

Larynx

1. Introduction

1.1 General Information and Aetiology

The larynx is found anterior in the neck, at the level of the C3-C6 vertebrae. It connects the inferior part of the pharynx (hypopharynx) with the trachea. The laryngeal skeleton consists of nine cartilages, three single (epiglottic, thyroid and cricoid) and three paired (arytenoid, corniculate and cuneiform). The hyoid bone is not part of the larynx, though it is connected to it. The larynx extends from the tip of the epiglottis to the inferior border of the cricoid cartilage and it can be divided into three subregions: supraglottis, glottis and subglottis.

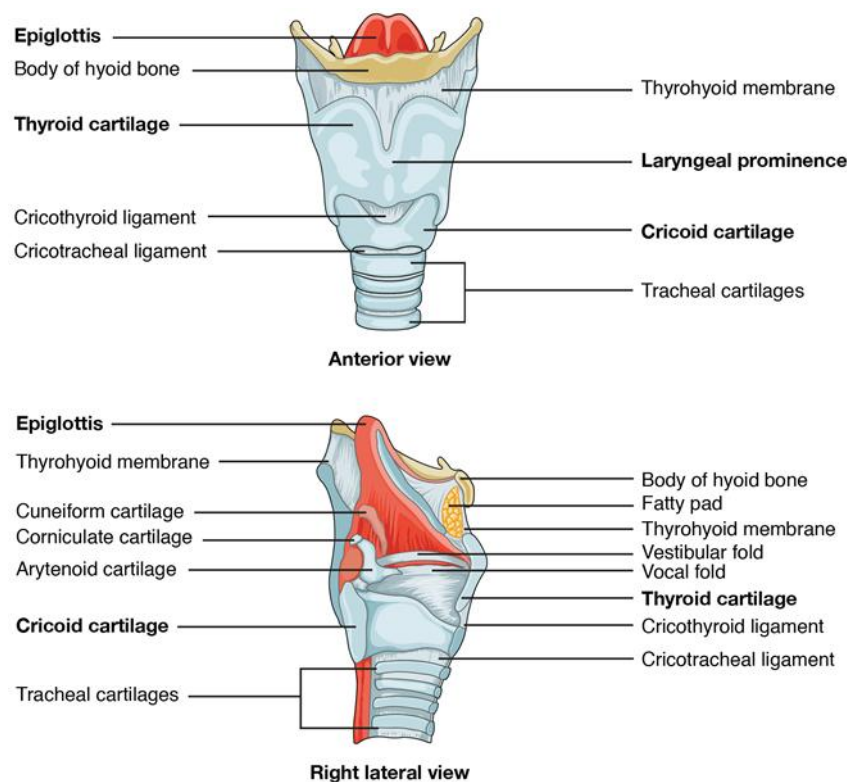


Figure 1: Anatomy of the larynx: anterior and right lateral view (OpenStax College. *Organs and Structures of the Respiratory System*, OpenStax CNX Web site. <http://cnx.org/content/m46548/1.8/>, Jul 8, 2013.)

In the Flemish Region, for the period 2004-2007, laryngeal cancer account for about 28% of all head-and neck cancers [1]. Squamous cell carcinomas (SCC) are the most frequent neoplasms at these sites and represent more than 95 % of all laryngeal cancers .

The main risk factors in the development of laryngeal cancer are alcohol drinking and tobacco smoking. No association with gastro-oesophageal reflux disease or immunosuppressive problems is known nor shown [2,3].

In laryngeal cancer, an important distinction between glottic and supra-glottic cancer needs to be made. Cancer of the vocal cords (glottic cancer) usually causes hoarseness and is therefore often recognised in an early stage. In addition, the lymphatic network of the vocal cords is very limited, preventing the cancer from spreading to regional lymph nodes. These factors contribute to a good prognosis of glottic cancer. In contrast, the supraglottic region is drained by an abundant network of lymphatic vessels [3]. Cancers originating from these region often present with lymph-node involvement and have a bad prognosis [3].

1.2 Diagnosis and Treatment

The first procedure in the diagnosis is the anamnesis, followed by a clinical examination. Afterwards directed technical examinations are performed, such as MRI, CT, PET, endoscopy,... Due to the higher risk of second primary cancers (lung and oesophagus), screening for these cancers is recommended [4].

In the treatment decision, it is import to differentiate between larynx preserving surgery and total laryngectomy. In case of a stage I laryngeal cancer, (endoscopic) surgery or radiotherapy can be performed as main treatment. Stage II is treated with radiotherapy or with surgery (partial or total laryngectomy depending on the location of the tumor) with or without adjuvant radiation therapy depending on the risk factors [5]. Stage III tumors are usually treated with a concomitant treatment of radiotherapy and chemotherapy. Sometimes surgery, with a complete resection of the larynx, is performed, followed by radiotherapy. In stage IV tumors, the cancer has at least spread into the surrounding area. Usually a total laryngectomy and lymphadenectomy is performed to remove the cancer and draining lymph nodes, followed by radiotherapy [4,6]. If surgery cannot be performed, for example for medical reasons, radio(chemo)therapy is a good alternative [6].

