Oesophageal intraepithelial and invasive neoplasia of squamous cell type : epidemiology and outcome in Luxembourg, 1980-2001

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Abstract

Background and study aims : **Oesophageal intraepithelial neoplasia of squamous cell type (INSC) and invasive oesophageal squamous cell carcinoma (IOSCC) are infrequent diseases in Western Europe. The aim of the present study was to collect population-based data of both entities over a 20 year-period and to look for concomitant neoplastic affections in order to define an adequate diagnostic strategy.**

Patients and methods : **The National Morphologic Tumour Registry allowed to review the data of all patients with INSC and IOSCC diagnosed between 1980 and 2001 and to record the time trends in incidence, the oncologic co-morbidity and the outcome of the patients.**

Results : **29 patients with INSC and 363 cases of IOSCC were identified. The overall age-standardized (world) incidence rate of intraepithelial neoplasia and invasive squamous cell carcinoma were 0.2 and 4.2 per 10^5, respectively, the M/F-ratio for both 3:1. During the study period, the incidence rate of invasive cancer remained stable in males but showed a 3-fold increase in females. There was a 2-fold increase of the intraepithelial neoplasia incidence in the last decade. The precancerous/cancerous-ratio increased slightly over the last 5 years. 31% of the patients with an INSC and 17.6% of those with IOSCC had concomitant precancerous and cancerous lesions especially of head and neck (laryngopharyngeal) or pulmonary origin. The observed 5-year survival rate was 8.8 +/- 3% (95% confidence interval) for IOSCC and 27.6% +/- 17% for INSC.**

Conclusions : **The incidence of invasive oesophageal squamous cell carcinomas remains stable whereas that of detected intraepithelial squamous cell neoplasias is remarkably low, indicating potential underdiagnosis. Considering the overall low incidence rates, mass screening for oesophageal cancer does not seem reasonable in Luxembourg. Nevertheless, patients at high-risk for oesophageal or head and neck or broncho-pulmonary cancer should be identified and surveilled by endoscopy, possibly with vital staining.** (Acta gastroenterol. belg., **2005**, 68, **302-307**).

Key words : oesophagus, intraepithelial neoplasia of squamous cell type, invasive squamous cell cancer, descriptive epidemiology, incidence, concomitant disease, outcome.

Introduction

In 2000, a new nomenclature of the oesophageal lesions was published by the WHO, discerning *intraepithelial squamous cell neoplasia (INSC)* of low grade (including slight and moderate dysplasia) and intraepithelial neoplasia of high-grade (including severe dysplasia and carcinoma in situ) (1). In fact, the intraepithelial neoplasias are often marginal areas of *invasive oesophageal squamous cell carcinoma (IOSCC)* (2,3). The aims of the present study were to determine the evolution of incidence of IOSCC and of INSC without synchronous invasive squamous cancer in a defined (low risk) population, to detect concomitant premalignant and malignant lesions in other organs and to document the outcome of oesophageal squamous cell carcinomas.

Patients and methods

Between January 1rst, 1980 and December 31st, 2001, the National Morphologic Tumour Registry (MTR) in Luxembourg (Western Europe) registered all new cases of oesophageal intraepithelial and invasive neoplasia of squamous cell type in a population increasing from 364.850 habitants in 1980 to 444.050 habitants in 2001 – an average increase of 0.9% per year (4). The registration of INSC and IOSCC, diagnosed by 12 pathologists in the sole department of anatomic pathology in the country, is mandatory. In this study, patients of all nationality living in Luxembourg were evaluated. To avoid multiple registrations, only the most severe degree of histopathological alteration was used to characterize each case. Only new primary malignant squamous cell tumours were considered. Recurrent local disease, manifestations of malignant lymphomas, mesenchymal malignant tumours or metastatic lesions were excluded. Although outside of the topic of our study, the number of oesophageal adenocarcinomas (AC) registered in Luxembourg during the study period was cited, to allow discussion. Please see below. The diagnoses of intraepithelial neoplasia of squamous cell type (INSC) were exclusively performed by biopsy forceps. No mucosectomy specimen was registered. The cases of invasive oesophageal squamous cell carcinoma (IOSCC) were first diagnosed by biopsy and confirmed by mucosectomy or surgery.

