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Original article

Squamous cell carcinoma and adenocarcinoma of the lower third of the esophagus and gastric cardia: similarities and differences

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SUMMARY. **Squamous cell carcinoma (SCC) and adenocarcinoma (ADC) of the lower esophagus and gastric cardia were compared in their clinical features and long-term prognosis. Two hundred and ninety-five patients with SCC and 263 with ADC were reviewed. Resectability rates for SCC and ADC were 74.2% and 73.2% respectively ($P = 0.8$). Among those who underwent resection, ADC was more advanced, with 22.3% at stage IV compared with 7.4% for SCC ($P = 0.001$). Postoperative cardiac events occurred in 24.2% of SCC patients and 14.7% of ADC patients ($P = 0.015$), and major respiratory complications in 20.1% and 8.6% respectively ($P = 0.001$). Thirty-day mortality rates were 2.7% and 4% ($P = 0.46$), and hospital mortality rates were 11.4% and 7.6% ($P = 0.19$). Median survival rates were 12.5 months for SCC and 11.6 months for ADC ($P = 0.99$) and 5-year survival rates were 19.9% and 17.6% ($P = 0.55$) respectively. Squamous cell carcinoma of the lower esophagus and ADC of the cardia differed in patient demographics and clinical features but long-term prognoses were similar.**

INTRODUCTION

Squamous cell carcinoma (SCC) and adenocarcinoma (ADC) of the esophagus and cardia are two distinct histological entities. Whether the two types of cancers differ in their natural history and treatment outcome remains controversial.

There has been a dramatic rise in the incidence of ADC in Western populations in the past decades, presumably secondary to gastroesophageal reflux and Barrett's esophagus.[1,2] In Eastern populations, SCC is still the predominant type, with no epidemiologic data to suggest an increase in ADC. Reports have shown better long-term survival with SCC[3] or similar[4] or inferior[5,6] survival when compared with ADC.

We have reported previously that the outcomes of treatment for SCC and ADC of the thoracic esophagus and cardia differed in postoperative morbidity but not in long-term prognosis.[7] It was emphasized that SCC was mostly situated in the middle third of esophagus, whereas ADC was almost exclusively located at the gastric cardia. The purpose of this study was to identify the similarities and differences between SCC and ADC of the lower esophagus and gastric cardia in terms of patients' demographics, treatment strategies, perioperative morbidity and mortality, and long-term prognosis.

MATERIALS AND METHODS

Patients with cancer of the thoracic esophagus and gastric cardia treated at the Department of Surgery, University of Hong Kong Medical Center, Queen Mary Hospital, were entered prospectively in a database. Patients with a diagnosis of cancer of the lower esophagus and cardia were identified and the clinical and pathological data of these patients examined and compared.

The lower esophagus was defined as the distal half of the esophagus between the tracheal bifurcation and the gastroesophageal junction.[8] For a tumor that straddled the gastroesophageal junction, if the main bulk was situated above the junction it was classified as lower third tumor; if below, it was called cardia cancer. Tumors at the gastric cardia were defined as those within 5 cm of the anatomical gastroesophageal junction.[9]

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Preoperative tumor staging and assessment of resectability were performed with clinical examination, chest radiography, barium contrast study, flexible endoscopy, and bronchoscopy. Computed tomographic (CT) scans and endoscopic ultrasonography have only been available in recent years and were not routinely performed in the earlier part of the study period.

The choice of surgical approach depended on the location and extent of the tumor and the cardiorespiratory assessment of the patient. The techniques of resection and anastomosis have been described previously.[10] In brief, most SCCs of the intrathoracic esophagus were resected via an abdomen and right thoracotomy approach, with intrathoracic esophagogastrostomy performed (Lewis–Tanner operation). For patients who had suboptimal cardiorespiratory reserve and whose tumors could be resected without a thoracotomy, transhiatal resection was carried out. For tumors of the cardia, the majority of patients underwent an esophagogastrectomy through a combined abdominal and right thoracic approach. A thoracotomy was avoided and the esophageal anastomosis carried out in the abdomen when an adequate length of proximal margin could be obtained, when advanced disease was encountered and the surgery was deemed palliative, or in patients in whom the risk of undergoing a thoracotomy was prohibitive.

Cardiovascular complications included any arrhythmia, heart failure, myocardial infarction, and pulmonary embolus. Major pulmonary complications were defined as the development of aspiration pneumonia, bronchopneumonia, shock lung, and respiratory failure. Minor pulmonary complications included the occurrence of bronchospasm, atelectasis, pleural effusion, pneumothorax, or sputum retention.

