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**Argon plasma coagulation compared with stent placement in the palliative treatment of inoperable oesophageal cancer**

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Keywords:	Argon plasma coagulation, Self-expandable metal stents, Oesophageal cancer, Endoscopy, palliation
Abstract:	<p><b>BACKGROUND:</b> Self-expandable metal stents (SEMS) are the main palliative modality used in inoperable oesophageal cancer. Other palliative modalities, including Argon plasma coagulation (APC), have also been used.</p> <p><b>OBJECTIVE:</b> To assess the relative efficacy of SEMS and APC regarding the survival of patients with inoperable oesophageal cancer, not receiving chemo/radiotherapy.</p> <p><b>METHODS:</b> Single centre, retrospective analysis of all patients (n=228) with inoperable oesophageal cancer between January 2000 and July 2014, not receiving chemo-radiotherapy, treated with SEMS (n=160) or APC (n=68) as primary palliation modalities. Cox-regression was performed to identify individual factors affecting survival and Kaplan-Meier curves were created for patients treated with APC and SEMS for stage III and IV disease. Survival intervals were compared by the log-rank test.</p>

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	<p>RESULTS: Type of treatment was the only statistically significant factor affecting survival, after disease stage stratification (hazard ratio-HR: 1.36, 95% CI:1.13-1.65 of SEMS over APC, p: 0.002). Median survival for patients treated with APC and SEMS was 257 (Interquartile range-IQR: 414, 124) and 151 (IQR: 241, 61) days respectively in stage III disease. It was 135 (IQR: 238, 43) and 70 (IQR: 148, 32) days respectively in stage IV disease. Both differences were statistically significant (p=0.02 and 0.05 respectively).</p> <p>CONCLUSIONS: APC is a promising palliation modality in inoperable oesophageal cancer, when patients are not candidates for chemo-radiotherapy. A randomized controlled trial will be needed to confirm those results.</p>

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3 **Title: Argon plasma coagulation compared with stent placement in the palliative**  
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5 **treatment of inoperable oesophageal cancer.**  
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10 **Short title: Comparison of 2 palliative modalities**

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## ABSTRACT

BACKGROUND: Self-expandable metal stents (SEMS) are the main palliative modality used in inoperable oesophageal cancer. Other palliative modalities, including Argon plasma coagulation (APC), have also been used.

OBJECTIVE: To assess the relative efficacy of SEMS and APC regarding the survival of patients with inoperable oesophageal cancer, not receiving chemo/radiotherapy.

METHODS: Single centre, retrospective analysis of all patients (n=228) with inoperable oesophageal cancer between January 2000 and July 2014, not receiving chemo-radiotherapy, treated with SEMS (n=160) or APC (n=68) as primary palliation modalities. Cox-regression was performed to identify individual factors affecting survival and Kaplan-Meier curves were created for patients treated with APC and SEMS for stage III and IV disease. Survival intervals were compared by the log-rank test.

RESULTS: Type of treatment was the only statistically significant factor affecting survival, after disease stage stratification (hazard ratio-HR: 1.36, 95% CI:1.13-1.65 of SEMS over APC, p: 0.002). Median survival for patients treated with APC and SEMS was 257 (Interquartile range-IQR: 414, 124) and 151 (IQR: 241, 61) days respectively in stage III disease. It was 135 (IQR: 238, 43) and 70 (IQR: 148, 32) days respectively in stage IV disease. Both differences were statistically significant (p=0.02 and 0.05 respectively).

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3 CONCLUSIONS: APC is a promising palliation modality in inoperable oesophageal  
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5 cancer, when patients are not candidates for chemo-radiotherapy. A randomized  
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7 controlled trial will be needed to confirm those results.  
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## INTRODUCTION

The crude incidence of oesophageal cancer in the European Union is 4.5 cases/10<sup>5</sup>/year and the mortality is 3.5/10<sup>5</sup>/year<sup>1</sup>. Even after complete tumour resection the long term survival in localized disease with lymph node involvement does not exceed 25%. In extensive disease the combination of surgery with other treatment modalities is a standard approach, but complete tumour resection is not possible in 30-50% of pT3-T4 cases<sup>1</sup>. The best palliative treatment for patients with inoperable oesophageal cancer has not yet been established. Treatment options most commonly used for palliation include self expandable metal stent (SEMS) placement<sup>2-4</sup>, thermal ablative techniques (laser, APC)<sup>5,6</sup>, external beam radiation in combination with brachytherapy<sup>7</sup>, brachytherapy as a single treatment<sup>8</sup> and chemotherapy<sup>9</sup>. In many cases combination of palliative treatments are implemented. Although SEMS have no direct antitumour activity, they are thought to extend the survival of symptomatic inoperable patients by improving nutritional intake and preventing starvation, dehydration, and aspiration. Other studies confirmed the effectiveness of APC as palliative treatment in oesophageal cancer, either alone<sup>10-12</sup> or in combination with other modalities<sup>13</sup>.

