

## Survival of patients after stent placement and chemotherapy in the treatment of esophageal cancer: A literature review

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### Abstract

Esophageal cancer is a disease that has a high mortality rate, and its main symptom is dysphagia, potentially requiring a stent placement. The performance of these patients is usually poor and the aim of this study is to analyze the survival of patients who underwent stent placement and chemotherapy. An integrative literature review in the National Library of Medicine and Cochrane Library databases was performed, using the descriptors “esophageal cancer” or “esophageal neoplasm” and “stent” and “chemotherapy”. Inclusion criteria were randomized and non-randomized clinical trials, between 1996 and 2022. Ten studies were included and information on the number of patients evaluated, tumor staging, histological subtypes and treatments prior to stent placement were gathered. The studies were heterogeneous and a systematic comparison was not possible, however there was a trend in patients who received systemic treatment +/- radiotherapy to have longer survival than patients which did not receive systemic treatment. Moreover, most studies report a small number of participants, and unparalleled comparisons. We concluded that survival data for patients who received stents and chemotherapy are scarce but this approach is possible for fit patients.

**Keywords:** Esophageal Neoplasms; Stents; Adjuvant Chemotherapy; Survival

### 1. Introduction

Esophageal cancer is associated with a limited prognosis. It is mainly represented by two main histological subtypes: adenocarcinoma and squamous carcinomas. In 2020, 572,000 new cases worldwide were estimated, with the incidence being twice as high in men as in women. Among all cancers, it is the seventh most common in men and the thirteenth most common in women. The highest incidence rates are found in countries such as China, Japan and the United Kingdom for both sexes. [1, 2]

Regarding mortality, in Brazil, in 2017, there were 6,647 deaths with a crude death rate of 6.58/100 thousand among men and 1,907 deaths with a crude rate of 1.84/100 thousand among women. Usually, patients receive late diagnosis and are not eligible to receive curative treatment. They may receive palliative treatment including anti-cancer therapies.

Malignant obstruction is a frequent consequence. The main complaint is dysphagia, present in more than 70% of patients with the disease, resulting in poor oral intake, weight loss and malnutrition. Symptom improvement options include feeding tube, ostomies, chemotherapy, radiotherapy and/or surgery. Another strategy is stent placement, the frequently chosen treatment for dysphagia in malignant diseases, as it promotes a quick and effective solution, restores permeability of luminal surface and, thus, improves oral intake and quality of life. [4-6]

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The procedure is commonplace in specialized centers with relative safety, but it can lead to acute, severe and late complications such as: esophageal bleeding, stent migration, aspiration, intense pain and fistula formation. In addition, several studies have reported that perforation during or shortly after stent placement can occur in less than 1% of patients, and it is more frequently in individuals previously treated with chemotherapy and/or radiotherapy. Mortality rates related to esophageal stent placement range from 3.9% to 27.2%. What is crucial to consider stent placement in case of esophageal cancer is not only the estimation of patient survival, but also the chance of complication in the procedure, in addition to anatomical issues. [7-10]

Stents are usually placed in patients with advanced stages of the disease and the prognosis even after the procedure is limited. On the other hand, there is no clear definition in the literature about which factors are prognostic for survival in patients undergoing stent placement. In a recent study, authors suggest that post-stent systemic treatment is associated with longer survival. [11] It is known that post-stent local radiotherapy does not offer improved survival and actinic esophagitis can occur in up to 28% of patients. On the other hand, very little is known about the survival related to systemic treatment in patients who received stents in trials. [6, 12-14]

Thus, this study was aimed at evaluating survival outcomes in patients who were selected to receive stent and chemotherapy.

