

Salivary Glands

1. Introduction

1.1 General Information and Aetiology

The salivary glands are exocrine glands that produce saliva. Besides the hundreds of minor salivary glands located throughout the palate, nasal, laryngeal and the oral cavity, there are three pairs of major salivary glands. The largest of these three are the parotid glands, which are located in front and just beneath the ears. The second are the sublingual glands which can be found under the tongue in the floor of the mouth. The third pair of salivary glands are the submandibular glands which are situated beneath the lower jaw (Figure 1). In this chapter, we will only describe the malignancies of the major salivary glands.

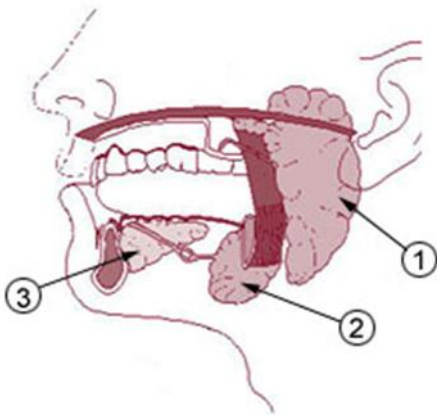


Figure 1. Anatomy of the Salivary Glands: the Parotid Gland (1), the Submandibular Gland (2) and the Sublingual Gland (3)

Tumours of the salivary glands are rather uncommon representing in the United States 0.5% of all malignancies and less than 5% of all head and neck cancers [1].

They originate most frequently from the parotid gland. Aetiology of these cancers is not completely established but has been associated with viral infections, exposure to ionising radiation and

occupational exposure to carcinogens. A relationship with smoking and estrogen/progesterone hormones has inconsistently been reported [2].

The malignancies of the salivary glands comprise of a morphologically diverse group of tumours , which have been divided by the World Health Organization into 24 different subtypes with different clinical courses and prognoses [2]. Sex-dependent differences in incidence of these subtypes are noted. Squamous cell carcinoma, adenocarcinoma-NOS and salivary duct carcinoma occur more often in males than females, while the opposite is true for acinic cell and adenoid cystic carcinoma [3]. Most of these subtypes have their highest incidence in the sixth and seventh decades. Among all patients, pleiomorphic adenoma occur most frequently.

1.2 Diagnosis and Treatment

The first step in the diagnosis is the anamnesis, followed by a clinical examination. Depending on the findings, technical examinations such as MRI, CT and ultrasound are performed with a preference for MRI scanning. When a suspicious lesion is diagnosed, histological confirmation is obliged and a biopsy is necessary. Different types of biopsies may be done, depending on the localization and the size of the lesion. Histological confirmation can be a difficult assignment given the morphological heterogeneities in this group of cancers. False negative diagnoses due to sampling errors can occur [1].

The basic treatment for salivary gland tumours is complete surgical excision, with or without postoperative irradiation. The choice for irradiation is dependent on the clinical stage and the histological grade of the tumour. It is indicated for stage II to IV high grade tumours and for stage III and IV low grade tumours. Additionally, it is also always advised when surgery was micro- or macroscopically incomplete, when there is neural or perineural invasion, when there are lymph node metastases or for adenoid cystic carcinoma. Chemotherapy is sometimes associated to the adjuvant radiation therapy.

Radiotherapy alone or in combination with chemotherapy is the choice for inoperable tumours or for patients unfit for surgery. Palliative chemotherapy, eventually combined with palliative radiation therapy, is the only treatment option in metastatic setting. Neck dissection is recommended when positive lymph nodes are observed [4,5].

2. Data Selection

All salivary gland cancers diagnosed between 2004 and 2007 for patients with an official residence in the Flemish Region are selected, resulting in 266 cases (for detailed information on selected topography and morphology codes, see Appendix A). As described in Figure 2, 31 of them are excluded, resulting in 235 patients for which results are presented in this chapter.

