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Oesophageal cancer in The Netherlands: Increasing incidence and mortality but improving survival ☆

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ARTICLE INFO

Article history:
Received 17 January 2007
Received in revised form 22 March 2007
Accepted 29 March 2007
Available online 23 May 2007

Keywords:
Oesophagus
Adenocarcinoma
Incidence
Mortality
Relative survival

ABSTRACT

Aim: Oesophageal cancer is highly lethal with a 5-year relative survival of 10–15%. An increasing incidence has been reported for several parts of the Western world. We studied time trends in incidence, mortality and survival for oesophageal cancer in the Netherlands during 1989–2003.

Methods: Data on incidence and survival were obtained from the Netherlands Cancer Registry and mortality data from Statistics Netherlands.

Results: The age standardised incidence increased by 3.4% ($p < 0.001$) and 1.9% ($p = 0.003$) per year for males and females, respectively. This increase was almost exclusively caused by oesophageal adenocarcinomas. Age standardised mortality increased 2.5% ($p < 0.001$) per year among males and 1.7% ($p = 0.002$) per year among females. Relative survival improved significantly from 8.1% in 1989–1993 to 12.6% in 1999–2003 ($p < 0.001$). Adjusted for age, stage, tumour location and surgery, the excess risk of death decreased by 22%.

Conclusion: Oesophageal carcinoma incidence is rising in the Netherlands. Mortality increased at a slightly lower pace due to improving survival.

1. Introduction

Oesophageal cancer is a relatively uncommon form of cancer in the Western world. The disease is highly lethal, with overall 5-year survival rates of only 10–15%.[1,2] The high mortality is due to the late onset of symptoms.[3] Frequently the diagnosis is made when the patients present with dysphagia due to an obstructing tumour. The disease is then already in an advanced stage with a high potential of occult metastases.[4] Histologically, there are two major subgroups of oesophageal cancer: adenocarcinoma and squamous cell carcinoma.[2] Particularly in the Western world, the incidence of

☆ All authors participated in the writing of the manuscript. Lucia M.A. Crane designed the study and wrote the manuscript; M. Schaapveld provided data, performed the analysis and wrote the manuscript; O.Visser and W.J. Louwman provided data, contributed to the design of the study and interpretation of the data; John T.M. Plukker and Gooitzen M. van Dam contributed to the design of the study and data interpretation.

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doi:10.1016/j.ejca.2007.03.024

adenocarcinomas is rising, while the incidence of squamous cell carcinomas remains stable.[5]

It remains difficult to address specific risk factors for the development of oesophageal cancer. Both smoking and alcohol abuse are known to be associated with an increased risk of squamous cell oesophageal carcinoma.[6] There is cumulating evidence that chronic gastro-oesophageal reflux, eventually leading to Barrett's oesophagus, is an important risk factor in the development of adenocarcinoma of the oesophagus.[7,8] Less convincing results have been published with regard to a high body mass index and dietary factors as risk factors in the Western world.[9–11] Furthermore, genetic predisposition may play a role in the development of oesophageal cancer, although the results are inconsistent.[10,11]

Over the years diagnostic techniques have improved, i.e. through the introduction of the multidetector computed tomography and the wider availability of PET-scan, which will have resulted in better staging of the tumour. Currently, the diagnosis and locoregional staging is based on endoscopic examination with endo-ultrasonography and eventually fine needle aspiration biopsy.[12–14] Endo-ultrasonography and CT scan of thorax and abdomen are used to evaluate nodal involvement and invasion of the tumour in adjacent structures.[12–15] Additionally, a positron emission tomography (PET) scan is used for determination of metastatic spread.[12,16] This improved staging may have resulted in stage migration and better stage-specific survival. However, this phenomenon generally does not improve survival of all stages combined.

Surgical resection is the standard treatment in oesophageal cancer.[17] Chemo-radiotherapy is still under investigation either combined with surgery as neoadjuvant therapy or alone as curative or palliative treatment.[18] Palliative radiotherapy alone can be valuable in reducing symptoms including pain, bleeding and dysphagia.[2]

This study was performed to gain insight into the current trends for oesophageal carcinoma in terms of incidence, mortality and survival in the Netherlands. Previous studies have shown an increase in the incidence of oesophageal cancer in the Western world[5,19–21], but the development of the disease in the Netherlands has not been studied specifically on a national level. Changing incidence rates may result in changes in patient admittance numbers for the specialised centres that perform oesophageal surgery. Specifically in the light of the discussion of centralisation of surgical procedures in the Netherlands and other European countries, the increases in resources required and rising costs may in itself necessitate a change in policy guidelines.

