Esophageal Cancer in Iran; a Population-based Study regarding Adequacy of Cancer Surgery and Overall Survival

Iraj Harirchi, M.D. Shadi Kolahdoozan, M.D., M.P.H. Somayeh Hajizadeh, MSc Fatemeh Safari, M.D. Zahra Sedighi, M.D. Azin Nahvijou, M.D. Mohammad-Reza Mir, M.D. Seyed-Mohsen Mousavi, M.D. Kazem Zendehdel, M.D., Ph.D.

PII: S0748-7983(13)00859-7
DOI: 10.1016/j.ejso.2013.10.011
Reference: YEJSO 3653

To appear in: European Journal of Surgical Oncology

Received Date: 26 May 2013
Revised Date: 15 September 2013
Accepted Date: 16 October 2013


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Title page:

Title: Esophageal Cancer in Iran; a Population-based Study regarding Adequacy of Cancer Surgery and Overall Survival

Short title: Surgery and Overall Survival

Authors list: Iraj Harirchi, M.D., Shadi Kolahdoozan, M.D., M.P.H., Somayeh Hajizadeh, MSc, Fatemeh Safari, M.D., Zahra Sedighi, M.D., Azin Nahvijou, M.D., Mohammad-Reza Mir, M.D., Seyed-Mohsen Mousavi, M.D., Kazem Zendehdel, M.D., Ph.D.

Affiliations list:
1: Cancer Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran.
2: Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran.
3: German Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany.
4: Department of Medical Epidemiology & Biostatistics, Karolinska Institute, Stockholm, Sweden.

Correspondence to: Dr. Iraj Harirchi, M.D., Associate Professor of medicine
Department of Surgery, Cancer Research Center, Cancer Institute, Tehran University of Medical Sciences.
Postal address: Qods Street, Enghelab Avenue, 1417863181, Tehran, Iran.
Tel: (+98 21) 66491070; Fax: (+98 21) 66419537;
E-mail: harirchi@sina.tums.ac.ir
**Key words:** Esophageal Cancer; Population-based; Surgery; Adequacy
Abstract:

**Aims:** Prognosis of esophageal cancer (EC) is poor. Population-based studies regarding EC survival and adequacy of cancer surgery (ACS) from developing countries are lacking. We aimed to evaluate EC patients’ survival and ACS in a population-based setting for the first time from Iran.

**Methods:** We randomly selected 409 cases from all 3048 newly diagnosed EC patients who were registered in the nationwide cancer registry in calendar year 2005-2006 and followed them until 2009. An expert panel in Cancer Institute of Iran reviewed adequacy of esophageal cancer surgery on a national basis.

**Results:** Overall three-year survival rate was 17%. The median (95% CI) survival time of all patients and cases who underwent surgery alone were 8.5 (6.9-10.1) and 6.0 (3.1-8.9) months, respectively. The hospital mortality was 27.8% among the operated patients. Only 6.8% of cases had documented free circumferential resection margin and merely 4.0% of patients experienced resection of more than 15 lymph nodes during surgery.

**Conclusions:** In Iran, the overall survival of EC patients with different treatment modalities are slightly less than those reported from high-income countries, but cases with surgery alone as the main treatment had worse outcome compared with their counterparts in developed countries. Surgery with curative intent has not been performed in most cases in Iran. It seems current clinical outcome of EC patients could be improved with surgical quality improvement and/or more use of chemoradiation in Iran.
Background

Esophageal carcinoma (EC) is the eighth most common cancer and the sixth most common cause of mortality due to cancer worldwide\(^1\). Incidence of EC varies widely across the world, with age-standardized rates (ASR) per 100 000 as low as 1.4 in Western Africa to over 20 in Southern Africa and in Eastern Asia\(^1\). Iran is on average an intermediate risk country, with ASRs around 7 for men and women\(^1\), but some parts of Iran are located in the high incidence Asian EC belt, with reported ASRs of as high as 100\(^2\).

Despite some improvements in treatment modalities of EC, its prognosis remains poor, even in developed countries. However, there is wide variation in reported survival rates. Five-year survival rate is estimated to be 13.6\% in the United States\(^3\), 8.0\% in England and Wales\(^4\), and below 5\% in developing countries including China (3.3\%)\(^5\) and Iran (around 0.8\%)\(^6\).

