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# Time trends in mortality of oesophageal cancer in Finland over 30 years

Ville E.J. Sirviö [a, *], Jari V. Räsänen [a], Joonas H. Kauppila [b, c]

[a] Department of Oesophageal and General Thoracic Surgery, Helsinki University Hospital and University of Helsinki, Finland
[b] Upper Gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[c] Surgery Research Unit, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

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ABSTRACT

*Introduction:* Oesophageal cancer survival is reported by epidemiological studies, but knowledge on survival trends regarding different histologies and operative treatment status is lacking.
*Materials and methods:* Data from all patients diagnosed with oesophageal cancer in Finland in 1987–2016 was collected from national registries. 1-, 3- and 5-year survival rates were examined stratified by histology (adenocarcinoma (OAC) and squamous cell carcinoma (OSCC)) and treatment strategy (surgery, no surgery). Hazard ratios (HR) with 95% confidence intervals (CI) for death were provided by multivariable Cox regression, adjusted for confounders.
*Results:* Of the 9102 patients, 3140 had OAC (1074 [34%] oesophagectomies), and 3778 had OSCC (870 [23%] oesophagectomies). Men were overrepresented in both OAC (77%) and OSCC (55%). The proportion of oesophagectomies decreased in both histologies. From 1987 to 1991 to 2012–2016, 5-year survival increased from 11% to 22% in OAC and from 7% to 13% in OSCC. For patients undergoing oesophagectomy, the corresponding increases were from 20% to 49% in OAC and from 11% to 54% in OSCC, and non-operated patients from 5% to 8% and from 5% to 7%, respectively. Earlier calendar period, older age and comorbidity were associated with mortality in both histologies. Female sex was a protective factor for patients operated for OSCC (HR 1.56 (95% CI 1.33–1.83), men versus women).
*Conclusions:* The prognosis of oesophageal cancer has improved in Finland over the last 30 years in both main histological types. The survival of patients undergoing oesophagectomy has drastically improved, while the prognosis of patients not undergoing surgery is slowly improving but remains poor.


## 1. Introduction

Oesophageal cancer is the 6th leading cause of cancer mortality worldwide [1]. In the USA, the 5-year survival for oesophageal adenocarcinoma (OAC) is estimated at 24% and for oesophageal squamous cell carcinoma (OSCC) at 21% in 2010 [2]. The latest pan-European survival data dates to 2007, estimating 12% of oesophageal cancer patients living 5 years after diagnosis [3]. According to the SURVMARK-2 project, the 5-year survival of oesophageal cancer has doubled in high-income countries during the last two decades [4]. Measures affecting the improvement of long-term survival include definitive chemoradiotherapy, routine neoadjuvant treatment, modern surgical technique and centralization of care along with higher center and surgeon volumes [5–8].

Epidemiological studies have reported long-term data on oesophageal cancer survival, but these studies mostly lack stratification for histology and operative treatment status. Mortality is mostly assessed as a whole, while survival regarding OAC and OSCC remain poorly known. The prevalence of these two main histologies have shifted in the recent years: OAC is becoming increasingly more prevalent, while the incidence rate of OSCC has decreased in Western countries [9]. Due to the shift in incidence trends, different risk factors (Barrett's oesophagus and gastro-oesophageal reflux disease in OAC, tobacco and alcohol consumption in OSCC) and different treatment strategies, these main histologies require separate assessment for survival [9]. Survival specifically among patients undergoing oesophagectomy and those not is even more unclear, as few studies assess the survival of non-operated patients separately [10]. As curative treatment of oesophageal cancer

* Corresponding author. Department of Oesophageal and General Thoracic Surgery, Helsinki University Hospital and University of Helsinki, Haartmaninkatu 4, PL 340 00029, HUS, Finland.
*E-mail address:* ville.ej.sirvio@helsinki.fi (V.E.J. Sirviö).

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**Table 1**
Characteristics of the 9102 patients diagnosed with oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, and any oesophageal cancer in Finland in 1987–2016.

| | Oesophageal adenocarcinoma | Oesophageal squamous cell carcinoma | Oesophageal cancer (any histology) |
|---|---|---|---|
| Category | Patients Number (%) | Patients Number (%) | Patients Number (%) |
| Total | 3140 (100.0) | 3778 (100.0) | 9102 (100.0) |
| Calendar period | | | |
| 1987–1991 | 202 (6.4) | 736 (19.5) | 1283 (14.1) |
| 1992–1996 | 300 (9.6) | 675 (17.9) | 1215 (13.3) |
| 1997–2001 | 437 (13.9) | 639 (16.9) | 1370 (15.1) |
| 2002–2006 | 632 (20.1) | 591 (15.6) | 1519 (16.7) |
| 2007–2011 | 818 (26.1) | 625 (16.5) | 1823 (20.0) |
| 2012–2016 | 751 (23.9) | 512 (13.6) | 1892 (20.8) |
| Age | | | |
| <50 | 207 (6.6) | 141 (3.7) | 456 (5.0) |
| 50–59 | 618 (19.7) | 569 (15.1) | 1460 (16.0) |
| 60–69 | 945 (30.1) | 1086 (28.7) | 2602 (28.6) |
| 70–79 | 892 (28.4) | 1134 (30.0) | 2664 (29.3) |
| 80–89 | 429 (13.7) | 749 (19.8) | 1672 (18.4) |
| ≥90 | 49 (1.6) | 99 (2.6) | 248 (2.7) |
| Sex | | | |
| Female | 710 (22.6) | 1701 (45.0) | 3289 (36.1) |
| Male | 2430 (77.4) | 2077 (55.0) | 5813 (63.9) |
| Comorbidity score | | | |
| 0 | 1799 (57.3) | 2319 (61.4) | 5159 (56.7) |
| 1 | 771 (24.6) | 883 (23.4) | 2244 (24.7) |
| 2 | 351 (11.2) | 371 (9.8) | 1056 (11.6) |
| ≥3 | 219 (7.0) | 205 (5.4) | 643 (7.1) |
| Surgical treatment status | | | |
| No | 2066 (65.8) | 2908 (77.0) | 6961 (76.5) |
| Yes | 1074 (34.2) | 870 (23.0) | 2141 (23.5) |

