

Survival After Esophageal Resection for Carcinoma: The Importance of the Histologic Cell Type

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Background. The significance of tumor cell type on survival after esophageal resection for carcinoma is uncertain. We reviewed our experience in order to compare the outcome in the two main histologic groups.

Methods. Between January 1987 and April 2000, 621 patients underwent esophagectomy with curative intention for squamous cell carcinoma or adenocarcinoma. The postoperative outcomes of patients with adenocarcinoma and squamous cell carcinoma were compared.

Results. Of the cohort, 424 patients had adenocarcinoma (group A) and 197 had squamous cell carcinoma (group B). The commonest approach in group A was a left thoracotomy (67%), while in group B, it was an Ivor Lewis resection (55%) ($p < 0.0001$). Operative mortality was 3.5% for group A and 8.1% for group B ($p = 0.03$). Cardiorespiratory complication rate was similar, but anastomotic leaks occurred more frequently in group B

(4.2% vs 8.6%, $p = 0.04$). Patients in group B tended to have earlier pathologic tumor, node, metastasis (pTNM) stage ($p = 0.06$). Overall, survival was significantly better for group B ($p = 0.003$). Group B had a significantly better survival than group A in lymph node (LN) negative status ($p = 0.01$), and a relatively improved survival in LN positive status ($p = 0.35$). On multivariate analysis, squamous cell subtype ($p = 0.034$), pTNM stage ($p = 0.005$), LN status ($p = 0.008$), and completeness of resection ($p = 0.028$) were significant predictors of survival.

Conclusions. After esophagectomy, patients with squamous cell carcinoma have a poorer perioperative outcome as compared with those with adenocarcinoma. However, in the longer term, squamous cell type appears to confer a significant survival advantage.

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Patients who undergo surgical resection for esophageal tumors have some of the poorest outcomes of all patients with gastrointestinal tumors [1]. The operations themselves are associated with considerable morbidity and mortality [2], and the long-term survival after resection remains suboptimal [3, 4].

Over the last decade there has been an epidemiologic change in the pattern of esophageal cancer in the Western world, with the incidence of adenocarcinoma now exceeding that of squamous cell carcinoma [5]. Despite the differing etiology and clinical characteristics of these two tumor types, there has been a tendency in most studies to regard patients who undergo resection for adenocarcinoma or squamous cell carcinoma as a homogenous group [5–8]. The purpose of our study was to analyze the impact of histologic cell type on the outcome after potentially curative resection for esophageal cancer.

Patients and Methods

This study was conducted under the supervision of the Thoracic Surgery Audit Office and fully meets the re-

quirements of the ethics committee at Nottingham City Hospital.

Between January 1987 and April 2000, a total of 642 patients underwent nonpalliative resectional surgery for carcinoma involving the esophagus or the esophagogastric junction in our unit. Of these 642 patients, 21 had a mixed histologic cell tumor or small cell cancer and were excluded from further analysis. The remaining 621 patients were divided in two groups according to the type of tumor cell type, namely 424 (68%) patients who had adenocarcinoma and 197 (32%) patients who had squamous cell carcinoma.

All operations were performed by a team of four thoracic surgeons who used similar surgical techniques and uniform preoperative and postoperative management. None of these patients underwent any preoperative or postoperative chemotherapy or radiotherapy. All patients who underwent transthoracic approach had an en bloc esophagectomy. This entailed local mediastinal dissection with mobilization of the intrathoracic portion of the esophagus using diathermy, followed by excision of all periesophageal tissue with the subcarinal and parahiatal lymph nodes; both parietal pleura overlying the esophagus and the aortic adventitia. Tumors at the level of the diaphragm were excised together with a cuff of diaphragm. In the abdomen, the lymph nodes from the left gastric artery pedicle were routinely excised and

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Table 1. Demographic and Clinical Features of the Two Groups

Parameter	AdenoCa	Squamous Cell Carcinoma	<i>p</i> Value
Age (years)	65.5 ± 10 (28-86)	64.3 ± 10 (37-85)	0.5
Male gender	336/424 (79.2%)	90/197 (45.6%)	< 0.0001
Tumor length	5.1 ± 2 (0.5-14)	4.9 ± 2 (1-11)	0.3
Site of tumor			
Tumor GOJ	166 (39.1%)	13 (6.6%)	< 0.0001
Tumor low 1/3	213 (50.2%)	87 (44.2%)	
Tumor mid 1/3	40 (9.4%)	84 (42.9%)	
Tumor upper 1/3	5 (1.18%)	13 (6.6%)	
Operative approach			
Left thoracotomy and phrenotomy	283 (66.7%)	59 (29.9%)	< 0.0001
Left thoracotomy and laparotomy	64 (15.1%)	19 (9.6%)	
Ivor Lewis	58 (13.7%)	108 (54.8%)	
Transhiatal	17 (4%)	11 (5.6%)	
McKeown	9 (0.5%)	0	
Pathological stage			
Stage I	25 (5.9%)	13 (6.6%)	0.059
Stage IIa	107 (25.2%)	67 (34%)	
Stage IIb	47 (11.1%)	16 (8.1%)	
Stage III	245 (57.8%)	101 (51.3%)	
Positive lymph nodes	275 (64.8%)	101 (55.3%)	0.028
Incomplete resection	52 (12.3%)	22 (11.2%)	0.79

