RESEARCH COMMUNICATION

# Impact of Lymph Node Metastases in Esophageal Carcinoma Patients is Independent of Patient Age

**Abidin Sehitogullari[1], Oztekin Cıkman[2], Fuat Sayir[3], Ufuk Cobanoglu[3], Cengiz Demir[4], Halit Demir[5*]**

## Abstract

**Objective: The purpose of the present study was to define the clinicopathological features and prognosis of esophageal cancer. Methods: Between 2004 and 2009, 128 patients with esophageal cancer were enrolled in a retrospective database and divided into two groups on the basis of number positive lymph nodes with the cut-off as four. Results: The findings for 18 patients (14.0%) Group A were compared with those of 110 patients Group B. In the group A, there were significantly more women (12/6 vs. 54/56, P < 0.001). In both groups, the most frequent histological morphology was squamous cell carcinoma (83% and 75%, respectively), although the percentages were significantly different (P < 0.005). In the group A, lesions were more frequently located in the middle one-third of the esophagus than in the group B (61% vs. 28%, P < 0.001). Group A was more likely to be Stage IIa. Survival rates in group A patients at 5 years after resection were 15.8%, similar to those in group B patients (12.1%, difference not significant). Local lymph node metastases and microscopic residual tumor at the line of resection were also more prevalent in the young patients, but not to a statistically significant degree. Conclusions: These findings suggested that the clinical and pathologic features of carcinomas of the esophagus in young patients do not significantly differ from those in older patients.**

**Keywords:** Esophageal cancer - survey - age groups - lymph node metastasis

*Asian Pacific J Cancer Prev,* **12**, 599-603

## Introduction

Esophageal cancer is one of the most lethal cancers and constitutes 7% of gastrointestinal cancers (Levine, 1997; Levine et al., 2000). Incidence rates vary greatly worldwide, with the highest rates in Asia, Southern and Eastern Africa, and Northern France. In these regions, annual mortality is near 100 per 100,000. The most common histologic types are squamous cell carcinoma (SCC) and adenocarcinoma (AC), which together constitute more than 90% of esophageal malignancies. Rarely, melanoma, sarcoma, small cell carcinoma, or lymphoma may arise in the esophagus (Tilanus, 1995; Wong et al., 2003; Demir et al., 2010).

Resection of the esophagus for malignant disease is associated with significant postoperative morbidity and mortality. Surgical technique is an important factor in preventing intraoperative and postoperative complications. The significant factors associated with preoperative complications are intraoperative blood loss, blood transfusion, splenectomy, and prolonged operation time rather than the extent of nodal dissection. Despite recent improvements, 5-year survival is still approximately 10% in most Western countries (Lagergren, 2005). Much of the research in esophageal cancer looks at prognostic factors with the number of metastatic lymph nodes, ratio of positive lymph nodes, volume of perioperative blood transfused, tumor size, and histologic type being all reported as prognostic variables (Cariati et al., 2002; Tachibana, 2002).

In this study, we tried to determine the survival rates of the patients under four number positive lymf nodes and 50 years of age and below as compared with those diagnosed upon four positive lymf nodes and upon 50 years of age.

## Materials and Methods

Materials were obtained from Thoracic Surgery Department of Van Training and Research Hospital. Demographic, clinical, treatment, and survival information from 128 patients (66 male (51.6%), 62 female (48.4%)) diagnosed with esophageal cancer after 2004 were collected. Patients were divided into two groups: Group A was under or 4 number of positive lymph nodes and 50 years of age and below, and group B upon 4 number of positive lymph nodes upon 50 years of age at diagnosis. Demographic, clinical, and treatment characteristics were comparedby using the chi-square test. The survival rates

*[1]Department of Thoracic Surgery, Van Training and Research Hospital, [2]Department of Thoracic Surgery, [3]Department of Hematology, Medical Faculty, [4]Department of Chemistry/ Biochemistry Section, Faculty of Science, Yuzuncu Yil University Hospital, Van, Turkey*
**For correspondence : halitdemir2005@yahoo.com*

