Esophageal cancer in India: Current Status and Future Perspectives

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Abstract

Esophageal cancer is the fourth common cause of cancer-related deaths in India. It is prevalent among both men and women. Squamous cell carcinoma (SCC) accounts for up to 80% of these cancers, although adenocarcinoma is on the increase due to changing lifestyles. The etiological factors for SCCs show a regional variation in different parts of India, but tobacco consumption in various forms, alcohol, hot beverages, and poor nutrition remain the predominant predisposing factors. Generally, these cancers present late and therefore have a poor prognosis. The current status of esophageal cancer in India in relation to the demographics, diagnosis, staging, multimodality treatment, surgical therapy, and the future perspectives are discussed in this review article.

Keywords: Carcinoma, current status, demographics, esophagus, India

INTRODUCTION

Worldwide, esophageal cancer is the eighth most common cancer with an annual incidence of 456,000 new cases. In India, it is the fourth most common cause of cancer-related deaths. There has been a significant increase in the incidence of esophageal cancer worldwide. Much regional variation exists in the incidence and pathology of esophageal cancer [Figure 1]. It has been reported that in countries with higher human development index (HDI), there is a higher incidence of adenocarcinoma (AC) of the esophagus.\(^1\) For example, in the US, the incidence of AC of the esophagus has increased by over 400% over the past 25 years.\(^2\) In contrast, in countries with low HDI, like India, there is a higher incidence of esophageal squamous cell carcinoma (SCC). Currently, SCC is the most common type of esophageal cancer in the Indian subcontinent and the most common location is the distal third of the esophagus.\(^3\) Approximately, 47,000 new cases are reported each year and the reported deaths reach up to 42,000 each year in India.\(^4\)

NATIONAL CANCER REGISTRY PROGRAMME

The National Cancer Registry Programme (NCRP) instituted by the Indian Council of Medical Research (ICMR) periodically publishes cancer statistics from registries across India. The latest publication is a report from 27 Population-Based Cancer Registries in the country. This publication has information on cancer incidence and mortality in the community covering 10% of the country’s population. Although the coverage is still low, it gives a fair idea of the pattern of cancer incidence emerging in various regions or parts of the country.\(^5\)

“Age-adjusted incidence rates” or age-standardized rate per 100,000 population are the two indices used to compare the incidence of cancer across registries. The Northeast registry tops the chart in relation to carcinoma of the esophagus, for both men and women. Cancer of the esophagus is the leading site in the registries in the states of Assam, Meghalaya, Mizoram, and Nagaland.\(^5\) The Kashmir valley is yet another high incidence area in the country. Estimates about the expected number of cancers are useful to plan and prioritize health care services. In a developing country like India, it also aids formulating government policies and appropriate allocation of resources. Table 1 shows the projected increase in number of cancers in India for selected sites between 2015 and 2020 for both sexes.\(^3\)

DEMOGRAPHICS

Population-based data suggest that esophageal cancer incidence peaks in the sixth decade in most parts of the world.\(^6\) The same trend has been reported in India, with the mean...
age in women slightly earlier than in men. SCCs are twice as common in men compared to women.

ACs again affect men more commonly than women, but the mean age is significantly lower, in the fourth decade of life. Esophageal AC has been reported to show a significant increase in the developed countries. The highest annual increase (10% per year) has been reported from the USA. Among the Asian countries, China and Singapore have also reported an increasing number of esophageal AC.

A retrospective study published in 2007 looked at the trends in histology and site-specific distribution of esophageal malignancy between 1989 and 2004 in the state of Tamil Nadu in the Indian subcontinent. This study concluded that esophageal SCC remained the most common esophageal malignancy. In contrast to reports of increasing incidence of esophageal AC from several countries worldwide, there was no such trend seen in our country. This was irrespective of the site, age, or gender.

More recent data from the author’s institute (Christian Medical College Hospital, Vellore), comprising of the 138 patients who underwent resectional surgery for esophageal cancer over the 7-year time period from 2010 to 2016, revealed the following. SCC was the most common histology (105 patients), as compared to AC (33 patients). The mean age was 52 years, mean body mass index was 21.5, and the male:female ratio was about 3:1. Most common geographical region in this cohort was the East and Northeast India (92 patients), followed by the South (36 patients) and the North (10 patients)

Table 1: The projected increase of cases for the 10 most common malignancies

| ICD-10 | Site name | Year 2015 | Year 2020 |
|--------|-----------|-----------|-----------|
| C1–C2  | Tongue    | 60,333    | 81,200    |
| C3–C6  | Mouth     | 89,645    | 128,451   |
| C12–C13| Hypopharynx| 19,700    | 20,948    |
| C15    | Esophagus | 49,059    | 53,898    |
| C16    | Stomach   | 44,998    | 54,108    |
| C18    | Colon     | 37,435    | 51,906    |
| C19–C20| Rectum    | 36,290    | 46,427    |
| C22    | Liver     | 36,255    | 49,844    |
| C23–C24| Gallbladder| 37,561    | 55,141    |
| C32    | Larynx    | 33,642    | 39,636    |