typically constitutes of multimodal therapy including surgery [11,12] and treatment strategies involving surgery are still superior to non-surgical approaches [13,14], separate assessment is important.

Despite these recognized differences, the survival trends remain poorly known in a nationwide setting. As the epidemiology of oesophageal cancer has been shifting during the last decades, up-to-date, nationwide, long-term information on survival trends with attention to histology and treatment strategy is needed.

The main aim of this study was to assess the recent developments in 1-, 3- and 5-year survival of oesophageal cancer in Finland stratified by surgical treatment and histology. The secondary aim was to assess risk factors for 5-year mortality in these patient groups.

## 2. Methods

### 2.1. Study design

This study was a nationwide Finnish, population-based, retrospective cohort study, including all patients diagnosed with oesophageal cancer in Finland from 1 January 1987 through 31 December 2016, with follow up for survival until 31 December 2019. Patients with oesophageal cancer were identified through the Finnish Cancer Registry (FCR) and the Finnish Hospital Discharge Registry (HILMO). Mortality was evaluated through the Death Registry. Data from these registries were combined using the unique 11-digit personal identification number assigned to all residents in Finland.

### 2.2. Data sources

According to Finnish law, all healthcare units in Finland are obligated to report data to national registries regardless of patient consent, resulting in highly comprehensive nationwide databases. The high quality of the data in these sources has been validated earlier [15,16], and their use concurrently yields a near complete reporting of oesophageal cancer in 1990–2014 [17].

The FCR maintains an accurate and close to complete national registry of all diagnosed cancers in Finland since 1953 [15]. Reporting by multiple healthcare professionals, both clinicians (general practitioners, surgeons, oncologists) and laboratories (pathology notifications), ensure up-to-date and non-biased data. Information retrieved from the FCR regarding the present study were the date of diagnosis (calendar period variable) and type of cancer and morphology (histology variable) information. The completeness in reporting of oesophageal cancer in the FCR is estimated at 91.8% [17].

HILMO is one of the oldest individual level nationwide hospital discharge registries in the world. It contains nationwide linkable data on all inpatient hospital discharges with personal identification codes since 1969. HILMO provided the diagnosis codes and operation codes recorded for patients before discharging from any medical facility [16]. Comorbidity- (diagnosis codes) and treatment variables (operation codes) were derived from this information. Comorbidity was defined as any disease the patient had before treatment, or at the time of the treatment, excluding oesophageal cancer, and was classified as 0, 1, 2 and more than 2 according to the well validated, modified Charlson Comorbidity Index (CCI) [18]. The completeness in reporting of oesophageal cancer in HILMO is estimated to be up to 97.7% [17].

The observed 1-year, 3-year and 5-year survivals were defined as death by any cause after the diagnosis of oesophageal cancer, based on a 100% complete death registry held by Statistics Finland, available until December 31, 2019.

### 2.3. Patient identification

Patients with cancer of the oesophagus (150.0–150.9 in the International Classification of Diseases (ICD)-8 and ICD-9, and C15 in the ICD-10) were identified through the FCR and HILMO. The time of diagnosis was defined by the first record of cancer diagnosis in