The relative effect of SEMS compared to APC on survival in patients with oesophageal cancer, who are not candidates for surgery or chemoradiotherapy, is unknown. In clinical practice, both modalities are available and in many cases they are both used in the same patients. The aim of this study was to compare the effectiveness of 2 different palliation strategies using either APC or SEMS as primary

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3 treatment, followed by the other as needed, on survival of patients with inoperable  
4 carcinoma of the oesophagus, not receiving other palliative treatments in the form of  
5 chemotherapy or radiotherapy.  
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## 10 11 METHODS

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16 This was a retrospective observational clinical study of consecutive patients  
17 with inoperable carcinoma of the oesophagus treated with SEMS or APC, conducted  
18 at a single centre over a 14-year period.  
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25 Patients referred for palliative treatment of oesophageal or oesophago-gastric  
26 junction cancers extending to the oesophagus were recruited. All had been assessed in  
27 a multidisciplinary upper GI cancer team (MDT) meeting, who agreed that surgery  
28 treatment was inappropriate because of locally advanced disease, metastases, severe  
29 comorbidity or combination of the above. The decision-making process was based not  
30 on predefined variables, but on consideration of multiple doctors' opinions and on an  
31 individual basis, taking into account age, serum albumin, magnitude of weight loss,  
32 comorbidities and performance status. The endoscopic palliative treatment modality  
33 was decided based on social circumstances and patient preferences after detailed  
34 discussion regarding each technique's characteristics. Informed consent was obtained  
35 from all patients prior to the initiation of treatment.  
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52 All patients diagnosed with inoperable oesophageal or oesophago-gastric  
53 junction cancer (Siewert type I) between January 2000 and July 2014 and received  
54 either APC or SEMS were considered eligible for inclusion in this study. Patients who  
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3 received chemotherapy or radiotherapy either before or after SEMS or APC were  
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5 excluded. Patients intolerant to the initial chemotherapy treatment, not being able to  
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7 conclude a cycle of therapy were also included, since a single dose of chemotherapy  
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9 was not considered as significant to alter the outcome. Patients lost to follow up or  
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11 with incomplete staging or treatment data were excluded.  
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16 Computerized medical records dated between 2000 and 2014 were searched  
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18 for patients meeting the inclusion criteria. Patient cases were identified using 4  
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20 different sources: hospital electronic records system (since 2004), the upper GI cancer  
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22 MDT records, the electronic endoscopy reporting system and the South-East of  
23  
24 Scotland Cancer network database. The following data were retrieved from the  
25  
26 medical, pathology and endoscopy records as well as the death register: gender, age,  
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28 date of diagnosis, date of first treatment, dates of subsequent treatments, date of death,  
29  
30 tumour location, histology, staging and comorbidities. For the latter, the comorbidity  
31  
32 component (Charlson Comorbidity Score-CCS) of Charlson Comorbidity Index (CCI)  
33  
34 was used. Charlson Comorbidity Index (CCI) has been widely used and proved to be  
35  
36 a reliable tool for use in trials of cancer patients. CCI score consistently correlated  
37  
38 with disease specific survival, overall survival, or treatment-related adverse events,  
39  
40 confirming its predictive validity. After controlling for age, cancer stage, and type of  
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42 treatment, increasing comorbidity remained significantly predictive of increased all-  
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44 cause mortality<sup>14</sup> and, as is the case with other comorbidity indices, has been shown to  
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46 be more predictive of disease outcome than single comorbid conditions<sup>15</sup>. For the  
47  
48 purposes of this study, the score was calculated taking into consideration all the  
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50 comorbidities known prior to the diagnosis of cancer. Therefore, patients without any  
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52 other health problems apart from oesophageal cancer were assigned a CCS of 0.  
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## STAGING PROCEDURE

Staging was based on endoscopic findings, histology and imaging studies. CT scan of abdomen and thorax was performed in all patients, as well as an endoscopic ultrasound (EUS) until 2010. Since 2010 positron emission tomography (PET) scan was also performed and EUS was used in cases of uncertainty. Oesophago-gastric junction cancers extending to the oesophagus (Siewert type I) were categorized as lower oesophageal. The most recent edition (6<sup>th</sup> or 7<sup>th</sup>)<sup>16, 17</sup> of the American Joint Committee on Cancer (AJCC) TNM classification for oesophageal cancer available at the date of diagnosis was used for each case.

## TECHNIQUES

Endoscopic procedure: All endoscopic procedures were performed under conscious sedation with the use of midazolam for biopsies to confirm the diagnosis of cancer. When EUS was performed, staging was done with a variety of radial or linear echoendoscopes (Olympus Corporation, Japan). In general, oesophageal dilatation was avoided prior to MDT discussion and management decision.

## ARGON PLASMA COAGULATION

The APC treatment goal was tumour debulking and oesophageal lumen recanalization. Argon gas flow was set at 2 L/min and power at 40- 65 W. Four different catheters were used; 2.3 mm axial beam catheters were used most commonly

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3 through standard scope channel, whereas the 3.2mm were used through an IT scope  
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5 for extensive tumour debulking. The side fire conical beam and the circumferential  
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7 beam catheters were used on few occasions. Both forced and pulsed APC techniques  
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9 were used as needed. During procedures, the gas produced was regularly aspirated and  
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11 coagulum from the tip of the probe was cleaned when necessary. The duration of each  
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13 session was between 25 and 40 min. Initially patients were treated at 2-4 week  
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15 intervals, until achieving lumen patency and symptom relief and then were regularly  
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17 treated at 8-12 weeks intervals. Those intervals were subject to change according to  
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19 tumour response and symptoms recurrence.  
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#### 27 OESOPHAGEAL STENTS

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31 For patients treated with stent placement a partially covered SEMS was used.  
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33 SEMS were available in lengths of 10, 12, and 15 cm with a proximal diameter of 23  
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35 mm and a distal diameter of 18 mm (Ultraflex, Boston Scientific, USA). The stent  
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37 was introduced and deployed either by direct endoscopic monitoring or a combination  
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39 of both endoscopic and fluoroscopic monitoring. When the latter was used, proximal  
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41 tumour margin was identified and marked internally by injection of a radiographic  
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43 contrast medium into the submucosa of the oesophageal wall through a sclerotherapy  
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45 needle. After placement, deployment of the stent was assessed endoscopically and  
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47 fluoroscopically.  
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#### 53 STATISTICAL ANALYSIS