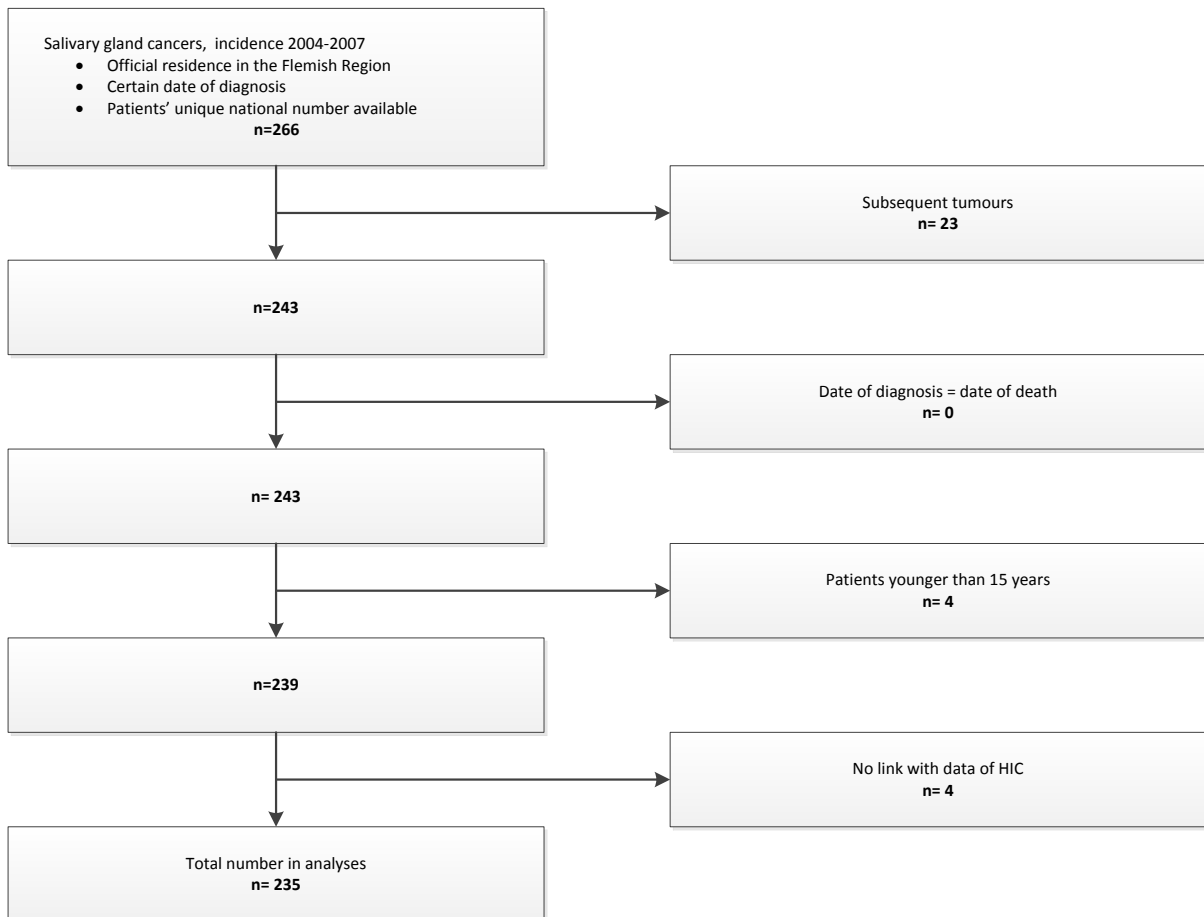


Figure 2. Selection of Cancers of Salivary Glands (Flemish Region, 2004-2007)

3. Patient Characteristics

During the period 2004-2007, slightly more males (n=129) than females (n=106) are diagnosed with an epithelial tumour of the major salivary glands in the Flemish Region (male/female ratio: 1.29). No clear trend in age-standardised rates can be observed over these incidence years.

The median age is 67 years for males and 61.5 years for females. Age at diagnosis ranges between 19 and 92 years. For further analyses, the patients are divided into three age groups: 15-59 years old, 60-74 years and 75+ years (Table 2).

