World Journal of Surgery

Published Online: 19 January 2006

World J Surg (2006) 30: 183–190
DOI: 10.1007/s00268-005-7861-6

Incurable Esophageal Cancer: Patterns of Tumor Spread and Therapeutic Consequences

Ines Gockel, MD, Werner Kneist, MD, Theodor Junginger, MD

Department of General and Abdominal Surgery, Johannes Gutenberg University of Mainz, Langenbeckstr. 1, D-55101 Mainz, Germany

Abstract

Background: The aim of the study was to determine if the two histologic tumor types in esophageal cancer exhibit different behavior at advanced tumour stages and require a differentiated therapy.

Patients and Methods: From November 1997 to December 2003, 268 patients presented with esophageal carcinoma. Esophagectomy was contraindicated in 88 (32.8%) patients (75 men, 13 women) with a median age of 64.7 (42–83) years. Fifty-six (63.6%) had squamous cell carcinoma; adenocarcinoma was identified in 31 (35.2%).

Results: The causes of incurable disease were non-resectable distant metastases in 32 (36.4%) patients, local tumor spread in 25 (28.4%), and general operative risk in 19 (21.5%). Surgical intervention was contraindicated in 7 patients because of a combination of general inoperability and local tumor spread, or the presence of distant metastases at the time of diagnosis (4 patients declined to undergo surgery and in one patient esophageal resection and reconstruction was technically not possible). The incurability rate for squamous cell carcinoma was 44.6% because of the presence of local tumor spread, compared to a rate of 12.4% for adenocarcinoma. Adenocarcinomas with proven hematogenic metastases were characterized by a higher incurability rate (64.5% vs. 21.4%) ($P = 0.0014$). The prevalence of technical causes of inoperability or of poor general condition was similar in both patient groups ($P > 0.05$). The median 1-year survival rates estimated (Kaplan-Meier) were 36.5% for patients with squamous cell carcinoma and 23.7% for patients with adenocarcinoma ($P = 0.051$). Therapeutic measures had a significant influence on the prognosis: patients without tumor-specific therapy survived 3.4 (0–24) months; those with radiochemotherapy 10.6 (0–25) months; those with radiotherapy 11.0 (0–65) months; and those with chemotherapy 16.5 [0–16.5] months (log-rank test: $P = 0.0229$). In the multivariate analysis, the therapeutic measures ($P = 0.0126$) and tumor localization ($P = 0.0474$) proved significant for prognosis, but were not the cause of incurability ($P = 0.0948$).

Conclusions: The histologic tumor type does not represent an independent prognostic factor in patients with incurable disease. Rather, the prognosis is dependent on the suitability of the induction of tumor-specific therapeutic measures. These are also recommended in patients with incurable disease after consideration of the extent of tumor spread, provided the performance of the selected measures is justified by the general condition of the patient and the expected prognosis.

Adenocarcinomas and squamous cell carcinomas are characterized by differences in biological behavior, pathogenesis, and location, three factors that establish the two tumor types as separate entities.[1,2] Although various investigations have demonstrated histologic differentiation as an independent prognostic factor after surgical therapy, results reported by other studies do not support this finding.[3–7] The purpose of the present

Correspondence to: Ines Gockel, MD, Department of General and Abdominal Surgery, Johannes Gutenberg University of Mainz, Langenbeckstr. 1, D-55101 Mainz, Germany, e-mail: gockel@ach.klinik.uni-mainz.de

retrospective investigation was to determine if the two histologic tumor types also exhibit different behavior at incurable tumor stages and require a differentiated therapy.

PATIENTS AND METHODS

Patients

From November 1997 to January 1, 2004, a total of 268 patients presented at our institution with esophageal carcinoma. Esophagectomy was contraindicated in 88 (32.8%) patients (75 men, 13 women) with a median age of 64.7 (42–83) years.

Over the same period of time, 180 patients with esophageal carcinoma (145 men, 35 women) underwent surgical therapy. Potentially curable esophageal cancer was defined by an R0 resection, which was assured by tumor-free resection margins, as assessed by pathological examination and by intraoperative findings described by the surgeon to rule out an R2-situation with macroscopic visible residual tumor.

