzak organ metastazı tespit edildi. Hastaların yaşı, cinsiyeti, tümörün lokalizasyonu, histolojik tipi, özofajektomi öyküsü, metastaz organı, tedavi şekli, survey sonuçları retrospektif olarak yeniden gözden geçirildi.

Sonuçlar: Karaciğer 24 (% 38,7) hasta ile en çok görülen uzak metastaz organıydı. İkinci olarak 21 (% 33.9) hastada akciğer metastazı tespit edildi. 5 hastada kemik metastazı, 4 hastada pankreas metastazı, 2 hastada plevral metastaz ve birer hastada dalak, periton, böbrek, surrenal, beyin ve diafragma metastazı tespit edildi. 9 hastada birden fazla organda metastaz mevcuttu. Genel olarak 6 aylık survey % 58, bir yıllık survey % 28, 2 yıllık survey ise sadece % 2 idi. İzole karaciğer

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metastazında ortalama survey 7,8 ay (1-18 ay arası), izole akciğer metastazında 7,1 ay idi (2-14 ay arası) idi. Multipl organda metastazı olanlarda ortalama survey 6,2 ay (1-32 ay arası), tek organ metastazı olanlarda ise ortalama survey 7,6 ay idi (1-18 ay arası). KT alan hastalarda ortalama survey 7,7 ay (1-18 ay arası), almayan hastalarda ise 7,1 ay idi (1-32 ay arası). Genel olarak hematojen yolla uzak organ metastazı yapmış hastalarda ortalama survey ise 7,3 ay olarak hesaplandı.

Tartışma: Elde ettiğimiz sonuçlar uzak organ metastazı bulunan özofagus kanserli hastalarda survey oranlarının farklı metastaz organlarında ve kemoterapi alan veya almayan hastalarda birbirine yakın olduğunu göstermektedir. Özofagus kanserinin metastazlarında yeni tedavi protokollerine ihtiyaç olduğunu düşünüyoruz.

Anahtar Sözcükler: Özofagus kanseri, metastaz, sağkalım

Introduction

Esophageal cancer ranks sixth in prevalence among all cancers worldwide. About 386,000 people per year die of esophageal cancer (1,2). Esophageal cancer is one of the most rapidly progressive and difficult to treat diseases. Regional lymph node involvement or distant organ metastasis may develop rapidly in this disease, with early and rapid spread to the esophageal wall and adventitia. In about 75% of patients local invasion, distant metastasis, or both may be observed at the time of diagnosis (3,4). Despite aggressive treatment, detailed 5-year survival is only as high as 20%. In the majority of patients, both locoregional recurrence and distant metastases develop following esophageal resection (3,4).

Esophageal cancer spreads in 3 ways: direct invasion, and via lymphatic or hematogenous routes. Most metastases in esophageal cancer cases are to the lymph nodes. Distant organ metastases in patients with esophageal cancer may vary, depending on location of the primary tumor and histological type. In the current study our aim was to assess the survival rates in esophageal cancer patients with hematogenous distant organ metastases, according to location, histological type of the primary tumor, location of metastases, and the treatment administered.

Materials and Methods

Medical records of 50 consecutive patients that presented to the Thoracic Surgery Department of Atatürk University between 2002 and 2007 in whom distant organ metastases were observed were retrospectively reviewed. Patient age and gender, tumor location, histological type, history of esophagectomy, organ of metastasis, type of treatment, and survival outcomes were reviewed. Metastases were detected in the patients with computerized tomography (CT), ultrasound examination (US), magnetic resonance imaging (MRI), bone scanning, and, in some patients, histological examination. Patients with lymph node metastases in the cervical/supraclavicular, thoracic, and abdominal regions, and locoregional recurrence were excluded from the study. Diagnoses of metastases were made during surgical exploration in 4 patients that were not diagnosed with metastasis following preoperative radiological examinations, and in all 4 cases surgery was terminated.

Results

Of the 50 esophageal cancer patients with hematogenous distant metastases 25 (50%) were female and 25 (50%) were male. Mean age was 59.0 years (range: 28-79 years). Tumor location included the upper esophagus in 4 (8%) patients, mid-thoracic esophagus in 22 (44%), and distal esophagus in 24 (48%). Histological type was squamous cell carcinoma in 38 (76%) patients and adenocarcinoma in 12 (24%). The liver was the most common organ of distant metastases, which occurred in 24 (38.7%) patients, followed by lung metastases in 21 (33.9%). Bone metastases were detected in 5 patients, pancreatic metastases in 4, pleural metastases in 2, and metastasis of the spleen, peritoneum, kidney, adrenal gland, brain, and diaphragm was each observed in 1 patient. In all, 9

patients had metastases in more than 1 organ (liver and lung metastases in 6 patients, bone and pleura metastases in 1, lung, liver, and bones in 1, and lungs, diaphragm, pleura, and adrenal gland in 1) (Table 1).

