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# CHAPTER 7

## An epidemiological evaluation of salivary gland cancer in het Netherlands (1989-2010)

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## ABSTRACT

### BACKGROUND

The relative 5-year survival rate of salivary gland cancer is moderate at best. This study was set up to evaluate whether the improvements in diagnosis and treatment in the last decades impacted the incidence, mortality and survival of salivary gland cancer.

### METHODS

Data on patients with salivary gland cancer from 1989 through 2010 were extracted from the Netherlands Cancer Registry (NCR); we examined incidence, mortality and relative survival. Furthermore, information on sex, age, tumor stage, histology, and treatment was taken into account.

### RESULTS

A total of 2737 patients were included. Fifty-three percent (53%) were males and 47% were females with a significant higher proportion of early stages in women. In 2010, the incidence rate (European Standardized Rate (ESR)) of salivary gland cancer was 0.9 per 100,000 per year. The estimated annual percentage change in incidence rate since 1989 equaled 0.6% (95%CI: 0.2–1.4). Mortality rates (ESR) decreased in men until 1997 and increased thereafter. Mortality in women remained stable at 1.5 per 100,000.

Over time more patients were treated by surgery and radiotherapy ( $p < .001$ ). The relative five-year survival rate equaled 69% and did not change in time.

### CONCLUSION

We observed no relevant changes in incidence or mortality rates in the last two decades. Despite the increased combined treatment by surgery and radiotherapy, survival did not improve. This implies an urgent need for the development of new effective treatment modalities

## INTRODUCTION

‘What progress has been made against cancer?’ is one of the most frequently asked questions in Western medicine. With this question in mind, several large cancer survival studies have been published over the past years, generally showing that incidence, as well as survival rates are rising<sup>1-5</sup>. Increasing incidence has mainly been explained by population aging and better cancer detection. Improvements in early detection and treatment may explain better survival rates. However, the war against cancer is still far from over<sup>3,4</sup>. Incidence trends of head and neck cancer differ by localization; the calculated incidence of oral cavity and pharyngeal cancer according to estimated annual percentage change EAPC increased with 1% per year for males and 2% for females since 1989, while the incidence in laryngeal cancer decreased with 2% per year for males and remained stable for females<sup>4</sup>. The most likely explanation for decreasing laryngeal cancer incidence in males is the decline in smoking prevalence<sup>6,7</sup>. Salivary gland carcinomas are a special group among head and neck carcinomas, because of its relatively rare occurrence at 150 new diagnoses per year in the Netherlands, and a greater variation in the histological subtypes. Also, malignancy rates differ by localization. About 80% of salivary glands tumors originate from parotid glands (25% malignant), 10% from the submandibular gland (50% malignant), 1% from the sublingual gland (95% malignant) and 9% from small submucous glands (60% malignant)<sup>8</sup>. Furthermore, the most important risk factors for head and neck cancer tobacco and alcohol use<sup>9</sup>, are less clearly associated to salivary gland tumors. Some reports suggest that exposure to ionizing irradiation<sup>10</sup> or Epstein Barr virus (EBV) infection<sup>11</sup> could be risk factors. Radiation was suspected based on the observation of high incidence rates among atomic bomb survivors in Japan<sup>12</sup> and patients who received radiation in childhood for indications like Hodgkin lymphoma<sup>10,13</sup>. The current knowledge suggests that only lymphoepithelial carcinoma, constituting 0.4% of all malignant salivary gland tumors, might be strongly associated with EBV<sup>11</sup>. This study was initiated to assess whether progress has been made regarding salivary gland cancer. Therefore, we calculated the changes in burden, indicated by incidence, mortality and survival rates over a 22-year period in the Netherlands.