**Table 1. Sex, Cell Type and Localization of the Subjects**

| | | Group A (%) | Group B (%) | Total (%) |
|---|---|---|---|---|
| Gender | Male | 6 (33) | 56 (53.7) | 62 (48.4) |
| | Female | 12 (67) | 54 (46.3) | 66 (51.6) |
| | Total | 18 (100) | 110 (100) | 128 (100) |
| Morphology | Squamous | 15 (83) | 82 (75) | 97 (76.1) |
| | Adenocarcinoma | 2 (11) | 24 (22) | 26 (21) |
| | Others | 1 (6) | 3 (3) | v |
| | Total | 18 (100) | 110 (100) | 128 (100) |
| Lesion locations | Upper one-third | 1 (6) | 5 (4.6) | 6 (4.7) |
| | Middle one-third | 11 (61) | 31 (28.3) | 42 (31.5) |
| | Lower one-third | 6 (33) | 74 (67.1) | 80 (63.8) |
| | Total | 18 (100) | 110 (100) | 128 (100) |
| | Stage I | 2 (11) | 0 | 2 (1.8) |
| | Stage IIa | 5 (28) | 16 (14.5) | 21 (16.4) |
| | Stage IIb | 1 (6) | 18 (16.3) | 19 (14.8) |
| | Stage III | 6 (33) | 52 (47.2) | 58 (45.2) |
| | Stage IV | 4 (22) | 24 (22) | 28 (21.8) |
| | Total | 18 (100) | 110 (100) | 128 (100) |

**Table 2. Survival Values of the Subjects Who have Undergone Surgical Resection**

| Duration (months) | Group A (%) | Group B (%) |
|---|---|---|
| 6 | 10 (89.2) | 57 (81.4) |
| 24 | 5 (40.4) | 27 (36.1) |
| 60 | 3 (15.8) | 27 (36.1) |

of the patients who were surgically treated were calculated and compared between the groups. Statistical analysis was performed using Stata 8.0 (Stata Corporation, College Station, TX, USA). All P values reported are two-tailed, and P =0.05 was considered to be statistically significant.

## Results

A total of 128 patients diagnosed with esophageal cancer were identified. Of these, 18 patients (14.0%) were under or 4 number of positive lymph nodes and younger (Group A) and 110 (85.9%) were upon 4 of positive lymph nodes and older (Group B) (Table 1). The mean age was 46 (18-65 years) in Group A and 62.16 in Group B. In Group A, 6 patients (33%) were male and 12 were female (67%), in Group B 56 patients (53.7%) were male and 54 (46.3%) were female. These sex differences between groups were statistically significant ($P$=0.001). In both groups, the most frequent histological morphology was squamous cell carcinoma (83% vs. 75%, $P$=0.005). Adenocarcinoma was the second most common type (11% vs. 22%, $P$=0.01) (Table 1). The difference between ratios of types of the two groups was statistically significant. In the group A, lesions were more frequently located in the middle one-third of the esophagus (61% vs. 28.3%, $P$=0.001), while in the group B, lesions were more frequently at the lower one third of the esophagus (33% vs. 67%, $P$=0.001) (Table 1). In the overall study group, 2 cases (1.8%) had Stage 1, 21 cases (16.4%) had Stage IIa, 19 cases (14.8%) had Stage IIb, 58 cases (45.2%) had Stage III, and 28 cases (21.8%) had Stage 4 cancers (Table 1). There was no patient with Stage 1 disease in Group B. The percentage of these patients in Group A was 2%. This difference was not statistically significant($P$=0.312). Group A patients were more likely to have Stage IIa disease than Group B patients who were upon 4 number positive lymph nodes and older (28% in Group A and 14.5% in Group B) and this difference was statistically significant ($P$=0.000). Stage IIb disease was present in 6% and 16.3% of Group A and B patients, respectively. The difference between two groups was not statistically significant ($P$=0.081). Stages 3 and 4 diseases were present in 33% and 22% of Group A patients, respectively; they were present in 47.2% and 22% of Group B patients. Differences between two groups were not statistically significant for both Stages 3 and 4 ($P$=0.324 for Stage 3 and $P$=0.321 for Stage 4). Among the surgically treated patients, the 6-month survival rates for Groups A and B were 89.2 % and 81.4 %, respectively; 24 months, 40.4% and 36.1%; 60 months 15.8% and 12.1% (Table 2). While the survival rates were decreased in the upon 4 number lymph nodes group and older, they were not statistically significant ($P$=0.05). For these calculations, operative mortalities were excluded.