2. Data Selection

All laryngeal cancers diagnosed between 2004 and 2007 for patients with an official residence in the Flemish Region are selected, resulting in 1,431 cases (for detailed information on selected

topography and morphology codes, see Appendix A). As described in Figure 2, 154 of them are excluded resulting in 1,277 patients for whom results are presented in this chapter.

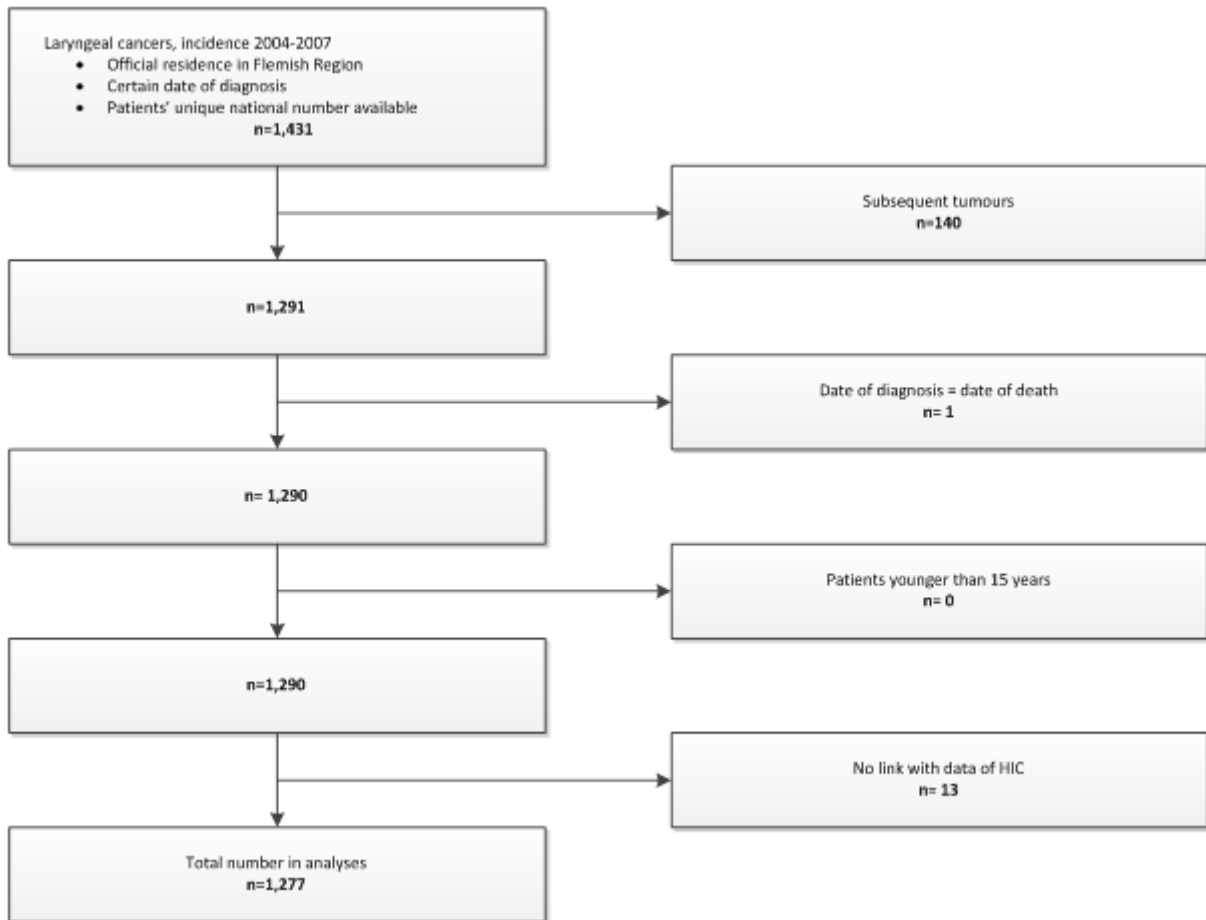


Figure 2. Selection of Laryngeal Tumours (Flemish Region, 2004-2007)

3. Patient Characteristics

Males are more often diagnosed with a laryngeal tumour than females (male/female ratio: 9.34) during the incidence years 2004-2007. No clear trend in age-standardised rates can be observed over the incidence years (Table 1).

The median age is 64 years for males and 63 years for females. Age at diagnosis ranges from 21 to 95 years. For further analyses, patients are divided into three age groups: 15-59 years, 60-69 years and 70+ years (Table 2).

