LARYNGECTOMY

Complications & Survival

Thomas Pézier

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Laryngectomy: complications & survival

Laryngectomie: complicaties & overleving
(met een samenvatting in het Nederlands)

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Introduction

HISTORICAL PERSPECTIVE

The larynx is the cartilaginous cavity guarding the entrance to the trachea. Our modern term larynx is derived from the Greek word λάρυγγας (láryngas) "the upper windpipe" which itself is probably derived from λαιμός (laimós)meaning "throat". Galen (129 AD – c. 200/c. 216) described the larynx as "first and supremely most important the instrument of the voice"[1]. We now recognize that in addition to phonation, the larynx plays an important role in breathing and protection from aspiration.

Diseases or traumas of the larynx thus manifest themselves with changes of voice, to breathing and/or aspiration. In ancient times, we can speculate that diseases such as diphtheria, tuberculosis, pseudo-croup, warts and syphilis were the most common pathologies of the larynx, alongside ever present trauma from sharp, blunt or strangulation injuries. Records exist of laryngotomy or tracheotomy being proposed by Asclepiades (c.124-40 BC)[2], Antyllus (2nd century AD) and Paul of Aegina (625-690), in order to prevent suffocation from obstructing masses[3] and indeed tracheotomy is depicted in far older Egyptian artifacts in the Abydos and Sakkara regions dating to 3600 BC[4-6]. There are similarly ancient writings from India which describe tracheotomy wounds healing spontaneously.

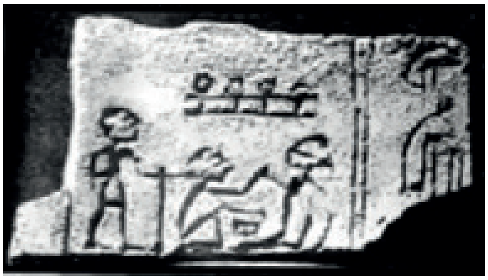

FIGURE 1: Egyptian artifacts in the Abydos and Sakkara

Whilst tracheotomy could alleviate some of the symptoms of obstructing masses, it was recognized that whilst it solved the airway compromise, it often would worsen phonation and aspiration. Furthermore, tracheotomy would also not solve the underlying pathology (though in the case of diphtheria, descriptions exist of the pseudomembrane being suctioned out through a tracheostomy).

Addressing the underlying pathology was hampered by a lack of anesthetic, hygiene and the ability to visualize the larynx. Indeed, it is not until the 18th and 19th centuries that we find reliable descriptions of laryngeal disease *in vivo*. Philipp Bozzini (1773-1809) and the André Levret (1703-1780) used warmed polished metal mirrors to view the larynx[7] but it was ultimately the singer Manuel Garcia (1805-1906) who first described a two mirror technique for visualizing his own vocal cords in 1854. For this finding, Garcia became known as the "father of laryngoscopy"[8].

FIGURE 2: Manuel Garcia (1805-1906), the "father of laryngoscopy"

Once a diagnosis could be established, treatment could follow. DeSault in Paris reported laryngofissure in 1813[9] and Brauets of Leeuven described the technique more fully in 1833[10].

In 1850, Charles-Henri Ehrmann (1792-1878), professor of anatomy and surgery in Strasbourg School of Medicine, published his treatise "Histoire des polypes de larynx" (History of laryngeal polyps) in which he describes a 33-year-old woman presenting with loss of voice in whom he diagnosed laryngeal polyps. After a preliminary tracheotomy, Ehrmann divided the patient's thyroid and cricoid cartilage and became the first surgeon to excise a laryngeal tumor by a direct route. The patient recovered well but without a voice and died seven months later of typhoid fever[7,11]. Some 19 years later, in

1869, the American laryngologist Jacob da Silva Solis Cohen (1838-1927) introduced the anterior laryngofissure for the management of laryngeal squamous cell cancer (LSCC). The patient recovered and lived a further 20 years[12].

In 1870, Czerny, one of Billroth's assistants from Vienna, laryngectomised 5 dogs resulting in four out the five dogs dying[13]. Undeterred, Billroth himself performed the first human laryngectomy in in 1873. The patient was a 36 year old male with a subglottic LSCC. Efforts to treat the cancer with topical silver nitrate cautery and intralesional injections of liquor ferri (a solution of iron perchloride) failed and Billroth performed a laryngofissure on 27th November 1873. A preliminary tracheotomy was performed and a tampon inserted to prevent aspiration. The thyroid cartilage was then divided just to the left of the midline exposing the tumor on the left side. The tumor was excised and its base curetted. The right vocal fold was able to be preserved and the wound was closed. Two weeks postoperatively, the patient was able to speak with a hoarse voice. However, during the night of 29th December, he became increasingly breathless due to tumor recurrence and the original tracheotomy wound was reopened with dilators. A further laryngofissure was performed on the 31st December but intra-operatively the tumor was found to be infiltrating the perichondrium of the thyroid cartilage. The chloroform anesthetic dose was lightened and the patient woken up and informed of the findings. Billroth advised that the only chance for cure was a laryngectomy. With the patient thus consented, he was re-anesthetized and the first ever human laryngectomy performed. The procedure lasted some 13 hours and was reconstructed with a T-shaped "artificial larynx" tube designed by Carl Gussenbauer (1842-1903). This consisted of three cannulas (tracheal, pharyngeal and phonation) and an artificial epiglottis. Phonation was produced by a vibrating metal reed located in the phonation cannula. Postoperatively, the patient was fed via a stomach tube and developed a pharyngocutaneous fistula. Two months later, this had healed and the patient was able to resume oral nutrition. The patient finally left hospital on 3rd May 1874 some 4 months after the operation. Three months later he died from recurrence[14-16].

Billroth's success (which brings to mind the Lancet medical journal's founding story of "the operation was a success, the patient nevertheless died") inspired other surgeons to attempt their own laryngectomies. In 1875, Enrico Bottini from Turin performed a total laryngectomy in a patient who survived for 10 years after surgery[17]. In 1880 Gluck reported a retrospective study, with a mortality rate of 50%. In 1908, he again published his case series, now with 128 total laryngectomies among which 20 patients were alive and free from recurrence at the end of three years. Over the years he had developed a two-step procedure, first by separating the trachea from the larynx and then 2 weeks later removing the larynx[18]. Sorenson (1862-1939) described in 1890, a new, one step total laryngectomy technique similar to the current retrograde approach. Martin and Ogura standardized the total laryngectomy with the addition of Crile's neck dissections around 1950[19].

FIGURE 3: Christian Albert Theodor Billroth (1829-1894)

FIGURE 4: "artificial larynx" tube designed by Carl Gussenbauer (1842-1903)

ANATOMY AND PHYSIOLOGY

Evolutionary origins

In evolutionary biology, the larynx can be viewed as a modification to a fish's gill arches and is present in most tetrapod species. Typically however, its structure is far simpler than that found in mammals. Frogs for example, only have the cricoid and arytenoid cartilages, whilst salamanders possess only the arytenoids[20]. Furthermore, only mammals have a thyroid cartilage and a true epiglottis, although a flap of non-cartilaginous mucosa is found in a similar position in many other groups.

Vocal folds are also almost unique to mammals, though they exist in a few lizards. As a result, many reptiles and amphibians are essentially voiceless; frogs use ridges in the trachea to modulate sound, whilst birds have a separate sound-producing organ, the syrinx[20] (located at the base of a bird's trachea).

Human embryology

In humans, during the 4th week of gestation, the trachea-bronchial diverticulum appears in the ventral wall of the primitive pharynx. The edges of this groove form the oesophago-tracheal septum which fuses caudally leaving a slit like opening cranially. The cranial end forms the larynx and trachea whilst the caudal end forms the bronchi and lungs. Arytenoid swellings appears on both sides of the trachea-bronchial diverticulum. These swellings grow upwards and deepen to form the aryepiglottic folds. The hyobrachial eminence forms the epiglottis. The thyroid cartilage forms from the 4th pharyngeal arch. The cricoid cartilage and tracheal cartilage rings form from the 6th pharyngeal arch. Superior and recurrent laryngeal branches of the vagus nerve derived from these two arches innervate the nascent larynx[21].

In infants, the larynx lies high in the neck and is softer, smaller and more funnel-like. Until puberty there is little difference between male and female larynx but after puberty the male larynx grows significantly larger with an anterior-posterior diameter of 36mm compared to 26mm in women. The angle of fusion of the thyroid cartilage is also more acute in men at roughly 90 degrees compared to 120 degrees in women, given the appearance of the "Adam's apple". In adults the larynx comes to lie at the level of the 3rd to 6th cervical vertebrae with the vocal cords lying at the level of C5. The cartilages stiffen with age and slowly calcifies.

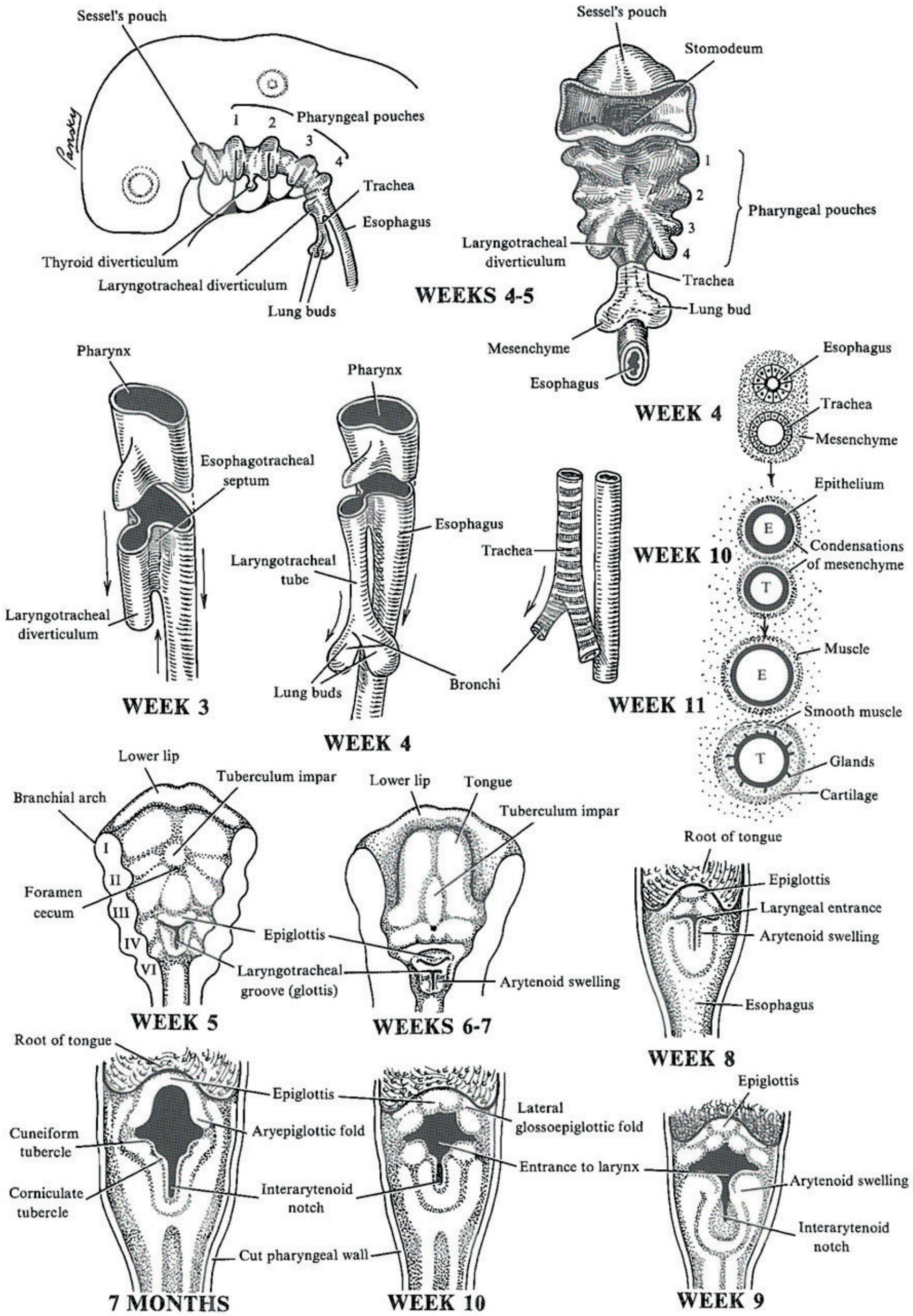

FIGURE 5: Embryological development of the human larynx

The larynx is formed of 3 paired cartilages (arytenoid, corniculate (of Santorini) and cuneiform (of Wrisberg)) and 3 unpaired cartilages (thyroid, cricoid and epiglottis). These are held together by various intrinsic/extrinsic ligaments and muscles. The larynx forms the entrance to the airway and extends from the tip of epiglottis to the lower edge of the cricoid cartilage. The cricoid cartilage is the only complete cartilaginous ring in the airway.

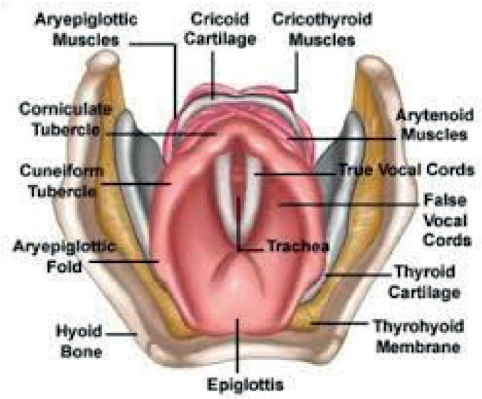

FIGURE 6: Axial view of the larynx

Anatomical divisions

The larynx can be divided in the coronal plane into the supraglottis, glottis and subglottis. The supraglottis extends from the tip of the epiglottis, a thin leaf like elastic fibrocartilage to the level on the laryngeal ventricles (sinus of Morgagni). It has a rich lymphatic drainage into levels II and III in the neck laterally. Tumors occurring here can often grow to a considerable size and metastasize before causing symptoms.

The area below the supraglottis to an imaginary line 1cm below the true vocal cords is termed the glottis. This region has poor lymphatic drainage and even small tumors can lead to hoarseness of voice meaning that many patients present early in the disease's course with small local tumors and no nodal spread.

The subglottis extends from 1cm below the vocal cords to the lower edge of the cricoid cartilage. Again it has poor lymphatic drainage and tumors here cause mostly obstructive symptoms. This said, the area is difficult to visualize in clinic and tumors can be missed.

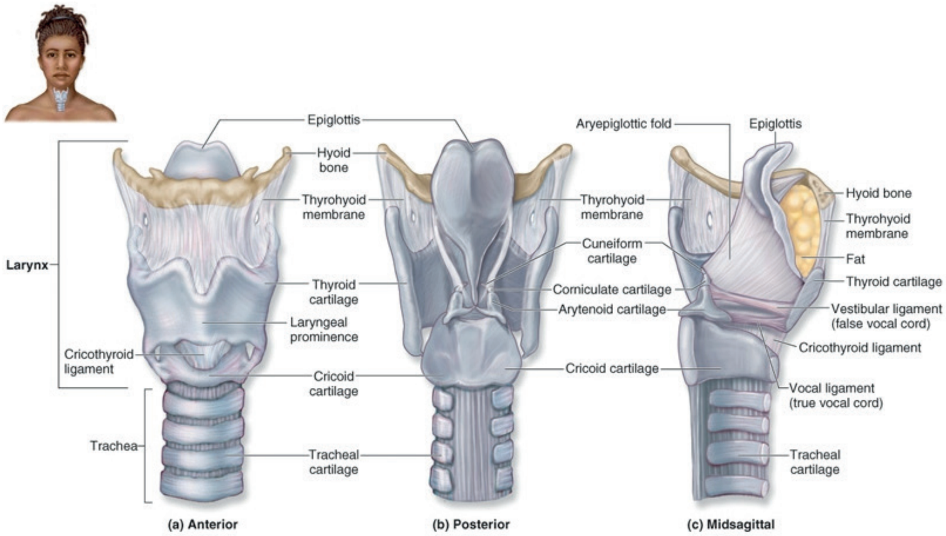

FIGURE 7: Front, rear and lateral views of the larynx

The larynx is covered in pseudo-stratified columnar respiratory type epithelium except for the upper half of the posterior epiglottis, upper part of the aryepiglottic folds, posterior glottis and vocal folds which are covered in non-keratinizing stratified squamous epithelium.

Innervation

Innervation is provided by the superior and recurrent (inferior) laryngeal nerves. The superior laryngeal nerve originates at the inferior ganglion of the vagus and also receives a branch from the superior cervical sympathetic ganglion. It descends lateral to the pharynx, behind the internal carotid artery and at the level of the greater horn of the hyoid, divides into external and internal branches. The external branch provides the motor supply for the cricothyroid muscle (useful for professional singers). The internal branch penetrates the thyro-hyoid membrane and divides into upper and lower branches providing sensory and secretory-motor function. The superior laryngeal nerve ends by piercing the inferior constrictor muscles and connecting to the ascending branch of the recurrent laryngeal nerve (Galen's anastomosis).

The right recurrent laryngeal nerve has a famously inconsistent course. In most cases however, it loops under the right subclavian artery before re-entering the neck at a variable angle to the trachea-oesophageal groove. The left recurrent laryngeal nerve loops under the aorta and follows a more consistent course, running in the trachea-oesophageal groove. Both left and right nerves can be identified where they enter larynx behind the cricothyroid joint. They then divide into motor and sensory branches. The former provides motor innervation for all the intrinsic laryngeal muscles except the cricothyroid. The latter provides sensory innervation below the level of the vocal cords.

Blood supply

The laryngeal blood supply consists of the superior laryngeal artery (a branch of the superior thyroid artery) which pierces the thyrohyoid membrane together with the superior laryngeal nerve. The inferior laryngeal artery arises from the inferior thyroid artery and enters the larynx below the lower border of the inferior constrictor. The cricothyroid artery may contribute to the supply of the larynx. It follows a variable course either superficial or deep to the sternothyroid muscle. If superficial, it may be accompanied by branches of the ansa cervicalis, and if deep, it may be related to the external laryngeal nerve. It can connect with the artery of the opposite side and with the laryngeal arteries.

EPIDEMIOLOGY

Head and Neck squamous cell carcinomas (HNSCC) are the seventh most-frequent cancer and the ninth most-frequent cause of cancer deaths in the world[22]. In 2018, head and neck cancers globally were diagnosed in more than 800,000 people: 354,864 lip & oral cavity, 177,472 larynx, 129,079 nasopharynx, 92,887 oropharynx and 80,608 hypopharynx. Dutch figures for 2018 show 699 laryngeal cancers and 194 hypopharyngeal cancers. Worldwide there were over 420,000 deaths: 177,384 lip & oral cavity, 84,771 larynx, 72,987 nasopharynx, 51,005 oropharynx, 34,984 hypopharynx.

Laryngeal squamous cell cancer (LSCC) comprises 2% to 5% of all malignant diseases diagnosed annually worldwide and is roughly a tenth as common as the commonest cancer, lung cancer. In recent years, age-adjusted incidence rates have decreased by about 2% annually, probably due to decreased rates of tobacco smoking. Patients are typically in their 60s when diagnosed[23] with a worldwide male-to-female ratio between 5:1 to 20:1 (with in recent years increasing numbers of women being diagnosed). There is a notable social class difference, with laryngeal cancer being twice as common in men with low socio-economic status compared to high socio-economic status. Approximately 65% laryngeal cancers are glottic in origin, 33% supraglottic and the remaining 2% subglottic.

TABLE 1: New cases and deaths worldwide for 36 cancers in 2018[24]

Cancer site	Number of new cases (%)	Number of deaths (%)
Lung	2,093,876 (11.6)	1,761,007 (18.4)
Breast	2,088,849 (11.6)	626,679 (6.6)
Prostate	1,276,106 (7.1)	358,989 (3.8)
Colon	1,096,601 (6.1)	551,269 (5.8)
Non-melanoma of skin	1,042,056 (5.8)	65,155 (0.7)
Stomach	1,033,701 (5.7)	782,685 (8.2)
Liver	841,080 (4.7)	781,631 (8.2)
Rectum	704,376 (3.9)	310,394 (3.2)
Esophagus	572,034 (3.2)	508,585 (5.3)
Cervix uteri	569,847 (3.2)	311,365 (3.3)
Thyroid	567,233 (3.1)	41,071 (0.4)
Bladder	549,393 (3.0)	199,922 (2.1)
Non-Hodgkin lymphoma	509,590 (2.8)	248,724 (2.6)
Pancreas	458,918 (2.5)	432,242 (4.5)
Leukemia	437,033 (2.4)	309,006 (3.2)
Kidney	403,262 (2.2)	175,098 (1.8)
Corpus uteri	382,069 (2.1)	89,929 (0.9)
Lip, oral cavity	354,864 (2.0)	177,384 (1.9)
Brain, nervous system	296,851 (1.6)	241,037 (2.5)
Ovary	295,414 (1.6)	184,799 (1.9)
Melanoma of skin	287,723 (1.6)	60,712 (0.6)
Gallbladder	219,420 (1.2)	165,087 (1.7)
Larynx	177,422 (1.0)	94,771 (1.0)
Multiple myeloma	159,985 (0.9)	106,105 (1.1)
Nasopharynx	129,079 (0.7)	72,987 (0.8)
Oropharynx	92,887 (0.5)	51,005 (0.5)
Hypopharynx	80,608 (0.4)	34,984 (0.4)
Hodgkin lymphoma	79,990 (0.4)	26,167 (0.3)
Testis	71,105 (0.4)	9,507 (0.1)
Salivary glands	52,799 (0.3)	22,176 (0.2)
Anus	48,541 (0.3)	19,129 (0.2)
Vulva	44,235 (0.2)	15,222 (0.2)
Kaposi sarcoma	41,799 (0.2)	19,902 (0.2)
Penis	34,475 (0.2)	15,138 (0.2)

TABLE 1: Continued

Cancer site	Number of new cases (%)	Number of deaths (%)
Mesothelioma	30,443 (0.2)	25,576 (0.3)
Vagina	17,600 (0.1)	8,062 (0.1)
All sites excluding skin	17,036,901	9,489,872
All sites	**18,078,957**	**9,555,027**

ETIOLOGY

Tobacco smoking and alcohol consumption are estimated to play a role in 89% of laryngeal cancer cases[25]. Both of them increase the risk of cancer in a dose-dependent way and the combination is multiplicative rather than additive. It appears that nicotine is not carcinogenic itself, but that the polycyclic aromatic hydrocarbons and nitrosamines are. Poor diet and oral hygiene, vitamin deficiency, cirrhosis and the depressed immune system often found in alcoholics may also contribute to cancerous process. Numerous other risk factors for laryngeal cancer have been investigated including:

- Anatomical malformations,
- Plummer-Vinson syndrome,
- Infections such herpes simplex and human papilloma virus (HPV),
- Gastroesophageal reflex disease,
- Chemicals such as formaldehyde, vinyl chloride and benzopyrenes,
- Thermal insults whether from steam, smoke or other heat inhalation,
- Ionizing radiation,
- Exposure to asbestos, nickel and textile fibers,
- Genetic factors.

PATHOPHYSIOLOGY

Roughly 95% of laryngeal malignancies are squamous cell carcinomas (SCC). Other laryngeal malignancies include: carcinoma in situ, verrucous, spindle cell and basaloid SCC, undifferentiated carcinoma, adenocarcinoma, miscellaneous carcinomas (adenoid cystic carcinoma, neuroendocrine carcinomas, etc.) and sarcomas.

Of the benign tumors of the larynx, papilloma is by far the most common, accounting for some 85%. Other types include: chondroma, haemangioma, lymphangioma, schwannoma, neurofibroma, adenoma, granular cell myoblastoma, leiomyoma, rhabdomyoma, fibroma, lipoma and paraganglioma[26].

Genetics

With modern pathological techniques, our understanding of the roles played by tumor suppressor genes and proto-oncogenes is improving and with it our understanding of malignant transformation[26]. In the future it is hoped that a precise genetic profiling of the cancer will allow us to better design management plans and predict outcomes.

In common with other SCCs, various chromosomal alterations have been observed in laryngeal SCC, such as 9p21 loss which contains the p16 gene, 11q13 which contains the CCND1 locus, 17p13 where the p53 gene is located, 3p with at least three putative tumor suppressor loci, 13q21, 6p and 8. Some of these alterations have been demonstrated to precede the development of cancer by several years, while others may be also detected as late occurring cytogenetic events.

Among the most frequent and relevant cellular changes in laryngeal carcinogenesis are those involving p53, cyclin D1 (CCND1), p16 and EGFR[26]. It is thought that early-on in the malignant transformation changes to these key genes combine to increase genetic instability and promote further genetic and chromosomal alterations.

p53

TP53 is a well known tumor suppressor gene which produces the nuclear phosphoprotein p53[27]. This is involved in gene transcription, DNA synthesis and repair, cell cycle coordination and apoptosis. Changes in p53 function have been detected not only in laryngeal SCC but in almost all head and neck cancers. p53 point mutations or deletions are frequent and p53 inactivation occurs in the transition from pre-invasive to invasive cancer. As such, alterations of p53 protein expression and mutations of the p53 gene have been proposed as independent predictors of recurrence in LSCC, however with controversial prognostic value. It seems that whilst p53 protein overexpression correlates well with p53 gene mutation, the latter is more reliable in, for example, predicting response to radiotherapy. Furthermore, changes in p53 can be found in healthy mucosa and precancerous lesions so p53 status should probably best be interpreted in combination with other genetic changes rather than as a discrete parameter itself. In most cases, tobacco is probably responsible for changes in p53 status though human papillomavirus (HPV) and E6 oncoproteins may represent alternative pathways leading to loss of p53 function.

In terms of using p53 as a target for therapy, a p53 gene therapy approach has already been shown to induce apoptosis and radio- and chemosensitisation in cell lines and this, in combination with radiotherapy or chemotherapy, may form part of a future personalized medicine treatment plan. Another potential use of p53 gene therapy is in the treatment of pre-cancerous lesions.

Cyclin D1

Cyclin D1 gene[27,28] is involved in cell cycle progression and interacts with cyclin-dependent kinases. Analogous to p53 as described above, early CCND1 gene overexpression is often detectable without evidence of gene amplification. Overexpression is necessary but not sufficient for gene amplification, which probably represents a non-reversible, alteration in tumor cells. Amplification rather than overexpression shows the best correlation with clinical behavior, relapse-free following treatment and overall survival in LSCC.

Human papilloma virus/p16

Human papillomavirus (HPV)[28] is an important prognostic biomarker for oropharyngeal squamous cell cancer and it has also been studied in the setting of laryngeal / hypopharyngeal cancer. Often two tests are performed, one for p16 protein over-expression (a cyclin dependent kinase inhibitor which becomes up-regulated in HPV-infected cells) and a second for HPV genotyping by ISH. Correlation between these tests in the oropharynx is above 90%[29] . However, outside the oropharynx, the correlation is far weaker. Chung et al.[30] analyzed pooed data of non-oropharyngeal squamous cell carcinoma cases from RTOG trials 0129, 0234 and 0255 demonstrating 42% were p16-positive with a positive predictive value for HPV of only 33%. A study of 324 laryngeal squamous cell cancer patients showed a p16 rate of 6% a positive predictive value of p16 for HPV of 50%[31]. No studies have identified HPV or p16 as prognostic in laryngeal or hypopharyngeal cancers.

EGFR

EGFR[32] is frequently and from any early time point overexpressed in LSCC, though mainly by post-translational mechanisms. EGFR expression retains a strong predictive value independently of treatment (surgery, chemotherapy and radiation) and adversely influences overall relapse-free and metastasis-free survival in LSCC. Indeed, at present, EGFR is the most reliable biological marker for molecular characterisation, aggressiveness and invasiveness of LSCC.

Other genetic changes

Many other genetic changes are observed in LSCC[26]. These include:

1. Increased telomerase activity.
2. Over-expression of metalloproteases, hyaluronidases and cathepsin D.
3. Over-expression of proteoglycan versican in the extracellular matrix.
4. Alterations in the sulphation pattern of chondroitin/dermatan sulphate, indicating altered expression of sulphotransferases.
5. Changes involving Type II oestrogen binding sites (EBS), normally found in laryngeal mucosa which may provide a target for hormonal therapies.
6. S100A2 has recently been described as an actual oncosuppressor with a prognostic significance stronger than simple histopathological grading. Its underexpression in cancer cells is inversely proportional to tumor differentiation.
7. Methyl-phydroxyphenyllactate esterase (MEPHLase) low activity in LSCC is associated with poor differentiation and shorter overall survival and metastasis-free survival.
8. Type 2 cyclo-oxygenase activity seems to promote tumour neo-angiogenesis. However, evidence exists that low COX2 expression indicates poor differentiation and higher aggressiveness and invasiveness.
9. Galectin-3 participates in a variety of cell processes and mediating cell-to-cell interactions. Its expression seems positively associated with tumour keratinisation and histological grade and a significant correlation was described between galectin-3 tumour positivity and longer metastasis-free and overall survival in LSCC patients.[26]

2

Clinical presentation & work-up

CLINICAL PRESENTATION

The presenting complaints of a patient with laryngeal cancer depend on the size and location of the tumor. Whilst hypopharyngeal cancers can present with difficulty swallowing, most laryngeal tumors present with a change in voice/hoarseness. Both types of tumor can also present with a nodal metastasis in the neck. A thorough ENT examination including transnasal fibre endoscopy together with radiological examination is usually able to delineate the tumor adequately, though often patients will require an anesthetic for the purpose of biopsy. Some centres are able to perform biopsy under local anesthetic using a transnasal approach in the outpatient setting. Sometimes specific questions need to be answered with an examination under anesthetic such as whether the tumor is amenable to laser treatment, whether a flap reconstruction will be required or whether a tumor is invading the pre-vertebral fascia or upper oesophageal sphincter.

IMAGING

Imaging plays an important complementary role to clinical examination and endoscopic biopsy in the evaluation of laryngeal cancers. Cross-sectional imaging with contrast-enhanced computed tomography (CT) and magnetic resonance (MRI) imaging allows excellent depiction of the intricate anatomy of the larynx and the characteristic patterns of submucosal tumor extension. CT, MRI and more recently PET-CT, also provide vital information about the status of cervical nodal disease, systemic metastases and any synchronous malignancies. Additionally, certain imaging-based parameters like tumor volume and cartilage invasion have been used to predict the success of primary radiotherapy or surgery. Integration of radiological findings with endoscopic evaluation greatly improves the pre-therapeutic staging accuracy of laryngeal cancers, and significantly impacts the choice of management strategies in these patients. Imaging studies also help in the post-therapeutic surveillance and follow-up of patients with laryngeal cancers and restaging when necessary[33].

STAGING

The American Joint Committee on Cancer (AJCC) uses the well-known TNM staging system, now in its 8th edition, for squamous cell laryngeal and hypopharyngeal cancers.

TABLE 2: T-stage for supraglottic laryngeal cancer

T-stage (supraglottis)	
pTx	Primary tumor cannot be assessed
pTis	Carcinoma in situ
pT1	Tumor limited to 1 subsite of supraglottis with normal vocal cord mobility
pT2	Tumor invades mucosa of > 1 adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g. mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
pT3	Tumor limited to larynx with vocal cord fixation or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space or inner cortex of thyroid cartilage
pT4a	Moderately advanced local disease: invades through the outer cortex thyroid cartilage or invades tissues beyond the larynx (e.g. trachea, soft tissues of neck including deep extrinsic muscle of tongue, strap muscles, thyroid or esophagus)
pT4b	Very advanced local disease: invades prevertebral space, encases carotid artery or invades mediastinal structure

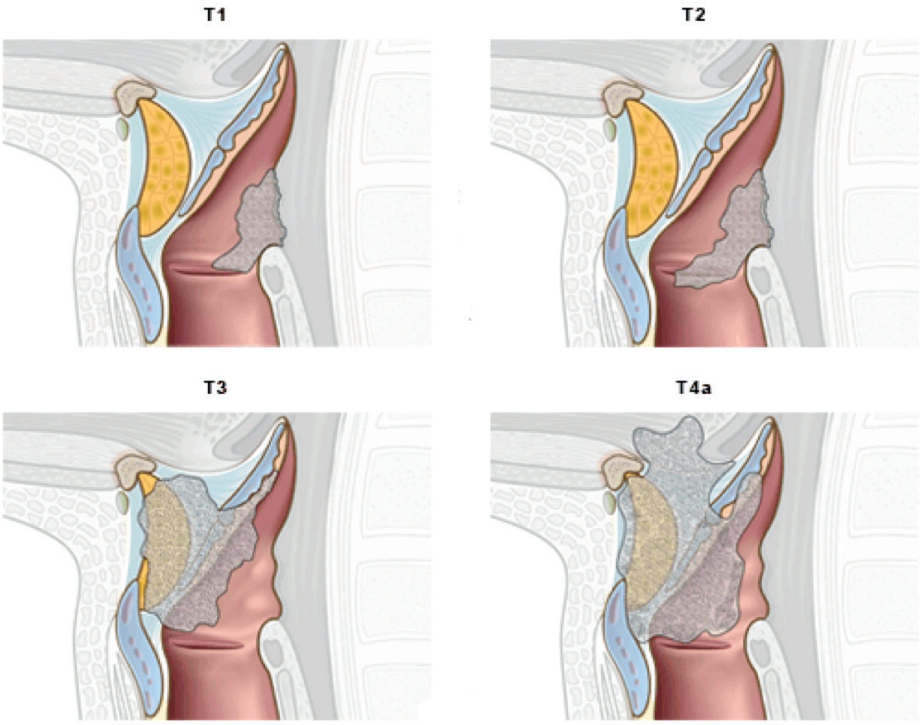

FIGURE 8: T-stage for supraglottic laryngeal cancer

TABLE 3: T-stager for glottic laryngeal cancer

T-stage (glottis)	
pTX	Primary tumor cannot be assessed
pTis	Carcinoma in situ
pT1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
pT1a	Limited to 1 vocal cord
pT1b	Involves both vocal cords
pT2	Tumor extends to supraglottis or subglottis or with impaired vocal cord mobility
pT3	Tumor limited to the larynx with vocal cord fixation or invasion of paraglottic space or inner cortex of the thyroid cartilage
pT4a	Moderately advanced local disease: invades through the outer cortex of the thyroid cartilage or invades tissues beyond the larynx (e.g. trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus)
pT4b	Very advanced local disease: invades prevertebral space, encases carotid artery or invades mediastinal structures

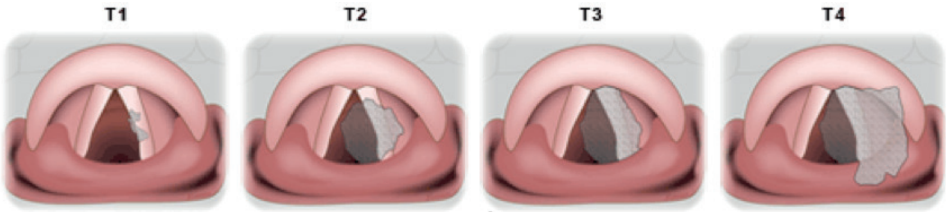

FIGURE 9: T-stager for glottic laryngeal cancer

TABLE 4: T-stage for subglottic laryngeal cancer

T-Stage (subglottis)	
pTX	Primary tumor cannot be assessed
pTis	Carcinoma in situ
pT1	Tumor limited to subglottis
pT2	Tumor extends to vocal cord(s) with normal or impaired mobility
pT3	Tumor limited to larynx with vocal cord fixation or invasion of paraglottic space or inner cortex of the thyroid cartilage
pT4a	Moderately advanced local disease: tumor invades cricoid or thyroid cartilage or invades tissues beyond the larynx (e.g. trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid or esophagus)
pT4b	Very advanced local disease: tumor invades prevertebral space, encases carotid artery or invades mediastinal structures

TABLE 5: T-stage for hypopharyngeal cancer

T-stage hypopharyngeal cancer	
pT1	Tumor limited to one subsite of hypopharynx and/ or 2cm or less in greatest dimension
pT2	Tumor invades more than sone subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4cm in greatest dimension, without fixation of hemilarynx
pT3	Tumor more than 4 cm in greatest dimension, or with fixation of hemilarynx or extension to oesophagus
pT4a	Tumor invades any of the following: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment, soft tissue
pT4b	Tumor invades prevertebral fascia, encases carotid artery, or invades mediastinal structures

TABLE 5: N-stage for laryngeal and hypopharyngeal cancer

Pathological regional lymph nodes (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in a single ipsilateral lymph node ≤ 3 cm in greatest dimension and extranodal extension (ENE)-
pN2a	Single ipsilateral lymph node ≤ 3 cm and ENE+ or single ipsilateral lymph node > 3 cm but ≤ 6 cm in greatest dimension and ENE-
pN2b	Metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE-
pN2c	Metastases in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension and ENE-
pN3a	Metastasis in a lymph node that is > 6 cm in greatest dimension and ENE-
pN3b	Metastasis in either: • Single lymph node, > 3 cm and ENE+ or • Multiple ipsilateral, contralateral or bilateral lymph nodes, any with ENE+ or

Notes on N-staging

The 8th edition of the AJCC cancer staging introduces the concept of extra-nodal extension for the first time. Clinically this manifests itself as fixed nodes and on imaging, this is seen as a loss of fat signal and growth into surrounding structures. On pathological examination extra nodal extension is defined as extension of metastatic tumor, present within the confines of the lymph node, through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction.

Distance of extension from the native lymph node capsule is now suggested (but not yet required) with the proposed stratification of ENE into macroscopic ENEma (> 2 mm) and microscopic ENEmi (≤ 2 mm).

However, pitfalls in the assessment of ENE (i.e. in larger, matted lymph nodes, in nodes post fine needle aspiration and in nodes with near total replacement of lymph node architecture) and the disposition of soft tissue deposits are still not resolved.

Soft tissue deposits for lymph node metastases based on limited studies appear to be the equivalent of a positive lymph node with ENE and should be recorded as such.

TABLE 6: Laryngeal and hypopharyngeal cancer stage

AJCC cancer stage	
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0 T1-3N1
Stage IVA	T4aN0-1M0 T1-4aN2M0
Stage IVB	T4bN0-3M0 T1-T4bN3M0

3

Management

ABLATION

In modern times, the surgical possibilities for the larynx have multiplied whilst conversely the indications have dwindled.

Small lesions can be treated very effectively with single modality, organ sparing approaches such as transoral carbon dioxide laser[34,35] excision or radiotherapy. Laser excision has the benefit of being repeatable and for the right tumor in the right patient should carry minimal morbidity. Its effectiveness has also been improved by the introduction of narrow band imaging[36].

Unfortunately, there are well known limitations to the technique, starting with the difficulty in positioning the patient appropriately on the operating table and gaining an adequate view of the tumor. Small lesions of the anterior commissure can be particularly frustrating and whilst some surgeons treat these in a staged fashion, many surgeons feel that despite their small size, this unfavorable location is better treated with radiotherapy. Overall, though are no direct trials of transoral laser excision versus radiotherapy[37], there are a plethora of analyses which ultimately show comparable local control and low risks of complication[38-40].

For larger tumors , those infiltrating more deeply, or those otherwise not amenable to laser excision the mainstay of treatment is radiotherapy. Though techniques such as laryngofissure and various forms of partial laryngectomy including vertical and horizontal (e.g. supracricoid with cricohyoidopexy (CHP) or cricohyoidoepiglottopexy (CHEP)), are described, radiotherapy has shown itself equally effective in oncological terms and with far less morbidity. The key functions of phonation, protection from aspiration and maintenance of a good airway with possibility for a strong cough and Valsalva are better maintained with radiotherapy rather than surgery. The recent off-label use of the Da Vinci robot for transoral surgery (even total laryngectomy[41]) is yet to have proven itself against conventional radiotherapy.

Radiotherapy protocols are commonly in the range of 60-70 Gray at 1.8-2 fractions. Hypofractionation, hyperfractionation and accelerated fractionation have also been investigated showing variations in cost-benefit, patient friendliness, local control and morbidity[42]. Some centres use carbogen and/or nicotinamide or hypoxic modifier nimorazole to further enhance the effect of radiotherapy[43]. For advanced stage laryngeal cancer, platinum based chemotherapy is often used concomitantly to radiotherapy.

Laryngectomy vs organ preserving therapy

For the largest tumors there has been a paradigm shift in treatment protocols since the 1990s. In 1991, the VA study[44] published in the *New England Journal of Medicine* and an EORTC trial[45] published in 1996 showed that even advanced stage laryngeal or hypopharyngeal cancer could be treated with induction chemotherapy and radiotherapy with similar survival outcomes to the previous gold standard of total laryngectomy, bilateral neck dissections and post-operative radiotherapy.

The benefit of the non-surgical management was clear – patients could keep their larynx and have better physical and psycho-social quality of life[46,47] . The term organ-preserving therapy was born, though it should be noted that organ preserving does not always imply a functioning organ. Indeed follow up of the EORTC cohort[48] reported in 2012 a 10 year survival rate of 13.8% for upfront laryngectomy patients versus 13.1% for patients treated initially with chemoradiation with more than half of the survivors in the latter group still having their larynx. A more recent study of T3/T4 patients initially treated with CRT shows that roughly a third will have a laryngectomy for recurrent disease, and around a further 10% will with have a permanent tracheostomy or laryngectomy for functional reasons[49].

In 2003 the RTOG group[50] addressed one of the concerns of the VA trial by showing the concomitant chemoradiotherapy was as good as, if not better than, induction chemotherapy followed by radiotherapy. The original VA trial had used induction chemotherapy and only patients whose tumors had responded to the induction chemotherapy had continued on for radiotherapy. Patients with chemotherapy resistant tumors had been treated with surgery. The RTOG trial showed that even without this selection of "good responders", chemoradiotherapy was a viable alternative to surgery. The RTOG group went on to show that even in "limited" T4 tumors, concomitant chemoradiotherapy was as effective as surgery (though discussion continues naturally on what "limited" means).

Current CRT protocols often consist of 7 weeks radiotherapy (fractions of 2 Gy, 5x /week) combined with cisplatin (100mg/m^2 in week 1, 4 and 7 of the radiotherapy).

It must also be emphasized that whilst surgical total laryngectomy has changed very little since the time of Martin and Ogura (with the exception of transoral robotic procedures), chemoradiotherapy has shown continuous improvement. Radiotherapy has benefitted from the introduction first of 3-dimensional conformal radiation therapy (3DCRT), then in 1994 intensity modulated radiation therapy (IMRT) and since 2007, volumetric modulated arc therapy (VMAT)[51]. Research is also continuing into the use of cisplatin, especially the dosage with various centres using a weekly dosing schedule and even trials looking at whether dosage based on body surface can be refined by looking at parameters of body composition.

Total laryngectomy is now reserved for the very largest tumors, or in cases of residual or recurrent disease following earlier radiotherapy. This means that in many centers, almost half of the laryngectomies performed will be post-organ preserving therapy.

This move towards organ preserving modalities has however been disappointing in terms of patient survival. Whereas for most cancers survival has been improving over the last 30 years, advanced laryngeal cancer survival seems if anything to have worsened. Some have therefore questioned the shift towards CRT and argue that we have been overenthusiastic in recommending it to patients[52-56]. A very recent analysis however concludes: "No survival difference were noted between surgical and nonsurgical approaches for patients with non-T4, low nodal burden laryngeal cancer. Patients with non-T4, high nodal burden disease may benefit from definitive CRT. Total laryngectomy remains advantageous in patients with T4 disease"[57].

The devil is therefore in the detail and lies in best stratifying patients in order to recommend a treatment option. Our challenge in the coming years will be not only to further refine our management modalities, but to improve our diagnostics and tailor our management plan as specifically as possible to the patient's individual situation.

Total laryngectomy

A total laryngectomy is often only one step in the surgical management of an advanced laryngeal cancer. Together with the laryngectomy, the surgical team must consider the indication for neck dissections, thyroidectomy, tracheoesophageal puncture and whether the pharynx will need to be reconstructed. Various techniques exist with modern possibilities including a "stapler gun" laryngectomy or even a transoral robot performed total laryngectomy. Here follows a simple description of the basic operative steps.

The patient is placed supine on the operating table with their feet towards the anesthetist. After the pre-operative checklists have been completed, the anesthetist usually performs a transoral endotracheal intubation with the tubing running superiorly over the patient's forehead, away from the operative field. At a later stage in the operation, the endo-tracheal tube will be removed and the patient ventilated via the tracheostomy with sterile tubing. Occasionally oral endo-tracheal intubation is not possible and other techniques for ventilation must be used.

A naso-gastric tube is placed and the patient prepped and draped ensuring adequate exposure for any necessary neck dissections or reconstructive flaps. A shoulder roll can be used to improve neck extension if required. Surgical landmarks are identified and a decision made as to whether to include the tracheotomy in the apron incision or whether to make a separate tracheotomy incision.

Skin incision is performed with either a scalpel or electrocautery and a subplatysmal flap raised superiorly to just above the hyoid and inferiorly to the clavicle. If no neck dissections are being performed, the surgeon can choose to either start inferiorly or superiorly. Inferiorly the inferior strap muscles are divided to reveal the thyroid. If the thyroid is to be preserved it is divided at its isthmus and the two lobes dissected laterally from the trachea. The inferior attachements of the sterno-cleido-mastoid muscles can be medially released to allow better exposure and for a less deep sitting stoma.