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3 The two treatment groups were compared with respect to base-line  
4 characteristics using Mann-Whitney U test for continuous variables and chi-square  
5 test for categorical variables. Analysis was based on intention to treat. Univariate  
6 analysis with cox-regression was performed for each of the patients' characteristics in  
7 order to assess its potential association with survival. Analysis was stratified for  
8 disease stage. Variables found to be associated with survival in Univariate analysis  
9 with  $p \leq 0.1$  were included in a multivariate cox-regression analysis. Statistical  
10 significance was set at 0.05 for the variables to be retained in the multivariate model.  
11 Differences in survival were tested with life-table analysis using the Kaplan-Meier  
12 method. This was constructed by using the number of days between the first  
13 procedure and death. Survival intervals were compared by the log-rank test. Survival  
14 comparisons were performed separately for stage III and IV. Survival of patients still  
15 alive at the time of the analysis was censored. In order to minimize the effect of  
16 potential selection bias (i.e. allocating more frail patients preferentially to one type of  
17 treatment), survival comparisons were also performed after excluding patients  
18 surviving less than a month. A p value of  $< 0.05$  was considered significant. All  
19 analyses were performed with IBM SPSS Statistics version 21.0 (IBM Corp, Armonk,  
20 NY, USA).  
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#### 45 ETHICS CONSIDERATION

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49 This study was conducted in accordance with UK research ethics guidelines. After  
50 review by the local ethics committee, further specific ethical review and approval  
51 were not required, as the study was considered as a retrospective clinical audit work,  
52 using data already obtained as part of regular patient care.  
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## RESULTS

Between January 2000 and July 2014 a total of 388 patients received a diagnosis of inoperable oesophageal cancer and were treated with a palliative modality. A total of 160 patients were excluded. Of them 86 were excluded because they were initially treated with chemotherapy, radiotherapy or laser. Fifty patients (10 in APC group and 40 in SEMS group) were also excluded due to inadequate staging data. In those patients it was unclear whether the local invasion of the tumour could be classified as T2 or T3 and thus it was unclear whether they should be categorized as stage II or III. Further 24 patients were also excluded due to inadequate data regarding their treatment. The majority of those patients were referred to our centre by other hospitals in Scotland for stent placement and then returned to the referring sites, being lost from our follow-up. Of the remaining 228 patients, 68 were treated with APC as a primary modality and 160 were treated with SEMS. There were 6 out of 228 (2.6%) patients still alive at the end of follow up, 5 of who were treated with APC and 1 with SEMS. A flow chart describing the exclusion process, as well as the need for further endoscopic interventions, in addition to the initial modality used, is presented in Figure 1.

A summary of the demographic and clinical characteristics of patients finally included in our study is presented in Table 1. Patients in APC groups were older and with a higher Charlson comorbidity score. Those differences were statistically significant. Stage distribution in the 2 groups was different, since the APC groups included more stage II and less stage IV patients. Stage III patients comprised

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3 approximately 40% of the population in both groups. Histology type distribution was  
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5 also different between groups with SEMS groups including squamous cancer patients  
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7 in a higher proportion (32.5%) compared to the APC group (15.7%). Tumour location  
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9 was not different between groups. There were no missing data for those variables,  
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11 with the exception of tumour length, where data on 55 patients were not available.  
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16 In the APC group, a median of 3 (IQR: 2, 5) APC sessions were required to  
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18 maintain lumen patency. In 44 (64.7%) of them, APC treatment was able to maintain  
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20 patency until death or end of follow up period (July 2014) in surviving patients.  
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22 Twenty four of them (35.3%) required an additional endoscopic palliative treatment  
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24 (20 stent placement, 3 balloon dilation, 1 laser). In the SEMS group, 24 (15 %)  
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26 patients required additional treatment. Nine of them (5.6%) required APC treatment  
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28 for tumour overgrowth, 10 (6.3%) at least a second stent, 3 required both an  
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30 additional stent and APC, 1 received laser treatment and 1 had eventually a  
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32 percutaneous endoscopic gastrostomy after a second stent placement.  
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39 Results of Univariate analysis of potential factors influencing survival, along  
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41 with the relevant hazard ratios (HR) and p values are presented in Table 2. Those  
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43 results are stratified for disease stage. Amongst the 7 factors examined, only  
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45 treatment type and tumour length met the criterion ( $p \leq 0.1$ ) for inclusion in the  
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47 multivariate model. Results of the multivariate cox-regression are also presented in  
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49 Table 2. Only treatment type was found to be independently associated with survival,  
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51 with a HR of 1.36 for SEMS over APC. Tumour length also exhibited a trend, with  
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53 longer tumours having a worse outcome, but this did not reach statistical significance  
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55 ( $p=0.07$ ).  
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5 The overall median survival was 257 (IQR: 485, 135) and 102 (188, 41) days  
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7 in the APC and SEMS group respectively. Patients treated with APC had significantly  
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9 better median survival (log rank  $p < 0.001$ ). Kaplan-Meier survival curves for stage III  
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11 and IV patients treated with APC or SEMS are presented in Fig. 2 and Fig. 3  
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13 respectively. Comparisons between treatment groups for patients belonging to less  
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15 advanced stages were not performed due to small numbers, especially in SEMS  
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17 group.  
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22 The overall median survival of stage III patients was 158 days (IQR: 285, 84).  
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24 Stage III patients treated with APC had a median survival of 257 days (IQR: 414,  
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26 124), while patients treated with SEMS had a median survival of 151 days (IQR: 241,  
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28 61). Survival of patients treated with APC was significantly better (log rank  $p = 0.02$ )  
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34 Stage IV patients had an overall median survival of 83 days (IQR: 158, 32).  
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36 Median survival of the APC group in stage IV disease was 135 days (IQR: 238, 43),  
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38 while patients treated with SEMS had a median survival of 70 days (IQR: 148, 32).  
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40 The difference was statistically significant (log rank  $p = 0.05$ ).  
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46 Patients treated with SEMS had a 14-days mortality rate of 8.1%, compared to  
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48 0% in patients treated with APC. The respective 30-days mortality rates for SEMS  
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50 and APC were 18.8% and 5.9%. Both differences were statistically significant  
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52 ( $p = 0.01$  for both).  
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3 Further analysis of the data set after excluding patients not surviving more  
4 than a month showed that again the type of treatment (APC or SEMS) was found as  
5 the only statistically significant factor in cox-regression, while stratifying for disease  
6 stage. In this sub-group analysis, median survival in stage III patients was 268 days  
7 (IQR: 425, 137) for APC, compared to 162 (IQR: 272, 99) for SEMS and in stage IV  
8 disease, median survival was 166 days (IQR: 243, 111) for APC compared to 97  
9 (IQR: 164, 59) for SEMS. The difference was statistically significant in stage III  
10 (p=0.04), whereas it was not in stage IV (p=0.07). The relevant Kaplan-Meyer curves  
11 are presented in Appendix Figures 1 and 2, while the relevant cox-regression analysis  
12 is presented in Appendix Table 1.  
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## 27 DISCUSSION