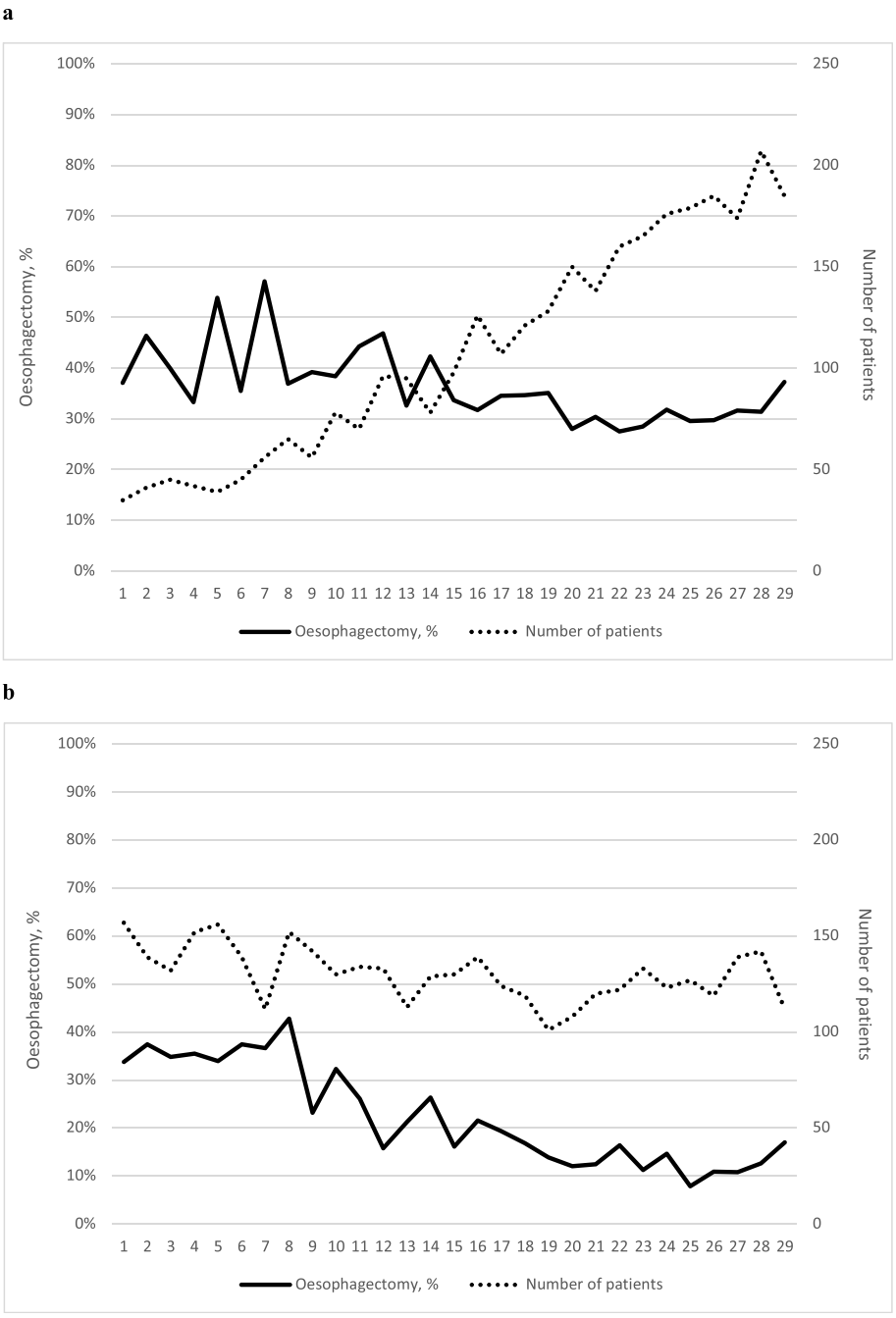


**Fig. 1.** Proportion of patients undergoing oesophagectomy (solid line) and number of patients (dotted line) diagnosed with oesophageal adenocarcinoma **a**, and oesophageal squamous cell carcinoma **b** in Finland in 1987–2016.

either of the registries. Surgical treatment status was defined based on operation codes for oesophagectomy [19].

### 2.4. Statistical analysis

The statistical analysis in the present study was conducted according to a detailed *a priori* study protocol. All analyses were carried out by using the software SPSS version 28 (Armonk, NY).

The 1- 3- and 5-year survivals were tabulated using life table method [20] for all patients diagnosed with oesophageal cancer, those undergoing surgery, and those not. The results were stratified for histological type, i.e. OAC and OSCC. Five-year survivals in each group were plotted using Kaplan-Meier curves. The survival was further stratified by calendar period (years 1987–1991, 1992–1996, 1997–2001, 2002–2006, 2007–2011 or 2012–2016), age (<50, 50–59, 60–69, 70–79, 80–89 or ≥90), sex (male or female) and comorbidity (CCI 0, 1,2 or ≥3).

For risk factor analysis, a multivariable Cox regression model provided the hazard ratios (HR) and 95% confidence intervals (CI), adjusted for calendar period, age, sex and comorbidity, with the aforementioned categorization. A p-value of <0.05 was considered significant.