The histopathological diagnoses of all lesions were realized following the WHO-classification (5,6). The slides of the intraepithelial neoplasias of squamous cell type (INSC) were reviewed in 2003 by one pathologist (RS). The complete histo-pathological charts of all patients with an INSC or an IOSCC were checked in order to determine the number and type of synchronous and metachronous cancerous lesions in other anatomic

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Table 1. — **Oesophageal intraepithelial neoplasia of squamous cell type (INSC, n = 29 cases) and invasive oesophageal squamous cell carcinoma (IOSCC, n = 363 cases) : period 1980-2001**

	Squamous cell type			
	Males	Females	Total	M:F
Intraepithelial neoplasia, low grade : ◦ mild dysplasia ◦ moderate dysplasia				
Intraepithelial neoplasia, high grade : ◦ severe dysplasia ◦ carcinoma in situ	3 19	1 6	4 25	
TOTAL :	22	7	29	3:1
Invasive squamous cell carcinoma INSC / IOSCC –ratio	288 1:13	75 1:11	363 1:13	4:1

sites. Patient survival was measured from the time of biopsy. The observed survival rates were available for all patients with an IOSCC and INSC. The relative survival rates were calculated in relation to the known expected survival rates from 1980 to 1994. This study did not have access to the clinical patients' charts and therefore, treatment modalities were only available concerning resection specimens.

The results were compared with the data of neighbouring geographical European regions published by the WHO in "Cancer in Five Continents, volume VI, VII and VIII" (7-9). The regions were selected for geographical proximity or comparable population-density and socioeconomic characteristics.

The statistical evaluations included the chi-square test with a level of significance $p < 0.05$ and the life-table survival analysis. The age-standardized incidence rates were calculated by the direct method, the standard error of the age-standardized rate by the Poisson approximation (10).

Results

29 new consecutive cases of *INSC* were found in 22 males (75.9%) and 7 females (24.1%) (Table 1). The M/F-ratio was 3.1:1. The mean age was 57.9 years (33 years-80 years). The age distribution of all patients with histologically confirmed INSC (n = 29 cases) and IOSCC (n = 363 cases) is documented in figure 1. 20.7% of all patients with an INSC were between 32 and 49 years of age ; 41.4% were between 50 and 59 years ; 20.7% between 60 and 69 years ; 13.8% between 70 and 79 years and one patient was 80 years of age.

363 patients with an *IOSCC* were found during the study period. 288 patients were males (79.3%) and 75 females (20.7%) (Table 1) ; the M/F ratio was 3.8:1. Of those patients, 33 (9.2%) had been resected surgically ; one patient underwent curative mucosectomy. The age distribution varied from 36 years to 92 years (mean : 62 years). As described in figures 1 we found that 16.5% of the patients with IOSCC (60/363) had less than 50 years of age, while 27.8% were between 50 and 59 years, 33.6% between 60 and 60 years, 18.2%

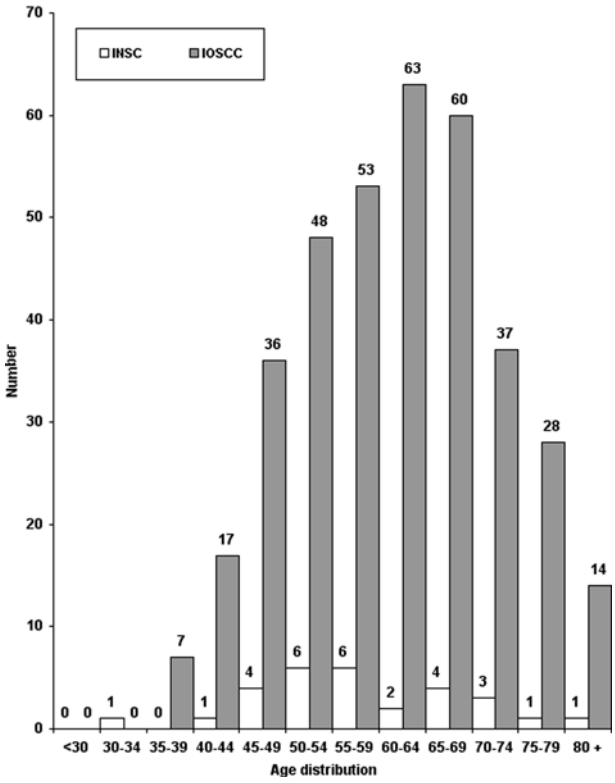

Fig. 1. — The age distribution of all patients with a histologically confirmed oesophageal INSC (n = 29 cases) or an IOSCC diagnosis (n = 363 cases), 1980-2001.

between 70 and 79 years and 3.9% of the patients with IOSCC were 80 years of age and above.