An R0-resection was accomplished in 165 (91.7%) of these 180 patients. The median age of R0-resected patients with squamous cell carcinoma was 59 years (Range: 34–77 years); of those with adenocarcinoma, 63 years (range: 35–78 years).

The course of the disease was known in 85 of 88 (96.6%) incurable patients on 1 January 2004; no data documenting the course were available in 3 patients at that time. Seventy-one (81.6%) of the patients with squamous cell carcinoma and adenocarcinoma ($n = 87$; one patient with undifferentiated carcinoma not considered for further evaluation) had died from the tumor; of the remaining 16 patients, 13 were alive and 3 were lost of follow-up with no information on survival.

Methods

In patients with histologically proven esophageal carcinoma, the following prognostic variables were recorded: American Society of Anesthesiologists (ASA) classification (I–IV) according to the preoperative anesthesiology evaluation, the body mass index (BMI) based on body weight and height in kg/m^2, and the nutritional status including tobacco and/or alcohol abuse. Tobacco abuse was defined by the consumption of at least 5 cigarettes a day over a period of >1 year, whereas alcohol abuse was defined by the regular intake of beer, wine or hard drinks, at least every second day. Among the preoperative diseases, cardiovascular risk factors were defined as a history of coronary heart disease, or myocardial infarction, arterial hypertension, valvular disease (>II°), arrhythmia requiring therapy (>III° according to the Lown classification), heart failure NYHA (New York Heart Association) > grade II, and peripheral occlusive arterial disease (>IIb according to Fontaine). A history of chronic obstructive pulmonary disease (COPD), regular tobacco consumption, and/or the use of bronchospasmolytics were subsumed under pulmonary diseases. The preoperative assessment of the vital capacity (VC) and forced exspiratory volume in 1 second (FEV_1 = Tiffeneau test) served to ensure a more accurate assessment. Preexisting cirrhosis of the liver (≥CHILD-Pugh A) was defined as hepatic disease, and determined on the basis of the assessment of serum albumin (g/dl), serum bilirubin (mg/dl), Quick value (%), and the presence of ascites or encephalopathy. The evaluation of additional risk factors included the prevalence of diabetes mellitus (insulin-dependent or requiring drug therapy), and the history of a secondary carcinoma.

In all patients, preoperative diagnostic measures after endoscopic-bioptic confirmation included, in addition to computed tomography of the neck, thorax, and abdomen, endosonography of the esophagus, barium swallow, percutaneous sonography of the abdomen, as well as positron emission tomography (PET), as previously described.[8] A conventional x-ray examination of the thorax and laboratory tests with tumor markers carcinoembryonic antigen (CEA), Ca 19-9, Ca 72-4, and alpha-fetoprotein (AFP) were routinely performed.

For a better comparison of staging procedures, the esophagus was considered in thirds, according to the endoscopic location of the tumor: upper third: dental front to 20 cm; middle third: 20–30 cm; lower third: 30 cm to the Z-line.

Hematogenic and lymphogenic metastases were proven by computed tomography (CT) examination (PET scan and endosonographic ultrasound). Lymph nodes larger than 0.8 cm on CT examination were suspicious for metastasis, abdominal, thoracic, or cervical. Local tumor spread was defined as wall-exceeding tumor extent to adjacent organs/structures (e.g., the main stem bronchi, the aortic wall. etc.); in summary a CT diagnosis of T4-tumor stage made an R0 resection impossible.

Patients with squamous cell carcinoma were treated by radiochemotherapy or radiation therapy alone, whereas patients with advanced adenocarcinoma were treated by chemotherapy with palliative intent. Palliative radiochemotherapy was carried out according to the *Herskovic* protocol (four courses of combined fluorouracil and cis-

platin plus 5000 cGy of radiation therapy).[9] Patients receiving chemotherapy alone were given a combination of fluorouracil and cisplatin. Patient groups were not randomized.