AdenoCa = adenocarcinoma; GOJ = gastroesophageal junction.

flush ligation of the left gastric pedicle was achieved by application of a vascular stapler.

Immediately after their operation, patients were nursed in the intensive care unit, typically overnight, to allow elective removal of the endotracheal tube. The patients were then transferred to the ward. Postoperative analgesia consisted of a continuous epidural infusion of bupivacaine and fentanyl. Barium swallow was performed on the seventh day after the procedure to assess the integrity of the anastomosis prior to commencing oral feeding. Patients did not routinely receive any postoperative enteral or parenteral nutrition.

Pathological analysis of the surgical specimens was performed by the same team of four histopathologists. The specimens were examined and the histologic subtype, resection margin status, tumor (T)-stage, and node (N)-stage were all recorded using the International Union Against Cancer tumor, node, metastasis (TNM) classification [9]. The overall stages of tumors were also categorized according to the American Joint Committee on Cancer staging system [10]. Incomplete resection was defined as the presence of microscopic tumor at the proximal or distal margins.

Follow-Up and Statistical Analysis

Patients were followed up for life after their operation, with outpatient clinic review every three months for the first year; every six months for the next four years, and yearly thereafter.

The case notes of these patients were reviewed along with data collected from a prospectively collated data-

base and comparisons made of the preoperative, perioperative, and postoperative courses of the two groups.

Statistical analysis was performed using a commercially available software package (SPSS version 11; SPSS Inc, Chicago, IL). Means were compared with the *t* test and proportions with the χ^2 or the Fisher exact tests as appropriate. Survival was calculated with the Kaplan-Meier method and the resulting curves compared with the log-rank test. Cox proportional hazards regression models were used to identify predictors of survival between the following variables: age, gender, tumor length, tumor site, operative approach, pathological stage, lymph nodal status, and incomplete resection (R1, 2). A *p* value less than 0.05 was considered significant.

Results

Demographics and Clinical Features

The demographics and clinical and pathological features of the two groups are summarized in Table 1. As shown, patients with squamous cell carcinoma tended to present with higher esophageal tumors and were more likely to have early disease.

Operative Mortality and Morbidity

The operative mortality and morbidity for both groups is summarized in Table 2. As shown, patients with squamous cell carcinoma had a significantly higher operative mortality (*p* = 0.03), as well as an increased risk of anastomotic leak (*p* = 0.043). Causes of death in the

Table 2. Operative Mortality and Morbidity for the Two Groups

Variable	Adenocarcinoma	Squamous Cell Carcinoma	p Value
Operative mortality	15 (3.5%)	16 (8.1%)	0.03
Respiratory complications	74 (17.5%)	36 (18.3%)	0.89
Cardiovascular T complications	17 (4%)	12 (6.1%)	0.35
Supraventricular T tachycardias	65 (15.3%)	40 (30.3%)	0.15
Anastomotic leak	18 (4.2%)	17 (8.6%)	0.043
Chylothorax	14 (3.3%)	9 (4.6%)	0.58

squamous group (n = 16, 8.1%) were pneumonia (5), anastomotic leak (4), stroke (2), myocardial infarction (2), pulmonary embolism (1), aortic rupture (1), and central venous line induced septicemia (1). Causes of death among patients having adenocarcinoma (n = 15, 3.5%) were pneumonia (7), anastomotic leak (6), adult respiratory distress syndrome (1), and pulmonary embolism (1). Operative mortality in the entire group according to the type of procedure performed was as follows: left thoracotomy and phrenotomy 4.9% (17 of 342), left thoracotomy and laparotomy 2.4% (2 of 83), Ivor Lewis resection 4.8% (8 of 166), transhiatal resection 14% (4 of 28), and McKeown resection 0% (0 of 2).