ICD=International Classification of Diseases

Table 2: Characteristics of patients that underwent esophageal resectional surgery at Christian Medical College, Vellore (2010-2016)

| Characteristics                                      | Value         |
|------------------------------------------------------|---------------|
| Total number of patients                              | 138           |
| Mean age, years                                      | 51.7          |
| Male:female                                          | 99:39         |
| Mean BMI, kg/sq.metre                                 | 21.5          |
| East/Northeast: South: North India                   | 92:36:10      |
| SCC:adenocarcinoma                                    | 105:33        |
| Middle:lower:GEJ                                      | 50:55:33      |
| Stage 1:Stage 2:Stage 3                               | 2:40:96       |
| McKeown’s:Ivor Lewis                                  | 107:31        |
| Minimally invasive esophagectomy (%)                  | 80:138 (58)   |
| pCR seen with NACRT (%)                               | 43:84 (51)    |

SCC=Squamous cell carcinoma, BMI=Body mass index, GEJ=Gastro esophageal junction, pCR=Complete pathological response, NACRT=Neoadjuvant chemoradiotherapy

Risk Factors

The major risk factors for SCC esophagus include poor nutritional status, low intake of fresh fruits and vegetables, consumption of hot beverages, excess tobacco and alcohol consumption, and possibly human papillomavirus infection. Understanding the etiology of esophageal cancer could inform interventions for primary prevention of this disease. Published data from different regions in India have indicated their observations on the local risk factors. For example, in
the northern state of Kashmir, smoking (hookahs), snuff, sundried spices and vegetables, hot salted tea with baking soda, and red chilies have been implicated as risk factors.\textsuperscript{[12]} ICMR data indicate a very high incidence of cancers in general and tobacco-related cancers in particular, in the northeastern region. The proportion of tobacco-related cancers relative to all sites is highest in Assam and Meghalaya. Pattern of tobacco use in Northeast India is different from the rest of the nation. The bidis and cigarettes available locally are different from the main land. Another publication from Ludhiana, Punjab, looked at the risk factors of esophageal SCC in women (who generally neither smoke nor consume alcohol). Poor nourishment and consumption of hot beverages were found to be linked to SCC carcinogenesis in this study.\textsuperscript{[13]}

The risk factors for AC esophagus include smoking, alcohol, obesity, chronic gastroesophageal reflux disease, and the presence of Barrett’s esophagus.

**Genetic Factors**

Notwithstanding the differences in demographics and putative etiological factors, genetic alterations have been consistently observed in esophageal SCC. These include (i) alterations in tumor suppressor genes, specifically p53; (ii) disruption of the G1/S cell cycle checkpoint and loss of cell cycle control; and (iii) activation of proto-oncogenes leading to deregulation of cellular signaling cascades. The most common gene alterations associated with esophageal SCCs are summarized in Table 3.\textsuperscript{[14‑17]}

**Diagnostic and Staging Investigations**

The clinical utility of a barium contrast study in the diagnosis of dysphagia is questionable. Moreover, there is a danger of a “normal” barium swallow missing an early esophageal mucosal lesion. However, it may be useful in a few instances such as to assess the length of the lesion (particularly in stricturing lesions not allowing passage of a scope) and to assess extraesophageal spread (axis deviation, sinus, fistula).

The upper gastrointestinal (GI) endoscopy remains the preliminary investigation of choice in a patient with dysphagia. What is the optimal number of biopsies that need to be taken for adequate diagnosis? In a small study attempting to answer this question, eight biopsies were performed. The first two specimens were diagnostic in 95.8% cases, and the yield incrementally increased to 100% with fifth and sixth specimens.\textsuperscript{[18]} A number of Indian studies have been published regarding the cytological diagnosis of esophageal cancer. Cytopathological correlation was found in about 80% cases, which raises the possibility of using brush cytology for screening and rapid diagnosis with minimal patient discomfort.\textsuperscript{[19]}

A contrast-enhanced computed tomography (CECT) scan of the thorax and upper abdomen is widely accepted as the preferred modality of staging for cancer of the esophagus in the Indian setting. It is highly effective in the assessment of the T stage, invasion of surrounding structures, and distant metastases. However, it is less useful in the assessment of nodal involvement.\textsuperscript{[20]}

Endoscopic ultrasound (EUS) helps to delineate the various layers of the esophagus and can be used in conjunction with the CT scan. It is very useful in early lesions, in particular early mucosal lesions that can be resected endoscopically. With regard to locoregional staging of tumor invasion and lymph nodal involvement, it is superior to CECT scan. However, an EUS may not be technically feasible in obstructive growths. Therefore, the routine use of EUS is debatable in the Indian setting, because of the advanced nature of disease at presentation as well as its limited availability in many centers. EUS only has a limited role in restaging after neoadjuvant therapy, because it cannot reliably differentiate between fibrosis and residual or recurrent disease.

