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Management and prognosis of esophageal cancers: Has progress been made?

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ABSTRACT

The aim of this study was to investigate time trends in treatment and prognosis of esophageal cancer in a well-defined French population. Data was obtained from the Burgundy Cancer Registry (France) and three time periods were defined: 1976–90, 1991–96 and 1997–2002. A logistic regression was used to identify factors associated with an R0 resection. A multivariate survival analysis was performed using a Cox model. From 1976 to 2002, 2267 patients were included. The R0 resection rate slightly increased from 20.9% to 25.8% ($P = 0.019$) then remained stable. Operative mortality decreased from 11.7% to 6.7% (NS). Age and subsite significantly influenced the rate of resection for cure whereas period had no effect. Chemotherapy alone was seldom used and radiotherapy alone dramatically dropped over time. Chemoradiation used as adjuvant treatment increased from 16.3% (1976–90) to 30.6% (1997–02) ($P < 0.001$) and as sole treatment from 16.0% to 48.5% ($P < 0.001$). The 3-year survival rates were respectively 10.1% and 9.7% (NS). Age and stage at diagnosis influenced the prognosis of esophageal cancer whereas time period and histology had no influence. This study claims that esophageal cancer remains a serious cancer problem and no improvement has been seen in the study population in France in its management over time.

1. Introduction

With nearly 5000 new cases in France during the year 2000, esophageal cancer ranks eleventh among cancers [1] and its prognosis remains among the poorest [2]. Although esophageal cancer accounts for one quarter of superior aerodigestive tract cancers, there are few reports on its management over time in the general population. The complexity of management strategies associated with short survival partly explains this situation. Most available reports are hospital or trial based. Due to selection bias, these data cannot be used as reference values. Yet, it is important to know the trends in outcome over time at a population level. Cancer registries recording accurate data about treatment and follow-up represent the only way to assess how patients are managed. The aim of this study was to assess time trends in treatment and prognosis of esophageal cancers diagnosed over a 27-year period in a well-defined French population.

2. Patients and methods

2.1. Population

A population-based cancer registry records all digestive tract cancers in two administrative areas in Burgundy (France): Côte-d'Or (507,000 inhabitants according to the 1999 census)

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and Saône-et-Loire (543,000 inhabitants). Cancer registration started in the Côte-d'Or area in 1976 and in the Saône-et-Loire area in 1982. Information is regularly obtained from pathologists, hospitals (university hospitals including the comprehensive-cancer centre, general hospitals), private physicians (gastroenterologists, surgeons, oncologists and radiotherapists) and general practitioners, as well as from the National Health system and monthly reviews of death certificates. Due to the multiplicity of information sources, it is assumed that nearly all newly diagnosed cancers are registered. The quality and comprehensiveness of registration is certified every 4 years by an audit of the Institut National de la Santé et de la Recherche Médicale (INSERM) and of the Institut de Veille Sanitaire (InVS). The data routinely collected are related to the clinical features, treatment, stage at diagnosis and survival of patients.

2.2. Studied variables

We reviewed a population-based series of 2267 patients diagnosed in Burgundy between 1976 and 2002. Diagnosis was based on endoscopy in 98% of the cases. Cancer site and histology were classified according to the International Classification of Diseases for Oncology [3]. Subsite included the upper third (C15.3, $n = 534$), the middle third (C15.4, $n = 912$) and the lower third (C15.5, $n = 727$). Precise localisation was unknown for 94 cases (C15.9). Histology included squamous cell carcinoma ($n = 1752$), adenocarcinoma ($n = 319$) and other types (malignant tumours not otherwise specified $n = 26$, undifferentiated carcinomas $n = 23$, signet ring cell carcinomas $n = 9$, colloid carcinomas $n = 8$, endocrine malignant tumours $n = 4$, sarcoma $n = 2$ and lymphomas $n = 2$). No pathological examination was performed for 122 cases. Time at diagnosis was tabulated into three periods: 1976–1990, 1991–1996 and 1997–2002.

