Original Research

Vascular invasion is not a risk factor in oesophageal cancer recurrence

N. Waraich a, F. Rashid a,*, A. Jan a, D. Semararo b, R. Deb c, P.C. Leeder a, S.Y. Iftikhar a

a Department of Surgery, Royal Derby Hospital, Derby, DE223NE, UK
b Department of Pathology, Royal Derby Hospital, Derby, DE223NE, UK
c Department of Oncology, Royal Derby Hospital, Derby, DE223NE, UK

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A B S T R A C T

Aim: The outcome of the treatment of oesophageal cancer remains poor despite improved treatment modalities and recurrence remains a major problem despite improved staging and treatment. The aim was to identify the independent risk factors responsible in the recurrence of oesophageal cancer.

Methods: The patients who had elective oesophagectomy (n = 244) with curative intent were studied. One hundred and eighty four patients had surgery alone, 44 patients had neo-adjuvant chemotherapy and surgery while 16 patients had neo-adjuvant chemotherapy, surgery and adjuvant chemotherapy. We have analyzed patients who had surgery alone (n = 184). Data was collected for demography, type of operation, histology, staging (TNM), vascular invasion (VI), differentiation of tumour, type of chemotherapy and recurrence of tumour.

Results: The median age was 67 years (IQR 60, 71). The T1, T2, T3 distribution was 10%, 24% and 66% respectively. Forty percent had no nodal involvement (N0) and 60% had N1 stage disease. Twenty three percent of patients had vascular invasion. Univariate analysis of histo-pathological factors identified lymph node yield (p = 0.06), curative resection R0 (p = 0.004) and vascular invasion (VI) (p = 0.69) as prognostic indicators of recurrence. Multivariate analysis showed that number of lymph nodes yielded (p = 0.01) and R0 resection remain independent indicators of recurrence of tumour. However, VI (p = 0.2) and age at disease onset (p = 0.8) were not indicators of recurrence in oesophageal cancer patients.

Conclusion: R0 and lymph node yield may help to predict the recurrence of oesophageal cancer. However the presence of VI may not be a significant risk factor in disease recurrence.

1. Introduction

Oesophageal cancer is currently the fifth most common cause of cancer related death in the world.1-2 The prognosis of both oesophageal squamous carcinoma and adenocarcinoma is dismal, with frequent metastasis and low survival rate despite improved multimodality treatment.3,4

The mainstay of treatment remains surgical resection, with some improvement in outcome in recent years.5 Griffin et al. highlighted the importance of availability of facilities, expertise, careful patient selection and execution of surgery, in order to reduce morbidity, mortality and improve survival outcome. However, recent advances have failed to translate into a substantial improvement in long-term survival after surgical resection with 5-year survival rates rarely exceeding 30%. This poses real challenges to improve the outcome of treatment in oesophageal cancer and need for alternative management strategies.5-9

Early tumour recurrence remains a significant problem. Clark et al. have reported nodal and systemic recurrence rates of 39.5%. Local anastomotic recurrence was 10.5% with mean follow-up of 16.5 months.10 Prognosis following recurrence remains extremely poor, with few exceptions. Isono et al. reported the median survival period after recurrence to be eight months after nodal, and four months for other types of recurrence. The survival period was reported as even worse, at only two months after peritoneal recurrence.11

Lymph node involvement in oesophageal carcinoma is identified as an independent factor influencing both disease recurrence and survival.12,13 The high frequency of recurrence and poor survival emphasise the need for additional, effective peri-operative treatment. The failure of current adjuvant therapy to significantly improve the prognosis of patients undergoing esophago-gastrectomy for cancer may be either because of poor patient selection or other patho-physiological factors.14,15

* Corresponding author. Division of GI Surgery, School of Graduate Entry Medicine and Health, University of Nottingham, Royal Derby Hospital, Uttoxeter Road, Derby DE223DT, UK. Tel.: +44 1332724702 (Office), +44 7817168102 (Mobile); fax: +44 1332787878.
E-mail address: farhan.rashid@nottingham.ac.uk (F. Rashid).

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Multiple causes and modes of recurrence have been discussed in the literature. These include delayed clinical presentation, or the presence of micro metastases spreading via longitudinal lymphatic drainage within the submucosal plexus at time of resection. The theory of micro metastasis is further supported by Sullivan et al. who identified the presence of rib marrow metastasis in patients undergoing curative resection of oesophago-gastric malignancies.