Positron emission tomography (PET) provides additional staging information, especially when combined with a CT (PET-CT) and is the best modality for detecting distant metastasis. In a study by Duong et al., a PET-CT changed the clinical management from either curative to palliative or vice versa in 40% patients.\textsuperscript{[21]} A similar finding has been published from Tata Memorial Hospital, Mumbai, where a PET-CT detected unsuspected metastatic disease in 16% patients.\textsuperscript{[22]} The practical difficulties in routine use of PET-CT in a country like ours are the cost, availability, and the high false-positive rate due to infections such as tuberculosis. However, most major centers in the country have included this investigation as part of the routine preoperative workup.

**Multimodality Treatment**

India has been late to embrace multimodality treatment for esophageal carcinoma. This may be because of the fact that the concept of a multidisciplinary team is still not

| Table 3: Gene alterations reported in esophageal squamous cell carcinoma |
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| **Gene symbol** | **TP53** | **NOTCH 1** | **PIK3CA** | **CDKN2A** | **CCND1** | **FAT1** |
| Chromosomal location | 17p13.1 | 9q34.3 | 3q26.3 | 9p21.3 | 11q13 | 4q35.2 |
| Gene alteration frequency (%) | Song et al.\textsuperscript{[14]} | 83 | 9 | 5 | 5 | 5 |
| | Lin et al.\textsuperscript{[15]} | 60 | 8 | 7 | 3 | 46 |
| | Gao et al.\textsuperscript{[16]} | 93 | 14 | 9 | 8 | 33 |
| | Zhang et al.\textsuperscript{[17]} | 88 | 21 | 17 | 8 | 64 | 15 |
The results of table 2. A total of 138 patients underwent resectional surgery for carcinoma esophagus in this time period. The majority of patients were in stage 3 at presentation. Patients with early tumor (T1 or T2 with NO) are treated with upfront surgery, while patients with advanced disease (T3 or T4 or N+) are treated by neoadjuvant therapy (NACRT/NACT) before surgery. The default option is NACRT for patients with SCC esophagus and NACT for AC esophagus. The pCR seen after NA therapy of 50% is indeed very encouraging.

The preferred choice of surgery is a transthoracic approach by the minimally invasive technique. Of the 138 resections, 80 (58%) were done by the minimally invasive approach. At our center, the minimally invasive approach was initiated in the year 2012 and was initially used selectively. The results

**Minimally Invasive Surgery**

Minimally invasive surgery (MIS) for the esophagus is performed at many centers in India, and there is published data from such high volume centers. The results of MIS are comparable to open surgery with respect to lymph nodal yield, duration of surgery, blood loss, and morbidities. However, the long-term survival data have not been published in these studies, but should be available in the near future. There are three different positions for MIS surgery – prone, lateral, and semi-prone, based on the surgeon’s preference. The author’s preferred position is the semi-prone approach, which combines the advantages of both the prone and lateral position.

Robotic surgery for the esophagus is at its initial phase in India, with a few centers reporting small case series. However, there is no distinct advantage over thoracoscopic surgery that has been demonstrated in these publications. The cost of robotic surgery is again an impediment for it to be practiced more widely in India.

**The Christian Medical College Hospital, Vellore Experience**

The 6-year experience (2010–2016) at the author’s institution is summarized in Table 2. A total of 138 patients underwent resectional surgery for carcinoma esophagus in this time period. The majority of patients were in stage 3 at presentation. Patients with early tumor (T1 or T2 with NO) are treated with upfront surgery, while patients with advanced disease (T3 or T4 or N+) are treated by neoadjuvant therapy (NACRT/NACT) before surgery. The default option is NACRT for patients with SCC esophagus and NACT for AC esophagus. The pCR seen after NA therapy of 50% is indeed very encouraging.

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were very encouraging, and currently, all patients undergo thoraco-laparoscopic minimally invasive esophagectomy. A two-field lymphadenectomy is done as the standard. The preferred conduit is stomach, and the preferred route of transposition is the posterior mediastinum.

**Future Perspectives**

Even though cancer registries under the NCRP have provided high-quality data on cancer occurrence, currently, the National Cancer Registry covers only 7% of the country’s population. This needs to be improved, and the data which will then be more robust and comprehensive can be used for estimation of disease burden for the country, establishment of management facilities, as well as developing strategies to combat cancer at a national level.

In the future, the molecular analysis of esophageal cancer cells will uncover key genetic and epigenetic alterations underlying the initiation and progression of tumors. These discoveries will pave the way for the development of targeted treatments for esophageal cancer.

Minimally invasive techniques are here to stay. Minimally invasive esophagectomy has been proven to be noninferior to open surgery in terms of oncological safety and is clearly beneficial to the patient in terms of postoperative recovery. We are due to see major strides in minimally invasive and robotic surgery in the country.

Multimodality treatment involving the treating surgeon, gastroenterologist, oncologist (medical and radiotherapy), radiologist, pathologist, and palliative care physicians needs to become the standard of care across the country. This is the way forward in the management of this disease, not only in improving the results of therapy but also in improving the quality of life of patients affected by this malignancy.

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**Conflicts of interest**

There are no conflicts of interest.

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