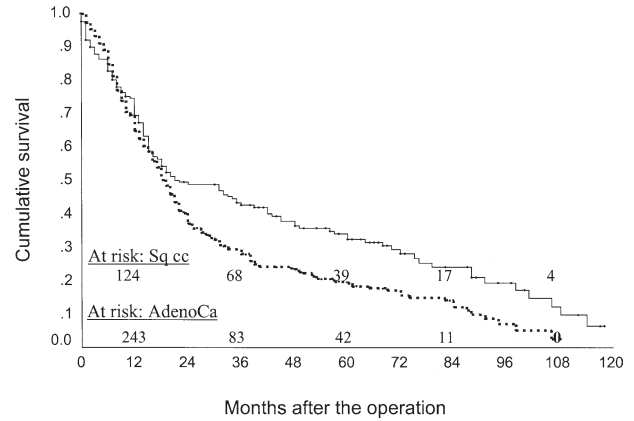


Fig 1. Kaplan Meier plot of overall survival according to cell type (continuous line = squamous cell carcinoma [Sq cc]; dotted line = adenocarcinoma [AdenoCa]).

Survival

The overall survival of the two groups and the survival according to pathological TNM stage and the lymph nodal status are summarized in Table 3. As shown in Figure 1, patients with squamous cell carcinoma had significantly improved survival as compared with those with adenocarcinoma. In addition, adenocarcinoma cell type was a significant independent predictor of adverse outcome on multivariate analysis as shown in Table 4. The type of operative procedure did not appear to influence long-term survival. In patients having adenocarcinoma, the Kaplan-Meier five years after a left thoracotomy with phrenotomy (or laparotomy) was 21 ± 2%,

Table 3. Kaplan-Meier 5-Year Survival and Median Survival Values for Squamous Cell and Adenocarcinoma Patients (Overall, According to TNM Stage and According to Lymph Nodal Status)

Histologic Group	5-Year Survival (%) ± SEM (Patients at Risk)	Median Survival Months (95% CI)	p Value
AdenoCa (overall survival)	19 ± 2 (42)	19 (17-21)	0.003
SCC (overall survival)	32 ± 4 (39)	21 (11-31)	
5-Year Survival by TNM Stage for Each Histologic Group			
AdenoCa (stage I)	55 ± 12 (5)	94 (32-155)	0.7
SCC (Stage I)	66 ± 17 (3)	72 (14-129)	
AdenoCa (stage IIa)	32 ± 5 (18)	33 (26-40)	0.01
SCC (Stage IIa)	52 ± 7 (23)	64 (34-93)	
AdenoCa (stage IIb)	17 ± 6 (5)	20 (15-27)	0.09
SCC (stage IIb)	42 ± 13 (5)	21 (1-64)	
AdenoCa (stage III)	10 ± 2 (14)	13 (12-14)	0.35
SCC (stage III)	14 ± 4 (6)	14 (12-16)	
5-Year Survival by Lymph Node Status			
AdenoCa (LN negative)	37 ± 5 (25)	36 (28-43)	0.01
SCC (LN negative)	53 ± 6 (29)	70 (52-88)	
Adeno Ca (LN positive)	11 ± 2 (18)	14 (12-16)	0.35
SCC (LN positive)	16 ± 4 (9)	14 (12-16)	

AdenoCa = adenocarcinoma; CI = confidence intervals; LN = lymph nodes; SCC = squamous cell carcinoma; SEM = standard error of the mean; TNM = tumor, node, metastasis.

Table 4. Multivariate Analysis for Survival

Variable	<i>p</i> Value	Hazard Ratio	95% CI for Hazard Ratios	
			Lower	Upper
Cell type	0.034	1.253	1.017	1.543
TNM stage	0.005	0.443	.224	.879
Lymph nodes	0.025	0.615	.274	1.380
Incomplete resection	0.028	0.719	.535	.966

CI = confidence interval; TNM = tumor, node, metastasis.

and after an Ivor Lewis procedure it was $14 \pm 6\%$ ($p = 0.8$). In patients having squamous cell carcinoma, the Kaplan-Meier five years after a left thoracotomy with phrenotomy (or laparotomy) was $35 \pm 6\%$, and after an Ivor Lewis procedure it was $32 \pm 5\%$ ($p = 0.5$).