## Discussion

The incidence of esophageal cancer varies considerably with geographic region and also within a common area among ethnic groups. Two of the locations where the highest rates are seen are Northern China and Northern Iran. In these regions, incidence exceeds 100 in 100,000 individuals (Fisher et al., 1998). While in Linxian, Hunan province, China, esophageal cancer is endemic, in the US, the incidence is less than five per 100,000 (Cheng et al., 1994; Fisher, 1998). In the east Anatolia region of Turkey, the incidence is similar to that of Iran. Although esophageal cancers are seen much more frequently in men in North America and Europe, in regions where prevalence is high, such as China, Japan, and Singapore, the rates are equal between men and women. Koshy and colleagues, in their article, have reported an approximate 3 : 1 male predominance in esophageal cancer incidence (Koshy et al., 2004). In addition, Eloubeidi and colleagues reported their patient population to be 72.9% male and 27.1% female (Eloubeidi et al., 2002).

In our institute, of the 128 patients diagnosed with esophagus cancer, 62 (48.4%) were male and 66 (51.6%) were female. Male-female ratio was similar in all patients. While in under 4 number positive lymf node and younger group, 33% were male, and in the upon 4 number positive lymf node and older group, 53.7% were male. In Group A, female gender was more frequent but survival rates were decreased more. The rates of esophageal cancer are extremely low in persons under 4 number positive lymf node group and younger than upon 4 number positive lymf node and older group and continue to rise with each decade of life. Eloubeidi et al. reported the median age as 68 in their study involving 10 441 patients. In their study, 0.1% of the patients were under age 30 and 1.1% of patients were under age 40 (Eloubeidi et al., 2002).

As to our study, the mean age was 36 in Group A, 62.36 in B, and 57.96 in the overall study group. Subjects in Group A were more frequently women, which is different than the overall patient population and reports in the literature. Of the 4 subjects under the

age of 35, 2 of the 10 were female. In both groups, the most common symptom was dysphagia, followed by chest pain and weight loss. These symptoms were not significantly different between our two groups. Axon et al. compared 24 patients with resectable hypopharynx and cervical esophageal carcinoma under the age of 45 with 156 patients who presented the same symptoms between the ages of 60 and 69. They stated that the young adults presented with less-advanced disease as assessed by tumor, node, metastasis (TNM) classification. They explained that this finding could indicate the younger patients' greater awareness of thegravity of their symptoms (Axon et al., 2000). The predominant histological types of esophageal carcinoma are squamous cell carcinoma and adenocarcinoma. Less common histologies include adenoid cystic, mucoepidermoid, adenosquamous, undifferentiated, and malignant melanoma. These rare types have poor prognoses. Small cell carcinoma can also be seen in the esophagus with a course similar to that in the lung (Imai et al., 1978) . Non-epithelial tumors in the esophagus, most of which is leiomyosarcoma, are rare. Metastatic tumors can also be found in the esophagus, most frequently from the breast (Fisher et al., 1998). In the 1960s, more than 90% of all esophageal tumor cases were squamous cell carcinomas in type. Esophageal adenocarcinoma is increasing in the Western countries and now equals or surpasses squamous cell carcinoma in many centers in the United States and Europe (Devesa et al., 1998; Daly et al., 2000). Whereas esophageal adenocarcinoma usually arises from areas with specialized intestinal metaplasia in the distal esophagus, squamous cell carcinoma is related to alcohol and nicotine abuse.

Mariette et al.'s study showed that, compared with squamous cell carcinoma patients, those with adenocarcinoma were significantly older, had a lower incidence of respiratory and otolaryngologic histories, and had more advanced tumors and a larger percentage of invaded lymph nodes (Mariette et al., 2005). In the past, squamous cell carcinomas accounted for over 95% of esophageal malignancies but over the past two decades, the incidence rates of squamous cell carcinomas have been decreasing whereas the incidence of adenocarcinoma of the esophagus has been dramatically increasing (Levine, 1997; Levine et al., 2000; Lightdale, 2000; Siewert et al., 2001; Mariette, 2005). In Eloubeidi et al.'s report, squamous cell carcinoma and adenocarcinoma also were the two most common morphologic types (53.6% and 36.9%, respectively) (Eloubeidi et al., 2002). Mariette and associates have reported that patients with adenocarcinoma compared with those that had squamous cell carcinoma were significantly older (Mariette et al., 2005). According to Mariette et al., it will be necessary to identify new molecular markers to better understand the specific pathogenesis and develop new therapeutic strategies for these tumors with diverse cell types (Mariette et al., 2005).

