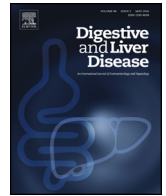




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### Review Article

# Prognostic factors in esophageal cancer treated with curative intent

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### ABSTRACT

The overall prognosis of patients with esophageal cancer has improved in recent decades due to surgical and medical progress, but overall survival remains poor. Better patient selection and tailored treatment are needed. Different prognostic factors linked with the patient, tumoral characteristics and treatment with curative intent have been identified and are the purpose of this review. Tumor detection at an earlier stage, the advent of new molecules and therapeutic combinations, and the centralization of management in high-volume centers should help to improve the prognosis of esophageal cancer. Improved imaging techniques and a better prediction strategy should guide future treatments.

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## 1. Introduction

Esophageal cancer ranks 6th among all cancers in mortality and 8th among the causes of cancer worldwide [1]. The prognosis of esophageal cancer remains globally poor due to the advanced stage at time of discovery, severe malnutrition induced by the digestive obstruction, and the background in which it usually occurs [2].

Surgery with perioperative treatment is the gold standard treatment for resectable esophageal cancer, and exclusive chemoradiotherapy (CRT) is an alternative for squamous cell carcinoma.

There was a significant improvement in overall survival (OS) at 5 years in the European registers (EUROCARE) from 5% in the years 1978–1980 to 9% in the years 1987–1989 [3], and a survival rate of 12.3% [4] was observed during the period of 1995–1999 in the EUROCARE-4 study. In France in the EUROCARE-5 study, the 5 year OS was 13.9% and 30% for patients who survived the first year (conditional survival) [5] and potentially reached 50% in the surgical series [6]. However, the 5-year OS rate in adenocarcinoma remains below 20% [7].

The main purpose of this review was to summarize the main prognostic factors of thoracic esophageal cancer after curative intent treatment as a guide for daily clinical practice according to the best evidence. The primary known predictive factors in esophageal cancer treated with curative intent are listed in Table 1.

## 2. Clinical prognostic factors

### 2.1. Malnutrition

Malnutrition, which is defined as a weight loss of more than 10% over the last 6 months, constitutes a major pejorative prognostic factor from the initial assessment and determines the response to CRT treatment and survival [8]. Food supplementation should be considered according to the clinical and biological nutritional balance as well as the calculation of the daily calorie intake with the intake aim of approximately 30 kcal/kg/day for patients confined to bed and 35 kcal/kg/day for ambulatory patients [9]. Dietetic advice, which is considered as the first line option, is not sufficient for malnourished patients, and artificial nutrition, as perioperative nutritional support, should be considered [9]. Enteral nutrition is recommended when the gastrointestinal tract is functional as it has superior efficacy, lower morbidity rates, and lower costs compared to parenteral nutrition [10–12].

In the case of expected duration of enteral nutrition of less than 2–3 weeks, a nasogastric or nasoenteric tube is proposed. How-

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**Table 1**  
Known prognostic factors in oesophageal cancer treated with curative intent.

	Negative prognostic factors on overall survival
Clinical factors	Malnutrition [8] Body mass index >30 kg m <sup>2</sup> in never smoker patients [18] Male sex [21] Charlson morbidity index of 2 or more [22] Previous myocardial infarction [22] Congestive heart failure [22] Tumor location in upper third of the oesophagus [25]
Socio-economic factors	Low socio-economic status [26] Residing in rural area [26]
Histological factors	Squamous cell carcinoma [27] Signet ring cells [28] Advanced tumor stage [27] Absolute number of invaded lymph nodes ≥4 [29] Ratio of invaded lymph nodes ≥0.2 [29] Number of harvested lymph nodes <23 [49] Capsular rupture [29]
Molecular imaging factor	MTV with a least 20% of SUV max ≥40 mL at pretherapeutic positron emission tomography [32]
Neoadjuvant treatment	Grade III/IV treatment toxicity [39] Pretherapeutic prosthesis [57]
Surgical factors	Incomplete resection [45] Transhiatal esophagectomy [51,52] Anastomotic leak [55] Low volume center [40,56]
Exclusive CRT factors	Age >65 years, WHO status >2, mediocre response to treatment [58] Malnutrition [59]
Salvage surgery after exclusive CRT	Previous radiotherapy dose ≥55 Gy [61] Low volume center [61]

MTV: metabolic tumor volume, SUV: standard uptake value, CRT: chemoradiotherapy, WHO: World Health Organisation.

ever, for duration of more than 2–3 weeks, direct access to the bowel is recommended through a gastrostomy or jejunostomy for esophageal cancer [13,14].

Despite surgical reluctances, many reports have shown that percutaneous esophageal gastrostomy or percutaneous radiological gastrostomy in esophageal cancer is safe and does not compromise the stomach or esogastric anastomosis without risk of tumoral dissemination [15–17].

In malnourished patients, perioperative immunonutrition is recommended and is more efficient than standard nutrition and preoperative immunonutrition alone [9].

## 2.2. Body mass index and tobacco

A study on 778 patients operated on for esophageal adenocarcinoma has shown that body mass index and smoking status (ever or never smoker) are associated with prognosis. Among never smokers, obesity is associated with a doubling of the adjusted overall mortality risk (HR 1.97; 95% CI 1.24–3.14) compared to normal weighted patients, while obesity had no prognostic influence on smokers [18].

## 2.3. Age and sex

Several studies have shown a lack of prognostic significance related to age. With similar treatment, survival is comparable in different age groups [19,20]. A recent American study has shown that female gender is a positive prognostic factor [21].

## 2.4. Comorbidities

The Charlson comorbidity index contains 19 parameters, each of which is weighted according to potential influence on mortality, and these parameters include diabetes with diabetic complications, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, mild and severe liver disease, hemiplegia, renal disease, leukemia, lymphoma, metastatic tumor, and acquired immunodeficiency syndrome, each of which was weighted according to their potential influence on mortality. A Charlson score of 2

or more is associated with an increase in postoperative and long-term mortality in esophageal cancer (HR 1.24; 95% CI 1.08–1.42), such as previous myocardial infarction (HR 1.23; 95% CI 1.01–1.49) and congestive heart failure (HR 1.31; 95% CI 1.04–1.67) [22].

## 2.5. Location of tumor

While post-treatment-specific survival for superficial esophageal cancer does not appear to be affected by tumor localization [23], several studies have identified tumor localization as an independent prognostic factor influencing survival for more advanced tumors [24]. Furthermore, the results of a large retrospective study have shown a 5-year OS rate of 33% for tumors of the upper third of the esophagus, 57% for the middle third and 66% for the lower third ( $p < 0.001$ ) [25].

## 3. Socio-economic factors

Certain socioeconomic factors may influence the prognosis in esophageal cancer patients, and the magnitude varies across populations. It has been shown that patients residing in rural areas have a higher incidence and worse prognosis than those in urban areas in developing regions. This phenomenon may be due to delayed access to care and, therefore, a diagnosis at a more advanced stage. Lower socio-economic status has also been associated with an increased incidence and reduced survival in esophageal cancer [26].

## 4. Histological prognostic factors

### 4.1. Histological type

Gravity related to the histological type, squamous cell carcinoma or adenocarcinoma remains a subject of controversy. According to population data, the prognosis of adenocarcinoma is hardly better than that of squamous cell carcinoma (HR = 1.15, NS) despite a greater probability of macroscopically and microscopically complete surgical resection (R0) [27]. Indeed, squamous cell carcinomas are mostly supracarinal and, therefore, are more rarely resected (R0).

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