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## 2. Methodology

We performed a bibliographic research, with a qualitative and descriptive approach through an integrative literature review using the National Library of Medicine (PubMed) and the Cochrane Library databases. The advanced search was used in the PubMed database by clicking on all fields and selecting the keywords in the following sequence: “((esophageal cancer) OR (esophageal neoplasm)) AND (stent) AND (chemotherapy)” with the Boolean operators “or” and “and”. The descriptors were used only in English. To prepare this literature review, the following steps were taken: topic selection; definition of eligibility parameters; definition of inclusion and exclusion criteria; verification of publications in databases; examination of the information found; analysis of the studies found and writing of the results [15]. After searching for the descriptors on the sites, inclusion and exclusion criteria were established. Search filters such as clinical trial and randomized controlled trial were applied. All original articles, clinical trials and randomized trials were included. In addition, articles published between 1996 and 2022 were included according to the inclusion criterion. Exclusion criteria were literature review articles, abstracts and meta-analysis. All articles that appeared in duplicate when selected by the inclusion criteria were excluded. Articles that did not match the context addressed, deviating from the topic about the survival of patients who received post-stent chemotherapy, were also excluded.

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## 3. Results

After associating all the descriptors in the databases accessed, 400 articles were found. 392 articles were found in the PubMed database and 8 articles in the Cochrane Library database. After applying the inclusion and exclusion criteria, 9 articles were selected in the PubMed database and 2 articles in the Cochrane Library, of which one was withdrawn because it was duplicated in both platforms, resulting in 1 article selected in the Cochrane Library, totaling 10 articles selected for the complete analysis, as shown in figure 1.

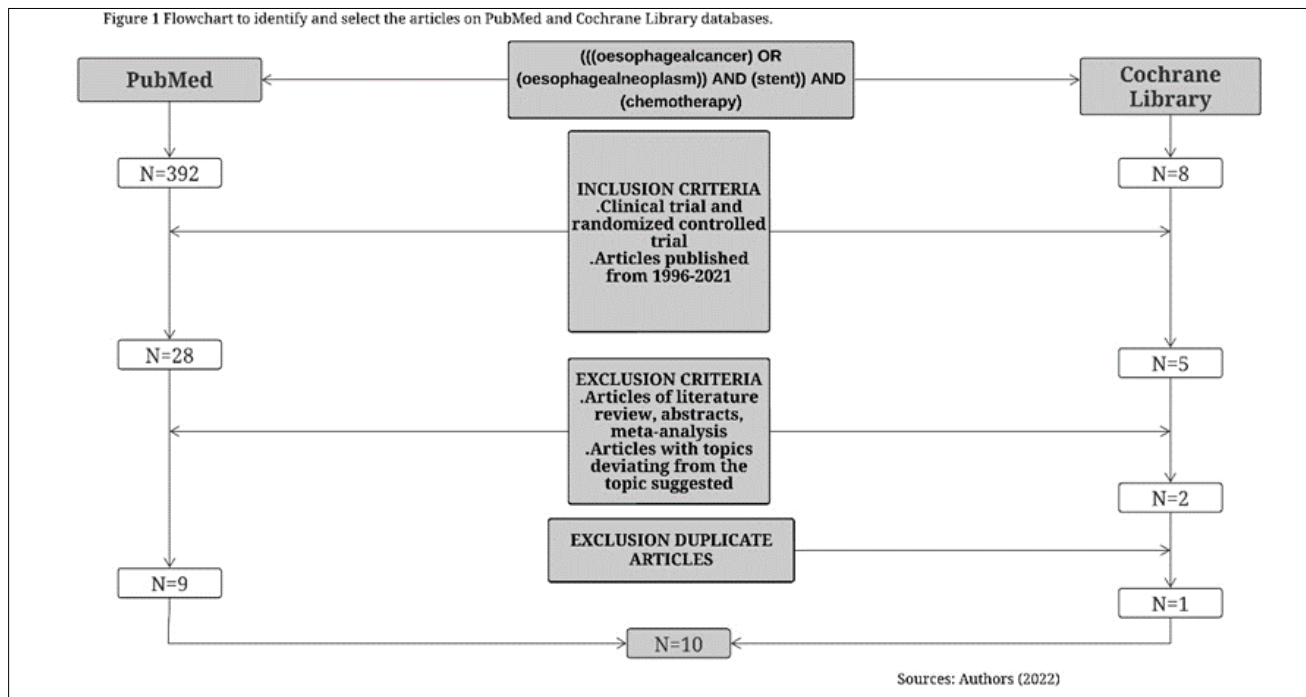
Of the 10 articles selected, information about the number of patients evaluated, the tumor staging, and the histological subtypes, squamous cell carcinoma or epidermoid carcinoma and adenocarcinoma was extracted. In addition, treatments performed prior to esophageal stent placement were considered, such as chemotherapy, radiotherapy, surgery, brachytherapy and thermotherapy. (Table 1)

