PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2006 July 14; 12(26): 4185-4190
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Predictive factors of survival in patients treated with definitive chemoradiotherapy for squamous cell esophageal carcinoma

Frédéric Di Fiore, Stéphane Lecleire, Olivier Rigal, Marie-Pierre Galais, Emmanuel Ben Soussan, Isabelle David, Bernard Paillot, Jacques-Henri Jacob, Pierre Michel

Frédéric Di Fiore, Stéphane Lecleire, Olivier Rigal, Emmanuel Ben Soussan, Bernard Paillot, Pierre Michel, Digestive Oncology Unit, Hepatogastroenterology Department, Rouen University Hospital, France
Marie-Pierre Galais, Jacques-Henri Jacob, Digestive Oncology unit, François Baclesse Centre, Caen, France
Isabelle David, Radiotherapy Department, Henri Becquerel Centre, Rouen, France
Correspondence to: Dr. Frédéric Di Fiore, Digestive Oncology Unit, Hepatogastroenterology Department, Rouen University Hospital- Charles Nicolle- France, 1, rue de Germont, 6031 Rouen Cedex, France. eliottdf@hotmail.com
Telephone: +33-2-32888101 Fax: +33-2-35151623
Received: 2006-01-25 Accepted: 2006-04-21

Key words: Definitive chemoradiotherapy; Esophageal squamous cell carcinoma; Predictive factors

Di Fiore F, Lecleire S, Rigal O, Galais MP, Ben Soussan E, David I, Paillot B, Jacob JH, Michel P. Predictive factors of survival in patients treated with definitive chemoradiotherapy for squamous cell esophageal carcinoma. *World J Gastroenterol* 2006; 12(26): 4185-4190

http://www.wjgnet.com/1007-9327/12/4185.asp

Abstract

AIM: The aim of the study was to evaluate the predictive factors of survival in patients with locally advanced squamous cell esophageal carcinoma (LASCOC) treated with definitive chemoradiotherapy (CRT) regimen based on the 5FU/CDDP combination.

METHODS: All patients with LASCOC treated with a definitive CRT using the 5FU/CDDP combination between 1994 and 2000 were retrospectively included. Clinical complete response (CCR) to CRT was assessed by esophageal endoscopy and CT-scan 2 mo after CRT completion. Prognostic factors of survival were assessed using univariate and multivariate analysis by the Cox regression model.

RESULTS: A total of 116 patients were included in the study. A CCR to CRT was observed in 86/116 (74.1%). The median survival was 20 mo (range 2-114) and the 5-year survival was 9.4%. Median survival of responder patients to CRT was 25 mo (range 3-114) as compared to 9 mo (range 2-81) in non-responder patients ($P < 0.001$). In univariate analysis, survival was associated with CCR ($P < 0.001$), WHO performance status < 2 ($P = 0.01$), tumour length < 6 cm ($P = 0.045$) and weight loss < 10% was in limit of significance ($P = 0.053$). In multivariate analysis, survival was dependant to CCR ($P < 0.0001$), weight loss < 10% ($P = 0.034$) and WHO performance < 2 ($P = 0.046$).

CONCLUSION: Our results suggest that survival in patients with LASCOC treated with definitive CRT was correlated to CCR, weight loss and WHO performance status.

INTRODUCTION

Esophageal cancer is a frequent gastrointestinal malignancy with 32 332 new cases per year in Europe. In France, esophageal carcinoma is the third most frequent digestive tract cancer with approximately 5000 new cases per year[1,2]. Approximately 50% of patients present a locally advanced esophageal carcinoma at diagnosis. To date, the incidence rate of adenocarcinoma is increasing but squamous cell carcinoma still remains the most frequent histological type in France[1,2]. The definitive chemoradiotherapy (CRT) based on the Herskovic regimen is considered as the standard medical treatment in non operated patients with locally advanced esophageal carcinoma[3,4]. Moreover, two phase III trials recently suggested that definitive CRT could be considered as an alternative treatment in patients with esophageal carcinoma[5,6].