Statistical Analysis

The SSPS 10.0 software package was used for statistical data analysis (SSPS, Chicago, IL, USA, 1999). Data were prospectively collected in a database established for internal quality control and analyzed retrospectively. The presented data are expressed as median values with ranges (minimum–maximum). In the comparative analysis of the different parameters between the two patient groups, the χ^2 test with Pearson's correction with cross-table calculations, or the Fisher's exact test was used for categorical parameters. The Mann-Whitney U-test served as the non-parametric method for quantitative variables. Survival probabilities were estimated with the method of Kaplan and Meier, and a log-rank analysis was carried out to determine significant differences between the patient groups. The Cox univariate regression model was used to analyze separately the influence of each prognostic factor on survival. Multivariate analysis of these factors was performed using Cox's proportional hazards model. A P value < 0.05 was considered statistically significant for all procedures.

RESULTS

Of the 268 patients who presented with esophageal cancer at our clinic between November 1997 and January 1, 2004, 88 (32.8%) did not receive surgical therapy. Of these 88 patients, 56 (63.6%) had squamous cell carcinoma; adenocarcinoma was identified in 31 (35.2%); and undifferentiated carcinoma was noted in 1 patient. In the curable group, squamous cell carcinoma was identified in 81 patients (49.4%), and adenocarcinoma was diagnosed in 75 patients (45.7%) after R0 resection (4.8% had undifferentiated carcinoma or other tumor types). In the curable group, 29 of 75 (38.7%) adenocarcinomas derived from Barrett's esophagus, and in the incurable group 7 of 31 cases (22.6%) were Barrett's.

Overall, patients with squamous cell carcinomas were more frequently found to have incurable disease (38.9%; n = 56) than patients with adenocarcinoma (27.4%; n = 31). Twenty-eight (31.8%) of the incurable carcinomas were located in the upper third of the esophagus, 19 (21.6%) in the middle third, and 41 (46.6%) in the lower third. An exploratory procedure (exploratory laparotomy, exploratory thoracotomy, or exploratory exposure) was carried out in 13 (14.8%) patients. Placement of a stent was required in 24 (27.3%) patients with tumor-related stenosis, and a tracheotomy was needed in one patient. Nine patients (10.2%) received chemotherapy, and another nine underwent irradiation therapy; 24 (27.3%) patients had combined radiochemotherapy, which was applied under neoadjuvant conditions in 5 of these patients. Patients undergoing surgery after receiving neoadjuvant treatment were excluded from the present study.

The causes of incurable disease were non-resectable distant metastases in 32 (36.4%) patients, local tumor spread in 25 (28.4%), and general operative risk in 19 (21.5%) patients. Surgical intervention was contraindicated in 7 patients because of a combination of general inoperability and local tumor spread, or the presence of distant metastasis at the time of diagnosis. Four patients declined operation. Reconstruction of the esophagus (gastric tube according to Billroth II resection, and colon interposition after sigmoidectomy due to the lack of a suitable colon segment demonstrated by angiography findings) was not possible in one patient.

Differences between Patients with Incurable Squamous Cell Carcinoma and Adenocarcinoma

At a median age of 61 (42–83.5) years, patients with incurable squamous cell carcinoma were significantly younger than patients with adenocarcinoma, whose median age was 69.9 (44.1–78.7) years (P = 0.0004). There were no significant differences with regard to sex distribution, BMI, and ASA classification. The evaluation of the patient's history showed a higher incidence of tobacco (61.9%) and alcohol abuse (71.4%) in the group with squamous cell carcinoma than in patients with adenocarcinoma (40.9% and 45.5%, respectively). Similarly, there was a higher incidence of pulmonary, cardiac, and hepatic risk factors in patients with squamous cell carcinoma. The majority of squamous cell carcinomas (48.2%) were located in the upper third of the esophagus, whereas adenocarcinomas were located primarily in the lower third (90.3%) (P = 0.0001). The incidence of distant metastases was significantly higher in patients with adenocarcinoma (58.1%) than in patients with squamous cell carcinoma (17.9%) (P = 0.0002). Metastases were significantly more often of the hematogenic type only in adenocarcinoma (58.1%), as compared to 17.9% in squamous cell carcinoma (P = 0.0373).