## 3. Results

### 3.1. Patients

A total of 9102 patients diagnosed with oesophageal cancer

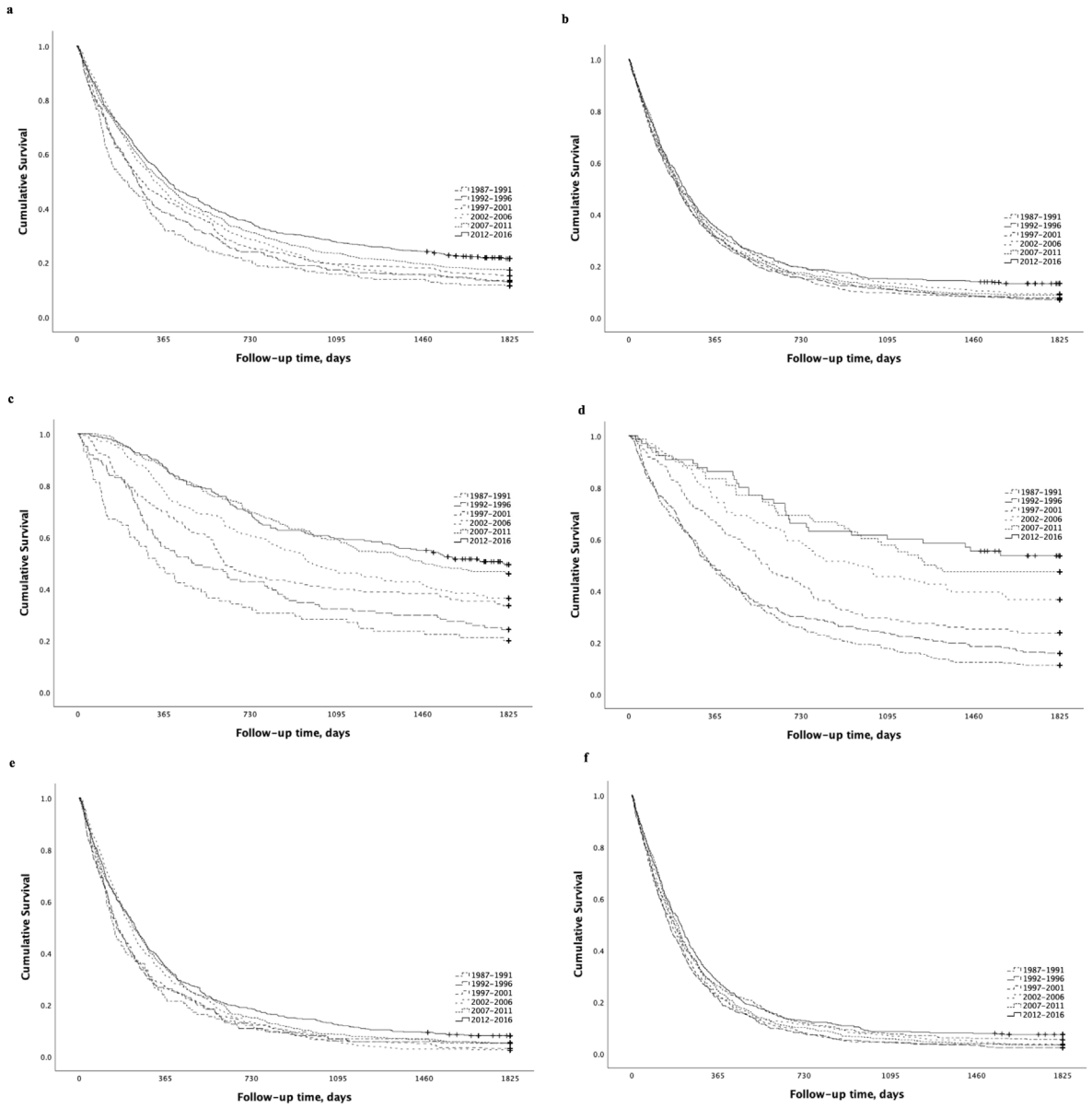


**Fig. 2.** 5-year survival of all patients diagnosed with oesophageal adenocarcinoma **a** and oesophageal squamous cell carcinoma **b**, patients undergoing oesophagectomy for oesophageal adenocarcinoma **c** and oesophageal squamous cell carcinoma **d**, and patients not undergoing surgery for oesophageal adenocarcinoma **e** and oesophageal squamous cell carcinoma **f** in Finland in 1987–2016, presented as Kaplan-Meier curves stratified for calendar period.

during the years 1987 through 2016 were identified in the registries, of which 2141 (23.5%) patients underwent oesophagectomy. The proportion of patients undergoing oesophagectomy decreased from 29% in 1987–1991 to 20% in 2012–2016 while the number of diagnosed oesophageal cancers increased through the study period. Median age of cancer diagnosis was 70 years. Men were over-represented in the patient population (64%) (Table 1).

Out of the total of 9102 patients, 1702 had unspecific tumors, 419 other or unclear carcinomas, 42 had neuroendocrine tumors, 5 had melanoma and 16 had mesenchymal tumors. Further, 3140 (34.5%) were diagnosed with OAC, of which 1074 (34.2%) had oesophagectomy. Out of the 9102 patients, 3778 (41.5%) were diagnosed with OSCC, of which 870 (23.0%) had oesophagectomy. The number of diagnoses of OAC increased almost 4-fold during the study period (Fig. 1a), whereas OSCC decreased to 70% of the initial number of diagnoses (Fig. 1b). 77% of patients diagnosed with OAC and 55% of patients diagnosed with OSCC were men. The proportion of patients undergoing oesophagectomy of all patients with OAC decreased from 42% in 1987–1991 to 32% in 2012–2016 (Fig. 1a). Similarly, in the OSCC group, the proportion decreased from 35% in 1987–1991 to 12% in 2012–2016 (Fig. 1b).

### 3.2. Survival trends in oesophageal adenocarcinoma

#### 3.2.1. All patients

The observed survival in patients diagnosed with OAC improved during the study period. The 1-year survival increased from 33% in 1987–1991 to 52% in 2012–2016. The 3-year survival increased from 16% to 28% and the 5-year survival increased from 11% to 22% in the same time period (Fig. 2a, Table 2).