Deaths within 30 days after surgery and hospital mortality within the same hospital admission were reported. Patients were followed up monthly for the first year and every 3 months afterwards. Statistical differences between groups were determined by the Student's *t*-test, the chi-square test, or Fisher's exact test where appropriate. Survival was calculated with the Kaplan–Meier method and difference compared by the log-rank test. Statistical significance was taken at $P < 0.05$. All calculations were performed with the program Statistical Package for the Social Sciences (SPSS version 9.0, Chicago, IL, USA).

RESULTS

Between July 1982 and March 1999, 1534 patients with cancer of the esophaghus and cardia were treated in the Department of Surgery, University of Hong Kong Medical Center at Queen Mary Hospital, and, of these patients, 1094 had SCC and 269 had ADC. There were 295 patients with SCC of the lower third of the esophagus and 263 patients with ADC of the gastric cardia, in addition to six patients with ADC of the lower esophagus. Of the patients with ADC of the lower esophagus, Barrett's esophagus was confirmed in only one Chinese and one Caucasian patient. The other four patients had no evidence of Barrett's mucosa either macroscopically or microscopically.

The mean age for all patients with SCC was 63.2 years (SEM = 0.57), and for those with ADC was 66.2 years (SEM 0.68) ($P = 0.001$). There were 263 men and 32 women in the SCC group (ratio 8:1) and 218 men and 51 women for the ADC group (ratio 4:1) ($P = 0.007$). Of the patients with SCC, a greater proportion were smokers [181 patients (83%) vs. 121 patients (61%), $P < 0.05$] or consumed either large or moderate amounts of alcohol [167 patients (76%) vs. 71 (36%), $P < 0.05$] compared with those with ADC.

Primary treatments given to patients in the two groups are listed in Table 1. The resectability rates for SCC and ADC were 74.2% and 73.2% respectively ($P = 0.8$). Significantly fewer patients with SCC (0.6%) had surgical exploration without resection compared with those with ADC (6.7%) ($P = 0.001$). The types of surgical resection are listed in Table 2. More patients with SCC underwent a transthoracic resection compared with those with ADC – 72.5% vs. 41% ($P = 0.001$). Overall, 47% of patients with SCC underwent curative resections compared with 38% of ADC patients ($P = 0.08$). Among patients who underwent transthoracic resection, similar proportions of patients with SCC and ADC had curative resections, 48% vs. 50% ($P = 0.2$).

Disease stage distribution and differentiation data are shown in Table 3. Most patients had stage III or IV disease but ADCs were more advanced.

Postoperative complications are listed in Tables 4 and 5. Cardiovascular and respiratory complications occurred more frequently with SCC than with ADC. This was true even when only transthoracic resections

Table 1. Summary of main treatments given to 295 patients with SCC and 269 patients with ADC of the esophagus and gastric cardia

Treatment	SCC	ADC
No intervention	27 (9%)	29 (11.3%)
Resection	219 (74.2%)	197 (73.2%)
Exploration only	2 (0.6%)	18 (6.7%)
Bypass	16 (5.5%)	6 (2.3%)
Radiotherapy	18 (6.3%)	1 (0.4%)
Chemotherapy	1 (0.3%)	9 (3.3%)
Intubation	10 (3%)	8 (2.9%)
Laser ablation	2 (0.6%)	1 (0.4%)
Total	295 (100%)	269 (100%)

Figures represent number of patients.

Table 2. Types of resections according to histology

	SCC	ADC	*P*-value
Thoracotomy	159 (72.5%)	82 (41%)	0.001
Three-phase esophagectomy	5 (2.3%)	0 (0%)	
Lewis–Tanner esophagectomy	109 (49.8%)	1 (0.5%)	
Esophagogastrectomy	45 (20.4%)	81 (40.5%)	
Non-thoracotomy	60 (27.5%)	115 (59%)	0.001
Total gastrectomy	0 (0%)	26 (13.4%)	
Proximal gastrectomy	0 (0%)	66 (33.9%)	
Abdominal esophagogastrectomy	6 (3%)	14 (7.1%)	
Transhiatal esophagectomy	49 (22.3%)	6 (3%)	
Thoracoscopic esophagectomy	5 (2.3%)	0 (0%)	
Other *	0 (0%)	3 (1.5%)	
Total	219 (100%)	197 (100%)	

* Staged operation (2), total esophagogastrectomy (1).
Figures represent number of patients.