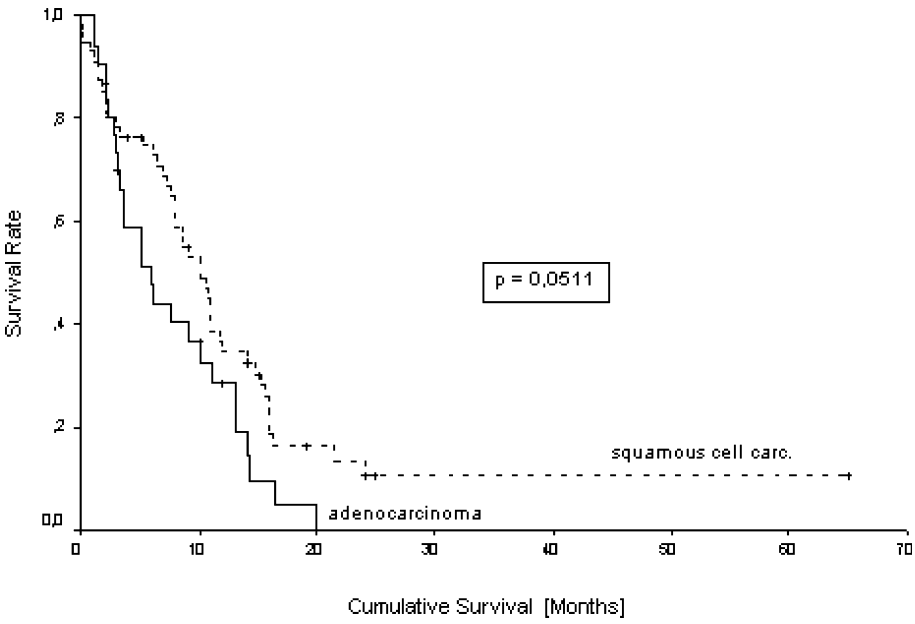

Figure 1. Kaplan-Meier survival curves in patients with incurable esophageal cancer, subdivided by histologic tumor type.

Likewise, the causes of incurability were different for the two types of tumors: The incurability rate for squamous cell carcinoma was 44.6%, due to the presence of local tumor spread, compared to a rate of 12.4% for adenocarcinoma. Adenocarcinomas with proven hematogenic metastasis were characterized by a higher incurability rate (64.5% vs. 21.4%) ($P = 0.0014$). The prevalence of general operative causes of inoperability as, for example, cardiopulmonary risk factors, or a poor general condition was similar in both patient groups (25.0% in sqamous cell carcinoma and 22.6% in adenocarcinoma) ($P > 0.05$). A combined poor general condition, local tumor spread and distant metastases as a contraindication for surgery was seen in 5.4% of patients with squamous cell carcinoma compared to 12.9% in adenocarcinoma.

Exploration laparotomy or thoracotomy was performed more often in the treatment of adenocarcinoma (19.4%) than in squamous cell carcinoma (10.7%) ($P = 0.0523$). With respect to therapeutic measures, radiotherapy and radiochemotherapy were applied more frequently in patients with squamous cell carcinoma than in those with adenocarcinoma (12.5% vs. 6.7% and 37.5% vs. 10.0%, respectively), whereas palliative chemotherapy was administered primarily in patients with adenocarcinoma (20% vs. 5.4%). Because their general condition was poor, 44.6% of patients with squamous cell carcinoma and 63.3% of those with adenocarcinoma did not undergo a tumor-specific therapy (e.g. esophageal stent only) ($P = 0.0405$).

Prognosis in Patients with Incurable Squamous Cell Carcinoma and Adenocarcinoma

The median survival time was 10 (0–65) months in patients with squamous cell carcinoma, and 6 (1–20) months in patients with adenocarcinoma. The 1-year survival rates estimated (Kaplan-Meier) for patients with squamous cell carcinoma and patients with adenocarcinoma were 36.5%, and 23.7%, respectively ($P = 0.051$) (Fig. 1).

The cause of incurability was also important for the prognosis: Patients with proven distant metastases had the worst prognosis with a median survival of 5.9 months (range: 0–16.5 months) as compared to patients with general (9.8 [0–24] months) and local incurability (11.0 [0–65] months) (log-rank test: $P = 0.0517$) (the 7 patients with a combined local and general incurability are not considered). Median survival was significantly worse in patients with hematogenic metastases (5.0 [0–16.5] months) than in those with lymphatic metastases (11.9 [0–24] months) (log-rank test: $P = 0.0284$) (considered are only patients with either hematogenic, lymphogenic, or no metastases).