In our younger group, the most common type was squamous cell carcinoma and this difference was statistically significant. In both of our groups, the most frequent histological morphology was squamous cell carcinoma, with adenocarcinoma being second most prevalent. Ten to twenty percent of esophageal cancers are located in the upper most third of the esophagus, 50% are in the middle third, and 30-40% are in the lower third. Moreover, according to Eloubeidi and colleagues, the most common primary tumor site is the lower one-third of the esophagus (44.6%) (Eloubeidi MA et al., 2002). In our younger group, lesions were more frequently located at the middle one-third of the esophagus (61%) than in the older group, and this feature was statistically significant. Esophagectomy remains the standard care for the treatment of early-stage tumors confined to the esophagus and paraesophageal region. In our institution, the selection of the therapeutic modality is based on resectability of the primary tumor and the patient's general status.

A primary surgical resectionis considered the therapy of choice if it is predicted that a complete tumor resection can be achieved and the patient can tolerate an extensive surgical procedure. Preoperative chemotherapy, combined radiochemotherapy, or both are used for the patients with T3/T4 tumors. When the patient's general status is not appropriate for an esophagectomy, primary radiochemotherapy is considered. In patients with systemic metastases or malignant esophagotracheal fistula, palliative methods (stents, chemotherapy, orradiochemotherapy) are employed in our institution. As it is not rare for the patients to refuse chemotherapy or radiochemotherapy in our region, our rates about these modalities remain low. The rate of resectability of esophageal cancer is reported to range from 60-90%, and the resulting 5-year overall survival rate ranges from 10-25% (Law et al., 1992; Chu et al.,1997; Ellis, 1999; Visbal et al., 2001). Five-year survival rates were reported for Stage 1 esophageal cancer, ranging from 80-94% and, for Stage 3, rates range from 10-14% (Ellis, 1999; Visbal et al., 2001). In our study, 12 (66%) subjects in Group A, and 56 (50.9%) subjects in Group B were operated on. While the ratio of overall resectability was determined to be 77.7, the unresectability rate on surgery was 9.7%. Nevertheless, 58 (45.3%) of the 128 subjects operated on were Stage 3.

Early surgical complications in our patients were wound infection (8.7%), gastric distention (7.4%), cardiac or pulmonary complications (8.1%), contralateral hydrothorax (8.2%), empyema (6.2%), anastomotic leak (2.5%), pneumothorax (2%), chylothorax (1%), and bleeding (2.2%). Late complications were stenosis (13.6%) and recurrence (6.2%). Overall mortality rate was 6.8%. A major problem in esophageal cancer is that half of the patients present with unresectable or metastatic cancers; if a screening program could detect the disease at an earlier stage, there could be a greater possibility for better long-term survival. Unfortunately, the value and cost-effectiveness of endoscopic surveillance for esophageal cancers has not been demonstrated. Esophageal carcinoma has a dismal prognosis (Watson et al., 1994; Boyle et al., 1999; Rindani et al.,1999). Five-year overall survival is still about 10-25% in most Western countries, although there have been recent improvements (Lagergren, 2005). Female sex, age less than 65 years, tumor size less than 5 cm, upper third esophageal location, have all positively influence outcome, while weight loss, low Karnofsky

performance status, deep ulceration of tumor, sinus tract formation, and fistula formation are all poor prognostic factors (Pearson, 1977; Hussey et al., 1980; Schrump et al., 2001). Tumor stage is still the most important prognostic factor, so early diagnosis and treatment are extremely important (Rice et al., 1997).