#### 3.2.2. Patients undergoing oesophagectomy

The 1-, 3- and 5-year survivals in patients treated surgically for OAC increased substantially during the study period. From 1987 to

**Table 2**
1-, 3- and 5-year survivals across calendar periods in oesophageal cancer in Finland in 1987–2016, stratified by treatment strategy.

| Calendar period | Oesophageal adenocarcinoma | | | | | Oesophageal squamous cell carcinoma | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Patients | | Survival % | | | Patients | | Survival % | | |
| | Number (%) | Median age | 1 year | 3 years | 5 years | Number (%) | Median age | 1 year | 3 years | 5 years |
| *All patients* | | | | | | | | | | |
| 1987–1991 | 202 (6.4) | 70.5 | 33.2 | 15.8 | 11.4 | 736 (19.5) | 72 | 34.0 | 11.1 | 7.3 |
| 1992–1996 | 300 (9.6) | 68 | 38.7 | 17.3 | 13.0 | 675 (17.9) | 71 | 31.1 | 11.0 | 7.0 |
| 1997–2001 | 437 (13.9) | 68 | 43.9 | 19.5 | 15.1 | 639 (16.9) | 71 | 31.3 | 9.7 | 7.7 |
| 2002–2006 | 632 (20.1) | 67 | 46.5 | 19.3 | 13.4 | 591 (15.6) | 69 | 31.8 | 13.4 | 9.1 |
| 2007–2011 | 818 (26.1) | 67 | 49.9 | 23.5 | 17.2 | 625 (16.5) | 68 | 31.7 | 12.2 | 8.8 |
| 2012–2016 | 751 (23.9) | 67 | 51.8 | 27.6 | 21.5 | 512 (13.6) | 70 | 35.2 | 15.0 | 13.2 |
| *Surgery* | | | | | | | | | | |
| 1987–1991 | 85 (7.9) | 67 | 48.2 | 28.2 | 20.0 | 258 (29.7) | 70 | 48.1 | 17.8 | 11.2 |
| 1992–1996 | 124 (11.5) | 67 | 56.5 | 32.3 | 24.2 | 233 (26.8) | 67 | 49.4 | 23.6 | 15.9 |
| 1997–2001 | 173 (16.1) | 66 | 69.9 | 39.9 | 33.5 | 135 (15.5) | 65 | 66.7 | 29.6 | 23.7 |
| 2002–2006 | 206 (19.2) | 63.5 | 78.2 | 47.1 | 36.4 | 101 (11.6) | 64 | 76.2 | 45.5 | 36.6 |
| 2007–2011 | 242 (22.5) | 64 | 86.8 | 59.1 | 45.9 | 78 (9.0) | 64 | 83.3 | 57.7 | 47.4 |
| 2012–2016 | 244 (22.7) | 65 | 87.3 | 59.4 | 49.4 | 65 (7.5) | 68 | 86.2 | 60.0 | 53.6 |
| *No surgery* | | | | | | | | | | |
| 1987–1991 | 117 (5.7) | 72 | 22.2 | 6.8 | 5.1 | 478 (16.4) | 74 | 26.4 | 7.5 | 5.2 |
| 1992–1996 | 176 (8.5) | 71 | 26.1 | 6.8 | 5.1 | 442 (15.2) | 74 | 21.5 | 4.3 | 2.3 |
| 1997–2001 | 264 (12.8) | 70 | 26.9 | 6.1 | 3.0 | 504 (17.3) | 73 | 21.8 | 4.4 | 3.4 |
| 2002–2006 | 426 (20.6) | 69 | 31.2 | 5.9 | 2.3 | 490 (16.9) | 69 | 22.7 | 6.7 | 3.5 |
| 2007–2011 | 576 (27.9) | 68.5 | 34.4 | 8.5 | 5.2 | 547 (18.8) | 70 | 24.3 | 5.7 | 3.3 |
| 2012–2016 | 507 (24.5) | 68 | 34.7 | 12.2 | 8.0 | 447 (15.4) | 71 | 27.7 | 8.5 | 7.4 |

1991 to 2012–2016 the 1-, 3- and 5-year survivals increased from 48% to 87%, 28%–59% and 20%–49%, respectively (Fig. 2c, Table 2).

#### 3.2.3. Patients not undergoing oesophagectomy

In patients not undergoing surgery, the 1-year survival increased from 22% in 1987–1991 to 35% in 2012–2016. The 3-year survival increased from 7% to 12% and the 5-year survival from 5% to 8% in the same time period (Fig. 2e, Table 2).

### 3.3. Survival trends in oesophageal squamous cell carcinoma

#### 3.3.1. All patients

The observed survival in patients diagnosed with OSCC improved during the study period. The 1-year survival increased moderately from 34% in 1987–1991 to 35% in 2012–2016, decreasing to the range of 31%–32% in the years between. The 3-year survival increased from 11% to 15% and the 5-year survival increased from 7% to 13% in the same time period (Fig. 2 b, Table 2).

#### 3.3.2. Patients undergoing oesophagectomy

The 1-, 3- and 5-year survivals in patients treated surgically for OSCC increased substantially during the study period. From 1987 to 1991 to 2012–2016 the 1-, 3- and 5-year survivals increased from 48% to 86%, 18%–60% and 11%–54%, respectively (Fig. 2d, Table 2).

#### 3.3.3. Patients not undergoing oesophagectomy

In patients not undergoing surgery, the 1-year survival increased from 26% in 1987–1991 to 28% in 2012–2016, decreasing to the range of 22%–24% in the years between (Table 1). The 3-year survival increased from 8% in 1987–1991 to 9% in 2012–2016, decreasing to 4% in 1992–1996 and 1997–2001. The 5-year survival increased from 5% to 7% in the same time period (Fig. 2f, Table 2).