2. Patients and methods

Data were obtained from the nationwide Netherlands Cancer Registry (NCR), which has complete data concerning the occurrence of cancer in The Netherlands since 1989. The Netherlands is now the second largest country in Europe, after the United Kingdom, with national cancer registration coverage. The NCR receives data from nine regional cancer registries, collaborating within the Association of Comprehensive Cancer Centres.

2.1. *Data collection by the regional cancer registries*

The Dutch nationwide network and registry of histo- and cytopathology (PALGA) regularly submits reports of all diagnosed malignancies to the regional cancer registries. The national hospital diagnosis databank, which receives diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. In the Netherlands, all patients are treated in public hospitals. Cancer registry clerks, which have full access to all medical records, including ambulatory care records, register data on diagnosis, stage and treatment, conform with the registration and coding manual of the NCR, within the hospitals. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O).[22] The TNM classification is used for the staging of the tumours[15] For the current analyses, the International Agency for Research on Cancer (IARC) criteria for multiple primaries were applied.[23]

Vital status was established either directly from the patient's medical record, through linkage of cancer registry data with the municipal population registries (which record information on their inhabitants' vital status), or through record linkage with the national death registry of the Central Bureau for Genealogy (CBG). The cohort used for survival analysis comprised data of patients diagnosed with oesophageal cancer in the Comprehensive Cancer Centre North (CCCN), South (CCCS) and Amsterdam (CCCA) regions from January 1989 until January 2004. These registries cover hospitals in the south-eastern and the northern part of The Netherlands with a total population of 7.3 million; about 45% of the Dutch population. Staging was based on pathological information; clinical information was used if pathology data were missing. The cohort was composed in accordance with privacy regulations of The Netherlands Cancer Registry.

3. Statistical analysis

Incidence rates were calculated per 100,000 person years according to gender, histological subtype and year of diagnosis. The population at risk was retrieved from Statistics Netherlands (http://statline.cbs.nl/StatWeb). Incidence rates were age-standardised using the European Standard Population.[24] Similarly, age standardised mortality rates were calculated per 100,000 person years according to gender. Trends were studied by calculating the Estimated Annual Percentage Change (EAPC), i.e. fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable.[25] This calculation assumes a constant rate of change over the entire studied period.

Survival was calculated as the time from the date of diagnosis until the date of death. Otherwise, patients were censored at the date of most recent linkage with the municipal population registries or the date of last contact if lost to follow-up. The overall survival probability was estimated using the Kaplan–Meier method and the distributions of crude survival were compared with the log rank test. The Expected Survival (ES) probability was calculated using age, sex and period matched mortality rates based on Dutch life expectancy tables (http://statline.cbs.nl/StatWeb), based on the

Ederer II method.[26] The cumulative relative survival, the ratio of the overall survival and the ES, was analysed using Stata (version 8.0) and a relative survival function written by Paul Dickman (www.pauldickman.com/teaching/tampere2004).

The relative survival can be considered as an estimator of the excess risk of death or the excess mortality ratio. The excess mortality rate was calculated by subtracting the expected number of deaths from the observed number of deaths and dividing this figure by the accumulated person–years. The excess mortality ratio is derived from the ratio of the excess mortality rates. Excess mortality ratios were estimated in a generalised linear model with a Poisson error structure based on collapsed relative survival data, using exact survival times.[27] For our relative survival analysis, the year of diagnosis was divided into three periods: 1989–1993, 1994–1998 and 1999–2003. Other variables included in the model were gender, the age at diagnosis, histology, location, TNM stage and surgical resection. All variables with a p-value <0.05 in univariate analysis were included in the multivariate model. The assumption of proportionality was verified by including interactions with follow-up time in the model. Model fit was evaluated with the model based Pearson Chi-square goodness-of-fit test statistics.[28] All reported p-values are two sided; the statistical significance level was set at a p-value <0.05.