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31 The aims of palliation in patients with advanced oesophageal cancer are to  
32 overcome dysphagia and optimize quality of life by using interventions that have  
33 minimal adverse events. Even though chemo-radiotherapy is an option for dysphagia  
34 palliation in advanced oesophageal cancer and also conveys an advantage in survival  
35 compared with palliative endoscopic stenting alone,<sup>18</sup> a significant proportion of  
36 patients are not candidates for such treatments. The palliation modalities most widely  
37 used in such patients is stent insertion, brachytherapy and thermal ablation  
38 techniques<sup>2-8</sup>. It has been shown, that that MDT assessment significantly improves  
39 staging accuracy for gastro-oesophageal cancer and ensures that correct management  
40 decisions are made for the highest number of individual patients. In an audit from our  
41 unit, overall staging accuracy as determined at the MDT meeting was high and  
42 resulted in only 2/118 (2%) patients being under-treated<sup>19</sup>.  
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5 SEMS are the mainstay of palliative treatment for malignant oesophageal  
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7 obstruction. The apparent advantage of this approach is the relative ease of  
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9 application in a single session achieving immediate results in relieving dysphagia. In  
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11 contrast, ablative techniques require multiple sessions and significant administrative  
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13 co-ordination efforts and therefore are less appealing, especially in busy tertiary  
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15 centres. Nevertheless, the apparent dominance of SEMS in oesophageal cancer  
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17 palliation over ablative techniques is not based on solid evidence. On the contrary, a  
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19 single centre, randomized, prospective study demonstrated a significantly longer  
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21 median survival of patients receiving Laser treatment for palliation of inoperable  
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23 oesophageal cancer compared to patients treated with stents<sup>5</sup>. An increased survival of  
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25 patients treated with various ablative techniques including APC, over SEMS, was also  
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27 documented in a randomized, controlled, multicentre study<sup>22</sup>. Those results raise the  
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29 question whether SEMS dominance on the field is at least partially explained by their  
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31 certain advantage in logistics rather than in a clear benefit in patient palliation and  
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33 survival. This study tried to provide some insight into this issue.  
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41 Most studies regarding SEMS included patients who were unfit for  
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43 chemotherapy and/or radiotherapy and hence median survival was low, ranging from  
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45 68 to 145 days<sup>2, 3, 5, 8, 18</sup>. This is in accordance with the results of this study which  
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47 showed an overall median survival of 102 days in patients receiving SEMS as a  
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49 primary palliation modality.  
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54 The effectiveness of APC in tumour debulking has been studied in a number  
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56 of studies. Eickhoff et al. showed a significant effect of both pulsed and forced APC  
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3 in achieving tumour debulking in GI cancers, with a response to treatment exceeding  
4 80%.<sup>10</sup> In a retrospective analysis<sup>6</sup> of 83 patients who had APC for oesophageal  
5 malignancy, Heindorff et al. reported a mean of six APC sessions to maintain lumen  
6 patency. This was higher compared with the median of 3 (mean=4), reported in this  
7 study. This could be explained by different intervals between the consecutive sessions  
8 adopted by each centre. The same study reported an average survival of 146 days in  
9 63 of patients who died in the investigation period, which is significantly lower  
10 compared with our study's overall median survival of 257 days. However, the  
11 proportion of stage IV patients in the aforementioned study was 41%, which was  
12 significantly higher compared with our study (25.7%) in the APC group.  
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27 To our knowledge, the only direct comparison of APC versus SEMS in  
28 inoperable oesophageal cancer so far, followed a different study design<sup>23</sup>. In that  
29 retrospective study by Kofoed et al. the study population was divided in 3 groups:  
30 patients receiving APC alone, SEMS alone and a combination of APC and SEMS. A  
31 proportion of patients in all categories also received chemo-radiotherapy. There was  
32 no difference in survival between "SEMS alone" and "APC alone" groups. The  
33 former had a mean survival of 134 days and the latter 114 days. Significantly better  
34 survival was observed in patients receiving a combination of both modalities  
35 compared to either modality alone. Additionally, patients receiving chemo-  
36 radiotherapy and SEMS plus/or APC had a better survival compared to the rest of the  
37 cohort. Direct comparison to our results is impossible since only patients with  
38 adenocarcinoma were included, the results were not stratified by disease stage (only  
39 distribution of T, N and M was reported) and patients also received chemo-  
40 radiotherapy. Furthermore, we chose not to compare APC or SEMS alone as distinct  
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3 modalities, but rather compare 2 different treatment strategies: APC first, followed by  
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5 SEMS when repeat APC was found ineffective and SEMS as primary modality,  
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7 followed by APC in cases of tumour overgrowth. In that sense, our analysis was more  
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9 on an intention to treat basis.  
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14 This study has certain caveats. It is a retrospective, single centre study and  
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16 results presented should be appreciated in that context. It is difficult to claim  
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18 immunity to selection bias in a retrospective study, especially when some baseline  
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20 characteristics are different between patient groups. Some of those patient  
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22 characteristics would be expected to negatively affect the prognosis in the APC group  
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24 (e.g. older age, higher Charlson comorbidity score), while the shorter median tumour  
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26 length could potentially improve it. In order to control for all those factors and find  
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28 the ones independently associated with survival, cox-regression was used after  
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30 stratification for disease stage. It was clear that treatment type was the only factor  
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32 independently correlated to survival after stratification for disease stage, in the  
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34 multivariate analysis.  
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41 In order to minimize any potential selection bias effect (i.e. assigning the most  
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43 frail patients in the SEMS group), further analyses, excluding the patients who died in  
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45 the first month, were performed and confirmed that the only factor found to be  
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47 statistically significant in the multivariate model was the type of treatment (data  
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49 shown in appendix Table 1). In addition, the survival benefit of APC remained, at  
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51 least in stage III disease.  
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3 The 30-day mortality in the SEMS group was comparable to previously  
4 reported results ranging from 11 to 40%<sup>24-27</sup>. Although such results could raise the  
5 concern that selection of more frail patients for SEMS could be an explanation for the  
6 higher mortality, it is certain from the demographic data that patient frailty was not a  
7 set criterion when discussing treatment options.  
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16 Cost is an important factor in every medical intervention and the need for  
17 repeat APC applications certainly needs further consideration from this point of view.  
18 Virtually all patients had more than one APC application and 35.3% needed other  
19 endoscopic procedures (mainly SEMS placement). However, 15% of patients in the  
20 SEMS group also required repeat endoscopic procedures including further stent  
21 insertions, while re-intervention rates as high as 38%<sup>28</sup> have  
22 been previously reported after SEMS placement. In view of the significantly higher  
23 cost of SEMS compared to APC catheters (approximately 5 times more expensive in  
24 UK), the actual difference in cost of the 2 treatment strategies appeared to be  
25 determined primarily by the costs related to the number of endoscopic procedures  
26 rather than the cost of consumables used. Patients treated with APC survived longer  
27 thus had higher number of interventions resulting in higher costs. Any future  
28 prospective studies should address the cost effectiveness of APC versus SEMS  
29 placement for palliation of esophageal cancer in detail.  
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49 This retrospective study has several strengths. We followed a rigorous  
50 protocol in patient inclusion and analysis. Staging was of very high standards, using  
51 all the available modalities available (CT, EUS, PET) and was based on a  
52 multidisciplinary decision thus making it as accurate as possible. Detailed  
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3 demographics were available for all patients included and procedure related factors as  
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5 well as mortality were documented prospectively with accuracy on case notes and  
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7 electronic records.  
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11 The palliation of inoperable oesophageal cancer is a challenging issue and  
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13 multiple factors should be taken into consideration. This study provided evidence that  
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15 a strategy based on APC as the primary palliation modality, supplemented by the  
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17 placement of SEMS only after APC failure or when patients become intolerable of  
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19 repeated endoscopies, might actually provide a significant survival benefit, compared  
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21 to SEMS as the primary treatment. Those findings need to be interpreted in the  
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23 context of a retrospective study and therefore, further, prospective, randomized  
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25 studies are needed to confirm those results.  
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Table 1. Baseline population characteristics in SEMS and APC treatment groups. Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Relevant p values are presented for each comparison.