Treatment was divided into four categories: 'R0' resection (when the distal and circumferential margins were free of tumour with no evidence of distant metastasis), 'R1/R2' resection (when there were positive margins or when the surgeon deemed the tumour not completely removed), 'palliative surgery' (bypass and exploratory laparotomy) and 'no surgery'. Operative mortality was defined as death within 30 days of surgery. Chemotherapy and radiotherapy were considered according to surgical procedures as adjuvant or as palliative therapy. Adjuvant chemo-radiotherapy was administered before surgery. Treatment procedures remained unknown for one case. T, N and M items were routinely collected. Cancer extension at the time of diagnosis was classified according to the 1997 TNM classification [4]: T1N0M0 (stage I), T2-3N0M0 (stage IIa), T1-2N1M0 (stage IIb), T3N1M0 (stage III) or T4N0-1M0 and M1 (stage IV). Those who underwent resection but were not staged were classified as unknown. Those in whom the cancer was not resected and with no evidence of visceral metastasis were considered as locally advanced stage ($n = 1299$).

2.3. Statistical method

Evolution of cancer characteristics according to study periods was performed with the χ^2 test. A logistic regression was used to identify factors associated with R0 resection. Age and sex were forced in the model. The other covariates were included in multivariate analysis if they were associated with R0 resection with a $P < 0.10$ in the univariate analysis. Results are expressed in terms of Odds Ratio (OR) and their 95% confidence interval (CI). The life status was known for 2183 patients (96%) in July 2004. Crude survival rates were calculated by the actuarial method and differences between survival curves were tested with the log-rank test. Prognostic factors were investigated using a Cox regression analysis. The significance of the covariates was tested using the likelihood ratio. Analysis was performed using the Stata V8 software.

3. Results

3.1. Clinical presentation

Overall, 90.3% of the cases were males. Mean age at diagnosis was 63.8 for males (standard deviation: 11.8) and 72.9 for females (standard deviation: 12.5) ($P < 0.0001$). The sex ratio decreased from 10.6 during the first study period to 7.5 during the last study period. Proportion of cases according to the localisation of cancer varied over time. There was a decrease of upper third and middle third cancers and an increase in lower third cancers ($P = 0.006$) (Table 1). Squamous cell cancers remained the most frequent histological type, however adenocarcinomas significantly increased over the 26 years of the study ($P < 0.001$). The ratio between these two histological categories decreased from 12.4 to 2.5. Seventy five cancers were stage I, 168 were stage IIa, 57 were stage IIb, 224 were stage III, 391 were stage IV and 53 were classified as unknown. Overall 1299 cases were considered as locally advanced stage (the cancer was not resected and there was no evidence of visceral metastasis). The decrease of locally advanced stages was associated with an increase of metastatic cases. There was no significant change over time for earlier stages.

3.2. Time trends in treatment

There was no significant variation in surgical treatment over the study period. Overall 22.8% of the patients were resected for cure. This proportion slightly varied from 20.9% (1976–90) to 25.8% (1991–96) then remained stable (Table 1). The proportion of patients resected for cure according to age varied little: 25.5% of the patients aged under 75% and 4.2% of the patients aged 75 and over during the first period and respectively 27.7% and 9.2% during the last one. Operative mortality for patients resected for cure was lower during the third study period (6.7%) than during previously (11.7%, $P = 0.286$). The proportion of curatively resected patients receiving radiotherapy as sole adjuvant treatment decreased over time whereas the combination of radio and chemotherapy increased (Table 2). During the last study period (1997–2002), 30.6% of the R0 resected patients had chemo-radiation. Adjuvant chemotherapy was rarely used over the three study periods. The use of palliative chemo-radiotherapy also increased over time from 16.0% to 48.5% ($P < 0.001$).