4. Results

4.1. Incidence and mortality

In the period 1989–2003, 15,739 patients were diagnosed with oesophageal cancer in the Netherlands of whom 10,752 (68.3%) were males and 4987 females. Among males the number of new cases of cancer increased rapidly, from 920 per year in 1989 to 2032 in 2003 and among females from 450 to 838 per year in the same period. The age-standardised incidence among males increased by 3.4% per year ($p < 0.001$; Fig. 1), among females the increase was slightly less by 1.9% per year ($p = 0.003$). The trends differed markedly by histological subgroup. While the number of male patients diagnosed with squamous cell carcinoma increased from 218 in 1989 to 285 in 2003, the number of males diagnosed with oesophageal adenocarcinoma increased strikingly from 207 in 1989 to 669 in 2003. Among females the increase in adenocarcinomas appeared less dramatic, from 74 in 1989 to 175 in 2003, compared to an increase in oesophageal squamous cell carcinomas from 125 in 1989 to 205 in 2003. The age standardised incidence among males remained stable for squamous cell cancers (EAPC −0.7%, $p = 0.143$), but increased markedly for adenocarcinomas by 6.4% per year ($p < 0.001$). Among females the incidence of squamous cell cancers also remained stable (EAPC 0.7%, $p = 0.318$), while the incidence of adenocarcinomas increased by 4.4% per year ($p < 0.001$).

Mortality trends for oesophageal cancer closely followed the trends in incidence. In the period 1989–2003, 15,335 patients died from oesophageal cancer in the Netherlands, of which 10,563 were male and 4772 were female. The age standardised mortality increased by 2.5% per year ($p < 0.001$) among males and slightly less among females by 1.7% per year ($p = 0.002$; Fig. 1).

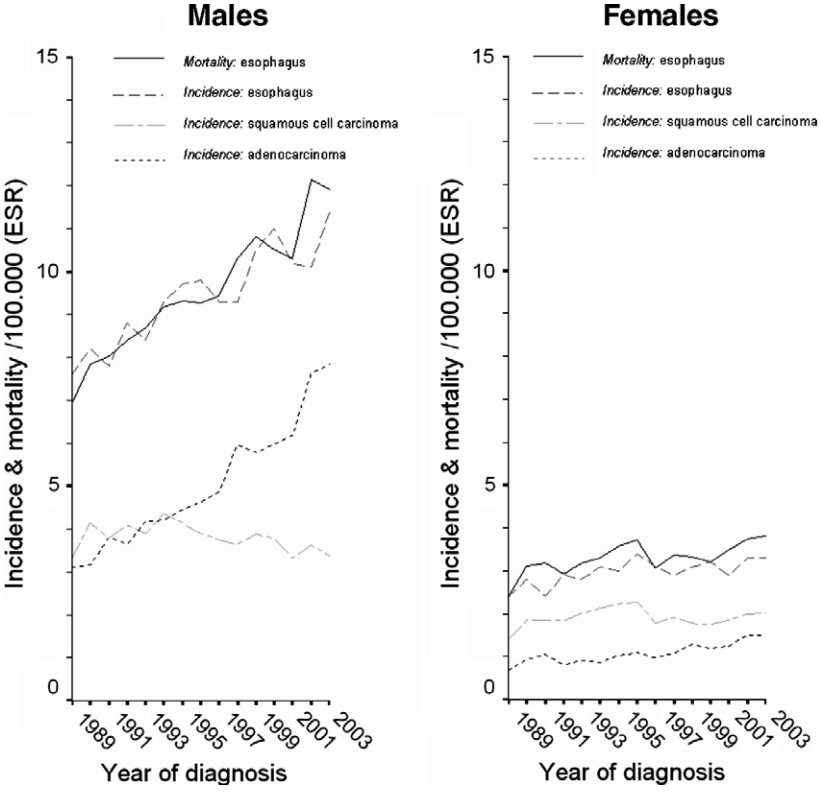

Fig. 1 – Incidence (total, squamous cell carcinomas and adenocarcinomas) and mortality of oesophageal cancer among males and females in The Netherlands in the period 1989–2003.