Table 1. Laryngeal Cancer: Incidence (Flemish Region, 2004-2007)

Incidence year	Males		Females		Total	
	n	ESR	n	ESR	n	ESR
2004	307	8.81	39	1.02	346	4.70
2005	268	7.48	27	0.70	295	3.91
2006	275	7.45	25	0.67	300	3.91
2007	295	8.06	41	1.02	336	4.38
2004-2007	1,145	7.94	132	0.85	1,277	4.22

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

Table 2. Laryngeal Cancer: Age Distribution (Flemish Region, 2004-2007)

	Males	Females	Total
15-59 years	384	54	438
60-69 years	383	34	417
70+ years	378	44	422

4. Tumour Characteristics

Sublocalisation, morphology, differentiation grade and stage (clinical, pathological and combined stage) of the selected laryngeal tumours are described in Table 3. The most affected localisations are the glottis and the supraglottis. While undifferentiated tumours are rarely diagnosed (0.6%), moderately differentiated tumours occur most frequent (37.7%). Almost all (99.7%) diagnosed laryngeal tumours are squamous cell carcinomas. About one-third of the patients are diagnosed with a stage I tumour, and more than one-fourth are diagnosed with a stage IV disease. 171 tumours (13.4%) can not be staged because of a localisation coded as C32.3 (laryngeal cartilage), C32.8 (overlapping lesion of larynx) or C32.9 (larynx, unspecified), or a morphology coded 8980 (carcinosarcoma). These tumours are displayed as stage 'NA'.

Table 3. Laryngeal Cancer: Tumour Characteristics (Flemish Region, 2004-2007)

	N	% of total	% of known
Localisation			
Glottis (C32.0)	747	58.5	67.0
Supraglottis (C32.1)	341	26.7	30.6

Subglottis (C32.2)	19	1.5	1.7
Laryngeal cartilage (C32.3)	8	0.6	0.7
Overlapping lesion of larynx (C32.8)	9	0.7	/
Larynx, unspecified (C32.9)	153	12.0	/
Morphology			
Squamous cell carcinoma	1,273	99.7	/
Other defined carcinoma	4	0.3	/
Differentiation grade			
Well differentiated	259	20.3	25.1
Moderately differentiated	482	37.7	46.7
Poorly differentiated	283	22.2	27.4
Undifferentiated	8	0.6	0.8
Unknown	245	19.2	/
Clinical stage			
0	2	0.2	0.2
I	337	30.5	37.2
II	170	15.4	18.8
III	141	12.7	15.6
IV	256	23.1	28.3
Unknown	200	18.1	/
Pathological stage			
I	91	8.2	29.6
II	39	3.5	12.7
III	54	4.9	17.6
IV	123	11.1	40.1
Unknown	799	72.2	/
Combined stage			
I	364	32.9	38.1
II	175	15.8	18.3
III	138	12.5	14.4
IV	279	25.2	29.2
Unknown	150	13.6	/

Note: 171 cases have a localisation or morphology for which staging is not applicable (NA)

Females are more frequently diagnosed with a stage IV tumour (males: 28.6%, females: 35.2%) and less frequently with a stage III tumour (males: 14.7%, females: 12.1%) than males (Figure 3). Stage distribution is similar for the different age groups, although there is a trend for less advanced tumours being more frequent in older patients (Figure 4).

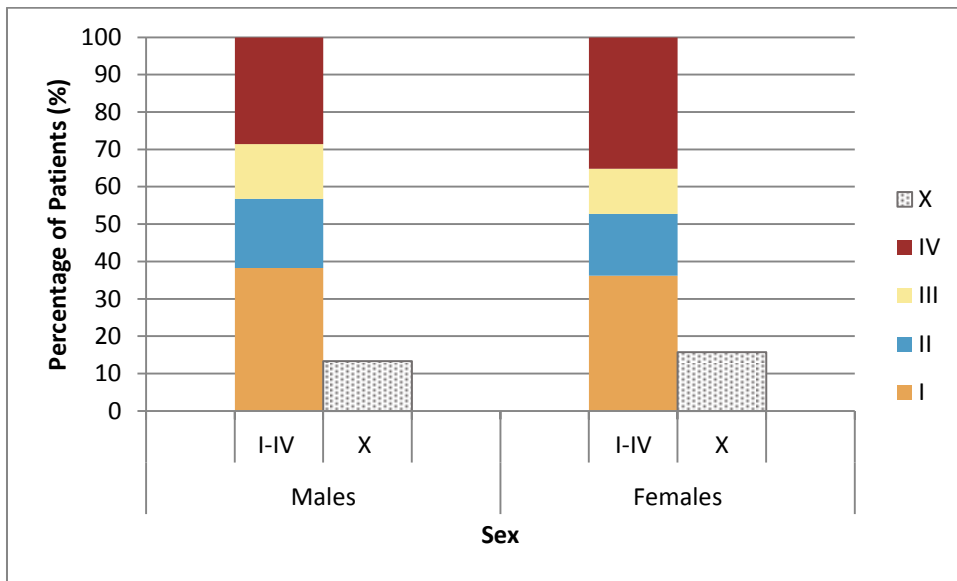


Figure 3. Laryngeal Cancer: Stage Distribution by Sex (Flemish Region, 2004-2007)