Table 3. Stage distribution and differentiation according histology

	SCC	ADC	*P*-value
Stage distribution			0.001
Stage 0*	2 (0.9%)	0 (0%)	
Stage I	11 (5.1%)	4 (2%)	
Stage IIa	34 (15.6%)	19 (9.6%)	
Stage IIb	12 (5.4%)	11 (5.6%)	
Stage III	144 (66.5%)	119 (60.4%)	
Stage IV	16 (7.4%)	44 (22.3%)	
Differentiation†			0.001
Good	57 (29.7%)	22 (12.5%)	
Moderate	89 (46.4%)	76 (43.2%	
Poor	46 (24%)	78 (44.3%)	

*Preoperative chemoradiation was given with pathologic complete response.
†Only including patients with data available.
Figures represent number of patients.

Table 4. Postoperative complications according to histology

Complication	SCC	ADC	*P*-value
Medical			
Cardiovascular	53 (24.2%)	29 (14.7%)	0.015
Pulmonary			
Major	44 (20.1%)	17 (8.6%)	0.001
Minor	137 (62.6%)	80 (40.6%)	0.001
Renal failure	4 (1.8%)	4 (2%)	0.88
Hepatic failure	2 (0.9%)	1 (0.5%)	0.625
Surgical			
Wound complication	21 (9.6%)	12 (6.1%)	0.187
Anastomotic leakage	11 (5%)	9 (4.6%)	0.829
Empyema thoracis	4 (1.8%)	6 (3%)	0.418
Hoarseness	6 (2.7%)	2 (1%)	0.201
Chylothorax	1 (0.5%)	1 (0.5%)	0.94
Loop gangrene	1 (0.5%)	0 (0%)	0.342

Figures represent number of patients.

were selected. Surgical complications were all relatively infrequent and were similar in the two groups. Anastomotic leakage occurred in 11 patients with SCC (5%) and in nine patients with ADC (4.6%) ($P = 0.83$).

Anastomotic recurrence was uncommon for both groups, occurring in only two patients (0.9%) in the SCC group and 11 patients (5.6%) in the ADC group ($P = 0.006$). The mean proximal resection margin was 6.1 cm (SEM = 0.2) for SCC and 3.5 cm (SEM = 0.23) for ADC ($P = 0.001$). Anastomotic recurrence rates stratified for the length of proximal resection margin are shown in Table 6. In 10 of the 11 patients with ADC and anastomotic recurrence, the resection was considered palliative, with the majority resected only through the abdomen.

Thirty-day and hospital mortality rates are shown in Table 7. Hospital mortality was higher, though not significantly so, among patients with SCC compared with those with ADC, at 11.4% and 7.6%, respectively ($P = 0.19$). When only patients who underwent thoracotomy were analyzed, the hospital mortality was 11.3% for SCC and 6.1% for ADC ($P = 0.15$).

Survival figures are summarized in Table 8 and Figs 1 and 2. No significant differences were found when SCC and ADC groups were compared. The most important determinants of survival were the stage of disease and the intent of the surgical resection, whether it was curative or palliative.

DISCUSSION

Squamous cell carcinoma and ADC are often reported together in the literature, presumably because surgical strategies in their treatment are similar and because tumors that traverse the gastroesophageal junction are often classified as primarily esophageal and not gastric in origin. It is not clear whether the two cell types differ only in location or also in their biological behavior. Our previous report has shown that the cardiopulmonary morbidity rates after resection were significantly higher for SCC, with no difference in long-term prognosis.[7] However, tumors of the upper and middle thirds of the esophagus accounted for 62% of the SCCs reported in that study. In the present study, only SCC of the lower third esophagus is included; thus, a better comparison of the two types of tumors can be made.