## 2. PATIENTS AND METHODS

### 2.1. PATIENTS

For this study, all primary cancers of the salivary glands diagnosed between 1989 and 2010 were extracted from the Netherlands Cancer Registry (NCR), leading to 2764 tumors in 2760 patients. We excluded 4 second primary salivary gland tumors, and 23 other non-carcinomas (sarcomas) resulting in data for 2737 patients. The NCR covers the total population of the Netherlands (16,574,989 inhabitants in 2010). The registry receives lists of all newly diagnosed cancers on a regular basis from the nationwide pathology network PALGA (all pathology laboratories in the Netherlands participate in PALGA). In addition, the NCR receives also diagnoses from the hospital discharge registries. The completeness of incidence of the NCR was estimated to equal at least 95%<sup>14</sup>. Following notification, trained tumor registration clerks abstract a minimum data set, including patient characteristics (sex, age at diagnosis), tumor information (date of diagnosis, topography, histology, stage at diagnosis) and treatment information from hospital records.

### 2.2. TUMORS

Topography was coded according to the international classification of diseases for oncology (ICD-O-3)<sup>15</sup>; codes C07 (parotid gland)–C08 (other salivary glands) were included. The histology was coded according to the ICD-O-3 morphology coding and categorized into 7 groups as described in Table 1. Tumor stage was recorded according to the International Union against Cancer (UICC) TNM classification according to the UICC 4th edition from 1989 through 1996 (1st and 2nd revision)<sup>16,17</sup>, the UICC 5th edition from 1999 until 2002<sup>18</sup>, the UICC 6th edition from 2003 to 2009<sup>19</sup> and the UICC 7th edition in 2010<sup>20</sup>. Major changes in classification were: from 5th to 6th edition all tumors >4 cm were considered T3 tumors (previous editions limited T3 tumors to tumors 4–6 cm in size) and T4 tumors were divided into T4a (tumor invasion of skin, mandible, ear canal and/or facial nerve) and T4b (tumor invasion of skull base, pterygoid plates and/or encasement of carotid artery). Scoring all T4, T4a and T4b as T4 tumor obviated the latter change. To evaluate changes over time, five equal time periods were defined: 1989–1993, 1994–1998, 1999–2002, 2003–2006 and 2007–2010.

Table 1 ICD-O-3 histology code grouping of salivary gland tumors.

Group	ICD-O code
Adenoid cystic carcinoma	8200
Muco-epidermoid carcinoma	8430
Acinic cell carcinoma	8550, 8551
Squamous cell carcinoma	8070, 8071, 8072, 8074, 8075, 8078, 8083
Adenocarcinoma NOS	8140, 8190, 8201, 8230, 8240, 8440, 8450, 8471, 8480, 8481, 8490, 8501, 8525, 8574
Carcinoma ex pleomorphic adenoma	8022, 8940, 8941
Myo-epithelial carcinoma	8562, 8982
Salivary duct carcinoma	8500
Other salivary gland carcinomas	See below
Neoplasm NOS	8000
Malignant tumor cells NOS	8001
Carcinoma NOS	8010
Large cell carcinoma NOS	8012
Neuro-endocrine carcinoma NOS	8013
Undifferentiated carcinoma	8020
Anaplastic carcinoma	8021
Large cell carcinoma	8031
Spindle cell carcinoma	8032
Sarcomatoid carcinoma	8033
Small cell carcinoma	8041
Lympho-epithelial carcinoma	8082
Basosquamous carcinoma	8094
Basaloidadenocarcinoma	8147
Neuro-endocrine carcinoma	8246
Merckel cell carcinoma	8247
Oxiphilic adenocarcinoma	8290
Clear cell adenocarcinoma	8310
Comedocarcinoma	8501
Medullary adenocarcinoma	8510
Adenosquamous carcinoma	8560
Metaplastic carcinoma	8575
Sialoblastoma	8974
Carcinoma sarcoma NOS	8980

Table 2 Patient, tumor and treatment characteristics in time.