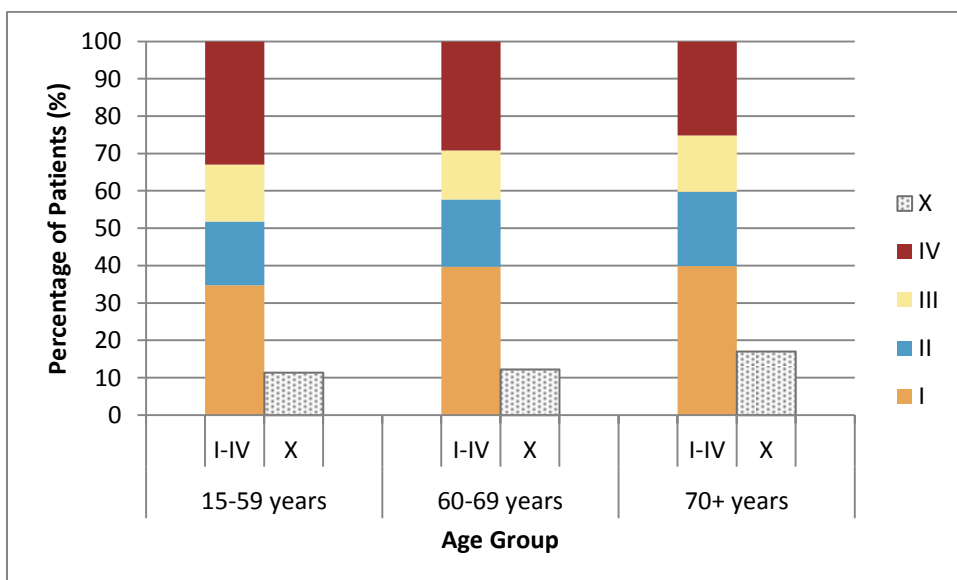


Figure 4. Laryngeal cancer: Stage Distribution by Age Group (Flemish Region, 2004-2007)

5. Diagnostic and Therapeutic Procedures

5.1 Diagnosis and Staging

Table 4 gives an overview of the diagnostic and therapeutic procedures for the laryngeal cancer patients in the Flemish Region diagnosed in the incidence years 2004 to 2007. Almost all cancers are confirmed by pathological examination (98.6%), which is always based on histology. The imaging

technique most frequently used is CT scanning (93.5%) but chest X-rays are also often performed (79.5%). All other imaging techniques are rather infrequently used compared with other head and neck tumours (range 8.3%-39.9%). PET scanning is charged in 22.4% of the patients and MRI in 22.8%. Screening for second primary cancers of the upper respiratory and digestive tract occurs in 11.6% and 48.1% of the patients, respectively.

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

Diagnostic Procedure (-3m<inc<+3m)	Total (N=1,277)		2004 (N=346)		2005 (N=295)		2006 (N=300)		2007 (N=336)	
	n	%	n	%	n	%	n	%	n	%
Tissue Examination	1,257	98.4	337	97.4	293	99.3	298	99.3	329	97.9
Histological Diagnosis	1,257	98.4	337	97.4	293	99.3	298	99.3	329	97.9
Cytology	168	13.2	42	12.1	35	11.9	41	13.7	50	14.9
Imaging	1,226	96.0	325	93.9	284	96.3	293	97.7	324	96.4
CT	1,194	93.5	313	90.5	273	92.5	288	96.0	320	95.2
MRI	291	22.8	78	22.5	61	20.7	67	22.3	85	25.3
Ultrasound Neck	106	8.3	30	8.7	22	7.5	24	8.0	30	8.9
PET Scan	286	22.4	64	18.5	71	24.1	70	23.3	81	24.1
Chest X-ray	1,015	79.5	277	80.1	240	81.4	230	76.7	268	79.8
Ultrasound Abdomen	509	39.9	119	34.4	114	38.6	131	43.7	145	43.2
Screening for Second Primary Malignancies	640	50.1	152	43.9	158	53.6	152	50.7	178	53.0
Respiratory Tract	148	11.6	37	10.7	39	13.2	31	10.3	41	12.2
Digestive Tract	614	48.1	145	41.9	154	52.2	145	48.3	170	50.6
Other Procedures										
Lymph Node Biopsy	25	2.0	11	3.2	3	1.0	6	2.0	5	1.5



5.2 Multidisciplinary Oncological Consult

About 59% of all laryngeal cancer patients are discussed at a multidisciplinary oncological consult (MOC) within one month before till three months after incidence date. An increase in the proportion of patients discussed at a MOC is observed over time, rising from 47.1% in 2004 to 72.0% in 2007 (Table 5).

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

Incidence year	MOC	
	n	%
2004 (n=346)	163	47.1
2005 (n=295)	173	58.6
2006 (n=300)	176	58.7
2007 (n=336)	242	72.0
Total (n=1,277)	754	59.0

5.3 Therapeutic Procedures

Three types of surgery are studied: major surgery (i.e. (sub)total laryngectomy), minor surgery (e.g. endoscopic surgery on the larynx) and lymphadenectomies. The major or minor surgery closest to the incidence date is selected as surgery. When none of them has taken place, lymphadenectomies are taken into account.