When comparing both of our groups, Stage 2 a was more frequent among Group A. However, survival rates were decreased in Group B. This can be attributed to the fact that across all stages, patient age and tumor site are important predictors of survival with esophageal carcinoma (Eloubeidi et al., 2002). Axon et al. reported that young adults presenting with squamous cell carcinoma of the hypopharynx and cervical esophagus had a tumor and nodal staging at presentation similar to that of patients between the ages of 60 and 69, and survival rates indicated no statistical difference after treatment (Axon et al., 2000). They suggested that patient age was not a significant factor for determining prognosis in esophageal carcinoma. Portale et al. studied 263 patients with resectable esophageal adenocarcinoma. Thirty-two patients (12.1%) were younger than 50 years old. In their study, the 5-year survival rate was 32.6% for patients younger than 50 years old and 45.5% for patients older than 50 years old. They reported that, with appropriate and aggressive treatment, the survival rate was similar (Portale et al., 2004).

Esophageal cancers are seen endemically in our region. Although it is very rarely seen in patients under the age of 50, in recent years the prevalence in this age group is increasing. In our cohort of under-11 patients, it is much more commonly seen in women. Younger patients are more likely to have cancers in the middle third of their esophagus, unlike their older counterparts. In both age groups, squamous cell carcinoma was more frequently seen. Survival, however, was not statistically different between the two age groups. Further studies are necessary to more fully understand the pathogenesis of esophageal cancers in younger patients.

Clarck et al., (1994) Studied Rates of lymph node metastases increase with the depth of the primary tumor. Patients with lymphatic metastases can be cured particularly if there are fewer than four nodes involved. Curative surgical therapy necessitates wide lymph node resection to ensure removal of all metastatic nodes. İn their study Patients with four metastatic nodes or less had a survival advantage over those with more than four ($p < 0.05$). There was no difference in survival according to location of nodal metastases. Two (22.2%) of 9 patients with celiac node metastases survived longer than 4 years (Clark et al., 1994). In our study local lymph node metastases were also more prevalent in the young patients, but not to a statistically significant degree. These findings suggested that the clinical and pathologic features of carcinomas of the esophagus in young patients were not significantly different from those in older patients.

## References


Axon PR, Simo R, Temple RH, et al (2000). Carcinoma of the hypopharinx and cervical esophagus in young adults. *Ann Otol Rhinol Laryngol*, **109**, 590-3.

Boyle MJ, Franceschi D, Livingstone AS (1999). Transhiatal versus transthoracic esophagectomy: complication and survival rates. *Am Surg*, **65**, 1137-41.

Cariati A, Casano A, Campagna A, et al (2002). Prognostic factors influencing morbidity and mortality in esophageal carcinoma. *Rev Hosp Clin Fac Med Sao Paulo*, **57**, 201-4.

Casas F, Ferrer F, Farrus B, et al (1997). Primary small cell carcinoma of the esophagus: a review of the literature with emphasis on therapy and prognosis. *Cancer*, **80**, 1366-72.

Cheng KK (1994). The etiology of esophageal cancer in Chinese. *Semin Oncol*, **21**, 411-5.

Chu KM, Law SY, Fok M, et al (1997). A prospective randomized comparison of transhiatal and transthoracic resection for lower third esophageal carcinoma. *Am J Surg*, **174**, 320-4.

Clark GW, Peters JH, Ireland AP, et al (1994). Nodal metastasis and sites of recurrence after enblock esophagectomy for adenocarcinoma. *Ann Thorac Surg*, **58**, 646-53.

Daly JM, FryWA, Little AG, et al (2000). Esophageal cancer: results of an American college of surgeons patient care evaluation study. *J Am Coll Surg*, **190**, 562-72.

Demir H, Akkus ZA, Cebi A, et al (2010). Catalase, carbonic anhydrase and other biochemical parameters in esophageal cancers in Turkey. *Asian Pac J Cancer Prev*, **11**, 1029-32.

Devesa SS, Blot WJ, Fraumeni JF (1998). Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer*, **83**, 2049-53.

Ellis FH Jr (1999). Standard resection for cancer of the esophagus and cardia. *Surg Oncol Clin N Am*, **8**, 279-94.

EloubeidiMA, Desmond R, ArguedasMR, et al (2002). Prognostic factors for the survival of patients with esophageal carcinoma in the U.S. The importance of tumor length and lymph node status. *Cancer*, **95**, 1434-43.