The overall low survival rate for esophageal cancer apart from aggressive behavior of the disease could possibly be related to the effectiveness of current treatments, so investigating the influence of treatment factors on survival is important. Surgery is an integral part of the localized EC treatment to obtain locoregional control and long-term survival. However, while performing esophagectomy, surgeons should apply the principles of “adequate cancer surgery (ACS)”, including en-bloc resection (free proximal and distal margins, circumferential resection margin (CRM)) and formal lymphadenectomy. ACS is believed to lower short-term mortality and morbidity rates, and use of neoadjuvant therapy could improve long-term survival\(^7\).

To the best of our knowledge, no population-based studies have been conducted to address the issues mentioned above in Iran. In this paper, we report on demographic, clinicopathological features, survival rates and predictors of EC survival in Iran with emphasis on the quality of surgery in patients with EC in a nationwide study.
Patients and methods

Patient selection and data collection

To obtain a nationally representative sample, we used simple random sampling to select newly-diagnosed EC patients from those who were registered in the 2005–2006 national cancer registry (NCR) databases. A detailed description of the nationwide pathology-based cancer registry of Iran is provided elsewhere. All patients had EC diagnosis confirmed by pathology. Of the 3048 new EC cases registered in NCR in 2005–2006, a total 409 cases were randomly selected for this study.

We followed the patients from the date of diagnosis until the date of death or the end of follow-up in 2009, whichever came first. We interviewed the patients or close relatives. We also interviewed the local health workers who are usually aware of and register the vital status of people living in the population under the coverage by the local health house.

We obtained the information on vital status (dead/alive), date of death, and type of treatment. The five most common treatment groups for EC patients in 2005–2006 were: 1) no oncologic treatment; 2) esophagectomy alone; 3) chemoradiotherapy or radiotherapy; 4) esophagectomy plus chemoradiotherapy or radiotherapy; 5) chemotherapy plus esophagectomy or only chemotherapy.

To evaluate the adequacy of surgery, we further studied pathology reports of 252 patients that were selected by cluster-random sampling from 39 pathologic centers throughout the country. Histological types of tumor, i.e., squamous cell carcinoma (SCC) or adenocarcinoma (AC); tumor location (upper, middle, lower thoracic and cervical); local tumor extension, involvement of the proximal, distal margin and CRM; and number of the dissected and number of positive lymph nodes (LN) were obtained from the pathology reports by an expert panel in Cancer Institute of Iran.
The Research Ethics Committee of Tehran University of Medical Sciences approved this study.

**Statistical Methods**

We estimated the median ± standard deviation (SD) survival using the descriptive statistics. Kaplan-Meier method was used to estimate 1 to 3 years survival rate of EC in overall and stratified by age and type of treatments. We used the log-rank tests to study the differences in the survival rates of different categories. We used Cox proportional hazards model to study the crude and adjusted relative risks and corresponding 95% confidence intervals (CI) of demographic and clinical factors on the mortality of EC. In all cases, two-sided P<0.05 was considered statistically significant. We used SPSS standard statistical software for the data analyses (SPSS, version 17.0; SPSS Inc, Chicago, Illinois).
Results

Patient characteristics

A total of 409 EC patients (235 men, 174 women) participated in this study. The mean (±SD) age at the time of diagnosis for these patients was 65.0 (±12.1) years; men were significantly older (66.9 years) than women (62.4 years) (p<0.001). Median survival (25th–75th percentile) for all patients was 8.5 months (3–24 months), therefore 25% of patients survived less than 3 months, half survived less than 8.5 months, and 75% survived less than 2 years. Proportions of patients who survived through the end of the first, second, and third year were 44.0%, 25.0%, and 15.0%, respectively.

Table 1 shows survival for different age and sex group and the five main treatment groups. Median survival time was 6, 6, 11, 12, and 8 month for those who were in treatment groups 1 to 5, respectively. Although survival was low in all groups, the highest survival time was observed among patients who underwent definite chemoradiotherapy (dCRT). Figure 1 illustrates the overall survival curve of EC and by different treatment groups.