Of all recorded surgeries, minor surgery is most frequently performed (73.4%), followed by major surgery (21.3%). Patients for which a lymphadenectomy is charged are uncommon (5.3% of all surgically treated patients).

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

Type of Surgery	n	%
Major Surgery	146	21.3
Minor Surgery	503	73.4
Lymphadenectomy	36	5.3

For 21 patients, the surgical procedure was carried out after radiotherapy and therefore considered as salvage surgery. For the remaining 664 surgically treated patients (52.0% of all patients), the

surgical procedure was considered to be the cornerstone of the treatment. For 187 patients surgery was the only oncological treatment. However, a majority of the surgically treated patients (n=459; 69.1%) received adjuvant radiotherapy with or without chemotherapy.

A large part of the patients only receives radiotherapy as the treatment for their laryngeal cancer (30.0%). Chemotherapy only or concomitant chemoradiotherapy are less frequently used (1.3% and 9.3% respectively). For about 6% of the patients, no charged primary oncological treatment can be found.

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

Treatment Scheme	n	%
Surgery	664	52.0
Adjuvant radiotherapy	357	28.0
Adjuvant chemoradiotherapy	97	7.6
No other therapy	187	14.6
Other therapy		
Surgery < chemotherapy	13	1.0
Chemotherapy < surgery	5	0.4
Chemotherapy < surgery < radiotherapy	3	0.2
Chemotherapy < surgery < chemoradiotherapy	2	0.2
Radiotherapy only	399	31.2
Chemoradiotherapy	124	9.7
Chemotherapy only	16	1.3
No primary treatment registered	74	5.8

6. Survival

6.1 Observed and Relative Survival

Patients with laryngeal cancers have a relative good prognosis compared with patients with other types of head and neck cancer. The five-year relative survival rate is 65.4% (Table 8).

Table 8. Laryngeal Cancer: 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
1,277	84.7	74.1	67.5	62.4	57.2	86.8	77.9	72.9	69.3	65.4

6.2 Relative Survival by Sex

In contrast to most cancer types, survival is slightly better for males than for females (Table 9).

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

	N at risk	%	Relative Survival (%)				
			1 year	2 year	3 year	4 year	5 year
Males	1,145	89.7	87.1	78.7	73.8	70.3	66.1
Females	132	10.3	84.6	71.1	65.1	61.2	59.7

6.3 Relative Survival by Age Group

Survival is lower for the oldest age group (5-year relative survival of 60.7%) than for the younger age groups (5-year relative survival of 65.7% and 68.5% for the age groups 15-59 years and 60-69 years respectively) (Table 10).

Table 10. Laryngeal Cancer: 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	438	34.3	89.3	78.5	73.8	69.5	65.7
60-69 years	417	32.7	89.5	80.2	74.4	71.5	68.5
70+ years	422	33.0	81.3	74.8	70.1	66.3	60.7

6.4 Relative Survival by Stage

Survival is highly dependent on the stage of the tumour. There is a much better survival for stage I tumours (5-year relative survival: 88.4%) compared with stage IV tumours (5-year relative survival: 38.5%). It should be noted that some locally or regionally advanced diseases are categorised as stage IV (stage IVA or IVB, more precisely) although laryngeal tumours with distant metastases are also categorised as stage IV (Stage IVC). Most stage IV tumours in this study (111) are stage IVA, only 17 tumours are staged as IVB and 22 as IVC.

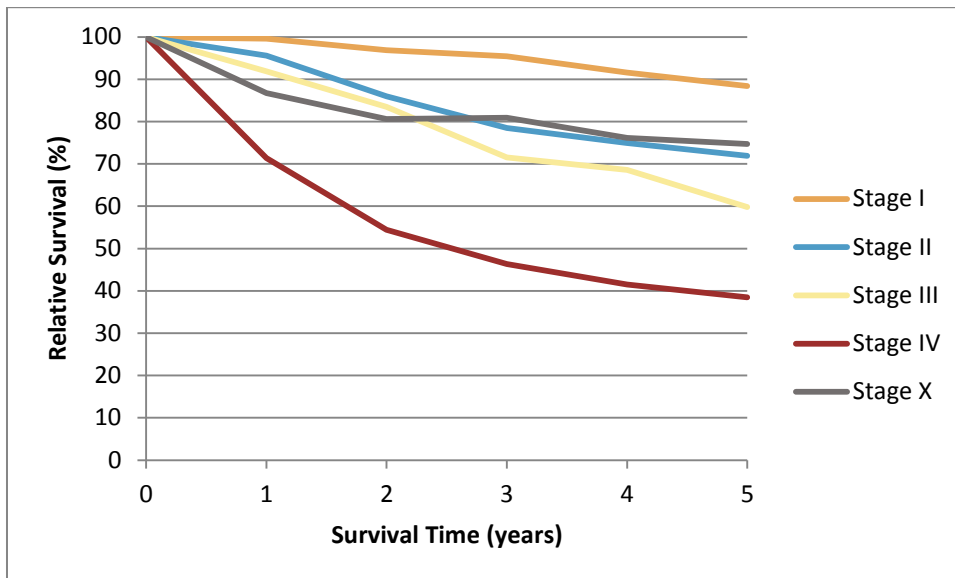


Figure 5. Laryngeal Cancer: Relative Survival by Stage (Flemish Region, 2004-2007)