The therapeutic measures were of influence on the prognosis. Patients without tumor-specific therapy survived 3.4 (0–24) months compared to patients with radiochemotherapy (10.6 [0–25] months), radiotherapy (11.0 (0–65) months) and chemotherapy (16.5 [0–16.5] months) (log-rank test: $P = 0.0229$).

Tumor localization (upper > middle > lower third of the esophagus) ($P = 0.0015$), therapeutic measures

Table 1.
Univariate analysis of potential prognostic factors of survival in patients with incurable esophageal cancer

Prognostic factor	Test	*P* Value
Tumor location	Cox	0.0015*
Therapy	LR	0.0229*
Type of metastasis	LR	0.0284*
Histologic tumor type	LR	0.0511
Cause of incurability	LR	0.0517
Gender	LR	0.1035
Age	Cox	0.3590

*Statistically significant.
LR: log-rank test; Cox: Cox regression.

($P = 0.0229$), and the type of metastasis (lymphogenic > hematogenic) ($P = 0.0284$) had a significant influence on survival in the univariate analysis. The histologic tumor type ($P = 0.0511$), the cause of incurability ($P = 0.0517$), the patient's gender ($P = 0.1035$), and the patient's age ($P = 0.3590$) were without significance (Table 1). In the multivariate analysis, the therapeutic measures (chemotherapy > radiotherapy > radiochemotherapy > no tumor-specific therapy) ($P = 0.0126$), and the tumor localization ($P = 0.0474$) proved to be significant for prognosis, but not the cause of incurability ($P = 0.0948$).

DISCUSSION

Squamous cell carcinoma and adenocarcinoma of the esophagus are separate tumor entities with regard to epidemiology, pathogenesis, location, and metastatic spread.[1,3,5,10–15] Although various studies[3,4] have described histologic differentiation as an independent prognostic factor after R0 resection, there is no conclusive evidence of the significance of this factor in incurable esophageal cancer. We therefore attempted to determine whether the two main tumor entities are, under conditions of incurable disease with different tumor spread and risk profiles, associated with a different prognosis and thus require a differentiated therapeutic approach.

Of the 268 patients diagnosed with esophageal carcinoma at our clinic from November 1997 to January 1 2004, 88 had incurable disease. There was a higher incidence (38.9%) of incurable disease in patients with squamous cell carcinoma than in those with adenocarcinoma (27.4%).

Interpreting the results, a major drawback of this study is the fact, that T-, N- and M-categories in incurable disease were proven by CT, endosonographic ultrasound, and PET scan only, with limited sensitivity and specifity.[8]

The documented differences in risk factors between squamous cell carcinoma and adenocarcinoma were confirmed in our patient population for both curable and incurable esophageal carcinomas. The incidence of pulmonary, cardiac, and hepatic risk factors in patients with esophageal carcinoma as a result of tobacco and alcohol abuse was higher in patients with inoperable disease than in those with operable disease. The higher BMI found in patients with operable adenocarcinoma was not demonstrated in the group with inoperable adenocarcinoma, a finding that may be attributable to the advanced tumor stage in the latter group (Table 2).

Patients with operable and inoperable squamous cell carcinoma were younger than patients with adenocarcinoma. The age difference was, however, larger in patients with incurable disease. Whereas the difference in median age was 4 years (59 years of age for patients with squamous cell carcinoma vs. 63 years for those with adenocarcinoma) in patients with curable disease, in those with incurable disease, it was 8 years (61.0 years squamous cell carcinoma vs. 69.0 years adenocarcinoma). The older age seen in adenocarcinoma is contrasted to other reported series and might be due to selection bias of the chosen study period. There were, however, significant differences in the causes of inoperability. Although a correlation was observed between local tumor spread and incurability in a plurality of patients with squamous cell carcinoma, distant metastasis accounted for incurable disease in the majority of patients with adenocarcinoma. This finding indicates the presence of a different tumor spread pattern for the two tumor entities: squamous cell carcinomas are characterized by a preference for regional tumor spread; furthermore, as a result of the local tumor extension, they are incurable after only a relatively short period of time. Gastroesophageal reflux disease is a frequently observed preneoplastic condition in adenocarcinoma and was seen in 85% of our patients.[5,10–12] Although the process of tumor formation and local tumor growth may be slower in these patients, the incidence of distant metastasis is comparatively higher, which makes the presence of distant metastasis an obstacle to surgical therapy in patients with incurable disease.