After adjusting for age and sex of the patients, in comparison with those who did not receive any oncologic treatment, patients who underwent esophagectomy alone (group 2) had a slightly and non-significantly lower risk of mortality (HR=0.86; 95% CI: 0.61-1.20). It is noteworthy that the hospital mortality was 27.8% among the operated patients. The 1 and 3-year survival rate of patients in this group who survived after 30-day were 55.0% and 26.0%, respectively and the median survival time was 13 months (38.0%, 18.0% and 6 month in all of this group, respectively. However, being in treatment groups 3 and 4, compared with group 1, both were associated with 40.0% (HR=0.60; 95% CI: 0.43–0.84) and 30.0% (HR=0.70, 95% CI: 0.50–0.99) lower risk of death.
The main pathologic characteristics of 252 patients with EC are shown in table 2. Evaluation of the pathological reports showed that 86.1% and 5.6% of patients were SCC and AC, respectively; 1.2% had other histological types; and 7.1% of patients had report of carcinoma without adequate information regarding the types of tumor.

In 52.4% of patients, the CRMs of the tumor were involved, while in 40.7% of patients, the margin involvement status was not evaluated by the treatment groups. The free CRMs were documented only in 6.8% of the patients (16.5% of the reported cases). Proximal and distal margins were free in 52.8% of the patients. One or both sides were involved in 7.2% of the cases; meanwhile proximal and distal margins of the specimen were not assessed in 40.1% of patients by the treatment groups at all.

In 47.6% of the specimens, one to 14 LNs were found and in 48.4% of the cases, no LNs were dissected during the surgery. Only in 4.0% of cases, 15 or more LNs were dissected, which is the recommended number of LN dissection in the esophageal resection.9

The average (±SD) longitudinal lengths of tumors were 4.2 (±1.8) centimeter (cm) and the majority of the tumors (48.1%) were located in the lower third of the esophagus.
Discussion

EC, a highly fatal malignancy, has an overall 5-year survival of 10.0%-13.0%, and even shorter survival periods have been reported in less developed countries. In Iran, EC is the 6th most common cancer (approximately 5.0% of total) overall. A few studies from high incidence areas in Iran have estimated the 5-year survival for this cancer to be around 0.8%-4.0%, although these rates are not obtained from population-based tumor registries.

In this study, the overall median survival for esophageal cancer was 8.5 months, which is almost similar to numbers reported from other developing countries. Median survival in Iran seems to be slightly less than those reported from high-income countries, according to population-based studies (9.2 months in the United States, 11.7 month in England), although these differences are not substantial. Also, 1-, 2-, and 3-year survival rates of 44.0%, 25.0%, and 17.0%, respectively, are only slightly lower than those reported from Sweden, which were 51.0%, 27.0%, and 19.0%, respectively. These data are also consistent with other studies conducted in developed countries that reported similar survival rates for EC cases in the general population. However, it should be noted that 5-year survival rate up to 40.0%-55.0% have also been reported for EC; although these outcomes are arisen from the centers with high quality cares. It should be noted, these reports should not be considered as a reference to be compared with population-based studies.

In this population-based study, the median survival time in “esophagectomy alone” group without any other neoadjuvant or adjuvant treatment was 6 months, as 1- and 3-year survival rate were 38.0% and 18.0%, respectively. A population-based study in Sweden, revealed 58.7% and 35.0% for 1- and 3-year survival rate of esophagectomy alone, respectively. In another population-based study from United States, the median and 3-year overall survival rate of similar group was 18 months and 30%, respectively; so the survival rate of surgery
alone group in Iran is significantly lower than developed countries despite slightly lower survival rate for all patients.

In comparison with other population-based studies that have reported the operative mortality rate following surgery within 30 day of 5.0% to 10.0%, findings of this study (30.3%, combined hospital and 30 day mortality and 27.8%, in-hospital mortality) were appalling high. In fact, it is supposed that low median survival time after esophagectomy is probably related to high perioperative mortality rate in this group. The 1and 3 year survival rate of patients in this group who survived after 30 day were 55.0% and 26.0%, respectively and the median survival time was 13 months (38.0%, 18.0% and 6 month in all of this group, respectively). The 30 day very high mortality rate after esophagectomy in this observational study is likely related to improper patient selection criteria, inappropriate preoperative preparation, insufficient surgical skills and poor postoperative cares.