The overall average, annual, incidence rate of INSC, over the period 1980-2001, was 0.3 per 100,000 both genders together (for males 0.5 per 10^5 and for females 0.2 per 10^5). The average, annual, age-standardized incidence rate (ASR-world population) of INSC was 0.2 per 100,000 (for males 0.4 per 10^5 and for females 0.1 per 10^5).

The average, annual, all ages specific incidence rate of IOSCC in Luxembourg, over the period 1980-2001, was 4.2 per 100,000 for both genders together, (for males 7.0 per 10^5 and for females 1.7 per 10^5). The

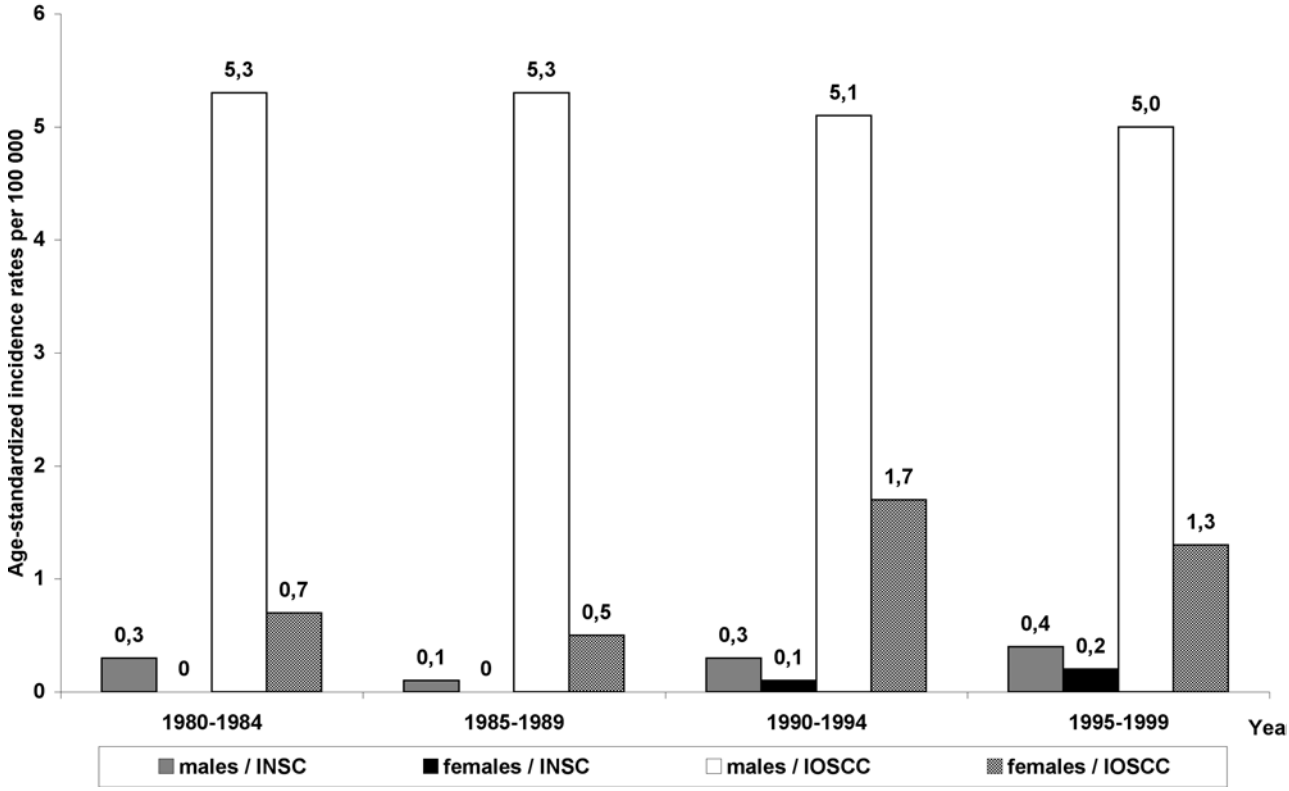

Fig. 2. — Age-standardized incidence rates (ASR(W) of intraepithelial squamous cell neoplasia (INSC, n = 19 cases) and invasive oesophageal squamous carcinoma (IOSCC, n = 330 cases) 5-year periods 1980-1999.