The different pattern of tumor spread presumably exerts an influence on the prognosis. In the present study, patients undergoing R0 resection for adenocarcinoma were found to have a more favorable long-term prognosis (median survival 39.9 [0–67.5] months) than those with squamous cell carcinoma (10.1 [0–64.7] months). However, in the patients with incurable disease a comparatively longer survival time was observed for the group with

Table 2.
Differences between incurable und curable (R0-resection) squamous cell- and adenocarcinoma of the esophagus (patient population between 11/1997 and 1/2004)

	Squamous cell carcinoma		Adenocarcinoma	
	Curable (n = 81)	Incurable (n = 56)	Curable (n = 75)	Incurable (n = 31)
Age (years)	59 (34–77)	61 (42–83.5)	63 (35–78)	69.9 (44.1–78.7)
Gender (% males)	63	89.3	82.7	77.4
BMI (kg/m^2)	24.0 (14.2–33.8)	24.3 (14.2–63.8)	26.1 (17.2–39.3)	24.9 (19.4–32.9)
ASA (%)				
II	38.5	40	51.4	20
III	57.7	50	48.6	65
IV	3.8	10	—	15
Nutritive factors (%)				
Tobacco abuse	63.2	61.9	35.2	40.9
Alcohol abuse	67.1	71.4	39.4	45.5
Risk factors (%)				
Pulmonary	18.8	53.3	12.0	21.7
Cardial	38.8	72.1	28.0	66.7
Hepatopathy	10.0	33.3	1.3	18.2
Diabetes mellitus	6.3	19.0	9.3	25.0
Secondary carcinoma	15.0	18.4	4.0	13.8
Tumor location (%)				
Upper third	9.9	48.2	—	3.2
Middle third	56.8	30.4	2.7	6.5
Lower third	33.3	21.4	97.3	90.3
Survival (months)	10.1 (0–64.7)	10.0 (0–65.0)	39.9 (0–67.5)	6.0 (1–20.0)

BMI: body mass index; ASA: American Society of Anesthesiologists classification.

squamous cell carcinoma (10 [0–65] months) than for the population with adenocarcinoma (6 [1–20] months). The reason for this is not yet fully understood.

The somewhat more favorable prognosis for incurable squamous cell carcinoma may be due to the administration of irradiation treatment or radiochemotherapy. The use of radiochemotherapy (5-FU and/or cisplatin) has resulted in response rates of 25%–97% in the primary tumor, and in median survival rates from 6 to 20 months.[16] While a more favorable effect of primary simultaneous or sequential radiochemotherapy compared to irradiation alone has been reported by a number of prospective studies (Table 3), [17–21] as well as by a meta-analysis of randomized trials,[22] only a small number of these trials differentiate between squamous cell carcinoma and adenocarcinoma. Although the cited prognostic advantage was not supported by the findings in our patient population, consideration needs to be given to the fact that the described therapeutic measures were carried out in a non-randomized study and data have to be regarded critically.

Palliative chemotherapy was the most frequently used therapeutic measure in patients with incurable adenocarcinoma and proven distant metastasis. The survival rates calculated by our study are in accordance with those reported in the literature (6–9 months).[23–26] The most unfavorable prognosis after symptomatic therapeutic measures was 3.4 months, which is also comparable to results obtained by other trials (68–309 days).[27–30]

In summary, the findings of this study hint at a difference in the tumor-biologic behavior of squamous cell carcinoma and adenocarcinoma of the esophagus at an incurable stage of disease, whether because of tumor extent or the patients' general condition. There seems to be a high incidence of locoregional spread in squamous cell carcinoma, which, because of the local conditions, is often incurable after only a short period of disease progression. In contrast, the incurability rate observed for adenocarcinoma might be accounted for by the development of distant metastasis, which, however, occurs only after longer duration of disease. This may explain the more favorable long-term survival after R0 resection for adenocarcinoma.