	Stent as first treatment, N=163	APC as first treatment, N=70	p value
Age, median (IQR)	76 (70,80)	80 (72,84)	<b>0.01</b>
Gender, Male N (%)	108 (66.3)	41 (58.6)	0.26
Charlson comorbidity score, median (IQR)	0 (0,2)	1 (0,2)	<b>0.02</b>
Tumour length, median (IQR)	6 (4,9)	5 (3,6)	<b>&lt;0.001</b>
Stage, N (%)			<b>&lt;0.001</b>
0	0 (0)	1 (1.4)	
I	1 (0.6)	13 (18.6)	
II	15 (9.2)	11 (15.7)	
III	65 (39.9)	27 (38.6)	
IV	82 (50.3)	18 (25.7)	
Tumour location, N (%)			0.34
Upper	4 (2.5)	3 (4.3)	
Mid	30 (18.4)	8 (11.4)	
Lower	129 (79.1)	59 (84.3)	
Histology type, N (%)			<b>0.03</b>
Adenocarcinoma	106 (65)	57 (81.4)	
Squamous carcinoma	53 (32.5)	11 (15.7)	
Other	4 (2.5)	2 (2.9)	

Table 2. Univariate and multivariate analyses of risk factors affecting the survival of patients with inoperable oesophageal cancer, not receiving chemo- or radiotherapy, who had APC or SEMS as primary palliation modality, after stratification for disease stage. The only statistically significant factor in both analyses was treatment type (APC or SEMS)