With the trachea thus exposed, tracheostomy can be performed remembering to allow for enough margin from any inferior extension of the tumor. The ventilation tubing is then switched with an appropriate tracheal tube (eg. Montadon). Ideally the tracheostomy incision is performed just inferior to a cartilaginous ring so that the remaining rings are protected by a cuff of soft tissue.

The dissection now proceeds superiorly with detachment of the constrictor muscles from the thyroid cartilage. An elevator can then be used to lift the piriform sinus off the thyroid ala, preserving as much mucosa as possible. The hyoid bone is identified and exposed by dissecting off the supra-hyoid muscles taking care not to damage the hypoglossal nerves laterally.

If oncologically safe, the larynx can now be entered from above. A long retractor can be placed via the mouth into the vallecula to guide the entry, or the epiglottis can be palpated directly. The epiglottis can be delivered through the incision allowing inspection of the larynx and tumor. The mucosa is then incised along the level of the arytenoids, leaving a 1 cm margin from the tumor. The larynx can now be released from the oesophagus.

The specimen is checked for adequate margins and can be marked and placed in formalin or sent dry according to local pathology laboratory protocol.

By placing a finger through the open pharynx inferiorly the crico-pharyngeus muscle can be identified and a myotomy performed. If a voice prosthesis is to be placed, it can be inserted according to the manufacturers guidelines. If there is sufficient pharyngeal mucosa, primary closure can be performed in either vertical, T or horizontal fashion.

Vicryl is often used in a running Connel suture but some surgeons prefer other materials, stitch techniques or even close over a salivary bypass tube. A second layer of interrupted sutures can be used to reinforce the pharyngeal closure by approximating soft tissue. Indeed, in selected cases a pectoralis major muscle only interposition flap can be used.

After thorough irrigation and hemostasis the neck can be closed leaving suction drains bilaterally.

Following total laryngectomy, patients can expect to spend the first night in a special, medium or intensive care unit and to be transferred to the general ward the following day. If the central compartment has been cleared, post-operative calcium checks will be performed. Progressively the various lines can be removed (for example, arterial line, central lines, urinary catheter, neck drains). Each center will follow its own protocols as to how long a patient is kept nil by mouth postoperatively with some centers starting as soon as 4 days postoperatively with fluids. Other centers keep a patient nil by mouth for up to 2 weeks, especially if the patient is thought to be at high risk of forming a pharyngo-cutaneous fistula (PCF). Some units check for a water tight closure with a contrast swallow, though others proceed directly to building up to a normal diet under the supervision of a speech and language therapist. No single protocol has been proved better than any other with roughly 20-30% of patients developing pharyngo-cutaneous fistulas. The variability in this rate between centers can to a large extent be explained in non-modifiable patient and tumor specific factors rather than operative / post-operative protocols[58]. If a total thyroidectomy has been performed, the patient will need to be started on hormone replacement.

If laryngectomy has been performed for primary disease, the patient will usually be treated with post-operative radiotherapy, ideally starting within 6 weeks of the surgery.

SPEECH REHABILITATION

Alongside the traditional focus on speech, swallow and airway issues, rehabilitation of patients following total laryngectomy must address the psycho-social dimension of being a cancer survivor and having a life-long stoma[59].

In terms of speech rehabilitation there are currently 3 used approaches: an external medical device, oesophageal speech or trachea-oesophageal speech.

Medical devices

Technological solutions include the pneumatic larynx and the electrolarynx. The former dates from the 1920s[60] and is now considered obsolete. It was a device which attached to the tracheostoma. Upon expiration a rubber reed would vibrate producing a tone which would be directed to the patient's mouth via an intra-oral tube for modulation into speech.

First introduced in the 1940s as a refinement of the pneumatic mechanical larynx, an electrolarynx is a battery-powered transducer that emits a buzz into the patient's vocal tract. The sound can be introduced via the neck using a handheld device, more or less the size of an electric razor, or into the oral cavity using an intraoral device[61]. Patients then articulate the sound into words using their mouth. The characteristic monotone robot voice of the earlier electrolarynxes has since been improved upon with the introduction in the 1990s of multi-tone devices. These could be controlled by variety of interfaces including switches, buttons and trackpads or even the electrical detection of neck muscle contraction[62]. This allowed for more natural intonations in speech as well as allowing speakers of tonal languages such as Mandarin to be more intelligible[63].

This form of rehabilitation is non-invasive, cheap and is easy to learn. However, despite improvements, the device still produces a mechanical sound and is dependent on batteries and maintenance.

Oesophageal speech

Conceptually the simplest, but with a large variation in success rates, is so called oesophageal speech. Essentially, the patient swallows air and whilst "burping" is able to achieve phonation. No devices or prostheses are required and it is a "hands-free" technique. Phonation however tends to be short (due to the limited amount of air in the stomach as compared to the lungs), and the reported success rate varies from 14-76%[64]. Side effects can include bloating and heart burn from swallowed air[65].

Tracheoesophageal speech

Tracheoesophageal speech is currently the most popular phonation option in the developed world. A tracheoesophageal fistula is made at the height of the stoma opening. A unidirectional valve is then inserted allowing air to pass from the trachea into the oeophagus, but stopping possible aspiration of oesophageal contents into the trachea. Phonation is achieved by blocking the external stoma and forcing air up through the oesophagus and neo-pharynx. The pharyngeal walls vibrate making a tone which can then be modulated by the mouth and tongue. Around 95% of patients achieve effective conversational speech with 88% achieving good voice quality[66].

Downsides to the technique mostly involve maintenance, dislocation and leakage of the prosthesis. Several manufacturers produce a variety of prostheses in the hope that one will ultimately "fit" the patient.

Of note, in the developing world where prosthesis maintenance is expensive and problematic, some surgeons attempt to make a one-way valve by careful fashioning of the trachea-oesophageal fistula with the patient's own tissues. An example is the Staffieri technique[67] first described in the Italian literature in 1969 and its various modifications e.g. by Sisson and Goldman[68]. This involves a low tracheostomy and a superior tracheal stump ending in a fistula. The fistula is made by a small vertical slit incision in the posterior wall of the tracheal stump. Intelligible speech without aspiration could be achieved in up to 80% of patients[69].

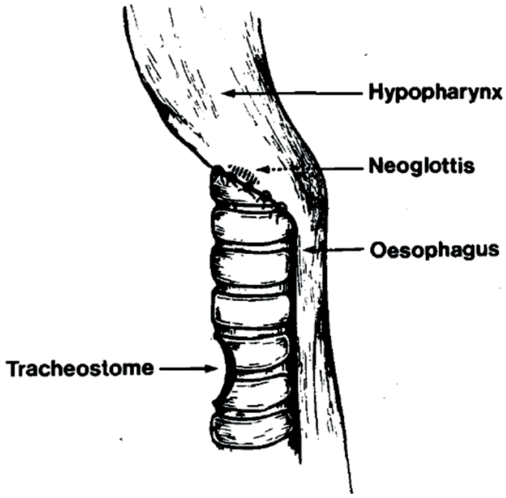

FIGURE 10: Staffieri voice rehabilitation technique

SWALLOW REHABILITATION

In many patients undergoing total laryngectomy only a minimal amount of pharyngeal tissue needs to be resected allowing primary closure of the neo-pharynx. However, whilst the mucosal surface can remain therefore relatively untouched, many of the muscles used in the normal swallow are resected including the inferior strap muscles. If a voice prosthesis is being used, a myotomy of the crico-pharyngeus muscle is also performed to allow better vibration of the neopharynx for speech purposes.

Furthermore, a proportion of patients, especially those with hypopharyngeal tumors, will need reconstruction of a mucosal pharyngeal defect. This can be achieved with a variety of flaps with the pectoralis major myocutaneous lap being one of the most common.

Whatever the method of pharyngeal closure and despite post-operative radiotherapy, the hope is that patients will be able to achieve a normal diet. Under guidance from a speech and language therapist, most patients achieve this, though roughly 23%[70] will need dilatation either endoscopically by a gastro-enterologist or under general anesthetic by a head & neck surgeon. Some patients unfortunately will need life-long tube feeding.

OLFACTION AND GUSTATION

By separating the trachea from the upper airway, olfactory acuity decreases due to loss of nasal airflow[71]. There is also resultant atrophy of the nasal mucosa with some patients complaining of sneezing (58%) and nasal discharge (20%)[72]. One study found 32% of patients performed well on smell testing, but 68% suffered anosmia[73]. Interestingly, gustation does not seem to be as badly affected by laryngectomy as olfaction[74].

An impaired sense of smell can have many effects of the patient's quality of life. Alongside its effect of the enjoyment of food, anosmia can important consequences for safety such as whether food is rotten or detecting smoke. The inability to detect bodily odors can cause insecurities in daily life, and the inability to perceive agreeable odors or fragrances can be experienced as a significant loss[75].

Several maneuvers have been proposed in order to restore some nasal airflow. These include the buccopharyngeal maneuver[76], buccopharyngeal sniffing[77] , glossopharyngeal press[78] and the so-called "polite yawn" technique[79]. Using this latter technique, the number of reported anosmic patients could almost be halved.

HEAT-MOISTURE EXCHANGERS (HMES)

After a total laryngectomy the patient breathes through a permanent stoma. By bypassing the upper airway, the air entering the lungs is therefore unfiltered, dry and cold compared to the normal physiological situation. Furthermore, heat and moisture is lost upon expiration, a loss of approximately 400–500 ml of water and about 300 kcal into the environment per day when compared to normal nasal breathing[80].

Heat-moisture exchangers (HMEs) aim to replicate the physiological benefits of nasal breathing, and are little more than a sponge like devices fitted over the tracheostoma. The sponge quickly becomes humidified and warmed through expiration and thus acts as a heat moisture exchanger to the inspired air[81]. In order to enhance the water-retaining capacity, the foam sponge can be impregnated with hygroscopic salts like CaCl2, AlCl3, MgCl2 or LiCl[82]. Despite numerous studies, it is however very difficult to quantify the exact impact of HMEs on the lower airways. This is due to often pre-existing lung disease, differences in minute ventilation in different settings, and the adaptation of the lower airways to the new physiology. It does seem clear however that patients who assiduously use their HMEs suffer fewer lower respiratory tract infections[83].

HMEs also have a filter effect though due to their large pore size, this is only for the largest of particles and certainly no barrier for microorganisms. The simple hygroscopic HMEs used by laryngectomy patients are therefore not comparable to the composite and pleated membrane HME filters used in anesthetic equipment [84,85].

Lastly, HMEs provide resistance to both inspiration and expiration, the latter effect resulting in a positive end expiratory pressure (PEEP) likely resulting in less alveolar collapse. Again, the pressure effects are difficult to study, though in general laryngectomy patients show a progressive obstructive pattern on pulmonary function testing[81].

LARYNGEAL REPLACEMENT

Given the rehabilitation difficulties discussed above, the question arises as to whether laryngeal replacement, either with a transplant or an artificial device is feasible.

Allografts

The first partial larynx transplant was reported by Kluyskens and Ringoir in 1969[86]. The patient was a 62-year-old man who had previously undergone an partial laryngectomy for carcinoma involving both vocal cords but without invasion of the perichondrium. The partial laryngeal graft was retrieved from an unmatched 40-year-old male cadaver, and no vascular or nerve anastomoses were performed. Episodes of rejection were treated with azathioprine, prednisolone, actinomycin C, and antilymphocyte serum. Eight months following the operation, a recurrence was discovered at the level of the stoma and was thought to be secondary to immuno-suppression as histopathology of the initial partial laryngeal resection had tumor-free margins. The rapidly fatal cancer recurrence overshadowed any graft survival, and further transplantation attempts in humans were abandoned for decades.

Although there are no published case series in the literature, there are several conference abstracts to suggest that Duque et al., Tinitinago et al., and Terris et al. have performed at least 14 cases of human laryngeal allotransplantation procedures since 2002[87-89]. Reported indications for these procedures were four cases of laryngeal trauma, eight cases of laryngeal stenosis, and two patients with laryngeal tumors. Terris et al. report that voice and deglutition recovered in most patients with some level of dysphonia, and that although there was a high index of rejection, most of their patients recovered with rescue therapy[89]. Similarly, it has been widely reported in the lay press that a group from Poland, who were involved in the world's first immediate face transplant[90], have also performed a laryngeal transplant. Although this case has not been reported in the English scientific literature, press reports in 2015 suggest that the larynx transplant recipient was a 37-year-old male who had previously undergone laryngectomy for advanced laryngeal cancer in 2009 and was already on immune-suppression following a kidney transplant in2001. If the press reports were true, this would be the first case of human laryngeal transplantation in the setting of cancer since Kluysken and Ringoir's operation in 1969.

To date there are 2 reports of successful total laryngeal transplantation[91]. Both cases were for non-functioning larynges following previous traumatic damage. The first patient was a 40 year old male with stenosis following a motorcycle accident 20 years previously. He was operated in 1998 at the Cleveland Clinic and received an allotransplantation from a 40 year old male who had died of a cerebral aneurysm. The second case was a 51 year old woman again with stenosis, this time secondary to multiple self-extubations following a prolonged intubation for renal failure. This patient was already under immune suppression following a kidney-pancreas transplant secondary to diabetes. Her donor was a 38 year old female who had suffered anoxic arrest. This operation took place in October 2010 at the University of California Davis Medical Center in Sacramento.

Despite two episodes of rejection treated with immunosuppressants, the first patient was able to keep his larynx for 14 years. Unfortunately, after 12 years, an infectious and chronic rejection pattern emerged and the larynx became progressively less functional leading to the decision for explantation. Histological evaluation showed extensive fibrosis, occlusive vasculopathy, marked acute and chronic inflammation, and acute chondritis. The second patient was doing well with no signs of rejection some 5 years after transplantation[92].

Rehabilitation of swallow was successful in both patients, though after a prolonged period of feeding tube dependency. During this time both patients also needed treatment for pooling of saliva (the first patient with glycopyrrolate and atropine, the second with botox injections into the major salivary glands).

Both patients showed evidence of reinnervation of the transplanted larynx both clinically and with electromyography, and both achieved near normal voice. This recovery however was measured in years rather than months. Furthermore, both patients remained tracheotomy tube dependent due to inadequate abduction of the vocal folds. Though adduction procedures were discussed with both patients, they were not willing to risk their quality of speech to be free of their tracheotomies.

Recently, a working party report from the Royal College of Surgeons of England acknowledged that there is potential for laryngeal transplantation to improve quality of life, but requires the expertise of a multidisciplinary team to define in advance the medical and psychological criteria for patient selection, and must involve the patient in the complex process of risk and benefit assessment[93]. For patients with LSCC there remains a concern that the necessary immunosuppression will adversely affect oncological outcomes

Prosthetic larynx

It is important to distinguish a "larynx prosthesis"[94] from an "artificial larynx", with the latter term having been hijacked in some sense by manufacturers of eletrolarynxs (see below). By larynx prosthesis we understand an implantable device which recreates the functions of the larynx.

In 2014, a French team from Strasbourg reported the first case in an ongoing clinical trial using a two part larynx prosthesis. The patient was a 65 year old with recurrent LSCC who had immediate implantation of the prosthesis at ablation. The prosthesis consists of a tracheal part with a porous titanium junction allowing colonization and ingrowth of respiratory epithelium and a second removable part inserted endoscopically. This second part consists of concentric valves enabling inhalation and exhalation whilst protecting the airway during swallow. The team report that at 8 months follow up, fibre-endoscopic, CT and barium swallow evaluation showed no issues. The patient was able to talk in a whispering fashion with the tracheostomy was temporarily closed (this could be for several hours).

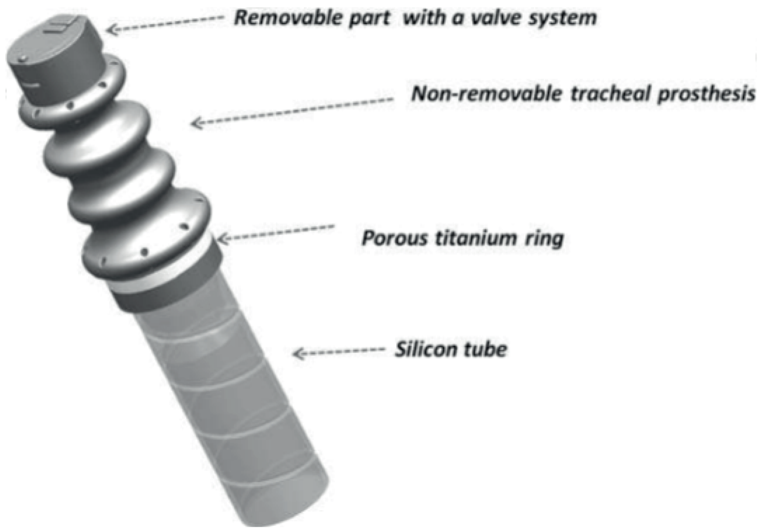

FIGURE 11: Modern artificial larynx

Surveillance

Often whilst patients are still recovering from their surgery, the post-operative histology will be discussed in the tumor board. Depending on the setting, patients may be candidates for post-operative (chemo)radiotherapy. Patients who have had their thyroid (and potentially parathyroid) glands removed will undergo endocrinology review. Indeed, even in patients where the thyroid has been preserved, postoperative radiotherapy can lead to hypothyroidism[95,96].

Alongside their rehabilitation program, laryngectomy patients enter a surveillance protocol for their cancer. The majority of recurrences happen within the first 2 years and most patients will be followed up at least 5 years. Primary laryngectomy followed by adjuvant radiotherapy provides excellent local regional control with 5 year loco-regional disease free rates of up to 87% reported in the literature[97]. For comparison, the same study showed distant recurrence free 5 year survival rates of 62%, disease specific survival of 51% and overall survival of 36%. This shows that whilst surgery and radiotherapy can provide excellent loco-regional control, distant recurrence and the inherent dangers of the treatments themselves lead to poor disease specific and overall survival rates. In order to diagnose distant recurrence, some units have argued for regular interval imaging though most rely on imaging based on clinical suspicion. The treatment of distant recurrence is also changing with oligometastases potentially being treated with radiotherapy at curative doses.

Loco-regional recurrence following laryngectomy is often associated with a poor prognosis. The patient may themselves notice changes to their speech/swallow or a lesion fungating through the skin. Some recurrences can however grow quite large before causing any symptoms and are also not apparent on clinical examination. Nevertheless, recurrences may be amenable to surgery or re-irradiation with or without chemotherapy.

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OUTLINE OF THESIS

The first section of this thesis investigates complications following total laryngectomy, specifically the troublesome and all to frequent complications of pharyngocutaneous fistulas (PCFs) and swallowing difficulties. The first paper describes a modern tertiary center experience of dealing with PCFs and outlines our management concept. Having provided context for the problem of PCFs we then try in the paper to more carefully delineate what PCFs are and whether they can be usefully stratified in terms of severity.

The following two papers look at patient risk factors for developing complications after total laryngectomy. Firstly we look at the biochemical marker of neutrophil-to-lymphocyte ratio which can be easily measured with a peripheral blood sample. This measure presumably relates to the patient's immune system and has been shown in a diverse group of solid tumors to correlate with outcomes. We then examine lean skeletal muscle mass and whether this correlates with complications/outcomes. Lean skeletal muscle mass is estimated from routine pre-operative imaging and informs the patient's general condition.

Having looked at patient related risk factors, we then look at some surgically related risk factors. Papers 5 and 6 look at airway intervention before definitive laryngectomy, firstly in a group of primary laryngectomy patients from London, and secondly in a group of salvage laryngectomy patients from Zürich. These papers were motivated by the all too frequent acute airway presentation of patients with advanced laryngeal disease. Patients may present with stridor to non-specialist centers without access to head & neck surgeons/relevant equipment. Here the general surgeon on-call will have to perform an emergency tracheostomy to stabilize the patient before transfer.

Paper 7 continues the theme of surgically-related risk factors for poor outcome, looking specifically at the role of elective neck dissection in picking up occult neck metastases in salvage patients.

Paper 8 provides an overview of the London primary laryngectomy cohort. The paper finds the somewhat surprising result that whilst pN>1 stage is associated with poor outcome, this poor outcome seems to be driven by distant recurrence and not by loco-regional failure. This is a somewhat sobering conclusion for a surgeon!

Next, in papers 9, 10 and 11 we investigate the effect of previous (chemo)radiotherapy on complications and survival in salvage patients. Of particular interest we report the same study question on two different data-sets, one slightly older (and smaller) data set from London and a more recent Utrecht data-set. Whilst the London data suggest a connection between timing of previous (chemo)radiotherapy and complications, the more recent data-set does not. A discussion of why this may be is included.

Finally, we investigate the need for post-laryngectomy dilatation in a combined Amsterdam/Utrecht data-set. Whilst there are innumerable publications on PCF and speech outcomes following laryngectomy, ours is one of only a few papers to deal directly with this common complication of total laryngectomy.

4

Pharyngo-cutaneous fistula formation following total laryngectomy: management, sequelae and outcomes

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ABSTRACT

Objective: To describe our experience of dealing with pharyngocutaneous fistulas (PCF) following total laryngectomy.

Design: Retrospective cohort

Setting: Tertiary referral center

Participants: All patients undergoing total laryngectomy at the [removed for blind peer review] over the 10 year period January 2008 to December 2017.

Main outcome measures: Incidence of PCF; treatment of PCF (conservative versus operative), closure success rate; time to closure; delay in adjuvant radiotherapy; increased the need of future neopharyngeal dilatations; overall survival.

Results: A total of 242 patients (199 males, 43 females) were analysed. One hundred and fifteen patients underwent primary laryngectomy, 102 salvage laryngectomy and 25 functional laryngectomy. Seventy five of 242 (31%) patients had a PCF. This was managed conservatively in 36/75 (48%) and operatively in 39/75 (52%) . Hospital length of stay was significantly longer in the PCF group (OR 2.38, p=<0.001). 5 year overall survival was 44% in the no PCF versus 24% in the PCF group, OR 1.7, p=0.001. PCF was not correlated with delay to adjuvant radiotherapy or the risk of neopharyngeal dilatation.

Conclusions: Despite efforts to identify risk factors and take preventive measures, PCF remains an all to frequent complication of total laryngectomy. PCF is associated with increased morbidity and significantly worse overall survival. The increased mortality is not a result of a delay in adjuvant radiotherapy.

INTRODUCTION

Total laryngectomy (TL) is used as a primary treatment for advanced stage laryngeal or hypopharyngeal cancer, as salvage in patients with recurrent disease after failure of organ preserving treatments or as a functional treatment in patients with a dysfunctional larynx [1-4].

Postoperative complications including pharyngocutaneous fistula (PCF) are common[1-5] with a recent systematic review[6] reporting rates of up to 58%. PCF often requires additional surgery, delays oral feeding/voice rehabilitation, decreases quality of life and increases hospital stay and costs[3,7,8]. Furthermore, PCF may delay postoperative (chemo) radiotherapy, thus jeopardizing optimal oncological treatment[4,9] and potentially lead to increased risk of neo-pharyngeal stricture formation.

Many papers describe risk factors for the occurrence of PCF including prior chemoradiotherapy, hypopharyngeal cancer, extensive pharyngeal resection and reconstruction, neck dissections, low BMI and low skeletal muscle mass (sarcopenia)[4,10,11]. Far fewer articles deal with the management of PCF and its consequences.

In this article we present our single center experience of 242 patients operated over a 10 year period. We evaluate our management strategy with regards to PCF (conservative versus operative), closure success rate and time to closure. We also evaluate whether PCF led to prolonged hospital stay, a delay in adjuvant radiotherapy, increased the need of future neopharyngeal dilatations, or had an adverse effect on overall survival. A rough estimate of extra cost incurred by PCF patients is also given.

MATERIALS AND METHODS

We performed a retrospective cohort study of all patients undergoing total laryngectomy at [blinded] over the 10 year period January 2008 to December 2017. The indication for total laryngectomy was either primary, salvage or functional.

Patients' demographic, staging, treatment and outcome data were collected using electronic patient records. All patients were discussed in our multidisciplinary tumour board and underwent total laryngectomy with or without (partial) pharyngectomy. For patients where the pharynx could not be closed primarily, a variety of flaps were used including pectoralis major with or without skin island, free radial forearm flap (FRFF), anterior lateral thigh flap (ALT), jejunum interposition and gastric pull up. Occasionally a pectoralis major muscle onlay flap (also reported in the literature as an interposition flap) was used to reinforce a primarily closed pharynx.

Postoperatively, all patients were fed via a feeding tube for the first 10 days before undergoing a contrast swallow. If this showed no leaks, the patient would begin with clear fluids and quickly build up to a normal diet. If there was a leak, the patient would be kept nil-by-mouth and a further contrast swallow study organised for the following week (unless a PCF manifested itself in during this period).

For this study, PCFs were defined by their clinical manifestation on the skin and patients who had leakage on the contrast swallow but never manifested a PCF were counted as not having a PCF.

The majority of PCFs occurred shortly after surgery, though some patients were discharged either with a feeding tube or on oral diet only to present with a PCF later. These patients were classified as having a PCF. Still further patients developed a PCF many months later secondary to an intervention such as dilatation of a stricture. These patients were classified as no PCF as the development of a PCF was considered a complication of the second procedure, not of the initial laryngectomy.

In those patients who developed a PCF, initial management was conservative using a variety of wound dressings. For fairly dry PCFs, Eusol (Edinburgh University solution of lime) wound dressings were used. For more productive PCFs either iodine soaked gauze or an alginate dressing. For the most productive a stoma bag had to be used. Occasionally scopolamine patches were used to reduce saliva production.

The indication for operative management of a fistula was up to the lead surgeon's judgement. This depended on many factors including the size of the fistula, its response to conservative therapy, the patient's fitness, and the availability of a suitable method of reconstruction (the favoured reconstruction being a salivary bypass tube and pectoralis major flap).

Outcomes of interest included the number of PCFs, duration of PCF, management of PCF (conservative vs operative) and method of reconstruction of the PCF. Some patients died from complications of the fistula and this was also noted. In the longer term, we looked at whether PCF led to a delay in adjuvant radiotherapy (delay was defined as starting radiotherapy >6 weeks after surgery) and whether the PCF correlated need for dilatation of a neopharyngeal stenosis during follow up. Lastly, we looked at PCF impact on overall survival and make a rough estimation of the extra costs involved in patients with PCF.

Statistical analyses were performed using SPSS® Statistics 20.0 (IBM, Armonk, NY). Overall survival and hospital length of stay was calculated using the Kaplan–Meier method and Cox-mantel log-rank test for comparison. The chi-squared test or binary logistic regression analysis was used as appropriate for univariate analysis.

RESULTS

A total of 242 patients (199 males, 43 females) underwent total laryngectomy (TL) with or without (partial) pharyngectomy (TLPP) in the study period. Treatment indication was primary (n=115), salvage (n=102) and functional (n=25). Details of the cohort general characteristics stratified by indication is shown in **table 1**.

Postoperative course /LOS

Mean average length of hospital stay was 21 days (16 days for patients without PCF and 30 days for patients with a PCF, OR 2.38, p=<0.001), **Figure 1**. Out of 242 patients, 51 (21%) returned to theatre: 39/51 (76%) for the treatment of PCF, 9/242 (4%) for hemostasis, 1/242 (0.4%) for a chyle leak and 2/234 (0.8%) for exploration of a free flap (one flap successfully salvaged, the other unfortunately lost (jejunum interposition) giving a free flap failure rate of 1/17 (4.5%)).

Incidence of PCFs

A total of 75/242 (31%) patients developed a PCF and these were managed as reported in **table 2**. In total, 61/75 (81%) fistulas were successfully closed, 2/75 (2.7%) fistulas were still open at last follow-up (respectively 3 and 29 months following laryngectomy) and 12 patients died with an open PCF. These patients are discussed in more detail below.

Conservative management of PCF

Initial PCF management was conservative with a feeding tube and a variety of wound dressings including Eusol, alginate dressings and/or iodine soaked gauze. Thirty-six out of 75 (48%) PCFs were treated this way with a success rate of 30/36 (83%). The remaining 6 patients died with open PCFs. Median time to closure was 41 days (see **figure 2**).

TABLE 1: Cohort characteristics. (TL= Total laryngectomy, TLPP=Total laryngectomy+(partial)pharyngectomy, PCF=pharyngo-cutaneous fistula, RT=radiotherapy)

		Salvage	Primary	Functional	
		n-102	**n=115**	**n=25**	**p value**
Gender	Male	90	91	18	
	Female	12	24	7	0.079
Age	<65	47	59	11	
	>65	55	56	14	0.67
Site	Supraglottic	22	18	5	
	Glottic	50	21	8	
	Subglottic	4	3	0	
	Post-cricoid	1	1	0	
	Piriform sinus	16	44	4	
	Transglottic	27	8	1	<0.001
Initial T-stage	T1	0	26	6	
	T2	0	42	11	
	T3	20	26	5	
	T4	95	8	2	<0.001
Initial N-Stage	N0	59	75	17	
	N1	8	8	3	
	N2a	1	1	0	
	N2b	21	12	4	
	N2c	24	5	1	
	N3	2	0	0	0.027
ASA	1	56	45	8	
	2	30	32	6	
	3	25	20	10	
	4	3	3	0	0.36
Operation	TL	77	63	14	
	TLPP/TLP	38	39	11	0.514
Neck dissection	None	29	54	20	
	Unilateral	45	35	4	
	Blateral	41	13	1	<0.001

TABLE 1: Continued

		Salvage	Primary	Functional	
		n-102	**n=115**	**n=25**	**p value**
Flap	None	77	62	13	
reconstruction	Pectoralis major	25	34	8	
	Radial forearm	7	0	0	
	Anterior lateral thigh	3	4	0	
	Gastric pull up	2	1	2	
	Jejunum interposition	1	1	1	0.071
PCF	No	82	72	13	
	Yes	33	30	12	0.151
Management	Conservative	17	13	6	
of PCF	Operative	16	17	6	0.801
PCF closed	No	2	8	4	
	Yes	31	22	8	0.04
Delay to	<7weeks	72			
adjuvant RT	>7weeks	28			0.06
Dilatation	No	96	84	18	
required	Yes	19	18	7	0.396

Operative management of PCF

The decision to return to theatre was taken by the lead surgeon and depended on a variety of factors including failure of conservative management and fitness of the patient. For most patients, this was during the same hospital stay as the initial laryngectomy, but for a few patients, the surgical management of the PCF was performed months later.

In 39/75 (52%) PCFs, the patient underwent at least one operation for their fistula. Twenty-three of 29 patients had one operation, 6 patients had 2 operations, 3 patients had 3 operations, 5 patients had 4 operations, 1 patient had 6 operations and 1 patient had 11 operations for his fistula. Twenty-two of 39 (56%) patients had a regional flap reconstruction (either pectoralis major or delto-pectoral). Of the operatively managed patients, the PCF healed in 31/39 (79%). Of the patients managed with regional flap reconstruction for their PCF 14/20 (70%) healed. Of the patients managed with local operative techniques 17/19 (89%) of PCFs healed.

Median time to closure in the operatively managed patients was 61 days. Kaplan-Meier analysis of time with fistula vs management (conservative vs operative) showed no significant differences (p= 0,119, see **Figure 2**).

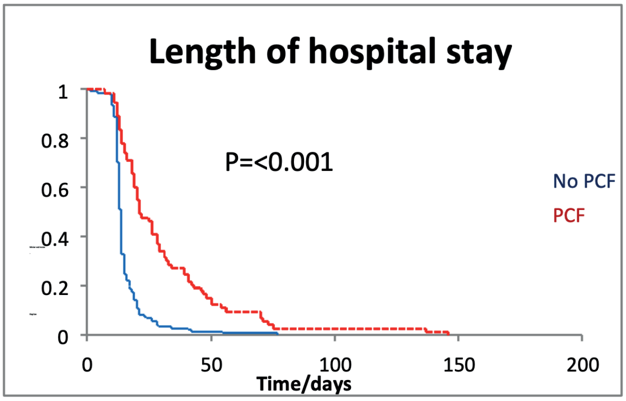

FIGURE 1: Length of hospital stay

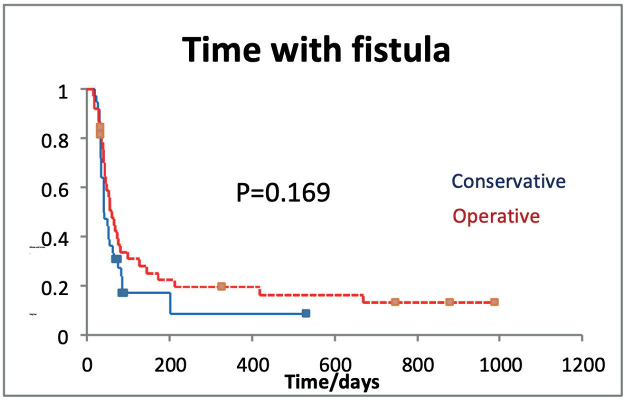

FIGURE 2: Time with fistula, conservative vs operative management.

TABLE 2: Management of pharyngo-cutaneous fistulas. (PCF= pharyngo-cutaneous fistula, LOS=length of hospital stay)

	N=242	Successfully closed (%)	Median LOS/ Days (range)	Median time till closure/ days (range)
No PCF	167	n/a	14 (1-77)	n/a
PCF	75	61 (81.3%)	21 (7-146)	43 (14-670)
Conservative	36	30 (83.3%)	20 (7-75)	40 (20-202)
Operative	39	31 (79.5%)	26 (11-146)	53 (14-670)
local technique	3	3 (100%)	21 (18-39)	17 (13-49)
local techqniue + salivary bypass	16	14 (87.5%)	22 (11-48)	47 (28-126)
regional flap	4	3 (75%)	49 (33-137)	55 (32-57)
regional flap + salivary bypass	16	11 (69%)	24 (11-146)	98 (18-670)

Salivary bypass tubes

In patients undergoing operative management of their PCF, a salivary bypass tube was used in 32/39 (82%) of operated patients. Of the 7 patients managed without a salivary bypass tube 4 had a regional flap reconstruction and 3 a local closure.

Does PCF lead to delayed adjuvant radiotherapy for primary laryngectomy patients?

Post-operative radiotherapy was indicated in 100/115 primary patients. Postoperative radiotherapy was started >7 weeks following operation in 28/100 primary patients. Twelve of 28 patients had a PCF versus 16/28 who had a delay despite no PCF. Binary logistic regression showed no correlation between PCF and delay to radiotherapy (p=0.06). Further worth noting is that 5 patients started adjuvant radiotherapy with an open PCF and in all these 5 patients the PCF closed during the radiotherapy.

Does PCF lead to increased risk of stricture formation necessitating dilatation?

Inflammation, multiple surgeries and prolonged tube feeding associated with PCF may plausibly lead to increased long-term risk of neopharyngeal stricture formation, potentially necessitating dilatation. In our cohort, a total of 44/242 (18%) of patients ultimately underwent dilatation during follow-up, 15/44 (34%) had had a PCF. Once again, binary logistic regression showed no statistically significant correlation between PCF and need for dilatation (p=0.623).

Does PCF adversely affect perioperative or long-term survival?

Laryngectomy is a physiologically demanding procedure, often performed in patients with little physiological reserve. In our cohort, there were 3/242 (1.2%) perioperative deaths (defined as deaths within 30 days of laryngectomy). One 76 year old patient had an injury to his common carotid artery intraoperatively which had to be ligated unfortunately leading to an ultimately fatal ischaemic stroke. A 67 year old patient had a fatal myocardial infarction on the first postoperative day. Finally a 76 year old male had necrosis of his pectoralis flap leading to carotid blow-out 1 month after laryngectomy.

In total 12/75 (16%) patients died with an open PCF which had never healed since the original laryngectomy. In these patients we considered the PCF a complication of the laryngectomy. (Other patients ultimately died of blow-outs associated with pharyngo-cutaneous fistulas due to either local recurrence or complications of dilatation. As the PCF in these cases was not considered a complication of laryngectomy, they are not described below.)

In 1/12 patients with a persistent fistula, the cause of death was unknown. In 3/12 patients there was a separate cause of death (lung embolus, peritonitis and small cell lung cancer). One patient died from distant metastasis. Three of 12 had complications due to their fistula (the blow-out mentioned above, 2 had spondylitis) but no sign of cancer. The remaining 4 patients had biopsy confirmed local residual disease (which retrospectively was probably the reason their PCF had not healed).

We can therefore say that 3/75 (4%) patients with PCF died as a direct result of it without sign of cancer.

When we analyzed long term overall survival comparing patients who developed a post-operative PCF and those who did not, we found a significant difference (5 year overall survival 24% versus 44% respectively, OR 1.7, p=0.001, **Figure 3**).

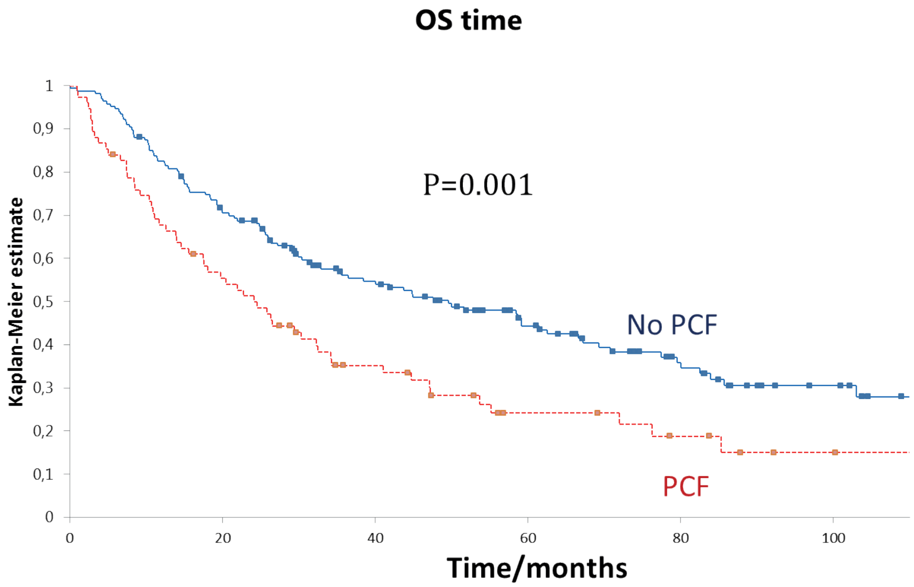

FIGURE 3: Kaplan Meier analysis of overall survival.

Costs associated with PCF formation

A complete analysis of the costs associated with PCF formation is beyond the scope of this article. A proper analysis would have to include not only inpatient costs, but also costs for outpatient care and costs associated with inability to work.

Given the differences in LOS and that a hospital bed in our institution very roughly costs 633 Euros per day we can estimate that a PCF patient costs an extra 8862 euros in bed costs alone. This substantial sum does not even take into account that many PCF patients underwent multiple admissions for the management of their PCF, with extra imaging and surgery (PCF patients underwent an average of 1.1 (81/75) operations compared to patients without PCF). Outside of the hospital, PCF patients also required more intensive nursing and tube feeding. Several patients with particularly persistent PCFs even underwent hyperbaric oxygen therapy. Along with delays in returning to work, all these factors vastly increase the costs to the healthcare system in case of PCF.

DISCUSSION

In line with the literature[6,12], roughly a third of our developed a PCF with a roughly 50/50 split between conservative and operative management. PCFs successfully closed in 61/75 (81%) cases with both conservative and operative approaches having a similar success rate. We can assume that smaller fistulas were treated conservatively and larger fistulas surgically and this high closure rate reflects the correct strategy for these PCFs. Three of 75 (4%) patients died of complications from their PCF without sign of cancer. Furthermore, PCF patients had a poorer overall survival (5 year overall survival PCF 24% versus 44% in the no-PCF group, OR 1.7, p=0.001). PCF does not however seem to delay the start of adjuvant radiotherapy (p=0.06). Indeed, in 5 patients the PCF was deemed small enough to all adjuvant radiotherapy to begin despite an open PCF. PCF also does not increase the risk of future dilatation.

Median length of hospital stay in our cohort was 14 days. This is somewhat higher than in other reports[13] and may be due to our protocol of keeping patients until their contrast swallow study at 10 days which then allows supervised initiation of feeding and voice rehabilitation. In any case, length of hospital stay was significantly longer in the PCF group than in the no-PCF group (**figure 1**) which together with the extra nursing care required, extra imaging studies, extra operations and delayed return to work vastly increase the costs associated with PCF.

Given the mortality and morbidity associated with PCF, many surgeons have suggested strategies to reduce their incidence. Pre-operatively there is unfortunately often little time for "pre-habilitation". Intra-operatively, modifications of technique such as the use of barbed sutures[14], stapler closure[15,16], salivary bypass tubes[17], sealants[18] or even transoral robotic total laryngectomy[19,20] have all been suggested. Reinforcing primary pharyngeal closure with a pectoralis major muscle-only overlay has also been suggested [21]. This latter strategy is clearly more invasive and is probably only appropriate in high risk patients, though the number-needed-to treat and the extra morbidities and costs associated with an interposition flap are all areas for further investigation. The extra hour of operative time and morbidity of such an interposition flap takes well outweigh the morbidity associated with dealing with a PCF at a later date. Even if patients do suffer a PCF after interposition, there is also the hope that the PCF will be less severe and could be conservatively managed.

Post-operative techniques to reduce the risk of PCF such as reducing saliva (scopolamine patches, botuline injections, parotid duct ligation)[22], early oral fluids[23] and vacuum drains[24]/endoscopic negative pressure therapy[25] all have their proponents though remain controversial.

Unfortunately, when there is such a plethora of varying advice in the literature, it is often because no single management option is particularly more effective than any other. Therefore, it remains unclear what the optimal management strategy for prevention and treatment of PCF is.

CONCLUSIONS

PCF remains a troublesome complication after total laryngectomy. Patients with PCF often have prolonged or multiple hospital admissions with associated higher morbidity and costs. Their overall survival is also significantly worse than patients who do not develop a PCF. The risk factors for PCF are numerous and described elsewhere in the literature, as are potential ways to reduce this risk. PCF however does not seem to lead to a delay to adjuvant radiotherapy, nor to an increased risk of stricture formation.

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5

Severity of pharyngo-cutaneous fistula following total laryngectomy: a comparison of three classifications

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ABSTRACT

Purpose: To evaluate 3 different classifications used to measure the severity of a pharyngocutaneous fistula (PCF) after total laryngectomy (TL).

Methods: Retrospective case note review of all patients undergoing TL at the University Medical Center, Utrecht, The Netherlands between January 2008 and December 2017. Data was stratified according to 3 classifications: Horgan & Dedo, Casasayas et al. and flap use for PCF reconstruction. The three classifications were then evaluated with regard to length of hospital stay, closure success, time to closure, delay to adjuvant radiotherapy, risk of future neopharyngeal dilatations and overall survival.

Results: Seventy-five of 242 (31%) laryngectomized patients developed a PCF. These were classified as minor vs major: Horgan & Dedo= 23 vs 52, Casasayas et al.= 3 vs 72 and according to flap reconstruction= 54 vs 21. Univariate analysis showed correlation between bilateral neck dissections being associated with *minor* PCFs (Horgan & Dedo and flap use classifications). The flap use classification also showed that primary TL patients are less likely to undergo flap reconstruction of their PCF than salvage or functional patients. Chance of closure, time to closure and length of hospital stay were statistically correlated with one or more classifications. The minor/major PCF distinction did not correlate with delay to adjuvant radiotherapy, risk of future dilatation and overall survival.

Conclusions: Efforts to classify the severity of PCFs seek to answer the short-term question of which patients benefit from a return to theatre and when this should happen. In this regard, the 3 evaluated classifications had differing strength/weaknesses. Classifications should also try to predict the longer term outcomes of delay to adjuvant radiotherapy, need for dilatation and overall survival. Unfortunately, all 3 classifications did not show correlation with these outcomes.

INTRODUCTION

Total laryngectomy (TL) with or without (partial) pharyngectomy (TLPP) is a highly invasive treatment often performed in patients with little physiological reserve. Postoperative complications are frequent, including the occurrence of a pharyngocutaneous fistula (PCF) [1-5]. A recent systematic review[6] found published PCF rates of up to 58%[7]. In a Dutch national study of 324 patients undergoing laryngectomy the overall PCF rate was 25.9%[2]. PCF often necessitates further surgery, delays oral feeding/prolongs feeding tube dependency, affects voice rehabilitation, decreases quality of life, increases hospital stay, costs and has an adverse effect on overall survival[3,8,9].

Numerous papers have described potential risk factors for the occurrence of a PCF including prior (chemo)radiotherapy, hypopharyngeal cancer, extensive pharyngeal resection/reconstruction, neck dissections, low BMI and low skeletal muscle mass (sarcopenia)[2,10,11]. Nearly all this literature, however, reports PCFs as a binary yes/no, making no distinction between a small PCF which can be conservatively managed and closes quickly, and a large PCF with extensive tissue loss, risk of carotid blow-out and potentially necessitating a return to theatre for flap closure. Though many severity classifications were proposed in the 1970s, none have been widely adopted. This is perhaps due to their overwhelming "retrospective" nature meaning they cannot be used to drive/inform management pre-, intra- and post-operatively. They do not provide a satisfactory answer to the questions of which PCFs can be managed conservatively, which need a return to theatre, and when should the return to theatre happen. Furthermore, the data used is now out-of-date in terms of predicting longer-term outcomes such as survival.