The histologic tumor type does not represent an independent prognostic factor for patients with incurable disease. The prognosis is probably dependent on the suitability of the induction of tumor-specific therapeutic measures, though this is not proven by randomized data in our patient population. Such therapeutic measures are

Table 3.
Randomized trials of simultaneous* and sequential† radiochemotherapy versus radiotherapy in patients with incurable esophageal cancer

Author (year)	Radiochemo–therapy (n)	Radiotherapy (n)	Histology (% SCC)	Median survival (months)
Roussel *et al.*† (1994)[17]	1 × CDDP;20 + 20 Gy (FD 4 Gy) (14-day interval) (n = 110)	20 + 20 Gy (n = 111)	100% vs. 100%	10.5 vs. 7.8
Lu *et al.*† (1995)[18]	2 × ADM, 5-FU, CDDP; 50 Gy (n = 30)	60–70 Gy (n = 30)	80% vs. 86%	n.m. 1-year survival:63% vs. 37%
Kaneta *et al.**(1997)[19]	CDDP (30 days);60 Gy(n = 12)	60 Gy (n = 12)	n.m.	7 vs. 9
Slabber *et al.** (1998)[20]	2 × 5-FU, CDDP; 40 Gy (n = 34)	40 Gy (n = 36)	100% vs. 100%	5.7 vs. 4.8
Cooper *et al.** (1999)[21]	2 × 5-FU, CDDP;50 Gy; 2 × 5-FU, CDDP (n = 61)	64 Gy (n = 82)	84% vs. 92%	14.1 vs. 9.3

CDDP: cisplatin; ADM: Adriamycin; 5-FU: 5-fluorouracil; SCC: squamous cell carcinoma ;FD: first dosage, n.m.: not mentioned.

also recommended in patients with incurable disease after consideration of the extent of tumor spread, provided the performance of the selected measures is justified by the general condition of the patient and the expected outcome.

REFERENCES

1. Bollschweiler E, Schroder W, Holscher AH, *et al.* Preoperative risk analysis in patients with adenocarcinoma or squamous cell carcinoma of the esophagus. Br J Surg 2000;87:1106–1110.
2. Siewert JR, Stein HJ, Sendler A. Esophageal cancer: clinical management. In Kelsen DA, ed., Principles and Practice of Gastrointestinal Oncology, Philadelphia, Lippincott Williams & Wilkins, 2001.
3. Siewert JR, Stein HJ, Feith M, *et al.* Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1000 consecutive resections at a single center in the Western world. Ann Surg 2001;234:360–369.
4. Holscher AH, Bollschweiler E, Schneider PM, *et al.* Prognosis of early esophageal cancer. Comparison between adeno- and squamous cell carcinoma. Cancer 1995;76:178–186.
5. Blot WJ, Devesa SS, Kneller RW, *et al.* Rising incidence of adenocarcinoma of the esophagus and gastric junction. JAMA 1991;265:1287–1289.
6. Fu JH, Rong TH, Li XD, *et al.* Cox regression analysis of the prognostic factors of unresectable esophageal carcinoma after stenting. Ai Zheng 2003;22:91–94.
7. Hagen JA, Peters JH, DeMeester TR. Superiority of extended en bloc esophagogastrectomy for carcinoma of the lower esophagus and cardia. J Thorac Cardiovasc Surg 1993;106:850–858.
8. Kneist W, Schreckenberger M, Bartenstein P, *et al.* Prospective evaluation of positron emission tomography in the preoperative staging of esophageal carcinoma. Arch Surg 2004;139:1043–1049.
9. Herskovic A, Martz K, al-Sarraf M, *et al.* Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;11:326:1593–1598.
10. Pera M, Cameron AJ, Trastek VF, *et al.* Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. Gastroenterology 1993;104:510–513.
11. Wang HH, Antonioli DA, Goldman H. Comparative features of esophageal and gastric adenocarcinomas: recent changes in type and frequency. Hum Pathol 1986;17:482–487.
12. Yang PC, Davis S. Incidence of cancer of the esophagus in the US by histologic type. Cancer 1988;61:612–617.
13. DeMeester SR, DeMeester TR. Columnar mucosa and intestinal metaplasia of the esophagus: fifty years of controversy. Ann Surg 2000;231:303–321.