However, some questions remain unsolved as regards the CRT regimen optimisation. Moreover, although most studies included both patients with squamous cell and adenocarcinoma, it has been suggested to consider these two tumours separately for treatment as regards their different risk factors, carcinogenesis pathways and treatment response[3-5,7-11]. Furthermore, the study of Rizk *et al* recently reported that long term prognosis in patients with esophageal carcinoma treated with preoperative CRT could be significantly different according to the histological type of tumour[11]. However, few reported series have specifically focused on the long-term survival analysis in patients with squamous cell carcinoma treated with definitive CRT using the 5FU/CDDP combination[12-20]. Moreover, most of these series included a limited number of patients or reported results with short follow-up[13-20].

The aim of the present study was to assess the long-

term results and the predictive factors of survival in a large series of patients with a locally advanced squamous cell esophageal carcinoma (LASCOC) treated with a definitive CRT regimen based on the 5FU/CDDP chemotherapy (CT) combination. Furthermore, knowledge of these prognostic factors could be useful for the management of individual patients as well as a stratification variable for the design of future randomised trials.

MATERIALS AND METHODS

Patient population

All consecutive patients with a LASCOC referred between January 1994 and the 31st December 2000 were retrospectively included for the study. Patients were selected based on the following criteria: a histologically confirmed squamous cell carcinoma; a first-line treatment with a definitive CRT regimen using the 5FU/CDDP CT and concomitant external radiotherapy (RT). Patients were excluded if they had previous a history of carcinoma during the past three years and if they had synchronous distant metastasis. In our centres, the definitive CRT regimen based on the 5FU/CDDP combination was the first therapeutic option used in patients with LASCOC.

For each patient, we routinely recorded all baseline clinical and tumour characteristics including age, sex, World Heath Organisation (WHO) performance status, dysphagia Atkinson score and weight loss at the beginning of treatment, median tumour length, esophageal tumour location, and tumour stage. Events and toxicity related to treatment were also included in the computer data base.

Tumour stage

The 1983 AJCC staging system was used in this study according to recently published recommendations[21]. Tumour evaluation was based on oesophagoscopy, barium oesophagography, chest and abdominal computed tomography (CT-scan), endoscopic bronchoscopy and esophageal ultrasonography when feasible.

Treatment schedule

CRT regimen was based on the 5 FU/CDDP CT combination associated with an external RT. The RT was delivered either by a dose of 50 Gy (50 Gy/25 fractions per 5 wk) with concomitant CT courses delivered on wk 1 and 5, or either a dose of 60 Gy (20 Gy/10 fractions × 3 courses separated by a 2-wk break) with concomitant CT courses delivered on wk 1, 5 and 9. The CT courses combined 5-FU (750 to 1000 mg/m^2 per day delivered by continuous infusion on 4 d) and CDDP (75 to 100 mg/m^2 delivered on 1 d). The target volume of RT was the macroscopic tumour and enlarged lymph nodes, if any, surrounded by 5 cm proximal and distal margins and a 2 cm radial margin. The target was extended to the inferior cervical area in cases of tumours located above the carina. The specified dose was delivered at the intersection of the central axis of the beams, according to international guidelines. The irradiation technique was applied in anterior and posterior opposed fields. At 40 Gy, the radiation portals were reduced to shield the spinal cord and encompass the primary tumour with a 2-3 cm craniocaudal margin.

Evaluation of clinical response and toxicity to CRT

Patients were considered to have a clinical complete response (CCR) to CRT when no residual tumour was identified on endoscopy and when no metastatic disease occurrence was observed on CT-scan. This evaluation was performed 2 mo after CRT completion.

Toxicity related to the treatment was evaluated using the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0). Toxicity was assessed in each patient at d 1 of each chemotherapy course. At each course, patients received the treatment when they exhibited a WHO performance status of 2 or less; satisfactory haematologic function (leucocytes count $\geqslant$ 3000 mm^{-3}, platelet count $\geqslant$ 100 000 mm^{-3}) and good renal function (creatine serum level $\leqslant$ 100 micromole/L). Patients with major complication i.e. heart disease, pulmonary fibrosis, or active carcinoma at the other site were not eligible for treatment.