Table 1 – Time trends in epidemiological characteristics of esophageal cancer

	n	1976–90	1991–96	1997–2002	*P*
		1114	629	524	
Sex					
Male	2047	91.4%	90.1%	88.2%	
Female	220	8.6%	9.9%	11.8%	0.121
Age					
<75 years	1766	78.7%	78.7%	75.2%	0.234
⩾75 years	501	21.3%	21.3%	24.8%	
Localisation[a]					
Upper third	534	27.0%	22.8%	21.7%	
Middle third	912	42.8%	42.9%	39.3%	
Lower third	727	30.2%	34.4%	39.0%	0.006
Histology					
Squamous cells	1752	83.3%	76.2%	65.8%	
Adenocarcinoma	319	6.7%	17.2%	26.0%	
Others	74	3.1%	3.3%	3.6%	
No histology	122	6.9%	3.3%	4.6%	<0.001
Stage resected[b]					
T1 N0 M0 (stage I)	75	6.9%	18.0%	15.6%	
T2-3 N0 M0 (stage IIA)	168	27.4%	28.9%	26.7%	
T1-2 N1 M0 (stage IIB)	57	9.7%	7.7%	11.1%	
T3 N1 M0 & T4 N0-1 M0 (stage III)	224	37.9%	34.0%	39.3%	
M1 (stage IV)	29	3.9%	5.6%	5.2%	<0.001
Not resected					
M1 (stage IV)	362	15.3%	25.3%	31.9%	
Locally advanced[d]	1299	84.7%	74.7%	68.1%	<0.001
Surgical treatment[c]					
R0	516	20.9%	25.8%	23.1%	
R1/R2	90	4.0%	5.1%	2.7%	
By pass/laparotomy	159	8.4%	5.7%	5.7%	
No surgery	1501	66.8%	63.4%	68.5%	0.019

a 94 cases with no precise information.
b 53 cases unknown.
c 1 case unknown.
d Cases in whom the cancer was not resected and with no evidence of visceral metastasis.

Table 2 – Time trends in non-surgical treatment of esophageal cancer

Treatment other than surgery	R0 resection				R1/R2 resection				No surgery			
	76–90	91–96	97–02	*P*[a]	76–90	91–96	97–02	*P*[a]	76–90	91–96	97–02	*P*[a]
Chemoradiotherapy	16.3%	41.4%	30.6%		18.2%	25.0%	42.9%		16.0%	42.6%	48.5%	
Chemotherapy alone	4.3%	1.8%	5.0%		0.0%	9.4%	7.1%		4.0%	7.3%	7.2%	
Radiotherapy alone	24.5%	8.6%	7.4%		15.9%	15.6%	14.3%		53.8%	21.1%	17.8%	
No cytotoxic therapy	54.9%	48.2%	57.0%	<0.001	65.9%	50.0%	35.7%	0.244	26.1%	29.1%	26.5%	<0.001

a χ^2 test for homogeneity.

After adjustment for sex, a multivariate logistic model identified age and localisation of the cancer as the only factors significantly and independently associated with R0 resection. Neither sex, period of diagnosis nor histology influenced R0 resection (Table 3).

3.3. *Survival*

The overall 1-, 3- and 5-year survival rates for esophageal cancers were 36.0%, 10.6% and 6.1%. Trends in three-year survival rates according to sex, stage, histology and treatment are

Table 3 – Factors associated with R0 resection

	%	P[a]	OR	95%CI	P[b]
Age					
<75 years	27.5		1.00		
⩾75 years	6.2	<0.001	0.14	[0.09–0.21]	<0.001
Sex					
Male	25.3		1.00		
Female	17.3	0.041	1.01	[0.67–1.51]	0.919
Histology					
Adenocarcinoma	29.1		1.00		
Squamous cell carcinoma	23.2	0.024	0.91	[0.66–1.24]	0.294
Period					
1976–90	20.9		1.00		
1991–96	25.8		1.26	[0.98–1.62]	0.055
1997–2002	23.1	0.067	1.03	[0.79–1.36]	0.844
Subsite					
Upper third	10.3		1.00		
Middle third	22.4		2.58	[1.86–3.59]	<0.001
Lower third	34.4	<0.001	5.57	[4.00–7.97]	<0.001

Logistic regression carried out among 2173 patients, excluding cases with unknown cancer site.
OR: odds ratio.
a χ^2 test.
b Probability for heterogeneity (likelihood ratio).