The effects on survival of CRMs involvement in patients with operated EC are well recognized, and regarded as a highly significant predictor of local recurrence, poor prognosis, and decreased survival rate. Therefore, CRMs could serve as a requirement for better local treatment, as a useful quality indicator of surgery\textsuperscript{21}. The CRMs were involved by tumor in 52.4% of esophagectomy procedure in this study. The free CRMs were documented only in 6.8% of the cases and the treatment group did not evaluate the CRMs margin involvement status in remaining of patients at all. On the other hand, proximal and/or distal margins were involved in 7.2% of the cases, while they are free in 52.8% of the patients. These margins of the specimen were not assessed in 40.1% of patients by the treatment teams. Although up to 87.0% rate of R0 resection has been reported in some esophagectomy series\textsuperscript{20}, it should be noted 40.0% of enrolled patients did not have complete resection of all gross disease and negative resection margins in a US Intergroup randomized controlled trial\textsuperscript{22} and 47.0% did
not have gross total resection with negative margins in a trial conducted by the Medical Research Council\textsuperscript{23}.

Most investigators believe that greater extent of lymphadenectomy was associated with increased survival for EC patients\textsuperscript{24} and was an independent predictor of survival after esophagectomy\textsuperscript{16}. Utilizing the Surveillance, Epidemiology and End-Results (SEER), overall and disease-free survival rate were also significantly longer in patients who had 30 or more LNs examined than the other groups\textsuperscript{24}. On the other hand, Hu Y, et al\textsuperscript{25} found that for advanced EC, if the number of resected LNs is less than 6, an occult positive regional LN might be missed. The National Comprehensive Cancer Network (NCCN) emphasizes on resection and examination of at least 15 LNs to achieve adequate staging of EC\textsuperscript{9}. In the current study, only 4.0\% of cases had experienced enough dissection of LNs 15 or more. In 27.4\%, 15.1\% & 5.2\% of cases 14, 59 & 1014 LNs were dissected, respectively; whilst no LNs was found in surgical specimen of 48.4\% of the patients.

"The only area of complete agreement in the appropriate surgical therapy of EC is that esophagectomy should not be performed if an R0 resection is not possible. In other words, if the surgeon does not believe he or she can remove all LNs invaded by cancer and provide a tumor-free radial margin and esophagus margins that are tumor free, then a resection should not be performed" pointed in the main textbook of surgery in Iran\textsuperscript{26}, but results of this study indicate that surgery with curative intention has not been performed for most EC patients in Iran.

This survey is an observational and non-randomized study, so the results cannot be used to compare different treatment modalities. Attention should be paid that the results of treatment options in community level and in different countries may vary substantially with referral and high quality care centers. Likewise, these results may differ with data obtained from clinical trials. As it is shown in table 1, the best survival rates were significantly higher in groups 3
and 4 ("chemo-radiotherapy or radiotherapy" and "esophagectomy plus chemo-radiotherapy or radiotherapy"). Surgery was the standard treatment of esophageal cancer at the time of patients’ registration, so one can argue patients who had refused surgery or those who had been considered high risk for surgery had been referred for treatment groups 3. Treatment groups 3 and 4 were not significantly different in terms of survival, raising the question whether addition of surgery to chemo-radiotherapy or radiotherapy could be effective or not in this setting.

This study has been carried out for the first time in Iran and to the best of our knowledge in other developing countries. Appropriate follow-up of patients in a national setting is a major strength of the study. The other strength of this study is evaluation of adequacy of esophageal cancer surgery in a national level by an expert panel in Cancer Institute of Iran.
**Limitation**

In Iran, cancer registry is in the early stages of its serving and the active and proper system of patient information records does not exist, so implementation of population-based studies with the appropriate follow-up is very difficult. The current survey has its own limitations, in addition to the intrinsic restrictions of such studies. Due to the lack of enough data, staging of tumors was not available in different subgroups of patients. Additionally, because of follow-up limitations and the type of primary design, survival rates in different surgical groups (with regard to ACS) have not been investigated. On the other hand, because of performing inadequate surgery in the most cases (which lead to limited access to appropriate staging data), comparison of different stage groups has not been possible.
Conflicts of interest: The authors have declared no conflicts of interest.
References


9 Esophageal and Esophagogastric Junction Cancers, National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology; available at:


Table 1: Survival by age group, gender, and therapy received among randomly selected esophageal cancer patients diagnosed in 2005-2006 in Iran