Table 1. Distribution of hematogenous distant organ metastases in the patients with esophageal carcinoma.

Metastatic organ	n	%
Liver	24	38.7
Lung	21	33.9
Bones	5	8.1
Pancreas	4	6.5
Pleura	2	3.2
Spleen	1	1.6
Peritoneum	1	1.6
Kidneys	1	1.6
Adrenal gland	1	1.6
Brain	1	1.6
Diaphragm	1	1.6
TOTAL	62	100

The most common organ of metastasis was the liver, followed by the lungs, regardless of primary tumor location (upper, middle, or lower esophagus). Metastases in other abdominal organs usually originated from tumors in the distal esophagus (Table 2).

When hematogenous distant organ metastases were evaluated according to histological type, the most common metastasis in squamous cell carcinomas was to the liver, followed by the lungs in adenocarcinomas, whereas metastasis into the liver, lungs, and pancreas was equal. In all of the 4 patients with pancreatic metastases, histological type was adenocarcinoma (Table 3).

Of the 50 patients with distant organ metastases, 15 (30%) (7 with liver metastases, 3 with lung metastases, 2 with liver-lung metastases, 1 with bone metastasis, 1 with kidney metastasis, and 1 with liver-lung-bone metastases) were deemed inoperable and received chemotherapy. The chemotherapy protocol consisted of cisplatin and 5-FU in 12 patients, cisplatin, 5-FU, and epirubicine in 1 patient, cisplatin, 5-FU, and leucovorin calcium in 1, and a combination of cisplatin and etoposide in 1. In all, 35 (70%) of the 50 patients underwent stent replacement for palliation; none of these patients underwent resection.

Overall, 6-month survival was 58%, 1-year survival was 28%, and 2-year survival was only 2%

Table 2. Distribution of hematogenous metastases according to primary tumor location.

Tumor location	Metastatic organ	n	%
UPPER	Liver	2	50
	Lung	1	25
	Bones	1	25
MIDDLE	Liver	11	40
	Lung	10	37
	Bones	4	15
	Kidney	1	4
	Pleura	1	4
LOWER	Liver	11	36
	Lung	10	33
	Pancreas	4	13
	Spleen	1	3
	Adrenal gland	1	3
	Peritoneum	1	3
	Brain	1	3
	Diaphragm	1	3
	Pleura	1	3

Table 3. Distribution of hematogenous metastases according to histological type in esophageal carcinoma patients.

Histological type	Metastatic organ	n	%
SQUAMOUS CELL	Liver	20	44.5
	Lung	17	37.8
	Bones	5	11.1
	Kidney	1	2.2
	Pleura	1	2.2
	Brain	1	2.2
ADENO-CARCINOMA	Liver	4	23.5
	Lung	4	23.5
	Pancreas	4	23.5
	Spleen	1	5.9
	Adrenal gland	1	5.9
	Peritoneum	1	5.9
	Diaphragm	1	5.9
	Pleura	1	5.9

(Figure). Mean survival was 7.8 months in isolated liver metastases cases (range: 1-18 months) versus 7.1 months (range: 2-14 months) in cases of isolated lung metastases. Mean survival was 6.2 months (range: 1-32 months) in patients with multiple organ metastases and 7.6 months (range: 1-18 months) in those with metastasis in 1 organ. Mean survival was 7.7 months (range: 1-18 months) in patients that underwent chemotherapy, as compared to 7.1 months (range: 1-32 months) in those that did not. Mean survival was 7.3 months in the patients with hematogenous distant organ metastases.

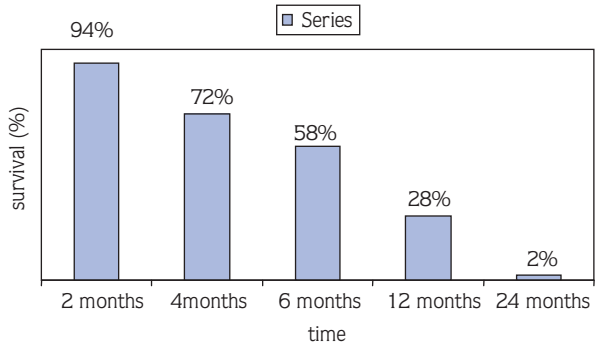

Figure. Survival rates in patients with esophageal cancer that metastasized via the hematogenous route.