Local and regional metastases often occur within one year of surgery, indicating that both must have been present at the time of operation. Distant metastases probably require more time to develop. This raises the concept of local and regional factors which influence the impact of disease. The prognostic factors identified by univariate analysis in different series are tumour size, depth of invasion, lymph node invasion, intra mural metastasis, lymphatic invasion and vascular invasion (Fig. 1). T-Stage, N-Stage and Grade of disease are already established key variables in the development of both locoregional and distant metastatic recurrence. However, the role of vascular invasion remains ill defined and therefore warrants further investigation.

2. Material and methods

2.1. Patients

All patients who underwent curative oesophageal resection for cancer of the oesophagus at Derby Upper GI cancer centre between 1995 and 2005 were included in the study. A dedicated team of surgeons, anaesthetists and pathologists managed all the patients. All cases were discussed preoperatively and post-operatively in a multidisciplinary team (MDT) meeting to determine the optimal treatment for each individual patient. All patients underwent oesophago-gastro-duodenoscopy (OGD), computed tomography (CT), endoluminal ultrasound (EUS), staging laparoscopy, echocardiogram and pulmonary function test (PFT), with gas exchange in selected cases prior to the surgical resection.

2.1.1. Inclusion criteria

a. Patients with operable cancer of the oesophagus
b. Patients with gastro-oesophageal junction (GOJ) cancer, Siewert I–III
c. Patients who underwent elective potentially curative resection

2.1.2. Exclusion criteria

a. Patients who had fixed unresectable tumour per-operatively
b. Patients who had Neo-Adjuvant chemotherapy
c. Patients who had Adjuvant Chemotherapy
d. Patients underwent oesophagectomy for non-cancer disease.

2.1.3. Surgical approach

Siewert type I–III oesophago-gastric cancers were resected via a single stage left thoracotomy and phrenotomy. The remainder of cancers were resected via an Ivor–Lewis two stage approach. All the patients had a standard two level lymph node clearance.

2.2. Data collection

Data was collected for age, gender, type of operation, histology type, lymph node yield, vascular invasion, differentiation of tumour, stage (TNM), type of chemotherapy, recurrence of tumour, date of operation and date of death (where applicable).

All the information was identified from hospital case notes and theatre records. Patient follow-up and date of death was determined from the hospital notes and patient administrative system (PAS).

2.3. Histology

In the initial phase, pathology specimens were analyzed by a non-dedicated pathologist, however after 2002 a dedicated team of upper GI pathologists examined all resection specimens. Specimen analysis was performed in a standardized fashion and the histological stage of tumour was classified according to TNM criteria for oesophageal cancer established by the International Union against Cancer/American Joint committee on cancer (Table 1). The pathologist identified all removed lymph nodes according to their location (coeliac axis, left gastric artery, lesser gastric curvature, left and right paracardial, para-oesophageal and subcarinal). Further- more Barrett’s metaplasia, lymphatic invasion, vascular invasion, the total number of lymph nodes retrieved and the presence of lymph nodes with tumour invasion were recorded.

2.4. Recurrence

Local, regional, transcoelomic (pleural or peritoneal) and distant (haematogenous) metastases were considered as manifestations of recurrence of disease. Recurrence at cervical, coeliac, mediastinal and para aortic lymph nodes was classified as locoregional recurrence. Disease recurrence was diagnosed on clinical grounds, identified on OGD or CT depending on the symptomatic presentation of the post-operative patient.

2.5. Follow-up

All patients were seen at the outpatient clinic at three monthly intervals for the first year and then every 6 months thereafter for five years. After five years, annual follow-up has been carried out on all surviving patients. Radiological modalities, haematological and endoscopic interventions were not used routinely during follow-up. However when recurrence was suspected, additional investigations were performed when clinically indicated.

2.6. Statistical analysis

Statistical package for social science (SPSS) version 15.0 was used to perform statistical analyses of the available data. Time to event was measured from the date of first definitive treatment (surgical) to the date of recorded death. Any cause of death was recorded as an event, which may have been directly related or unrelated to disease progression or relapse.