Risk factor	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Treatment type	1.86 (1.34-2.59)	<0.001	1.36 (1.13-1.65)	0.002
Age	0.99 (0.98-1.01)	0.27		
Gender	0.98 (0.74-1.3)	0.88		
Tumour length	1.06 (0.99-1.13)	0.08	1.06 (0.99-1.13)	0.07
Charlson comorbidity score	1.04 (0.95-1.14)	0.38		
Histology		0.29		
Adenocarcinoma	(1.00)			
Squamous	1.27 (0.94-1.72)			
Other	1.14 (0.39-3.34)			
Tumour location		0.15		
Lower	(1.00)			
Middle	1.15 (0.78-1.68)			
Upper	2.07 (0.96-4.46)			

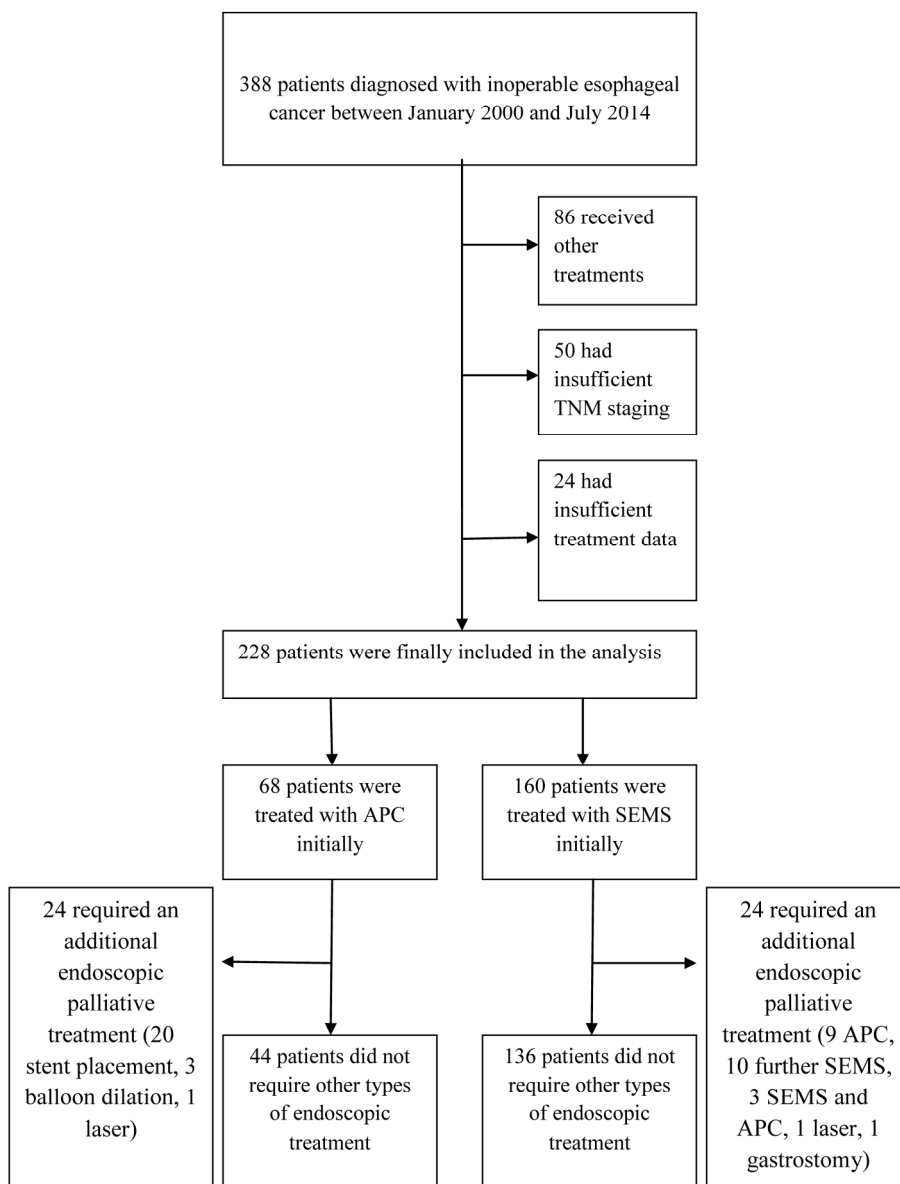


Figure 1. Flow chart describing the screening and exclusion process of patients with inoperable oesophageal cancer diagnosed between 2000 and 2014, as well as the type of initial treatment they received (APC or SEMS). Further types of treatments required are also presented for both the APC and SEMS groups.  
165x215mm (300 x 300 DPI)