	1989–1993	1994–1998	1999–2002	2003–2006	2007–2010	p-value
<b>Sex</b>						
Women	276 (51.1%)	310 (55.5%)	288 (54.7%)	246 (48.3%)	353 (56.1%)	0.057b
Men	260 (48.5)	249 (44.5%)	239 (54.3%)	263 (51.7%)	276 (43.9%)	
<b>Age</b>						
Median (p25–p75)	64 (50 – 74)	64 (50-74)	62 (48-74)	64 (52-75)	64 (52-75)	0.623a
<b>Localisation</b>						
Parotid gland	416 (77.7%)	418 (74.9%)	436 (82.7%)	388 (76.2%)	505 (80.3%)	0.012b
Minor salivary glands	120 (22.3%)	141 (25.1%)	91 (17.3%)	121 (23.8%)	124 (19.7%)	
<b>Histology</b>						
Adenoid cystic carcinoma	86 (16.0%)	116 (20.7%)	81 (15.4%)	88 (17.3%)	84 (13.4%)	0.001b
Muco-epidermoid carcinoma	87 (16.4%)	61 (10.9%)	80 (15.2%)	65 (12.8%)	80 (12.7%)	
Acinic cell carcinoma	65 (12.1%)	79 (14.3%)	78 (14.8%)	75 (14.7%)	109 (17.3%)	
Carcinoma ex pleiomorphic adenoma	43 (8.0%)	35 (6.2%)	39 (7.4%)	52 (10.2%)	38 (6.0%)	
Adenocarcinoma, NOS	99 (18.4%)	102 (18.2%)	73 (13.8%)	84 (16.5%)	93 (14.8%)	
Squamous Cell Carcinoma	55 (10.2%)	62 (11.1%)	59 (11.2%)	42 (8.3%)	59 (9.4%)	
Other salivary gland ca	101 (19.0%)	104 (18.7%)	117 (20.2%)	103 (20.2%)	166 (26.4%)	
<b>Stage</b>						
1 & 2	260 (48.5%)	286 (51.2%)	277 (52.6%)	250 (49.1%)	297 (47.2%)	0.001b
3 & 4	198 (36.9%)	207 (37.0%)	201 (38.1%)	221 (43.4%)	282 (44.8%)	
X	78 (14.6%)	66 (11.8%)	49 (9.3%)	38 (7.5%)	53 (8.0%)	
<b>Therapy</b>						
No therapy	26 (4.9%)	27 (4.8%)	26 (4.9%)	27 (5.3%)	38 (6.0%)	<0.001b
Surgery	158 (29.5%)	144 (25.8%)	132 (25.1%)	106 (20.8%)	118 (18.8%)	
Radiotherapy	29 (5.4%)	34 (6.1%)	53 (10.1%)	34 (6.7%)	65 (10.3%)	
Surgery & radiotherapy	316 (59.0%)	349 (62.4%)	309 (58.6%)	334 (65.6%)	393 (62.5%)	
Other treatment	7 (1.3%)	5 (0.9%)	7 (1.3%)	8 (1.6%)	15 (2.4%)	
<b>Total</b>	536 (19.4%)	559 (20.3%)	527 (19.1%)	509 (18.4%)	629 (22.8%)	

a Fisher's exact, b Chi-square.

### 2.3. STATISTICAL ANALYSIS

Differences between groups were assessed using Fischer's exact test or chi-square test (whichever was appropriate). Trends in incidence and mortality were evaluated using Joinpoint Regression Program, Version 3.5.3. May 2012; Statistical Research and Applications Branch, National Cancer Institute<sup>21</sup>, calculating the estimated annual percentage change (EAPC) over the European Standardized rates. Overall survival was analyzed using Kaplan–Meier estimations. Relative survival rates were calculated using Paul Dickman's STATA model for relative survival (Ederer II method)<sup>22</sup>. In relative survival analyses the ratio of observed survival to the expected survival was calculated. Survival time was defined as date of diagnosis to date of death or date of censoring (date of emigration or date of record linkage to the municipal records to assess the vital status). The administrative censoring date was December 31, 2010. Patients with a survival time of 0 days were excluded (N = 1). Poisson regression modeling was used to calculate the multivariable relative excessive risk of dying (RER)<sup>22</sup>. All statistical analyses were performed using STATA data analysis and statistical software (version 10.0, StataCorp LP, TX, 1996).