Follow-up

The follow-up was performed on clinical basis, endoscopy and CT scan. Histopathological confirmation of the recurrence was not routinely required. Follow-up was performed either until death or for the purpose of this study until October 2005.

Statistical analysis

Analysis was performed in October 2005 and was considered the cut-off date. Survival curves according to the putative prognostic factors were established using the Kaplan-Meier method and were compared with a log-rank test. The effects of clinical characteristics at baseline related to prognosis using univariate analysis were further evaluated in multivariate analysis using Cox regression model. A two-side *P*-value equal or less than 0.05 was considered to indicate statistical significance. Data from patients who had been lost to follow-up were censored at the time of last obtained information. The date of CRT initiation was the starting point for the analysis of overall survival. The date of CRT response evaluation was the starting point for the analysis of the disease free survival.

RESULTS

Patients characteristics

Between the first of January 1994 and the 31st December 2000, one hundred and sixteen consecutive patients were treated with a CRT based on the 5FU/CDDP CT combination. The majority of patients had a good performance status and the dysphagia score prior to CRT reflected their ability to eat a normal or semisolids diet for approximately 90% of these patients (Table 1). Among patients who were estimated with T1-T2 tumour on CT-scan, 14 were estimated to present with a T1-T2 N0 tumour. These latter patients were treated with a definitive CRT as regards age and/or comorbidities.

Safety and toxicity per patient

Significant toxicities per patient are shown in Table 2.

Table 1 Patient characteristics

	n = 116	%
Mean age (yr)	61.3 (40-90)	
Male	101	87.1
Female	15	12.9
WHO performance status (OMS)		
0	32	27.6
1	70	60.3
2	14	12.1
Dysphagia (Atkinson score)		
0	2	1.7
1	21	18.1
2	58	50
3	26	22.4
4	9	7.8
Weight loss ⩾ 10% at CRT		
Initiation	30	25.9
TNM		
T 1-2	27	23.3
3-4	89	76.7
N 0	50	43.1
1	54	46.5
x	12	10.4
M 0	116	100
1	-	-
Esophageal location		
Upper one-third	35	30.2
Middle one-third	53	45.7
Lower one third	28	24.1
Mean tumour length (cm)	4.9 (0-15)	
Histopathology		
Squamous cell carcinoma	116	

Table 2 Significant treatment toxicities per patient (%)

	Grade 3 (%)	Grade 4 (%)
Haematological		
Neutropenia	9	3
Anemia	11	-
Thrombopenia	1	1
Mucositis		
Oral	4	-
Esophageal	16	-
Gastrointestinal		
Nausea	12	-
Diarrhoea	4	-
Neuropathy	1	-
Alopecia	3	-

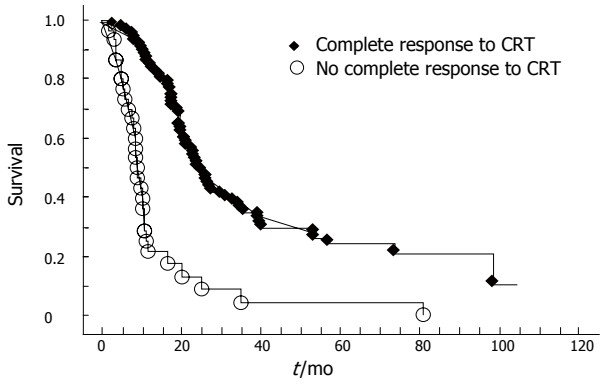

Figure 1 Survival according to response to CRT. The median overall survival of patients who had a complete clinical response (CCR) to the chemoradiotherapy (CRT) was 25 mo as compared to 9 mo in non-responder patients ($P < 0.001$).

There was no death related to CRT. Moreover, 75 patients (64.6%) experienced grade 3-4 toxicities and 112 (96.5%) patients achieved the planned concomitant CRT regimen. Dose modification to the planned CT regimen were required in 55 patients (47.4%) and 18 patients (15.5%) received at least one of their CT courses with a delay of more than 1 wk. The mean delivered radiation dose was 53.2 Gy.