average, annual, age-standardized incidence rate (ASR-world) of IOSCC was 2.9 per 100,000 (2.9 +/- 0.5 with 95% confidence interval. c.i.), for males 5.0 per 10^5 and for females 1.1 per 10^5.

During the study period, 74 new cases of oesophageal AC had been registered, corresponding to 16.9% of all oesophageal cancers morphologically diagnosed in Luxembourg.

Figure 2 displays the age-standardized incidence rates (ASR-world) of INSC (n = 19 cases) and IOSCC (n = 330 cases), divided by four 5-year categories (period 1980-1999) and by gender. There is a significant ($p < 0.05$), 2-fold increase of IOSCC in females during the last decade and a significant increase of the INSC-diagnoses in males and in females. In the years 2000 and 2001 the average, annual, age-standardized incidence rate of INSC for both genders remained stable, 1.1 per 100,000.

Table 2 documents the world age-standardized incidence rates (ASR/W) of invasive oesophageal squamous cell carcinomas in the Luxembourgish population, during the period 1983-1997 in comparison to other European countries (6,7,8).

Over the last five-year period (1993-1997) we found in *males* an ASR/W of 6.9, which is 2-fold lower than the data reported from the limitroph French region of Bas-Rhin (ASR/W : 13.9), comparable to that of the Saarland in Germany (ASR/W : 7.4) but slightly higher than the ASR/W of 5.6 in the Dutch Maastricht county. On the other hand females in Luxembourg (ASR/W : 1.9) had a higher value than those in the Saarland (ASR/W : 1.3) and those in the Bas-Rhin or Maastricht region, both with an ASR/W of 1.1.

In table 3, the concomitant neoplasias of INSC and IOSCC patients are summarized. In the INSC-group, 31% (9/29) of the patients had an associated invasive squamous cell carcinoma, (oral cavity, tonsil, larynx (3×), pharynx (2×), lung) and one patient had a neuro-endocrine carcinoma of the mediastinum. For the IOSCC cohort such an association was found in 18.5% (67/363) of these patients and 68.7% of the them (46/67) had a concomitant squamous cell cancer of head and neck or pulmonary origin (Table 3).

The overall observed survival rates of the 363 patients with IOSCC, calculated by the actuarial method (life-table) and stratified by years were : first year 27 +/- 5% (n = 97/363) ; second year 15 +/- 4% (n = 55/363) ; third year 12 +/- 3% (43/363) ; forth year 9 +/- 3% (n = 34/363) and after five years 8 +/- 3% (n = 31/363). Between 1980 and 1994 (n = 236 cases) the relative 5-year survival rates of the patients with an invasive squamous cell carcinoma was 2.4%. For this period the observed 5-year survival rate was 2.1%.

The observed survival rates for IOSCC of the last 20 years (1980-1999) were compared by 5-year segments. Thus, the 5-year survival rates improved from

Table 2. — **Invasive oesophageal squamous cell carcinoma and concomitant precancerous and cancerous lesions (n = 67/ 363)**

	In situ	Invasive
◦ squamous cell carcinoma of the oral cavity		7
◦ squamous cell carcinoma of the tongue	1	6
◦ squamous cell carcinoma of the tonsils	1	4
◦ squamous cell carcinoma of the larynx		11
◦ squamous cell carcinoma of the pharynx		1
◦ squamous cell carcinoma of the oesophagus	1	4
◦ squamous cell carcinoma of the lungs		10
◦ adenocarcinoma of the breast		3
◦ adenocarcinoma of the uterus		1
◦ adenocarcinoma of the prostate		1
◦ adenocarcinoma of the pancreas		
◦ adenocarcinoma of the stomach	1	2
◦ adenocarcinoma of the colo-rectum		5
◦ adenocarcinoma of the kidney		1
◦ transitional carcinoma of the bladder	2	
◦ malignant melanoma of the skin	1	
◦ sarcoma of the retroperitoneal region		1
◦ malignant lymphoma and leucemie of the bone		3

3% in the beginning of the 1980's to 8% in the late 1990's.