Also concerning these 10 articles, information about the details of chemotherapy treatment, such as the substances used – Cisplatin, 5-Fluorouracil, etoposide, paclitaxel, docetaxel and carboplatin, was gathered. Regarding radiotherapy, external beam radiation, cobalt-60 in individual doses, radiofrequency therapy and brachytherapy were used. Patients' survival in relation to the treatment chosen was also addressed, with the results obtained in the form of survival rate, median survival, survival time, survival in years or overall median survival. The results of the works selected were evaluated and shown in a comparative table, Table 2.

Four of the ten selected articles (40%) used staging as a criterion for patient eligibility. Thus, 75% included stage I carcinomas, 100% stage II, 75% stage III and 50% included stage IV cancers in the study. The histological subtype of cancer was mentioned by nine of the ten articles (90%), 66.7% of the articles included studies with patients with

adenocarcinoma and 88.9% included patients with squamous cell carcinoma. Two of the ten selected articles (20%) used staging and histological subtype as eligibility criteria. (Table 1)

Treatments performed prior to esophageal stent placement in patients were evaluated in 90% of the studies. 88.9% of the studies used chemotherapy and 77.8% used radiotherapy, and 66.7% included combined therapy with chemotherapy and radiotherapy. In addition, 22.2% of the studies included surgery, 11.1% included brachytherapy, 11.1% thermotherapy, and 11.1% mentioned the use of proton pump inhibitors. (Table 1)



**Figure 1** Flowchart to identify and select the articles on PubMed and Cochrane library databases

**Table 1** Characterization of articles according to year of publication, number of individuals approached, staging, histological subtype, lines of previous treatments

Author	Year	N	Staging	Histological subtype	Previous treatments
Anand, B. et al. <sup>16</sup>	1998	15	-	Squamous cell carcinoma (n=15)	Chemotherapy and radiotherapy (n=15); Surgery (n=2)
Siersema, P. et al. <sup>17</sup>	2001	57	-	Squamous cell carcinoma (percentage not available)	Chemotherapy and radiation therapy (percentage not available)
Akiyama, S. et al. <sup>18</sup>	2006	18	Stage IIA (n=1); Stage III (n=10); Stage IVA (n=1); Stage IVB (n=6). T3 or T4	-	Thermotherapy and surgery (n=5); Thermotherapy and chemotherapy (n=8); Thermotherapy and Chemotherapy (n=5)
Iraha, Y. et al. <sup>19</sup>	2006	19	-	Squamous cell carcinoma (n=19)	Radiotherapy and/or Chemotherapy (n=12)
Hirdes, M. et al. <sup>20</sup>	2012	19	-	Adenocarcinoma (n=16); Squamous cell carcinoma (n=3)	Brachytherapy (n=19)