## 3. RESULTS

### 3.1. PATIENTS, TUMOR AND TREATMENT CHARACTERISTICS

A total of 2737 patients were included in the study. This cohort consists of 1464 (53.5%) male patients and 1273 (46.5%) female patients (Tables 2 and 3). The median age of male salivary gland cancer patients was 64 years, while female patients had a median age of 62 years ( $p = 0.03$ ). In this cohort 78.3% of the tumors were from the parotid gland. The other 21.7% were found in submandibular, sublingual or minor salivary glands (Tables 2 and 3). Most patients were treated with a combined scheme of surgery and postoperative radiotherapy (61.8%), sometimes combined with chemotherapy. Other treatment modalities included only surgery (23.8%) and only primary radiotherapy (7.8%). A total of 5.1% of the patients did not undergo any form of treatment (only best supportive care) (Tables 2 and 3). The distribution of all different histological types of salivary gland cancer over the years is shown in Table 2.

Table 3 Patient, tumor and treatment characteristics by sex			
	Male	Female	p-value
Age			
Median, years	64	62	0.032a
Year of diagnosis			
1989 – 1993	276 (18.9%)	260 (20.2%)	0.064b
1994 – 1998	310 (21.0%)	249 (19.5%)	
1999 - 2002	288 (19.5%)	239 (18.5%)	
2003 – 2006	246 (16.7%)	263 (20.4%)	
2007 - 2010	353 (23.9%)	276 (21.4%)	
Histology			
Adenoid cystic carcinoma	184 (12.5%)	271 (21.0%)	<0.001b
Muco-epidermoid carcinoma	184 (12.5%)	189 (14.6%)	
Acinic cell carcinoma	189 (12.8%)	217 (16.9%)	
Carcinoma ex pleiomorphic adenoma	114 (7.7%)	93 (7.2%)	
Adenocarcinoma NNO	279 (18.9%)	172 (13.3%)	
Squamous cell carcinoma	199 (13.5%)	78 (6%)	
Other salivary glandcarcinoma	324 (22.0%)	267 (20.8%)	
Localisation			
Parotid gland	1167 (79.3%)	996 (77.4%)	0.244b
Minor salivary gland	306 (20.8%)	291 (22.6%)	
Stage			
1 & 2	623 (42.3%)	747 (58.0%)	<0.001b
3 & 4	697 (47.3%)	412 (32.0%)	
X	152 (10.3%)	128 (10.0%)	
Therapy			
No therapy	79 (5.4%)	65 (5.1%)	0.013b
Surgery	322 (21.9%)	336 (26.1%)	
Radiotherapy	130 (8.8%)	85 (6.6%)	
Surgery + radiotherapy	914 (62.1%)	787 (61.2%)	
Other therapy	28 (1.9%)	14 (1.1%)	
Total	1473 (53.4%)	1287 (46.6%)	
a) Fisher exact, b) Chi square			

Over the total study period there was a significant change in stage. The proportion of patients with unknown stage, due to missing data, declined over time from 8.4% to 5.4%. The proportion of patients treated by surgery only declined over time and most likely shifted toward surgery with radiotherapy (Table 2). There were striking differences between male and female patients (Table 3). While adenoid cystic carcinoma is most common in female patients (21%), adenocarcinoma NOS was most common in male patients (19%,  $p < 0.001$ ). Also, male patients had a significant higher disease stage than female patients at first diagnosis (stages III and IV disease, respectively 47.5% and 31.6%) ( $p < 0.001$ ). More primary radiotherapy was reported in men (8.7% vs. 6.7% in women), while surgery only was more frequent in women (26.1% vs. 21.7% in men,  $p = 0.012$ ).