Table 4 – Time trends in 3-year survival rate[a] of esophageal cancer

	1976–90	1991–96	1997–2002
Overall	10.1%	11.9%	9.7%
Sex			
Male	9.8%	12.1%	9.8%
Female	13.6%	10.0%	9.3%
Age			
<75 years	11.1%	14.2%	12.3%
⩾75 years	6.1%	3.4%	2.6%
Subsite			
Upper third	6.8%	10.4%	7.2%
Middle third	9.1%	14.1%	8.9%
Lower third	14.9%	10.7%	12.5%
Stage			
T1 N0 M0 (stage I)	53.3%	51.1%	43.5%
T2-3 N0 M0 (stage IIa)	24.7%	22.7%	29.3%
T1-2 N1 M0 (stage IIb)	30.8%	35.8%	49.5%
T3 N1 M0 & T4 N0-1 M0 (stage III)	16.1%	11.6%	17.6%
M1 (stage IV)	0.8%	1.1%	1.0%
Locally advanced cancers[b]	6.1%	8.9%	5.6%
Histology			
Adenocarcinoma	23.3%	10.5%	13.0%
Squamous cell carcinoma	9.6%	12.8%	9.2%
Other	10.1%	0.0%	7.6%
No histology	3.9%	9.5%	4.6%
Treatment			
R0 resection	25.6%	27.7%	29.6%
R1/R2 resection	16.1%	3.1%	0.0%
Chemoradiotherapy without surgery	9.0%	9.6%	5.1%
Chemotherapy alone	7.1%	7.2%	0.0%
Radiotherapy alone	6.0%	10.8%	5.1%
By pass/laparotomy	2.2%	0.0%	4.8%
Symptomatic treatment	3.3%	1.4%	2.9%

a 84 cases lost to follow-up.
b Cases not resected and with no evidence of visceral metastasis.

given in Table 4. There was no significant change in prognosis over time. Overall, stage at diagnosis and treatment were the most important determinants of survival. Long-term survival was only observed after R0 resection and early stage at diagnosis. Adenocarcinomas was associated with a better prognosis than the other histological types (log-rank test between survival curves according to histological categories after exclusion of cases with no histology: $P = 0.006$).

In the multivariate analysis, age, subsite, histology and treatment were independent significant prognostic factors (Table 5). Treatment procedure was the major prognostic factor. Compared to R0 resection, the relative risk of death was 2.08 [1.64–2.66, $P < 0.0001$] for R1/R2 resection and 1.66 [1.44–1.91, $P < 0.0001$] with chemo-radiation as main treatment. Survival was higher for adenocarcinomas than for squamous cell carcinomas. The period did not influence prognosis.

4. Discussion

Many studies concerning the management and the prognosis of esophageal cancers have been published. Most of them were hospital-based and often limited to surgically treated patients. Data from this study have the advantage of including all the cases diagnosed in a well-defined French population, including those not operated on, over a long time period. Due to the multiplicity of information sources we assumed that nearly all newly diagnosed cases were recorded. Information on treatment, morphological features and follow-up was nearly complete. Thus this report has the advantage of including a large number of patients and of providing a non-biased view on the trends in management and survival of esophageal cancer.

Our study showed an increasing frequency of adenocarcinomas over time. They represented more than one quarter of esophageal cancers during the last study period. This shift from squamous cell carcinoma to adenocarcinoma was reported in several population-based studies in Western countries [5]. Obesity, diet and gastroesophageal reflux disease may contribute to the development of this cancer [6]. A recent population-based case–control study suggests that 79% of esophageal could be attributed to smoking, body-mass index, gastroesophageal reflux and low intake of fruits and vegetables [7]. Studies aimed at unravelling the determinants of this disease in the general population are needed.