Table 1. Cancer of Salivary Glands: Incidence (Flemish Region, 2004-2007)

Incidence year	Males		Females		Total	
	n	ESR	n	ESR	n	ESR
2004	35	0.97	19	0.49	54	0.68
2005	31	0.85	37	0.98	68	0.89
2006	26	0.72	25	0.66	51	0.66
2007	37	1.00	25	0.59	62	0.77
Total	129	0.88	106	0.68	235	0.75

ESR: age-standardised rate, using the European Standard Population (n/100,000 person years)

Table 2. Cancer of Salivary Glands: Age Distribution (Flemish Region, 2004-2007)

	Males	Females	Total
15-59 years	39	47	86
60-74 years	49	35	84
75+ years	41	24	65

4. Tumour Characteristics

Sublocalisation, morphology, differentiation grade and stage (clinical, pathological and combined stage) of the selected salivary glands cancer are described in Table 3. The majority of the tumours with a known localisation are located in the parotid glands. The second most frequent localisation are the submandibular glands, tumours of the sublingual glands are rare. The differentiation grade is unknown in almost half of the tumours (45.9%). Amongst tumours with a known differentiation grade, all possible grades occur although undifferentiated tumours are rare (only 7.0% of the tumours with a known grade).

Table 3. Cancer of Salivary Glands: Tumour Characteristics (Flemish Region, 2004-2007)

	N	% of total	% of known
Localisation			
Malignant neoplasm of parotid gland (C07.9)	164	69.8	84.9
Submandibular gland (C08.0)	24	10.2	12.4

Sublingual gland (C08.1)	5	2.1	2.6
Major salivary gland, unspecified (C08.9)	42	17.9	/
Morphology			
Mucoepidermoid carcinoma (high and low grade)	23	9.8	9.9
Low grade salivary gland	48	20.4	20.7
- <i>Acinic cell carcinoma</i>	26	11.1	11.2
- <i>Other specified carcinoma - Low grade</i>	22	9.4	9.5
High grade salivary gland	161	68.5	69.4
- <i>Adenoid cystic carcinoma</i>	34	14.5	14.7
- <i>Carcinoma ex-pleomorphic adenoma</i>	17	7.2	7.3
- <i>Other specified carcinoma – High grade</i>	110	46.8	47.4
Other	3	1.3	/
Differentiation grade			
Well differentiated	40	17.0	31.5
Moderately differentiated	29	12.3	22.8
Poorly differentiated	49	20.9	38.6
Undifferentiated	9	3.8	7.0
Unknown	108	45.9	/
Clinical stage			
I	25	10.6	23.8
II	21	8.9	20.0
III	18	7.7	17.1
IV	41	17.5	39.0
Unknown	130	55.3	/
Pathological stage			
I	20	8.5	18.5
II	23	9.8	21.3
III	21	8.9	19.4
IV	44	18.7	40.7
Unknown	127	54.0	/

Combined stage			
I	31	13.2	21.7
II	26	11.1	18.2
III	25	10.6	17.5
IV	61	26.0	42.7
Unknown	92	39.1	/

Males are more frequently diagnosed with stage III-IV tumours than females (stage III – IV in males: 71.4% of known stages, in females: 47.0%; Figure 3). Older patients (60-74 years and 75+ years) present more often with advanced stage disease than younger patients.