### 3.2. TRENDS IN INCIDENCE AND MORTALITY RATES

The incidence (ESR) of salivary gland cancer changed from 0.63 per 100,000 per year in 1989 to 0.74 per 100,000 per year in 2010 with an estimated average annual percentage change (EAPC) of 0.6% (95%CI: 0.2; 1.4) (Fig. 1). This trend was similar in males and females. Mortality rates declined statistically significantly between 1989 and 1997 with an EAPC of 6.3% (95%CI: 10.7; 1.6), while from 1997 onwards the EAPC was positive, indicating stable/increasing mortality rates (the EAPC equaled 2.0% (95%CI: 0.3; 4.4)) (Fig. 2). The changes in mortality rates showed a similar pattern in males, whereas female mortality rates remained stable over the entire period.

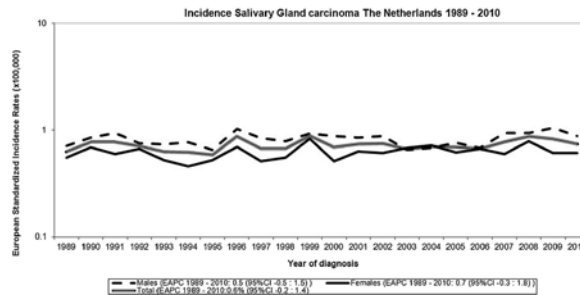


Fig. 1. Incidence of salivary gland cancer in the Netherlands 1989–2010

### 3.3. SURVIVAL

The overall 5-year survival was 59.6% (95%CI: 57.7–61.5); 10-year survival equaled 46.1% (95%CI: 44.0–48.2). The 5- and 10-year relative survival rate equaled 69.1% (95%CI: 66.8–71.3%) and 61.7% (95%CI: 58.8–64.5%), respectively. Relative survival stratified by sex and time period is visualized in Fig. 3. Males had a significant lower relative survival than female patients. Five-year relative survival in male patients was 63%, compared to 76% for females ( $p < 0.001$ ). Relative survival did not change over the years as shown in Fig. 3. The relative survival differed by histology: the best 5-year relative survival rate was observed for acinic cell carcinoma 97% (95%CI: 93–99%), while intermediate rates were found for adenoid cystic carcinoma 79% (95%CI: 75–84%) muco-epidermoid carcinoma 76% (95%CI: 70–81%), and carcinoma ex pleomorphic carcinoma 72% (95%CI: 63–80%).



Fig. 2. Mortality of salivary gland cancer in the Netherlands 1989–2010.

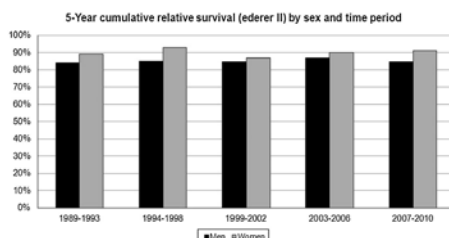


Fig. 3. Five-year relative survival estimates by sex and time period.



Worse 5-year relative survival rates were observed for other salivary gland carcinomas 59% (95%CI: 54–64%), adenocarcinoma NOS 54% (95%CI: 48–60%), and especially squamous cell carcinoma 44% (95%CI: 36–51%). Table 4 shows the multivariate relative excess risk of dying for malignant salivary gland tumors in the Netherlands. Patients with adenocarcinoma NOS and primary SCC were twice as likely to die compared to patients with adenoid cystic carcinoma. Patients with acinic cell carcinoma had the least relative excess risk of dying (0.44 (95%CI: 0.25–0.79). Females had a RER of 0.88 (95%CI: 0.74– 1.04), which was not statistically significant.