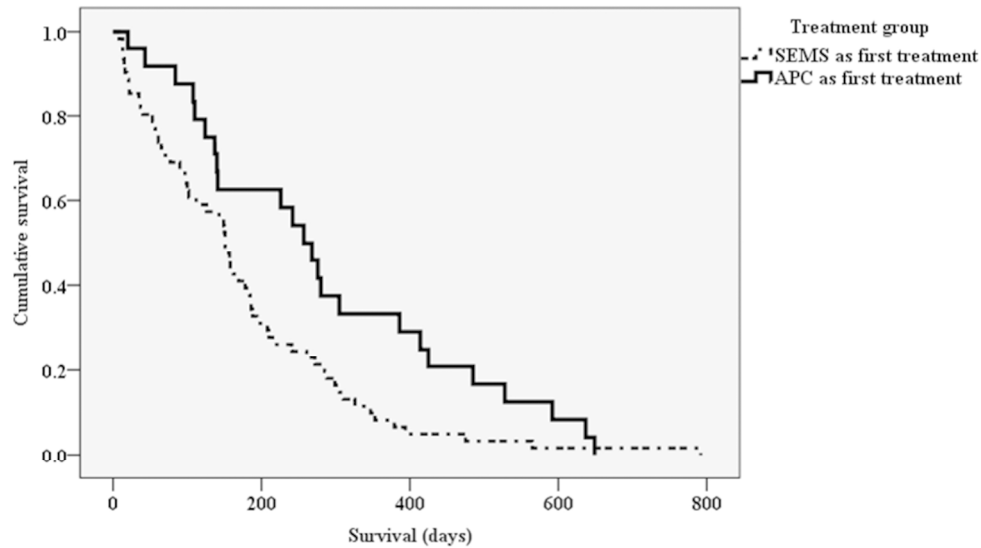


Figure 2. Kaplan-Meier survival curves for patients with stage III inoperable, oesophageal cancer, not receiving chemo- or radiotherapy, having either APC or SEMS as initial palliative treatment. Median survival was higher in the APC group (257 days, IQR: 414, 124) compared to SEMS group (151 days, IQR: 241, 61). This difference was statistically significant (log rank  $p=0.02$ ).  
252x157mm (300 x 300 DPI)

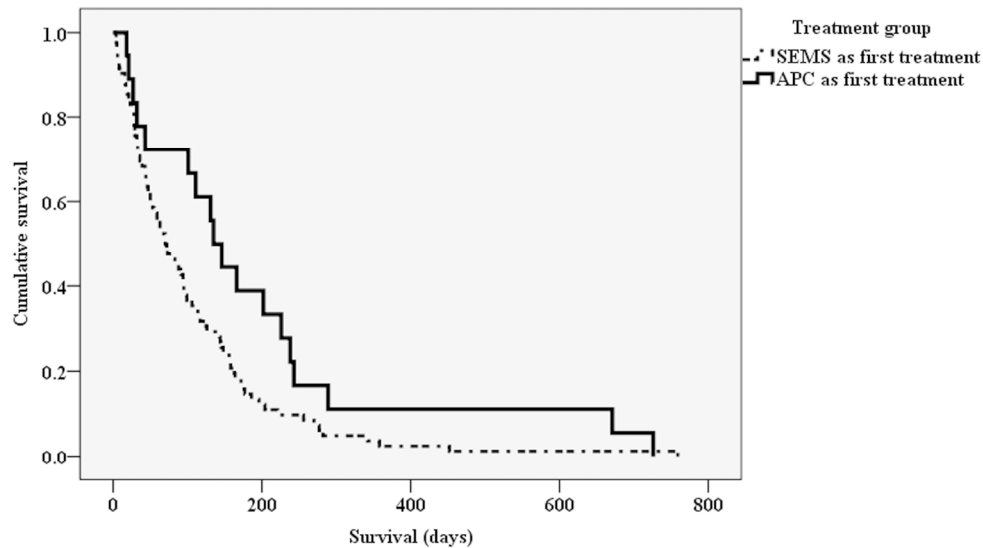
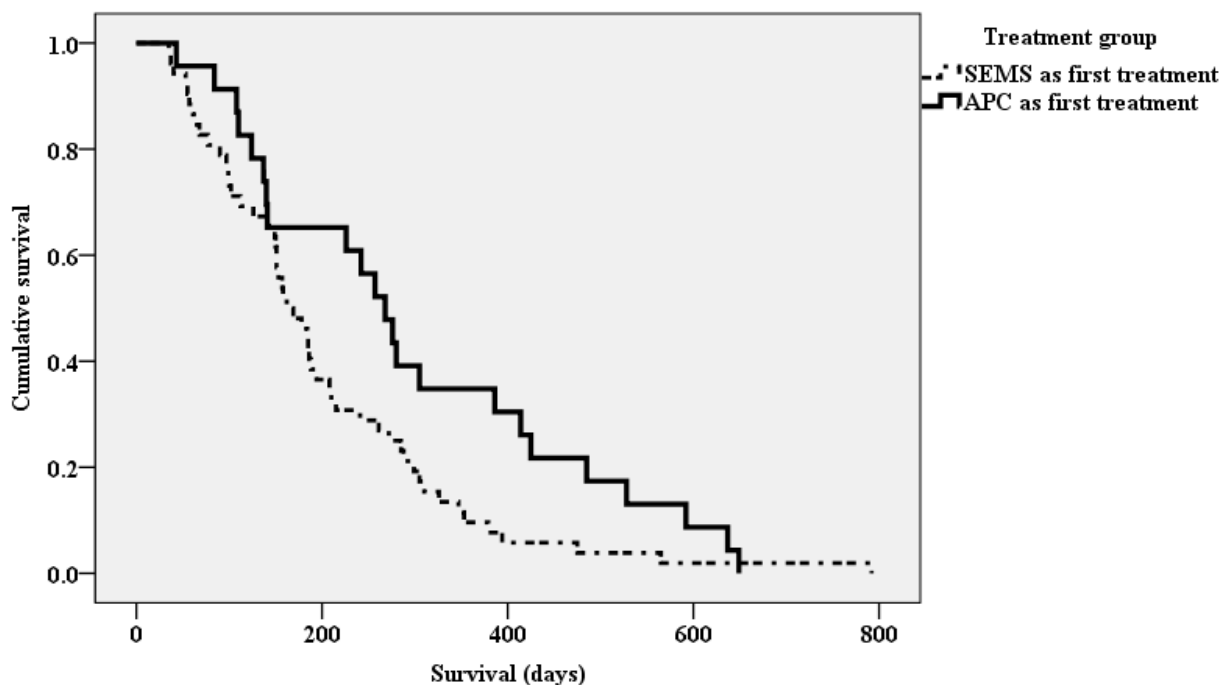
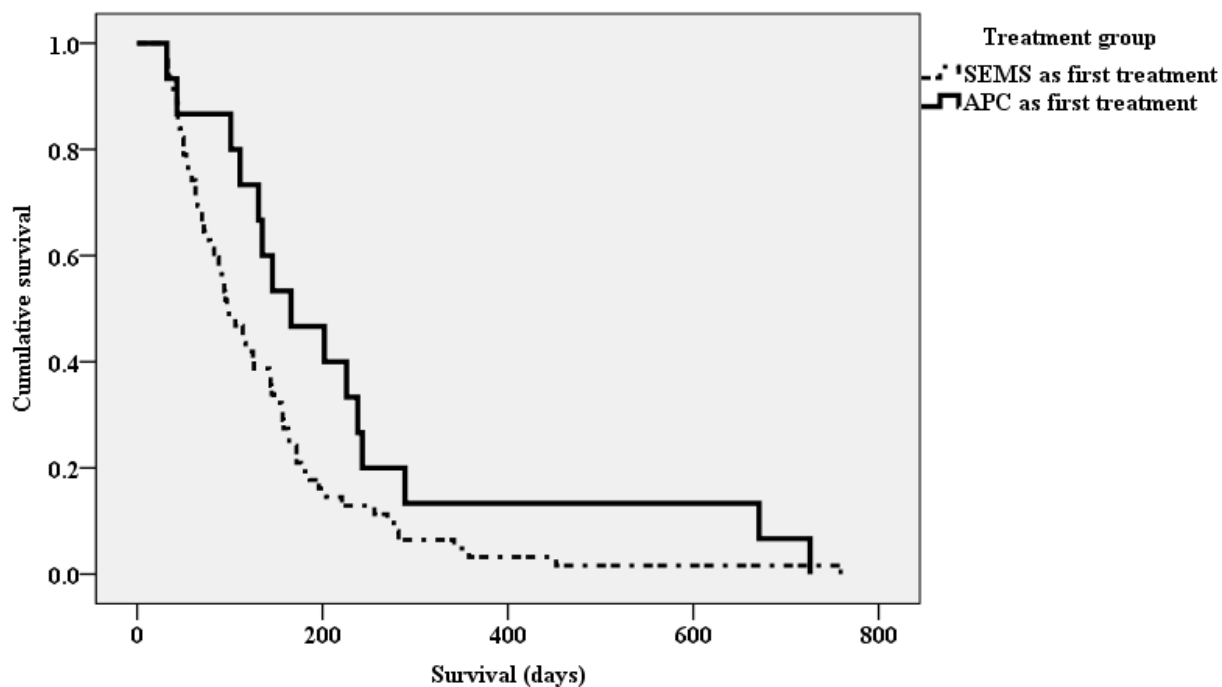