During the CRT treatment, 18 patients (15.5%) required nutritional enteral feeding. In contrast, palliation of the dysphagia by endoscopic stenosis dilation was performed in 25 patients (21.6%). A self expandable metallic stent was inserted in 6 patients (5.1%) during CRT treatment.

Clinical complete response (CCR) to CRT

A total of 86/116 patients (74.1%) achieved a CCR to CRT. In the remaining 30 non-responder patients, a self expanding metallic stent was inserted in 12 for dysphagia palliation after completion of CRT, a CT treatment was initiated in 1 patient and salvage surgery was performed in 2 patients.

Patient outcome

In October 2005, 7/116 patients (6%) were still alive. The median follow-up of these surviving patients was 79 mo (range 56-104) and the median follow-up of the 11 patients who were lost to follow-up during the study was 45.1 mo (range 9-68).

The median overall survival was 20 mo (range 2-114) and the 2-years and 5-years survival rates were 39.6% and 9.4%, respectively. Moreover, the median overall survival of the 86 patients who had CCR to CRT was 25 mo (range 3-114) as compared to 9 mo (range 2-81) in non-responder patients ($P < 0.001$) (Figure 1). The median disease free survival of responder patients to CRT was 17 mo.

During the follow-up, 34 of responder patients (39.5%) experienced a local disease recurrence, 37 patients (43%) experienced metastatic disease and 19 of them experienced both of these recurrences.

Prognostic factors of survival

As regards univariate analysis (Table 3), survival was correlated to CCR to CRT ($P < 0.001$), WHO performance status < 2 ($P = 0.01$) and tumour length < 6 cm ($P = 0.045$). In contrast, weight loss > 10% at the start of CRT was in limit of statistical significance and was included in multivariate analysis ($P = 0.053$). In a Cox regression model (Table 3), the independent covariates significantly associated with survival were the CCR to CRT ($P < 0.0001$; Odds Ratio (OR): 0.121; IC95 = 0.06-0.24), the weight loss < 10% ($P = 0.034$; OR: 0.53; IC95 = 0.29-0.95) and a WHO performance status < 2 ($P = 0.046$; OR: 0.495; IC95 = 0.24-0.99).

DISCUSSION

To date, definitive CRT based on the 5FU/CDDP combination is considered as standard treatment in non operable patients with locally advanced esophageal carcinoma whatever the histological tumour phenotype[3-5]. Some authors recently suggested that histological types of oesophagus tumour could be considered separately regarding their significant different treatment response and long term prognosis[9-11]. Therefore, we performed a retrospective analysis of the long term outcome and predictive factors of survival in 116 patients with LASCOC treated with a definitive CRT using the 5FU/CDDP CT combination.

In our study, the 5-year survival was 9.4% and the median overall survival was 20 mo. We also found that responder patients to CRT had a significantly increased median survival as compared to non-responders patients (24 mo *vs* 9 mo; $P < 0.001$). This result was supported by the multivariate analysis which identified the CCR as an independent prognostic factor of survival. In definitive CRT series using the 5FU/CDDP combination, a survey of literature showed that median overall survival ranged from 17 to 26 mo and the 5-year survival rate from 20% to 30%[12-20]. The 5-year survival rate in our study was slightly lower as compared to those reported in these series. This result could be explained by the patient selection bias in these prospective trials, whereas our retrospective study possibly reflected the outcome of non-selected patients with LASCOC treated with definitive RT.

The CCR to CRT was obtained in 75.9% of patients in our series. Moreover, a CCR was identified as an independent prognostic factor of long-term survival in our multivariate analysis. Although the prognostic significance of pathological complete response after preoperative CRT was well documented[22-24], to our knowledge, there are no previous studies that have reported similar result in patients with LASCOC treated with definitive CRT using the 5FU/CDDP combination. In fact, the significant impact of CCR to CRT in long-term survival in patients treated with the same definitive CRT regimen was reported in series which included patients with mixed histological tumour types[12,25,26]. Moreover, in the reported Ohtsu *et al* study focusing exclusively on patients with LASCOC, the CCR to CRT was identified as a predictive factor of the progression free survival but not for overall survival[18]. In our study, 39.5% of responder patients to CRT had a local disease recurrence. In previous studies, local recurrences were reported to be as high as 38% to 48% after definitive CRT[12,18]. Furthermore, a distant metastasis occurred in 43% of responder patients to CRT in our series. This result compared less favourably to other series including patients with squamous cell carcinoma treated with the same CT combination, where less than 30% of responder patients to CRT experienced a distant metastasis[12,18]. The frequent use of additional CT in responder patients to CRT in these latter series could probably explain the difference in metastasis frequency. Indeed, only 44% of patients received additional CT after the CRT completion in our study.