Martin, R. et al. <sup>21</sup>	2014	52	Clinical stage IIIB or lower	Adenocarcinoma (n=43); Squamous cell carcinoma (n=9)	Chemotherapy (n=36) and Radiotherapy (n=27); Isolated chemotherapy (n=16)
Wen, L. et al. <sup>22</sup>	2014	126	-	Adenocarcinoma (n=21); Squamous cell carcinoma (n=105)	-
Philips, P. et al. <sup>23</sup>	2015	40	T3N0 / 1 or T2N0 / symptomatic 1	Adenocarcinoma (n=40)	Proton pump inhibitors (n=25); Neoadjuvant chemotherapy or chemoradiation (95% of patients)
T. Maishman et al. <sup>24</sup>	2020	12	-	Adenocarcinoma (n=10); Squamous cell carcinoma (n=2)	Chemotherapy (n=12)
Adamson, D. et al. <sup>25</sup>	2021	220	Stage I - III vs. IV	Squamous cell carcinoma; Non-squamous cell carcinoma (percentage not available)	Chemotherapy in patients with usual care only (n=15); Chemotherapy in patients who underwent external beam radiotherapy (EBRT) and usual care (n=23)

Source: authors 2022

Of the ten articles, five (50%) mentioned the chemotherapeutic agents used, in which all studies used cisplatin, 80% used 5-Fluorouracil and 40% combined cisplatin with some other chemotherapeutic substance. (Table 2)

Eight articles (80%) addressed radiotherapy as a treatment. External beam radiation was used in 37.5% of the studies, cobalt-60 in 12.5%, and radiofrequency therapy in 25% and brachytherapy in 25% of the studies. (Table 2)

Overall survival after treatment was addressed in seven of the ten articles (70%). The survival measures of the studies and populations are different and have had a significant impact on their combined assessment. Median survival was assessed by two of the ten articles (20%), resulting in 90 days for patients who received chemotherapy and brachytherapy and 61 days for those who received brachytherapy, chemotherapy and radiotherapy. (Table 2)

**Table 2** Characterization of the articles above regarding radiotherapy and/or chemotherapy and overall survival

Author	Year	Radiotherapy	Chemotherapy	Overall survival
Anand, B. et al. <sup>16</sup>	1998	External beam radiation; Cobalt-60 (n=15)	Cisplatin; 5-Fluorouracil (n=15)	Two-year survival rate was 25% (14 ± 18)
Siersema, P. et al. <sup>17</sup>	2001	External beam radiation of 50 to 60 Gy + 2 doses of brachytherapy of 6 Gy (n=5); 2 doses of brachytherapy 6 Gy (n=9)	Cisplatin and etoposide (n=3); Cisplatin and paclitaxel (n=4)	Average survival (all patients) was 61 days
Akiyama, S. et al. <sup>18</sup>	2006	The radiation dose was 2 Gy/day, 5 days/week, for a total dose of 60-70Gy (n=5)	5-Fluorouracil (5-FU) and Cis-diaminodichloroplatinum (n=12); Oral Fluoropyrimidine and Cis-diaminodichloroplatinum (n=1)	-
Iraha, Y. et al. <sup>19</sup>	2006	-	-	Survival time (days, mean and range) in patients with previous Radiotherapy and/or Chemotherapy: 139.8 (32–253); without previous Radiotherapy and/or Chemotherapy: 165.2 (23–323)

Hirdes, M. et al. <sup>20</sup>	2012	Brachytherapy: a dose of 12Gy administered with 192iridium at 1cm from the applicator source axis (n=19)	Palliative chemotherapy (n=7)	Average survival was 90 days (IQR 51-140).
Martin, R. et al. <sup>21</sup>	2014	Three-dimensional conformal radiation with a planned mean dose of 5,040 (4,500–6,600) cGy	5-Flouracil and Cisplatin (n=26); 5-Flouracil and Carboplatin (n=4); 5-Flouracil, Cisplatin and Taxol (n=4); 5-Flouracil, Cisplatin and Carboplatin (n=2)	-
Wen, L. et al. <sup>22</sup>	2014	Radiofrequency Therapy (Group C)	Local chemotherapy with 5-Flouracil and Cisplatin and metal stent (Group A); Local chemotherapy with 5-Flouracil and Cisplatin and stent with particles of iodine-125 (Group B)	Two-year survival: Group A: 45.65% Group B: 52.63% Group C: 21.21%
Philips, P. et al. <sup>23</sup>	2015	-	-	-
T. Maishman et al. <sup>24</sup>	2020	20Gy radiotherapy in 5 fractions (n=10); Radiotherapy 30 Gy in 10 fractions (n=1)	-	25% of the patients survived 52 weeks after the date of registration
Adamson, D. et al. <sup>25</sup>	2021	Post-stent radiotherapy: EBRT 20 Gy in 5 fractions or 30 Gy in 10 fractions (n=97)	Post-stent intended chemotherapy: Patients with usual care only (n=36) and patients with EBRT and usual care (n=34)	Overall average survival: 19.7 weeks with usual care only and 18.9 weeks with EBRT and usual care