Concerning the survival of the 29 INSC cases, the observed 5-year survival rate was 27.6 +/- 17%. 10 out of these patients died of cancers, 8 of squamous cell type of non-oesophageal origin and 2 due to invasive squamous cell cancer of the oesophagus.

Discussion

Squamous cell carcinoma is the most frequent histological subtype of oesophageal cancer, although adenocarcinomas show a remarkably rising incidence (11). The incidence of oesophageal AC has increased tremendously in the United States and other Western countries over the last three decades, while the incidence of IOSC has remained unchanged. Today in the U.S. the incidence of oesophageal AC approaches or exceeds that of squamous cell oesophageal cancer (12-15). In Luxembourg we did not find a similar trend as reported in the USA. In analogy to some other European regions such as the Saarland (Germany), Tyrol (Austria) or St. Gallen (Switzerland) we registered over the last decades a 2-fold increase of the oesophageal AC-diagnoses, which never surpassed 20% of all the oesophageal carcinomas (15). The intraepithelial neoplasias of squamous cell type are often situated in proximity to invasive squamous cell carcinomas and are about eight times more common in high cancer-risk areas than in low-risk areas (2,3). Mandard *et al.* described in a series of 100 oesophagectomy specimens, that 95% of the resected oesophagi contained at least one focus of INSC, for the most part adjacent to IOSCC ; in 14% of the cases INSC were detected at some distance from the IOSCC (3). Because in the literature most cases of INSC were reported in combination with IOSCC, we reviewed our files in order to detect, in a defined population, the incidence of INSC not associated to an IOSCC.

In our series the detection of INSC-cases is obviously exceedingly low and the detection of IOSCC-cases in an advanced and irresectable stage, very high. 90.9% of our IOSCC were diagnosed in stages T3 and T4 with poor prognosis and were probably treated by chemo- and /or radiotherapy or endoscopic stent.

As in many European countries, with exception of the Calvados and the Alsace regions in France or some provinces in Northern Italy, epidermoid oesophageal cancer is a rare disease in Luxembourg considering the incidence rate of 5.4 cases per 10^5 (7-9).

IOSCC has a multifactorial etiology involving environmental and/or genetic factors (16). It is generally accepted that smoking and alcohol are the major risk factors for squamous cell carcinoma and its precursors (17,18). A transversal survey comparing tobacco

Table 3. — **Invasive squamous cell oesophagus cancer in the European Community : World age standardized incidence rates (ASR(W)*), time trends : 1983-1987 ; 1988-1992 ; 1993-1997 (6,7,8)**

Males	83-87	88-92	93-97		Females	83-87	88-92	93-97	
F/Bas Rhin	18.7	16.3	13.6	–	IRL/Southern	4.2	3.4	3.8	–
UK/South Western	6.5	7.4	8.5	–	UK/South Western	3.3	3.7	3.7	–
IRL/Southern	4.5	6.5	8.0	–	L/Luxembourg	0.9	1.4	1.9	–
D/Saarland	6.1	6.7	7.4	–	DK/Denmark	1.3	1.4	1.7	–
L/Luxembourg	6.7	5.6	6.9	–	SF/Finland	2.2	1.7	1.4	–
E/Navarra	6.6	7.0	6.5	–	D/Saarland	0.8	0.8	1.3	–
DK/Denmark	3.9	4.8	5.8	–	F/Bas Rhin	0.9	1.2	1.1	–
NL/Maastricht	3.7	4.0	5.6	–	NL/Maastricht	0.9	1.2	1.1	–
CH/St.Gall	5.5	5.5	4.6	–	I/Parma	0.6	0.8	1.0	–
I/Parma	4.2	3.9	4.0	–	S/Sweden	0.9	1.0	0.9	–
SF/Finland	3.3	3.5	3.2	–	CH/St.Gall	0.5	0.7	0.6	–
S/Sweden	3.2	3.1	3.1	–	E/Navarra	0.7	0.7	0.6	–
USA/Seer**, white	4.0	4.5	4.7	–	CND/Canada	1.3	1.3	1.3	–
CND/Canada	4.2	4.1	4.2	–	USA/Seer**, white	1.3	1.2	1.2	–