Table 4. Multivariate RER of dying from salivary gland cancer in the Netherlands			
Variable		RER multivariate	95% confidence interval
Sex	Male	1	reference
	Female	0.91	0.77 – 1.06
Stage	I	1	reference
	II	2.79	1.77 – 4.40
	III	5.59	3.58 – 8.72
	IV	9.77	6.50 – 14.67
Histology	Adenoid cystic carcinoma	1	reference
	Muco-epidermoid carcinoma	1.51	1.07 – 2.13
	Acinic cell carcinoma	0.46	0.25 – 0.80
	Ca ex pleiomorphic adenoma	1.50	1.01 – 2.23
	Adenocarcinoma NOS	1.92	1.42 – 2.59
	Squamous cell carcinoma	2.47	1.79 – 3.39
	Other salivary gland carcinoma	2.18	1.63 – 2.93
Treatment	No therapy	1	reference
	Surgery	0.20	0.15 – 0.28
	Radiotherapy	0.50	0.37 – 0.67
	Surgery + radiotherapy	0.18	0.14 – 0.24
	Other	0.65	0.42 – 1.02
Year of diagnosis grouped	1989 – 1993	1	reference
	1994 – 1998	0.96	0.75 – 1.23
	1999 – 2002	1.04	0.81 – 1.33
	2003 – 2006	0.98	0.76 – 1.26
	2007 – 2010	0.77	0.60 – 1.01

## 4. DISCUSSION

### 4.1. MAIN FINDINGS

Over the past 22 year, the standardized incidence rate of salivary gland carcinomas in the Netherlands was stable, but hospitals still see a greater number of patients due to population growth and aging. The most remarkable findings are related to sex differences in mortality (stable in women; significantly decreasing until 1997 in men and stable, but tending toward increasing afterwards) and relative survival (63% for men and 76% for women). These differences could be explained by the finding that male patients more often presented with higher stage disease than female patients and with different histological subtypes (male more often adenocarcinoma NOS and women adenoid cystic carcinoma).

### 4.2. COMPARISON INCIDENCE TO LITERATURE AND POSSIBLE EXPLANATIONS OF CHANGES/TRENDS

Crude incidence of salivary gland carcinoma in the Netherlands is 0.9 per 100,000 in 2010, and equals other international studies reporting crude incidences from 0.7 per 100,000 per year to 1.3 per 100,000 per year<sup>23-29</sup>. Age standardized (ESR) incidence rate in this cohort is approximately 0.8 per 100,000 per year in the Netherlands. The male: female ratio of 1:0.87 is in agreement with the international literature, which ranges from 0.67 to 1.04<sup>23,24,30-32</sup>.

Furthermore, the mean and median age of patients found in this study corresponds well to the ages reported in the literature<sup>23,24,28,32,33</sup>. Over the years, we found a stable incidence rate, although a tendency toward an increase could not be neglected. Changes in incidence rate may sometimes reflect the improvement of the diagnosis or reclassification of benign salivary gland tumors to malignant salivary gland tumors<sup>23</sup>.

The diagnosis is clearly a challenge for epithelial salivary gland carcinoma since they are uncommon and very heterogeneous appearance (anatomy as well as histology). The current World Health Organization (WHO) categories no less than 24 different malignant salivary gland lesions. It is the general opinion of experts in the field that from the moment pathologists in the Netherlands started to centralize the pathological review of parotid tumors, often consulting their experts in case of difficult classification, a higher percentage of malignancies have been diagnosed. Because this trend started slowly a clear starting year cannot be given. Interestingly, there was an absolute increase observed of T1-T2 tumors. This could be due to the widespread use of ultrasound-guided fine-needle-aspiration cytology (FNAC)<sup>34</sup> and magnetic resonance imaging (MRI)<sup>35</sup> in the Netherlands. In this cohort, the most common histological type was adenoid cystic carcinoma, followed by adenocarcinoma NOS, acinic cell carcinoma, and muco-epidermoid carcinoma (respectively 16.56%, 16.5%, 14.78% and 13.6%).

Adenocarcinoma NOS, was the number one diagnosis in male patients, whereas adenoid cystic carcinoma was most common in females. Internationally, muco-epidermoid carcinoma represents the major subtype, followed by adenoid cystic carcinoma and adenocarcinoma NOS<sup>23,24,26,30-32,36-40</sup>. Two studies described the same pattern of sex difference in histology<sup>23,24</sup>. This phenomenon is not well understood. The significantly higher tumor stage at diagnosis in male patients compared to female patients (stage IV: 36.2% vs. 21.3%, respectively  $p < 0.001$ ), may be related to the greater attention of women to their appearance and to disease, as has been suggested by Micheli et al<sup>41</sup>.