One recent attempt to revive interest in stratifying the severity of PCFs is by Casasayas et al.[12] who propose a modification of the Horgan and Dedo [13] criteria. The benefit of this modification however remains unclear as they do not compare the two classifications in their data series, nor with many important outcomes. Once again, we are none-the-wiser as to which patients can be conservatively managed, which might benefit from operative closure of their PCF and what the severity of PCF says about longer term outcomes.

In this article we present our single center experience of 242 laryngectomized patients operated over a 10 year period. In order to try and identify the patients requiring flap reconstruction of their PCFs, we stratify our patients according to this intervention and compare/contrast this criteria with the published classifications of Horgan & Dedo and Casasayas et al. (see **table 1**). Most importantly, we evaluate these 3 classifications in terms of risk factors for minor vs major PCF and the important short term outcomes of hospital length of stay, chance of successful PCF closure, duration of the PCF and the longer term outcomes of delay to adjuvant radiotherapy, risk of future neopharyngeal dilatation and overall survival.

TABLE 1: Major pharyngo-cutaneous fistula criteria for the 3 classifications used

Horgan and Dedo13 major PCFs	**Cassayas et al.12 major PCFs**	**Flap use major PCFs**
PCF lasting >8 weeks	PCF lasting >4 weeks	All PCFs treated with flap reconstruction
Operative management performed	Operative management performed	
	Associated with perioperative mortality	

MATERIALS AND METHODS

We performed a retrospective cohort study of all patients undergoing total laryngectomy at the University Medical Center Utrecht over the 10 year period January 2008 to December 2017. The indication for total laryngectomy was either as primary treatment for cancer, as salvage treatment for cancer following (chemo)radiotherapy or as a treatment for an afunctional larynx.

Patients' demographic, staging, treatment and outcome data were collected using electronic patient records. We recorded TNM classification according to the then applicable AJCC manual. All patients were discussed in our multidisciplinary tumour board and underwent total laryngectomy with or without (partial) pharyngectomy. For patients where the pharynx could not be closed primarily, a variety of flaps were used including pectoralis major (with or without skin island), radial forearm free flap (RFFF), anterior lateral thigh flap (ALT), jejunum interposition and gastric pull up. Occasionally a pectoralis major muscle onlay flap (also reported in the literature as an interposition flap) was used to reinforce a primarily closed pharynx.

In those patients who developed a PCF, initial management was conservative using a variety of wound dressings. For fairly dry PCFs, Eusol (Edinburgh University solution of lime) wound dressings were used. For more productive PCFs either iodine soaked gauze or an alginate dressing were used. For the most productive, a stoma bag had to be used.

The indication for operative management of a fistula was up to the lead surgeon's judgement. This depended on many factors including the size of the PCF, its response to conservative therapy, the patient's fitness, and the availability of a suitable method of reconstruction (the favoured reconstruction being a salivary bypass tube and pectoralis major flap). Some patients with very small fistulas ultimately accepted the situation and managed with a combination of tube feeding and modified oral feeding.

PCFs were stratified as minor or major according to our 3 classifications: Horgan and Dedo13, Casasayas et al12, and our own classification as to whether a patient underwent flap reconstruction of their PCF or not. **Table 1** shows the criteria for a major PCF for the 3 classifications. Having stratified our patients in this way, we performed univariate analysis for the risk factors across a number parameters. We also evaluated the effect on hospital length of stay, chance of successful PCF closure, duration of the PCF, delay to adjuvant radiotherapy, risk of future neopharyngeal dilatation and overall survival.

Statistical analyses were performed using SPSS® Statistics 20.0 (IBM, Armonk, NY). Overall survival and hospital length of stay was calculated using the Kaplan-Meier method and Cox-mantel log-rank test for comparison. The chi-squared test or binary logistic regression analysis was used as appropriate for univariate analysis.

This study does not fall under the scope of the Medical Research Involving Human Subjects Act and the institutional review board approved this study.

RESULTS

A total of 242 patients (199 males, 43 females) were operated in the study period. Treatment indication was primary (n=115), salvage (n=102) and functional (n=25). Seventy five patients (31%) developed a PCF. **Table 2** shows the univariate analysis of these 75 patients stratified into minor and major PCFs by the 3 classifications.

Expressed as a percentage of the total patient cohort we had a Horgan & Dedo major fistula rate of 52/242 (21%) and minor rate of 25/242 (10%). Using the Casasayas classification, we have a major fistula rate of 72/242 (30%), and a minor rate of 3/242 (1%). Lastly, 21/242 (9%) underwent flap reconstruction of their PCF and 54/242 (22%) did not.

TABLE 2: Univariate analysis of the 75 patients who developed PCFs

		PCF flap use			Horgan & Dedo			Casasayas		
		No flap	Flap	P value	minor	major	P value	minor	major	P value
N=75		**54**	**21**		**25**	**52**		**3**	**72**	
Indication	Primary	28 (85%)	5 (15%)		13	20		1	29	
	Salvage	17 (57%)	13 (43%)		8	22		2	31	
	Functional	9 (75%)	3 (24%)	**0.044**	2	10	0.356	0	12	0.638
Gender	Male	39 (89%)	15 (11%)		18	40		3	55	
	Female	15 (89%)	2 (11%)	0.09	5	12	0.898	0	17	0.339
ASA	1	25 (76%)	8 (24%)		12	21		1	32	
	2	17 (71%)	7 (29%)		6	18		1	23	
	3	12 (67%)	6 (33%)		5	13		1	17	
	4	0	0	0.778	0	0	0.626	0	0	0.907
Age	<65	26 (67%	13 (33%)		10	29		1	38	
	>65	28 (78%)	8 (22%)	0.284	23	52	0.326	2	34	0.509
Tumor Site	Supraglottis	10	3		4	9		0	13	
	Glottis	13	6		7	12		1	18	
	Subglottis	0	2		0	2		0	2	
	Post cricoid	1	0		0	1		0	1	
	Piriform sinus	23	8		9	22		2	29	
	transglottic	5	2	0.329	3	4	0.829	0	7	0.915
T-stage	T1	6	1		3	4		0	7	
	T2	13	8		4	17		1	20	
	T3	10	6		6	10		1	15	
	T4	25	6	0.311	10	21	0.530	1	30	0.900
N-stage	N0	31	13		14	30		1	43	
	N1	2	3		0	5		0	5	
	N2a	1	0		0	1		0	1	
	N2b	8	5		2	11		1	12	
	N2c	10	0		5	5		1	9	
	N3	1	0	0,213	1	0	0.109	0	1	0.913
Operation	TL	27	13		13	27		1	39	
	TLPP/TLP	27	8	0.355	10	25	0.713	2	33	0.479
Neck dissection	None	21	9		8	22		0	30	
	Unilateral	19	12		6	25		1	30	
	Bilateral	14	0	**0.026**	9	5	**0.009**	2	12	0.076
Initial flap	None	27	13		13	27		1	39	

TABLE 2: Continued

		PCF flap use			Horgan & Dedo			Casasayas		
		No flap	**Flap**	**P value**	**minor**	**major**	**P value**	**minor**	**major**	**P value**
Recons-truction	Pectoralis Major	20	7		8	19		1	26	
	Free radial forearm	3	0		1	2		1	2	
	Anterior lateral thigh	2	1		1	2		0	3	
	Gastric pull-up	1	0		0	1		0	1	
	Jejunum	1	0	0.785	0	1	0.964	0	1	0.208
Closure	No	8	6		0	14		0	14	
achieved	Yes	46	15	0.170	23	38	**0.006**	3	58	0.397
Later dilatation	No	43	17		17	43		2	58	
	Yes	11	4	0.898	6	9	0.381	1	14	0.556
Delayed start of	No	7	1		4	4		1	7	
Radio-therapy	Yes	17	4	0.677	8	13	0.561	2	27	0.462

Statistically significant findings

Of all the pre-operative parameters included in **table 2**, it is worth highlighting that a bilateral neck dissection was associated with *minor* PCFs and that patients undergoing bilateral neck dissection were *less* likely to undergo subsequent flap reconstruction should they develop a PCF.

The other statistically significant pre-operative finding in **table 2** is that patients undergoing primary TL who develop a PCF are less likely to undergo flap reconstruction than salvage or functional TL patients.

Hospital length of stay

Turning our attention to the post-operative parameters described in **table 2** we find that both the Horgan & Dedo and flap reconstruction classifications showed statistically significant differences between minor and major PCFs on Kaplan Meier analysis of hospital length of stay (see **figure 1**).

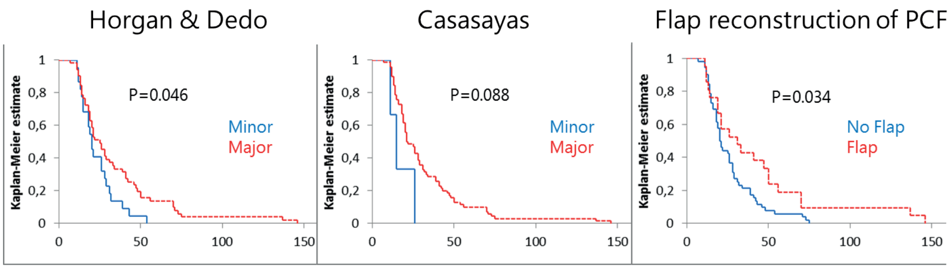

FIGURE 1: Length of hospital stay, time/days

Duration of PCF and chance of ultimate closure

Looking at how many patients had ultimate closure of their PCF we found that in sixty-one of 75 (81%) fistulas ultimately closed, 2/74 (2.7%) fistulas were still open at last follow-up (respectively 3 and 29 months following laryngectomy) and 12 patients died with an open PCF.

The minor/major distinction according to Horgan & Dedo classification showed that the minor PCFs were statistically significantly more likely to ultimately close (38/52 (73%) major versus 23/23 (100%) minor PCFs p=0.006).The Casasayas classification and flap use classification were not statistically significantly associated with chance of closure (p=0.397 and p=0.170 respectively)

All three classifications however showed statistical correlation with the speed of closure of PCF. Kaplan Meier analysis in **figure 2** shows the median time to closure for minor vs major PCFs was according Horgan & Dedo classification 35 vs 76 days, OR 3.9, p=<0.001 , according Casasayas classification 21 vs 55 days, OR 15.3, p=<0.001 and according flap use classification 42 days vs 172 days, OR 2.5, p=<0.0001.

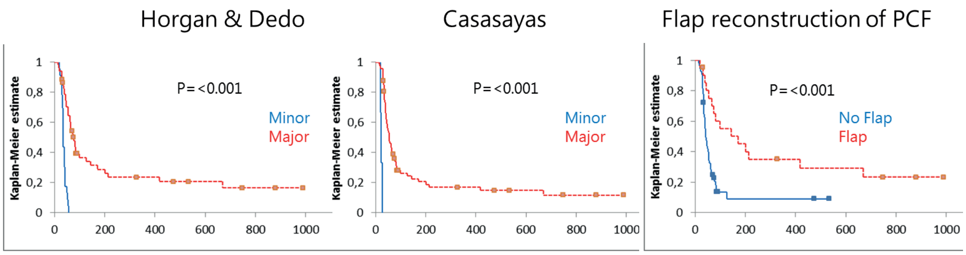

FIGURE 2: Time with fistula, time/days

With regard to the later complications of delayed start of radiotherapy and need for neopharyngeal dilatation, **table 2** shows no statistically significant result for the minor/major distinction for all three classifications.

Overall survival

Figure 3 shows the overall survival for the 75 patients with PCF stratified into minor/major for the 3 classifications. Using the Horgan & Dedo classification the 5-year survival was 21% vs 25% respectively (p=0.584), for the Casasayas classification 24% vs 33% respectively, p=0.928), for the flap use classification, 5-year survival was 22% vs 32% (p=0.550).

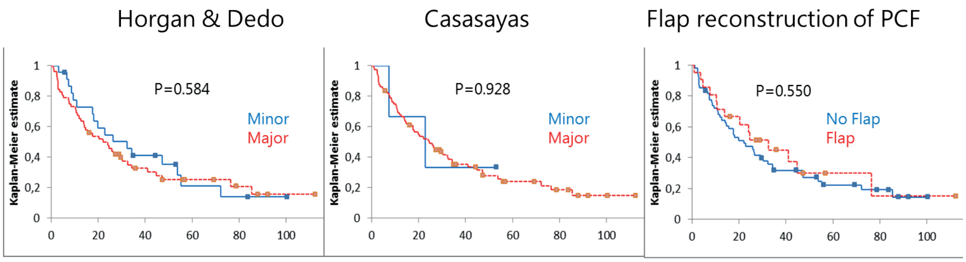

FIGURE 3: Overall survival, time/months

DISCUSSION

Efforts to classify the severity of PCFs are not new. Indeed, beginning in the 1970s, several classifications for PCFs were proposed. The simplest is a measurement of the PCF skin defect either as an absolute measurement in millimeters, or as measurement relative to the pharyngeal circumference. The timing however of these measurements is clearly critical, with the possibility of a small PCF progressing to a larger one before spontaneously regressing and potentially closing without ever the need for operative management. This timing issue also means measurement based classifications cannot be easily used to drive management protocols.

Another approach is to look at risk factors for a PCF healing or not. For example the Vilar-Sancho classification separates patients into those post-radiotherapy or not, recognizing the effect radiotherapy has on tissue quality.

A more management focused classification is Funk et al's from 1978[14]. A Funk Type 1 PCF involves either the carotid artery or a microvascular anastomosis (further split into type 1a for patients with previous radiotherapy and 1b for patients without previous radiotherapy). Type 2 PCFs are pharyngostomas with accompanying skin loss. This classification clearly relates to the need for operative intervention and perhaps more accurately stratifies patients needing major operations, for example with flap reconstruction, as opposed to more minor operations such as freshening wound edges and primary closure.

The Horgan and Dedo criteria analyzed in this paper was first proposed in 1979[13]. Though what counts as "operative management" is left somewhat vague in their publication, this classification does crucially recognize the time duration element of a PCF and the chance of spontaneous closure. This is also the focus of Casasayas et al's modification from 2018 reducing the time criteria from 8 weeks to 4 weeks. The value of this modification is discussed below.

Our data set, consistent with the literature[6,15], shows roughly a third of patients undergoing laryngectomy develop a PCF. Roughly half of these could be conservatively managed and 28% underwent flap reconstruction.

In terms of risk factors, we found that the various parameters measured including TNM stage, tumor location and extent of operating did not predict risk of a major PCF as opposed to a minor PCF. Indeed, we found the counter intuitive result of a bilateral neck dissection being associated with minor PCF and that primary TL patients are less likely to undergo flap reconstruction should they develop a PCF. These results can be explained. The former is likely because of the higher number of bilateral neck dissections performed in the primary setting and the latter is likely due to the perceived need to bring fresh, non-irradiated tissue into the wound bed in the post-radiotherapy setting.

It is also worth highlighting that the indication for TL did not correlate with the severity of PCF. It might have been thought that patients with irradiated tissues would have more severe PCFs but this is not borne out in our data series. This may due to the more frequent use of upfront flaps in patients who had previous (C)RT. Ultimately though it is disappointing that we could not identify any pre-operative features which might have allowed us to take action in preventing a major PCF.

In terms of the time duration with an open PCF and the chance of this ultimately closing, we found that whilst all three classifications for minor/major distinction showed correlation with the chance of ultimate closure, only the Horgan & Dedo classification showed a correlation with the duration of PCF. Significance was also found in length of hospital stay but this is hardly surprising given that these classifications include a time parameter.

In terms of the longer term complications, there was no statistically significant difference in the groups in terms of delay to adjuvant radiotherapy, risk of future neopharyngeal dilatation or overall survival

The Casasayas modification of Horgan & Dedo

Horgan & Dedo's original publication of 178 laryngectomies reported a PCF rate of only 14.8% (8.9% minor, 4.9% major) compared to data-set's 31% PCFs (9.5% minor, 21.4% major). Casasayas et al. unfortunately do not analyze their 400 patients under the Horgan & Dedo criteria, instead reporting a PCF rate of 23.3% (minor 5.3% , major 18%) according to their criteria. Whilst the Casasayas data reflects our data with a higher proportion of major than minor PCFs, it is striking that in our data set, only 3/75 (4%) PCFs meet their minor criteria. This remarkable difference is worthy of discussion.

Firstly, the differences in time with PCF shows that in our data, 20/75 (27%) patients were able to be conservatively managed and achieve closure of their PCF between 4 and 8 weeks. All is therefore not lost if a conservatively managed PCF patient hasn't closed within the first few weeks.

The finding however begs the question, why did patients managed conservatively in Barcelona heal so much *faster* than patients managed conservatively in Utrecht? Looking at the patient cohorts, it does not seem that there are major differences between our data set and the Casasayas data set in terms of previous radiotherapy, T-stage, neck dissections and other parameters. The only striking difference is that during the initial surgery, only 12% of the Casasayas patients had a flap reconstruction compared to 37% of our patients and that 44/400 (11%) of the Casasayas patients had stapler closure of their pharynx compared to a negligible number in our data set.

To discuss the latter difference first, could stapler closure reduce the risk of fistula? Unfortunately we cannot answer this question in our dataset as staplers were only occasionally used, and it is also cofounded by extent of surgery (i.e. stapler laryngectomies can only be performed when no pharyngeal resection is required).

With regards to upfront flap reconstruction we must be careful not to miss a subtlety. Upfront flap reconstruction can be used when there is a need to fill the pharyngeal defect, or it can be used as reinforcement over a primarily closed pharynx. Casasayas et al do not report this disctionction in their paper. In our data, 9 flaps were used for reinforcement and 59 for a partial pharyngeal defect and 22 for a circumferential reconstruction of the pharynx. Interpreting this data is difficult. On the one hand, using a flap to close a pharyngeal defect implies a larger pharyngeal defect in the first place and a much longer suture line. This might lead us to expect a higher risk of leak. On the other hand, whilst a primarily closed pharynx has a shorter suture line, presumably a reinforcement interposition overlay flap would have only be used in those patients thought to be at particularly high risk of leak. The mitigating affect therefore of the onlay flap is therefore lost in the analysis because it is only used in the highest risk patients.

This notwithstanding, some authors argue that bringing a "fresh" flap into the neck, whether for reconstruction of a pharyngeal defect or for reinforcement, might reduce not only the incidence, but also the *severity* of any post-laryngectomy PCF[16]. It seems disappointing therefore that despite our extensive use of upfront flaps, we still have a higher rate of PCFs, and also of major PCFs than Casasayas. Although data to support this are lacking, it is likely that the mix of patients and management in both studies is different.

Another explanation for why the conservatively managed patients healed faster in the Casasayas et al cohort could be that we are overly inclined to operative management. This however does not seem to be the case, as highlighted above when we show a good number of patients healing with conservative management >4 weeks postoperatively. Indeed, the major driver in our data set of whether a patient is a minor or major PCF according to Casasayas is the time with fistula, not whether they required an operation.

More generally speaking, an ideal severity classification system would allow us to change management in order to mitigate risks of severe PCFs, or at least to better counsel a patient. Since both the Horgan & Dedo and Casasayas classifications offer a post-hoc definition of a major PCF, they unfortunately do not fulfil these key features. Our effort to discover risk factors for a later flap reconstruction of a PCF comes from the hypothesis that in these patients, an "upfront" flap reconstruction would be more desirable than one performed later in the setting of a large contaminated PCF.

Indeed, if we had been able to correlate the severity of a PCF with the parameters in **table 2**, it may have allowed us to make recommendations about management. Being able to identify the patients at risk for severe PCFs might lead to changes in pre- and intra-operative management. Post operatively, we might be inclined to earlier operative intervention in those patients who have a small PCF but with known risk factors for developing a more severe PCF. This would allow the intervention to take place before the wound was heavily contaminated and the patient potentially weaker. Further investigations in this direction are required to answer these questions.

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6

Does the preoperative neutrophil-to-lymphocyte ratio predict formation and severity of pharyngo-cutaneous fistula and overall survival in patients undergoing laryngectomy?

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Submitted

ABSTRACT

Objectives: To evaluate the correlation between the neutrophil-to-lymphocyte ratio (NLR) and pharyngo-cutaneous fistula (PCF) formation/severity, hospital length of stay (LOS) and survival following total laryngectomy.

Materials and Methods: Retrospective cohort review of patients undergoing total laryngectomy at our institution over the 10 year period January 2008 to December 2017. The NLR was calculated from the most recent pre-operative blood count. Univariate and multivariate analyses were used to see if NLR correlated with the outcomes stated above.

Results: A total of 225 patients were analyzed. Median follow up was 36 months and 5 year overall survival was 38%. Patients underwent primary laryngectomy (n=110), laryngectomy following radiotherapy (n=94) or laryngectomy following chemoradiotherapy (n=21). NLR did not correlate with risk and severity of PCF (p=0.728) nor LOS (p=0.498). On multivariate analysis NLR was a statistically significant predictor of survival (OR 1.048, p=0.001).

Conclusions: Increased NLR correlates with adverse survival in patients undergoing laryngectomy. Having identified this high risk group, strategies to mitigate this risk are discussed.

INTRODUCTION

The link between carcinogenesis and inflammation was first proposed by Virchow in 1863 with the observation of infiltrating leucocytes in the tumor microenvironment. Our understanding of the role the immune system plays in carcinogenesis and cancer suppression has however been limited until the availability of modern pathological techniques. It has now become clear that tumor cells change their microenvironment seeking to evade the immune system 1 and indeed that this process can be measured in order to provide prognostic information and even modulated/targeted with immunotherapy. Furthermore, the persistent local inflammation in the tumor microenvironment is reflected by chronic systemic inflammation with resulting changes to the patient's general condition such as weight loss [2,3], loss of lean tissue [4] and decreased performance status and survival [3]. This systemic inflammation can be measured using simple blood tests, for example measuring leucocyte counts and differentiation.

The neutrophil-to-lymphocyte ratio (NLR) is one such measure with high NLR values having been shown to correlate with adverse outcomes in cancers as diverse as esophageal [5], gastric, colon [6], liver [7], cervical [8] ,prostate [9], gallbladder [10], renal [11], breast [12] and head and neck cancers [13-16]. In addition, high NLR has also been extensively studied in other settings, for example as a cardiovascular risk factor [17].

Many studies focus on the correlation between survival and NLR but far fewer on whether NLR correlates for example with post-operative complications such as pharyngo-cutaneous fistula (PCF) following total laryngectomy. Indeed, a reliable marker of this all too frequent complication might allow changes to decision making, for example intraoperatively with the use of an interposition flap to reinforce the pharyngeal closure, or post operatively in determining whether a patient is better managed conservatively or with early operative intervention. More generally, if NLR did correlate particularly strongly with adverse outcomes, it might influence the decision for laryngectomy at all, especially in the salvage setting.

In this paper we investigate a cohort of patients undergoing laryngectomy and correlate the NLR with the risk and severity of pharyngo-cutaneous fistula (PCF) formation, length of hospital stay (LOS) and overall survival (OS).

MATERIALS AND METHODS

Patient group

We performed a retrospective cohort study of all patients undergoing total laryngectomy (TL) at our tertiary head & neck referral center over the period January 2008 to December 2017. The indication for total laryngectomy was either as primary treatment for squamous cell carcinoma, salvage treatment for squamous cell carcinoma following (chemo)radiotherapy or treatment for a dysfunctional larynx following oncologically successful (chemo)radiotherapy. For the purposes of analysis, the patient group was split into patients without previous treatment (primary laryngectomies), patients with previous radiotherapy and patients with previous chemoradiotherapy (which included patients previously treated with either cisplatin, carboplatin or cextuximab).

Patients' demographic, staging, treatment and outcome data were collected using electronic patient records. We recorded TNM classification according to the then applicable AJCC manual. All patients were discussed in our multidisciplinary tumour board and underwent total laryngectomy (TL) or total laryngectomy with (partial) pharyngectomy (TLPP).

Blood counts

Pre-operative work up of these patients routinely included a complete blood count from which we were able to analyse the neutrophil and lymphocyte counts. Patients whose blood samples which were taken more than 30 days before the operation were excluded. If more than one sample was available within the 30 days before the operation, the blood count closest to the operation date was recorded.

From these data, the neutrophil-lymphocyte ratio (NLR) was calculated. For the sake of univariate analysis a cut-off of 5 was used to categorise patients with high NLR (NLR≥5) or low (NLR <5) as per previous landmark studies[18,19]. For multivariate analysis, NLR was used as a continuous variable.

For this study data from the Utrecht Patient Oriented Database (UPOD) were used. UPOD is an infrastructure of relational databases comprising data on patient characteristics, hospital discharge diagnoses, medical procedures, medication orders and laboratory tests for all patients treated at the University Medical Center Utrecht (UMC Utrecht) since 2004. UPOD data acquisition and management is in accordance with current regulations concerning privacy and ethics. The structure and content of UPOD have been described in more detail elsewhere(13).

Outcomes

The preoperative NLR was then analysed with relation to: the chance of postoperative pharyngo-cutaneous fistula (PCF) formation, the need for operative management of PCF, duration of PCF, ultimate chance of closure of PCF, length of hospital stay (LOS) and overall survival (OS).

Statistical analysis

Statistical analyses were performed using SPSS® Statistics 20.0 (IBM, Armonk, NY). Overall survival was calculated using the Kaplan–Meier method and Cox-mantel log-rank test for comparison. The chi-squared test or binary logistic regression analysis was used as appropriate for univariate analysis.

For multivariate analysis we included four prognostic factors deemed clinically relevant with regard to overall survival: age, gender, T-stage and previous treatment. With regard to the latter, patients were categorized primary laryngectomy, post-RT and post-CRT (which included patients previously treated with either cisplatin, carboplatin or cetuximab). A multivariable logistic regression analysis was performed with five variables and eight degrees of freedom. By doing so, the balance between the degrees of freedom and the survivors and deceased was no lower than 10 survivors per degree of freedom. Starting with a full model with five potential predictors, backward elimination was used to exclude predictors with a p-value of more than 0.157[20].

Our institutional review board found that this study does not fall under the scope of the Medical Research Involving Human Subjects Act.

RESULTS

NLR data was available for 225 patients (185 males, 40 females). Median follow up was 36 months and 5 year survival was 38%. NLR values ranged from 1.3 to 35.5 with a mean of 6.1. A histogram showing the distribution of NLR is shown in **table 1**. For univariate analysis, an NLR cut off value of 5 split our patient group fairly evenly into 126/225 (56%) patients with an NLR<5 and 99/225 (44%) patients had NLR≥5, see **table 2**. For multivariate analysis, NLR was used as a continuous variable.

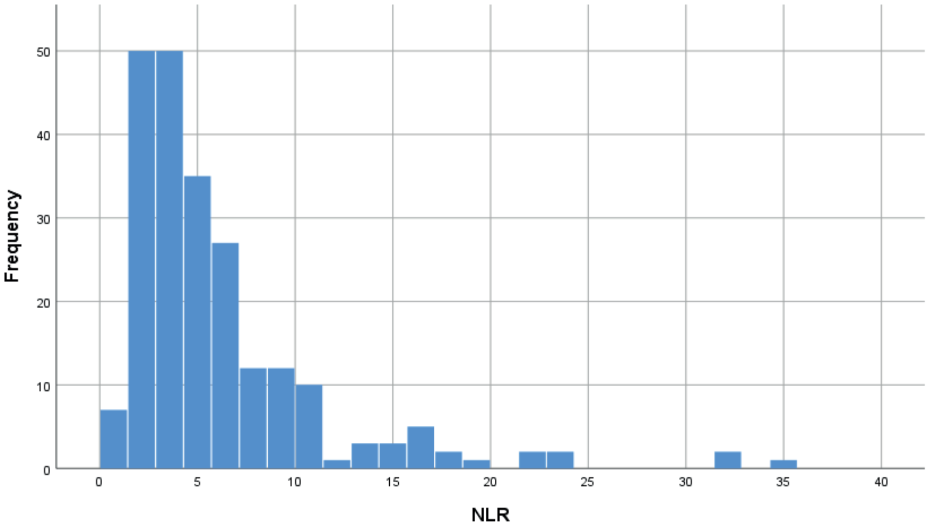

TABLE 1: Histogram showing distribution of NLR values.

Pharyngo-cutaneous fistula formation

For the cohort as a whole, 70/225 (31%) patients developed a PCF post-operatively of which 38/126 (30%) had an NLR<5 and 32/99 (32%) with an NLR≥5. On binary logistic regression analysis this was not statistically significant (p=0.728). Multivariable logistic regression analysis using age, gender, T-stage and previous therapy showed NLR did not correlate with risk of PCF formation.

Severity of PCF

We further investigated if in the patients with a PCF, whether the NLR correlated the severity of the PCF. This notion of severity was broken down into: 1. the likelihood of surgical management, 2. prolonged duration of PCF and 3. the chance of ultimate closure.

In terms of operative management, PCFs were managed operatively in 35/70 (50%) of cases. Of these 35 operatively managed patients, 17 had an NLR<5 versus 18 with an NLR≥5. NLR did not correlate with risk of operative management on binary logistic regression (p=0.338).

TABLE 2: Univariate analysis of various parameters for NLR<5 vs NLR≥5.

		NLR<5	NLR≥5	p=value
Gender	Male	105	80	
	Female	21	19	0.623
Age	<65	58	47	
	>65	68	52	0.829
Site	Supraglottic	19	24	
	Glottic	49	26	
	Subglottic	3	4	
	Transglottic	11	20	
	Post-cricoid	1	1	
	Piriform sinus	38	22	
Indication	Primary	71	39	
	Post RT	47	47	
	Post CRT	8	13	0.025
T-stage	T1	17	12	
	T2	27	24	
	T3	21	22	
	T4	60	41	0.657
pN-Stage	N0	80	64	
	N1	8	7	
	N2a	1	1	
	N2b	16	18	
	N2c	20	7	
	N3	0	2	0.231
Operation	TL	87	56	
	TLPP/TLP	39	43	0.053
ASA	1	59	46	
	2	33	28	
	3	31	19	
	4	3	3	0.835
Neck dissection	None	46	52	
	Unilateral	45	31	
	Bilateral	35	16	0.032
flap	None	87	56	

TABLE 2: Continued.

		NLR<5	NLR≥5	p=value
reconstruction	Pectoralis major	28	34	
	Radial forearm	4	2	
	Anterior lateral thigh	2	5	
	Gastric pull up	3	1	
	Jejunum interposition	2	1	0.274
PCF	No	88	67	
	Yes	38	32	0.728

To investigate the duration of an open PCF we performed a Kaplan Meier analysis (see **Figure 1**). Stratified by NLR, median duration of PCF was 61 days for patients with NLR≥5 and 43 days for patients with NLR <5. Using the Cox-mantel log-rank test, this difference was not statistically significant (p=0.652).

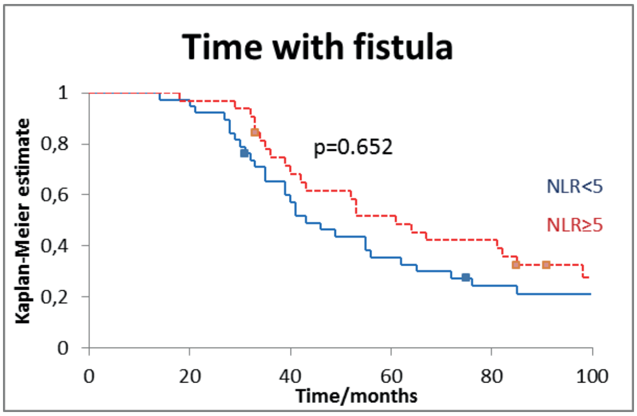

FIGURE 1: Time with fistula vs NLR (whole cohort)

Our final measure of PCF severity was to look at whether the PCF ultimately closed or not and whether this correlated with NLR. In total 57/70 fistulas closed during follow-up: 30/38 (79%) closed in the NLR<5 group and 27/32 (84%)in the NLR≥5 group. On binary logistic regression analysis this difference was not statistically significant (p=0.562).

On our 3 measures of PCF severity, NLR did not correlate with adverse outcomes.

Length of hospital stay

As a marker of overall complications and speed of recovery, we performed a Kaplan Meier analysis comparing LOS for patients with NLR<5 and patients with NLR≥5 (see **figure 2**). A Cox-mantel log-rank test showed no statistically significant difference (p=0.498) in LOS. Multivariable analysis using a Cox-proportional hazards model including age, gender, T-stage and previous therapy again showed not significant correlation between NLR and LOS.

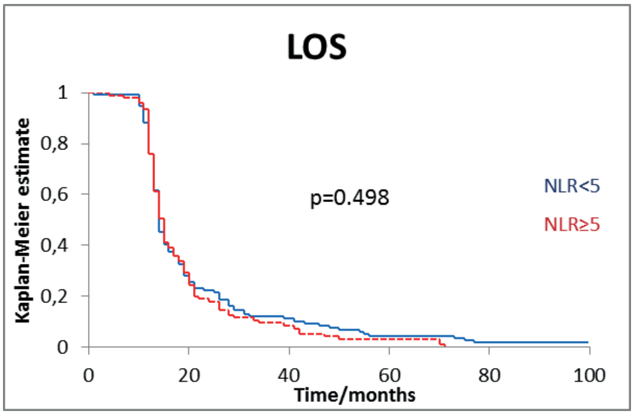

FIGURE 2: NLR versus LOS (whole cohort)

Survival

Kaplan Meier survival analysis of the whole cohort showed a 5 year overall survival of 45% for NLR<5 patients versus 30% for NLR≥5 patients (p=0.007; see **Figure 3**). To investigate this result further, we split the patients into primary, post-RT and post-CRT groups. Interestingly we found the NLR was no longer associated with poor survival for the primary and CRT groups, but remained statistically significantly correlated with poor survival in post RT group on univariate analysis (5 year survival 48% vs 27% p=0.014) – **figure 4**.

Multivariable analysis of the whole cohort using age, gender, T-stage and previous therapy showed that increasing age (OR 1.026, p=0.005) and increasing NLR (OR 1.048, p=0.001) were associated with worse survival and despite the univariate analysis result, previous therapy did not seem to correlate with survival. Running the multivariate analysis on the subgroups primary / post-RT / post-CRT showed that that age remained a prognosticator for survival, but that NLR only correlated independently with worse survival in the *primary* laryngectomy group (OR 1.057, p=0.06). The multivariate analysis therefore shows the opposite result from the univariate analysis.

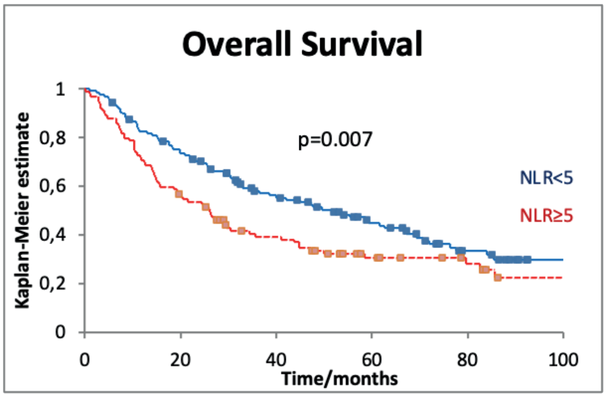

FIGURE 3: Overall survival for NLR<5 and NLR≥5 patient groups (whole cohort)

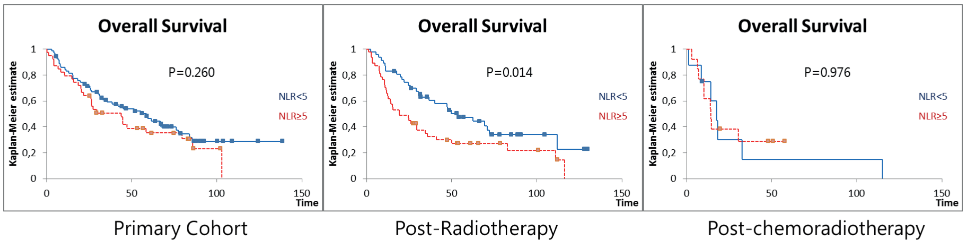

FIGURE 4: NLR versus overall survival stratified by previous therapy

DISCUSSION

NLR is a simple, inexpensive and minimally invasive test which has been shown to correlate with adverse outcomes in cancer patients. For head and neck oncologists there are papers describing its value in oral, oropharyngeal, nasopharyngeal, laryngeal and hypopharyngeal cancers 16,18,19,21-28 both in patients treated with surgery and with primary (chemo)radiotherapy. In terms of laryngeal cancer, there is evidence that a raised NLR correlates with increased risk of recurrence and transformation into cancer for vocal fold leukoplakia and small tumors [24,29]. For larger laryngeal tumors, there is also the suggestion that a high NLR might be an indication for concomitant chemotherapy in patients who are currently treated with radiotherapy as a single modality [30], or even that these patients might be candidates for upfront surgery.

Despite these findings, NLR does not currently drive management and can be considered similarly to low skeletal muscle mass[31] or HPV status in oropharyngeal patients, i.e. it has a clear prognostic value, but does not as yet influence management [32].

One of the reasons for this is a lack of understanding of what NLR is actually measuring. As mentioned in the introduction, it is only recently with advent of new pathological techniques that we are beginning to our understand the role of the immune system in carcinogenesis. Many discrete inflammatory markers such C-reactive protein, leucocytosis and thrombocytosis show significant correlation with outcomes in cancers as diverse as breast, cervical and anal cancer [33-35], but NLR seems to be even more robust in predicting adverse outcomes. However this clinical observation is yet to be supported by a detailed immunological understanding. Indeed, the precise role neutrophils play in the tumor microenvironment remains controversial[36-38] and how tumor microenvironment neutrophilia is reflected by systemic neutrophil counts is similarly poorly understood.

One controversy is whether or not these systemic inflammatory markers are elevated due to the cancer itself or some concurrent infection. For example, in our specific patient cohort, laryngeal tumors can easily lead to lung infections as well as local infective issues. Experiments performed in mice have shown that inflammation caused by a completely separate infection can promote tumor growth and metastasis[39]. It is as if the immune system in this situation has been distracted by the infection, allowing the cancer to progress. This phenomenon has also been reported with early postoperative infections which also seem to increase the risk of cancer progression40. This latter result might have implications for our patients with PCFs with their resultant inflammatory consequences. The occurrence of PCF might distract the immune system from dealing with any remaining cancer cells.

Another controversy is that some reports show that the NLR correlates with overall survival but not necessarily with disease specific survival[23]. This again implies that NLR is measuring something other than tumor immunogenicity only.

Most importantly, whether NLR plays a role in only a subset of patients is unclear. Generalizing from a small subset to a large patient population is clearly hazardous and the data presented in this paper show for example conflicting results between multivariate and univariate analyses as to whether NLR is useful depending on prior therapy. Whilst the univariate analysis Kaplan Meier curves in **Figure 4** imply that NLR is only a prognosticator in the post-RT group, the multivariate analysis shows the opposite result, namely that NLR is only a prognosticator in the primary group. Whether much can be said regarding CRT group is debatable. This group is small and has in any case poor outcomes. The CRT patient group are on the one hand sicker than the RT patients (hence the recommendation for concomitant chemotherapy) but yet fit enough to have chemotherapy. It may be that confounding our data are patients in the RT group who preferably would have undergone CRT but were deemed unsuitable.

Why should NLR be a prognosticator in the primary group and not the post-RT group? One possibility is that the host immune system is activated differently in the two groups. For post-RT patients, radiotherapy induced tumor lysis occurs during the initial treatment and the patient's immune system is presumably activated by the local tumor micro-environment and may play a role in many aspects of tumor proliferation, invasion, migration, angiogenesis, radio-resistance and host response[41,42.] Radiotherapy is performed over many weeks and dead tumor cells are processed by the immune system for potentially many months after the radiotherapy has finished.

In surgically treated patients the situation is markedly different. Tumor cells are proliferating up until the point of surgery when they are removed rather than killed. With such different tumor antigen presentation, it should be no surprise that the host immune response is markedly different and that this is reflected in the difference we see between the primary and salvage groups.

Limitations

Despite a reasonably large cohort of patients, this study is limited in its multivariate analysis by the number of events. Ideally, we would have included more variables in the multivariate analysis and the choice of age, gender, T-stage and previous therapy as co-variates is open to discussion. Furthermore, the analysis can be further confounded by patient choice of treatment and also the complexities of the treatment protocols. As mentioned in the discussion, an example of this is the post-CRT group. This patient group is difficult to analyze as it may represents a group of patients with significant tumor burden who are however fit enough to undergo a potentially toxic treatment plan. It also includes patients who may have chosen CRT over primary laryngectomy for their own reasons.

Conclusions

The data presented adds to the growing literature on NLR in head and neck cancers. Whilst NLR did not correlate with risk PCF formation/ severity or length of hospital stay, it did correlate with poor survival in the primary laryngectomy group. It is difficult to see how this group could be treated more aggressively, other than by the addition of chemotherapy to the adjuvant radiotherapy. This would greatly increase toxicity and further studies would be required to see if there was a survival benefit. Another approach might be more intensive follow-up with the hope of detecting any recurrent tumors early, though whether a patient could be treated for any such recurrence is also unclear. Further research needs to be carried out into what drives the increased NLR and whether these underlying factors could be addressed.

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7

Pre-operative low skeletal muscle mass as a risk factor for pharyngocutaneous fistula and decreased overall survival in patients undergoing total laryngectomy

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ABSTRACT

Background: Low skeletal muscle mass (SMM) is associated with postoperative complications, prolonged hospital stay, and short overall survival (OS) in surgical oncology. We aimed to investigate this association in patients undergoing total laryngectomy (TL).

Methods: A retrospective study was performed of patients undergoing TL. SMM was measured using CT or MRI scans at the level of the third cervical vertebra (C3).

Results: In all, 235 patients were included. Low SMM was observed in 109 patients (46.4%). Patients with low SMM had more pharyngocutaneous fistulas (PCFs) than patients with normal SMM (34.9% vs 20.6%; $P = .02$) and prolonged hospital stay (median, 17 vs 14 days; $P < .001$). In multivariate analysis, low SMM (hazards ratio, 1.849; 95% confidence interval, 1.202-2.843) and high N stage were significant prognosticators of decreased OS.

Conclusion: Low SMM is associated with PCF and prolonged hospital stay in patients undergoing TL. Low SMM is an independent prognostic factor for shorter OS.

INTRODUCTION

Total laryngectomy (TL) with or without (partial) pharyngectomy, often followed by postoperative (chemo)radiotherapy is a curative treatment option for patients with advanced stage primary laryngeal or hypopharyngeal cancer. TL can also be used to salvage patients with recurrent disease after failure of initial organ preserving treatment with (chemo)radiotherapy or in patients without (current) cancer but with a dysfunctional larynx[1,2]. TL is an invasive surgical procedure and is associated with significant morbidity and mortality, as well as a reduced quality of life after surgery[3].

Postoperative complications including the occurrence of a pharyngocutaneous fistula (PCF) are common and difficult-to-treat problems after TL[1-4]. Up to 30% of patients develop PCF, which may require additional surgery, prolongs feeding tube dependency, and increases hospital stay[5]. Previously described risk factors for the occurrence of a PCF include prior chemoradiotherapy with platinum-based chemotherapy, hypopharyngeal cancer, extensive pharyngeal resection and reconstruction, additional neck dissection, and low BMI. The occurrence of a PCF may also cause delay of postoperative (chemo) radiotherapy, thus jeopardizing optimal oncological treatment[6,7].

The radiological assessment of body composition has increasingly gained attention in oncological research over the last decade[8,9]. Specifically a low skeletal muscle mass (SMM), also termed sarcopenia, has been related to negative outcomes in variety of tumour types and treatments. In geriatric patients, sarcopenia is defined as a geriatric syndrome characterized by the age-related loss of muscle mass and/or muscle function or decreased physical status[10]. In oncological patients, often only SMM assessed as muscle function is rarely measured during routine clinical practice[11].

In oncological patients, SMM is most commonly assessed on abdominal CT imaging at the level of the third lumbar vertebra (L3)[12,13]. Abdominal CT is routinely performed during diagnostic work-up and follow-up of many patients with cancer, and thus imaging is routinely available for analysis without any extra burden for the patient or health care-related costs.

Low SMM has been related to more postoperative com- plications, prolonged hospital stay and decreased survival in surgical oncology[14,15]. In head and neck cancer (HNC), the predictive and prognostic value of low SMM has not yet been researched as thoroughly. Abdominal CT imaging is not routinely performed in patients with HNC and is often only available in a preselected patient group with advanced disease and high-risk features for distant metastasis. Recently, a novel SMM assessment method at the level of the third cervical vertebra (C3) was published[16]. Imaging at the level of C3 is almost always available in patients with HNC, allowing for the routine assessment of SMM.

In this article, we aim to investigate whether preoperative low SMM, as measured using CT or MRI at the level of C3, is a significant predictor of postoperative complications including PCF, prolonged hospital stay, and decreased overall survival (OS) in a large consecutive cohort of patients undergoing TL for any indication.

METHODS

Patients and methods

The design of this study was approved by the Medical Ethical Research Committee of the University Medical Centre Utrecht (ID 17-365/C). The research was conducted in accordance with the Declaration of Helsinki.