Disappointingly there was no increase in the proportion of patients resected for cure. The development of endoscopy was not followed by an increase of operative indications or earlier diagnosis of esophageal cancers. This may be explained by the fact that most of the time, cancer is already advanced when dysphagia occur. Development of CT scan and endo-ultrasonography allow a more precise diagnosis [8]. Among cases found to be unresectable, the proportion of

Table 5 – Multivariate survival analysis in esophageal cancer (operative mortality excluded)

	RR	95%CI	P
Age			
<75 years	1.001		
⩾75 years	1.16	[1.03–1.31]	0.017
Treatment			
R0 resection	1.00		
R1/R2 resection	2.08	[1.64–2.66]	<0.001
Derivation/laparotomy	3.04	[2.47–3.74]	<0.001
Chemoradiotherapy without surgery	1.66	[1.44–1.91]	<0.001
Chemotherapy without surgery	2.63	[2.00–3.39]	<0.001
Radiotherapy without surgery	1.93	[1.67–2.23]	<0.001
Symptomatic treatment	3.82	[3.24–4.49]	<0.001
Period			
1976–90	1.00		
1991–96	0.95	[0.84–1.05]	0.321
1997–2002	0.98	[0.88–1.13]	0.974
Subsite			
Upper third	1.00		
Middle third	1.16	[1.03–1.31]	0.013
Lower third	1.12	[0.99–1.28]	0.110
Histology			
Adenocarcinoma	1.00		
Squamous cell carcinoma	1.15	[0.99–1.30]	0.066
Other histological types	1.18	[0.88–1.57]	0.270

Cox model: 1987 patients were studied, excluding cases with unknown life status at endpoint date, cancer site or histology.

cases with an identified visceral metastasis increased over time. Operative mortality dropped from 11.7% to 6.7%. Improvements in surgical procedures, peri-operative management and post-operative resuscitation can explain this trend. However, due to the small number of resected cases, this trend was not significant. In population-based series, operative mortality is higher than in hospital-based series. In this latter group, it is around 5% [9–11].

Some changes in the management of esophageal cancer had occurred: chemotherapy was increasingly associated with radiotherapy with the aim to reach distant metastasis and to achieve a radiosensitising effect. This trend was associated with a decrease in the use of radiotherapy alone. Chemo-radiation was either associated with surgical resection or exclusive. It is still debated whether pre-operative chemo-radiation improves the prognosis of operable cancer or not [12]. It has been demonstrated very recently, in patients responding to radiochemotherapy, that this treatment alone was as effective as surgery [13,14]. During the studied period, radiochemotherapy was not used in this indication. It was mainly used as palliative treatment in non-operable patients. In this indication, it has been demonstrated to be more effective than radiotherapy or chemotherapy alone [15,16] but has mainly improved short-term survival. So it is not surprising that the reported trend of more frequent use of chemo-radiation in the treatment of esophageal cancers has had no significant effect on 3-year survival.

One of the main results of this study was the absence of improvement in survival between 1976 and 2002. The prognosis of esophageal cancer remained dramatically low with less than 10% survivors five years after diagnosis. Only R0 resections and early stages were associated with a better survival. They were the major determinants of prognosis. Multivariate analysis confirmed that prognosis after resection did not improve over the 27 years of the study. The improvement underlined in some surgical series probably results from a better selection of the resected patients [17,18]. Our analysis also indicated that age and histology significantly influenced the prognosis. Adenocarcinoma had a modest but significant better prognosis than squamous cell carcinoma, which is consistent with the results of a large series recently published [19]. Only development of more effective chemo-radiation regimens, together with earlier diagnosis, could contribute to improving the prognosis of this cancer which remains a serious concern.

Conflict of interest statement

None declared.

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