Table 5. Cardiopulmonary complications for patients who underwent transthoracic resection only according to histology

	SCC	ADC	Total	*P*-value
Cardiovascular	45/159 (28.3%)	10/82 (12.2%)	55/241 (22.8%)	0.005
Pulmonary				
Major	31/159 (19.5%)	6/82 (7.3%)	37/241 (15.4%)	0.013
Minor	95/159 (59.7%)	35/82 (42.7%)	130/241 (53.91%)	0.012

Table 6. Anastomotic recurrence rate stratified for length of proximal resection margin in SCC and ADC patients

Proximal resection margin (cm)*	SCC	ADC
0–2	1/7 (14.3%)	8/59 (13.5%)
2–4	1/37 (2.8%)	1/52 (1.9%)
4–6	0/62 (0%)	2/32 (6.25%)
6–8	0/49 (0%)	0/13 (0%)
8–10	0/31 (0%)	0/10 (0%)
< 10	0/22 (0%)	0/10 (0%)
Unknown	0/13 (0%)	0/21 (0%)
Total	2/219 (0.9%)	11/197 (5.6%)

*Measured in resected specimen before fixation.
Figures represent number of patients.

Table 7. Thirty-day mortality, mortality after 30 days, and hospital mortality for patients undergoing resection for carcinoma of the lower third of esophagus and cardia

	SCC	ADC	*P*-value
Thirty-day mortality	6 (2.7%)	8 (4%)	0.46
Mortality after 30 days	19 (8.6%)	7 (3.5%)	0.03
Hospital mortality	25 (11.4%)	15 (7.6%)	0.19

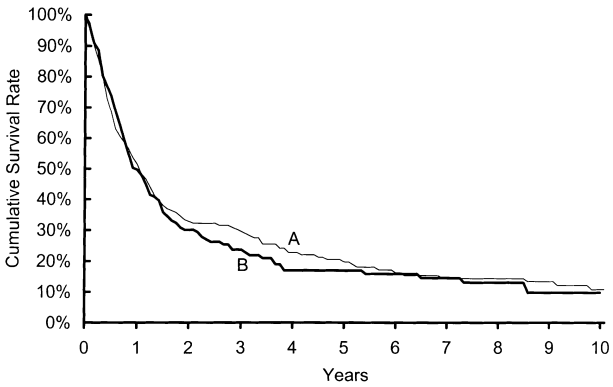

Fig. 1 Survival curves for patients with squamous cell or adenocarcinoma of the esophagus or cardia who underwent resection, according to histology. Median survival:A, SCC = 13.4 months; B, ADC = 13.5 months (P = 0.99).

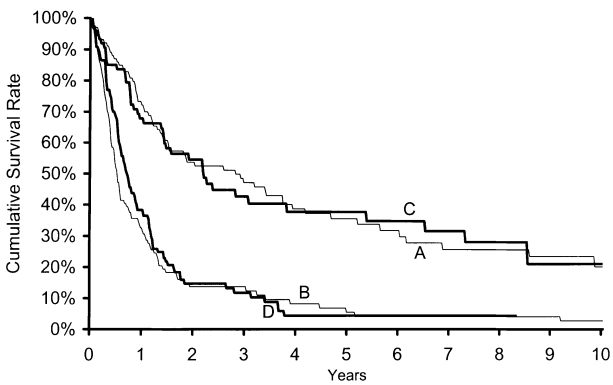

Fig. 2 Survival curves for patients with squamous cell or adenocarcinoma of the esophagus or cardia who underwent resection, stratified for histology and intent of resection. Median survival: A: SCC, curative = 34 months; B, SCC, palliative = 6.2 months; C, ADC, curative = 26.7 months; D, ADC, palliative = 8.5 months. A vs. B, P = 0.0001; C vs. D, P = 0.0001; A vs. C, P = 0.66; B vs. D, P = 0.1.

In the West there has been a dramatic increase in the incidence of ADC of the lower esophagus and gastric cardia, with gastroesophageal reflux disease, Barrett's esophagus, and subsequent progression to cancer being implicated.[1,11,12] A similar rise in incidence of ADC has not been seen in Eastern countries, and SCC of the middle third of the esophagus is still most prevalent. In terms of the classification of ADC of the gastroesophageal junction, in this population they are confined to types II and type III.[9] The rarity of Barrett's cancer is confirmed in the present series. Only six of the patients with ADC had lower third tumors, and true Barrett's cancer was confirmed in a single Chinese patient.

The gender distribution showed a male predominance for SCC, and the average age of patients with ADC was older. A greater proportion of the patients with SCC were smokers and consumed either moderate or large amounts of alcohol. Geographical variations have been similarly reported.[11,12]

Resectability rates were similar comparing the two groups, with about three-quarters of patients undergoing resection for each group. Over this series of patients, there have been evolving patterns of treatment, with greater selection of patients for curative surgery in parallel with the availability of effective and less invasive forms of palliation. The authors are of the opinion that, in some patients with advanced disease, surgical resection with low morbidity and mortality may be justifiable for good palliation. In the series, stage IV disease was found in 22% of patients with ADC who underwent resection. Among patients who in whom exploratory surgery revealed the tumor to be unresectable, those with SCC had a bypass procedure more frequently than those with ADC.