6.5 Relative Survival by Sublocalisation

Survival is highly dependent on the sublocalisation (Figure 6). Tumours located in the glottis have a much better survival (5-year relative survival: 77.2%) than tumours originating from the supraglottis (5-year relative survival: 48.1%) and tumours with an unspecified laryngeal localisation (5-year relative survival: 53.8%).

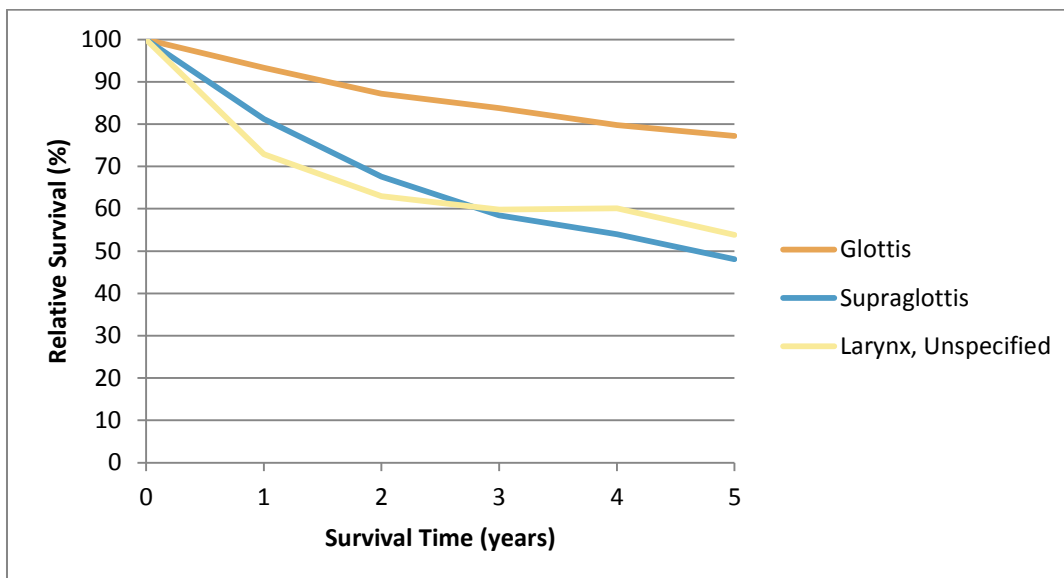


Figure 6. Laryngeal Cancer: Relative Survival by Sublocalisation (Flemish Region, 2004-2007)

6.6 Relative Survival by Primary Treatment

Survival results by primary treatment are reported separately for the lower and higher stages, because treatment choice and survival are dependent on the stage of the tumour.

For the lower stages (stage I and II), survival is comparable between patients treated with RT and patients treated with surgery (only few patients were treated with chemoradiotherapy and are therefore not shown in Figure 7).

Survival patterns are different for the higher stages (stage III to IVb), where similar results are seen for patients treated with chemoradiotherapy and surgery, and worse results for those treated with radiotherapy only.

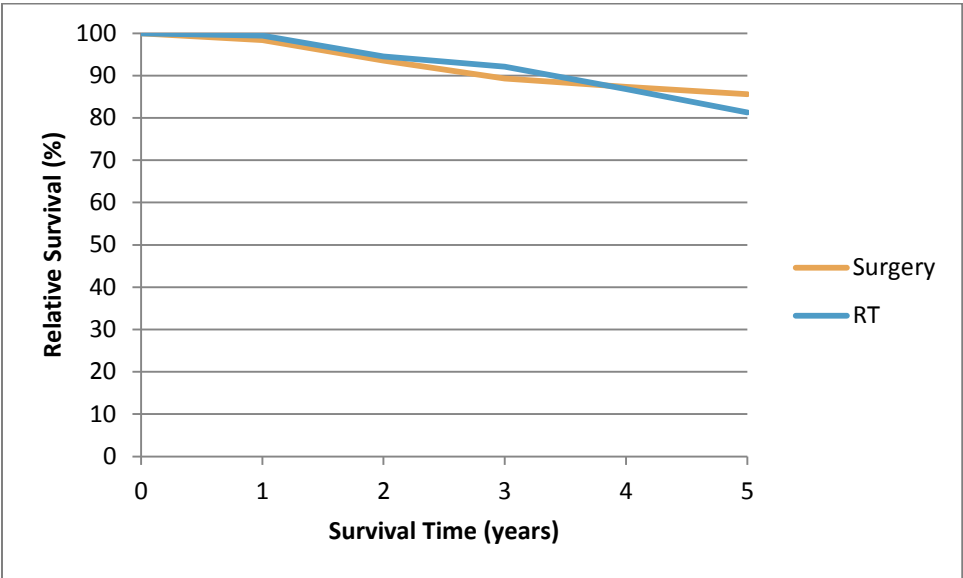


Figure 7. Laryngeal Cancer: Relative Survival by Primary Treatment for Tumours with Stage I-II (Flemish Region, 2004-2007)