### 3.4. Risk factors for 5-year mortality in oesophageal adenocarcinoma

In OAC, earlier calendar periods and older age were risk factors for 5-year mortality. HR for first vs last calendar period was 1.61 in all patients, 3.12 in operated and 1.32 in non-operated patients, and HR for age 80–89 vs < 50 was 1.86 in all patients, 2.00 in operated and 1.24 in non-operated patients. Sex did not affect the HR of mortality in any patients with OAC. In all patients with OAC, comorbidity had a higher HR for 5-year mortality (HR 1.28, CCI ≥3 vs no comorbidities), whereas it was not a risk factor for death in patients undergoing surgery nor in those not (Table 3).

### 3.5. Risk factors for 5-year mortality in oesophageal squamous cell carcinoma

Risk factors for 5-year mortality in OSCC were similar in patients undergoing oesophagectomy and those not: earlier calendar period, older age group and higher comorbidity were associated with a higher adjusted HR for mortality. Female sex was a protective factor in patients with OSCC: HR for male vs female sex was 1.56 in operated and 1.28 in non-operated patients (Table 3).

## 4. Discussion

The present study reports overall improved prognosis trends in oesophageal cancers in a 30-year period in Finland. The prognosis has improved in both OAC and OSCC, especially in those receiving surgical treatment. Factors associated with a higher risk of all-cause mortality in patients with OAC and OSCC were earlier calendar period of diagnosis, older age and comorbidity, and additionally male sex in OSCC.

The main strengths of this study include the nationwide, population-based design. The two registries used concurrently assured a validated, highly complete dataset for the study, allowing robust analyses in the subgroups of patients [15–17]. The limitations in this study include the few missing data on histological confirmation of cancers, which might slightly decrease the accuracy of the histological subtype analyses. Unavailable variables, such as the use of neoadjuvant treatment and other oncological treatments, and lack of TNM stage information prevented more granular analysis. However, the trends in a larger perspective could still be well described.

Comparing to the available histology-specific survival data, the prognosis of patients in Finland follows similar improvement rates.

**Table 3**
Multivariable analysis of risk factors for 5-year mortality as hazard ratios (HR) and 95% confidence intervals (CI) for oesophageal adenocarcinoma and oesophageal squamous cell carcinoma in Finland in 1987–2016.