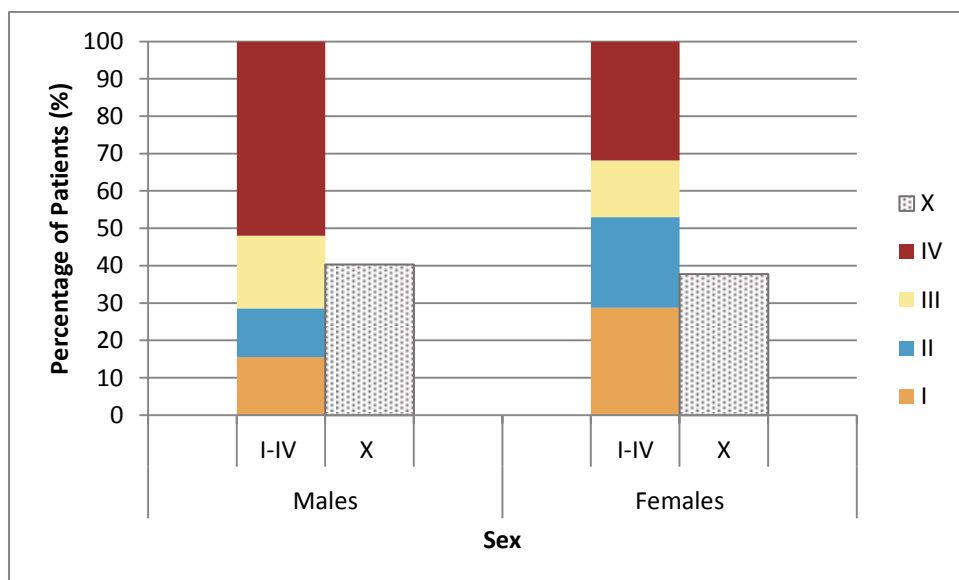


Figure 3. Cancer of Salivary Glands: Stage Distribution by Sex (Flemish Region, 2004-2007)

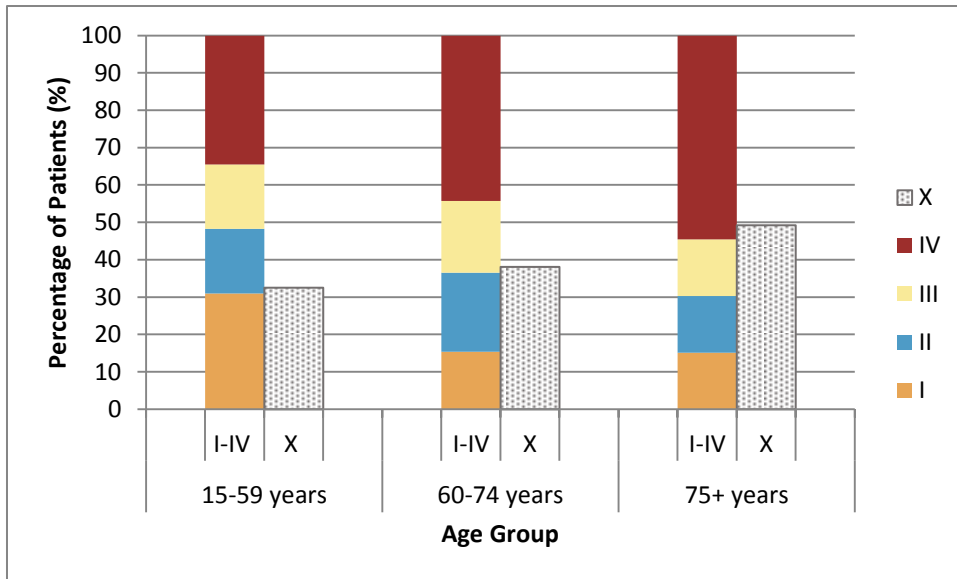


Figure 4. Cancer of Salivary Glands: Stage Distribution by Age Group (Flemish Region, 2004-2007)

5. Diagnostic and Therapeutic Procedures

5.1 Diagnosis and Staging

An overview of the diagnostic and staging procedures for the patients with cancer of salivary glands diagnosed in the Flemish Region between 2004 and 2007 is given in Table 4.

Almost all cancers are confirmed by pathological examination within three months around incidence date (97.9%). This pathological confirmation is most often based on histology (97.0%), only a small part of patients have undergone a cytology examination (30.6%). Two patients are found to be only charged for cytology examination, without histological examination. The number of patients who are examined by imaging is high (96.6%). The most frequently used imaging technique is CT scanning (87.7% of all patients) followed by X-ray of the chest (68.9%). MRI is performed in 39.1% of the patients, a PET-scan in about one fourth (27.2%).