Table 1 – Relative survival according to period of diagnosis, tumour and patient characteristics

	Period of diagnosis													
	1989–1993					1994–1998					1999–2003				
	N	%	Relative survival (%)			N	%	Relative survival (%)			N	%	Relative survival (%)		
			1 year	3 year	5 year			1 year	3 year	5 year			1 year	3 year	5 year
All patients	1704	100	33	12	8	2049	100	35	15	11	2516	100	38	16	13
Gender															
Male	1101	65	33	10	7	1369	67	34	15	12	1763	70	38	16	12
Female	603	35	35	14	9	680	33	37	16	11	753	30	39	16	13
Age (years)															
<50	131	8	36	16	13	177	9	46	22	17	184	7	45	19	13
50–59	272	16	38	9	7	385	19	42	18	13	553	22	43	20	17
60–69	471	28	35	13	9	578	28	35	17	13	656	26	42	18	13
70–79	520	31	30	13	9	560	27	32	15	11	737	29	39	16	12
80+	308	18	30	9	4	349	17	33	9	5	386	15	30	11	12
Histology															
Adenocarcinoma	680	40	36	12	7	943	46	38	16	13	1438	57	40	17	12
Squamous cell	875	51	33	12	9	934	46	34	15	11	865	34	37	16	14
Undifferentiated	94	6	26	11	6	107	5	18	4	3	161	6	26	9	10
Other	15	1	52	28	10	26	1	42	11	6	17	1	49	17	0
No histological confirmation	40	2	16	6	0	39	2	26	15	10	35	1	40	24	–
Location															
Cervical	19	1	27	9	10	52	2	42	13	10	55	2	37	15	16
Upper thoracic	110	6	32	11	7	125	6	30	10	6	131	5	33	10	10
Middle thoracic	404	24	37	14	10	452	22	33	14	10	457	18	39	14	12
Lower thoracic	992	58	35	12	8	1245	61	37	17	14	1710	68	39	17	13
Overlapping	162	10	21	7	5	147	7	28	12	7	109	4	28	12	9
NOS	17	1	16	8	–	28	1	21	5	–	54	2	31	13	10
TNM stage															
I	74	4	54	30	26	91	4	87	83	79	110	4	89	72	75
IIA	205	12	68	26	19	213	10	63	33	27	255	10	62	38	23
IIB	170	10	37	9	8	234	11	43	15	9	247	10	51	16	12
III	265	16	31	12	7	370	18	39	14	10	533	21	47	17	12
IV	370	22	13	2	1	502	25	15	2	1	830	33	18	4	2
Unknown	614	36	32	11	7	631	31	30	10	7	535	21	33	12	11
Not applicable	6	0	65	44	22	8	0	40	13	13	5	0	44	24	0
Tumour resected															
Yes	360	21	62	28	21	526	26	68	41	33	528	21	74	43	33
No	1342	79	25	7	4	1519	74	24	6	4	1979	78	29	9	7

4.2. *Survival*

Survival was poor for most patients, with an overall 5-year relative survival rate of 10.9% (95% confidence interval (CI) 10.0–12.0%) over the period 1989–2003. Although modest in absolute terms, survival did improve significantly over the study period (Table 1). The 5-year survival increased from 8.1% (95% CI 6.6–9.8%) for patients diagnosed between 1989 and 1993 to 12.6% (10.5–14.8%) for patients diagnosed between 1999 and 2003 ($p < 0.001$). The increase in relative survival was most pronounced between the period 1989–1993 and 1994–1998 (AER for 1994–1998 0.87, 95% CI 0.80–0.93). Survival did not improve markedly between 1994–1998 and 1999–2003 (AER for 1999–2003 0.96, 95% CI 0.89–1.03). Table 1 further shows a shift in the stage distribution over time with a decrease in the proportion of tumours staged as 'unknown', while the proportion of stages III and IV tumours increased ($p < 0.001$). The proportion of patients who underwent surgery did differ between the study periods. It was 21.2% for the period 1989–1993, 25.7% for 1994–1998 and 21.0% for 1999–2003 ($p = 0.010$). There was a rather large difference in survival for stage I patients between the years 1989–1993 and later years ($p < 0.001$), with 5-year survival rates of 26% (95% CI 15.4–39.1%) for the period 1989–1993 versus 79% (95% CI 67.3–83.9%) for 1994–1998.