Patient and study design

A retrospective case note review was performed of all consecutive patients who had undergone TL between January 2008 and May 2017 at the University Medical Centre, Utrecht, the Netherlands, a tertiary referral centre for patients with HNC. All patients were discussed in the local multidisciplinary tumour board prior to and after surgery. Patients without recent CT or MRI scans (less than 1 month old) of the head and neck area prior to TL were excluded. Patients who had severe dental artefacts at the level of C3 that impeded accurate assessment of SMM were also excluded.

Patients' demographic, staging, treatment, and outcome data were collected using electronic patient records. Both versions 6 and 7 of the American Joint Committee on Cancer (AJCC) manual were used for staging as the study period straddled the change in 2009[17]. All patients were discussed in local tumour board meetings and underwent TL with or without (partial) pharyngectomy and with or without additional lymph node dissection either as a primary treatment, a salvage treatment, or a functional treatment for a dysfunctional larynx. Five dedicated head and neck surgical oncologists performed all total laryngectomies during the time period. Operating records were checked for details of the surgery, neck dissection, and primary pharyngeal closure or flap reconstruction of the pharynx. Prior treatment with radio- therapy or chemoradiotherapy for HNC was recorded. Postoperative adjuvant treatment was also recorded. The American Society of Anaesthesiologist's physical status classification was recorded as a surrogate marker for comorbidities[18]. Postoperative complications were graded according to the Clavien-

Dindo classification of Surgical Complications[19]. Severe complications were defined as Clavien-Dindo grade 3A or higher. Of specific interest was the occurrence of PCF which was scored separately to the other postoperative complications. The occurrence of PCF was defined as a clinical fistula requiring any form of conservative or surgical treatment. Duration of hospital stay was recorded as the time in days between the date of TL and date of first hospital discharge.

Follow-up/survival data were retrieved up until August 31st, 2017. OS was defined as the time elapsed between the date of TL and the date of death. Disease-specific survival (DSS) was defined as any patient who had died as a result of the current HNC diagnosis or as a result of the surgical procedure. Survival status was checked in the patient medical records in our hospital. Patients are routinely contacted during the first 5 years of follow-up after TL.

SMM measurement

SMM was measured on pre-treatment CT or MRI scans of the head and neck area at the level of C3 using a previously published method[16]. Whenever possible, CT imaging was used instead of MRI. In brief, the first slide at the level of C3 when scrolling from caudal to cranial direction to show both transverse processes and the entire vertebral arc was selected for segmentation of skeletal muscle (SM) tissue. For CT imaging, SM area was defined as the pixel area within a radiodensity between −29 and +150 Hounsfield units (HU), which is specific for SM tissue[20]. For MRI, SM tissue was carefully segmented and any intramuscular fatty tissue was manually excluded. Segmentation of SM tissue was manually performed by a single researcher (S.B.) using the commercially available software package SliceOmatic (Tomovision, Magog, Quebec, Canada). An example of SM tissue segmentation at the level of C3 is shown in **Figure 1**. After a learning period, the measurement of SMM requires 5 to 10 minutes per CT scan, and up to 15 minutes per MRI scan.

From SM area at C3, SM area at the level of L3 was predicted using the previously published formula 1[16]. The SM area at L3 was then normalized for height to calculate the lumbar skeletal muscle index (lumbar SMI), as shown in formula 2[12]. Low SMM was defined as a lumbar SMI lower than 43.2 cm^2/m^2. This recently published cut-off value was established in a separate cohort of patients with HNC[21].

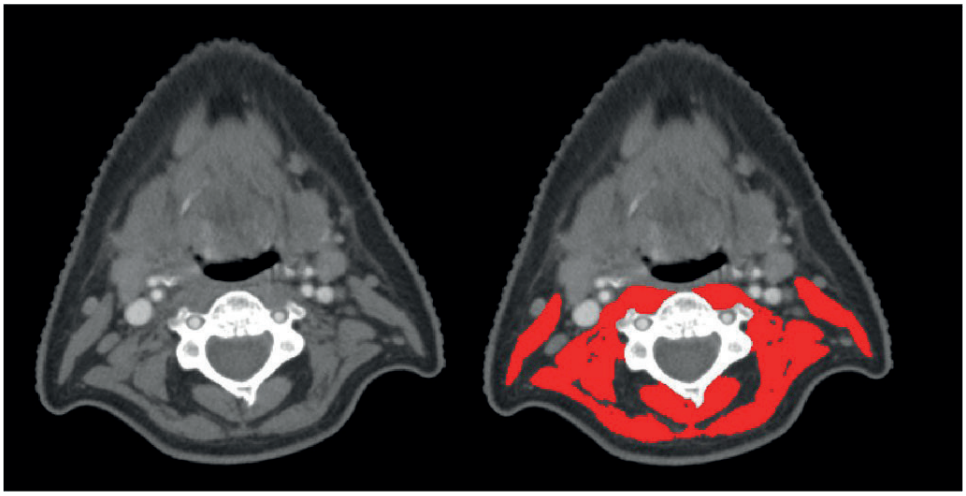

FIGURE 1: Example of segmentation of skeletal muscle tissue at the level of third cervical vertebra (C3). Two identical axial CT-slides at the level of C3; the left CT slide shows the skeletal muscle tissue unsegmented, while the right image shows the paravertebral muscles and both sternocleidomastoid muscles segmented in red, using SliceOmatic software. Hounsfield unit (HU) ranges are set at −29 to +150 HU for optimal identification of skeletal muscle tissue

Formula 1:

$$CSA\ at\ L3\ cm^2 = 27{:}304 + 1{:}363 * CSA\ at\ C3\ (cm^2)$$
$$- 0{:}671 * Age\ (years) + 0{:}640 * Weight\ (kg)$$
$$+ 26.442 * Sex\ (Sex = 1\ for\ female,\ 2\ for\ male)$$

Formula 2:

$$Lumbar\ SMI\ (cm^2/m^2) = CSA\ at\ L3/length\ (m^2)$$

Statistical analysis

Categorical data are represented as a number and percentage of the total. All statistical analyses were performed using the IBM SPSS Statistics version 21.0 software package (Chicago, Illinois). A test for normality (Kolmogorov-Smirnoff test) and histograms were used to assess whether continuous variables were normally distributed. Continuous data are represented as mean ± SD if normally distributed, and median ± interquartile range if skewed. Fisher's exact tests, Pearson Chi square tests, independent sample *t* tests, and Mann-Whitney *U* tests were used to assess group differences. Binary logistic regression analysis was used to assess the association between low SMM and the occurrence of

PCF. Kaplan-Meier estimates were used to visualize the relationship between low SMM and survival outcomes. Univariate and multivariate Cox proportional hazard models were used to assess the association between low SMM and OS. Parameters entered as covariates in regression analysis were chosen based on known or expected association with outcomes. All analyses were two-sided and $P \leq .05$ was considered significant.

RESULTS

Between January 2008 and June 2017, 245 patients underwent TL at our institution. Of these 245 patients, 235 (95.9%) had appropriate imaging available and were included in this study. Mean interval between imaging and TL was 3 weeks; maxi- mum was 3 months. Four patients without recent imaging available that were excluded from this study were diagnosed with a dysfunctional larynx and underwent functional laryngectomy, two patients had severe dental artefacts on the imaging impeding accurate SMM assessment at the level of C3, and four patients had irretrievable scans.

Patient demographics

Patient, disease, and surgical characteristics are presented in **Table 1** and the outcomes after surgery in **Table 2**. During the study period, 108 patients underwent primary TL, 114 patients underwent salvage TL, and 13 patients underwent a functional TL. A complication of any grade occurred in 64.3% of patients after TL. The most commonly noted complication was a Clavien-Dindo grade I transient hypocalcaemia after surgery, necessitating short-term calcium monitoring and supplementation. Severe complications occurred in 69 patients (29.4%). A PCF occurred in 64 patients (27.2%), which required surgical closure in 40 patients (17.0%). Mean duration of hospital stay after TL was 21 days. There were four postoperative deaths (1.7%). At the time of concluding this study, with a median time of 62.7 months after TL, 134 (57.0%) patients had died of any cause and 101 (43.0%) were alive.

Body composition

SMM measurement at the level of C3 was successful in all 235 patients. The lumbar SMI was calculated from the SM area at C3 as described in Section 2. Using the lumbar SMI cut-off point of <43.2 cm^2/m^2, 109 patients (46.4% of total) had low SMM. Patients with low SMM had a tendency to be female, had a lower BMI, had a larger primary tumour and AJCC stage, were more likely to have undergone primary TL, and more frequently had flap reconstruction of the pharynx.

TABLE 1: Patient, disease, and surgical characteristics

Characteristic	All patients (*n* = 235)	Patients with low SMM (*n* = 109)	Patients with normal SMM (*n* = 126)	*P* value
Gender				
Male	193 (82.1)	72 (66.1)	121 (96.0)	<.001[a]
Female	42 (17.9)	37 (33.9%)	5 (4.0)	
Age	64.7 (9.1)	65.6 (8.9)	63.8 (9.3)	.13[b]
BMI	23.9 (5.0)	21.1 (3.8)	26.4 (4.6)	<.001[b]
Smoking				
Never	6 (2.6)	4 (3.7)	2 (1.6)	0.04[c]
Current	112 (47.6)	60 (55.0)	52 (41.3)	
Former	117 (49.8)	45 (41.3)	72 (57.1)	
Alcohol abuse				
No	159 (67.7)	72 (66.0)	87 (69.0)	0.72[c]
Yes, current	26 (11.1)	14 (12.8)	12 (9.5)	
Yes, former	50 (21.3)	23 (21.1)	27 (21.4)	
ASA classification				
I	19 (8.1)	7 (6.4)	12 (9.5)	0.23[c]
II	109 (46.4)	46 (42.2)	63 (50.0)	
III	107 (45.5)	56 (51.4)	51 (40.5)	
Localization tumor				
Larynx	175 (74.2)	75 (68.8)	99 (78.6)	.09[c]
Hypopharynx	61 (25.8)	34 (31.2)	27 (21.4)	
T classification				
T 0	13 (5.5)	10 (9.2)	3 (3.2)	0.008[c]
T 1-2	75 (31.9)	26 23.9)	49 (38.9)	
T 3-4	147 (62.6)	73 (67.0)	74 (57.9)	
N classification				
N0	152 (64.7)	64 (58.7)	88 (69.8)	.19[c]
N1	17 (7.2)	7 (6.4)	10 (7.9)	
N2	64 (27.2)	37 (33.9)	27 (21.4)	
N3	2 (0.9)	1 (0.9)	1 (0.8)	
AJCC stage[d]				
0	13 (6.0)	10 (9.2)	3 (2.4)	.009[c]
I	28 (11.9)	6 (5.5)	22 (17.5)	
II	35 (14.9)	16 (14.7)	19 (15.1)	

TABLE 1: Continued

Characteristic	**All patients (*n* = 235)**	**Patients with low SMM (*n* = 109)**	**Patients with normal SMM (*n* = 126)**	***P* value**
III	35 (14.9)	14 (12.8)	21 (16.7)	
IV	124 (52.8)	63 (57.8)	61 (48.4)	
Indication for TL				
Primary HNC[e]	108 (46.0)	57 (52.3)	51 (40.5)	0.004[c]
Recurrent/residual HNC	114 (48.5)	42 (38.5)	72 (57.1)	
Dysfunctional larynx	13 (5.5)	10 (9.2)	3 (2.4)	
Prior treatment				
None	106 (45.1)	55 (50.5)	51 (40.5)	.30[c]
Radiotherapy	106 (45.1)	44 (40.4)	62 (49.2)	
Chemoradiotherapy	23 (9.8)	10 (9.2)	13 (10.3)	
Type of resection				
Laryngectomy (LE)	159 (67.6)	66 (60.6)	93 (73.8)	.04[c]
LE + pharyngectomy	76 (32.4)	43 (39.4)	33 (26.2)	
Closure of neopharynx				
Vertical	129 (54.9)	49 (45.0)	80 (63.5)	.12[c]
T-closure	21 (8.9)	9 (8.3)	12 (9.5)	
Flap closure	85 (36.2)	51 (46.8)	34 (27.0)	
Lymph node dissection				
None	99 (42.1)	45 (41.3)	54 (42.9)	0.46[c]
Unilateral	88 (37.1)	38 (34.9)	50 (39.7)	
Bilateral	48 (20.4)	26 (23.9)	22 (17.5)	
Primary flap reconstruction				0.002[a]
No	150 (63.8)	58 (53.2)	92 (73.0)	
Yes	85 (36.2)	51 (46.8)	34 (27.0)	

Continuous variables are represented as mean (SD) and categorical variables are represented as number (percentage of total). Abbreviations: AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologist's physical status classification; BMI, body mass index; SMM, skeletal muscle mass; HNC, head and neck cancer; TL, total laryngectomy.

[a] *Fisher's exact test.*

[b] *Independent sample t test.*

[c] *Pearson Chi squared test.*

[d] *Before 2009: according to the 6th AJCC staging manual. After 2009: according to the 7th AJCC staging manual.*

[e] *Two patients with primary HNC underwent prior radiotherapy for non-Hodgkin lymphoma.*

TABLE 2: Short-term and long-term outcomes after total laryngectomy (TL)

Outcome	All patients (n = 235)	Patients with low SMM (n = 109)	Patients with normal SMM (n = 126)	P value
All grade complications	151 (64.3)	74 (67.9)	77 (61.1)	0.38[a]
Severe complications[b]	69 (29.4)	38 (34.9)	31 (24.6)	0.11[a]
Postoperative mortality	4 (1.7)	4 (3.7)	0 (0)	0.05[a]
PCF	64 (27.2)	38 (34.9)	26 (20.6)	0.02[a]
Treatment PCF				
Conservative	24 (10.2)	14 (12.8)	10 (7.9)	0.05[c]
Surgical	40 (17.0)	24 (22.0)	16 (12.7)	
Duration of hospital stay in days	14 [13-21]	17 [13-28]	14 [12-17]	<0.001[d]
Overall survival after TL				
Alive	101 (43.0)	30 (27.5)	71 (56.3)	<0.001[a]
Deceased	134 (57.0)	79 (72.5)	55 (43.7)	

Duration of hospital stay was skewed and is represented as median [interquartile range]. Categorical variables are represented as number and percentage of total. Abbre- viations: PFC, pharyngocutaneous fistula; SMM, skeletal muscle mass.

[a] *Fisher's exact test.*

[b] *Severe complications: Clavien-Dindo Classification of Surgical Complications grade 3A or higher.*

c Pearson Chi squared test.

[d] *Mann-Whitney U test.*

Association between low SMM, postoperative complications, PCF, and hospital stay

Table 2 shows the associations between low SMM and outcomes after TL. Patients with low SMM had more severe complications than patients with normal SMM (34.9% vs 24.6%, difference not statistically significant, P = .11). All four patients who died in hospital had low SMM (P = .05). PCF occurred significantly more often in patients with low SMM than in patients with normal SMM (P = .02), and surgical treatment of the PCF was more often necessary (P = .05). Hospital stay was significantly longer in patients with low SMM (median, 17 days vs 14 days; P < .001).

Logistic regression analysis was performed to identify predictors of the occurrence of PCF. Variables were selected for logistic regression based on known or hypothesized association with PCF. T stage and AJCC stage were not entered in logistic regression analysis because of interaction with the indication for TL. Results of the univariate and multivariate logistic regression analysis are shown in **Table 3**. In univariate logistic regression analysis, localization of the tumour (hypopharynx), the type of resection (laryngectomy+ pharyngectomy), flap closure of the pharynx, low SMM, and a dysfunctional larynx as the indication for TL were significant predictors for PCF. In multivariate logistic regression analysis, only a hypopharyngeal tumor (odds ratio [OR], 3.348; 95% confidence interval [CI], 1.740-6.443), low SMM (OR, 1.950; 95% CI, 1.038-3.664), and a dysfunctional larynx (OR, 4.881; 95% CI, 1.375-17.325) remained significant predictors of PCF.

Survival analysis

On univariate analysis, OS at the end of follow-up was significantly lower in patients with low SMM than in patients with normal SMM (median OS was 18.5 months in patients with low SMM vs 30.1 months in patients with normal SMM, $P < .001$), which is visualized in **Figure 2**. DSS was significantly lower in patients with low SMM, as shown in **Figure 3**.

Table 4 shows the results of the univariate and multivariate regression analysis for OS. In univariate Cox proportional hazard regression analysis, high N stage (N2 and N3) and low SMM were significant prognosticators for OS. A higher BMI appeared to be associated with longer OS. In multivariate Cox regression analysis, N2 nodal status (OR, 1.494; 95% CI, 1.023-2.182; P= 0.04), N3 nodal status (OR, 16.040; 95% CI, 3.691-69.710; $P < .001$) and low SMM (OR, 2.096; 95% CI, 1.494-2.920; $P < .001$) remained independent prognosticators for decreased OS.

TABLE 3: Univariate and multivariate logistic regression analysis for the occurrence of pharyngocutaneous fistula (PCF)

	Univariate analysis[a]		Multivariate analysis[b]	
Risk factor	**Odds ratio (95% CI)**	***P* value**	**Odds ratio (95% CI)**	***P* value**
Sex				
Male	1.00 [reference]			
Female	1.633 (0.803-3.319)	.18	1.091 (4.72-2.521)	.84
Smoking				
Never	1.00			
Current	1.747 (0.196-15.583)	.52		
Former	2.048 (0.231-18.188)	.62		
Alcohol abuse				
Never	1.00			
Yes, current	1.322 (0.534-3.274)	.55		
Yes, former	1.400 (0.700-2.802)	.34		
Prior treatment				
None	1.00			
Radiotherapy	1.330 (0.725-2.473)	.35		
Chemoradiotherapy	1.728 (0.656-4.550)	.27		
Localization tumor				
Larynx	1.00			
Hypopharynx	3.276 (1.757-6.107)		3.348 (1.740-6.443)	<.001
Type of resection				
Laryngectomy (LE)	1.00			
LE + pharyngectomy	3.003 (1.646-5.478)	<.001	1.799 (0.852-3.798)	.12
Closure of neopharynx				
Vertical	1.00			
T closure	1.492 (0.496-4.489)	.18	1.581 (0.511-4.896)	.43
Flap closure	3.238 (1.734-6.047)	0.001	1.580 (0.525-4.753)	.42
LND				
None	1.00			
Unilateral	1.458 (0.767-2.772)	.25		
Bilateral	1.042 (0.469-2.316)	.92		
Indication for TL				
Primary HNC	1.00			
Recurrent/residual HNC	1.126 (0.614-2.067)	.70	1.560 (0.809-3.011)	.19
Dysfunctional larynx	5.046 (1.518-16.775)	.008	4.881 (1.375-17.325)	.01

TABLE 3: Continued

	Univariate analysis[a]		Multivariate analysis[b]	
Risk factor	**Odds ratio (95% CI)**	***P* value**	**Odds ratio (95% CI)**	***P* value**
BMI				
<18.5	1.191 (0.373-3.801)	.77		
18.5-25.0	0.935 (0.374-2.340)	.89		
25.0-30.0	0.479 (0.163-1.405)	.18		
>30.0	1.00			
Low SMM	2.059 (1.148-3.692)	.02	1.950 (1.038-3.664)	.04

Abbreviations: BMI, body mass index; CI, confidence interval; HNC, head and neck cancer; LND, lymph node dissection; SMM, skeletal muscle mass; TL, total laryngectomy.

[a] Univariate binary logistic regression analysis.

[b] Multivariate binary logistic regression (Backward Wald selection model).

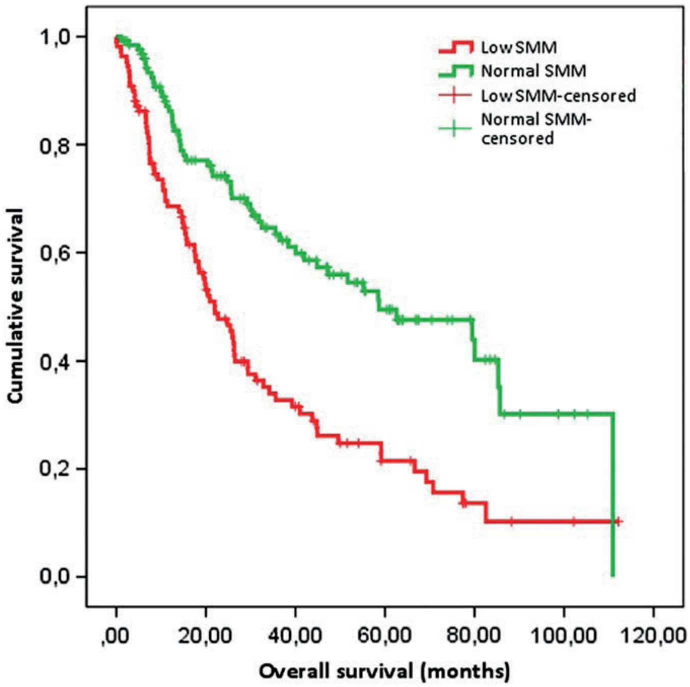

FIGURE 2: Kaplan-Meier survival curve for overall survival (OS) after total laryngectomy (TL). Kaplan-Meier survival curve showing OS in patients with low and normal skeletal muscle mass (SMM). OS for patients with low SMM was the median OS for patients with low SMM after laryngectomy was 18.5 months, compared to 30.1 months in patients with normal skeletal muscle mass ($P < .001$). OS at 5 years after TL was 32.1% for patients with low skeletal muscle mass vs 61.1% for patients with normal skeletal muscle mass (log rank test: $P < .001$)

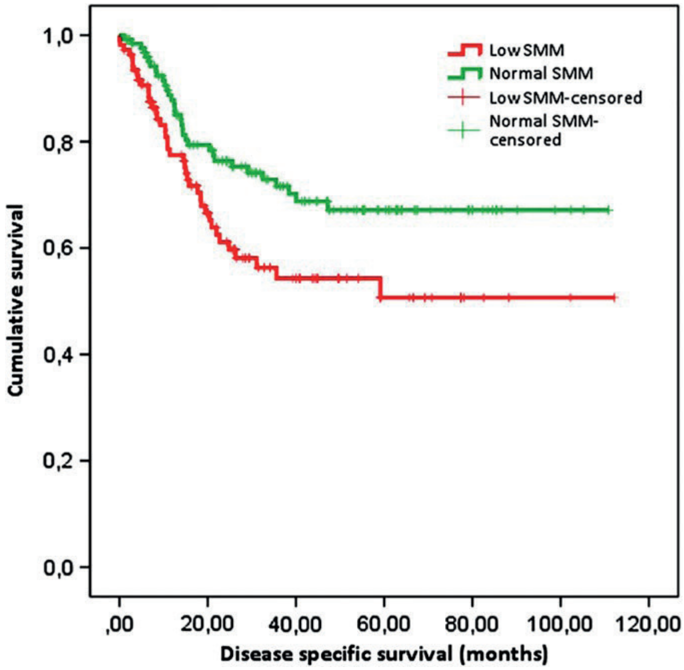

FIGURE 3: Kaplan-Meier survival curve for disease-specific survival (DSS) after total laryngectomy (TL). Kaplan-Meier survival curves showing DSS in patients with low and normal skeletal muscle mass (SMM). DSS and 5-year DSS were equal; DSS was 63.3% for patients with low SMM vs 73.8% for patients with normal SMM (log rank test: $P = .02$) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4: Univariate and multivariate Cox regression analysis for overall survival

Risk factor	Univariate analysis[a]		Multivariate analysis[b]	
	Odds ratio (95% CI)	***P* value**	**Odds ratio (95% CI)**	***P* value**
Sex				
Male	1.00			
Female	0.940 (0.603-1.465)	.78		
Indication for TL				
Primary HNC	1.00 [reference]			
Recurrent/residual HNC	1.308 (0.923-1.855)	.13		
Dysfunctional larynx	1.017 (0.439-2.355)	.97		
N classification[c]				
N0	1.00			
N1	1.771 (0.979-3.201)	.06	1.452 (0.783-2.692)	.24
N2	1.763 (1.214-2.560)	.004	1.313 (0.892-1.932)	.17
N3	17.091 (3.939-74.153)	<.001	17.4170 (3.919-77.410)	<.001
Postoperative treatment				
None	1.00			
Radiotherapy	0.756 (0.524-1.092)	.14		
Chemoradiotherapy	0.834 (0.461-1.509)	.55		
ASA classification				
I	1.00			
II	1.286 (0.638-2.590)	.48		
III	1.746 (0.868-3.511)	.12		
BMI				
<18.5	1.237 (0.605-2.528)	.56	0.710 (0.332-1.568)	.39
18.5-25.0	1.193 (0.662-2.150)	.56	0.904 (0.487-1.679)	.75
25.0-30.0	0.494 (0.246-0.989)	.05	0.538 (0.267-1.081)	.08
>30.0	1.00			
Low SMM	2.217 (1.566-3.137)	<.001	1.849 (1.202-2.843)	.005

Abbreviations: ASA, American Society of Anaesthesiologist's physical status classification; BMI, body mass index; HNC, head and neck cancer; SMM, skeletal muscle mass; TL, total laryngectomy.
[a] Univariate Cox survival regression analysis.
[b] Multivariate Cox survival regression analysis (Backward Wald selection model).
[c] Patients with N3 nodal status: n = 2.

DISCUSSION

It can be anticipated that low SMM has a high prevalence in patients with HNC, at least partly due to the location of the tumour and/or poor physical condition of patients with HNC[22,23]. Many patients with HNC experience dysphagia and odynophagia, especially after initial (chemo)radiotherapy, leading to malnutrition at diagnosis[24,25]. A recent study in patients with advanced stage head and neck squamous cell carcinoma undergoing primary chemoradiotherapy, in which SMM was measured at the level of C3, found that 54.5% of patients had low SMM prior to start of treatment[21]. Another study, in which SMM was measured at the level of L3, found that 77% of patients undergoing TL had low SMM[26]. In the latter study, low SMM was a significant independent predictor for the occurrence of PCF[26]. One shortcoming of this study was that abdominal imaging was available in only 57% of patients and consequently only in these patients SMM could be assessed. Because it might be expected that whole body imaging is only routinely performed in selected patients, for example, with advanced stage disease and at high risk of distant metastases, a substantial risk of bias has been introduced.

This study is the largest to date in patients with HNC to show that low SMM is a powerful negative prognostic factor in patients undergoing primary, salvage, or functional TL. Patients with low SMM are at increased risk of developing PCF after TL compared to patients with nor- mal SMM, and the OS of patients with low SMM is only half of the OS of patients with normal SMM. Our data suggest that a simple preoperative measurement of SMM may aid in identifying patients at risk for severe complications, in particular of PCF, and prolonged hospital stay. It may also function as a strong negative prognostic parameter for OS after TL.

Our study is the first to use routinely performed CT or MRI of the head and neck area to assess preoperative muscle status in patients undergoing TL, and the largest to do so in patients with HNC. The main benefit of SMM measurement at the level of C3, compared to SMM measurement at the level of L3, is that almost all patients have appropriate imaging available. In this current study, only 10 out of 245 (4.1%) patients had to be excluded[26].

The relationship between low SMM and negative short- term outcomes and prolonged hospital stay is consistent with previous publications in surgical oncology. In abdominal surgery, a recent systematic review and meta-analysis showed that low SMM is a significant risk factor for major postoperative complications, postoperative mortality, and shorter 1-year, 3-year, and 5-year survival[15]. In hepatopancreatobiliary cancer, low SMM is associated with reduced OS[14]. In patients with resectable early stage non-small-cell lung cancer, low SMM is associated with poor short-term and long-term outcomes after surgery[27,28]. Low SMM has also been associated with prolonged hospital stay and increased health care-related costs. A recent study in 452 patients undergoing abdominal surgery for cancer of the alimentary tract showed that patients with low SMM had a significantly longer hospital stay and significantly higher hospital costs than patients with normal SMM[29]. In our study, patients with low SMM had a significantly longer hospital stay than patients with normal SMM. Although not investigated, it can be anticipated from our results that health care-related costs have been higher in patients with low SMM as well. Our study also showed a clear relationship with poor OS and DSS in patients with low SMM. This is in line with previous publications in other types of cancer[30]. This may be due to patients not being fit enough to receive adjuvant treatment, or severe postoperative complications resulting in mortality or delaying necessary adjuvant treatment.

In our study, a cut-off value to define low SMM that has been developed in a separate cohort of Dutch patients with HNC was used[21]. Although exact definitions and cut-off values for low SMM differ between studies, patient groups and ethnicities, it does appear that low SMM is consistently associated with adverse short-term and long-term outcomes in surgical oncology. A potential hypothesis for this may be that patients with low SMM have a decreased capability for recovery after major cancer surgery, for instance due to an altered protein metabolism or a decreased physiological reserve to deal with surgical stress[31,32]. Another hypothesis is that low SMM indirectly reflects an overall poorer physical functioning in patients, which is not as distinctly found as using other routinely used risk stratification methods.

Future research should be aimed at proactive interventions to improve patient's physical and nutritional status, to clarify whether the adverse effects of low SMM are prognostic only, or if they can be overturned by intensive preoperative optimization and postoperative rehabilitation with physical therapy and nutritional support. Feasibility studies in patients with HNC have shown that resistance training programs in patients under- going chemoradiotherapy or radiotherapy are feasible and show high patient satisfaction[33,34]. A randomized controlled trial in patients with lung cancer undergoing short-term intensive rehabilitation prior to radical surgery showed positive results, with a significant decrease in hospital stay after surgery[35]. However, most current trials are small; larger randomized controlled trials should clarify whether a multimodal rehabilitation program can reduce the negative effects of low SMM in patients undergoing TL. Alternatively, treatment planning could take the low SMM into account. For example, this could lead the head and neck surgeon to more frequently use overlay pectoralis major flaps for reinforcement in order to decrease the risk of PCF in patients at high risk of PCF[36]. In our cohort, an overlay pectoralis major flap was only used in nine patients; as such, no conclusions could be drawn of its protective effect.

There are some limitations of our study to discuss. The cut-off value that we used to define low SMM in patients is not a sex-specific cut-off value. We do believe that a sex-specific cut-off value would be superior to the cut-off value currently used. However, particularly in female patients, we currently do not have enough data to reliably formulate sex-specific cut-offs for patients with HNC. We also evaluated using other published sex-specific and BMI-specific cut-offs for low SMM, which have been formulated in large cohorts of patients with different types of cancer[12,37]. Using these cut-offs, approximately 80% of patients are classified as having low SMM. Thus, these cut-offs seem to lose their clinical discriminative power in patients with HNC.

We found some discrepancies between the results of the recent Dutch Head and Neck Society Audit for risk factors of PCF after TL, and our current research[7]. For instance, previous chemoradiotherapy was a risk factors for PCF occurrence after TL in the Dutch Head and Neck Society Audit, and it was not a significant predictor for PCF in our cohort. This may be explained by the fact that relatively few patients in our cohort had chemoradiotherapy before TL (9.8% in our cohort compared to 15.6% in the Dutch Head and Neck Society cohort). As we did find a slightly higher albeit nonsignificant risk of PCF in patients who had chemoradiotherapy prior to TL, we believe that our analysis was underpowered for this risk factor.

Due to the retrospective nature of the research, all relevant research parameters for body composition or nutritional status may not have been documented or measured during normal clinical practice. In this study, this was particularly true for the plasma albumin level, which was often not measured in our cohort of patients undergoing TL. Also, the ASA classification for physical status was used as a surrogate marker for representing comorbidity. Unfortunately, more specific comorbidity scales could not be determined in this retrospective study because of missing information, particularly in the first 3 years of the study period. Muscle function was not assessed in this study, as muscle function is not tested during routine clinical practice in our institution. Possibly, a measurement of muscle mass and muscle function and/or physical condition (following the geriatric definition of sarcopenia[10]) may provide a more accurate risk profile of muscular status in patients undergoing TL than CT or MRI measured muscle mass alone.

Concerning the imaging techniques used to assess SMM, we decided to include both CT scans and MRI scans of the head and neck area to assess SMM, in order to maximize the number of patients that could be included. Whenever available, we used CT imaging instead of MRI because most research on SMM in patients with cancer is performed using CT imaging. However, the CT measurement method for SMM was formulated on MRI-based research[12,13]. Theoretically, there is no difference in SMM between CT imaging and MRI, as both methods are very accurate for SMM assessment. Therefore, we believe it is acceptable to use MRI for SMM measurement when CT imaging is not available. Also, a measurement of SM density, which is the mean HU value of the SM area, was not included in this analysis. A recent study showed that SM area does not differ significantly between CT with and without contrast, but SM density does differ significantly[38]. As we used both CT with and without contrast for measurement of SMM, we decided not to include SM density in this analysis.

CONCLUSIONS

In this study, we found that preoperative low SMM is statistically associated with more frequent PCF, prolonged hospital stay and reduced OS in patients undergoing TL for any indication. A measurement of SMM at the level of C3 allows for routine SMM assessment in diagnostic imaging, without the need for additional abdominal imaging. Our results advocate a preoperative assessment of SMM in patients under- going TL to identify high risk patients. Possibly, intensive prehabilitation strategies aimed at increasing SMM may reduce these negative outcomes, or wider use of flap reconstruction in patients with low SMM may prevent complications from occurring. Prospective research is needed to evaluate this.

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8

Pre-operative tracheostomy does not impact on stomal recurrence and overall survival in patients undergoing primary laryngectomy

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ABSTRACT

Pre-operative tracheostomy (POT) to secure a critical airway up to several weeks before definitive laryngectomy in patients with laryngeal cancer has been proposed as a risk factor for poor oncologic outcome. Few modern papers, however, examine this question. The aim of this study is therefore to determine whether POT affects oncologic outcome with an emphasis on stomal/peristomal recurrence. This is a retrospective case note review of 60 consecutive patients undergoing curative primary total laryngectomy (TL) for advanced laryngeal squamous cell carcinoma (SCC). Demographic, staging, treatment and outcome data were collected. 27/60 (45 %) patients had POT and 33/60 did not. No patient underwent laser debulking. Median age was 62 years (39–90 years) and median follow-up of survivors was 31 months. 5-year overall survival (OS), disease-specific survival (DSS) and local recurrence-free survival (LRFS) of patients undergoing POT versus no POT was 28 versus 39 % ($p = 0.947$), 55% versus 46 % ($p = 0.201$) and 96 versus 88 % ($p = 0.324$) respectively. No statistically significant difference in OS, DSS and LRFS was found between patients undergoing POT and those not. Despite the relatively small case series, this evidence should reassure surgeons without the ability to perform trans-oral debulking that they should not hesitate to perform tracheostomy on a patient with airway obstruction due to laryngeal cancer. Appropriate definitive treatment meant that POT was not a risk factor for poor oncological outcome in our series.

INTRODUCTION

Even in the present day, the initial presentation of a patient with advanced laryngeal cancer can be imminent airway obstruction. Three options exist to relieve this problem: trans-oral debulking (TOL) often with a laser, tracheostomy and emergency laryngectomy. The latter technique has largely been abandoned[1] and there has been a move away from pre-operative tracheostomy (POT) towards TOL in recent years. This move has been driven by studies which showed that POT was associated with a higher risk of stomal/peristomal recurrence[2-5], and that TOL could reliably secure the airway[6]. However, on occasion, POT is the easiest way of securing a critical airway. Indeed, TOL can be limited in its application as it requires specialist equipment and experience, in both surgical and anaesthetic fields. TOL also has the potential disadvantage of post-operative oedema[7] and rapid tumour re-growth necessitating repeat debulking. Many studies investigating the oncological risk of POT are now quite old. Furthermore, the treatment paradigms and modalities for laryngeal cancer have changed significantly in the last 20 years and it is not clear whether the previous studies on POT are still applicable.

Our unit regularly receives patients who have presented with airway compromise to surrounding smaller hospitals where they have undergone emergency tracheostomy before being transferred to us for definitive management. Indeed, our unit still prefers POT to TOL and the aim of this study was therefore to analyse the impact of POT on oncological outcome in a contemporary patient cohort undergoing primary TL.

MATERIALS AND METHODS

After local ethics and audit committee approval, a retrospective case note review was performed of 60 consecutive patients who underwent primary TL for locally advanced laryngeal squamous cell carcinoma (SCC) performed with curative intent between 2003 and 2010. Patients who underwent primary chemoradiotherapy, partial laryngectomy or those treated palliatively from the outset were therefore excluded.

Patients' demographic, staging, pre-operative imaging, treatment and outcome data were collected using case notes, surgeons' logbooks and electronic patient records (EPR). Patient factors analysed included age at procedure and gender which were retrieved from the hospital electronic database. Primary site, cTNM classification, type of procedure, extent of neck dissection (ND) and pre-operative tracheostomy (POT) were retrieved from operative records and radiological imaging reports. Histological features such as degree of differentiation, the presence of extra-capsular spread, sarcolemmal/perineural/perivascular invasion, the presence of a cohesive front, thyroid gland involvement and adequacy of the pathological margin of excision were collected from surgical histopathological results.

All patients underwent pre-operative computerized tomography (CT) scanning of the neck and thorax, magnetic resonance (MR) scanning when indicated and had their treatment planned in our multidisciplinary head and neck tumour (MDT) board meeting. All patients were staged M0 and treated with curative intent. Both version 6 and 7 of the AJCC staging manual[8,9] were used as the study period straddled the change in 2009. At the time of POT, the approach outlined in **Table 1** was systematically adopted whenever possible.

TABLE 1: Modern approach to total laryngectomy

At the time of POT
Excision and histological analysis of the excised tracheal window and the thyroid isthmus and Delphian node at POT Placement of the tracheostomy between the 2nd and 4th tracheal rings Inspection of the lower margin of the trachea before tube placement
At the time of definitive TL
Minimal interval time between POT and TL Comprehensive wide field TL with lateral compartment neck dissections Excision of the tracheostomy tract at definitive surgery Critical appraisal of thyroid involvement, including evaluation of the invasion of the thyroid gland, ipsilateral hemithyroidectomy with isthmusectomy on the side of the tumour or total thyroidectomy when indicated Frozen section margin control especially of the lower tracheal margin Central compartment (level VI) neck dissection Post-operative management
Post-operative
Radiotherapy or chemo-radiation therapy

All patients underwent primary TL in our unit, including comprehensive central compartment (level VI) neck dissection[10] with lateral neck dissections as agreed by the MDT board meeting. All patients with POT had the tracheal window excised and sent for histological analysis. At the time of definitive surgery, frozen sections were used to confirm satisfactory margins with critical analysis of the lower tracheal margins following excision of the POT tract as part of an en bloc surgical specimen. All patients had critical evaluation and management of the thyroid gland. This included ipsilateral thyroid lobectomy with isthmus-ectomy on the side of the tumour or total thyroidectomy when pre-operative staging suggested thyroid involvement, an approach validated by earlier research[11]. The treatment plan included post-operative radiotherapy (PORT) for all patients and after 2008, patients with positive margins or extra-capsular spread were planned for post-operative chemoradiotherapy (CRT). For a variety of reasons, not all patients were able to complete adjuvant treatment.

Local recurrence (LR) was defined as recurrent squamous cell carcinoma (SCC), diagnosed within 5 years of initial treatment involving the immediate stomal and peri-stomal region. Regional recurrence (RR) was defined as recurrent SCC involving the cervical nodes level 1–5. Distant recurrence was diagnosed either clinically or on imaging studies including ultrasound guided fine needle aspiration, CT or positron emission tomography (PET) scanning. All recurrences were biopsy proven except in those patients in which it was felt that either co-morbid status or disease progression meant that invasive biopsies were not indicated. All cases were discussed within the MDT, and those patients not fit for biopsy were considered as recurrence by consensus based on clinical or imaging examination.

Evidence of patients' death was taken from hospital records and death certificates where available. All patients with active disease at last follow-up who died of unknown causes were considered as having died of disease.

Statistical analysis of overall survival (OS), disease- specific survival (DSS) and local recurrence-free survival (LRFS) were calculated using the Kaplan–Meier method. The log-rank test was used for univariate, and cox-regression model for multivariate analysis (SPSS, Chicago, Illinois, v19). Comparison of subgroups was performed using the Fishers exact test.

RESULTS

Sixty patients with median age of 62 years (39–90 years) were analysed. Forty-nine were male (82 %), 11 were female (18 %). The median follow-up was 16 months (range 1–91 months), with a median follow-up for survivors of 31 months (range 4–91 months). 27/60 (45 %) patients had POT. No patients had TOL. The majority of patients undergoing POT had awake fibreoptic intubation in line with anaesthetic guidelines[12].

TABLE 2: Description of patients and disease

Factor	Number of patients (%)
Ablative	
Total Laryngectomy	31 (52%)
Plus Pharyngectomy	29 (48%)
Location	
Subglottic	1 (2 %)
Glottic	4 (7%)
Supraglottic	22 (37%)
Transglottic	20 (33%)
Hypopharynx	12 (20%)
Incomplete records	1 (2%)
pT stage	
T3	15 (25%)
T4	44 (73%)
Incomplete records	1 (2%)
pN stage	
N0	18 (30%)
N1	10 (17%)
N2a	1 (2%)
N2b	13 (22%)
N2c	14 (23%)
N3	1 (2%)
Incomplete records	3 (5%)
Histological differentiation	
Well differentiated	3 (5%)
Moderately differentiated	25 (42%)
Poorly differentiated	29 (48%)
Incomplete records	3 (5%)
Extranodal spread in N+	(n=39)
Yes	27 (69%)
No	11 (28%)
Incomplete records	1(3%)
Tracheostomy	
POT	27 (45%)
No POT	33 (55 %)

Procedure, location of primary, pT and pN stage and histology are shown in **Table 2**. All patients underwent TL and 29 also had partial pharyngectomy (48 %). Forty-eight had laryngeal (80 %) and 12 hypopharyngeal primaries (20 %). All patients had comprehensive central neck dissection. Fifty-five patients underwent bilateral (92 %) lateral neck dissection and five patients had unilateral (8 %) neck dissection.

Two patients died within 30 days of surgery (peri- operative deaths) due to carotid blow out. Both had extensive disease peeled off the carotid during surgery and had involved margins. A further 34 patients died during follow-up, 24 of these from their disease (5 LR, 2 RR and 17 DR).

For the whole cohort of patients, 5-year overall survival (OS), disease-specific survival (DSS) and local recurrence- free survival (LRFS) were 36, 51, 92 % respectively (**Fig. 1**). As expected, the presence of nodal metastasis predicted worse disease-specific survival (pN0 5y DSS 74 vs pN+ 32 %, p =0.008). This was, however, most likely because N = stage is a predictor of distant metastasis. Indeed loco-regional control rates were excellent. No significant association was found between tumour site and risk of recurrence, though this was probably due to small numbers.

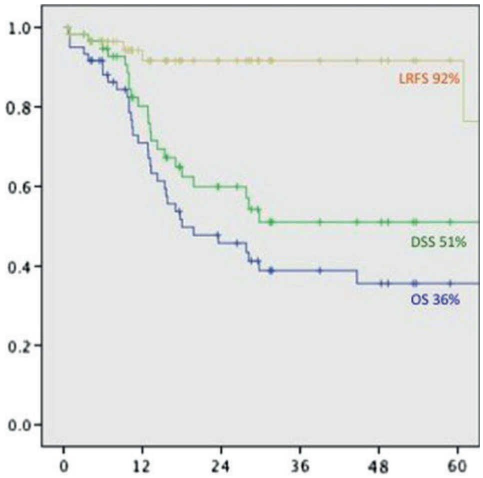

FIGURE 1: Kaplan–Meier survival for the whole cohort

POT versus no POT

1/27 (3.7 %) patients with POT had local recurrence during follow-up compared to 4/33 (12 %) patients without POT. 5-year overall survival (OS), disease-specific survival (DSS) and local recurrence-free survival (LRFS) of patients undergoing POT versus no POT was 28 versus 39 % (p = 0.947), 55 versus 46 % (p = 0.201) and 96 versus 88 % (p = 0.324), respectively. POT was therefore not statistically associated with poorer outcome in terms of OS, DSS or LRFS (Figs. 2, 3, 4).

Subgroup analysis/bias

Due to the non-randomised nature of our study, we analysed whether the POT and non-POT group were similar in terms of ages, co-morbidities and TNM classification. The groups were similar though the POT group had a higher rate of pT3 than pT4 disease (**Table 3**). This counter- intuitive result did not show any significant correlation with likelihood of POT (data not shown). Further subgroup analysis was performed by pT classification. Again, POT was not predictive of outcome in either subgroup when analysed separately. POT remained a non-significant prognostic factor in outcome analysis of the T-classification subgroups i.e. pT3 POT versus pT3 non-POT and pT4 POT versus pT4 non-POT.