Mean and median values were compared by statistical analysis. Death within 30 days of surgical resection and time of survival were used as endpoints for assessing post-operative death and prognostic factors. Survival probabilities were calculated using the Kaplan–Meier method and difference in survival was assessed by the log rank test. A multivariate Cox regression analysis was performed to assess

| Table 1
| Clinical characteristics of 184 patients submitted to potentially curative resection for oesophageal cancer. |
|-----------------|-----------------|
| Variables       | Number of patients |
| Gender M/F      | 146/38           |
| Age             | 67 (60,71)       |
| Histology       |                 |
| Adenocarcinoma  | 146 (79.3%)      |
| Squamous        | 38 (20.7%)       |
| Well differentiated | 22 (12%)       |
| Moderately differentiated | 67 (36%) |
| Poorly differentiated | 95 (52%) |
| pT1/pT2/pT3     | 18/44/122 (10%, 24%, 66%) |
| pN0/pN1         | 73/111 (40%, 60%) |
| Vascular invasion | 41 (22.2%)   |
| RO              | 129 (70%)        |
| Recurrence      | 70 (38%)         |
3. Results

Our cohort included 244 patients who had curative elective oesophagectomy at Derby upper GI cancer centre between 1995 until 2005.

Out of 244 patients 184 had surgery alone while 44 patients had preoperative chemotherapy followed by surgery and 16 patients had preoperative chemotherapy followed by surgery and subsequent post-operative chemotherapy. Therefore, 60 patients were excluded from the study, in order to eliminate the effects of neo-adjuvant and adjuvant chemotherapy on recurrence and over-all patient survival.

The median age of study patients was 67 years (IQR 60–71) at the time of surgical resection with a male to female ratio of 4:1. One hundred and forty six patients had oesophageal adenocarcinoma and 38 had squamous cell cancer.

T1, T2, and T3 stages were identified respectively, in 10% (n = 18), 24% (n = 44) and 66% (n = 122) of patients’ post-operative histological staging.

Forty percent (n = 73) of patients had no nodal involvement and 60% (n = 111) had N1 stage. The median lymph node yield was 11 (IQR 8, 20) and median number of positive lymph nodes was two (IQR 0, 8).

Twenty-two patients (12%) had well differentiated oesophageal carcinoma, 67 (36%) had moderately differentiated cancer and 95 (52%) had poorly differentiated tumour. One hundred and twenty-nine patients (70%) had microscopically clear resection margins (R0). Twenty three percent of patients (n = 41) had vascular invasion (Table 1).

Patients were followed up regularly every three months post surgery. Thirty eight percent (n = 70) of patients developed recurrence during the study period and more than half of these patients n = 40 had recurrence within one year of their surgery. Only three patients (6%) with T1 disease had recurrence (p = 0.61), 14 patients (32%) with T2 disease developed (p = 0.01) recurrence and 57 patients (47%) with T3 disease had disease recurrence (p = 0.001).

Fifty percent of patients with N1 disease (n = 55) showed recurrence of disease and 28% of patients with N0 (n = 21) disease had recurrence following intentionally curative resection.

Univariate analysis of histo-pathological factors indicated that lymph node yield (p = 0.06), curative resection (R0) (p = 0.004) and vascular invasion (VI) (P = 0.69) were all prognostic indicators of recurrence.

Multivariate analysis confirmed total lymph node yield (p = 0.01) and R0 (0.003) resection to be independent indicators of disease recurrence. However, vascular invasion (p = 0.2) and age (P = 0.8) were not the indicators of recurrence in oesophageal cancer patients.

4. Discussion

Despite comprehensive preoperative staging to carefully select patients for potentially curative surgery for oesophageal cancer, recurrence remains a problematic and frequent issue. Lymphatic and haematogenous dissemination probably both occur in parallel. The vast majority of the patients develop either locoregional disease or distant metastases within two years after surgery. Early recurrence indicates that many patients have unrecognised micro metastatic disease at the time of surgery and present later with locoregional, haematogenous, and/or transcelomic recurrences.8,21–25

Multiple pathological factors are known to play an important role in the prognosis and final outcome of patients with oesophageal cancer, even after potentially curative resection of cancer. These factors included T-stage, N-stage, differentiation of tumour, R0 (microscopic clearance) resection, and R1 (macroscopic clearance) resection. However the role of vascular invasion in oesophageal carcinoma remains unclear.