Thus, our results suggest that further optimisations of the definitive CRT regimen are required for both local and systemic disease control improvement. To date, the 5FU/CDDP combination used in our study is still considered the standard for the CRT regimen. Evaluation of novel chemotherapy regimens which include new drugs such as irinotecan and new cancer therapies encompassing those directed against vascular growth factor and epidermal growth factor pathways may be usefully associated with RT to provide improved sustained CCR and therefore optimal long-term survival[27-30]. Furthermore, CRT regimen optimisation should determine the optimal radiotherapy dose in order to achieve a sustained local disease control. In our study, patients received a mean dose of 52.1 Gy of external RT in the tumour bed, which was a similar dose as that used in the standard regimen described by Herskovic *et al*[3]. Recently, Zhang *et al* reported, in a retrospective study, that patient who received a dose of RT more than 51 Gy had a statistically better local disease-free survival and overall survival as compared to patients treated with a dose of RT less than 51 Gy[31]. Minsky *et al* specifically investigated dose escalation in RT. In this prospective study, patients were randomised in a CRT regimen using either 50.4 Gy of RT or 64.8 Gy of RT[32]. However, the unexplained excess of death frequency (9%) which occurred prior to the dose escalation in patients treated in the 64.8 Gy arm did not permit a valid conclusion as regards the optimal dose of RT. In our study, no death due to CRT was observed. However, we found that 64.6% of patient experienced grade 3-4 toxicities, which was a similar result to that usually reported[3,4]. As regards the new RT techniques including three dimensional CT planning with conformal beam, dose escalation in the definitive CRT regimen could be reconsidered. Further studies including these new RT techniques may be helpful to evaluate the optimal and safety dose of RT in patients with LASCOC.

Multivariate analysis identified the WHO performance status less than 2 as the second independent predictive factor of long-term survival in patients treated with definitive CRT for a LASCOC. The WHO performance status has been previously identified as prognostic factor in patients with esophageal cancer treated by radiotherapy alone or in patients with metastatic oesophago-gastric cancer in previous studies[21,33]. Moreover, Polee *et al* also identified this variable as a prognostic factor of survival in

Table 3 Predictive factors of survival, univariate and multivariate analysis

	Univariate	Multivariate		
	P	*P*	OR	IC95
Sex	0.507	-		
Age < 70	0.745	-		
WHO performance status < 2	0.01	0.046	0.52	0.28-0.99
Weight loss < 10%	0.053	0.034	0.53	0.29-0.95
Dysphagia	0.074	-		
T	0.273	-		
N	0.499	-		
Tumour location	0.501	-		
Tumour length < 6 cm	0.045	0.534	0.86	0.53-1.38
Complete response to CRT	< 0.001	< 0.000	0.21	0.13-0.36

a meta-analysis performed in six prospective trials which included several CRT regimens and mixed histological type of esophageal tumour[34]. However, to our knowledge, this result had never been previously reported in patients with LASCOC treated in curative intent with definitive CRT using the 5FU/CDDP combination. The WHO performance status evaluation provides useful information on the patient's general well-being indirectly reflecting the impact of the malignancy on the physiological individual condition. Although the evaluation of the WHO performance status seems to be subjective, our results showed that this variable was significantly correlated with survival. Moreover, weight loss before treatment starting was also identified as prognostic factor in our work. This variable was recently to be correlated with prognosis in a meta-analysis by Thomas *et al* in patient treated by definitive CRT for esophageal cancer[30].