Table 4. Cancer of Salivary Glands: Overview of Diagnostic and Staging Procedures (Flemish Region, 2004-2007)

Diagnostic Procedure (-3m<inc<+3m)	Total (N=235)		2004 (N=54)		2005 (N=68)		2006 (N=51)		2007 (N=62)	
	n	%	n	%	n	%	n	%	n	%
Tissue Examination	230	97.9	51	94.4	66	97.1	51	100.0	62	100.0
Histological Diagnosis	228	97.0	51	94.4	65	95.6	50	98.0	62	100.0
Cytology	72	30.6	20	37.0	19	27.9	16	31.4	17	27.4
Imaging	227	96.6	51	94.4	67	98.5	49	96.1	60	96.8
CT	206	87.7	45	83.3	59	86.8	44	86.3	58	93.5
MRI	92	39.1	18	33.3	28	41.2	21	41.2	25	40.3
Ultrasound Neck	89	37.9	21	38.9	27	39.7	19	37.3	22	35.5
PET Scan	64	27.2	13	24.1	15	22.1	16	31.4	20	32.3
Ultrasound Abdomen	67	28.5	17	31.5	21	30.9	18	35.3	11	17.7
Chest X-ray	162	68.9	42	77.8	44	64.7	35	68.6	41	66.1
Other Procedures										
Biopsy Lymph Nodes	24	10.2	4	7.4	5	7.4	11	21.6	4	6.5

5.2 Multidisciplinary Oncological Consult

More than half of the patients are discussed at a multidisciplinary oncological consult (MOC) within 1 month before till three months after incidence date (Table 5). The proportion of discussed patients greatly differs between the incidence years under consideration: from 44.4% (2004) to 80.4% (2006).

Table 5. Cancer of Salivary Glands: Frequency of Multidisciplinary Oncological Consult (Flemish Region, 2004-2007)

Incidence year	MOC	
	n	%
2004 (n=54)	24	44.4
2005 (n=68)	34	50.0
2006 (n=51)	41	80.4
2007 (n=62)	41	66.1
Total (n=235)	140	59.6

5.3 Therapeutic Procedures

According to the nomenclature codes, three groups of surgery are taken into account in the analyses. The first group are codes used for surgeries of the salivary glands itself. The second group are surgeries that are invoiced with nomenclature codes for surgeries of the head or mouth region. When both types of surgery have taken place within the timeframe one month before until six months after diagnosis, the surgery closest to incidence is selected. If none of them has taken place, surgeries that are invoiced as lymphadenectomies are taken into account as a third group of surgeries. This is done because intermediate results showed that a considerable number of patients is charged for a lymphadenectomy without any other registered type of surgery and because lymphadenectomies without surgery of the tumour itself are regarded as rather unlikely.

Table 6 gives an overview of the selected surgeries. The majority of patients who has undergone surgery within the time period, was charged for a salivary gland surgery. Surgeries of the head and mouth are taken into account in 13.2% of the surgically treated patients while patients treated with a lymphadenectomy comprise 16.2% of the surgically treated patients.

Table 6. Cancer of Salivary Glands: Overview of the Selected Surgeries (Flemish Region, 2004-2007)

Type of Surgery	n	%
Salivary Gland Surgery	144	70.6
Head and Mouth Surgery	27	13.2
Lymphadenectomy	33	16.2

Treatment schemes for all patients are displayed in Table 7. More than 85% of the patients is primarily treated with surgery (204 patients). For 76 of these patients, surgery is the only treatment. A larger group (126 patients) receive adjuvant radiotherapy, mostly alone and only exceptionally in combination with chemotherapy. Adjuvant chemotherapy without radiation is given in a minority of cases.

A small part of the patients receive radiotherapy as the primary treatment (9.0%), sometimes combined with chemotherapy (2.6%) but most often alone (6.4%).

No registered primary treatment is found within the time frame for 9 patients (3.8%).

Table 7. Cancer of Salivary Glands: Overview of Treatment Schemes (Flemish Region, 2004-2007)

Treatment Scheme	n	%
Surgery	204	86.8
Adjuvant radiotherapy	115	48.9
Adjuvant chemoradiotherapy	11	4.7
Adjuvant chemotherapy	2	0.9
No other therapy	76	32.3
Radiotherapy only	15	6.4
Chemoradiotherapy	6	2.6
Chemotherapy only	1	0.4
No primary treatment registered	9	3.8

6. Survival

6.1 Observed and Relative Survival

Survival decreases from diagnosis to reach a 5-year observed survival of 55.7% and a 5-year relative survival of 64.1% (Table 8).