| **Category** | Oesophageal adenocarcinoma | | Oesophageal squamous cell carcinoma | |
|---|---|---|---|---|
| | **Patients** Number (%) | **HR** (95% CI)[a] | **Patients** Number (%) | **HR** (95% CI)[a] |
| *All patients* | | | | |
| Calendar period | | | | |
| 1987–1991 | 202 (6.4) | 1.61 (1.35–1.90) | 736 (19.5) | 1.20 (1.07–1.36) |
| 1992–1996 | 300 (9.6) | 1.42 (1.22–1.65) | 675 (17.9) | 1.29 (1.14–1.46) |
| 1997–2001 | 437 (13.9) | 1.29 (1.13–1.47) | 639 (16.9) | 1.24 (1.10–1.40) |
| 2002–2006 | 632 (20.1) | 1.20 (1.06–1.35) | 591 (15.6) | 1.13 (1.00–1.29) |
| 2007–2011 | 818 (26.1) | 1.11 (0.99–1.24) | 625 (16.5) | 1.08 (0.96–1.23) |
| 2012–2016 | 751 (23.9) | 1 (reference) | 512 (13.6) | 1 (reference) |
| Age (years) | | | | |
| <50 | 207 (6.6) | 1 (reference) | 141 (3.7) | 1 (reference) |
| 50–59 | 618 (19.7) | 1.00 (0.84–1.19) | 569 (15.1) | 0.99 (0.81–1.20) |
| 60–69 | 945 (30.1) | 1.10 (0.93–1.30) | 1086 (28.7) | 1.06 (0.87–1.28) |
| 70–79 | 892 (28.4) | 1.23 (1.04–1.46) | 1134 (30.0) | 1.25 (1.03–1.51) |
| 80–89 | 429 (13.7) | 1.86 (1.54–2.24) | 749 (19.8) | 1.70 (1.39–2.07) |
| ≥90 | 49 (1.6) | 2.41 (1.74–3.35) | 99 (2.6) | 2.48 (1.89–3.26) |
| Sex | | | | |
| Male | 2430 (77.4) | 0.98 (0.89–1.08) | 2077 (55.0) | 1.43 (1.33–1.54) |
| Female | 710 (22.6) | 1 (reference) | 1701 (45.0) | 1 (reference) |
| Comorbidity score | | | | |
| 0 | 1799 (57.3) | 1 (reference) | 2319 (61.4) | 1 (reference) |
| 1 | 771 (24.6) | 1.07 (0.97–1.17) | 883 (23.4) | 1.09 (1.01–1.19) |
| 2 | 351 (11.2) | 1.24 (1.09–1.40) | 371 (9.8) | 1.18 (1.05–1.32) |
| ≥3 | 219 (7.0) | 1.28 (1.10–1.49) | 205 (5.4) | 1.44 (1.24–1.68) |
| *Surgery* | 1799 (57.3) | | | |
| Calendar period | | | | |
| 1987–1991 | 85 (7.9) | 3.12 (2.30–4.24) | 258 (29.7) | 3.60 (2.45–5.29) |
| 1992–1996 | 124 (11.5) | 2.32 (1.76–3.06) | 233 (26.8) | 3.37 (2.29–5.00) |
| 1997–2001 | 173 (16.1) | 1.79 (1.38–2.32) | 135 (15.5) | 2.46 (1.64–3.71) |
| 2002–2006 | 206 (19.2) | 1.42 (1.11–1.83) | 101 (11.6) | 1.67 (1.08–2.57) |
| 2007–2011 | 242 (22.5) | 1.08 (0.85–1.39) | 78 (9.0) | 1.10 (0.68–1.76) |
| 2012–2016 | 244 (22.7) | 1 (reference) | 65 (7.5) | 1 (reference) |
| Age (years) | | | | |
| <50 | 97 (9.0) | 1 (reference) | 50 (5.7) | 1 (reference) |
| 50–59 | 253 (23.6) | 0.98 (0.73–1.33) | 166 (19.1) | 0.99 (0.68–1.44) |
| 60–69 | 370 (34.5) | 1.01 (0.75–1.35) | 311 (35.7) | 1.07 (0.75–1.53) |
| 70–79 | 303 (28.8) | 1.13 (0.84–1.52) | 272 (31.3) | 1.37 (0.96–1.97) |
| 80–89 | 49 (4.6) | 2.00 (1.33–3.02) | 67 (7.7) | 2.26 (1.48–3.45) |
| ≥90 | 2 (0.2) | 6.90 (1.63–29.17) | 4 (0.5) | 2.16 (0.75–6.26) |
| Sex | | | | |
| Male | 877 (81.7) | 1.10 (0.90–1.34) | 436 (50.1) | 1.56 (1.33–1.83) |
| Female | 197 (18.3) | 1 (reference) | 434 (49.9) | 1 (reference) |
| Comorbidity score | | | | |
| 0 | 713 (66.4) | 1 (reference) | 638 (73.3) | 1 (reference) |
| 1 | 226 (21.0) | 1.09 (0.89–1.33) | 171 (19.7) | 1.14 (0.93–1.38) |
| 2 | 87 (8.1) | 1.15 (0.86–1.55) | 45 (5.2) | 1.50 (1.09–2.08) |
| ≥3 | 48 (4.5) | 1.48 (1.03–2.14) | 16 (1.8) | 1.51 (0.85–2.67) |
| *No surgery* | | | | |
| Calendar period | | | | |
| 1987–1991 | 117 (5.7) | 1.32 (1.07–1.63) | 478 (16.4) | 1.14 (0.99–1.31) |
| 1992–1996 | 176 (8.5) | 1.31 (1.09–1.56) | 442 (15.2) | 1.33 (1.16–1.52) |
| 1997–2001 | 264 (12.8) | 1.31 (1.12–1.53) | 504 (17.3) | 1.26 (1.10–1.43) |
| 2002–2006 | 426 (20.6) | 1.17 (1.03–1.34) | 490 (16.9) | 1.16 (1.02–1.33) |
| 2007–2011 | 576 (27.9) | 1.10 (0.97–1.25) | 547 (18.8) | 1.11 (0.97–1.26) |
| 2012–2016 | 507 (24.5) | 1 (reference) | 447 (15.4) | 1 (reference) |
| Age (years) | | | | |
| <50 | 110 (5.3) | 1 (reference) | 91 (3.1) | 1 (reference) |
| 50–59 | 365 (17.7) | 0.92 (0.74–1.15) | 403 (13.9) | 0.95 (0.75–1.21) |
| 60–69 | 575 (27.8) | 1.08 (0.87–1.33) | 775 (26.7) | 0.97 (0.77–1.21) |
| 70–79 | 589 (28.5) | 1.10 (0.89–1.36) | 862 (29.6) | 1.03 (0.82–1.29) |
| 80–89 | 380 (18.4) | 1.24 (0.99–1.55) | 682 (23.5) | 1.17 (0.93–1.47) |
| ≥90 | 47 (2.3) | 1.49 (1.04–2.12) | 95 (3.3) | 1.71 (1.27–2.30) |
| Sex | | | | |
| Male | 1553 (75.2) | 1.02 (0.92–1.14) | 1641 (56.4) | 1.28 (1.18–1.39) |
| Female | 513 (24.8) | 1 (reference) | 1267 (43.6) | 1 (reference) |
| Comorbidity score | | | | |
| 0 | 1086 (52.6) | 1 (reference) | 1681 (57.8) | 1 (reference) |
| 1 | 545 (26.4) | 0.94 (0.84–1.05) | 712 (24.5) | 1.04 (0.95–1.14) |
| 2 | 264 (12.8) | 1.11 (0.96–1.28) | 326 (11.2) | 1.05 (0.92–1.19) |
| ≥3 | 171 (8.3) | 1.06 (0.89–1.25) | 189 (6.5) | 1.34 (1.14–1.56) |

[a] Adjusted for calendar period, age, sex and comorbidity.