Interestingly, tumour characteristics were not identified as prognostic factors in our study. Indeed, the tumour diameter and the tumour length were only significant in univariate analysis. In surgical series, the extent of the tumour infiltration in the esophageal wall and the lymph node involvement were frequently closely correlated with survival[23,24,35]. Although an underpowered significance could not be excluded in the analysis, our results could also reflect the limited accuracy of the usual staging evaluation including oesophagography, oesophagoscopy and thoraco-abdominal computed tomography used during the period of the study. However, these imaging modalities appear to be more accurate for the CRT response assessment as regards the significant link that was observed between the CCR and survival. The high rate of early disease recurrence in our study could reflect an overestimation of the CCR rate by modalities used in our study. Thus, the further use of endoscopic ultrasound and PET-FDG, may be helpful to provide better correlative data for initial tumour staging and for tumour response assessment[36-38].

In conclusion, based on a large series of patients with LASCOC, our results suggest that survival of these patients treated with definitive CRT using the 5FU/ performance status. These prognostic factors could be considered for the management of individual patients as well as a stratification variable for the design and interpretation of further randomised trials. However, as regards the retrospective design of our study, further prospective studies are necessary to investigate the impact of these prognostic factors.

ACKNOWLEDGMENTS

The authors thank Richard Medeiros, Rouen University Hospital medical Editor, for his valuable advice in editing the manuscript.

REFERENCES

1 **Keighley MR**. Gastrointestinal cancers in Europe. *Aliment Pharmacol Ther* 2003; **18** Suppl 3: 7-30
2 **Ménégoz F**, Black RJ, Arveux P, Magne V, Ferlay J, Buémi A, Carli PM, Chapelain G, Faivre J, Gignoux M, Grosclaude P, Mace-Lesec'h J, Raverdy N, Schaffer P. Cancer incidence and mortality in France in 1975-95. *Eur J Cancer Prev* 1997; **6**: 442-466
3 **Herskovic A**, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, Cooper J, Byhardt R, Davis L, Emami B. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992; **326**: 1593-1598
4 **Cooper JS,** Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, Byhardt R, Russell AH, Beitler JJ, Spencer S, Asbell SO, Graham MV, Leichman LL. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999; **281**: 1623-1627
5 **Bedenne L,** Michel P, Bouche O, Triboulet JP, Conroy T, Pezet D, Roullet B, Seitz JF, Lacourt J, Milan C. Randomized phase III trial in locally advanced esophageal cancer: radiochemotherapy followed by surgery versus radiochemotherapy alone (FFCD 9102). *Proc Am Soc Clin Oncol* 2002: 519a
6 **Stahl M,** Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005; **23**: 2310-2317
7 **Burmeister BH,** Denham JW, O'Brien M, Jamieson GG, Gill PG, Devitt P, Yeoh E, Hamilton CS, Ackland SP, Lamb DS. Combined modality therapy for esophageal carcinoma: preliminary results from a large Australasian multicenter study. *Int J Radiat Oncol Biol Phys 1995*; **32**: 997-1006
8 **Chan A**, Wong A. Is combined chemotherapy and radiation therapy equally effective as surgical resection in localized esophageal carcinoma? *Int J Radiat Oncol Biol Phys* 1999; **45**: 265-270
9 **Terry P,** Lagergren J, Ye W, Nyrén O, Wolk A. Antioxidants and cancers of the esophagus and gastric cardia. *Int J Cancer* 2000; **87**: 750-754
10 **Enzinger PC,** Mayer RJ. Esophageal cancer. *N Engl J Med* 2003; **349**: 2241-2252
11 **Rizk NP,** Bains MS, Ilson DH, Minsky B, Rush VW. The AJCC Staging System Does Not Predict Survival in Patients Receiving Multimodality Therapy for Esophageal Cancer. *Proc Am Soc Clin Oncol* 2005: 4005a
12 **Seitz JF**, Milan C, Giovannini M, Dumas F, Cauvin JM, Conroy T, François E, Renard P, Votte-Lambert A, Paillot B, Bedenne L. [Concurrent concentrated radio-chemotherapy of epidermoid cancer of the esophagus. Long-term results of a phase II national multicenter trial in 122 non-operable patients (FFCD 8803)]. *Gastroenterol Clin Biol* 2000; **24**: 201-210
13 **Leichman L,** Herskovic A, Leichman CG, Lattin PB, Steiger Z, Tapazoglou E, Rosenberg JC, Arbulu A, Asfaw I, Kinzie J. Nonoperative therapy for squamous-cell cancer of the esophagus. *J Clin Oncol* 1987; **5**: 365-370
14 **Seitz JF,** Giovannini M, Padaut-Cesana J, Fuentes P, Giudicelli R, Gauthier AP, Carcassonne Y. Inoperable nonmetastatic squamous cell carcinoma of the esophagus managed by concomitant chemotherapy (5-fluorouracil and cisplatin) and radiation therapy. *Cancer* 1990**; 66**: 214-219
15 **Reddy SP,** Lad T, Mullane M, Rosen F, Carroll R, Marks JE. Radiotherapy alone compared with radiotherapy and chemotherapy in patients with squamous cell carcinoma of the esophagus. *Am J Clin Oncol* 1995; **18**: 376-381
16 **Murakami M,** Kuroda Y, Okamoto Y, Kono K, Yoden E, Kusumi F, Hajiro K, Matsusue S, Takeda H. Neoadjuvant concurrent chemoradiotherapy followed by definitive high-dose radiotherapy or surgery for operable thoracic esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 1998; **40**: 1049-1059
17 **Minsky BD,** Neuberg D, Kelsen DP, Pisansky TM, Ginsberg RJ, Pajak T, Salter M, Benson AB 3rd. Final report of Intergroup Trial 0122 (ECOG PE-289, RTOG 90-12): Phase II trial of neoadjuvant chemotherapy plus concurrent chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 1999; **43**: 517-523
18 **Ohtsu A,** Boku N, Muro K, Chin K, Muto M, Yoshida S, Satake M, Ishikura S, Ogino T, Miyata Y, Seki S, Kaneko K,