Table 8. Cancer of Salivary Glands: Observed and Relative Survival (Flemish Region, 2004-2007)

N at risk	Observed Survival (%)					Relative Survival (%)				
	1 year	2 year	3 year	4 year	5 year	1 year	2 year	3 year	4 year	5 year
235	82.6	72.3	66.4	59.1	55.7	85.3	76.7	72.2	66.2	64.1

6.2 Relative Survival by Sex

Survival is clearly better for females than for males (Table 9). This sex difference arises shortly after diagnosis and enlarges continuously thereafter.

Table 9. Cancer of Salivary Glands: Relative Survival by Sex (Flemish Region, 2004-2007)

	N at risk	%	Relative Survival (%)				
			1 year	2 year	3 year	4 year	5 year
Males	129	54.9	82.5	72.2	67.4	59.3	57.2
Females	106	45.1	88.5	81.9	78.0	74.0	72.0

6.3 Relative Survival by Age Group

Survival is best in the youngest age group (15-59 year), with a 5-year relative survival of 70.7%. In the older age groups the survival is less good, with a 5-year relative survival of 64.8% and 53.7% for the age groups 60-74 years and 75+ years, respectively.

Table 10. Cancer of Salivary Glands: Relative Survival by Age Group (Flemish Region, 2004-2007)

	N at risk	%	Relative Survival (%)				
			1 year	2 year	3 year	4 year	5 year
15-59 years	86	36.6	92.1	85.4	80.9	74.1	70.7
60-74 years	84	35.7	92.0	79.9	75.0	68.7	64.8
75+ years	65	27.7	65.9	59.2	55.2	50.2	53.7

6.4 Relative Survival by Stage

Due to the low number of stage I (n=31), stage II (n=26) and stage III (n=25) cancers, they are grouped together in the analysis of survival by stage and indicated with stage I-III. Survival is highly dependent on the stage of the tumour. There is a pronounced difference between stage IV and the non-stage IV lesions, with a difference of relative survival at 5 years of almost 50% (Figure 5).

It should be noted that, in line with other head and neck cancers, some locally or regionally advanced diseases are also categorised as stage IV (stage IVA or IVB, more precisely). Salivary gland tumours with distant metastases are defined as Stage IVC. Most stage IV tumours in this study are stage IVA (n=46), only 4 tumours are staged as IVB and 11 as IVC.

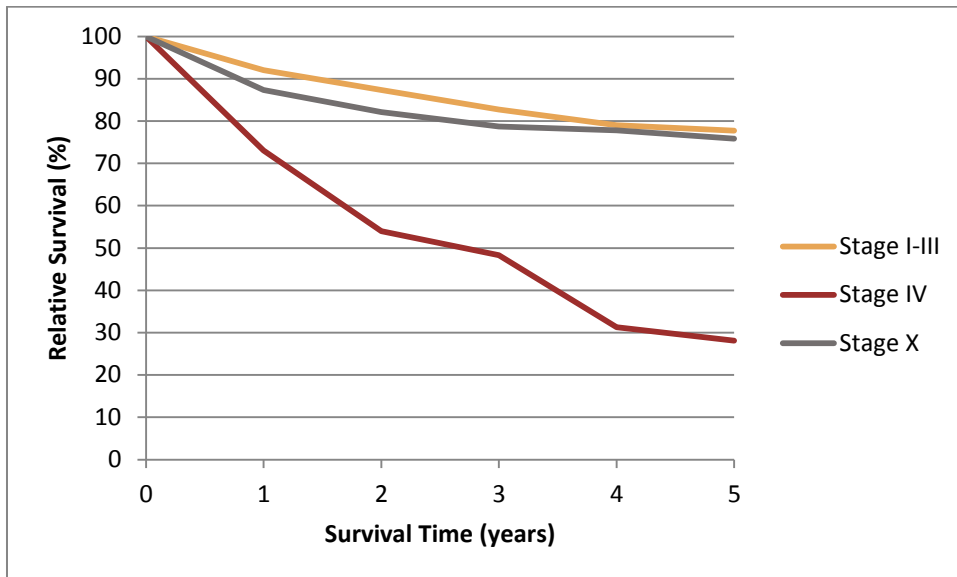


Figure 5. Cancer of Salivary Glands: Relative Survival by Stage (Flemish Region, 2004-2007)

6.5 Relative Survival by Morphology Groups (Low versus High Grade)

There is a significant difference between low and high grade salivary gland cancers. The 5-year relative survival for low grade cancers is about 85%, in high grade cancers this is about 55% (Figure 6).