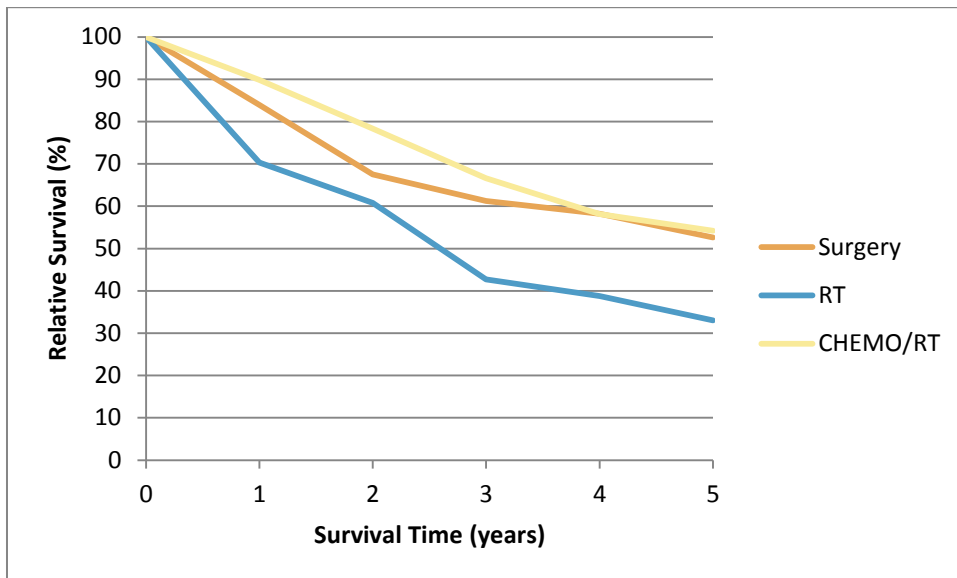


Figure 8. Laryngeal Cancer: Relative Survival by Primary Treatment for Tumours with Stage III to IVB (Flemish Region, 2004-2007)

7. Analyses by Volume

During the period 2004-2007, Belgian patients with laryngeal cancer are treated in 55 different Flemish hospitals. The mean number of patients (during the period 2004-2007) treated or followed for laryngeal cancer by hospital is 22.0 and the median is 11, with a range between 1 and 170. The distribution of the number of patients (=volume) per hospital is displayed in Figure 9..