Nakamura A. Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J Clin Oncol* 1999; **17**: 2915-2921

19 **Hironaka S**, Ohtsu A, Boku N, Muto M, Nagashima F, Saito H, Yoshida S, Nishimura M, Haruno M, Ishikura S, Ogino T, Yamamoto S, Ochiai A. Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T(2-3)N(any) M(0) squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 2003; **57**: 425-433

20 **Kaneko K,** Ito H, Konishi K, Kurahashi T, Ito T, Katagiri A, Yamamoto T, Kitahara T, Mizutani Y, Ohtsu A, Mitamura K. Definitive chemoradiotherapy for patients with malignant stricture due to T3 or T4 squamous cell carcinoma of the oesophagus. *Br J Cancer* 2003; **88**: 18-24

21 **Coia LR**, Minsky BD, Berkey BA, John MJ, Haller D, Landry J, Pisansky TM, Willett CG, Hoffman JP, Owen JB, Hanks GE. Outcome of patients receiving radiation for cancer of the esophagus: results of the 1992-1994 Patterns of Care Study. *J Clin Oncol* 2000; **18**: 455-462

22 **Forastiere AA,** Orringer MB, Perez-Tamayo C, Urba SG, Zahurak M. Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. *J Clin Oncol* 1993; **11**: 1118-1123

23 **Fujita H,** Sueyoshi S, Tanaka T, Tanaka Y, Sasahara H, Shirouzu K, Suzuki G, Hayabuchi N, Inutsuka H. Prospective non-randomized trial comparing esophagectomy-followed-by-chemoradiotherapy versus chemoradiotherapy-followed-by-esophagectomy for T4 esophageal cancers. *J Surg Oncol* 2005; **90**: 209-219

24 **Berger AC,** Farma J, Scott WJ, Freedman G, Weiner L, Cheng JD, Wang H, Goldberg M. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *J Clin Oncol 2005*; **23**: 4330-4337