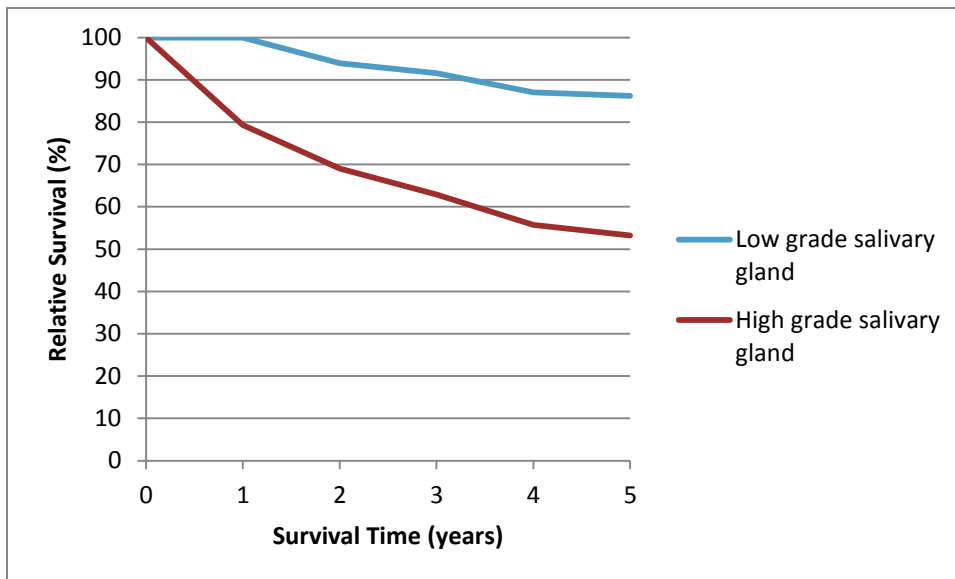


Figure 6. Cancer of Salivary Glands: Relative Survival by Morphology Groups (Flemish Region, 2004-2007)

6.6 Relative Survival by Treatment

Looking at the patients who are primarily treated by surgery (excluding stage IV disease), the addition of adjuvant radiation seems to be associated with worse prognosis. This confirms the clinical practice of preserving adjuvant radiation for cases with more aggressive cancers.

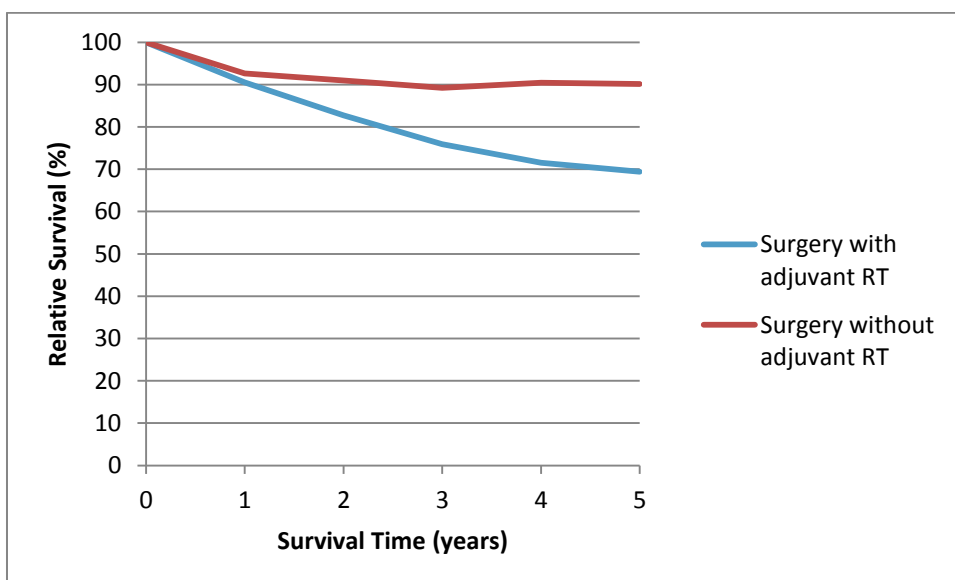


Figure 7. Cancer of Salivary Glands : Relative Survival by Treatment – Excluding Stage IV