* Cancer incidence in five continents. Vol VI ; Vol VII ; Vol VIII (6,7,8).
** SEER : Surveillance, Epidemiology and End Results Program.

and alcohol consume in young Luxembourgish people in 1990 and in 1998 showed an increase of 5% of girls beginning to smoke and of 1% of young men. The mean age of young people smoking the first cigarette was 12.8 years and consuming the first time alcohol was 12.9 years. At the age of 18, 34% of young people smoked and 4% consumed alcohol every day (19). The increase of INSC and IOSCC concerning women might thus be explained by changes in lifestyle. Other risk factors include radiotherapy for bilateral breast cancer, tylosis, celiac disease, Plummer-Vinson syndrome, achalasia and caustic lesions (20-28). As confirmed in our series, Mc Guirt *et al.* reported in 1982 that patients with head and neck, oropharyngeal and broncho-pulmonary cancer suffer from an increased risk of oesophageal cancer, of about 2-4% (29). We found one case of high-grade intraepithelial neoplasia associated with an Human-Papilloma-Virus-infection (HPV) in a patient who has no Chinese origins. The positive rates of HPV16-E6 and E7 in intraepithelial neoplasia and oesophageal carcinoma, especially in the Chinese population, are significantly higher than those in normal mucosa and are associated with oesophageal squamous cell carcinogenesis (30).

Dawsey *et al.* published an endoscopic survey of 682 patients, showing that low- and high grade intraepithelial neoplasia were associated with a significantly increased risk of developing squamous cell carcinoma of the oesophagus within 3.5 years after endoscopy (31). In our series 2 patients out of 29, who had a histologic follow-up of INSC showed transformation into an IOSCC within 2 years (22 to 23 months). Other authors reported similar progression of severely dysplastic lesions into invasive cancer of the oesophagus (32,33). We found 8 (27.8%) oro-pharyngeal and broncho-pulmonary cancers associated with oesophageal INSC and 64 (17.6%) cancers of other organs associated to oesophageal IOSCC, confirming the high-risk situation of these patients (Table 2). The difference in percentages of other associated tumours between INSC and IOSCC is probably due to a bias introduced by the fact that these patients were screened as part of a general staging for lung or head and neck tumours.

IOSCC of the oesophagus appears mainly as an isolated tumour, frequently diagnosed in its latest stage, with a poor prognosis. However, current advances in endoscopy should allow the detection of early lesions such as intraepithelial neoplasia of low and high grade, especially with vital staining or magnification techniques (34-36). As mass screening for oesophageal cancer in a low-risk population is neither feasible nor reasonable, we believe in accordance to Scherubl *et al.* 2002, that high-risk groups should be identified (Table 2) and surveilled with endoscopy (37). Lugol staining has proven to be an elegant, easy, inexpensive and accurate endoscopic method of squamous cell neoplasia detection (34,35). The underuse of such techniques in non-academic structures or in current clinical practice might explain the very low rate of INSC detection in Luxembourg. Conventional oesophagoscopy in asymptomatic individuals exposed to known risk factors (abuse of smoking and alcohol, status after diagnosis of head and neck or pulmonary cancer, status of radiotherapy, oropharyngeal HPV-lesions) may be not accurate enough. To improve prognosis it is essential to detect and to treat the early oesophageal lesion endoscopically by new techniques such as magnification endoscopy or high resolution chromoendoscopy (38,39). We found an overall observed 5-year survival rate for INSC of 27% and for IOSCC of 8%. This finding is in accordance with data of other authors, who reported 5-year survival rates below 10% (40,41), confirming that current modalities of therapy for IOSCC offer poor survival and cure rates (42). Due to methodological restrictions, we were unable to provide individual patient's data regarding comorbidity and treatment modalities, possibly explaining these low survival rates ; we cannot exclude suboptimal treatment modalities.

The endoscopic management of early cancer and intraepithelial neoplasia of squamous cell type by minimally invasive techniques such as mucosal resection has become attractive for many of these patients often in a poor general health status (43-45).

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