25 **Lim JT,** Truong PT, Berthelet E, Pai H, Joe H, Wai E, Larsson S, Kader HA, Weinerman B, Wilson K, Olivotto IA. Endoscopic response predicts for survival and organ preservation after primary chemoradiotherapy for esophageal cancer. *Int J Radiat Oncol Biol Phys* 2003; **57**: 1328-1335

26 **Tahara M,** Ohtsu A, Hironaka S, Boku N, Ishikura S, Miyata Y, Ogino T, Yoshida S. Clinical impact of criteria for complete response (CR) of primary site to treatment of esophageal cancer. *Jpn J Clin Oncol* 2005; **35**: 316-323

27 **Ilson DH**, Forastiere A, Arquette M, Costa F, Heelan R, Huang Y, Kelsen DP. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. *Cancer J* 2000; **6**: 316-323

28 **Ajani JA**, Walsh G, Komaki R, Morris J, Swisher SG, Putnam JB Jr, Lynch PM, Wu TT, Smythe R, Vaporciyan A, Faust J, Cohen DS, Nivers R, Roth JA. Preoperative induction of CPT-11 and cisplatin chemotherapy followed by chemoradiotherapy in patients with locoregional carcinoma of the esophagus or gastroesophageal junction. *Cancer* 2004; **100**: 2347-2354

29 **Michel P,** Mirabel X, Galais M, Dahan L, Conroy T, Boucher E, Oprea C, Paillot B. Weekly cisplatin/irinotecan and radiotherapy (RT) in patients with locally advanced esophageal cancer : multicenter FFCD phase II trial. *Proc Am Soc Clin Oncol* 2005: 4060a

30 **Thomas CR Jr,** Berkey BA, Minsky BD, Gaspar LE, Herskovic A, Rich TA, Gunderson LL. Recursive partitioning analysis of pretreatment variables of 416 patients with locoregional esophageal cancer treated with definitive concomitant chemoradiotherapy on Intergroup and Radiation Therapy Oncology Group trials. *Int J Radiat Oncol Biol Phys* 2004; **58**: 1405-1410

31 **Zhang Z,** Liao Z, Jin J, Ajani J, Chang JY, Jeter M, Guerrero T, Stevens CW, Swisher S, Ho L, Yao J, Allen P, Cox JD, Komaki R. Dose-response relationship in locoregional control for patients with stage II-III esophageal cancer treated with concurrent chemotherapy and radiotherapy. *Int J Radiat Oncol Biol Phys* 2005; **61**: 656-664

32 **Minsky BD,** Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA, Kelsen DP. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; **20**: 1167-1174

33 **Chau I,** Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. *J Clin Oncol* 2004; **22**: 2395-2403

34 **Polee MB**, Hop WC, Kok TC, Eskens FA, van der Burg ME, Splinter TA, Siersema PD, Tilanus HW, Stoter G, van der Gaast A. Prognostic factors for survival in patients with advanced oesophageal cancer treated with cisplatin-based combination chemotherapy. *Br J Cancer* 2003; **89**: 2045-2050

35 **Kato H**, Miyazaki T, Nakajima M, Takita J, Kimura H, Faried A, Sohda M, Fukai Y, Masuda N, Fukuchi M, Manda R, Ojima H, Tsukada K, Kuwano H, Oriuchi N, Endo K. The incremental effect of positron emission tomography on diagnostic accuracy in the initial staging of esophageal carcinoma. *Cancer* 2005; **103**: 148-156

36 **Flamen P,** Van Cutsem E, Lerut A, Cambier JP, Haustermans K, Bormans G, De Leyn P, Van Raemdonck D, De Wever W, Ectors N, Maes A, Mortelmans L. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. *Ann Oncol* 2002; **13**: 361-368

37 **Wu LF,** Wang BZ, Feng JL, Cheng WR, Liu GR, Xu XH, Zheng ZC. Preoperative TN staging of esophageal cancer: comparison of miniprobe ultrasonography, spiral CT and MRI. *World J Gastroenterol* 2003; **9**: 219-224

38 **Rice TW.** Clinical staging of esophageal carcinoma. CT, EUS, and PET. *Chest Surg Clin N Am* 2000; **10**: 471-485

S- Editor Wang J **E- Editor** Liu Y