Discussion

Esophageal cancer is known to have an aggressive course. Local infiltration, adjacent lymph node involvement, and hematogenous distant organ metastases are common. Most patients with esophageal cancer die within 1 year of diagnosis. Only 8%-20% of patients survive for 5 years. In the majority of these patients the primary cause of death is metastasis (3-5).

The most common therapy for patients in the early stages of esophageal cancer is esophagectomy. Some patients, however, may relapse with metastatic disease, even though no metastases were observed at the time of primary surgery and despite chemotherapy. Furthermore, detailed survival following planned curative surgery does not exceed 25% and disease-free survival is only 12 months (5). This could be due to the presence of micrometastases or metastases that are not detected during surgery (6). Depth of tumor invasion is considered the most important predictor of postoperative recurrence (7).

Appropriate staging of esophageal carcinoma based on BT and endoscopic US examination will preclude unnecessary surgery. PET provides more accurate data than BT for detecting distant metastases. With the standard diagnostic strategy, however, more than 30% of distant metastases are radiologically occult and surgery is still performed in a substantial number of patients with distant metastases (8). This highlights the fact that current staging methods alone fail to identify disseminated tumor cells. Thus, sensitive molecular processes are being developed to identify disseminated tumor cells in the lymph nodes and distant organs (9).

The metastatic process consists of several steps that are quite organized and organ-selective (10,11). Early metastatic relapse following complete resection of a localized tumor suggests disseminated tumor cells or micrometastases that could not be detected with routine imaging methods during surgery. The first step of the metastatic cascade consists of tumor cell adhesion loss, induction of cellular motility, and local tumor cell invasion (12). These steps are followed by dissemination to regional lymph nodes or hematogenous circulation. In this case, the tumor reaches secondary organs via immovable or dormant cells. Some of these cells may be precursors of metastases that may appear several years after curative resection of the primary tumor.

Two histopathological types are most commonly seen in esophageal carcinoma. A high recurrence rate and the fact that recurrence is predominant in patients with tumors of the lower third of the esophagus suggest biological differences between adenocarcinomas and squamous cell carcinomas (7). Esophageal adenocarcinoma tends to grow locally. It may lead to invasion to adjacent organs, causing local complications, and may lead to death. Invasion into the periadventitial tissue, esophageal muscle layer, and adjacent tissues is seen in about 80% of patients, whereas lymphatic spread occurs in 70% of patients (13). In particular, metastases into the mediastinal, abdominal, and cervical lymphatic ganglia are common. Lymphatic spread with submucosal invasion is responsible for intra-

esophageal tumor growth. Hematogenous spread is less common and is seen later in these cancers (13).

The most common sites of hematogenous metastases in esophageal cancer cases are the liver, lungs, and bones (14). In the present study most hematogenous metastases were observed in these organs. Rarely, hematogenous spread into other various organs may be seen; its incidence, however, is about 1%-2%. These organs include the brain, spleen, pancreas, stomach, kidneys, adrenal gland, peritoneum, pleura, diaphragm, and chest wall (15-17). It has been noted that there is a tendency for hematogenous recurrence in esophageal cancer, especially in cases of negative E-cadherin in liver and lung metastases (18). As for lymphatic recurrence, the hematogenous type also significantly correlates with positive node sites and number (15,18). Although liver metastases were more common in adenocarcinoma cases than in cases of squamous cell carcinoma in a study by Quint et al. (15), liver metastases were more common in cases of squamous cell carcinoma than in adenocarcinoma cases in the present study (44.5% and 23.5%, respectively). Furthermore, in the present study hematogenous metastases were most common in the liver, followed by the lungs in esophageal cancers in which the primary tumor was located in the upper, middle, or lower esophagus.

Systemic metastases are seen in about 25% of patients within 20 months of curative resection. Patients with metastatic esophageal carcinoma have a poor prognosis due to their general medical status; therefore, these patients usually cannot tolerate aggressive medical treatment. Even palliative surgery to relieve dysphagia may result in high morbidity rates in these patients. Resection may be performed in rare cases in metastatic patients. Resection criteria are as follows in cases of metastatic disease (19): functional status of the patient must be good, no local recurrence of the primary tumor, well-limited solitary metastasis, tumor must be completely resected without significant dysfunction, and at least 1 year must have elapsed from the time of initial treatment of the primary esophageal carcinoma.