Fisher S, Brady L. Esophagus. In: Perez CA, Brady LJ (eds) (1998). *Principles and Practice of Radiation Oncology*, 3rd edn. Philadelphia, PA: lippincott-raven, 1241-56.

Holmes RS, Vaughan TL (2007). Epidemiology and pathogenesis of esophageal cancer. *Semin Radiat Oncol*, **17**, 2-9.

Holscher AH, Bollschweiler E, Schneider PM, et al (1995). Prognosis of early esophageal cancer: comparison between adeno- and squamous cell carcinoma. *Cancer*, **76**, 178-86.

Hussey DH, Barakley T, Bloedorn F (1980). Carcinoma of the esophagus. in: Fletcher G H (ed.). *Textbook of Radiotherapy*, 3rd edn. Philadelphia, PA: Lea & Febiger, 688.

Imai T, Sannohe Y, Okano H (1978). Oat cell carcinoma (apudoma) of the esophagus: a case report. *Cancer*, **41**, 358-64.

Koshy M, Esiashvilli N, Landry JC, et al (2004). Multiple management modalities in esophageal cancer: epidemiology, presentation and progression, work-up, and surgical approaches. *Oncologist*, **9**, 137-46.

Lagergren J (2005). Adenocarcinoma of oesophagus: what exactly is the size of the problem and who is at risk? *Gut*, **54**, 1-5.

Law SY, Fok M, Cheng SW (1992). A comparison of outcome after resection for squamous cell carcinomas and adenocarcinomas of the esophagus and cardia. *Surg Gynecol Obstet*, **175**, 107-12.

Levine MS (1997). Esophageal cancer: radiologic diagnosis. *Radiol Clin North Am*, **35**, 265-79.

Levine MS, Halvorsen RA (2000). Carcinoma of the esophagus. in: Gore RM, Levine MS (eds). *Textbook of Gastrointestinal Radiology*. Philadelphia, PA: WB Saunders, 403-33.

Lightdale CJ (2000). Positron emission tomography: another useful test for staging esophageal cancer. *J Clin Oncol*, **18**, 3199-201.

Mariette C, Finzi L, Piessen G, et al (2005). Esophageal

carcinoma: prognostic differences between squamous cell carcinoma and adenocarcinoma. *World J Surg*, **29**, 39-45.
Pearson JG (1977). The present status and future potential of radiotherapy in the management of esophageal cancer. *Cancer*, **39**, 882-90.
Portale G, Peters JH, Hsieh CC, et al (2004). Esophageal adenocarcinoma in patients _50 years old: delayed diagnosis and advanced disease at presentation. *Am Surg*, **70**, 954-8.
Rice TW, Adelstein DJ (1997). Precise clinical staging allows treatment modification of patients with esophageal carcinoma. *Oncology*, **11**, 58-62.
Rindani R, Martin CJ, Cox MR (1999). Transhiatal versus ivor- lewis oesophagectomy: is there a difference? *Aust N Z J Surg*, **69**, 187-94.
Schrump D, Altorki N, Forastiere A (2001). Cancer of the esophagus. in: De Vita VT Jr, Hellman S, Rosenberg SA (eds). Cancer: *Principles and Practice of Oncology*, 6th edn. Philadelphia, PA: Lippincott-Williams & Wilkins, 1319-42.
Siewert JR, Stein HJ, Feith M, et al (2001). 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*, **234**, 360-7.
Tachibana M, Dhar DK, Kinugasa S, et al (2002). Esophageal cancer patients surviving 6 years after esophagectomy. *Langenbecks Arch Surg*, **387**, 77-83.
Tilanus HW (1995). Changing patterns in the treatment of carcinoma of the esophagus. *Scand J Gastroenterol Suppl*, **212**, 38-42.
Visbal AL, Allen MS, Miller DL, et al (2001). Ivor lewis esophagogastrectomy for esophageal cancer. *Ann Thorac Surg*, **71**, 1803-8.
Watson A (1994). Operable esophageal cancer: current results from the west. *Word J Surg*, **18**, 361-6.
Wong RK, Malthaner RA, Zuraw L, et al (2003). Combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: a practice guideline. *Int J Radiat Oncol Biol Phys*, **55**, 930-42.