#### 4.3. COMPARISON MORTALITY TO LITERATURE AND POSSIBLE EXPLANATIONS OF CHANGES/TRENDS

Mortality showed an interesting difference between men and women. We have no explanation for the trend break in 1997 for men. As far as we know, such a trend break has not been described before.

#### 4.4. COMPARISON RELATIVE SURVIVAL TO LITERATURE AND POSSIBLE EXPLANATIONS OF CHANGES/TRENDS

The relative survival curve was significantly lower for male patients compared to female patients for all time periods. This can partly be explained by an early stage at diagnosis and more favorable histological subtypes in women.

A prognostic benefit in women for adenoid cystic carcinoma of the head and neck has been described previously<sup>42</sup>, while sex differences for other types of salivary gland carcinomas have never been described before. However, in the multivariate RER analysis the sex difference, in favor of females, disappeared. Differences in the trend analysis were thus mainly determined by stage and histology.

#### 4.5. TREATMENT IN RELATION TO INTERNATIONAL TRENDS AND RELATION TO PROGNOSIS

Since 1989 treatment regimens consist of primary surgery, with or without adjuvant irradiation. More recent literature demonstrates that chemo-radiotherapy as part of the treatment leads to better survival<sup>43,44</sup>. Pederson et al showed better 5-year locoregional progression free survival (96% vs. 86%) for adjuvant chemo-radiotherapy compared to surgery with radiotherapy for loco-regionally advanced and high-risk salivary gland cancer in a series of 24 consecutive patients<sup>43</sup>. Another study found a 92% 3-year overall loco-regional control rate in the post surgery chemo-radiotherapy group, even though more high-risk patients (high-risk included: T3-T4 disease, nodal positivity and positive resection margins) were included in the chemo-radiotherapy group<sup>44</sup>. In our cohort, only 22 patients were treated by chemoradiotherapy for advanced disease.

This treatment modality did not increase over the years. It is doubtful whether chemoradiotherapy contributes to outcome of our study, but future analysis of adjuvant chemo-radiation should certainly be performed in a prospective randomized fashion. This initiative should be taken up by the International Head and Neck Oncological societies to combine efforts for improving the survival rates for patients with head and neck cancer.

#### 4.6. CHANCES FOR IMPROVEMENT

For several tumors (e.g. esophagus, pancreas and bladder), a positive relationship between higher surgical volume and better outcome has been shown<sup>45-48</sup>. Since salivary gland cancer, and in fact all head and neck cancers, can be qualified as rare disease, the volume-outcome relationship is likely to be positive, although a recent editorial showed the lack of good studies confirming this relationship<sup>49</sup>. A fact is that rare tumors require experienced decision-making, so the Dutch head and neck cancer co-operative group started centralizing head and neck cancer in 1984<sup>50</sup>. However, due to the low incidence rate the mean number of salivary gland carcinomas per head and neck cancer center does not exceed 15 new patients per year. Compared to other major clinics in the world, this remains a very low number. It may be expected that further centralization of this rare disease will improve patient outcomes.

#### 4.7. LIMITATIONS AND ASSETS

Compared to other salivary gland carcinoma epidemiological studies in the literature, we describe one of the largest populationbased cohorts from the Western world. In this study, information over a total of 22 years was available, which made it possible to evaluate time trends. However, the numbers still did not permit extensive subgroup analyses. And since it was retrospective, some data was missing.

#### 5. CONCLUSION

Summarizing, incidence, mortality and relative survival did not improve. Progress may be possible by further centralizing the treatment of salivary gland carcinomas by exploring multimodality therapies and by increasing the public awareness to prevent high stage cancers in male patients.

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