Figure 3. Kaplan-Meier survival curves for patients with stage IV inoperable, oesophageal cancer, not receiving chemo- or radiotherapy, having either APC or SEMS as initial palliative treatment. Median survival was higher in the APC group (135 days, IQR: 238, 43) compared to SEMS group (70 days, IQR: 148, 32). This difference was statistically significant (log rank  $p = 0.05$ ).  
282x176mm (300 x 300 DPI)



Appendix Figure 1. Kaplan-Meier survival curves for patients with stage III inoperable, oesophageal cancer, not receiving chemo- or radiotherapy, having either APC or SEMS as initial palliative treatment. Patients surviving less than 30 days were excluded. Median survival was higher in the APC group (268 days, IQR: 425, 137) compared to SEMS group (162 days, IQR: 272, 99). This difference was statistically significant (log rank  $p=0.04$ ).



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Appendix Figure 2. Kaplan-Meier survival curves for patients with stage IV inoperable oesophageal cancer, not receiving chemo- or radiotherapy, having either APC or SEMS as initial palliative treatment. Patients surviving less than 30 days were excluded. Median survival in the APC group was 166 days (IQR: 243, 111). Median survival in SEMS group was 97 days (IQR: 164, 59). This difference was not statistically significant (log rank  $p=0.07$ ).

Appendix Table 1. Univariate and multivariate analyses of risk factors affecting the survival of patients with inoperable oesophageal cancer, not receiving chemo- or radiotherapy, having either APC or SEMS as primary palliation modality, after stratification for disease stage. Patients not surviving more than 30 days following the first treatment session (either APC or SEMS) were excluded. The only statistically significant factor in both analyses was treatment type (APC or SEMS). Tumour length was included in the multivariable analysis despite not being statistically significant, to enable direct comparison with the analysis presented in Table 2 of the main manuscript.

Risk factor	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Treatment type	1.82 (1.28-2.58)	0.001	1.34 (1.09-1.64)	0.005
Age	0.99 (0.98-1.01)	0.46		
Gender	0.97 (0.71-1.3)	0.83		
Tumour length	1.05 (0.98-1.13)	0.15	1.06 (0.98-1.14)	0.13
Charlson comorbidity score	1.04 (0.94-1.15)	0.47		
Histology		0.34		
Adenocarcinoma	(1.00)			
Squamous	1.28 (0.92-1.78)			
Other	0.99 (0.29-3.41)			
Tumour location		0.63		
Lower	(1.00)			
Middle	1.14 (0.36-3.6)			
Upper	1.22 (0.81-1.84)			