In the USA, 5-year survival improved from 5% to 24% in OAC and from 4% to 21% in OSCC between 1973 and 2010 [2]. In the SURVMARK-2 study conducted for 7 high-income countries, 3-year survival improved from 10%-21% to 22%–29% in OAC and from 8%-24% to 20%–29% in OSCC during 1995–1999 to 2010–2014 [21]. Both of these studies lacked stratification for surgical treatment status. Survival trends similar to the present study reported from Sweden were expected due to the similar populations and publicly funded healthcare systems in Finland and Sweden. From 1990 to 1994 to 2010–2013, the 5-year survival in Sweden increased from 12% to 15% in OAC patients, and from 9% to 12% in OSCC patients [10]. In the present study, 5-year survival improved from 11% to 22% in OAC and from 7% to 13% in OSCC during 1987–1991 to 2012–2016. In patients undergoing oesophagectomy, the improvements observed in Finland seem to be superior to those of Sweden: In Finland, the 5-year survival improved from 20% in 1987–1991 to 49% in 2012–2016 in OAC (22%–40% in Sweden 1990–1994 to 2010–2013) and from 11% to 54% in OSCC (20%–39% in Sweden 1990–1994 to 2010–2013) in the same time period.

The overall survival improvement of operated patients in this study is due to many factors. Changes in surgical technique, including lymphadenectomy and minimally invasive approach may have improved the prognosis of operated patients in Finland [6,22,23]. The use of minimally invasive oesophagectomy in Finland has increased rapidly in the 2000s, with 35% of all oesophagectomies being minimally invasive in 2010–2014 [24]. Centralization of surgery in Finland is ongoing, yet most centers would still be classified as low volume (median of Finnish centers at 3.7 per hospital per year in 2010–2014) [24]. Hospital and surgeon volume of oesophagectomy have been shown to affect long-term survival [7,25,26]. Neoadjuvant treatment has been standard-of-care in Finland for over a decade (first implemented around the year 2000), which might show in the rapid developments in survival in the 2000s [5]. The CROSS trial demonstrated a higher responsiveness of OSCC to chemoradiotherapy [12], which may be reflected in the greater increase in the 5-year survival of OSCC patients compared to OAC in the current era of routine neoadjuvant therapy. Other factors playing a role in the improved survival of patients undergoing surgery might include improved staging (e.g. positron emission tomography, PET-CT) and careful selection of surgery-eligible patients (especially regarding the elderly [27] and comorbid patients [28]), as reflected in the declining proportion of surgically treated cancers.

Regarding the patients not undergoing surgery, the 1-, 3- and 5-year survivals were better during years 1987–1991 than in the following time period in patients with OSCC. It could be speculated that the survival numbers in 1987–1991 are inflated due to the lower surgical treatment rate in these years, why some surgery-eligible patients might not have received surgical treatment, consequently causing longer survival periods in the non-operated group. Another possibility could be missing operation codes, which may cause misclassification of patients as non-operated. Regardless, the non-surgical management of the disease, i.e. definitive chemoradiotherapy may have been improved and more often used, explaining the improved prognosis in patients not undergoing surgery. Improvements in definitive chemoradiotherapy include recent technological evolutions in radiotherapy such as intensity modulation (higher dosage and dose conformity) and volumetric arc radiotherapy (shorter treatment time), and the introduction of two- or three agent chemotherapy regimens. Other factors include targeted agents such as trastuzumab for HER2-positive disease and the increased knowledge in adverse effect management. Due to the high responsiveness of OSCC to chemoradiotherapy, definitive chemoradiotherapy is considered an alternative curative-intent treatment in selected cases of OSCC [12]. However, in the present study, the better responsiveness was not seen in non-operated patients: 5-year survival in OAC was 8% whereas it was 7% in OSCC in 2012–2016, and 1-year survival was 34% in OAC and 28% in OSCC in the same time period. These improvements considered, the prognosis of non-operated patients in Finland is still poor.

The risk factors for 5-year mortality in oesophageal cancer were as expected. Earlier calendar periods were a risk factor for mortality. As also previously shown, increasing age and comorbidity were risk factors for mortality [27–29]. The main difference between the histological subgroups was female sex being a positive prognostic factor in OSCC, but not OAC. The same was observed in a Swedish study, and similarly, no association between sex and greater risk for 5-year mortality in OAC was found [10]. The issue was further assessed in another Swedish study, in which a positive influence of female sex on prognosis was observed after adjustment for known prognostic factors (tumor stage, comorbidities, educational level, neoadjuvant treatment and surgeon volume) [30]. The mechanisms behind the observed differences are unclear and call for further research.

The present study has several implications. First, the major improvements in survival observed in this study suggest that the changes in the operative care of oesophageal cancer have been correct, but there is still room for improvement especially in patients not receiving operative treatment. The next few years will show whether the implementation of checkpoint inhibitors will bring awaited improvements at population level in these patients. Second, the reasons behind the better prognosis for women with OSCC should be further investigated: if part of the difference can be explained with lifestyle factors rather than with biological differences, the positive effects could also be implemented in men, e.g. with better health-education and knowledge of early symptoms. Finally, a degree of missing histologies indicate that reporting to national registries should be done even more carefully to ensure the data is as complete as possible.

To conclude, this population-based, nationwide study shows an improvement in the survival and prognosis of oesophageal cancer patients over time. Significant improvements in survival were seen in surgically treated patients, with possibilities for even further improvements in the future. While the prognosis of patients not undergoing surgery remains poor, the observed conservative improvements are encouraging.

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## Ethics statement

The study has been approved by the ethical committee in Northern Ostrobothnia (EETMK 115/2016), and governmental agencies and hospital districts involved in the study. The requirement for individual consent was waived by the Finnish Institute for Health and Welfare.

## Disclosures of interest

None.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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