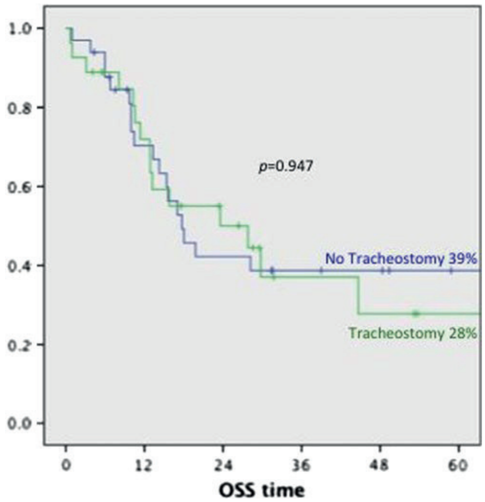

FIGURE 2: Overall survival stratified by POT

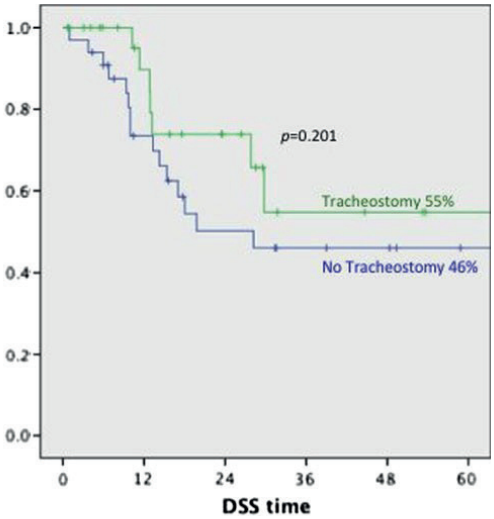

FIGURE 3: Disease-specific survival stratified by POT

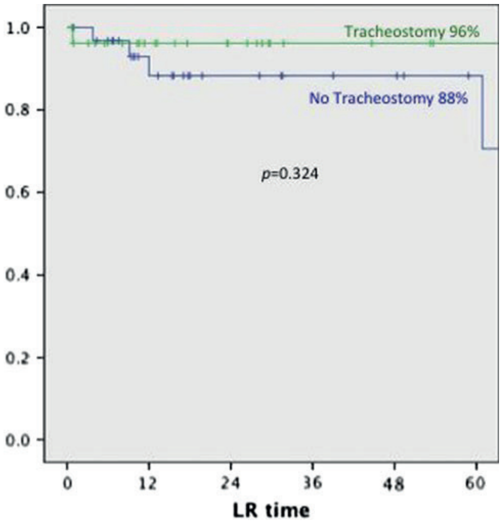

FIGURE 4: Local recurrence-free survival stratified by POT

TABLE 3: Comparison of POT and non-POT groups

	Number of patients undergoing POT N=27	Number of patients without POT N=33	P-value (Fischer's exact test)
Gender			
Male	23	24	0.53
Female	4	7	
Age (years)			
<60	10	16	0.80
>60	17	17	
pT stage			
T3	10	5	0.03
T4	17	27	
N0/N+			
N0	9	9	1.00
N+	17	22	
Stage			
Stage III	4	3	0.17
Stage IV	23	30	

We further reanalysed our data assuming the incomplete records were either "positive" or "negative". In no instance did this change our result that there was no statistically significant association between POT and outcome.

Overall, we feel the patients who underwent POT were globally more compromised by their disease and co-morbidities and therefore would have expected these patients to perform worse than patients who did not undergo POT. The fact that we did not find a significant difference is therefore all the more striking.

DISCUSSION

Laryngeal cancer is the only cancer for which survival rates have worsened over the last 20 years[13,14]. The reasons for this have been contested[14-16] and potentially include worsening co-morbidities and the increased use of chemoradiation. Surgically speaking we can only focus on local and regional control and this paper addresses an important question regarding the risk of stomal/local recurrence.

Stomal recurrence following primary total laryngectomy (TL) for squamous cell carcinoma occurs in 2–15 %[17,18]and has been defined as "a diffuse infiltration of neoplastic tissue at the junction of the trachea and skin"[17]. It is difficult to distinguish from spread from local level VI lymph nodes and the thyroid gland. Indeed, in this paper we have not attempted to distinguish between these particular types and classify all stomal/peri-stomal recurrences as LR. Patients presenting with local recurrence have a dismal outcome with approximately 50 % presenting in the first year after completion of treatment[3,4] and 80 % dying in the first 2 years after completion of treatment[19].

Pre-operative tracheostomy (POT) performed up to several weeks before definitive laryngectomy is one of several risk factors identified originally in the 1960s as being associated with increased risk of LR (**Table 4**). Since that time several papers have shown a poor outcome with POT[3,5,20] and others have found no relation[21-26]. Intuitively it seems plausible that POT might disrupt the primary tumour, seed the tract and therefore lead to worse local control (**Fig. 5**). Some authors have argued to place the tracheostomy low[27] in order to avoid any subglottic extension of the tumour, whereas others have argued for a high tracheostomy[17] which can then be more easily completely excised at the time of definitive laryngectomy. Theoretically also any time delay between the POT and the definitive TL would allow the seeded cancer to more effectively establish itself in the fresh tracheostomy wound bed.

TABLE 4: Risk factors thought to be associated with poor outcome following total laryngectomy [4]

Size of tumour
Location of tumour (e.g. subglottic)
Lymph node involvement (e.g. paratracheal)
Incomplete removal of tumour
Inoculation of tumour cells
Pre-operative tracheostomy
Endotracheal intubation

Evidence for the intuitive risk of POT comes from diverse sources. For example, there are case reports describing stomal recurrence in the setting of non-laryngeal/hypopharyngeal primaries. This raises the suspicion that cancer cells are able to inoculate the fresh tracheostomy wound[28,29]. Stell[4] reported one case of a patient who had a maxillectomy performed with a covering tracheostomy who developed recurrence around the tracheostomy site 2 years later. McGurk[30] also reports three cases of patients who had a prophylactic tracheostomy for intra-oral resections that developed recurrence at the tracheostomy site. Clayman et al.[31] reported two cases of stomal recurrence with oropharyngeal primaries. There are even case reports of gastric metastasis from oral squamous cell carcinoma following PEG insertion[32]. Supporting these case reports are laboratory studies which have investigated vital looking tumour cells recovered from tracheal swabs or endo-tracheal tubes[33]. Though these could not be grown on intact mucosa, suspicions remain about them seeding a fresh tracheostomy wound.

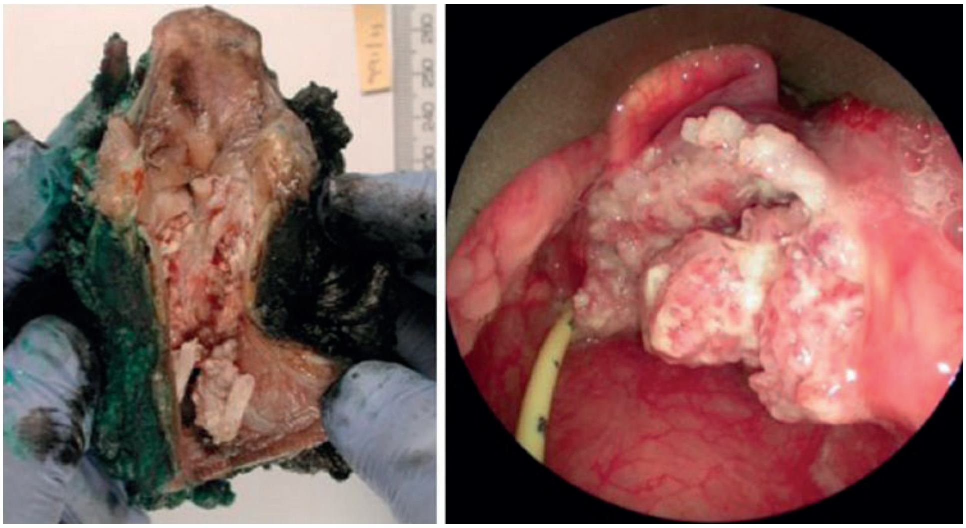

FIGURE 5: Involvement of POT site in cancer

Overall, however, we do not have a particularly good understanding of how LR occurs[19]. The terminology used in the literature is not necessarily consistent making meta-analyses difficult. Some authors use the word "recurrence" when actually describing residual disease following incomplete excision or when potentially positive central compartment lymph nodes have not been addressed as part of the definitive treatment. Other papers use the term stomal recurrence and it is not clear if this would include direct spread from level VI or the thyroid. Others do not differentiate between primary and salvage laryngectomy.

Furthermore, much of the literature quoted is quite old. Nowadays, with the increasing use of chemoradiotherapy, primary laryngectomy is often reserved for patients with the most advanced local disease meaning that it is not necessarily possible to compare old data with modern series. The exact description of TL is also missing from many papers (for example whether the central compartment or thyroid was removed) again making comparisons difficult. We therefore felt that a consistent modern surgical approach in a modern patient cohort was needed to look at whether POT affects outcome following primary TL.

This is an important question, as even in the twenty-first century, many patients with advanced laryngeal cancer present with such severe airway compromise as to require emergency airway management. Though several protocols exist as to how to judge how severely compromised an airway is[12,34], often objective measures of respiratory rate, fatigue, pulse oximetry etc. interplay with subjective measures of stridor and feelings of panic from both the patient and surgeon.

Securing a safe airway allows for appropriate investigations and staging as well as allowing fully informed consent before definitive treatment. Although laser surgery has theoretical oncological advantages, as it prevents disruption to tissue planes and minimises the chance of tumour seeding, it intuitively is not quite as safe as a POT in terms of securing the airway as there remains the potential risk of post-operative oedema[7], aspiration, and tumour re-growth. Furthermore, both the surgical and anaesthetic skills and instruments required to perform such procedures are often not available out of office hours or in smaller hospitals where such patients may present. Even if patients can be temporarily stabilised with inhalational therapies, some more advanced lesions are just not amenable to TOL. In such patients, POT may be the only safe option for the airway, irrespective of oncological concerns. It must be stated, however, that our study is not a comparison of TOL versus POT, but rather a reassurance to surgeons who can be faced with a critical airway and no access to more advanced airway techniques. Our contention is that with sufficiently aggressive definitive management as described in **Table 1**, carried out within a reasonably short timeframe from the POT, that any increased risk associated with POT can be eliminated.

We would also like to highlight the multi-modal nature of our treatment which uses adjuvant post-operative irradiation of the surgical bed and bilateral neck nodes to reduce the risk of loco-regional recurrence[35]. To further improve locoregional recurrence rates[36,37], post-operative chemoradiation[38] with high dose cisplatin and 60–66 Gy in 30–33 daily fractions has become the standard of care in our unit since 2008 for patients with positive margins and/or extracapsular spread[39], the two most unfavourable parameters.

In conclusion, management of the compromised airway in advanced laryngeal carcinoma remains a challenge. Whilst it is important that teams dealing with head and neck cancers are familiar with the use of TOL and endo- laryngeal surgical techniques, our results are in keeping with more recent studies, which suggest that POT is not necessarily related to poor oncological outcome. It is a technique that can be easily taught, requires standard equipment available in all operating theatres and is suited to almost all advanced laryngeal lesions. Despite limitations imposed by the cohort size and potential lack of power, this paper provides evidence that POT is not a risk factor for poor outcome.

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9

Does airway intervention before primary non-surgical therapy for T3/T4 laryngeal squamous cell carcinoma impact on oncological or functional outcomes

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SUMMARY

Questions under study: Even today, some patients with laryngeal cancer present with airway obstruction necessitating an intervention in the form of either a tracheostomy or transoral laser debulking (TOL). Controversy exists as to whether such an intervention is a risk factor for poor oncological or functional outcome in patients who then undergo primary (chemo)radiotherapy.

Methods: Retrospective chart review of all patients undergoing primary curative nonsurgical treatment for T3/T4 laryngeal squamous cell cancer at the University Hospital Zurich between 1981 and 2011.

Results: A total of 29/114 patients had an airway intervention before initiation of (chemo)radiotherapy (21/29 tracheostomies, 8/29 TOL). Kaplan-Meier analysis showed no statistical difference in oncological outcomes between the groups with and without intervention (5 year overall survival: 52% vs 70%, disease specific survival: 73% vs 79%, recurrence free survival: 53% vs 63%). In functional terms, we report an overall functional larynx rate of 60%.

Conclusions: Airway intervention was not found to be a risk factor for poor oncological or functional outcome in this patient group.

INTRODUCTION

In the western world, laryngeal cancer was until recently the most common non-cutaneous cancer of the head and neck[1]. It is now the second most common after the recent precipitous increase in oropharyngeal cancers.

Traditionally, treatment for advanced laryngeal cancer was a total laryngectomy. However, after the landmark Department of Veterans Affairs study[2] in 1991 and subsequent studies[3], many centres worldwide now treat all but the most advanced tumours with primary (chemo)radiotherapy, saving surgical treatment in the form of total laryngectomy for residual or recurrent disease or only the most bulky primary disease. This “organ preserving” approach is believed to achieve similar oncological outcomes to a primary surgical approach, with the benefit of retained laryngeal function for breathing, speaking and swallowing. Selection of patients for either primary (chemo) radiotherapy or primary total laryngectomy is normally made in a tumour board setting and depends on local protocols, expertise and, of course, patient choice. One factor which is weighed in the balance is whether the patient has had to have an airway intervention prior to definitive treatment. Even with good access to medical care, some patients’ first presentation of their laryngeal cancer will be with acute airway obstruction, necessitating an emergency/ urgent airway intervention. This airway intervention is life-saving in the short term and often performed outside of head and neck cancer centres by noncancer specialists. Patients are then referred on for definitive treatment of their laryngeal cancer. The Tumour Board must then decide if the airway intervention has disrupted/seeded the primary cancer and decide how this would influence the decision as the primary treatment modality.

For patients who undergo primary (chemo)radiotherapy, there also exists the possibility of requiring airway intervention either during or after their (chemo)radiotherapy. For example, tumour oedema from (chemo)radiotherapy may compromise the airway during therapy. There are also a few patients who, despite a satisfactory oncological out- come, have a non-functioning larynx and may require permanent tracheostomy or even laryngectomy potentially months or even years after the (chemo)radiation was completed.

The aim of this study was to retrospectively analyse a cohort of patients undergoing primary nonsurgical treatment for laryngeal cancer and see how many patients required an airway intervention, when it was performed, and what form this took (tracheostomy or transoral laser debulking [TOL]). Special emphasis is placed on patients who underwent airway intervention prior to definitive treatment and results are expressed in terms of both oncological and functional outcomes.

MATERIALS AND METHODS

A retrospective case note review was performed of all patients who underwent primary curative non-surgical treatment for T3/T4 laryngeal squamous cell cancer at the University Hospital Zurich between 1981 and 2011. Patients with less advanced disease, treated primarily with an- other modality or treated with palliative intent from the beginning, were excluded.

Patients' demographic, staging, treatment and outcome data were collected with use of electronic patient records. Staging was based on both a clinical and a radiological ex- amination of the patient and both versions 6 and 7 of the American Joint Committee on Cancer (AJCC) manual[4] were used as the study period straddled the change in 2009. Airway interventions in the form of tracheostomy or TOL were recorded, as was the date of eventual reversal of the tracheostomy if this was done. Patients who suffered from residual or recurrent disease were also recorded, along with their management.

All patients were discussed in our tumour board meeting and underwent primary nonsurgical treatment. Over such a long time-period one can imagine that the tumour board's attitude to surgery or nonsurgical treatment changed. Anecdotally, it is probably fair to say that the more recent patients were more likely to have (chemo)radiotherapy than surgery, even those with advanced disease. Ultimately, the patients also have the final decision as to which treatment they will choose. Also of note, for patients with T4 disease and cartilage involvement, surgical treatment was recommended. The radiotherapy protocols evolved during the study period, notably with the advent of intensity modulated radiation therapy (IMRT) in March 2002 (consecutively since June 2003). All patients after this date were treated with IMRT, all those before underwent traditional multiplanar external beam radiotherapy. Details of the exact regimen have been published elsewhere[5].

Patients undergoing tracheostomy had this performed in the traditional open manner in all cases. No percutaneous tracheostomies were performed. Transoral debulking was performed using a CO_2 laser. The indication for a tracheostomy was the same regardless of whether it was pre-, during or post- definitive treatment, i.e., a compromised airway with either inadequate ventilation or recurrent aspiration.

In terms of oncological outcomes, local recurrence (LR) was defined as either residual or recurrent squamous cell cancer (SCC) of the larynx or level 6. Regional recurrence

(RR) was defined as either residual or new disease in the lateral neck, levels 1–5. Distant recurrence (DR) was diagnosed on imaging studies unless with possibility for cytological/histological confirmation existed.

Statistical analysis of overall survival (OS), disease specific survival (DSS), local recurrence-free survival (LRFS) and regional recurrence-free survival (RRFS) was calculated using the Kaplan-Meier method. The log-rank test was used for univariate analysis (SPSS, Chicago, Illinois,v21) and Pearson's chi-squared or Fisher's exact test for comparison of subgroups, as appropriate.

Functional outcomes are expressed as descriptive statistics of how many patients were able to be weaned off their tracheostomies, how many patients had permanent tracheostomies and how many progressed to total laryngectomy.

RESULTS

A total of 114 patients (106 men, 8 women) were included in this study. Median age at diagnosis was 62 years. A more detailed description of patients and extent of disease can be found in **table 1**, which also compares the non-airway intervention group with the airway intervention group.

Oncological outcomes and timing of airway intervention

For the cohort as a whole, 5 year OS, DSS, LRFS were 65%, 78% and 56% respectively (**fig. 1**). Only 4/114 patients had evidence of disease less than 4 months after the end of primary therapy, implying that they had residual tumours that had been incompletely treated (persistent dis- ease). A further 43/114 patients had recurrence of disease >6 months after end of therapy. Forty of 47 recurrences occurred within the first 2 years after initial therapy. Recurrences were treated with total laryngectomy (33/47 patients), neck dissection (1/47 patient) or palliative therapies (13/47).

Twenty-nine of the 114 patients had an airway intervention before commencement of radiotherapy (21/29 tracheostomies, 8/29 laser debulking [TOL]). One of these patients initially had an unsuccessful TOL which needed to be con- verted to a tracheostomy. During treatment, a further 3/114 patients had tracheostomy performed. After completion of treatment 19 patients underwent tracheostomy, and 5 patients had TOL.

TABLE 1: Comparison of patients and disease characteristics between intervention and non-intervention groups

	No airway intervention	Pretherapy airway intervention	Chi-squared/ Fisher's exact	Total
Gender				
Female	6	2	1	8
Male	79	27		106
Age				
<60	37	10	0.389	47
>60	47	20		67
cT-stage				
T3	58	19	0.678	77
T4	25	10		35
T4b	1	1		2
cN-stage				
N0	54	22	0.358	76
N1	9	4		13
N2a	2	0		2
N2b	4	3		7
N2c	12	1		13
N3	3	0		3
Stage				
III	47	19	0.772	66
IVa	33	10		43
IVb	4	1		5
Site				
Glottic	28	10	0.649	38
Supraglottic	41	17		58
Subglottic	2	1		3
Transglottic	13	2		15

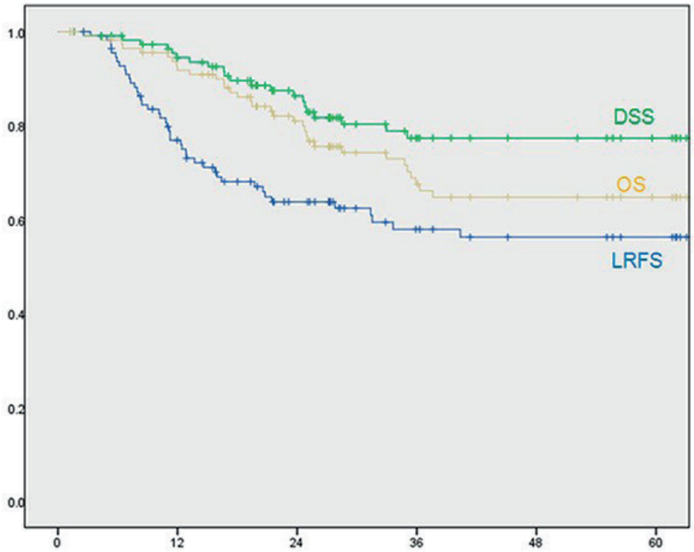

FIGURE 1: Five-year (60-month) comparison of overall survival (OS), disease specific survival (DSS) and local recurrence-free survival (LRFS). Note that the LRFS lies under the other two curves, indicating that despite local recurrence, patients can often be successfully salvaged.

No intervention vs pre-definitive therapy airway intervention

To ensure that our comparison between the intervention and non-intervention groups was unbiased, we analysed the demographics and disease burden of the two groups to en- sure comparability. Where 2x2 tables could be constructed, a two-tailed Fischer's exact test was used, otherwise Pear- son's chi-squared test (**table 1**). This showed no significant differences in terms of age, gender or disease burden between the two groups.

Kaplan Meier survival analysis was then performed to compare the oncological outcomes in the two groups. No statistically significant differences in 5 year OS (70% vs 52%, p = 0.176), DSS (79% vs 73%, p = 0.768) and LRFS (58% vs 50%, p = 0.661) between no airway intervention vs pre-therapy airway intervention was found (**fig. 2**).

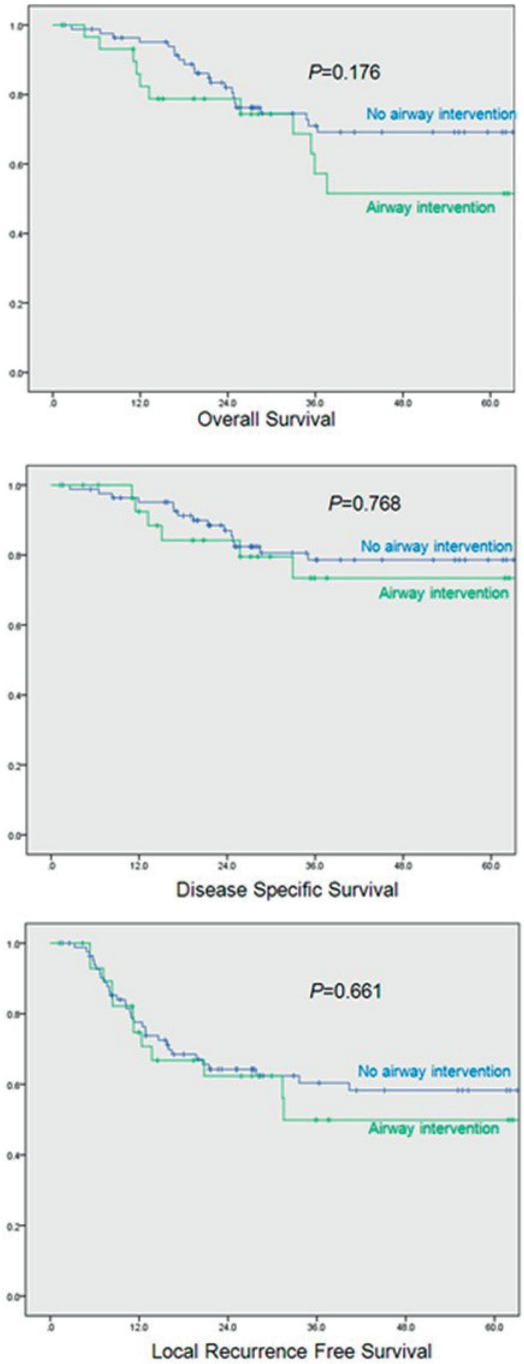

FIGURE 2: Pretreatment airway intervention vs no airway intervention: 5-year survival.

Pre-treatment tracheostomy vs no tracheostomy / TOL

In the pre-definitive therapy setting, it might be argued that there are fundamental differences between endoscopic approaches to securing the airway such as TOL and the intuitively more "risky" tracheostomy. The latter might cut directly into the tumour, seeding the tract and also runs the risk of disrupting lymphatics. Furthermore, the AJCC staging does not necessarily capture the subtleties of tumour burden and perhaps tracheostomies are still performed on the more severely affected patients, despite our negative chi-squared and Fischer's tests outlined above. We there- fore performed an analysis of the 21 patients undergoing pretherapy tracheostomy against the remaining 93 patients (i.e. those with TOL or no intervention). Once again, no statistically difference in disease burden or demographics was found between the two groups. Five-year LRFS was 51.3% vs 54.5% for the no-tracheostomy vs tracheostomy groups respectively (p = 0.633).

Functional outcomes

In total, 43/114 of patients had a tracheostomy at some stage of their treatment (21 pre-treatment, 3 during treatment and 19 after). Thirteen of the 43 patients were able to be successfully weaned from their tracheostomies, 19/43 ultimately had a laryngectomy and 11/43 can be deemed to have a permanent tracheostomy despite an anatomical in- tact larynx (**table 2**).

TABLE 2: Overview Any Recurrence free survival and functional larynx rate

Airway intervention	Tracheostomy	Debulking	Recurrence-free survival (%)	Functional larynx rate (%)
None (n=58, 51%)	0	0	63	61
Airway Intervention (n=56, 49%)	43	13		
Pretherapy (n=29, 25%)	21	8	53	54
During therapy (n=3, 3%)	3	0	26	26
Post-therapy (n=24, 21%)	19	5	26	26
Total (n = 114)			61	60

Despite the initially "organ-preserving" approach, 46/114 (40%) patients ultimately lost their laryngeal function, resulting in 35 laryngectomies and 11 permanent tracheostomies. Whilst 33/35 laryngectomies were performed for onco- logical reasons, 2/35 were performed for purely functional reasons without any sign of cancer. For the cohort as a whole we therefore have a "functional larynx" rate of 68/ 114 (60%). Of the patients who needed pretherapy tracheostomy, this "functional larynx" rate was 12/21 (57%) and for patients undergoing no pretherapy intervention of 56/93 (60%).

DISCUSSION

Laryngeal cancer is the second most common non-cutaneous cancer of the head and neck. Cure rates are excellent for early disease, but problematic in more advanced disease. Indeed, laryngeal cancer is the only cancer for which survival outcomes have worsened in the last 20 years[1]. Many reasons have been put forward to explain this, including the increasing use of primary nonsurgical therapy[6].

Organ-preserving treatment of laryngeal cancer aims to achieve the same oncological outcomes as surgical approaches with the benefit of maintaining laryngeal function (speech and swallow). Laser ablation for T1 tumours or partial laryngectomies for more advanced tumours are surgical possibilities, but (chemo)radiotherapy is currently the most widespread treatment modality, especially since the advent of IMRT. Advances continue apace with dose painting being the latest innovation leading many units and patients to prefer a primarily nonsurgical approach to laryngeal cancer in all but the most advanced cases. In a few centres worldwide, organ-preserving surgery in the form of transoral robotic surgery (TORS) is once again being preferred to (chemo) radiotherapy.

Before deciding which treatment to recommend a patient, the tumour board must carefully decide the oncological risks and the functional risks. These questions must be answered not only before the start of treatment but throughout the patient's management. For example, one key question is how to identify those patients who are non-responders to (chemo)radiotherapy as early as possible. Our unit, in common with many others, use a positron emission tomography / computed tomography (PET-CT) scan at 3 months post-treatment, but ideally, some form of test *during* or even *before* the treatment would be far better (e.g. diffusion-magnetic resonance imaging [MRI], PET- CT).

One factor which might push tumour boards towards a surgical management plan is an antecedent airway intervention. It seems plausible that patients who have presented with airway obstruction and needed some form of surgical intervention might have sub-optimal outcomes with (chemo)radiotherapy and might therefore be more appropriately treated with a total laryngectomy with adjuvant radiotherapy. A recent publication showed that an antecedent airway intervention followed by primary total laryngectomy with adjuvant radiotherapy was not associated with adverse outcomes[7]. So if antecedent airway intervention was associated with increased risk in primary (chemo)radiotherapy patients then the message would be clear: patients with antecedent airway interventions should be counselled towards a primary surgical treatment.

Overall the literature in this area is confusing. Many articles have discussed the possibility of tumour inoculation[8] or seeding[9] during intubation[10], tracheostomy[11] or other operative manipulation of a laryngeal tumour. Some articles find that tracheostomy is a risk factor[12-14] whilst others find no increased risk[7,15,16].

The picture is further confused as studies often suffer from heterogeneous patient groups (for example mixing primary and salvage laryngectomies together) or from small sample size (for example fewer than 100 patients).

Furthermore, the key question, namely, if the patient has an antecedent airway intervention, what should the definitive management plan be, is not addressed. The airway intervention is often a "given" and may have been performed in non-head and neck units outside of normal hours as a life- saving procedure. To simply tell the patients that they are possibly at increased oncological risk does not seem particularly helpful.

We purposively picked a highly homogeneous patient group in order to answer a very specific question. Do patients with antecedent airway intervention undergoing primary nonsurgical treatment have worse outcomes than those without the antecedent airway intervention? Our data would suggest that there is no increased risk, though we accept the limitations of the retrospective nature of our data and small sample size. It is however in keeping with the largest series looking at this problem from Zhao et al.[15] (548 patients) and Petrovic et al. [16] (402 patients), who could also find no increased risk.

During treatment, some patients whose airway was initially deemed safe, suffer radiation-induced swelling which further reduces the diameter of the already compromised airway and necessitates airway intervention. This was the situation for three of our patients and, unfortunately, our data show that such circumstances are fore-bears of a dismal outcome.

The last group of patients who need tracheostomy after completing radiotherapy often require it because of an aspiration risk as much as for ventilation. These patients can sometimes be helped with intensive swallow physiotherapy and develop tricks to minimise their aspiration risk. Some however will find their voice next to useless and their aspiration risk so high as to justify a total laryngectomy for functional reasons. This was the case for 2/114 patients.

Having answered our primary oncological question, we have also looked at functional results associated with antecedent airway intervention. Overall, we report a functional larynx rate of 60% for the cohort as a whole is fairly similar to published figures (which often include less advanced cancers)[2,3].

CONCLUSIONS

Our data would suggest that pre(chemo)radiotherapy air- way intervention, whether in the form of tracheostomy or TOL does not negatively impact on oncological outcome. This adds to the considerable debate on this topic as many surgeons instinctively feel that it must increase risk.

In terms of functional outcomes, we report that of 114 patients initially undergoing primary nonsurgical treatment,33 needed laryngectomy for oncological control, 2 for frozen larynx and a further 11 will remain tracheostomy de- pendent. This latter group may have a preserved larynx, but it is unfortunately, non-functional. This gives a "functional" larynx rate of 68/114 (60%) which is similar to other published figures[2,3].

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Should elective neck dissection be routinely performed in patients undergoing salvage total laryngectomy?

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ABSTRACT

Background: The prevalence of occult neck metastasis in patients undergoing salvage total laryngectomy remains unclear, and there is controversy regarding whether elective neck dissection should routinely be performed.

Method: A retrospective case note review of 32 consecutive patients undergoing salvage total laryngectomy in a tertiary centre was performed, in order to correlate pre-operative radiological staging with histopathological staging.

Results: The median patient age was 61 years (range, 43–84 years). With regard to lymph node metastasis, 28 patients were pre-operatively clinically staged (following primary radiotherapy or chemoradiotherapy) as node-negative, 1 patient was staged as N1, two patients as N2c and one patient as N3. Fifty-two elective and seven therapeutic neck dissections were performed. Pathological analysis up-staged two patients from clinically node-negative (following primary radiotherapy or chemoradiotherapy) to pathologically node-positive (post- surgery). No clinically node-positive patients were down-staged. More than half of the patients suffered a post-operative fistula.

Conclusion: Pre-operative neck staging had a negative predictive value of 96 per cent. Given the increased complications associated with neck dissection in the salvage setting, consideration should be given to conservative management of the neck in clinically node-negative patients (staged following primary radiotherapy or chemoradiotherapy).

INTRODUCTION

Radiotherapy (RT) and chemoradiotherapy have become standard treatments for patients with all but the most advanced squamous cell carcinoma (SCC) of the larynx. Laser excision is an option for early cancer. Primary total laryngectomy is often performed for advanced bulky disease, though some patients with quite advanced cancer are still also suitable for chemo- radiotherapy[1]. High local control has been reported in randomised controlled trials of chemoradiotherapy. Nevertheless, around 10 per cent of patients undergo salvage total laryngectomy because of persistent or recurrent disease.

Elective neck dissection performed at the time of primary total laryngectomy is recommended for supraglottic and glottic grade 4 tumours (National Comprehensive Cancer Network Guidelines). In this way, occult neck disease, which can be missed in up to 30 per cent of patients on pre-operative staging, is treated.

However, the position is less clear in the salvage setting. Salvage neck surgery is challenging, and affected patients are at a high risk of post-operative complications and prolonged hospital stay[2,3]. If such patients could be reliably pre-operatively staged, those considered free of neck disease could potentially be managed without elective neck dissections. This would reduce post-operative complications such as pharyngocutaneous fistula.

The frequency of occult nodal disease in recurrent laryngeal cancer has been reported to range from 3 to 17 per cent, with a higher trend of up to 28 per cent in supraglottic recurrence[2,4,5]. It is unclear why such variation exists in the literature. Furthermore, techno- logical radiological developments continue apace, meaning that historical datasets may not be applicable to current practice.

This study aimed to assess the negative predictive value of contemporary pre-operative investigation in patients undergoing salvage laryngectomy. We also briefly describe our complication rates though these are more thoroughly described in a previous publication from our unit[6].

MATERIALS AND METHODS

After local ethics committee approval, a retrospective analysis was performed of 32 consecutive patients who underwent salvage total laryngectomy following primary RT or chemoradiotherapy for laryngeal SCC between 2003 and 2010.

All patients underwent pre-operative computed tomography (CT) scanning of the neck and thorax, magnetic resonance imaging (MRI), and fine needle aspiration cytology (FNAC) when indicated. Patients' treatment was planned in our multidisciplinary head and neck tumour board meetings. Only patients with no evidence of distant metastasis and those treated with curative intent were included in this analysis.

In line with our multidisciplinary team's normal approach, salvage laryngectomy patients with evidence of neck disease were managed with bilateral modified radical neck dissections. Patients without evidence of neck disease underwent bilateral selective neck dissection of levels 2–4.

Following surgery, routine pathological analysis of neck specimens was performed. These results were then compared with the tumour board pre-operative documentation. As a secondary exercise, we collected survival data from follow-up consultations to investigate survival outcomes associated with pathological lymph node metastasis stage using the Kaplan–Meier method.

RESULTS AND ANALYSIS

Patients

A total of 32 patients underwent surgery between October 2003 and July 2010. Twenty-nine patients were male, three were female. The median patient age at the time of the procedure was 61 years (range, 43–84 years). All patients underwent total laryngectomy, and 9 of the 32 patients (28 per cent) also under- went partial pharyngectomy. Twenty-nine patients (91 per cent) underwent bilateral neck dissections, one (3 per cent) underwent a unilateral neck dissection and two (6 per cent) had no neck dissection.

Oncological outcomes

With a median follow up of 18 months (range, 1–106 months) for the whole cohort, 5-year overall survival was 37 per cent, disease-specific survival was 47.4 per cent, loco-regional recurrence free survival was 71.7 per cent and distant recurrence free survival was 95.5 per cent (**Figure 1**).

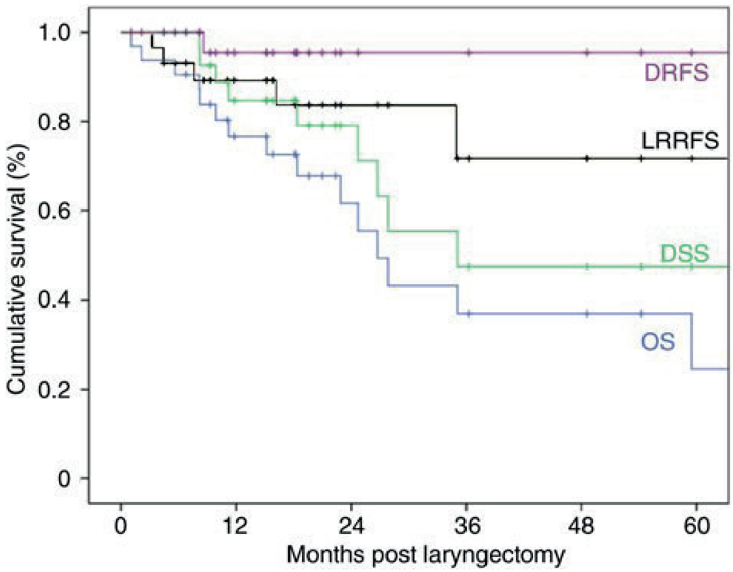

FIGURE 1: Kaplan–Meier survival curves following salvage laryngectomy. DRFS = distant recurrence free survival; LRRFS = locoregional recurrence free survival; DSS = disease-specific survival; OS = overall survival

The pathological lymph node metastasis (N) stage is known to be an important predictor of outcome in head and neck cancer. However, possibly because of our small cohort, overall survival of pathologically staged N+ patients was not statistically significantly worse than pathologically staged N_0 patients ($p > 0.05$) (**Figure 2**).

Negative predictive value

Twenty-eight patients were pre-operatively clinically staged (following primary RT or chemoradiotherapy) as N_0 and four were staged as N+ (one patient was staged as N_1, two were N_{2c} and one was N_3). In the 28 N_0 patients, 52 elective dissections were performed, and in the 4 N+ patients, 7 therapeutic neck dissections were performed, based on pre-operative investigations. A total of 1277 lymph nodes were retrieved from the 59 neck dissections. Of the 1277 nodes, 17 (1.3 per cent) were positive in 6 patients. Only two patients clinically staged as N_0 (following primary RT or chemo- radiotherapy) were proven to have occult metastasis on post-operative pathological examination. This gives an occult metastasis rate (per neck) of only 2 out of 52 (4 per cent).

No patients were down-staged from clinical N+ (following primary RT or chemoradiotherapy) to pathological N_0 (post-surgery).

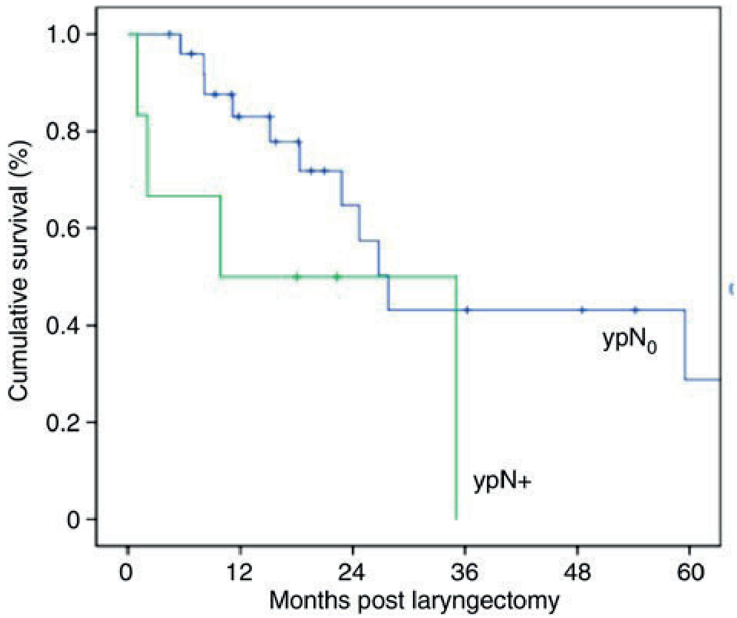

FIGURE 2: Kaplan–Meier overall survival curves for patients pathologically staged as node positive ('ypN + ') versus those staged as node- negative ('ypN0') ($p > 0.05$).

The sensitivity, specificity, and positive and negative predictive values are outlined in **Table 1**.

TABLE 1: Diagnostic value of CT in detecting post-(chemo)radiotherapy neck metastasis

Parameter	Value (%)
Sensitivity	78
Specificity	100
Positive predictive value	100
Negative predictive value	96

Key points

- Various imaging and minimally invasive interventional techniques are available to stage the neck in primary and salvage laryngectomy
- Computed tomography has better negative predictive value in ruling out neck metastasis in salvage rather than primary laryngectomy
- Salvage neck dissection is associated with a high risk of complications
- Conservative management may be considered for the clinically node-negative neck in the salvage laryngectomy setting

Complications

The very high rate of complications suffered by this patient cohort has been described previously[6]. In brief, more than half of our patients had post-operative infections despite antibiotic prophylaxis. All patients with wound infections ultimately developed pharyngo- cutaneous fistulas at an average of 12 days post- operatively.

Univariate analysis revealed three variables with significant correlation to wound infection: alcohol consumption ($p = 0.01$), clinical lymph node metastasis stage ($p < 0.01$) and pre-operative albumin levels of less than 3.2 g/l ($p = 0.012$). Trans-oesophageal puncture was not associated with a higher risk of complications. The time delay from completion of RT or chemoradiotherapy and salvage surgery was correlated with post-operative complications. The median time interval in patients that developed fistulas was 16.5 months whereas those who did not develop fistulas underwent surgery an average 27 months later.

Tumour stage was not associated with an increased risk of complications. Counterintuitively, N_0 was associated with more complications than N+ disease, despite the fact that the former group underwent selective neck dissection at levels 2–4, compared with modified radical neck dissection in the N+ group.

DISCUSSION

Laryngeal cancer is the only cancer for which survival rates have worsened over the last 20 years[7,8]. The reasons for this have been contested[8-10], but potentially include worsening co-morbidities and the increasing use of RT or chemoradiotherapy as the primary treatment modality.

Although surgeons' workload for primary laryngectomy has decreased, the need for salvage laryngectomy has increased. Indeed, persistent or recurrent disease following RT or chemoradiotherapy has been reported to be as high as 50 per cent[11].

In some of these patients, salvage surgery is still feasible and can achieve cure. However, the effects of high- dose RT and chemotherapy on tissue mean that these patients are at a higher risk for post-operative complications[2,3,12]. Salvage surgery is defined as 'clean-contaminated' surgery, and local wound infection rates range from 40 to 61 per cent[13-16]. The reasons for this high complication rate are discussed elsewhere, but it seems to be driven more by the extent of surgery than by nodal stage[13,17,18]. Chemoradiation also seems to be associated with more complications than RT[15,19,20],though we found no significant difference, which is in agreement with an earlier study[21].

Given the above, the surgeon must be convinced of the survival benefit of carrying out a neck dissection before recommending it to a patient. This survival benefit is clear in N+ patients, but the question of how much occult disease is missed on pre-operative investigation is a matter of contention. If pre-operative investigation was reliable, we could spare the patient the morbidity of an elective neck dissection[2,4,22,23] without impacting on oncological outcome. On the other hand, this might be the last chance for cure that the patient has, and if the occult metastasis rate is too high, then the surgeon should recommend elective neck dissection[22,24]. It must also be emphasised that despite aggressive treatment, the overall prognosis for these patients is dire, with a five-year overall survival rate of less than 50 percent.

Novel pre-operative staging techniques

In the primary laryngectomy setting, despite the variety of possible investigations (endoscopy, MRI, CT, positron emission tomography (PET), or ultrasound with or without FNAC), it is not uncommon for the pre- operative investigation to either over-estimate[25] or under-estimate[26-29] the extent of disease. Overall, occult metastasis rates of roughly 30 per cent are reported for primaries of the oral cavity, oropharynx and larynx[30].

In order to increase the accuracy of pre-operative staging and reduce the occult metastasis rate, several new techniques have been tested. Three of the more promising techniques are PET-CT, sentinel lymph node biopsy and diffusion-weighted MRI.

The PET-CT technique has been widely studied, and has been reported to have a significant therapeutic impact in changing the management of patients under- going surveillance[31]. A review of studies on PET-CT for recurrent laryngeal cancer found pooled estimate sensitivity of 89 per cent and specificity of 74 per cent[32]. However, few studies have addressed regional disease specifically. A recent publication on the use of PET-CT for detecting regional disease in patients undergoing salvage laryngectomy concluded that the negative predictive value was too low to allow conservative management of the neck[23].

Sentinel lymph node biopsy is gaining popularity in the management of early oral SCC, with negative predictive values of more than 95 per cent[33]. Though there are reports of sentinel lymph node biopsy used in recur- rent carcinoma of the vulva[34], and in oral or oropharyngeal cancer[35], to date there are no published studies on recurrent laryngeal cancer. In theory, the post-RT or post-chemoradiotherapy neck may well have aberrant drainage patterns, and it is unclear whether this would make sentinel lymph node biopsy unreliable. The technique would also need some modification to allow 'on-table' injection of the nanocolloid.

Diffusion-weighted MRI has only recently been introduced for head and neck cancers[36]. In the setting of post-RT or post-chemoradiotherapy laryngeal cancer, it has been reported to have better sensitivity and specificity than PET-CT (up to 96 per cent and 100 per cent in some series[37]), although this is not specifically in terms of evaluating the neck. There is little doubt though that diffusion-weighted MRI complements existing techniques and can be easily added to routine follow-up protocols.

Limitations

There remains a concern that micro-metastatic deposits of tumour in the neck will be well under the resolution of even the most advanced imaging technique. Furthermore, these micro-metastases might be currently under-estimated as they may be missed on routine pathological examination[38]. Indeed, roughly 10 per cent of historical pathologically staged N_0 neck specimens show micro-metastasis on careful re-analysis.

This raises the possibility that our pathologically staged N_0 patients actually did have micro-metastatic disease resected during elective neck dissection. This would presumably have a survival benefit though the exact survival significance of micro-metastatic disease is controversial. For example, Bohannon *et al.*[2] and Temam *et al.*[39] showed no survival benefit associated with elective neck dissection in the pathologically staged N_0 neck. This implies that the impact of any micro-metastatic disease missed on routine pathological examination would be too small to have a significant effect on survival.

CONCLUSION

Although limited by small numbers and its retrospective nature, our data suggest that the rate of occult neck disease in the salvage laryngectomy patient group is low. With the high rates of post-operative complications associated with salvage neck dissection, a conservative approach to the neck may be considered for patients clinically staged as N_0 (following primary RT or chemoradiotherapy). This would help to limit the significant morbidity of salvage surgery without adversely affecting the oncological outcome. Larger, preferably prospective studies are needed to further evaluate this suggestion.