7. Analyses by Volume

During the period 2004-2007, Belgian patients with salivary glands cancer are managed in 46 different Flemish hospitals. The mean number of patients (during the period 2004-2007) by hospital is 5.1 and the median number of patients is 3, with a range between 1 and 33. The distribution of the number of patients (=volume) per hospital is displayed in Figure 8.

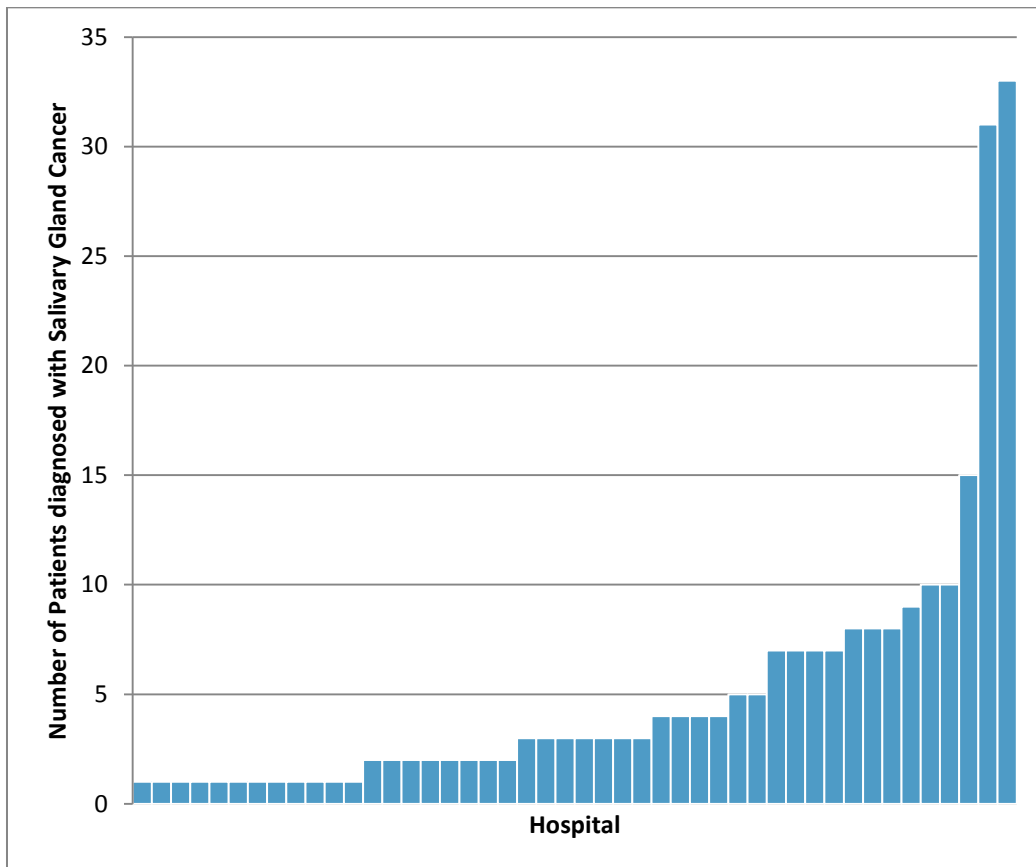


Figure 8. Cancer of Salivary Glands: Distribution of Patients by Hospital (Flemish Hospitals, 2004-2007)

228 Flemish patients (97.0%) can be assigned to a hospital (see Methodology for the rules applied to assign a patient to one hospital). Because of the low number of patients diagnosed with a tumour of the salivary glands who are treated in a large number of different hospitals, the maximum number of patients per hospital is very small. Therefore, no further analyses on the volume of the hospital are performed.

8. References

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