Patients with distant organ metastases usually have a poor general medical status at the time of presentation and receive only palliative treatment. Squamous cell carcinoma of the esophagus is known to respond well to chemotherapy. Standard treatment for liver metastases of the distal esophagus and cardia adenocarcinomas is chemotherapy (20). Systemic chemotherapy is still considered the most common standard treatment for patients with distant organ metastases. Nakada et al. (21) reported that they achieved complete response with chemotherapy consisting of 5-fluorouracil and cisplatin in a patient with esophageal cancer and liver metastasis. Sueyama et al. (22) achieved survival for more than 3 years with cisplatin and continuous 120-h 5-fluorouracil infusion in an advanced esophageal cancer patient with lung and liver metastases. Uchikado et al. (23) reported that treatment with low doses of 5-fluorouracil and cisplatin was quite successful in a patient with adenosquamous carcinoma of the esophagus with liver metastasis, and reported that successful outcomes could be achieved with the same chemotherapy protocol in patients with esophageal cancer and visceral metastasis. In randomized trials, however, the duration of response was short and mean survival was less than 1 year, although symptoms were relieved by the chemotherapy in the majority of patients (24). The mortality rate related to the treatment was high, even in a series in which the response rate was 35% in patients with metastatic esophageal carcinoma in response to a combination of 5-fluorouracil and cisplatin. Therefore, no standard treatment regimen exists for metastatic esophageal carcinoma. High tumor burden, advanced age, smoking, alcohol consumption, and comorbid conditions reduce the tolerance to toxic chemotherapy regimens in patients with metastatic esophageal carcinoma. Furthermore, the effect of chemotherapy on survival is unclear. Nevertheless, chemotherapy is the most studied treatment option for relieving symptoms and prolonging survival. Mean survival was 7.7 months in 15 of our patients that received cisplatin-based chemotherapy and no significant improvement was observed in survival as compared to the patients that did not receive chemotherapy.

Hepatic arterial infusion chemotherapy, or aggressive hepatectomy, has been performed recently in cases of liver metastases of gastric or

colorectal cancers; however, the success rate of surgery or chemotherapy in the case of liver metastasis in patients with esophageal carcinoma is low. Thus, Ikeda et al. (25) propose treatment with radiotherapy in cases of liver metastases in patients with esophageal squamous cell carcinoma.

Kato et al. (26) reported that the 3-year survival rate is only 0.3% in patients with esophageal cancer and distal organ metastases. In the present study, survival at 2 years was seen in only 1 (2%) patient (a 65-year-old woman with lung and liver metastases). The patient had not undergone surgery for the primary disease and she declined chemotherapy). Mean survival in the current study was 7.3 months in the patients with hematogenous metastases. In the case of lung and liver metastases, mean survival was similar in the patients that received and did not receive chemotherapy (7.8 and 7.1, and 7.7 and 7.1 months, respectively).

In summary, hematogenous spread in esophageal cancer most commonly occurs in the liver, lungs, and bones. The most common treatment is chemotherapy. The most commonly used chemotherapy protocol consists of cisplatin and 5-fluorouracil. In metastatic patients the complete response rate is low with chemotherapy; therefore, a standard chemotherapy protocol has yet to be determined for metastatic esophageal carcinoma. Based on the results we obtained, survival rates were similar in patients with hematogenous metastases in different organs, whether or not they received chemotherapy–about 6-8 months. In conclusion, current staging techniques alone fail to detect disseminated tumor cells. Thus, sensitive molecular processes are required for detecting disseminated tumor cells in distant organs at early stages. Furthermore, chemotherapy protocols that are less toxic and more effective at prolonging survival must be developed. Thus, patients with distant organ metastases may be diagnosed at earlier stages, unnecessary surgery can be avoided, and patient comfort and survival can be improved with appropriate treatment combinations.