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Factors predictive of outcome following primary total laryngectomy for advanced squamous cell carcinoma

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ABSTRACT

The increasing use of primary chemoradiation (CRT) for laryngeal squamous cell carcinoma (SCC) means that historical surgical data sets are not representative of the modern laryngectomy patient. We analyse a contemporary total laryngectomy (TL) cohort to identify factors predictive of outcome. This is a retrospective consecutive case note review in a UK tertiary referral centre. Demographic, staging, treatment and outcome data were collected. Oncological outcomes are expressed using the Kaplan–Meier method. The log-rank test was used for univariate analysis and cox regression for multivariate analysis. Sixty consecutive patients between 2003 and 2010 underwent primary TL, 28 including partial pharyngectomy. Median age was 61 years and mean follow-up was 24 months (1–78 months). Thirty six patients died during the study period, 24 of their disease. Of the disease- specific deaths, two occurred peri-operatively, four from local, two from regional and 18 from distant disease [two patients had simultaneous local and distant recurrence (DR)]. Five-year overall survival, disease-specific survival, loco-regional recurrence-free survival and distant recurrence-free survival (DRFS) were 36, 51, 87, 62 %, respectively. Of 17 parameters analysed, pN-stage, extra-capsular spread, a non-cohesive tumour front, thyroid infiltration and involvement of level 6 were significant predictors of disease-specific survival (DSS) on univariate analysis. pN>1 and the presence of adverse histological features were found to be independent predictors of DSS and DRFS on multivariate analysis. Neither was significantly associated with loco-regional recurrence-free survival. Around half of patients who undergo TL for stage IV SCC will die of disease within 5 years, with most deaths attributable to DR. Surgery provides excellent loco-regional control but patients, especially those with advanced nodal disease and/or adverse histological features, should be thoroughly screened for occult distant disease.

Level of evidence 4.

INTRODUCTION

Squamous cell carcinoma (SCC) of the larynx is one of the most common cancers of the upper aero-digestive tract accounting for about 0.7 % of all cancer deaths worldwide[1,2]. Overall mortality from laryngeal cancer in the USA fell by 24.5 % between 1990 and 2004, but this reduction is thought to be exclusively due to a decrease in incidence, driven by a reduction in smoking[1]. Indeed, 5-year overall survival (OS) rates for laryngeal cancer have fallen from 67 % in 1997 to 64 % in 2004[1] making laryngeal SCC the only cancer for which survival rates have worsened over the last 20 years[3]. The reasons for this have been contested[4-6].

In this context, the aim of our study was to report our experience of outcome following TL in a contemporary cohort of patients, managed by a major UK head and neck cancer unit and analyse factors predictive of outcome.

PATIENTS AND METHODS

After local ethical approval, we performed a retrospective case note review of 60 consecutive patients operated with total laryngectomy (TL) or pharyngo-laryngectomy (TPL) for SCC between 2003 and 2010 in our unit. All patients had bulky stage IV disease felt to be unamenable to primary chemoradiotherapy. Patients with other cancers or previous treatment of a laryngeal cancer were excluded. Following operation, all patients were planned for adjuvant therapy.

Patients' demographic, staging, pre-operative imaging, treatment and outcome data were collected using case notes, surgeons' logbooks and our institutional electronic patient, radiology and pathology database. 17 variables were available for analysis: two demographic (age at procedure and gender), three tumour-specific (primary site, T-stage, N-stage), four therapeutic [TL or TPL, neck dis- section (ND), thyroidectomy, pre-operative tracheostomy] and eight histological variables (differentiation, the presence of extra-capsular spread, sarcolemmal/perineural/ perivascular invasion, cohesive front, thyroid involvement and margin of excision). Unfortunately, as a retrospective study, some data were either unclear or missing. Unless absolutely clear, such data have been omitted from the analysis.

For the purposes of multivariate analysis, we considered the presence of one or more of sarcolemmal or perineural or perivascular invasion as representing adverse histological features. As a histologically non-cohesive front was present in the majority (89 %) of patients it was excluded from the multivariate analysis.

All patients underwent pre-operative Computerized Tomography (CT) scanning of their neck and thorax and Magnetic Resonance (MRI) scanning when indicated and were discussed in our multidisciplinary head and neck tumour board meeting (MDT). All patients were considered M0 and were treated with curative intent (palliative cases and those undergoing primary CRT were excluded). Both versions 6 and 7 of the AJCC staging manual were used as the study period straddled the change in 2009.

The surgical approach to laryngectomy during this time includes comprehensive wide field TL/TPL with central compartment clearance, lateral ND when indicated, excision of a tracheostomy tract if one exists, critical appraisal of thyroid involvement, including ipsilateral hemithyroidectomy with isthmusectomy on the side of the tumour or total thyroidectomy when indicated, frozen section surgical margin control and post-operative chemoradiotherapy for patients treated with primary surgery. All patients, there- fore, underwent TL or TPL with central ND. Therapeutic comprehensive lateral ND was performed when metastases were identified pre-operatively. Elective lateral ND was performed when there was no suspicion of nodal metastases, unless the risks of comorbidities were felt to outweigh the potential for benefit.

Local recurrence (LR) was defined as recurrent SCC, diagnosed within 5 years of initial treatment involving the immediate peristomal region. Regional recurrence (RR) was defined as recurrent SCC involving the cervical nodes (level 1–6). Distant recurrence (DR) was diagnosed either clinically or on imaging studies including ultrasound-guided fine needle aspiration, CT or Positron Emission Tomography (PET–CT) scanning. All recurrences were biopsy proven except in those patients in which it was felt that either comorbid status or disease progression meant that invasive biopsies were not indicated. All cases were discussed within the MDT, and those patients not fit for biopsy were considered as recurrence by consensus based on clinical or imaging examination.

Evidence of patients' deaths was taken from hospital records, and death certificates were available. All patients with active disease at last follow-up who died of unknown causes were considered as having died of disease.

Statistical analysis of OS, disease-specific survival (DSS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS) and distant recurrence- free survival

(DRFS) were calculated using the Kaplan– Meier method. The log-rank test was used for univariate, and cox regression model for multivariate analysis (SPSS, Chicago, Illinois, v19).

RESULTS

Sixty patients with a median age of 62 years (39–89 years) were identified. 49/60 (82 %) were male, 11/60 (18 %) were female. Mean follow-up was 25 months (0–108 months) for the whole group and 33 months (4–78 months) for the survivors.

All patients underwent primary laryngectomy, 29/60 (48 %) also had partial pharyngectomy. 47/60 (78 %) patients were treated for laryngeal primaries, 13/60 (22 %) for hypopharyngeal primaries. All patients had level 6 central compartment clearance, 55/60 (92 %) had bilateral lateral NDs, 5/60 (8 %) had unilateral lateral NDs.

Thirty-six patients died during the study period, 24 (67 %) of disease. Of the disease-specific deaths, two occurred peri-operatively (considered as dying from local disease for the purpose of outcomes analysis), four from local, two from regional and 18 from distant disease (two patients had simultaneous local and DR). Five-year overall survival, disease-specific survival, loco-regional recurrence-free survival and DRFS were 35.6%, 51.0%, 86.8% and 62.0 %, respectively (**Fig. 1**).

Univariate analysis was performed for all factors analysed across all outcome measures—**Table 1**. The strongest predictive factor for outcome was pN-stage though interestingly this failed to achieve significance in terms of loco- regional recurrence.

Multivariate analysis was then performed to identify independent prognostic factors. Due to the limited numbers of patients, only two variables could be combined in a multivariate analysis. We, therefore, defined one or more of peri- neural or perivascular or sarcolemmal spread together under the title of adverse histological features. pN>1and the presence of an adverse histological feature remained independent predictors of outcome, conferring a x6 and x3.5 greater risk of disease-specific death, respectively (**Table 2**).

TABLE 1: Cohort's characteristics and 5-year univariate analysis for OS, DSS, LRRFS and DRFS

	N	OSS	P	DSS	P	LRRFS	P	DRFS	P
Demographic									
Gender									
Female	11	30.3	0.356	35.4	0.104	88.9	0.607	39.8	**0.008**
Male	49	37.2		55.7		86.5		69.3	
Age									
<60	26	42.6	0.148	56.1	0.312	82.4	0.747	68.5	0.403
>60	34	31.2		45.9		93.6		55.3	
Disease									
Site									
Subglottic	1	0	0.124	100	0.324	100	0.262	100	0.8555
Glottis	4	66.7		66.7		100		66.7	
Supraglottic	22	36.1		47.1		89.9		59.6	
Transglottic	20	47.8		60		93.3		68.9	
Hypopharynx	12	0		20		56.3		46.7	
Site									
Laryngeal	47	42.3	0.055	55.3	0.143	92.3	0.063	64.1	0.646
Hypopharyngeal	12	0		20		56.3		46.7	
T-stage									
T3	15	43.3	NS	66.7	0.42	100	0.158	71.4	0.495
T4	44	33.8		46.5		82.7		59.6	
pN									
N0	18	60.6	0.084	74.4	**0.025**	92.9	0.377	82.1	0.132
N+	39	23.4		32.4		82.5		44.2	
pN									
N0	18	60.6	**0.01**	74.4	**0.001**	92.9	0.073	82.1	**0.022**
N1	10	53.6		85.7		100		85.7	
N>1	29	16.4		21.1		75.9		32.1	
Treatment									
Tracheostomy									
Yes	33	38.7	0.947	46	0.201	79.9	0.132	61.1	0.34
No	27	27.8		54.7		96.2		60	
Ablative									
TL	31	51.4	0.064	65.0	0.085	92.2	0.414	74.3	0.228
TL+	29	19.3		33.3		92.2		43.8	
Neck dissection									
Unilateral	5	0	**0.024**	33.3	0.52	66.7	0.347	66.7	0.836
Bilateral	55	39.5		52.5		88.5		62.1	
Thyroidectomy									
Hemi-	5	40.0	0.83	33.3	0.566	50.0	0.529	75	0.932
Total	49	34.6		47.4		87.2		58.6	

TABLE 1: Continued

	N	OSS	P	DSS	P	LRRFS	P	DRFS	P
Histology									
Differentiation									
Well	3	66.7	0.786	100	0.35	100	0.827	100	0.348
Moderate	25	38.5		44.8		79.1		56.4	
Poor	29	32.6		44.7		90.4		56.0	
Tumour front									
Cohesive	6	37.8	0.809	42.3	**0.042**	82.7	0.221	54.7	0.131
Non-cohesive	48	33.0		66.7		100		80	
ECS									
No	29	49.5	0.152	63.6	**0.027**	91.1	0.346	73.2	0.108
Yes	27	19.8		27.7		79.3		42.2	
Perineural									
No	46	32.9	0.575	46.5	0.27	85.6	0.514	59.6	0.183
Yes	7	30		30		75		40	
Perivascular									
No	35	35	0.523	52	0.061	86	0.718	63.6	**0.037**
Yes	18	25.7		26.4		84		41.9	
Sarcolemmal									
No	46	35.7	0.346	49.2	0.085	88.7	**0.026**	59.7	0.372
Yes	6	0		0		33		0	
Thyroid involved									
No	49	31.4	0.079	43.6	**0.023**	88.7	**<0.001**	55.4	0.076
Yes	1	0		0		0		0	
Level 6 involved									
No	46	31.9	**0.001**	43.5	**0.003**	88.5	**<0.001**	55.3	0.426
Yes	4	0		0		0		50	
Margins									
Clear	14	51.9	0.812	62.5	0.198	88.9	0.941	73.5	0.378
Close	32	33.1		51.3		87.5		62.1	
Involved	11	26.9		23.1		81.8		31.2	

Values in bold are statistically significant at p< 0.05

TABLE 2: Multivariate analysis using Cox regression

Variable	N	OSS			DSS			LRRFS			DRFS		
		HR	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
N-stage													
pN0/1	27		Referent			Referent			Referent			Referent	
pN2/3	29	3.15	1.45-6.83	0.04	5.88	2.06-16.8	0.001	6.28		0.98	5.25	1.59-17.3	0.0006
Adverse Histological features													
Absent	34		Referent			Referent			Referent			Referent	
Present	18	1.53	0.7-3.33	0.287	3.512	1.41-8.72	0.007	3.55	0.72-17.5	0.12	3.43	1.17-10.1	0.025

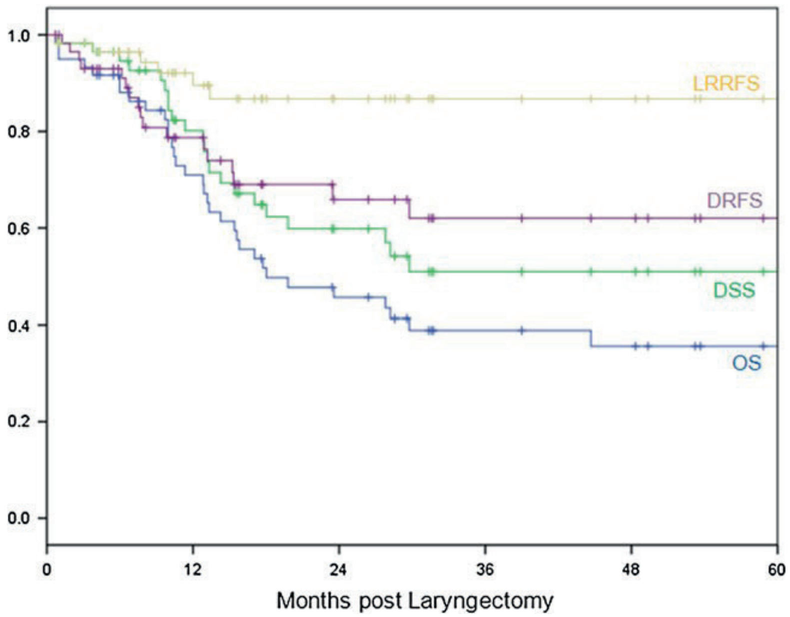

FIGURE 1: OS, DSS, LRRFS, DRFS 5-year Kaplan–Meier curves

DISCUSSION

We present in this paper a homogeneous group of Stage IV laryngeal squamous cell cancer patients. Furthermore, all the patients had disease unamenable to an organ preserving approach with primary chemoradiotherapy. This meant that they were treated in uniform fashion with TL and adjuvant treatment. These patients represent possibly the worse end of the scale and indeed, we show a five OS of 36 %. Of interest, the loco-regional recurrence-free 5-year survival was 87 % implying that surgery followed by adjuvant therapy is a very effective method of achieving loco- regional control. Unfortunately, many patients die of comorbidities or DR, both of which are more difficult for the surgeon to prevent.

Declining survival rates

Recent statistics demonstrate worsening survival rates for laryngeal cancer over the last 20 years. If we accept these survival statistics are true, the deterioration in outcomes may reflect changes in (1) patient, (2) tumour or (3) treatment characteristics.

Patients presenting with laryngeal cancer are predominately older men with a history of smoking. Whether or not this demographic may have changed significantly over the last 20 years is not the focus of this paper.

In terms of tumour characteristics, it is interesting to speculate whether for example the public health campaigns aimed at reducing smoking have subtlety changed the nature of the disease we treat today as compared to 20 years ago.

Of these three possible causes, however, the only one directly under the influence of the clinician is the approach to treatment. This has changed significantly in the last 20 years especially in view of evidence provided by the Veteran's Affairs Laryngeal Cancer Study group[7] and Radiation Therapy Oncology Group[8]. These landmark trials showed that selected patients with laryngeal cancer treated with induction chemotherapy followed by chemo- radiation (CRT) achieved survival rates comparable to those treated with TL and adjuvant radiotherapy. Since this time, CRT has gained popularity as an organ preserving approach. Indeed, the RTOG paper showed that laryngeal preservation rates of up to 88 % at 2 years were achievable, though of course organ preservation does not necessarily imply organ function[9,10].

Recent advances such as intensity-modulated radiotherapy (IMRT) have further boosted CRT's appeal. Discussion continues, however, as to how best to select patients for CRT instead of the more traditional TL with adjuvant RT. It must also be remembered that the VA study gave a full CRT course to patients who initially responded to chemotherapy. Non-responders, who represent a group of patients with a significantly poorer outcome, underwent TL. Many units, ours included, often recommend CRT to patients without a trial of induction chemotherapy to select responders.

In persistent or recurrent disease post-CRT, surgery can still achieve cure. Indeed, the rate of salvage laryngectomy in patients undergoing CRT in advanced laryngeal cancer is reported as high as 50 %[11]. Sometimes conservative surgical procedures such as partial laryngectomy are possible, but more advanced post- CRT residual or recurrent disease requires TL with or without partial pharyngectomy. Patients with unresectable recurrence, clinical trials aside, are only candidates for palliative chemotherapy.

This trend towards CRT, however, means at the same time as surgeon's case loads have been decreasing due to an overall decrease in laryngeal cancer incidence and the move to CRT, TL has increasingly become reserved for either the most advanced (bulky) primary lesions where cartilage destruction or airway compromise is present or for salvage following persistent/recurrent disease post- CRT. This means that today's

TL patients are clearly not comparable with historical series as contemporary surgical series of patients considered for TL are likely to represent those with the most advanced disease. Given the worsening survival rates for laryngeal cancer, this paper focuses on survival measures rather than performance-related or quality of life measures. We have selected a total of 17 factors which might reasonably be thought to influence survival and disease-related outcomes. Furthermore, our data analysis benefits from the consistent approach taken to laryngeal cancer by our department over the last 10 years.

Important non-predictive factors

As interesting as those factors which achieved significance were the factors which did not achieve significance. For example, amongst the patient and treatment factors, age, lateral ND, pre-operative tracheostomy and T-stage failed to achieve significance. Amongst the individual histological factors, differentiation, perineural spread and surgical margins failed to achieve significance.

This may be partly because the group was fairly homogeneous with respect to certain factors (e.g. all patients were T3/T4 and 95 % had bilateral ND) and partly because certain procedures appear effective at controlling disease (e.g. lateral ND at controlling limited regional metastasis). However, our patient numbers are too small to draw any firm conclusions from these non-significant results.

N-stage

N-stage is the most consistently reported factor predictive of survival in the literature[11-16] and again was the strongest predictive factor in our study. There are several subtleties which should, however, be highlighted.

First, pN-stage failed to achieve significance in terms of loco-regional survival, implying that a surgical approach followed by CRT is an excellent method of loco-regional control.

Second, multivariate analysis showed no statistically significant difference between N0 and N1 necks, whilst N0/ N1 versus >N1 was associated with a hazards ratio of 5.9 (range 2.1–16.8, $p = 0.001$). Similarly, Ganly et al.[11] analysing a dataset of purely supra-glottic carcinomas similarly found that N1 necks had better OS and DSS than N0. The paper's discussion puts this counter-intuitive result down to differences between clinical and pathological staging. In our study, however, we only use pathological stage. The implication in both sets of data is that, with suitably aggressive treatment, including surgery and post- operative radiation therapy, N-stage only becomes predic- tive of outcome at N>1.

Last, and perhaps most importantly, N-stage seems to be a predictor not of regional failure but of DR. Our multi- variate analysis showed a statistically insignificant result for pN-stage in terms of LRRFS, but a hazards ratio of 95.3 (p = 0.006, range 1.6–17.3) for DRFS. Similarly, Ganly et al. reported that patients with N3 disease were five times more likely to develop DR than those with N0 dis- ease. Neither our paper nor Ganly's found N-stage to predict loco-regional failure.

Therefore, patients with pN1 necks can expect survival outcomes similar to those patients with a pN0 neck. N>1 patients, whilst, having good regional control are at a significantly higher risk of developing DR. More careful staging of N>1 patients, potentially with new radiological modalities may allow identification of patients with early distant metastasis prior to surgical intervention.

Adverse histological features

Although intuitively, adverse histological features may predict survival, they are not part of AJCC staging. Currently, whilst extra-capsular extension[17] is considered an indication for the addition of chemotherapy to post-operative radiation, perineural, perivascular or sarcolemmal spread do not currently influence management decisions. Our multivariate analysis shows a DSS hazard ratio of x3.5 associated with the presence of one or more of these features. Again, this was insignificant for LRRFS but had a DRFS hazards ratio of x3.4 (p = 0.025, range 1.17–10.1). Like N-stage, adverse histological features can be well- controlled in the neck with current techniques, but predict a higher degree of risk for DR.

Our study is limited by its retrospective nature and by the limited number of patients available for analysis. Despite that, the accurate recording of clinical, pathological, treatment and outcome data allows for detailed analysis of this cohort. Whilst greater numbers would be advantageous, with the trend away from TL for primary disease, surgical series are limited. Despite this, all efforts must be made to understand the changes in survival observed in laryngeal cancer, and the outcomes expected following contemporary management of advanced disease.

Conclusions

Patients with stage IV disease undergoing TL have a roughly 50 % 5-year DSS rate. Both advance neck disease (p>N1) and the presence of adverse histological features were independently predictive of outcome. Despite the effectiveness of surgery in local–regional control, more than half of these patients will die from distant metastasis. This implies that both improvements in pre-operative evaluation and more effective systemic therapies are needed.

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12

What is the effect of previous (chemo) radiotherapy on pharyngocutaneous fistula formation, management, duration and closure in patients undergoing total laryngectomy?

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ABSTRACT

Background: Prior (chemo)radiotherapy ((C)RT)is thought to impact on the risk of post-laryngectomy pharyngocutaneous fistula (PCF) formation, duration of PCF and need for operative closure.

Methods: Retrospective case note review of all patients undergoing laryngectomy over a 10 year period in our institution.

Results: A total of 242 patients (199 males, 43 females) were analyzed. 116 patients underwent primary laryngectomy, 101 had previous RT and 25 had previous CRT with either cisplatinum or cetuximab. Seventy-five of 242 (31%) patients developed a PCF. Previous (C)RT was not statistically significant correlated with PCF formation but should PCF occur, it did increase its severity as reflected by longer duration and less chance of closure.

Conclusions: Previous (C)RT need not be a risk factor for developing a post laryngectomy PCF. However, should these patients develop a PCF it is more severe than if they had not had previous treatment.

INTRODUCTION

Total laryngectomy (TL), often followed by postoperative (chemo)radiotherapy is a curative treatment option for patients with advanced stage primary laryngeal or hypopharyngeal cancer. Total laryngectomy can also be used to salvage patients with recurrent disease after failure of initial organ preserving treatment and can also be performed in patients with a dysfunctional larynx either due to previous treatment, treatment of a nearby organ (proximal oesophagus or base of tongue) or trauma[1-4].

Postoperative complications including the occurrence of a pharyngocutaneous fistula (PCF) are common and difficult to treat problem[1-5]. PCF is a communication between the pharynx and the skin, mostly between mucosal suture line and surgical skin suture line, including(less frequently) around the tracheostoma. Though saliva usually promotes both mucosal and skin healing [6], continuous leakage through the fistula often hinders PCF closure and roughly half of patients undergo further operation(s) to close the PCF.

A recent systematic review[7] found published PCF rates of up to 58%[8]. In a Dutch national study with 324 patients undergoing laryngectomy the overall PCF rate within 30 days after discharge from the hospital was 25.9%[4]. PCF often necessitates further surgery, delays oral feeding, prolongs feeding tube dependency, affects voice rehabilitation, decreases quality of life and increases hospital stay and costs[3,9,10]. PCF carries a high risk of further wound breakdown and subsequent damage to nearby tissues and structures, including potential carotid artery blowout. The occurrence of a PCF may also cause delay of postoperative (chemo)radiotherapy, thus jeopardizing optimal oncological treatment[4,11].

Prior (chemo)radiotherapy is one of many potential risk factors for PCF formation. Other factors are hypopharyngeal cancer, extensive pharyngeal resection and reconstruction, neck dissections, low BMI and low skeletal muscle mass (sarcopenia) [4,12,13]

In this article we present our single center experience of 242 laryngectomized patients operated over a 10 year period. We stratify these patients according to whether they underwent (chemo)radiotherapy prior to laryngectomy and see whether this increased the risk of PCF formation and severity of the PCF as measured by chances of operative management, duration of PCF and chance of ultimate closure.

MATERIALS AND METHODS

We performed a retrospective cohort study of all patients undergoing total laryngectomy at the University Medical Center Utrecht over the 10 year period January 2008 to December 2017. The indication for total laryngectomy was either as primary treatment for cancer, as salvage treatment for cancer following (chemo)radiotherapy or as a treatment for an afunctional larynx.

Patients' demographic, staging, treatment and outcome data were collected using electronic patient records. We recorded TNM classification according to the then applicable AJCC manual. All patients were discussed in our multidisciplinary tumour board and underwent total laryngectomy with or without (partial) pharyngectomy. For patients where the pharynx could not be closed primarily, a variety of flaps were used including pectoralis major (with or without skin island), radial forearm free flap (RFFF), anterior lateral thigh flap (ALT), jejunum interposition and gastric pull up. Occasionally a pectoralis major muscle onlay flap (also reported in the literature as an interposition flap) was used to reinforce a primarily closed pharynx.

The majority of PCFs manifested themselves during the inpatient stay, though some patients were discharged home either with a feeding tube or on oral diet only to present with a PCF later. These patients were classified as having a PCF. Still further patients developed a PCF many months later secondary to an intervention such as dilatation of a stricture. These patients were classified as no PCF as the development of a PCF was considered a complication of the second procedure, not of the initial laryngectomy.

In those patients who developed a PCF, initial management was conservative using a variety of wound dressings. For fairly dry PCFs, Eusol (Edinburgh University solution of lime) wound dressings were used. For more productive PCFs either iodine soaked gauze or an alginate dressings were used. For the most productive, a stoma bag had to be used.

The indication for operative management of a fistula was up to the lead surgeon's judgement. This depended on many factors including the size of the fistula, its response to conservative therapy, the patient's fitness, and the availability of a suitable method of reconstruction (the favoured reconstruction being a salivary bypass tube and pectoralis major flap). Some patients with very small fistulas ultimately accepted the situation and managed with a combination of tube feeding and modified oral feeding.

PCFs were stratified according to whether they had no previous treatment (TL group), previous radiotherapy (RT group) or previous concomitant cisplatinum/cetuximab and radiotherapy (CRT group) - see **table 1**. Having stratified our patients in this way, we evaluated the risk of PCF formation, risk of operative management of the PCF, the time to closure of the PCF and the chance of successful PCF closure.

Statistical analyses were performed using SPSS® Statistics 20.0 (IBM, Armonk, NY). Duration of fistula was calculated using the Kaplan–Meier method and Cox-mantel log-rank test for comparison. The chi-squared test or binary logistic regression analysis was used as appropriate for univariate analysis.

This study does not fall under the scope of the Medical Research Involving Human Subjects Act and the institutional review board approved this study.

RESULTS

A total of 242 patients (199 males, 43 females) were operated in the study period. One hundred sixteen of 242 (48%)patients had no previous radiotherapy (TL group) whilst 101/242 (42%) had previous radiotherapy as a single modality (RT group), 16/242 (7%) patients had cisplatin with radiotherapy and 9/242 (4%) patients had cetuximab with radiotherapy . These latter two groups were analysed together as the CRT group (see **table 1**).

Many of the differences seen in **table 1** are due to the way in which patients are selected for either primary surgery or primary organ-preserving treatment. Features we feel are important to highlight however include the rate of elective neck dissections and the use of flap reconstructions.

Neck dissections

When analyzing neck dissections, in the primary cohort 86/115 (75%) patients underwent a total of 127 neck dissections including 44 prophylactic dissections. This gives an elective neck dissection rate of 44/230 (20%).

In the RT group, 36/101 (36%) patients underwent 46 neck dissections including 36 elective neck dissections. This gives an elective neck dissection rate of 36/202 (18%)

In the CRT group 17/25 (70%) patients underwent 21 neck dissections including 4 elective neck dissections. This gives an elective neck dissection rate of 4/50 (8%).

TABLE 1: Univariate analysis of cohort stratified by primary / RT / CRT.

		Primary TL	Prior RT	Prior CRT	P value
		n	n	n	
Indication	Primary	115	0	0	
	Salvage	0	83	19	
	Functional	1	18	6	n/a
Gender	Male	91	87	21	
	Female	25	14	4	0.325
ASA	1	56	48	5	
	2	30	24	14	
	3	26	25	4	
	4	3	2	1	0.043
Age	<65	59	46	12	
	>65	57	55	13	0.736
Tumor Site	Supraglottis	18	23	4	
	Glottis	21	57	1	
	Subglottis	3	3	1	
	Transglottic	27	8	1	
	Post cricoid	1	0	1	
	Piriform sinus	44	8	12	<0.001
T-stage	T1	0	30	2	
	T2	0	45	8	
	T3	20	23	8	
	T4	95	3	7	<0.001
N-stage	N0	60	84	7	
	N1	8	8	3	
	N2a	1	0	1	
	N2b	21	7	9	
	N2c	24	1	5	
	N3	2	0	0	<0.001
Operation	TL	78	70	6	
	TLPP/TLP	38	31	19	<0.001
Neck dissection	None	30	65	8	
	Unilateral	45	26	13	
	Bilateral	41	10	4	<0.001
Initial flap	None	78	69	5	

TABLE 1: Continued.

		Primary TL	Prior RT	Prior CRT	P value
		n	n	n	
reconstruction	Pectoralis major	25	25	18	
	Radial forearm free flap	7	0	0	
	Anterior lateral thigh	3	4	0	
	Gastric pull-up	2	2	1	
	Jejunum	1	1	1	<0.001
Fistula	No	83	68	16	
	Yes	33	33	9	0.678
Fistula management	Conservative	17	16	3	
	Operative	16	17	6	0.624
Fistula closed	No	2	8	4	
	Yes	31	25	9	0.018

Flap reconstruction

Twenty of 25 (80%) CRT patients had a flap reconstruction of their pharynx, vastly more than 38/116 (33%) in the primary TL and 32/101 (32%) in the RT group. A distinction can also be made between flaps used for reconstruction of a mucosal defect vs onlay reinforcement (also called interposition) flaps. Two of 20 flaps in the CRT group were onlay flaps compared with 5/32 flaps in the RT group.

Previous (C)RT and risk of PCF formation

A total 75/242 (31%) of patients developed a PCF. 33/116 (28%) primarily surgical patients developed a PCF, 33/101 (33%) prior RT patients and 9/25 (36%) prior CRT patients. On binary logistic regression analysis neither previous RT nor previous CRT were significant risk factors for the development of a PCF.

Are patients with prior RT more likely to need operative management of their PCF?

Sixteen of 33 (48%) patients with no prior radiotherapy needed operative management of their PCF versus 17/33 (52%) patients with prior radiotherapy and 6/9 (67%) patients with prior CRT. These differences were not statistically significant on binary logistic regression.

Does a PCF after prior (C)RT take longer to heal?

Figure 1 shows a Kaplan Meier analysis of time to closure of the PCFs for the three groups. Patients without previous therapy had a median duration of fistula of 42 days vs 81 days in RT group vs 172 days in the CRT group. Comparing TL and RT groups, p=<0.001, TL vs CRT p=0.028 and RT vs CRT p=0.598 was found.

Is a PCF after prior (C)RT less likely to heal?

61/75 (81%) fistulas ultimately closed, 2/74 (2.7%) fistulas were still open at last follow-up (respectively 3 and 29 months following laryngectomy) and 12 patients died with an open PCF.

31/33 (94%) PCFs healed in the no prior therapy cohort. This compares to 25/33 (76%) in the prior RT cohort and 5/9 (56%) in the prior CRT cohort . On binary logistic regression this difference was statistically significant (p=0.008).

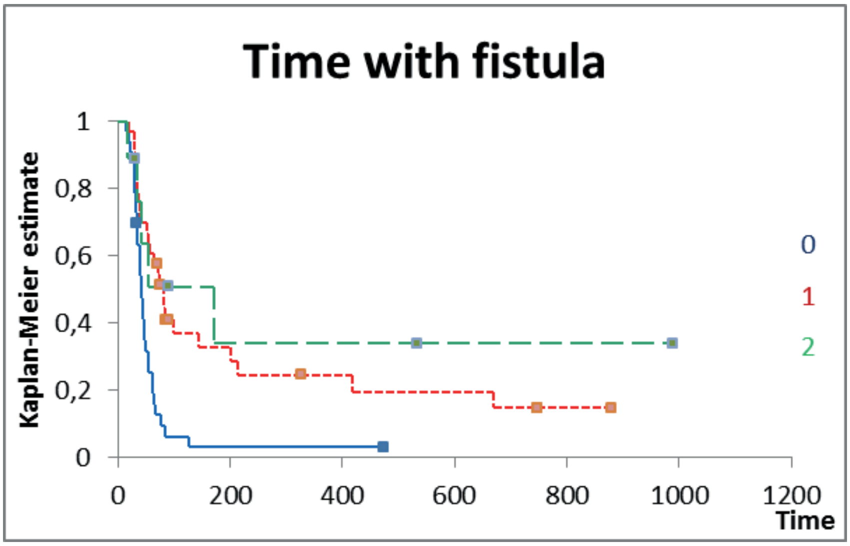

Figure 1: Time to closure of PCF stratified by no previous therapy (blue 0), previous RT (red 1) and previous CRT (green 2) (p= <0.001 between no RT and RT groups, p=0.002 between no RT and CRT groups, p=0.598 between RT and CRT).

DISCUSSION

We present a single tertiary referral center's experience of pharyngo-cutaneous fistulas stratified by previous RT or CRT. Consistent with the literature[7,14], roughly a third of patients undergoing laryngectomy had a PCF. However this did not seem to be related to whether a patient had undergone previous RT or CRT. This is in contrast to some older data sets which suggest RT is a risk factor for the development of PCF[3,14-16], but in keeping with some more modern datasets which find a no convincing correlation between radiotherapy as a single modality and PCF[4,17]. These more recent publications do however find that previous CRT is a risk factor. In our data, though there seems to be a trend for CRT to be a risk factor, this was not statistically significant. This could be because of small numbers, or because our CRT patients were managed differently.

There are many potential reasons for the apparent difference between the older and more modern data sets. Firstly, in the more recent data sets, the diagnostic techniques have changed significantly. With improvements in diagnostics we have been able to reduce the extent of prophylactic radiotherapy. Secondly, radiotherapy techniques have changed significantly with IMRT and VMAT. These techniques have allowed a more targeted approach with less damage to surrounding tissues.

These improvements in diagnostics and radiotherapy have allowed surgeons to also be more targeted in their salvage laryngectomies. Fewer elective neck dissections are being performed despite some recent publications showing rates of occult metastases of up to 24% in supraglottic recurrences[18] and other papers showing that elective neck dissection do little to add to morbidity or mortality[19]. However, neck dissection was one of the most important predictive factors for PCF development in Dutch multicenter study[4]. Awareness of the risks for PCF has also led surgeons to change their operative technique, for example by making more frequent use of flaps. Indeed there is evidence that this might reduce not only the incidence, but also the severity of any post-laryngectomy PCF[20]. In our data set, 20/25 (80%) CRT patients had a flap reconstruction of their pharynx, vastly more than 38/116 (33%) in the primary TL and 32/101 (32%) in the RT group. The distinction between a mucosal reconstruction flap and an overlay flaps could not be analyzed as the number of overlays flaps was too small for their impact to be statistically analyzed.

With regard to neck dissections, though the rate of prophylactic neck dissection in the CRT group was less than half that of the RT or primary group, there was unfortunately a high level of nodal disease meaning that only 8/25 (32%) patients were able to avoid some form of neck dissection. This is no doubt due to the high level of nodal disease in this group pre-CRT.

It seems therefore that despite the high (though necessary) number of neck dissections performed in the CRT group along with the accepted increased risk CRT plays in PCF formation, this was mitigated by the judicious use of flaps to the extent that prior CRT no longer was statistically associated with increased risk of PCF. In those patients who did develop a PCF we still see that the severity of the PCF is higher than in the primary group despite the extra flaps.

CONCLUSIONS

PCF remains a common and troublesome complication after total laryngectomy. Fortunately, previously identified risk factors such as prior RT and prior CRT have been to a large extent mitigated in our data set by the judicious use of flaps and a reduction in elective neck dissections. However, when patients do have a PCF, previous RT or CRT means that despite the extra flaps, the PCF will take far longer to close and has significantly less chance of healing at all.

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Time interval between primary radiotherapy and salvage laryngectomy: a predictor of pharyngocutaneous fistula formation

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ABSTRACT

Salvage laryngectomy (SL) is associated with high levels of morbidity. Rates of pharyngocutaneous fistulae (PCF) are as high as 35 % in some series. Patients at highest risk of such complications may be candidates for altered surgical management in terms of additional tissue transfer, or delayed tracheoesophageal puncture. This study investigates the relationship between the time from primary radiotherapy (RT) to salvage surgery and the development of PCF. 26 consecutive patients who underwent SL between 2000 and 2010 were identified from our institutional data- base. Demographic, staging, treatment and complication data were collected. Subgroup analysis was performed using the Student's *t* test or Mann–Whitney *U* test for continuous variables and either Chi-squared test or Fisher's Exact test for categorical variables. 26 patients underwent SL between October 2003 and July 2010. Of these, 15 (58 %) developed a PCF. On analysis of the time between pre-operative RT and surgery, a significant difference was seen, with a mean time of 19.5 months in those who developed a PCF versus 47.0 months in those who did not ($p = 0.02$). Patient characteristics, treatment, and pathology results were comparable between the two groups. There was no significant difference in distribution of the other covariates between the PCF and non-PCF groups. We reported a high rate of PCF and identified an association between PCF and a short time from primary treatment to salvage surgery. Identifying factors associated with higher rates of post-operative morbidity allows surgeons to adapt surgical planning in an attempt to minimize rates of PCF.

INTRODUCTION

Over the past two decades, non-surgical organ preservation therapies such as radiotherapy (RT) and chemotherapy (CT) have become increasingly important in the management of advanced stage squamous cell laryngeal carcinoma[1-3]. In appropriately selected patients, such treatment strategies offer high rates of loco-regional control and in many cases preserve laryngeal function[4]. However, despite these improvements, the maximum laryngectomy-free survival at 10 years for patients receiving RT and induction chemo- therapy is 28.9 %[3]. In these situations, salvage total laryngectomy (SL) may be the only curative option[5,6].

As a consequence of co-morbidities and poor pre-operative performance status, patients undergoing SL are at high risk of post-operative complications. Post-operative infection rates, even with prophylactic antibiotic coverage, range from 40–61 %[7-10]. The most common infective complication reported is pharyngocutaneous fistulae (PCF), with an incidence of up to 35 %[11,12]. These patients may benefit from additional steps to avoid such complications such as use of interposed free flaps and pectoralis myofascial onlay flaps[13,14].

A wide range of risk factors have been associated with PCF formation, although due to limited sample sizes and heterogeneity of surgical cohorts, not all have proven significant. Risk factors include pre-operative RT and CT, male gender, increased age, low body mass index, poor nutritional status, tobacco and alcohol history, tumour site, size and stage, intra-operative flap reconstructions, trans-oesophageal puncture (TOP) and pre-operative tracheostomy[6,9,12,14-16].

Although pre-operative RT is recognised as a significant risk factor for PCF formation in head and neck oncological surgery[5,12,17-19], little data are reported on the association of time interval between primary RT and salvage surgery in relation to PCF formation.

The purpose of this study was to investigate the whether there was a relationship between the time interval from primary RT to salvage surgery and the development of PCF in patients undergoing salvage total laryngectomy.

MATERIALS AND METHODS

A retrospective case note review of 26 consecutive patients who underwent SL at our unit between 2000 and 2010 was carried out. From 2003, all patients were discussed and their management was agreed at the Multidisciplinary Head and Neck Oncology Tumour Board Meeting before surgical management was undertaken.

All patients received primary 3 dimensional radiation treatment as they predated the introduction of intensity modulated radiotherapy at our institution. Patients with cN0 node disease underwent a selective neck dissection (SND) of levels II–IV, while those with nodal disease (cN1 and 2) underwent a modified radical neck dissection (MRND) of levels I–V. All complications were recorded in the medical records as well as the head and neck ward complications record book. Wound infections were categorized according to Tabet and Johnson's manual on control of infection in surgical patients. Grade 4 is classified as a purulent discharge either spontaneous or by surgical drainage, and Grade 5 is classified as a muco-cutaneous or PCF[20].

All patients received antibiotic prophylaxis according to the standard prophylactic antibiotic policy. This involved giving intravenous teicoplanin 400 mg, cefuroxime 1.5 g and metronidazole 500 mg at induction and then three further doses over the following 24 h. All patients who developed post-operative infection received initially empiric antibiotics which were modified following results of culture and sensitivity of the samples.

The following parameters were also collected; age, smoking history, alcohol, co-morbidities, BMI, pre- and post-operative serum albumin concentrations, history of radio- and chemo-radiotherapy (RT, CRT), intra-operative TOP, and tumour stage both at the time of primary diagnosis and recurrence (T, N and Overall stage). Patients were categorized into those who developed a PCF and those who did not.

An independent *t* test was carried out to compare the time interval between RT/CRT and salvage surgery in each group. A further analysis was undertaken to determine potential associations between baseline demo- graphic, staging, treatment characteristics and PCF formation.

Statistical analysis was undertaken using SPSS for Windows (version 19; SPSS Inc., Chicago, IL).

RESULTS

26 patients were identified and included in this study. The primary tumour staging was T1 in 6 patients (23 %), T2 in 11 patients (42 %), T3 in 8 patients (31 %) and T4 in 1 patient (4 %). Nodal stage was N0 in 25 patients (96 %), and N2 in 1 patient (4 %). All patients were considered free of distant metastases. Overall stage was I in 5 patients (19 %), II in 12 patients (46 %), III in 7 patients (26 %) and IV in 2 patients (8 %) at time of primary surgery. At the time of recurrence, tumour staging was T2 in 3 patients (12 %), T3 in 7 patients (27 %) and T4 in 16 patients (62 %). Nodal stage was N0 in 20 patients (77 %), N1 in 3 patients (12 %) and N2 in 3 patients (12 %). Overall stage was II in 2 patients (8 %), III in 7 patients (27 %) and IV in 17 patients (65 %) at time of salvage surgery. All patients were considered free of distant metastases. Progression of disease stage from initial treatment to recurrence is shown in **Table 1**.

TABLE 1: Comparison of primary versus recurrent tumour stage

Stage (i = primary, r = recurrence)	**rT1**	**rT2**	**rT3**	**rT4**
iT1	–	2 (8 %)	2 (8 %)	2 (8 %)
iT2	–	1 (4 %)	4 (15 %)	6 (23 %)
iT3	–	–	1 (4 %)	7 (26 %)
iT4	–	–	–	1 (4 %)
Stage (i = primary, r = recurrence)	**rN0**	**rN1**	**rN2**	**rN3**
iN0	20 (77 %)	3 (11 %)	2 (8 %)	–
iN1	–	–	–	–
iN2	–	–	1 (4 %)	–
iN3	–	–	–	–
Stage (i = primary, r = recurrence)	**rStage I**	**rStage II**	**rStage III**	**rStage IV**
iStage I	–	–	2 (8 %)	3 (11 %)
iStage II	–	2 (8 %)	4 (15 %)	6 (23 %)
iStage III	–	–	1 (4 %)	6 (23 %)
iStage IV	–	–	–	2 (8 %)

TABLE 2: Stratification of groups by co-variate

Characteristic	Overall	PCF	No PCF	p-value
Time interval RT to SL (months)	31.2 (5.5–104)	19.5 (5.5–55.4)	47 (7.2–104)	0.02[a]
Mean age (years)	60.9 (44.7–79.7)	59.9 (44.7–73.2)	64.7 (44.7–79.7)	0.31[a]
Gender (n)				
Male	24	14	10	0.68[b]
Female	2	1	1	
Diabetes (n)				
Yes	3	1	2	0.38[b]
No	23	14	9	
Alcohol (current)				
Yes	6	5	1	0.20[b]
No	20	10	10	
Smoking (current)				
Yes	7	6	1	0.18[b]
No	19	9	10	
BMI	22.8 (16.7–31.7)	23.2 (16.7–31.7)	22.3 (18.9–27.5)	0.20[a]
Albumin (g/l)	31.7 (10–44)	33.3 (15.0–43.0)	29.9 (10–44)	0.41[a]
Primary TOP (n)				
Yes	15	9	6	0.55[b]
No	11	6	5	
T stage primary (n)				
T1 and 2	17	8	9	0.11[b]
T3 and 4	9	7	2	
N stage primary (n)				
N0	25	14	11	0.58[b]
N1 and 2	1	1	0	
Overall stage primary (n)				
I and II	17	8	9	0.11[b]
III and IV	9	7	2	
T stage recurrence (n)				
T1 and 2	3	2	1	0.69[b]
T3 and 4	23	13	10	
N stage recurrence (n)				
N0	20	11	10	0.23[b]
N1 and 2	6	4	1	

TABLE 2: Continued

Characteristic	Overall	PCF	No PCF	p-value
Overall stage recurrence (n)				
I and II	2	1	1	0.51[b]
III and IV	24	14	10	
CCRT				
Yes	5	3	2	
No (RT only)	21	12	9	0.91[b]
Primary TOP (n)				
Yes	15	9	6	0.55[b]
No	11	6	5	

The mean age of patients was 61 years, 24 (92 %) patients were male, 3 (12 %) had diabetes, 15 (58 %) had a TOP intra-operatively, average alcohol intake was 46 U per week, average BMI pre-operatively was 23, average albumin pre-operatively was 32 g/l, and average smoking history was 33 pack years (data not included in **Table 2**). The demographic and staging data are shown in **Table 2**.