Comment

Although our study highlights a number of differences in the characteristics of patients with squamous or adenocarcinoma, it should be noted that some of the differences observed are to be expected. For example, the higher prevalence of female patients in the squamous cell carcinoma group and the differing tumor locations of the two groups are hardly surprising and have been previously documented [11]. Our finding is that patients with squamous cell carcinoma appear to have a poorer perioperative outcome as compared with those with adenocarcinoma. Although respiratory and cardiovascular complications occurred with similar frequency in both groups, a significantly higher proportion of squamous cell carcinoma patients developed anastomotic leak. In addition, operative mortality was significantly higher among patients having squamous cell carcinoma. These findings cannot be explained by differences in preoperative regime of the two groups as during the study period none of the patients received any neoadjuvant chemotherapy or radiotherapy. Similarly, these findings cannot be explained by differences in tumor bulk as patients with squamous cell carcinoma tended to have smaller tumors and earlier TNM-staged disease. One explanation could lie in the fact that the majority of patients with squamous cell carcinoma underwent the Ivor Lewis procedure, while the majority of patients with adenocarcinoma underwent a left thoracotomy. However, operative mortality in the entire group after a left thoracotomy (4.9%) and an Ivor Lewis procedure (4.8%) was identical in our study. The importance of operative approach has been addressed by a number of groups, most notably Hulscher and colleagues [12], who found that en bloc esophagectomy was associated with an increased postoperative morbidity. However, this explanation cannot account for the differences seen in this study as the vast majority of our patients in both groups underwent extended en bloc lymphadenectomy. Previous studies have also failed to demonstrate the superiority of left thoracotomy over the Ivor Lewis approach in terms of opera-

tive morbidity or mortality [13], whereas a report from the Mayo Clinic has quoted a 1.4% operative mortality in 220 consecutive patients undergoing an Ivor Lewis esophagectomy for carcinoma [14]. Nevertheless, in view of the lack of another convincing explanation, it could be argued that the higher intrathoracic tumor position (that renders resectional surgery technically more demanding) may account for the higher anastomotic leak and operative mortality rates in the squamous cell carcinoma group. One could also speculate that the differing perioperative outcomes seen in the two groups may reflect an underlying biological difference between the two cell types.

A rather unexpected finding in this study is the poorer long-term outcome of the patients with adenocarcinoma as compared with those with squamous cell carcinoma. A number of studies have attempted to ascertain predictors of long-term survival after esophageal resection, often with contradictory results [5-7]. Although the majority of studies have failed to show any survival differences between the cell types, there have recently been a number of reports showing adenocarcinoma to be a predictor of better prognosis [11, 15, 16]. Our study appears to contradict these findings; within our cohort, patients with squamous cell carcinoma were more likely to have earlier tumor stage and less likely to have lymph nodes involved by the disease process. In addition, squamous cell carcinoma was, on multivariate analysis, a significant independent predictor of improved long-term outcome. This effect is particularly pronounced in patients with node negative disease. We have previously reported this observation in a smaller study that was limited to patients undergoing esophageal resection and having node negative disease [17]. The present study, in addition to confirming the previous report [17], shows that patients with squamous cell carcinoma have a better survival in the node positive group too. This survival benefit, however, does not attain statistical significance. Why this pattern is seen is unclear. In a recent editorial, Stein and Siewert [16] hypothesized that adenocarcinomas are less aggressive and have a lower tendency for lymphatic vessel invasion as compared with squamous cell carcinomas. While we would agree with their premise that differing cell types do indeed have differing biological behavior, our results would suggest that it is squamous cell carcinomas, as opposed to adenocarcinomas, that have a more clinically benign course, both in terms of lymphatic spread and in overall survival.

We accept that this study has potential limitations. None of our patients underwent preoperative chemotherapy as this study was conducted prior to the publication of unequivocal evidence of the efficacy of this treatment [18]. We are therefore unable to comment on whether the differences in outcome we observed between the two groups will be replicated in patients who undergo neoadjuvant therapy. This said, the survival figures recorded in our study seem to compare well with those seen after the use of neoadjuvant therapy. Similarly, this study predates the introduction of large-scale endoscopic surveillance programs for patients with Bar-

rett's esophagus. It is possible that the introduction of such screening programs may improve the long-term survival of patients with adenocarcinoma as opposed to squamous cell carcinoma [19]. Nonetheless, despite these provisos, the relatively standardized nature of our preoperative, operative, and postoperative management regime, together with the large size of our cohort, does allow us to make a meaningful analysis of the importance of histologic cell type on outcome after surgical resection.

In conclusion, we have found that patients with squamous cell carcinoma appear to have a poorer perioperative outcome as compared with those with adenocarcinoma. However, in the longer term, squamous cell histology appears to confer a significant survival advantage. This is particularly pronounced in the early stage disease, and persists after adjusting for the differences that were observed in other parameters between the two groups. These findings support the contention that squamous cell and adenocarcinoma of the esophagus should be regarded as two distinct tumor entities.

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