Older age at the time of diagnosis and higher tumour stage were associated with lower survival (Table 2). Tumour location and histology were only weakly associated with survival with worse survival for patients with overlapping or unclassified lesions. Gender showed no association with survival. In

Table 2 – Relative excess risks of death according to tumour and patient characteristics

	Univariate[a]			Multivariate[b]		
	RER	95% CI	*p*-Value	RER	95% CI	*p*-Value
Period			$p < 0.0001$			$p < 0.0001$
1989–1993	1.00			1.00		
1994–1998	0.86	0.80–0.93		0.90	0.83–0.97	
1999–2003	0.83	0.77–0.89		0.78	0.72–0.84	
Gender			0.4203			NS
Male	1.00			–		
Female	0.98	0.91–1.04		–		
Age group			$p < 0.0001$			$p < 0.0001$
<50	1.00			1.00		
50–59	1.05	0.93–1.18		1.05	0.93–1.18	
60–69	1.12	1.00–1.26		1.15	1.02–1.29	
70–79	1.30	1.15–1.45		1.32	1.18–1.49	
80+	1.66	1.46–1.87		1.56	1.36–1.78	
Histology			$p < 0.0001$			0.0382
Adenocarcinoma	1.00			1.00		
Squamous cell	1.08	1.01–1.15		1.04	0.97–1.11	
Undifferentiated	1.56	1.38–1.76		1.20	1.06–1.36	
Other	0.93	0.69–1.25		1.03	0.71–1.49	
No histological confirmation	1.51	1.21–1.89		1.14	0.91–1.43	
Location			$p < 0.0001$			$p = 0.0002$
Cervical	1.00			1.00		
Upper thoracic	1.08	0.86–1.36		0.94	0.75–1.19	
Middle thoracic	0.96	0.78–1.18		0.91	0.73–1.12	
Lower thoracic	0.91	0.74–1.11		0.94	0.76–1.16	
Overlapping	1.31	1.04–1.64		1.17	0.93–1.47	
NOS	1.41	1.05–1.90		1.27	0.94–1.71	
TNM stage			$p < 0.0001$			$p < 0.0001$
I	1.00			1.00		
IIA	2.53	1.98–3.24		2.23	1.75–2.84	
IIB	4.20	3.30–5.33		3.21	2.52–4.08	
III	4.38	3.47–5.52		3.78	3.00–4.77	
IV	9.00	7.15–11.33		5.92	4.68–7.47	
Unknown	5.84	4.64–7.35		3.09	2.44–3.91	
Not applicable	3.91	2.26–6.76		2.29	1.17–4.47	
Tumour resected			$p < 0.0001$			$p < 0.0001$
Yes	1.00			1.00		
No	3.03	2.80–3.28		2.09	1.91–2.29	

RER, relative excess risk of death; NS, not significant.
a Adjusted for time since diagnosis.
b The multivariate model contained time since diagnosis, period of diagnosis, age, tumour histology, localisation, TNM stage and resection.

univariate analysis the strongest predictor for survival besides stage was surgical resection of the tumour. While 5-year survival was only 4.9% (95% CI 4.1–5.8%) for patients without surgery, it was 30.1% (95% CI 27.1–33.1%) for patients who underwent surgery.

Multivariate relative survival analysis confirmed an improving prognosis of oesophageal cancer over time (Table 2). Adjusted for age, stage, tumour location and surgery, the excess risk of death decreased by 22% (95% CI 16–28%) in the period 1999–2003 compared to 1989–1993. Patients aged 60 years or over had worse outcomes compared to younger patients and the excess risk of death increased markedly with more advanced stage. The excess risk of death was more than halved by surgical resection of the tumour.