A total of 15 of the 26 patients (58 %) developed an infection after SL during the study period. Of these 15 patients, all developed PCF. All of these patients required post-operative antibiotic therapy, and the time to infection post-operatively ranged from 2 to 26 days, with an average time to onset of 12 days.

When stratified by development of PCF, the groups were similar in terms of age, gender, co-morbidities and both initial and recurrence staging. In contrast, those patients that developed a PCF had a shorter mean time between RT and salvage surgery, 19.5 months (range 5.5–55.4 months) versus 47.0 months (range, 7.2–104 months) ($p = 0.02$) (**Table 2**).

The rate of PCF in those patients who had initial Stage I/II disease was 47 % compared with 78 % those who had Stage III/IV, $p = 0.11$.

DISCUSSION

The success of treatment of early laryngeal cancers with radiation alone gave rise to interest in management of more advanced disease. With the publication of the VA study in 1991[1], a change in standards of care was seen with patient who present with Stage III and IV laryngeal cancers now being considered for an organ preservation approach using chemoradiotherapy. Although the practice of induction chemotherapy with an assessment of response used to triage towards either laryngectomy or further non-surgical management has not become widespread, the use of CCRT for advanced laryngeal cancer is now well accepted and represented in the British Association of Head and Neck Oncologists current management guide- lines[21].

Given the increasing use of non-surgical, organ preservation strategies with or without RT and CT for the primary treatment of laryngeal cancer, contemporary total laryngectomy (TL) is increasingly performed in the salvage setting. This *may* result in high rates of post-operative complication[22], the most common and often difficult to manage is PCF formation [9], occurring in up to 35 % of patients[5,11]. As highlighted by Weber et a.l[23], those patients who are most likely to have a favourable outcome following salvage head and neck surgery include those with a disease-free interval between initial treatment and recurrence. The finding of rapidly recurrent or persistent disease is predictive of poor surgical outcome.

In this study, 58 % of patients developed PCF which is higher than previous reports. The reasons for this are unclear but may include the aggressive approach to organ preservation now adopted by our unit, the advanced disease stage encountered at recurrence (92 % Stage III or IV) and also the high rates of resistant infection, with the most commonly isolated organism being MRSA (41 %)[6]. These high rates of MRSA infection were encountered during the period when MRSA was a significant issue in the institution. PCF results in prolonged hospitalization and higher resource utilization, potentially life threatening complications such as carotid rupture[24] as well as delay of any further post-operative adjuvant chemo/re-irradiation therapy[25-29].

It is generally accepted that pre-operative RT is a risk factor for PCF in head and neck surgery[12,13,19,30,31], in particular increasing the rate, severity and duration of wound breakdown[17,19,32-34]. However, the association between time from RT to surgery and PCF formation is more controversial and a paucity of evidence exists in the literature. A meta-analysis by Paydarfar et al.[12] failed to demonstrate an association between time interval and PCF. A retrospective cohort study by Van der Putten et al.[35] failed to show an association between time interval and major complications, though it is worth noting that major complications here include all those that "needed surgery or admission to the intensive care unit or led to death". In contrast, a more recent retrospective study by Basheeth et al.[36] has shown that performance of laryngectomy within 1 year of completion of RT is a significant risk factor for development of PCF. A study by Stenson et al.[37] looking at optimal timing of post-CRT neck dissection (ND) for advanced head and neck cancer suggested a safe window of surgery somewhere between 4 and 12 weeks. However, a more recent study comparing complications between groups undergoing ND less than 12 weeks or 12 weeks and more showed no difference in overall complication rates[38]. Therefore, given the importance of pre-operative RT as a risk factor for PCF, and the lack of evidence on whether time interval is associated with formation after SL specifically, in this study, we sought to answer the question of whether time interval was associated with PCF post-SL.

The median time between RT and SL in this present study was 16.5 months slightly higher than the 10 months recorded by Grau et al.[5], while the mean time was 31.2 months. We found a significant association between PCF and time between RT and SL, with a mean interval of 19.5 months (range 5.5–55.4 months) in the group who developed a PCF versus 47.0 months (range 7.2–104.0 months) in those who did not ($p = 0.02$). Analysis of all other variables stratified by development of PCF identified no other significant differences between groups in terms of age, gender or stage.

It is known that the acute biological effects of radiation (mucositis and dermatitis) continue for 2–3 months after RT treatment, leading to impaired healing and increased risk of infection [6]. In addition, it has been shown that the accuracy of post-treatment imaging studies, particularly dual-modality PET/CT, increases when delayed to greater than 3-month post-primary treatment[39-42]. The evidence suggests that for neck dissections, delaying past the 3-month window does not increase surgical complications or decrease disease control or survival [38]. The general consensus is that surgery should be performed after the resolution of these acute RT toxicities but before the onset of chronic vascular radiation injury[43,44]. This chronic phase is characterized by endarteritis obliterans, subintimal fibrosis and thrombus formation, which leads to a hypovascular, hypocellular and hypoxic tissue bed[45]. Hopewell et al. [46] showed that this initial endothelial injury, resulting in a reduction in the size of the capillary bed, occurs within 2–4 months of RT, but that later changes in the vasculature associated with loss of smooth muscle were more variable with the upper limit occurring up to 18 months later. They also noted that the presence of vascular changes does not necessarily imply that gross evidence of damage will develop in the parenchyma of the tissue supplied.

It is likely that our finding that a shorter time interval between RT and SL predisposes to PCF is related to multiple factors including both these acute-phase and chronic tissue toxicities in addition to factors, such as malnutrition related to therapy, and the increased risk of resistant bacterial colonization for those recently dis- charged from hospital. The high incidence of MRSA infection detected by the senior authors in a previous study is also a factor that might have had some influence on the development of PCF and cannot be overestimated[47].

This study has significant limitations. We describe a single UK tertiary referral centre's experience, which limits our cohort size and also impacts on the applicability to other groups' practice. Our data are retrospective and, therefore, subject to bias, although comparison of all other covariates in our study suggested that the two groups were similar in terms of demographics and staging both in terms of primary tumour and at time of recurrence. We acknowledge that the small sample size means that there may be covariates that are associated with PCF formation apart from time interval which fail to reach statistical significance in our study. For this reason, we feel that a multi-centre prospective study is needed to address these issues.

Another limitation is lack of data on dose and fields of primary RT given. It is likely that the dose of RT delivered and the modality used to treat patients (IMRT versus 3D- RT) will impact on the tissue toxicity and the potential for PCF following SL. When stratified by development of PCF, however, our data did not support this. Those patients with Stage I/II disease at presentation were treated with narrow field radiation, given the low rates of nodal metastases. Those patients who presented with advanced disease (Stage III/IV) were treated with chemotherapy where fit, and concurrent wide field radiation including the larynx and bilateral nodal basins. Although we did not have specific details on RT dose, our cohorts were balanced in terms of initial stage suggesting that treatment approaches were likely to be similar for both those that developed PCF and those that did not.

Patients at highest risk of such complications may be candidates for altered surgical management in terms of incision placements, use of flaps, indications for neck dissection or delayed TOP[48]. Recent work looking at pharyngeal closure technique during salvage laryngectomy suggests that non-irradiated, vascularized flaps reduce the incidence and duration of PCF formation and should be considered[14]. In addition, following on from the results of this study, the timing of previous RT treatment should also be taken into consideration in surgical planning of patients undergoing salvage total laryngectomy.

CONCLUSION

This study shows a significant association between PCF formation and time interval from primary RT to salvage laryngectomy. Identifying factors associated with higher rates of post-operative morbidity allow surgeons to adapt surgical planning in terms of considering the need for additional tissue transfer, or delayed TOP, in an attempt to minimize rates of PCF.

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Time interval between (chemo)radiotherapy and subsequent laryngectomy is not prognostic for pharyngocutaneous fistula formation nor overall survival

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ABSTRACT

Purpose: Pharyngocutaneous fistula (PCF) formation and swallowing difficulties are common and troublesome complications following total laryngectomy (TL). Prior (chemo)radiotherapy ((C)RT) is thought to be a risk factor for these complications, but there is conflicting evidence as to whether the time interval between (C)RT and TL is important. The impact of time interval on these complications and also its impact on overall survival are investigated.

Methods: Retrospective case note review of all patients undergoing TL at the University Medical Center, Utrecht, The Netherlands over the 10 year period January 2008 to December 2017. The cohort was split into those who underwent TL within a year of finishing (C)RT and those longer than 1 year.

Results: One hundred and twenty six patients (108 males, 18 females), with a mean age of 66 underwent total laryngectomy after prior (C)RT in the study period. Overall 5 year survival was 35% with a median follow up of 30 months. Fifty-four patients underwent laryngectomy within a year of their (C)RT versus 72 patients who had a time interval of more than one year. No differences in PCF rate, risk of dilatation or overall survival could be found between the two groups.

Conclusions: In this modern cohort, time interval between (C)RT and surgery did not impact PCF rate, risk of dilatation or overall survival.

INTRODUCTION

NCCN guidelines for the treatment of advanced stage laryngeal cancer[1] include laryngectomy, (chemo)radiotherapy or some combination thereof. Following the move towards organ sparing approaches driven by the VA[2], RTOG and other studies [3,4], surgeons are increasingly performing total laryngectomy as a salvage procedure following failed (chemo)radiotherapy ((C)RT), or as functional treatment for recurrent aspiration and airway issues following successful (C)RT setting. Indeed, for many units, there is now an almost 50/50 split between primary patients and patients who have undergone prior radiotherapy. This latter group can be split into patients with or without cancer and therefore includes patients undergoing salvage laryngectomy and a proportion of patients undergoing functional laryngectomy.

From our knowledge of radio-biochemistry we know that radiotherapy is toxic to both cancerous and healthy cells. An initial acute inflammation lasts 2-3 months and includes endothelial injury resulting in a reduction in the size of the capillary bed[5]. Chronic changes include increased subintimal fibrosis, loss of vascular smooth muscle and endarteritis obliterans leading to fragile hypovascular, hypocellular and hypoxic tissue[6], a situation which generally stabilizes after 12-18 months.

These changes have several implications for post-radiotherapy management. Perhaps the best investigated is the timing of imaging. For example, the timing of response evaluation by PET/CT has been extensively studied with a consensus that this is best performed after 3 months, i.e. after the initial acute inflammatory phase[7-10]. Another implication for post-radiotherapy management concerns the timing of surgery. Whilst some surgeries are strongly indicated (e.g. recurrent cancer), others may be relatively indicated (e.g. stricture release) and the timing of especially these latter operations can be informed by our understanding of the tissue toxicity. The timing of neck dissections following (C)RT has also been well studied. Stenson et al. [11] suggests a safe window of surgery somewhere between 4 and 12 weeks though a more recent study comparing complications between groups undergoing neck dissection less than 12 weeks or 12 weeks and more showed no difference in overall complication rates[12].

Total laryngectomy is however an order of magnitude more invasive than a neck dissection with implications for speech[13], swallow[14] and breathing. It is associated with high levels of complications, particularly of pharyngo-cutaneous fistula (PCF) formation[15] with published results with rates of up to 58% in patients after prior (chemo) radiotherapy[16]. Several authors have highlighted the time interval between radiotherapy and subsequent laryngectomy as being a risk factor for PCF[17,18] whilst others finding no effect[19,20]. One even finds a longer time interval as a risk factor for PCF[21]. Various cut-offs are used to describe a short vs long interval and few papers report overall survival outcomes or other complications such as swallowing difficulties needing dilatation.

This paper investigates the impact of time interval between primary (chemo)radiotherapy and laryngectomy with regards to PCF, risk of dilatation and overall survival.

MATERIALS AND METHODS

A retrospective cohort study of all patients undergoing total laryngectomy following prior (chemo)radiotherapy at the University Medical Center, Utrecht over the 10 year period Jan 2008 to Dec 2017 was performed. The indication for total laryngectomy was either as salvage treatment for residual or recurrent cancer following (chemo) radiotherapy or as a treatment for a dysfunctional larynx following successful (chemo) radiotherapy.

Patients' demographic, staging, treatment and outcome data were collected using electronic patient records. TNM classification according to the then applicable AJCC manual was recorded. All patients were discussed in our multidisciplinary tumour board and underwent total laryngectomy with or without (partial) pharyngectomy. For patients where the pharynx could not be closed primarily, a variety of flaps were used including pectoralis major with or without skin island, radial forearm free flap (RFFF), anterior lateral thigh flap (ALT), jejunum interposition and gastric pull up. We did not make routine use of salivary bypass tubes during laryngectomy, preferring to use them only if patients developed a PCF.

Patients were stratified by time interval between end of (chemo)radiotherapy and date of laryngectomy. As per Basheeth et al.18 a cut off of 1 year was used to split our patient group into two cohorts for comparison. At one year, the damage from radiotherapy to healthy tissue should have stabilised in the majority patients. Specific outcomes of interest included the short term complication of pharyngo-cutaneous fistula formation (defined as a clinical fistula visible on the skin), the longer term complication of swallowing difficulties necessitating dilatation and the 5 year overall survival, using the date of laryngectomy as the start point.

Statistical analyses were performed using SPSS® Statistics 20.0 (IBM, Armonk, NY). Overall survival was calculated using the Kaplan–Meier method and Cox-mantel log-rank test for comparison. The chi-squared test or binary logistic regression analysis was used as appropriate for univariate analysis.

This study does not fall under the scope of the Medical Research Involving Human Subjects Act and the institutional review board approved this study.

RESULTS

A total of 126 patients (108 males, 18 females) with a mean age of 66 years (range 44-87years) underwent total laryngectomy after prior (chemo)radiotherapy in the study period. One hundred and twenty-two patients were operated as a salvage procedure due to recurrent cancer, 24/126 were operated for an afunctional larynx. Median follow up following laryngectomy was 30 months (range 1 to 130 months). Overall 5 year survival following laryngectomy for the cohort was 35%. A total of 54 patients underwent laryngectomy within a year of their radiotherapy versus 72 patients who had a >1 year time interval until laryngectomy. Univariate comparison of the cohort stratified by time interval of 1 year can be found in **table 1**. No significant differences were found across a range of parameters between the two groups.

Time delay to laryngectomy and overall survival

Time interval between end of radiotherapy and laryngectomy is plotted in **Figure 1**. The mean time interval was 36 months, the median interval 15 months (range 3 -196 months). **Figure 2** shows the different time delays stratified for treatment indication: median interval 5.3 months (salvage) versus 48 months (functional), p= 0.101.

The 5-year survival was 38.5% (n=54) for the <1 year cohort versus 32.4% (n=72) for the >1 year interval cohort (p= 0.987, see **figure 3**). Once again, we stratified our cohort by treatment indication. For the salvage patients, 5 year survival was 35%, with the <1 year cohort having a 5 year survival of 40% versus 30% for the >1 year cohort (p=0.688, see **Figure 3**). For the functional laryngectomies, the 5 year survival was 39% (33% in the <1y cohort versus 40% in the >1y cohort, p=0.46, see **figure 3**).

We also analyzed our patients with regard to whether the primary tumor was in the larynx or hypopharynx. For the whole cohort the 5 year survival was 39% for laryngeal tumors vs 28% for hypopharyngeal, p=0.244)

Using alternative time interval measures

We further analyzed our cohort by splitting them at 6 months, 18 months, 24 months and 30 month intervals. The overall survival differences between the groups thus stratified remained statistically not significant (6 months p=0.936, 18 months p=0.955, 24 months p=0.587, 30 months p=0.407).

TABLE 1: Univariate comparison stratified by >1 year time interval

		Time interval from end of radiotherapy to laryngectomy		
		<1 year	**>1 year**	**P value**
N		54	72	
Indication	Salvage	45	57	
	Functional	9	15	0.556
Gender	Male	47	61	
	Female	7	11	0.713
ASA	1	25	28	
	2	18	20	
	3	10	19	
	4	1	2	0.660
Age	<65	27	31	
	>65	27	41	0.439
Tumor Site	Supraglottis	8	19	
	Glottis	23	35	
	Subglottis	1	3	
	Post cricoid	1	0	
	Piriform sinus	12	8	
	Transglottic	7	2	0.113
Previous Cextuximab	No	50	67	
	Yes	4	5	0.920
Previous Cisplatinum	No	45	65	
	Yes	9	7	0.247
rT-stage	rT0 (functional)	9	15	
	rT1	5	5	
	rT2	16	18	
	rT3	12	7	
	rT4	12	27	0.181
rN-stage	rN0	46	60	
	rN1	1	5	
	rN2a	0	0	
	rN2b	6	4	
	rN2c	1	2	
	rN3	1	1	0.440

TABLE 1: Univariate comparison stratified by >1 year time interval

		Time interval from end of radiotherapy to laryngectomy		
		<1 year	**>1 year**	**P value**
Operation	TL	35	41	
	TLPP/TLP	19	31	0.372
Neck dissection	None	33	40	
	Unilateral	15	24	
	Bilateral	6	8	0.790
Initial flap reconstruction	None	33	41	
	Pectoralis Major	20	23	
	Radial forearm free flap	0	0	
	Anterior lateral thigh	1	3	
	Gastric pull-up	0	3	
	Jejunum	0	2	0.414
Later dilatation	No	42	59	
	Yes	12	13	0.562
Pharyngocutaenous fistula	No	36	48	
	Yes	18	24	0.999

Pharyngo-cutaneous fistula formation

A total of 42/126 (33%) patients developed a PCF postoperatively. When stratified according to time interval from radiotherapy to surgery, 18/54 (33%) of <1 year interval patients developed a PCF versus 24/72 (33%) in the >1 year cohort (p=0.999). Once again, stratifying patients at time intervals of 6, 18, 24 and 30 months did not reveal any significant differences in risk of PCF formation. (6 months p=0.631, 18 months p=0.523, 24 months p=0.597, 30 months p=0.689)

Risk of future dilatation

A later complication of total laryngectomy can be swallowing difficulties. Reported rates of such difficulties severe enough to require dilatation are roughly 23%[14]. In our cohort, 25/126 patients (20%) underwent dilatation, 12/54 (22%) in the short interval cohort vs 13/72 (18%) in the long interval cohort. On binominal logistic regression, this difference was not statistically significant, p=0.562.

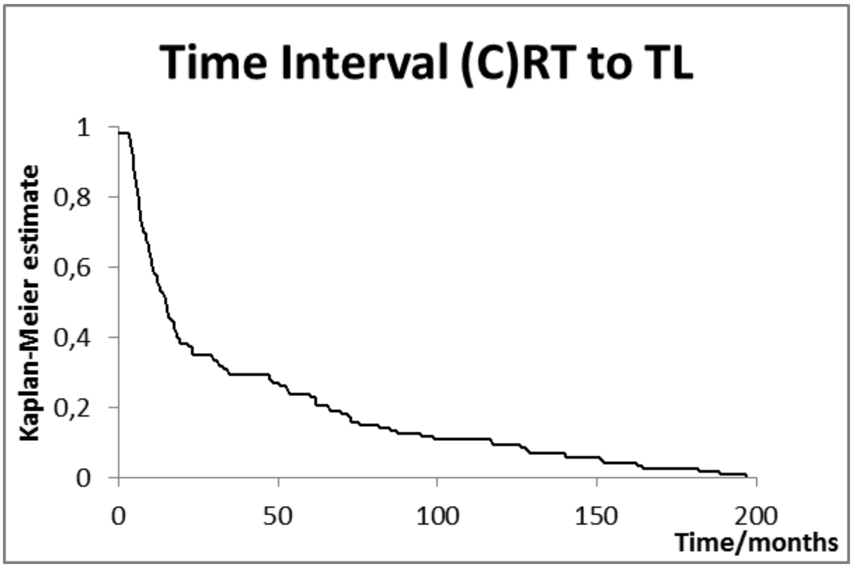

FIGURE 1: Time interval in months between end of radiotherapy and subsequent total laryngectomy (n=126)

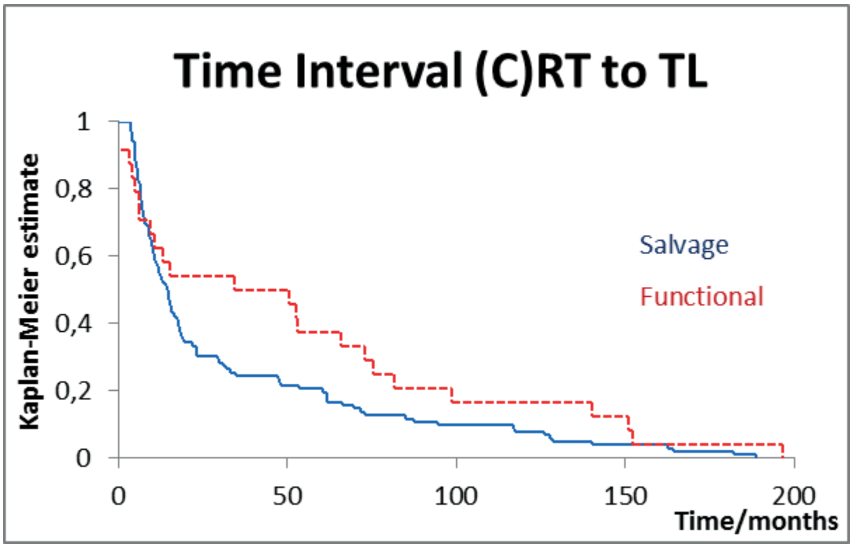

FIGURE 2: Time interval stratified for salvage (n=102) vs functional (n=24, p=0.101).

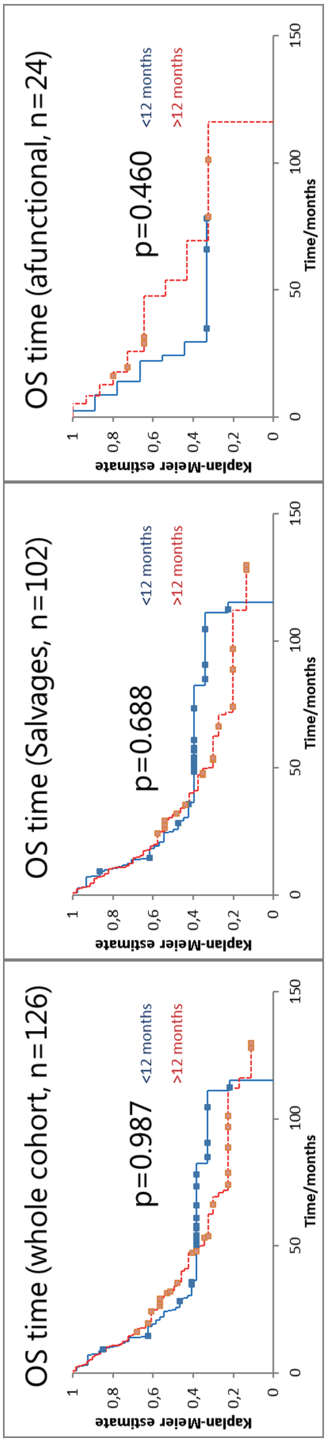

FIGURE 3: Overall survival for cohorts, stratified by <1 year time interval vs >1 year time interval

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DISCUSSION

We present a single tertiary institution's experience of laryngectomy in patients who have undergone previous (chemo)radiotherapy, specifically focusing on whether the time interval between end of (chemo)radiotherapy and laryngectomy is correlated with risk of PCF, need for dilatation and changes in overall survival.

Intuitively, it seems that the time interval to surgery would stratify patients in an informative way following (chemo)radiotherapy. In the salvage group, the time interval might imply radio-resistance on the part of the tumor. The distinction between residual and recurrent disease is debatable, but patients who were operated shortly after finishing their (chemo)radiotherapy might well have had more aggressive/advanced disease or at least more radio-resistant tumors than those only salvaged years later. Indeed, Weber et al.[22] argue that patients with a longer disease-free interval between initial treatment and recurrence are more likely to have a favorable outcome and that the finding of rapidly recurrent or persistent disease is predictive of poor outcomes, though this is not supported by our data. Note however that the most aggressive tumors presumably led to loco-regional irresectable disease or distant metastasis meaning that the patients were no longer candidates for salvage total laryngectomy and are not in our data set.

Furthermore, from a radiobiological point of view, it is clear that tissue quality after (chemo)radiotherapy is generally worse particularly in a subset of patients who ultimately require functional laryngectomy. It might also be expected that this problem is particularly acute in patients operated soon after radiotherapy and that this would be reflected in increased rates of complications in both the salvage and functional groups.

The literature however contains conflicting evidence. A meta-analysis by Paydarfar et al.[19] found no association between time interval and PCF though he doesn't mention survival outcomes. Van der Putten et al. [23] similarly showed no association between time interval and major complications, though it is worth noting that major complications here include all those that "needed surgery or admission to the intensive care unit or led to death" and the time interval used is not described.

In contrast, Basheeth et al.[18] and Scotton et al.[17] have shown that a short interval between radiotherapy and laryngectomy is a significant risk factor for development of PCF. We could find no literature regarding the longer term complication of swallowing difficulties requiring dilatation.

Our data shows not only similar PCF and dilatation rates between the short and long interval patients, but also similar overall survival. It is also noteworthy that we describe 126 modern patients; this is 3 times[18] and 5 times[17] larger than single institution series discussed, without having the shortcomings of being a pooled analysis of data as in the DAHANCA[24] and American studies[19]. Furthermore, these 4 publications also relate to datasets dating as far back as the late 1970s when presumably radiotherapy techniques were less effective at sparing healthy tissue.

In other ways though, it seems our data is fairly consistent with these publications. Though they do not publish a figure similar to our **figure 1**, our median interval of 15 months compares to with Grau et al.'s [24] 10 months and Scotton et al.'s 16.5 months. Paydarfar et al. and Basheeth et al. do not report median intervals. The latter however states that 30/47 (64%) patients underwent salvage laryngectomy within 1 year of (chemo)radiotherapy compared to our 54/126 (43%).

The incidences of PCF formation also seem similar in 3 of the 4 data sets with only Scotton et al.'s incidence of PCF is 58% being markedly higher. Our incidence is 33% compares with Basheeth et al's 34%, Payfardar et al's 25.7% and Grau et al's 30% (in the more modern patients). Only Grau et al report a 5 year overall survival of 36% (vs our 35%), though not stratified for time interval.

Interestingly, the most recent analysis of time interval and PCF is a Dutch audit of 190 post (C)RT laryngectomies[21] which found that a *longer* interval between (chemo) radiotherapy and laryngectomy was a risk factor for PCF. Also, the cut-off used for short and long interval was 30 months (deemed as "clinically relevant") which would stratify patients well into the chronic phase of inflammation and perhaps better delineate those with *ongoing* inflammation and those with a stable situation. When we analyse our data however with this 30 month cut-off, again we find no statistically significant differences in PCF rate (27/84 (32%) short interval PCFs vs 15/42 (36%) long interval PCFs, p=0.689) or in overall survival (5y overall survival 35% vs 35%, p= 0.407).

Flap use

Though not one of our primary aims in this investigation, no discussion of PCF can be complete without a mention of flaps. A total of 21/54 (39%) patients in the <1y cohort and 31/72 (43%) patients in the >1y cohort had a flap during their laryngectomy (see **table 1**). Analysis of whether this reduced the PCF rate is unfortunately confounded by the fact that many of these flaps would have been used precisely in patients who were deemed at high risk of PCF. Furthermore, our data did not allow us to see whether in cases of PCF or flap-failure, this was due to problems with the flap itself (for example, thrombosis) or problems with the in-setting (for example, dehiscence). It could be imagined that a healthy flap might well dehisce from an irradiated wound bed and that therefore a flap is not necessarily a panacea for PCFs.

CONCLUSIONS

We present a modern, large, homogenous cohort of patients undergoing total laryngectomy after prior (chemo)radiotherapy. We find no association between the time interval between prior therapy and surgery and the risk of PCF formation, risk of dilatation or post-operative overall survival.

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Dilation after laryngectomy: Incidence, risk factors and complications

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ABSTRACT

Background: Neopharyngeal stenosis is a recognized sequela of total laryngectomy (TL). We aim to investigate the incidence of stenosis requiring dilation, risk factors for stenosis and complications of dilation.

Methods: Retrospective cohort study of patients undergoing TL in two dedicated head and neck centres in the Netherlands.

Results: A total of 477 patients, (81% men, median age of 64 at TL) were included. Indication for TL was previously untreated primary tumour in 41%, salvage following (chemo)radiotherapy (CRT) in 44%, dysfunctional larynx in 9% and a second primary tumour in 6%. The cumulative incidence of dilatation at 5 years was 22.8%, and in total 968 dilatations were performed. Median number of dilations per patient was 3 (range 1–113). Female gender, a hypopharynx tumour, and (C)RT before or after the TL were significantly associated with stenosis requiring dilation. We observed 8 major complications (0.8%) predominantly during the first dilation procedures. Use of general anaesthesia is a risk factor for complications. The most frequent major complication was severe oesophageal perforation (n = 6 in 5 patients).

Conclusion: The cumulative incidence of pharyngeal stenosis needing dilation was 22.8% at 5 years. Roughly half of these patients could be treated with a limited number of dilations, the rest however needed ongoing dilations. Major complications are rare (0.8%) but can be life threatening. General anaesthetics is a risk factor for complications, and complications occurred predominantly during the first few dilations procedures. This should alert the physician to be extra careful in new patients.

INTRODUCTION

Total laryngectomy (TL) with or without (partial) pharyngectomy and adjuvant radiotherapy (RT) is often recommended for bulky advanced stage cancer of the larynx or hypopharynx whilst less bulky disease is often treated with (chemo)radiotherapy (CRT) for organ preservation[1-5]. However, despite initial organ preservation, TL is subsequently still performed in roughly a third of advanced stage patients, either as salvage procedure for a recurrence, treatment of a second primary or for functional reasons[4,6,7].

Rehabilitation following TL largely focuses on speech rehabilitation. Most Western countries use indwelling voice prostheses (VP) and with this, up to 90% of patients achieve satisfactory speech[8,9]. Less attention however is paid to swallowing function after TL. The majority of patients are expected to return to a normal diet, but some find that swallowing becomes difficult[10,11]. This can be due to anatomical reasons such as narrowing of the neopharyngeal lumen (a lumen <12 mm invariably leads to dysphagia[12]), pseudo-diverticulum formation[13], or due to functional problems changes in the quality/ quantity of saliva, poor pressure built up at the base of tongue or loss of coordinated muscular contraction in the neopharynx. Rates of anatomical pharyngeal stenosis have been reported as high as 33% in surgically treated patients[14] and over 50% in patients treated with CRT[15]. Severe dysphagia negatively effects patients' quality of life and can lead to nutritional deficiencies and increased healthcare costs[16]. The diagnosis of dysphagia is almost entirely from the patient's self- reported symptoms and the threshold for intervention depends on whether a patient's nutritional status is affected and/or their perceived quality of life. Stepwise interventions can involve dietary advice/ modification, the use of supplementary nutritional drinks, dental rehabilitation, proton pump inhibitors, tube feeding, dilation or surgical reconstruction of the neo-pharynx.

Not all patients with dysphagia are suitable for dilation. Some patients have no clear radiographic or endoscopic evidence of a stricture. In these patients it is thought that the dysphagia is more "functional/ physiological" than "anatomical"[17,18]. Other patients have clear radiographic evidence of a diverticulum or pseudo-epiglottis[19] which is also not amenable to dilation.

Dilation for benign oesophageal strictures caused by inflammation of the oesophagus or post-operative stenosis of the anastomosis after oesophagectomy is reported to be highly successful[12,20-22]. However, among TL patients who are often treated with chemoradiotherapy before or after the TL and thereby represent a distinct patient group, only small case series have described the effect of dilation procedures in this group of patients[23].

In this paper we aim to investigate in a cohort of patients having undergone TL:

1. The cumulative incidence of pharyngeal stenosis requiring dilation
2. Risk factors for stenosis requiring dilation
3. The incidence and risk factors for complications following dilation

MATERIALS AND METHODS

We performed a retrospective cohort study of all patients under- going total laryngectomy in two dedicated Head and Neck Centres in The Netherlands: the University Medical Centre Utrecht, Utrecht (Jan 2008–Dec 2016) and The Netherlands Cancer Institute, Amsterdam (Jan 2000–Dec 2012). Patients' demographic, staging, treatment and outcome data were collected using (scanned) electronic patient records. We recorded TNM classification according to the then applicable AJCC manual, (5th, 6th and 7th editions). All patients underwent total laryngectomy with or without (partial) pharyngectomy either as a primary treatment, salvage treatment, treatment for a second primary or as a functional treatment for a dysfunctional larynx. TLs were performed by a variety of surgeons during the study period and details on the surgical techniques could not be found in all patients. Specifically, myotomy of the cricopharyngeal muscle and neurectomy of the pharyngeal plexus, as well as the method of closure (vertical, T, horizontal, suture type, stitch type) were not well documented and differed between surgeons. For each dilation procedure we recorded the maximum size of dilation (in mm), type of dilator, type of anaesthetic, which physician group performed the dilation (head & neck surgeons or gastro-enterologist) and whether any complications occurred. We excluded dilation procedures where the stenosis was due to tumour recurrence. Complications following dilation were grouped into minor or major. Major complications were defined as complications for which the patient had to be admitted to the ward for > 24 h and received medical treatment other than analgesics, antiemetics, and antipyretics. Minor complications were defined as complications which resolved within < 24 h after dilation, for which no medical treatment was necessary (other than replacement of a dislocated voice prosthesis).

Dilation technique

In our institutes, dilation is performed either by a gastroenterologist or a head and neck surgeon. The gastroenterologist generally uses procedural sedation (using a combination of fentanyl and midazolam or propofol) whereas the head and neck surgeon dilates under general anaesthesia. The gastroenterologists routinely use a flexible endoscope to inspect the oesophagus and stomach and place a guidewire for Savary bougies (Savary Gilliard technique [13]). The head and neck surgeons use the same bougies but without placing a guidewire and generally visualize only the upper oesophagus with a rigid oesophagoscope. For both physician groups, the stenosis is dilated by passing bougies of increasing diameter through the stenosis until either the maximum diameter is reached (18 mm) or until too much resistance is felt by the operator. Whilst achieving small mucosal tears is necessary to treat the stenosis, an oesophageal perforation is a well-known major complication of this procedure that has to be avoided.

Statistical analysis

Statistical analyses were performed using SPSS® Statistics 20.0 (IBM, Armonk, NY) and R studio. Descriptive analysis was used to summarize patient and treatment characteristics. We used a cumulative incidence technique to assess the effect (expressed as a hazard ratio) of patient and treatment characteristics on dilatation, which is a time dependent outcome, using the R-package 'cmprsk'[24]. Death was treated as a competing risk and patients were censored when lost-to- follow-up. The same technique was used to assess the cumulative incidence of dilatation with death as a competing risk. To calculate the cumulative incidence, we used time in days since TL to date of first dilatation procedure.

Using this technique, we performed univariate and multivariate regression analyses to identify patient and treatment characteristics that correlate with the patient having a dilation. Odds ratios on a complication following a dilatation procedure, which was not considered time dependent, were calculated using univariate and multivariate logistic analyses.

Ethical considerations

This study does not fall under the scope of the Medical Research Involving Human Subjects Act and the institutional review boards of both centres approved this study.

RESULTS

Patients

A total of 477 patients (81% men) with a median age at TL of 64 (range 38–91) were included in this study. Median follow-up time in months since TL was 81 months (95% CI 69–96). Indication for TL was salvage surgery in 211 (44%), primary surgery in 193 (41%), a dysfunctional larynx in 45 (9%) and second primary tumour in 28 (6%), see **Table 1** for patient characteristics.

Dilations

In our cohort 111/477 (23%) patients underwent a total of 968 dilations for symptomatic pharyngeal stenosis. The cumulative incidence of dilatation (with death as a competing risk) increased over time. At 5, 10 and 15 years this was respectively 22.8%. 26.5% and 29.0%, see **Fig. 1** for a plot of the cumulative incidence. The median number of dilations performed per patient was 3 (range 1–113). Median time to first dilation was 9 months after TL (95% CI 7–11). Twenty- seven (27/111 = 24%) patients underwent one dilation, 23 (21%) re- quired two dilations, 13 (12%) three dilations and the remaining 48 patients (43%) had more than 3 dilations.

The gastroenterologists performed 91% of all dilations, 9% was performed by the head and neck surgeons, though there was considerable cross-over with patients being dilated by both types of specialists. On a patient level, 43 patients (39%) underwent their first dilation procedure by the head and neck surgeon. Of these 43 patients, 13 patients were also dilated by the gastroenterologists at a later time point. Of the 68 patients who were initially dilated by gastro-enterologists, 8 patients were also dilated by the head and neck surgeon at a later time point.

The stenosis was dilated to a mean maximal diameter of 13 mm (range 6–18 mm) which was similar among dilation procedures by the head and neck surgeons and gastroenterologists. All patients were dilated using silicon bougie dilatators. In 67% of procedures a combination of fentanyl and midazolam for sedation was used, in 18% propofol, 8% was performed under general anaesthetics and in 7% the type of sedation was not reported. One patient performed self-dilations at home. Because the frequency and complication rate of these dilations were unknown, we did not include these dilations in our analysis.

Table 1: Characteristics of dilation vs non-dilation groups and univariable analysis presented in adjusted hazard ratios* with corresponding p-values**

	Total N (%)	Non-dilation group N (%)	Dilation group N (%)	Univariate analysis OR (95% CI)	P value
Mean age at TL (SD)	64 (10.0)	64 (10.2)	64 (9.4)	1.00 (0.98-1.02)	0.890
Gender					
Male	385 (81)	306 (84)	79 (71)	1.00	
Female	92 (19)	60 (16)	32 (29)	1.87 (1.24-2.81)	**0.003**
Tumour site					
Larynx	344 (72)	277 (76)	67 (60)	1.00	
Hypopharynx	98 (21)	66 (18)	32 (29)	2.06 (1.34-3.15)	**<0.001**
Other	35 (7)	23 (6)	12 (11)	1.86 (0.98-3.55)	0.057
Initial T-stage					
Tls/T1	71 (15)	52 (14)	19 (17)		
T2 (vsT1)***	106 (22)	79 (22)	27 (24)	1.11 (0.60-1.87)	0.84
T3 (vsT2)	102 (21)	81 (22)	21 (19)	0.74 (0.42-1.32)	0.31
T4 (vsT3)	189 (40)	149 (41)	40 (36)	1.01 (0.59-1.72)	0.99
Unknown	9 (2)	5 (1)	4 (4)	–	–
Initial N-stage					
N0	294 (62)	234 (64)	60 (54)	1.00	
N positive	178 (37)	129 (35)	49 (44)	1.46 (1.00-2.13)	0.050
Unknown	5 (1)	3 (0.8)	2 (1.8)	–	–
Indication TL					
Primary	193 (41)	158 (43)	35 (32)	1.00	
Salvage	211 (44)	167 (46)	44 (40)	1.24 (0.80-1.94)	0.34
2nd primary	28 (6)	14 (4)	14 (13)	2.90 (1.62-5.19)	**<0.001**
Dysfunctional	45 (9)	27 (7)	18 (16)	2.70 (1.54-4.72)	**<0.001**
Neck dissection					
None	183 (38)	137 (37)	46 (41)		
Unilateral (vs None)***	142 (30)	111 (30)	31 (28)	0.92 (0.59-1.45)	0.73
Bilateral (vs Unilateral)	152 (32)	118 (32)	34 (31)	0.94 (0.58-1.53)	0.81
Primary puncture					
No	65 (14)	48 (13)	17 (15)	1.00	
Yes	412 (86)	318 (87)	94 (85)	0.78 (0.47-1.32)	0.36
(Chemo)radiotherapy					

Table 1: Characteristics of dilation vs non-dilation groups and univariable analysis presented in adjusted hazard ratios* with corresponding p-values**

	Total N (%)	Non-dilation group N (%)	Dilation group N (%)	Univariate analysis OR (95% CI)	P value
Never	56 (12)	53 (15)	3 (3)	1.00	
Before TL	310 (65)	227 (62)	83 (74)	5.42 (1.71-17.2)	**0.004**
After TL	104 (22)	82 (23)	22 (20)	3.69 (1.10-12.4)	**0.035**
Before and after TL	7 (1.5)	2 (0.5)	5 (4)	19.3 (5.04-73.8)	**<0.001**
Flap					
None	295 (62)	240 (66)	55 (49)	1.00	
PM to reconstruct	105 (22)	71 (20)	34 (30)	1.99 (1.30-3.04)	**0.002**
PM to overlay	24 (5)	18 (5)	6 (5)	1.48 (0.65-3.38)	0.350
FRFF	14 (3)	8 (2)	6 (5)	2.80 (1.17-6.72)	**0.021**
ALT	13 (3)	8 (2)	5 (4)	2.39 (0.97-5.87)	0.057
Gastric pull up	10 (2)	7 (2)	3 (3)	1.60 (0.50-5.18)	0.43
Other	8 (2)	7 (2)	1 (0.9)	0.81 (0.10-6.45)	0.84
Unknown	8 (2)	5 (1)	3 (3)	–	–
Post-operative clinical fistula < 30 days after TL					
None	347 (73)	275 (75)	72 (65)	1.00	
Yes	126 (26)	87 (24)	39 (35)	1.68 (1.14-2.48)	**0.009**
Unknown	4 (0.8)	4 (1)	–	–	–

** Hazard ratios are calculated using a cumulative incidence technique using (time to) dilatation or death as competing events. Hazard ratios shown here are hazard ratios on first dilatation procedure.*

*** Bold faced p-values are significant.*

**** In the univariate analysis the ordinal variables T-classification and type of neck dissection were compared with the nearest lower category to assess the effect of 1 higher stage (T3 versus T2, etc.)*

Risk for stenosis requiring dilation

We performed a univariate analysis to assess risk factors for dysphagia requiring dilation using the cumulative incidence technique described in the methods section (see **Table 1**). Statistically significant variables on univariate analysis included female gender, a hypopharynx tumour (ref = larynx), TL for a dysfunctional larynx or for a second primary (ref = primary TL), (C)RT before, after or before and after TL (ref = no (C)RT), a pectoralis major (PM) flap to reconstruct a mucosal defect (i.e. not as overlay reinforcement), a free radial forearm flap (FRFF (ref = no flap)), and the development of a pharyngo-cutaneous fistula < 30 days after TL.

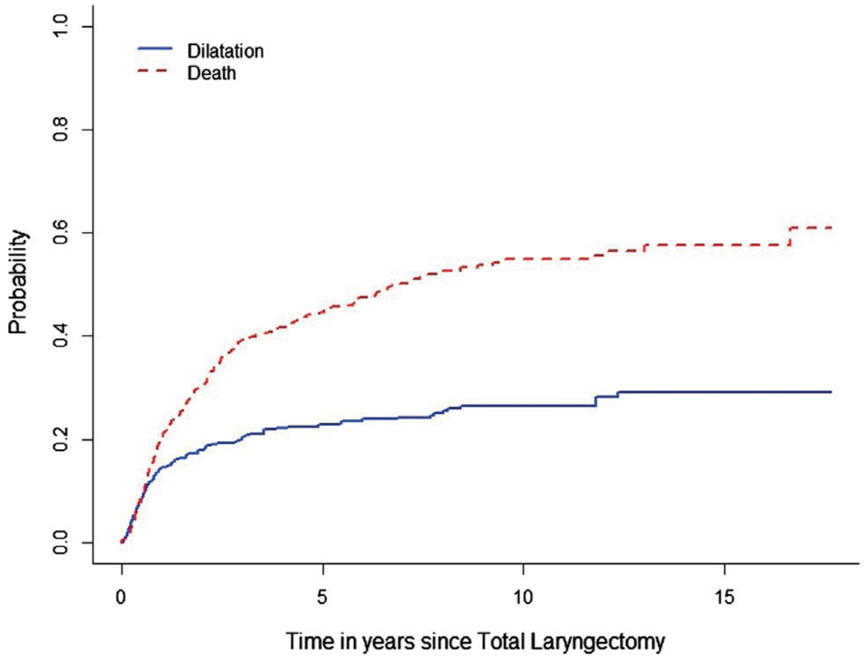

Figure 1: Cumulative incidence of dilatation. The X-axis depicts the time in years since total laryngectomy, the Y-axis depicts the cumulative probability on a dilatation procedure (blue straight line) or death (red, dashed line).

We subsequently performed a multivariate analysis including the parameters that showed significant interaction with stricture formation on univariate analysis. Using a binary logistic backwards regression model the following parameters remained statistically significantly associated with stricture formation necessitating dilation: female gender (HR 1.87, $p = 0.006$), a hypopharynx tumor (ref = larynx) (HR 2.12, $p = 0.001$), (C)RT before TL (HR 6.13, $p = 0.003$), (C)RT after TL(HR 3.65, $p = 0.04$), and (C)RT before as well as after the TL (HR 25.09, $p < 0.0001$) (ref = no (C)RT) (see **Table 2**).

Complications following dilation

On a procedure level we observed 27 complications during the 968 dilations (2.8%), of which 19 minor (2.0%) and 8 major (0.8%). On a patient level, 7 patients (6%) suffered 8 major complications.