14. Tachimori Y, Kato H, Watanabe H, *et al.* Difference between carcinoma of the lower esophagus and the cardia. World J Surg 1996;20:507–511.
15. Nigro JJ, Hagen JA, DeMeester TR, *et al.* Prevalence and location of nodal metastases in distal esophageal adenocarcinoma confined to the wall: implications for therapy. J Thorac Cardiovasc Surg 1999;117:16–23.
16. Fritz P, Stoll P, Wannenmacher M, *et al.* Primäre Radiochemotherapie inoperabler fortgeschrittener Ösophaguskarzinome. Strahlenther Onkol 2003;179:328–336.
17. Roussel A, Haegele P, Paillot B, *et al.* Results of the EORTC-GTCCG Phase III trial of irradiation versus irradiation and CDDP in inoperable esophageal cancer. For the Gastrointestinal Tract Cancer Cooperative Group. Proc Am Soc Clin Oncol 1994;13:583.
18. Lu XJ, Miao RH, Li XQ. Combination of selective arterial infusion chemotherapy with radiotherapy in the treatment of advanced esophageal carcinoma. Chin J Clin Oncol 1995;22:262–265.
19. Kaneta R, Takai Y, Nomoto K, *et al.* Effect of combination chemotherapy with daily low-dose CDDP for esophageal cancer: results of a randomized trial. Jpn J Cancer Chemother 1997;24:2099–2104.
20. Slabber CR, Nel JS, Schoeman L, *et al.* A randomized study of radiotherapy alone versus radiotherapy plus 5-fluorouracil and platinum in patients with inoperable, locally advanced squamous cancer of the esophagus. Am J Clin Oncol 1998;21:462–465.
21. Cooper JS, Guo MD, Herskovic A, *et al.* Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG 85–01). JAMA 1999;281:1623–1627.
22. Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus (Cochrane Review). Oxford: The Cochrane Library, Issue 4 (actualized software).
23. Urba SG, Chansky K, van Veldhuizen PJ, *et al.* Gemcitabine and cisplatin for patients with metastatic or recurrent esophageal carcinoma: a Southwest Oncology Group study. Investigational New Drugs 2004;22:91–97.
24. Bleiberg H, Conroy T, Paillot B, *et al.* Randomized phase II study of cisplatin and 5-fluorouracil versus cisplatin alone in advanced squamous cell carcinoma. Eur J Cancer 1997;33:1216–1220.
25. Conroy T, Etienne PL, Adenis A, *et al.* European Organisation for Research and Treatment of Cancer. Gastrointestinal Tract Cancer Cooperative Group. Ann Oncol 2002;13:721–729.
26. Webb A, Cunningham D, Scarffe JH. Randomized trial comparing epirubicin, cisplatin and fluorouracil versus fluorouracil, doxorubicin and methotrexate in advanced esophagogastric cancer. Br J Cancer 1996;73:1260–1264.
27. Szentpali K, Palotas A, Lazar G, *et al.* Endoscopic intubation with conventional plastic stents: a safe and cost-effective palliation for inoperable esophageal cancer. Dysphagia 2004;19:22–27.
28. May A, Selmaier M, Hochberger J, *et al.* Memory metal stents for palliation of malignant obstruction of the esophagus and cardia. Gut 1995;37:309–313.
29. Dormann AJ, Eisendrath P, Wigginghaus B, *et al.* Palliation of esophageal carcinoma with a new self–expanding plastic stent. Endoscopy 2003;35:207–211.
30. Dallal HJ, Smith GD, Grieve DC, *et al.* A randomized trial of thermal ablative therapy versus expandable metal stents in the palliative treatment of patients with esophageal carcinoma. Gastrointest Endsoc 2001;54:549–557.