<table>
<thead>
<tr>
<th>Demographics data</th>
<th>Number (%)</th>
<th>Survival (months); Median (95% CI)</th>
<th>P Value*</th>
<th>Survival % + (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Demographics data</strong></td>
<td></td>
<td></td>
<td>59</td>
<td>37</td>
</tr>
<tr>
<td><strong>Age group (years)</strong></td>
<td></td>
<td>0.01</td>
<td>12.0 (9.9-14.1)</td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>49 (12.2)</td>
<td>12.0 (9.9-14.1)</td>
<td>59</td>
<td>37</td>
</tr>
<tr>
<td>50-60</td>
<td>89 (22.1)</td>
<td>13.0 (8.8-17.2)</td>
<td>53</td>
<td>31</td>
</tr>
<tr>
<td>61-70</td>
<td>115 (28.5)</td>
<td>9.0 (7.1-10.9)</td>
<td>41</td>
<td>23</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>150 (37.2)</td>
<td>6.0 (4.6-7.4)</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>235 (57.5)</td>
<td>10.0 (8.3-11.7)</td>
<td>48</td>
<td>26</td>
</tr>
<tr>
<td>Female</td>
<td>174 (42.5)</td>
<td>8.0 (6.5-9.5)</td>
<td>39</td>
<td>24</td>
</tr>
<tr>
<td><strong>Therapy received</strong></td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No oncologic treatment</td>
<td>86 (21.0)</td>
<td>6.0 (4.5-7.5)</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Esophagectomy alone</td>
<td>79 (19.3)</td>
<td>6.0 (3.1-8.9)</td>
<td>38</td>
<td>27</td>
</tr>
<tr>
<td>Chemo-radiotherapy or radiotherapy</td>
<td>87 (21.3)</td>
<td>11.0 (8.3-13.7)</td>
<td>49</td>
<td>32</td>
</tr>
<tr>
<td>Esophagectomy plus chemo-radiotherapy or radiotherapy</td>
<td>92 (22.5)</td>
<td>12.0 (9.5-14.5)</td>
<td>53</td>
<td>32</td>
</tr>
<tr>
<td>Chemotherapy plus esophagectomy or only chemotherapy</td>
<td>53 (13.0)</td>
<td>8.0 (4.9-11.1)</td>
<td>42</td>
<td>17</td>
</tr>
</tbody>
</table>

CI: Confidence Interval,
* Univariable log-rank,
* Raw percentage of respective subgroups
**12 cases received none of these treatments
Table 2: Histopathological Characteristics of the 252 Patients with esophageal cancer patients

<table>
<thead>
<tr>
<th>Pathologic findings</th>
<th>Number (% of 252)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Circumferential resection margin</strong></td>
<td></td>
</tr>
<tr>
<td>Free</td>
<td>17 (6.8)</td>
</tr>
<tr>
<td>Involved</td>
<td>132 (52.4)</td>
</tr>
<tr>
<td>Not evaluated by treatment group</td>
<td>103 (40.7)</td>
</tr>
<tr>
<td><strong>Margin involvement status</strong></td>
<td></td>
</tr>
<tr>
<td>Both sides free</td>
<td>133 (52.8)</td>
</tr>
<tr>
<td>Proximal side involved only</td>
<td>10 (4.0)</td>
</tr>
<tr>
<td>Distal side involved only</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Both sides Involved</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Not evaluated by treatment group</td>
<td>101 (40.1)</td>
</tr>
<tr>
<td><strong>No. of Dissected Lymph Node; Median (range)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>122 (48.4)</td>
</tr>
<tr>
<td>1-4</td>
<td>69 (27.4)</td>
</tr>
<tr>
<td>5-9</td>
<td>38 (15.1)</td>
</tr>
<tr>
<td>10-14</td>
<td>13 (5.2)</td>
</tr>
<tr>
<td>≥ 15</td>
<td>10 (4.0)</td>
</tr>
<tr>
<td><strong>No. (%) of Lymph Node Involvement in dissected group</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>73 (56.1)</td>
</tr>
<tr>
<td>1</td>
<td>31 (23.8)</td>
</tr>
<tr>
<td>2-3</td>
<td>20 (15.3)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>6 (4.1)</td>
</tr>
</tbody>
</table>