5. Discussion

Using data from the Netherlands Cancer Registry (NCR), we have shown a substantial increase in the incidence of oesophageal cancer in the Netherlands. This increase was almost exclusively caused by adenocarcinomas, the incidence of squamous cell carcinoma of the oesophagus did not increase. An increase in incidence has already been shown in other countries, especially in the Western world.[19–21,29,30]

Barrett's oesophagus is an important risk factor for the development of oesophageal cancer. Lowering the incidence of Barrett's oesophagus through better prevention or earlier treatment of gastro-oesophageal reflux could be a step in decreasing the incidence of oesophageal adenocarcinoma. Questions are raised whether patients who are diagnosed with Barrett's oesophagus should be screened endoscopically on a more regular basis, in order to detect early cancerous lesions when the tumour is still small and thus suitable for radical resection.[7] However, whereas Barrett's oesophagus can progress to carcinoma, only a small number of patients with Barrett's oesophagus die as a result of oesophagus cancer.[31] There is still a fair amount of discussion on the subject of screening and results are not consistent.[32]

Mortality due to oesophageal cancer also increased, but at a slightly lower pace than the incidence, suggesting improved survival. This was confirmed by survival analysis which showed an increase in 5-year relative survival from 8% in 1989–1993 to 13% in 1999–2003.

We have shown in this study that while incidence and mortality of oesophageal cancer are rising, at the same time survival has improved. This increase in survival is most likely explained by increasing concentration of oesophageal surgery, an increase in and better selection of the proportion of patients who underwent resections and increasing use of (neo)adjuvant treatment. With the introduction of spiral/multidetector CT and endoscopic ultrasonography (EUS), staging has become increasingly more accurate.[12–14] Additionally, the value of positron-emission tomography (PET) with 18F fluoro-deoxyglucose for detection of systemic metastases has recently been shown.[16] The effects of improved staging are shown in this study with the proportion of tumours staged as 'unknown' decreasing over time. The increase in survival of patients with stage I cancer observed in our study is probably also related to improved accuracy of staging. Besides, there was an increase in the proportion of stage I patients who underwent surgery in the later periods. However, coincidence may also play a role as the number of stage I patients was rather low.

Another advantage of the improved diagnostic (staging) techniques is that patient selection for surgery is more adequate, which will prevent futile esophageal resections. Consequently, it will diminish the demand for scarce surgical resources. Anaesthesiological techniques and postoperative care have improved over the past few years, which results in better postsurgical outcomes. The type of surgical intervention depends mainly on the extent of the tumour. Surgical techniques improved greatly with the introduction of en-bloc resection of the tumour combined with two-field lymphadenectomy, resulting in improved survival.[2–4]

The increased incidence of adenocarcinomas observed in this study is unlikely to be fully explained by changes in registration practises. Although some adenocarcinomas of the distal oesophagus may have been classified erroneously in the Netherlands Cancer Registry as cancers of the gastric cardia or as gastric cancers with unspecified subsite, this unlikely explains the magnitude of change in the incidence of oesophageal adenocarcinomas. Furthermore, adenocarcinomas of the gastric cardia show a similar incidence trend as adenocarcinomas of the oesophagus in the Netherlands (data not shown).

All Comprehensive Cancer Centres in The Netherlands collect and have collected their data in the same standardised way using internationally agreed coding systems for describing morphology, topography and histology. Furthermore, these data are verified by trained personnel directly from the patients' medical charts using all available information. Mortality data were collected from the National Death Registry to which all physicians submit data concerning cause of death. All data used for statistical analysis were thus directly comparable and no additional conversion was needed. Survival data were only available from three of nine Comprehensive Cancer Centres, covering 45% of the population in the Netherlands. The three regions covered (North, Amsterdam and South) are however diverse with respect to population, level of urbanisation and ethnicity and a good representation of the country as a whole.

From this study it is clear that the incidence of oesophageal cancer in the Netherlands is rising. Studies have shown a relationship between hospital type, hospital volume and survival for various cancers,[33,34] which has had a substantial impact on referral patterns, ICU admissions and duration of hospital stay in specialised centres. Furthermore, due to changes in pre-operative treatment protocols, more patients will be treated with a combination of chemoradiation followed by surgical resection.

The increase in incidence will undoubtedly lead to a significant increase in overall demand on resources, mainly in specialised centres, and to increasing costs in these centres. Continuing improvements in staging techniques may further improve patient selection for curative therapies. Although the prognosis of oesophageal cancer is still very poor, the increase in survival observed in this study, albeit small, allows a glimmer of hope for the future.

Conflict of interest statement

None declared.

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