The important prognostic role of vascular invasion has been widely discussed in the literature in thyroid, colorectal, hepatopancreaticobiliary, breast and prostate cancer, as well as sarcoma. Its exact role in oesophageal cancer is yet to be established. The presence of vascular invasion has not been found to be a consistent finding and to date has not been reported to be associated with an increased incidence of lymph node or distant metastasis.26–30

The impact of tumour stage (T), lymph noted stage (N), curative resection (R0) and vascular invasion have been widely discussed in the context of survival from oesophageal cancer.12,13,31 However, vascular invasion has not been assessed fully as a potential predictor of tumour recurrence.

Multivariate analysis in our study identified lymph node yield to be a significant prognostic indicator of locoregional recurrence. Our results are inconsistent with studies performed by Hulscher et al. (cohort n = 137) and Dressener et al. (Cohort n = 176). However both of these studies failed to describe the exclusion of patients who had neo-adjuvant chemotherapy.

In our cohort of 184 patients, Univariate analysis of radicality of resection (R0) showed a significant (P = 0.004) impact on over-all recurrence of the disease following potentially curative resection. Multivariate analysis confirmed that R0 resection was an independent prognostic indicator of tumour recurrence. The microscopic clearance of disease following surgery is a good indicator of over-all survival. However most of the previous studies have sparse data, without clear exclusion criteria of patients who had neo-adjuvant or adjuvant chemio-radiotherapy. The current cohort included patients who underwent surgical resection only. This excludes the potential bias in the study, as neo-adjuvant and adjuvant chemotherapy are both known to influence recurrence rates and potentially improve over-all survival. The Medical Research Council (MRC) OE02 trial found a significantly improved survival following neo-adjuvant chemotherapy in oesophageal cancer as compared to surgery alone.32 Preliminary results from the Medical Research Council (MRC UK) Multi centre trial (MAGIC) of patients with resectable adenocarcinoma of the stomach, gastros- oesophageal junction and lower oesophagus has also suggested the survival benefits of neo-adjuvant chemotherapy.33

Over half of study patients with recurrent tumour had vascular invasion. Neither univariate nor multivariate analysis identified a significant impact of vascular invasion on disease recurrence. The present study is contrary to the study by Zaferillis et al. which showed that vascular invasion was an independent prognostic indicator; however, this study did not describe exclusion and inclusion criteria which may have added potential bias. In a similar study, Osugi et al. recruited patients with surgical resections only and excluded the patients with neo-adjuvant chemotherapy. Multivariate analysis in their study suggested that vascular invasion seems to play no significant role in the prognosis of oesophageal cancer (p = 0.65). The significance of lymphatic invasion was found to be better than vascular invasion for generalized metastasis and there was equal specificity for lymphatic invasion suggesting the presence of micro metastasis at time of resection.31,34

Our findings confirmed that the vascular invasion is not a significant indicator of recurrence of oesophageal cancer.

Porschen et al. studied the vascularization of both normal oesophagus and carcinoma of the oesophagus. They demonstrated less capillary volume, less total volume, less vascular surface area and less vascular length in oesophageal cancer than the normal oesophagus.35 The oesophagus is a tubular structure with comparatively more tenuous vascularity than other organs. It relies on
branches from the inferior thyroid artery, aorta and short gastric arteries for its blood supply. A possible explanation of less vascular invasion could be related to either the anatomy of oesophagus or carcinogenesis of oesophageal malignancy. This may explain our findings that vascular invasion may not play any role in recurrence as compared to lymphatic invasion.

The retrospective nature of data has imposed some limits on our study. Also introduction of dedicated pathologist may have contributed towards improved median number of yielded lymph nodes.

5. Conclusion

Curative resection R0 and total lymph node yield may predict the recurrence of oesophageal cancer. However, the presence of vascular invasion has not been shown consistently to be an independent pathological risk factor in the recurrence of oesophageal malignancy.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

None.

Author’s contributions

NW, FR have designed and carried out the study. NW, AJ, DS, RD, PCL and SYI helped in data collection. SYI provided the supervision. NW, AJ and FR wrote the manuscript. DS, RD, PCL and SYI helped in data collection. SYI provided the super-
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A FINAL RESEARCH