Source: authors 2022

#### 4. Discussion

The review included studies which evaluated esophageal cancer patients receiving stents. This approach can provide acute relief from malignant dysphagia with an immediate success rate of > 90%. On the other hand, chemotherapy and radiation therapy could provide long-term relief from dysphagia and potentially survival gain.<sup>[26]</sup> Therefore, as shown by the results, 88.9% of the studies included chemotherapy and 77.8% used radiotherapy, and in 66.7%, the combination of chemotherapy and radiotherapy was used, and all procedures were prior to stent placement.

As the results show, 40% of the articles included in this study used staging as an eligibility criterion for considering the stent patients. Once the diagnosis of esophageal cancer is made, staging must be performed before the beginning of treatment. The most used system is the Classification of Malignant Tumors TNM, which considers the characteristics of the tumor (T), of the lymph node involvement (N) and the presence or absence of distant metastases (M). When made correctly, it leads to well-applied therapeutic approaches. Therefore, it is possible to determine whether the tumor is resectable or unresectable.<sup>[27]</sup> This study shows that 22.2% of the selected articles mentioned surgery prior to stent placement.

In addition, the histological subtype is considered, such as adenocarcinoma, which was included in 66.7% of the articles evaluated, or squamous cell carcinoma, present in 88.9%. According to Anne-Michelle Noone et al<sup>[28]</sup>, the relative survival of five years for esophageal tumors shows a modest increase over time for men and women. Survival is higher among those with adenocarcinoma compared with squamous cell cancer among men. However, there was no difference in survival between the subtypes for women.<sup>[28]</sup> In the present study, there was no comparison of survival between men and women.

A trial published in 2013 by Ravi Shridhar et al<sup>[29]</sup> was performed in patients with gastroesophageal junction cancer or stomach cancer, in which they were randomly assigned for surgical and postoperative treatment with chemoradiotherapy or surgery alone, demonstrating greater survival rates in the former. In addition, a Chinese study on stages II and III of squamous cell esophageal cancer was conducted, resulting in greater survival in patients treated with pre- and postoperative chemoradiotherapy compared to those undergoing surgery alone. No benefits were seen when comparing preoperative versus postoperative chemoradiation. Therefore, the studies proved to be insufficient to draw conclusions.<sup>[29]</sup>

Finally, the study conducted by Wen et al<sup>[22]</sup> shows survival data in a population of 126 patients, of which 49 belonged to group A, 41 to group B and 36 to group C, the survival rate for patients who received chemotherapy was more than two times higher than that of those who did not.<sup>[22]</sup> This corroborates recently published data on a real-world cohort of patients.<sup>[11]</sup>

Although this review might highlight the lack evidence in literature to assure survival benefit of chemotherapy in patients which underwent to esophageal stenting, it should be seen in the light of its limitations. The studies were significantly heterogeneous in inclusion criteria and treatment regimen, which significantly impairs a proper comparison amongst them. On the other hand, this study might reinforce the potential benefits of chemotherapy in selected patients who are fit to receive.

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## 5. Conclusion

Survival data of patients who received stent and chemotherapy in clinical trials is scarce, and the studies are generally limited in number of participants and are generally incomparable. Chemotherapy could be considered for patients fit enough to receive but factors to guide patient selection warrants investigations in prospective studies.

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## Compliance with ethical standards

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