References

1. Kamangar F, Malekzadeh R, Dawsey SM, Saidi F. Esophageal cancer in Northeastern Iran: a review. Arch Iran Med 2007; 10: 70-82.
2. Kollarova H, Machova L, Horakova D, Janoutova G, Janout V. Epidemiology of esophageal cancer--an overview article. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2007; 151: 17-20.
3. Millikan KW, Silverstein J, Hart V, Blair K, Bines S, Roberts J et al. A 15-year review of esophagectomy for carcinoma of the esophagus and cardia. Arch Surg 1995; 130: 617-24.
4. Carlisle JG, Quint LE, Francis IR, Orringer MB, Smick JF, Gross BH. Recurrent esophageal carcinoma: CT evaluation after esophagectomy. Radiology 1993; 189: 271-5.
5. Flanagan FL, Dehdashti F, Siegel BA, Trask DD, Sunderasan SR, Patterson GA et al. Staging of esophageal cancer with 18F-fluorodeoxyglucose positron emission tomography. AJR 1997; 168: 417-424.
6. Wright C, Mathisen D, Wain J, Grillo HC, Hilgenberg AD, Moncure AC et al. Evolution of treatment strategies for adenocarcinoma of the esophagus and GE junction. Ann Thorac Surg 1994; 58: 1574-1579.
7. Mariette C, Balon JM, Piessen G, Fabre S, Van Seuningen I, Triboulet JP. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. Cancer 2003; 97: 1616-23.
8. Rice TW. Clinical staging of esophageal carcinoma: CT, EUS and PET. Chest Surg Clin N Am 2000; 10: 471-485.
9. Kaifi JT, Yekebas EF, Schurr P, Obonyu D, Wachowiak R, Busch P et al. Tumor-cell homing to lymph nodes and bone marrow and CXCR4 expression in esophageal cancer. J Natl Cancer Inst 2005; 97: 1840-7.
10. Izbicki JR, Hosch SB, Pichlmeier U, Rehders A, Busch C, Niendorf A et al. Prognostic value of immunohistochemically identifiable tumor cells in lymph nodes of patients with completely resected esophageal cancer. N Engl J Med 1997; 337: 1188-94.
11. Pantel K, Brakenhoff RH. Dissecting the metastatic cascade. Nat Rev Cancer 2004; 4: 448-56.
12. Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. Nat Rev Mol Cell Biol 2003; 4: 915-25.
13. Feith M, Stein HJ, Siewert JR. Pattern of lymphatic spread of Barrett's cancer. World J Surg 2003; 27: 1052-7.
14. Lindenmann J, Matzi V, Porubsky C, Maier A, Smolle-Juettner FM. Complete resection of an isolated chest wall metastasis from esophageal carcinoma after transhiatal esophagectomy and gastric pull-up at one and a half-year follow-up. J Thorac Oncol 2007; 2: 773-6.

15. Quint LE, Hepburn LM, Francis IR, Whyte RI, Orringer MB. Incidence and distribution of distant metastases from newly diagnosed esophageal carcinoma. Cancer 1995; 76: 1120-5.

16. Weinberg Js, Suki D, Hanbeli F, Cohen ZR, Lenzi R, Sawaya R. Metastasis of esophageal carcinoma to the brain. Cancer 2003; 98: 1925-33.

17. Kimura Y, Miyazaki M, Saeki H, Ohga T, Nozoe T, Sugimachi K. Solitary splenic metastasis derived from esophageal cancer. Hepatogastroenterology 2003; 50: 1336-7.

18. Kato H, Miyazaki T, Nakajima M, Sohda M, Fukai Y, Masuda N et al. Prediction of hematogenous recurrence in patients with esophageal carcinoma. Jpn J Thorac Cardiovas Surg 2003; 51: 599-608.

19. Mao YS, Suntharalingam M, Krasna MJ. Management of late distant metastases after trimodality therapy for esophageal cancer. Ann Thorac Surg 2003; 76: 1742-3.

20. Seitz JF, Duffaud F, Dahan L, Pies P, Ville E, Laugier R. Adenocarcinomas of the distal esophagus and gastric cardia: what chemotherapy or chemoradiotherapy for recurrent or metastatic disease? Cancer Radiother 2001; 5: 107-12.

21. Nakada T, Nagayama K, Hiramato J, Tsuruta Y, Murakami S, Sakabe S. Complete regression of esophageal cancer with concomitant liver metastasis achieved by concurrent chemoradiation therapy. Int J Clin Oncol 2002; 7: 192-6.

22. Sueyama H. A case of esophageal carcinoma with the lung and liver metastases surviving more than 3 years. Nippon Gan Chiryo Gakkai Shi 1990; 25: 1668-72.

23. Uchikado Y, Natsugoe S, Okumura H, Matsumoto M, Setoyama T, Takigawa J et al. A case of successful treatment by low-dose 5-fluorouracil and cisplatin for liver metastases of esophageal adenosquamous carcinoma. Gan To Kakagu Ryoho 2006; 33: 83-5.

24. Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, et al. Randomized phase II study of cisplatin and 5-fluorouracil versus cisplatin alone in advanced squamous cell esophageal cancer. Eur J Cancer 1997; 33: 1216-20.

25. Ikeda Y, Niimi M, Kan S, Shatari T, Takami H, Kodaira S. Conformal radiation therapy for liver metastasis of esophageal carcinoma. Hepatogastroenterology 2003; 50: 532-4.

26. Kato H, Tachimori Y, Watanabe H, Iizuka T. Evaluation of the new (1987) TNM classification for thoracic esophageal tumors. Int J Cancer 1993; 53: 220-223.