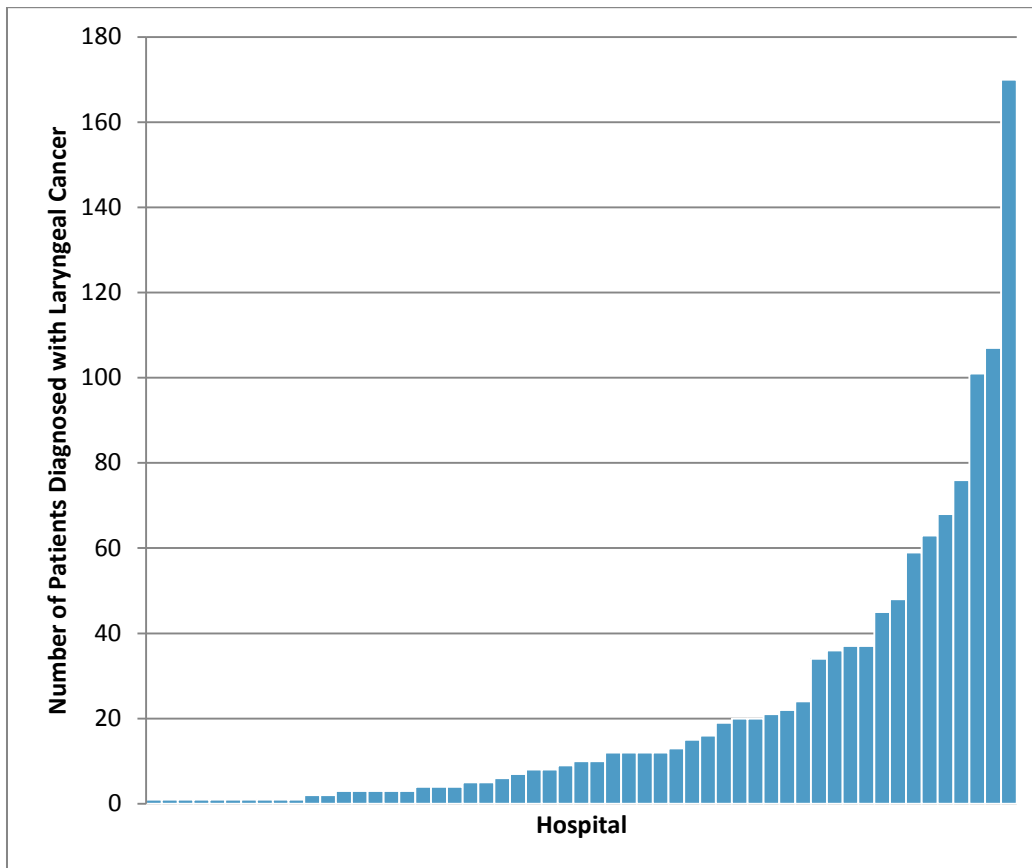


Figure 9. Laryngeal Cancer: Distribution of Patients by Hospital (Flemish Hospitals, 2004-2007)

1,215 of the Flemish patients (95.1%) can be assigned to a hospital (see Methodology for the rules applied to assign a patient to one hospital). Considering a hospitals having taken care of 60 or more patients diagnosed during the period 2004-2007 as high-volume hospitals, 568 patients are assigned to high-volume hospitals and 647 are assigned to low-volume hospitals.

Treatment schemes are different for high-volume and low-volume hospitals (Figure 10). In high-volume hospitals, 43.7% of the patients are primarily treated with radiotherapy, while another 12.7% are treated with chemoradiotherapy. Another 41.0% of the patients are primarily treated with surgery (with or without (neo-) adjuvant therapy). For low-volume hospitals only 21.6% of the patients are primarily treated with radiotherapy and another 8.0% are treated with chemoradiotherapy. The proportion of patients primarily treated with surgery is much larger than for the high-volume hospitals (66.5%).

Patients only treated with chemotherapy or without any registered oncological treatment are rare in both high- and low volume hospitals.

It should be noted that the difference in the proportion of patients treated with radio- or chemoradiotherapy in the high-volume versus low-volume hospitals can at least partly be explained because the RT centres are overrepresented in the high-volume group due to the rules for assignment that give a rather high priority to the hospital where the RT has taken place.

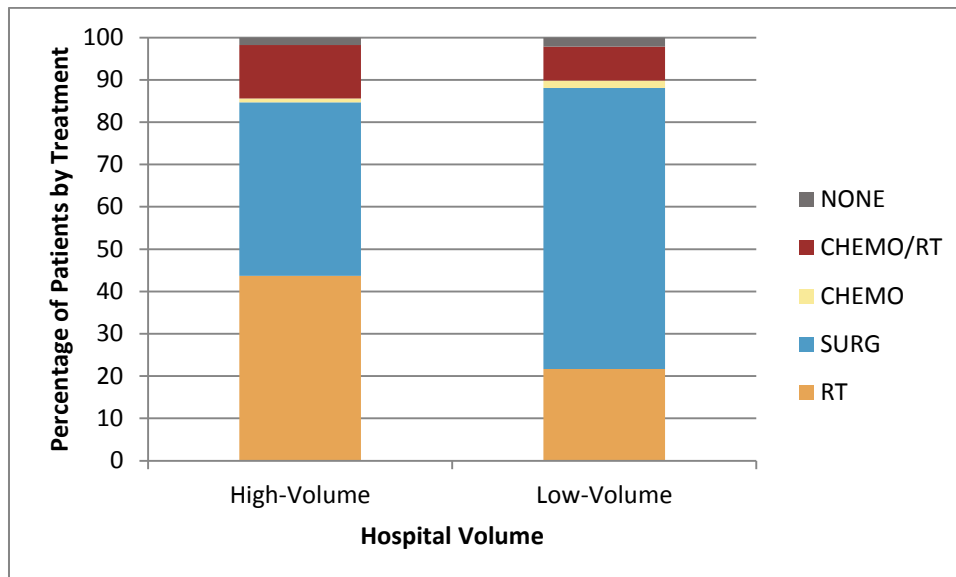


Figure 10. Laryngeal Cancer: Primary Treatment by Hospital Volume (High-Volume versus Low-Volume Hospitals) (Flemish Region, 2004-2007)

8. References

1. Cancer Survival in Belgium, Belgian Cancer Registry, Brussels 2012.
2. Muscat J and Wynder E. Tobacco, alcohol, asbestos, and occupational risk factors for laryngeal cancer. *Cancer* 1992; 69: 2244-2251.
3. Raitiola H, Pukander J and Laippala P. Glottic and supraglottic laryngeal carcinoma: differences in epidemiology, clinical characteristics and prognosis. *Acta Otolaryngol* 1999; 119: 847-851.
4. NCCN guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed on October 01 2013.
5. Mendenhall W, Werning J, Hinerman R, Amdur R and Villaret D. Management of T1-2 glottic carcinomas. *Cancer* 2004; 100: 1786-1792.
6. Forastiere A, Goepfert H, Moar et al. Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer. *N Eng J Med* 2002; 349: 2091-2098.