The anatomic location and the more advanced disease stage of ADC accounted for the difference in surgical approach. A similar proportion of patients

Table 8. Survival rates according to histology

	SCC		ADC		
	Curative $n = 102$	Palliative $n = 117$	Curative $n = 75$	Palliative $n = 122$	Overall $n = 416$
Median survival (months)	34	6.2	26.7	8.5	12.3
Five-year survival	35.8%	5.5%	37.8%	4.4%	18.6%
Overall median survival (months)	12.5		11.6		
Overall 5-year survival	19.9%		17%		

with ADC and SCC had a curative resection when a thoracotomy was performed. More transthoracic resections were performed for SCC, with those patients with suboptimal cardiorespiratory reserve usually undergoing transhiatal resection. For cancers of the gastric cardia, in the face of advanced disease, when feasible, palliative resections were sometimes attempted through the abdomen, with the aim of avoiding the morbidity associated with a thoracotomy. Significantly more patients with ADC than with SCC underwent palliative resection to avoid thoracotomy.

Cardiovascular and pulmonary complications were more frequent among patients with SCC than among patients with ADC. This was probably related to both the higher frequency of thoracotomy and the greater extent of thoracic mobilization and dissection in patients with SCC. Surgical complications, in particular anastomotic leakage, were infrequent and were similar in patients with the two cancer types.

Anastomotic recurrence negates one of the most important goals of treatment, which is the relief of dysphagia. In this study, the total anastomotic recurrence rate was significantly higher for the ADC group than for the SCC group (5.6% vs. 0.9%). The likelihood of anastomotic recurrence is related to the length of proximal margin attained at operation.[13] The average lengths of proximal resection margin between SCC and ADC differed significantly ($P = 0.001$). The proximal resection margin was more than 4 cm in 75% of patients with SCC but in only 45% of patients with ADC.

Some of these differences in surgical outcome stem from a difference in the surgical philosophy on management in terms of palliation. In some patients with advanced ADC of the lower esophagus and gastric cardia, resection was carried out as the best available palliative therapy at the time. In these patients, compromise over the extent of resection margin was made in order to avoid the morbidity and mortality associated with thoracotomy. This explains the differences in the two groups in terms of the number of patients with stage IV disease undergoing resection and the higher incidence of recurrence following resection in the patients with ADC. In this series, survival rates were similar in both groups of patients.

A Japanese report showed that, although there was no overall difference in survival between patients with SCC of the lower esophagus and those with ADC of the cardia, when mediastinal lymph nodes were involved, the prognosis was worse for patients with ADC.[11] In Western literature, prognostic differences have been variably reported. A study from Germany found that patients with early ADC of the esophagus fared much better than those with early SCC, and this was attributed to a higher recurrence rate and more frequent development of other primary tumors for SCC.[5] A multicenter retrospective analysis of 2400 patients reported a survival advantage with ADC compared with SCC, with 5-year survival rates of 27% and 16% respectively.[6] In a second German study, it was shown that, among patients resected with curative intent, those with ADC had a better long-term prognosis.[14] Other series report a better survival for patients with SCC[3,15,16] while some showed no difference in long-term prognosis.[4,17] Various multivariate analyses have not identified cell type to be an independent prognostic factor.[4,18,19] When only ADC was studied, most reports showed that patients with tumors of lower third and cardia were similar in demographics, clinical features, and prognosis, and were distinct from patients with subcardial gastric cancers.[20,21] Esophageal and cardia ADC may share the same etiology, i.e. Barrett's dysplasia; however, as has been confirmed in this study, Barrett's esophagus and esophageal ADC are very uncommon in the East. In the absence of a surveillance program in Eastern countries, both SCC and ADC are diagnosed only when patients are already symptomatic. The prognosis is equally poor.

We have shown in our population that SCC and ADC of the lower esophagus and cardia are different entities and should be reported separately. They differ in patient demographics and clinical features, with patients with ADC also presenting with more advanced disease. The anatomic location and the stage of disease often dictate different operative strategies and this may impact on surgical outcome. Their long-term prognoses, however, were similar and the stage of the disease is a much more important determinant of survival than is cell type.

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