TABLE 2: Multivariate analysis demonstrating adjusted hazard ratio for development of stricture formation necessitating dilation after total laryngectomy.*

	Hazards ratio (95% C.I.)	P-value
Gender		
Male	1.00	
Female	1.87 (1.20-2.91)	0.006
Tumour site		
Larynx	1.00	
Hypopharynx	2.12 (1.34-3.35)	0.001
Other	1.37 (0.61-3.08)	0.38
Indication TL		
Primary	1.00	
Salvage	0.80 (0.69-2.61)	0.43
2^{nd} primary	1.42 (0.67-3.01)	0.36
Dysfunctional	1.42 (0.71-2.84)	0.32
(Chemo)radiotherapy		
Never	1.00	
Before TL	6.13 (1.86-20.22)	0.003
After TL	3.65 (1.06-12.60)	0.04
Before and after TL	25.09 (5.76-109.35)	<0.001

** Hazard ratios are calculated using a cumulative incidence technique using (time to) dilatation or death as competing events. Hazard ratios shown here are hazard ratios on first dilatation procedure.*

The major complications were: anaphylactic shock caused by NSAIDs taken before the dilation procedure (n = 1), a voice prosthesis dislodged into the bronchus causing severe cardiac stress, intensive care stay and a Tsako-Tsubo cardiomyopathy (n = 1) and transmural oesophageal perforations (n = 6 in 5 patients).

Two proximal perforations caused leakage laterally to the carotid artery (n = 1) and leakage posteriorly to the pre-vertebral space (n = 1). The former developed a pharyngo-cutaneous fistula which was managed conservatively with wound dressings. The latter underwent multiple surgeries including stabilization of the vertebral column by the spinal surgeons. One distal perforation required intensive care admission (n = 1) and another distal perforation necessitated laparotomy (n = 1) and direct repair. One patient suffered two major complications at dilation number 1 and 2, both involving proximal perforations which could be managed conservatively.

Five of the 8 major complications occurred in the first or second dilation procedure of this patient. The other three occurred during respectively the 8th, 12th and 31st dilation procedure. Of note, two of these "late" complications were unusual in that one was a distal oesophageal perforation in a patient with a hiatus hernia and one was the dislodged voice prosthesis. We observed only one 'late' proximal oesophageal perforation in a patient during his 31st dilation.

Minor complications were: loss of voice prosthesis during dilation or < 24 h due to oedema (n = 6), suspected mucosal tear/hematemesis for which the patient was observed but that resolved spontaneously < 24 h after dilation (n = 7), oedema temporarily worsening dysphagia (n = 3), fever with unknown cause which resolved < 24 h after dilation (n = 1), exacerbation COPD (n = 1) and transient but significant desaturation during the procedure without any further consequences (n = 1).

Risk factors for complications

We performed a univariate analysis to assess risk factors for major complications. The following variables were entered into univariate analysis: age, gender, T-stage, N-stage, tumour localization, indication for TL, (C)RT pre- or post TL, clinical fistula after TL, flap reconstruction, maximum size of bougie used (6–12 mm, 12.5–14 mm or 14.5–18 mm), dilation performed by head and neck surgeon or gastroenterologists, type of anaesthetic used, and first dilation versus sub- sequent dilation. The following variables were significantly related to a higher risk on a major complication: first dilation procedure (OR 4.7, 95% CI 1.12–20.1, p = 0.04), general anaesthetic (OR 9.15, 95% CI 1.81–46.10, p = 0.007, ref = other anaesthetics (fentanyl, midazolam) and dilation performed by the head and neck surgeon (OR 5.95, 95% CI 1.40–25.30, p = 0.016, ref = gastroenterologist).

We subsequently entered the variables into a multivariate analysis, except for type of physician. Since only head and neck surgeons per- form dilations under general anaesthesia, these two variables are over- lapping, thus the variable type of physician was barred from entering the multivariate model. Using a binary logistic backward regression model, only a dilation procedure under general anaesthetics remained significantly associated with a higher risk on a major complication (OR 9.15 95% CI 1.81–46.10, p = 0.007).

Gastric pull-up

During follow-up, two patients with symptomatic stenosis under- went a gastric pull up reconstruction of the stenotic segment following failed dilations. One of the patients suffered a heart attack intra-operatively and died, the other made an unremarkable recovery although his swallowing function remained impaired, as the jejunostomy tube could not be removed.

DISCUSSION

In this consecutive cohort of 477 patients who underwent a laryngectomy, almost a quarter of all patients underwent one or more dilations for dysphagia, with a median of 3 procedures per patient. The cumulative incidence of dilatation increased over time from 22.8% at 5 years to 29% 15 years after TL. Risk factors for dysphagia requiring dilation were female gender, a hypopharynx tumour, and (chemo) radiotherapy before or after TL. On a procedure level, we observed a major complication rate of 0.8%, which was significantly higher among patients dilated under general anaesthesia.

The incidence of pharyngeal stenosis requiring dilation

The cumulative incidence of 22.8% requiring dilation at 5 years means that dysphagia is one of the most common sequelae of a TL[25]. Indeed, other studies found (dilation and non-dilation necessitating) rates of dysphagia as high as 50–72% after TL[17] and stricture formation rates of 13–50%[26-31]. Due to the retrospective nature of the cohort, we were unable to reliably evaluate the incidence of dysphagia not necessitating dilation. Therefore, the actual incidence of dysphagia in our cohort is probably higher.

Risk factors for stenosis requiring dilation

Not surprisingly, (C)RT before or after the TL was the most important risk factor for dysphagia requiring dilation besides female gender and a hypopharynx tumour. Dysphagia as a complication after CRT for head and neck cancer has been described by Kraaijenga et al. in a long-term follow-up study. In their cohort, at a median follow-up time of 11 years, 54% had moderate to serious swallowing problems, and 14% was still tube feeding dependent [15]. In another retrospective study of 199 patients receiving CRT mainly for T3/T4 larynx, hypo- pharynx and oropharynx cancer, 21% of patients developed symptomatic strictures. Similarly to our data set, risk factors for stricture formation in their cohort were female gender and a hypopharynx tumour, but also patients receiving twice daily radiotherapy showed an in- creased risk for stenosis[32].

In our cohort, patients were laryngectomized in the time period 2000–2016 and received RT before (66%) or after (22%) the TL. Only 12% was not treated with RT. Given the time frame in which patients were included and the fact that patients might have had radiotherapy several years before their TL, patients in this cohort were treated with several different radiotherapy techniques. Details regarding type of radiotherapy and dosage were missing not at random, rendering an analysis based on radiotherapy details impossible. The incidence of dysphagia and the necessity for dilatations in future patients treated with IMRT or VMAT might be lower as this technique aims to spare organs at risk[33]. Christianen et al. recently demonstrated how swallowing sparing IMRT (SW-IMRT) with dose constraints for both parotid glands and the swallowing organs at risk, can indeed lead to reduced swallowing dysfunction 6 months after completion of treatment[34]. It is however important to note that also preventive swallowing therapy and a dedicated rehabilitation program following (C)RT might further decrease the incidence of dysphagia and necessity for dilatation in future patients[35].

Due to the retrospective nature of our study we were unable to reliably analyse closure technique and its relation to dysphagia. The specific stich technique used (eg. Conley, interrupted, stapler), the suture material (monofilament, polyfilament, barbed), the closure form (vertical, T, horizontal) are all of particular interest and have their proponents in the surgical community. Furthermore, whether the pharynx could be primarily closed or whether partial reconstruction with for example a pectoralis major skin island flap or full 360-degree reconstruction should intuitively impact on dysphagia post-operatively. Indeed, in univariate analysis the PM to reconstruct was statistically significant, as was the free forearm flap but these did not remain significant on multivariate analysis.

The incidence and risk factors for complications following dilation

In the literature, the most important risk factor for a complication of dilation, is the presence of a malignant or complex stricture, or a caustic induced stricture[12,36,37]. Complex strictures are described as narrower or more angulated strictures. Piotet et al. described their experience in 1826 endoscopic dilations in which they observed a complication rate of 0.8% for benign strictures and 4.6% for malignant strictures[12]. These figures have been indeed reported by other studies[38,39], and the 0.8% is similar to our major complications rate. In our cohort, 7 patients (6%) suffered 8 major complications, of which 6 perforations. Five of the 6 perforations occurred during the first or second dilations. This should alert the operator to be particularly careful with new patients. On multivariate analysis dilation under general anaesthesia was associated with the highest OR for a complication. It is possible that the muscle relaxant used during anaesthesia mitigates feedback from the patient, leading to overly ambitious dilation and a higher risk on an oesophageal perforation. Furthermore, the indication for the first dilation is invariably given by the head and neck surgeon, who then chooses whether this will be done by a head and neck surgeon under general anaesthesia or as an endoscopic procedure by the gastro-enterologist. Reasons to perform the dilatation under general anaesthesia by the head and neck surgeon may be to exclude recurrent tumour in the neopharynx or to evaluate severe stenosis for other treatment options like surgical reconstruction of the neo-pharynx. It can be anticipated that these cases are more difficult and harbours a higher risk of complications.

Success rate of dilation

In our data set, 57% of patients who were dilated required 1-3 dilations. The remaining 43% underwent repeated dilations due to on- going dysphagia (one patient had >100 dilations). In these patients, surgical reconstruction of the stenotic segment (for example with a flap or gastric pull up) can be offered. It must however be noted that our experience with gastric pull-up as a functional procedure to treat dysphagia was limited to two patients, making the numbers too small for any meaningful conclusions.

Conclusion

With a cumulative incidence rate of 22.8% at 5 years, dysphagia necessitating dilation is a common sequela following laryngectomy, and is more common in female patients, patients with hypopharynx tumours and in association with (chemo)radiotherapy before or after the TL. Roughly half the patients requiring dilation could be treated with a limited number of dilations, the others however needed serial dilations. Major complications such as perforations are rare and occur almost exclusively in the first and second dilations. This should alert the physician to be extra careful in new patients.

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- # Summary
- # Samenvatting

SUMMARY

This thesis is the culmination of some 10 years' interest in laryngectomies. The data has been collected from 3 separate units, namely Guy's & St. Thomas' in London (60 laryngectomy patients from 2003-2010), the UniSpital in Zurich (114 patients with T3/T4 disease treated with organ-preserving protocols between 1981-2011) and the University Medical Center, Utrecht (242 laryngectomy patients from 2008-2017). Chapter 15 uses a combined dataset from the Netherlands Cancer Institute and the UMC Utrecht for a total of 477 patients. Whilst it was tempting to combine all the data-sets for a meta-analysis we have chosen not to do so as there are clearly differences in each country's tumour board preferences and the timelines involved make analysis of combined data-sets problematic.

In chapter 4 we analyse the largest and most modern data-set, namely that from the UMC Utrecht. This chapter investigates 242 consecutive patients undergoing laryngectomy specifically looking at incidence of PCF, treatment of PCF, PCF duration/closure success rate, delay to adjuvant radiotherapy, risk of future neopharyngeal dilation and survival. These outcome measures recur throughout the thesis, especially with respect to the UMC Utrecht data-set. Chapter 4 thus sets the scene and tries to provide some measure of the problems encountered following laryngectomy. We see that laryngectomy is predominately performed in older men with a more or less even split between primary and salvage cases. The length of stay is on average 16 days for patients without a PCF and 30 for patients with a PCF. Roughly half of the patients with PCF will return to theatre and of these, 20% will return to theatre more than once. PCF is also significantly associated with a worse 5 year survival rate (5 year overall survival of 44% no PCF vs 24% PCF, OR 1.7, p=0.001). Whether this correlation implies causality is a difficult question to answer, though the suspicion is that lower fitness patients with larger resections for more aggressive disease are more likely to suffer PCF *and* poor survival rather than the PCF itself being the cause of poor survival. That said, in a few cases that the PCF itself was the cause of death due to carotid blow-out.

Chapter 5 tries to more subtly classify PCFs, separating the small spontaneously healing PCF requiring little more than delayed oral feeding and wound dressings, from the large "pharyngo-stomas" leading to flap reconstruction. The 3 proposed classifications however are all fairly retrospective and lack the predictive capacity to drive management decisions. For example, they do not help answer the questions of which patients may benefit from an upfront interposition flap, or who might best benefit from an early return to theatre for their PCF. Ultimately, this attempt to classify PCFs as minor or major, whilst theoretically an interesting exercise, is thus abandoned for the rest of the thesis. This is not to say however that this approach might not have benefits in the future, particularly in the retrospective analysis of PCFs. The message remains – not all PCFs are equal.

Having set the context and outcomes of interest, we move on and try to identify risk factors. Generally speaking, we can divide these factors into patient specific (e.g. diabetes, smoking history), procedure specific (e.g. extent of resection, nature of reconstruction) and tumour specific (e.g. size, location, aggressive features).

Chapters 6 and 7 look at two fairly novel patient specific markers and attempt to correlate them with the outcomes first outlined in chapter 4. The NLR has been shown to be correlated with outcomes (both in terms of complications and long-term survival) for a wide range of cancers. Whilst NLR>5 correlates with poorer survival for our data-set as a whole, we find on further analysis a somewhat confusing picture with conflicting univariate and multi-variate analyses specifically with regard to the subgroups of primary vs salvage laryngectomy. As discussed at the end of chapter 6 this may have some basis in that patients following radiotherapy have no doubt had their immune system stimulated over a period of weeks by dead cancer cells, whereas in the primary setting the cancer is simply removed. More speculatively, it may be that the very patients who are candidates for salvage laryngectomy have by definition failed primary radiotherapy and therefore may have a different immune / host interaction.

Chapter 7 looks at an area of ongoing research at the UMC Utrecht, namely using skeletal muscle mass as estimated from routine staging CT scans to drive management. Low SMM is a powerful predictor of PCF formation and poor survival. Current research is now using low SMM to change the dosing of chemotherapy in patients undergoing chemo-radiotherapy, and more interestingly for the surgeon, to recommend an interposition pectoralis major flap. These data will be published by the UMC Utrecht group in the coming years.

Chapters 8 and 9 look the procedure specific issue of pre-definitive treatment airway intervention. Acute airway obstruction remains an all too common presenting complaint for patients with laryngeal cancer and in the Guy's & St. Thomas' dataset investigated in Chapter 8, 45% of patients had a tracheotomy before undergoing definitive laryngectomy. Furthermore, many of these patients had their tracheotomies performed by non-head & neck specialists in smaller hospitals. This is a strikingly high figure and indeed, was the initial impetus for my interest in laryngectomies.

The unit at Guy's & St. Thomas' at the time would always excise the tracheotomy tract and use intra-operative frozen sections to check adequate clearance of tumour. Using such an approach, the data showed the pre-operative tracheotomy was not associated with worse survival.

Chapter 9 again examines the effect of pre-laryngectomy airway intervention, but this time in the setting of patients treated with definitive (chemo)radiotherapy. The Zurich dataset included 114 patients with T3/T4 disease treated with (chemo)radiotherapy of whom 21 had an antecedent tracheotomy and a further 8 had antecedent transoral laser debulking. Interestingly, 3 further patients had to have a tracheotomy performed during radiotherapy and a further 19 afterwards. Only 11 of the patients who had a tracheotomy were able to have this reversed. Again, pre-laryngectomy airway intervention was not statistically associated with poorer survival. Furthermore, despite the initial organ-preserving approach, 46/114 (40%) of patients lost their laryngeal function either with a permanent tracheotomy (n=11) or a laryngectomy (n=35).

Continuing the theme of procedure specific risk factors, chapter 10 returns to the Guy's & St. Thomas' dataset and looks at the salvage laryngectomy patients (n=32). The treatment protocol meant that all these patients had a bilateral neck dissection at the time of laryngectomy. This meant we could compare the post-(chemo)radiotherapy cN stage with the pN stage to calculate a negative predictive value 96% of pre-operative CT for the detection of lymph node metastases. This very high negative predictive value, together with the fear of increased morbidity associated with elective neck dissections led to a change in management protocols. Indeed, this data has now been superseded by further research which is discussed in the General Discussion.

Chapter 11 performs a complete multivariate analysis of the Guy's & St. Thomas' dataset with the most striking finding being that pN>1 was the strongest predictor of poor survival, but that it was most intimately related to *distant failure*. This finding should give surgeons pause for thought. Simply put, a cancer which has demonstrated its metastatic potential is very difficult to cure with loco-regional modalities such as surgery or radiotherapy. Better systemic therapies are therefore needed, whether in the form of refinements to existing protocols or in the form of new modalities (e.g. immunotherapy).

Chapters 12-14 all focus on the salvage laryngectomy patients. Chapters 13 and 14 are more or less the same, but use data from London and Utrecht respectively. Perhaps analogous to the situation of pre-laryngectomy tracheotomy, what we find is that salvage patients need not be at increased risk of PCF formation, as long as they are appropriately managed. For the Utrecht data, this means forgoing elective neck dissection and only performing superselective (only level of residual disease) in N+ necks. It also involves a more liberal use of flaps, including pectoralis major interposition. It is also interesting to note the conflicting findings between the London data set and Utrecht data set regarding whether the time interval between end of (chemo)radiotherapy and salvage laryngectomy impacts risk of PCF formation. The London dataset would suggest that a short interval between (chemo)radiotherapy and surgery increased the risk of PCF formation which would seem to fit our conceptual understanding of wound-healing following radiotherapy. Indeed, radiotherapists will not offer re-irradiation to patients recently irradiated for fear of complications. The longer the time interval, the more comfortable they are to offer re-irradiation and it would not be surprising if this concept held for surgical complications as well. However, the Utrecht data-set finds no such correlation, and indeed a cross-sectional study of Dutch laryngectomies suggested that a *longer* time interval may be a risk factor.

Chapter 15 analyses a combined UMC Utrecht / Netherlands Cancer Institute data set with regard to post-laryngectomy neo-pharyngeal dilatation. The idea for the article first came about after a patient suffered a distal oesophageal perforation during a dilatation procedure. When we consulted the literature we realised that there was a dearth of publications on this topic in the laryngectomy setting, despite us knowing that swallowing difficulties are a fairly common. One reason for this may be that swallowing difficulties are difficult to objectify/quantify. The most objective measure we could reliably find in patient notes was whether or not dilatation had been performed, and this became thus our marker for significant functional impairment. This measure however introduces a somewhat subjective/patient centred bias which may explain why females were more "at risk" of dilatation.

Whilst not discussed in the chapter, within the UMC Utrecht data, we did find a correlation between PCF and later dilatations but this finding disappeared when the data-sets were combined. The remaining risk factors for dilatation were female gender, a hypopharynx primary and (C)RT either before or after laryngectomy. Most striking is perhaps that 111/477 (22.8%) patients underwent at least 1 dilatation and in total, 968 dilatations were performed in the study period. This is a considerable burden of morbidity which is perhaps under-appreciated.

SAMENVATTING

Dit proefschrift is het resultaat van zo'n 10 jaar interesse in laryngectomieën. De gegevens zijn verzameld van 3 ziekenhuizen, namelijk Guy's & St. Thomas in Londen (60 laryngectomiepatiënten van 2003-2010), de UniSpital in Zürich (114 patiënten met T3 / T4-ziekte behandeld met orgaansparende protocollen tussen 1981- 2011) en het Universitair Medisch Centrum Utrecht (242 laryngectomiepatiënten uit 2008-2017). In hoofdstuk 15 wordt gebruik gemaakt van een gecombineerde dataset van het Nederlands Kanker Instituut en het UMC Utrecht van in totaal 477 patiënten. Hoewel het verleidelijk was om alle datasets voor een meta-analyse te combineren, hebben we ervoor gekozen dit niet te doen, aangezien er duidelijke verschillen zijn in de voorkeuren van de landelijke en lokale multidisciplinaire teams en de lange periode waarover deze gegevens verzameld zijn.

In hoofdstuk 4 analyseren we de grootste en meest recente dataset, namelijk die van het UMC Utrecht. Dit hoofdstuk onderzoekt 242 opeenvolgende patiënten die een laryngectomie ondergaan, waarbij specifiek wordt gekeken naar de incidentie van pharyngocutane fisteling (PCF), behandeling van PCF, PCF-duur / sluitingspercentage, vertraging tot adjuvante radiotherapie, risico op toekomstige neofaryngeale dilatatie en overleving. Deze uitkomstmaten komen gedurende het proefschrift terug, vooral met betrekking tot de dataset van het UMC Utrecht. Hoofdstuk 4 zet dus de toon en probeert een overzicht te geven van de problemen die optreden na een laryngectomie. We zien dat een laryngectomie voornamelijk wordt uitgevoerd bij oudere mannen met een min of meer gelijkmatige verdeling tussen primaire en salvage ingrepen. De verblijfsduur in het ziekenhuis is gemiddeld 16 dagen voor patiënten zonder PCF en 30 dagen voor patiënten met PCF. Ongeveer de helft van de patiënten met PCF moet een keer opnieuw geopereerd worden, en van hen zelfs 20% meerdere keren. PCF is ook significant geassocieerd met een slechtere 5-jaarsoverleving (5-jaars overleving van 44% geen PCF vs. 24% PCF, OR 1,7, p = 0,001). Of deze correlatie causaliteit impliceert, is een moeilijke vraag om te beantwoorden, hoewel het vermoeden is dat deze patiënten door hun slechtere algehele conditie bij een grote operatie voor een agressieve ziekte meer kans hebben op een PCF en een slechtere overleving, dan dat de PCF zelf de oorzaak is van een slechte overleving. Dat gezegd hebbende, in een paar gevallen was de PCF zelf de doodsoorzaak als gevolg van een schade van de halsslagader door PCF, met een bloeding als gevolg.

In hoofdstuk 5 proberen we PCF's subtieler te classificeren, door de kleine, spontaan genezende PCF die weinig meer nodig heeft dan vertraagde start van orale voeding en wondverbanden, te scheiden van de grote "faryngo-stoma's" die leiden tot een heroperatie vaak met een lapreconstructie. De drie voorgestelde classificaties zijn echter allemaal retrospectief en missen het voorspellende vermogen om managementbeslissingen te sturen. Ze helpen bijvoorbeeld niet bij het beantwoorden van de vragen welke patiënten baat zouden kunnen hebben bij een voorafgaande interpositieflap, of welke patiënten het beste kunnen profiteren van een vroege terugkeer naar de operatiekamervoor hun PCF. Uiteindelijk is deze poging om PCF's als minor of major te classificeren, hoewel theoretisch een interessante oefening, is dit niet verder meer onderzocht in dit proefschrift. Dit wil echter niet zeggen dat deze benadering in de toekomst mogelijk geen voordelen kan hebben, met name bij de retrospectieve analyse van PCF's. De boodschap blijft: niet alle PCF's zijn gelijk.

Nadat we de context en de uitkomsten van interesse hebben benoemd, gaan we verder om risicofactoren te identificeren. Over het algemeen kunnen we deze factoren onderverdelen in patiëntspecifiek (bijv. diabetes, rookgeschiedenis), procedure specifiek (bijv. mate van resectie, soort van reconstructie) en tumorspecifiek (bijv. grootte, locatie, agressieve kenmerken).

In hoofdstukken 6 en 7 kijken we naar twee vrij nieuwe patiëntspecifieke markers en proberen deze in verband te brengen met de uitkomsten die voor het eerst in hoofdstuk 4 zijn geschetst. Er is aangetoond dat het neutrophil-to-lymphocyte ratio (NLR)correleert met uitkomsten (zowel in termen van complicaties als overleving op lange termijn) voor een groot aantal kankers. Hoewel NLR> 5 correleert met een slechtere overleving voor onze dataset als geheel, vinden we bij verdere analyse een enigszins verwarrend beeld met tegenstrijdige univariate en multivariate analyses, specifiek met betrekking tot de subgroepen van primaire versus salvagelaryngectomie. Zoals besproken aan het einde van hoofdstuk 6 kan dit enige basis hebben in het feit dat patiënten die radiotherapie hebben ondergaan ongetwijfeld hun immuunsysteem gedurende een periode van weken hebben gestimuleerd door dode kankercellen, terwijl in de primaire setting de kanker wordt verwijderd uit het lichaam. Meer speculatief kan het zijn dat juist de patiënten die in aanmerking komen voor salvage laryngectomie per definitie gefaald hebben bij primaire radiotherapie en daarom mogelijk een andere immuun - kanker interactie hebben.

In hoofdstuk 7 behandelen we lopend onderzoek in het UMC Utrecht, namelijk het gebruik van skeletspiermassa (SMM), zoals geschat op basis van voor de diagnostiek van de primaire tumor routinematig vervaardigde CT-scans, als predictieve en prognostische factor. Lage SMM is een krachtige voorspeller van PCF-vorming en slechte overleving. Huidig onderzoek maakt nu gebruik van een lage SMM om de dosering van chemotherapie te bepalen bij patiënten die chemoradiotherapie ondergaan, en, nog interessanter voor de chirurg, om een interpositie pectoralis major flap aan te bevelen. Deze gegevens zullen de komende jaren door de UMC Utrecht-groep worden gepubliceerd.

In hoofdstukken 8 en 9 gaan we in op de procedure specifieke kwestie van luchtweginterventie voor de definitieve laryngectomie. Acute luchtwegobstructie blijft een maar al te vaak voorkomende klacht bij patiënten met larynxcarcinoom en in de Guy's & St. Thomas' dataset die in Hoofdstuk 8 werd onderzocht, had 45% van de patiënten een tracheotomie voordat ze een definitieve laryngectomie ondergingen. Bovendien was bij veel van deze patiënten de tracheotomie in een kleiner ziekenhuis niet door een hoofd-/halschirurg-verricht. Dit is een opvallend hoog cijfer en was inderdaad de eerste aanzet voor mijn interesse in laryngectomieën.

De chirurgen van Guy's & St. Thomas’ namen het weefsel rondom deze tracheotomie altijd mee in de resectie van de larynx en gebruikten vriescoupes van de resectieranden om peroperatief te beoordelen of de tumor voldoende was verwijderd. Data toonden aan dat een dergelijke benadering (tracheotomie voorafgaand aan laryngectomie) niet leidde tot een slechtere overleving.

In hoofdstuk 9 onderzoeken we opnieuw het effect van een luchtweginterventie, maar dit keer in de setting van patiënten behandeld met definitieve (chemo)radiotherapie. De Zurich-dataset omvatte 114 patiënten met T3 / T4-ziekte die werden behandeld met (chemo)radiotherapie, van wie 21 een tracheotomie voor de laryngectomie kregen en nog eens 8 transorale laser debulking. Nog 3 patiënten moesten een tracheotomie ondergaan tijdens radiotherapie en nog 19 daarna. Bij slechts11 van de patiënten die een tracheotomie hadden, kon deze gesloten worden. Ook in deze studie was een luchtweginterventie niet statistisch geassocieerd met een slechtere overleving. Bovendien verloren 46/114 (40%) van de patiënten, ondanks de initiële orgaanspatrende therapie hun larynxfunctie met een permanente tracheotomie (n = 11) of een laryngectomie (n = 35).

Blijvend bij het thema van procedure specifieke risicofactoren, keren we in hoofdstuk 10 terug naar de dataset van Guy's & St. Thomas’ en kijken we naar de salvage laryngectomie patiënten (n = 32). Het behandelprotocol hield in dat al deze patiënten een bilaterale halsklierdissectie kregen op het moment van de laryngectomie. Hierdoor konden we de post-(chemo)radiotherapie cN-stage vergelijken met de pN-stage. Hierbij werd voor de detectie van lymfekliermetastaseneen negatief voorspellende waarde van 96% van preoperatieve CT gevonden. Deze zeer hoge negatief voorspellende waarde, samen met het risico van een verhoogde morbiditeit door electieve halsklierdissecties, leidde tot een verandering in de management protocollen. Deze gegevens zijn nu enigszins achterhaald door verder onderzoek dat wordt besproken in de algemene discussie.

In hoofdstuk 11 voeren we een complete multivariate analyse uit van de Guy's & St. Thomas' dataset met als meest opvallende bevinding dat pN> 1 de sterkste voorspeller was van slechte overleving, en dat deze meest nauw verband hield met metastasen op afstand. Deze bevinding zou chirurgen aan het denken moeten zetten. Simpel gezegd, een kanker die zijn metastatische potentieel heeft aangetoond, is zeer moeilijk te genezen met locoregionale modaliteiten zoals chirurgie of radiotherapie. Betere systemische therapieën zijn daarom nodig, hetzij in de vorm van verfijning van bestaande protocollen, hetzij in de vorm van nieuwe modaliteiten (bv. immunotherapie).

In de hoofdstukken 12-14 richten we onsop patiënten die een salvage laryngectomie hebben ondergaan. De hoofdstukken 13 en 14 zijn min of meer hetzelfde, maar gebruiken gegevens uit respectievelijk Londen en Utrecht. Misschien analoog aan de situatie van tracheotomie voor laryngectomie, vinden we dat salvage patiënten geen verhoogd risico op PCF-vorming hoeven te lopen, zolang ze op de juiste manier worden behandeld. Voor de Utrechtse gegevens betekent dit afzien van electieve halsklierdissectie voor cN0 patiënten en alleen selectieve halsklierdissecties uitvoeren bij cN+. Het houdt ook een meer liberaal gebruik van flappen in, inclusief pectoralis major interpositie. Het is ook interessant om de tegenstrijdige bevindingen op te merken tussen de Londense dataset en de Utrechtse dataset met betrekking tot de vraag of het tijdsinterval tussen het einde van (chemo)radiotherapie en salvage chirurgie het risico op PCF-vorming beïnvloedt. De Londense dataset zou suggereren dat een kort interval tussen (chemo)radiotherapie en chirurgie het risico op PCF-vorming vergroot, wat lijkt te passen bij ons conceptuele begrip van wondgenezing na radiotherapie. Radiotherapeuten willen inderdaad geen herbestraling aanbieden aan patiënten die kort tevoren bestraald zijn uit angst voor complicaties. Hoe langer het tijdsinterval, hoe geruststellender het is om herbestraling aan te bieden en het zou niet verrassend zijn als dit concept ook zou gelden voor chirurgische complicaties. De Utrechtse dataset vindt een dergelijke correlatie echter niet, en inderdaad suggereerde een cross-sectionele studie van Nederlandse laryngectomieën dat een *langer* tijdsinterval een risicofactor kan zijn.

In hoofdstuk 15 analyseren we een gecombineerde dataset van het UMC Utrecht en het Nederlands Kanker Instituut met betrekking tot dilatatie van de neofarynx na totale laryngectomie. Het idee voor het artikel ontstond na geconfronteerd te zijn geweest met zeldzame complicatie na een dilatatieprocedure. Toen we in de literatuur gingen kijken, realiseerden we ons dat er een gebrek aan publicaties over dit onderwerp was, ondanks dat we wisten dat slikproblemen vrij vaak voorkomen. Een reden hiervoor kan zijn dat slikproblemen moeilijk te objectiveren / kwantificeren zijn. De meest objectieve maatstaf die we betrouwbaar konden vinden in de notities van patiënten was of er al dan niet dilatatie was uitgevoerd, en dit werd dus onze marker voor significante functionele beperkingen. Deze maatregel introduceert echter een wat subjectieve / patiëntgerichte.

Hoewel niet besproken in dit hoofdstuk, vonden we binnen de UMC Utrecht-data wel een verband tussen PCF en latere dilataties, maar deze bevinding verdween toen de datasets werden gecombineerd. De overige risicofactoren voor dilatatie waren vrouwelijk geslacht, een primaire hypofarynx en (C)RT zowel voor als na laryngectomie. Het meest opvallende is wellicht dat 111/477 (22,8%) patiënten ten minste 1 dilatatie ondergingen en in totaal 968 dilataties werden uitgevoerd in de onderzochte periode. Dit is een aanzienlijke ziektelast die misschien wel ondergewaardeerd wordt.

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General discussion and future perspectives

In this thesis we have investigated laryngectomy complications and survival. We have put this in the context of improved diagnostics and non-surgical treatments which have over the years changed the indication for laryngectomy and associated neck dissections, speech valve placement etc. In this section we examine the various steps in a patient's pathway, discussing the relevance of the research contained in this thesis, recent thinking and what the future might hold.

SCREENING

Whilst not investigated in this thesis, screening for cancers attempts to identify them in their early stages when they may be more effectively treated with less associated morbidity. Several countries have attempted screening programs for at-risk groups for particular cancers. Some of the best known screening programs are for breast[1] and cervical[2] cancer, but arguments continue as to how to balance costs and the risk of over-treatment on the one hand, with the improving outcomes on the other. For example, the recent explosion in the number of thyroid cancers being diagnosed does not seem to be mirrored by an increase in mortality and it is not clear if the costs as measured not only in time and money but also in psychological stress, recurrent laryngeal nerve palsies, hypocalcaemia and lifelong thyroxine replacement therapies are really justified[3].

In the setting of laryngeal cancer, early diagnosis might allow trans-oral techniques such as laser resection or narrow field radiotherapy to be used leading to laryngectomy being reserved for recurrence. However, to our knowledge, worldwide no screening programs exist and unless there is a change in current technology it seems difficult to envisage such a program. Instead there are guidelines for rapid referrals particularly if a patient is deemed to be in a high risk group. For example, the European Make Sense campaign (https://makesensecampaign.eu) recommends that primary practitioners refer any patient with persistent unexplained hoarseness of voice >3 weeks for specialist for evaluation, even if the patient is a young non-smoker. Unfortunately, using persistent hoarseness as the screening tool, whilst sensitive is highly non-specific.

Perhaps in the future a simple routine blood test may identify those at particular risk, or indeed those with small cancers. Even if such tests were not perfect in terms of their sensitivity and specificity, they might be good enough to justify the relatively non-invasive investigation of a trans-nasal fibre-endoscopy.

PRE-TREATMENT WORK-UP

Today's patients with confirmed laryngeal cancer benefit from a pre-operative work-up which puts Billroth's simple mirror examination of the larynx to shame. There now exists a plethora of imaging modalities including "chip on the tip" outpatient transnasal fibre-endoscopy, ultrasound, CT and MRI as well functional modalities such as stroboscopy and PET-CT. Together with an examination under anaesthetic with a Hopkin's rod and narrow band imaging, not to mention advances in pathological characterisation of the cancer, the tumour board has a huge amount of information to discuss before making its recommendation.

Imaging modalities are continuously improving both in speed and accuracy though there is still of course room for improvement. The infamous "retro-spectro-scope" can still show a missed distant metastasis or similar such crucial finding. Furthermore, it can feel that the TNM staging system is too heavily based on imaging, ignoring potential patient or cancer specific features. These various patient and/or cancer markers will no doubt be more frequently used in the future to risk stratify patients. Chapters 6 and 7 discuss NLR and skeletal muscle mass respectively and one can imagine a future in which these together with genetic profiling of the cancer itself will be used in a nomogram to give a patient specific treatment recommendation. This would complement the blunt TNM staging, perhaps pushing some patients who would have previously be considered for organ-preserving treatment towards surgery and vice-versa.

Efforts in this direction are still largely matters of research rather than clinically put in practice. One exciting development is the use of radiomics. Radiomics involves machine learning algorithms which analyze scans with known outcomes (training sets). The algorithm can then be validated by applying it to a validation set and checking its predictive value[4]. The approach is especially advanced in lung cancer[5] and is now being used in non-surgically treated head & neck cancer, for example with functional MRI[6] and 18F-FDG PET[7]. Whilst the details of what the machine learning algorithm focuses on can be often unintelligible to the clinician they can outperform visual analysis in terms of accuracy. One simple to understand concept is that of tumor volume which can be easily calculated by the computer, but is not routinely calculated by the clinician. Indeed whilst the T in TNM-staging reflects size, it does so in a very 2 dimensional manner and it would seem intuitively plausible that a three dimensional volume would be more closely correlated with survival. In terms of laryngeal cancer such an approach may help the crucial decision between organ-preserving treatment and laryngectomy.

There are some features of this approach which merit caution. For example, focusing on survival as the only outcome may not be of the utmost importance to a patient. There may be patients willing to run the risk of failed organ-sparing treatment in order to keep laryngeal function for another year or two. Building such functional endpoints into the machine learning is especially difficult as good quality data on functional outcomes is often difficult to find and measure meaningfully.

Even more precisely, pre-intervention predictive models may refine the exact treatment beyond simple triaging of a patient to laryngectomy or organ-sparing. An example might be to stop performing elective bilateral neck dissections in primary laryngectomy. This has already occurred to a large extent in the salvage laryngectomy setting following publications such as chapter 10. The search for markers for PCF could similarly inform the surgeon as to whether an interposition overlay flap was justified. Chapters 4, 5, 7 and 8 all look at various possibilities to stratify patients according to their PCF risk and our unit in Utrecht is currently running research using skeletal muscle mass measurements to recommend interposition muscle flap reinforcement of primary pharyngeal closure.

For the radiotherapist, better pre-treatment analysis may allow for dose painting to achieve escalation/de-escalation using both anatomical and functional parameters.

THE CN0 NECK

Management of the cN0 neck in laryngeal cancer deserves special discussion. Traditionally, all candidates for total laryngectomy would invariably undergo elective bilateral neck dissections. Over the last 10 years though, the management of the cN0 neck has been a topic of vigorous debate.

The rationale to offer elective neck dissections at the time of laryngectomy is to treat potential occult metastasis. The higher the risk of occult metastasis, the more sensible it would seem to electively treat the neck, though this must be balanced against firstly the morbidity associated with elective neck dissection, secondly the potential or not for future salvage and thirdly and, perhaps counterintuitively, the effectiveness or not of a neck dissection in treating neck metastases.

Let us begin by addressing the somewhat less contentious situation of the salvage laryngectomy. In Chapter 10 we investigated the occult metastasis rate by comparing pre-operative CT scanning with pathological analysis of elective neck dissections of levels II-IV. The rate of occult metastasis was found to be 4%. Though not included in this thesis, a study was made of the very high rate of pharyngo-cutaneous fistula in this group[8] which was thought to be partly related to the elective neck dissections. Crucially, chapter 10 does not answer the question as to whether elective neck dissections provided any survival benefit.

This question however was addressed by Freiser et al.'s study[9] in 2016 which showed that whilst patients with N+ necks have a poorer outcome than N0, this is *irrespective of whether a neck dissection is performed*. In their data, the elective neck dissection is of prognostic value but does not confer a survival benefit, a situation somewhat analogous to melanoma.

This counter-intuitive finding has been further supported by a very recent meta-analysis[10] of 19 articles detailing 1353 patients and 1552 elective neck dissections. This found an overall occult metastasis rate of 14% balanced against the relative risk of developing complications of 1.3 in the elective neck dissection patients compared to patients without elective neck dissection (CI 0.86-1.92). Whilst elective neck dissection decreased the risk of regional recurrence (RR 0.62, CI 0.35-1.08) there was *no statistically significant difference in disease specific or overall survival* between the elective neck dissection and no elective neck dissection groups. On the basis of such studies, many units now recommend no elective neck dissections in the cN0 salvage setting and a super-selective neck dissections in the cN+ neck[11].

Moving now to the primary laryngectomy setting. For cN+ necks, there is general agreement that neck dissection should be performed at the time of laryngectomy. There is however discussion as to which levels, most specifically as to whether IIB and V should be included[12-14]. A recent systematic review showed the incidence of occult metastases in levels I, IV and V was 2.4%, 2.0% and 0.5% respectively and recommended therefore that in the absence of extensive nodal disease, dissection of levels I, IIB and V could be avoided[15].

The situation becomes even more contentious in the cN0 neck. In principal there are three options: surveillance, node sampling (e.g. sentinel lymph node biopsy) or elective dissection. The above mentioned systematic review showed the incidence of occult metastases to be 19.9% for supra-glottic tumours and 8% for glottis tumours[15]. A very small pilot study of the sentinel node technique is difficult to evaluate as it mixed primary and salvage patients and analysed the sentinel nodes as part of an elective neck dissection. Here, sentinel node was found to be 80% sensitive for picking up occult metastasis[16]. Another group investigated supra-glottic cancers amenable to transoral laser resection (T1-T3) by performing sentinel lymph node biopsy followed by immediate bilateral neck dissection, finding a sensitivity of 100% and a specificity of 78%[17].

It is however interesting to speculate whether the primary laryngectomy situation will ultimately prove similar to the salvage laryngectomy situation. It must also be remembered that not performing an elective neck dissection does not mean that the neck will not be electively treated. Almost without exception, primary laryngectomy is followed by a course of adjuvant radiotherapy and this may be enough to sterilise isolated tumour cells and other occult tumour deposits in the neck. There is also little published data as to how salvageable a recurrent neck node is in this setting.

ANAESTHETICS / PERI-OPERATIVE CARE

In addition to characterising the cancer as outlined above, there have also been huge advances in characterising the patient's fitness for surgery. This together with modern anaesthetic agents and ventilators/intensive care units mean that patients can expect to survive their surgery.

There now also now exists the concept of *pre*-habilitation. This involves optimizing the patient prior to treatment in order to improve treatment effectiveness and reduce complication risks and morbidity. The concept has become well established across a broad range of treatments[18-20] and despite the time constraints of cancer surgery, simple interventions such as increasing exercise or stopping smoking have been shown to be effective. That said, a recent editorial in the British Medical Journal highlighted potential concerns including that resources could be better used elsewhere and that it could in some ways be perceived as "blaming" the patient[21].

In chapter 7 we highlighted skeletal muscle mass as a risk factor for poor outcome and we can speculate as to whether a prehabilitation program might be of use. Patient motivation/concordance would obviously play an important role, but even in a short time-frame measurable improvements in cardio-vascular fitness could potentially be achieved. It can be striking during for example during pectoralis major flap harvest how one patient has a thick "steak" whilst another barely a layer of fascia. This is an area for further research.

TRANS-ORAL ROBOTIC SURGERY

Though Billroth would immediately recognise today's laryngectomy procedure, this is not to say that advances have been made on the surgical side. In addition to improvements in sterile technique, suture materials and haemostasis, there exists now the option of trans-oral robotic surgery (TORS). This has renewed interest in larynx-sparing surgery/partial laryngectomy. These various operations (vertical[22], horizontal, crico-hyoido-pexy[23]) had fallen largely out-of-favour in the Anglo-Saxon world, but have continued to be used to some extent, especially in Germany, Italy, France and Spain. One reason for the loss in interest in these procedures was the difficulty in maintaining a functional, sensate larynx after extensive resection especially given the option of radiotherapy, the ultimate organ preserving therapy[24].

Trans-oral robotic surgery can be used for partial[25] and even total laryngectomy[26], though it is still in its infancy with both refinements in equipment and surgical indications continuing apace. Partly due to these issues together with increases costs and the time needed, TORS is yet to find widespread use for laryngeal cancer. Its role may ultimately be in the salvage setting where small residual/recurrent tumours can be resected. This would greatly reduce the surgical insult thereby reducing the wound healing difficulties post chemo-radiotherapy. It might even be combined with a super-selective neck dissection as described above.

RECONSTRUCTION

Billroth would have certainly been impressed by the improvements in lighting, suture materials and microscopes which allowed the introduction of free flaps some 50 years ago. This allows for more aggressive resections and better patient rehabilitation[27]. 360 degree reconstructions are now possible, as are procedures such as a gastric pull-up. There is even the possibility of laryngeal transplant surgery[28] as mentioned in the introduction.

Bringing non-irradiated, well vascularised tissue into the neck reduces is thought to not only fistula rates but also the time they take to heal should they occur. A systematic review by Paleri et al[29] published in 2014 showed a relative risk of fistula formation of RR 0.63, (CI 0.47-0.85) in patients with flaps and a further systematic[30] review of only pectoralis major flaps again showed a risk reduction of -0.22 (CI -0.29-0.14).

Whilst we have not examined flaps explicitly, we report our experiences throughout this thesis. Chapters 12-14 investigate the salvage setting where but perhaps surprisingly, our data do not show an increased risk of PCF formation when compared to primary laryngectomies. We believe that the higher risk of PCF in the salvage setting had been mitigated by the judicious use of flaps. We did find however that if a fistula occurred in the salvage setting, it took longer to heal or indeed had a higher risk of not healing at all, than in the primary setting.

Some observations, particularly about the workhorse pectoralis major pedicled flap need to be made. Firstly, a surprising amount of pharyngeal mucosa can be resected but still allow primary closure. Hui et al. report that just 2.5cm of stretched pharynx is sufficient to allow primary closure and good swallow function[31]. This is important, as if the flap is used to reconstruct the pharynx (sometimes called "patch" reconstruction), it will "double" the length of the suture line, potentially increasing the risk of suture failure and fistula formation. Of course, this doubling only happens when some pharyngeal mucosa has been preserved. This, together with the fact that the pharyngeal remnant has been previously irradiated and therefore often of poor quality, can lead one to argue that any pharynx that cannot be closed primarily should simply be resected and a 360 degree reconstruction performed[32]. Secondly, the skin paddle of a pectoralis major flap is notoriously unreliable, especially in patients with a thick layer of intervening subcutaneous fat where the well vascularised muscle can be several centimetres away from the skin. This makes patch reconstructions only slightly less at risk of fistula formation than primarily closed pharynxs[32].

Due to the still quite high rates of fistula formation especially in the salvage setting, the concept of a primarily closed pharynx with a "reinforcement" flap (variously described in the literature as a pectoralis major myofascial overlay or interposition flap) has grown in popularity. Whilst the efficacy of these interposition flaps in preventing fistulas is generally accepted, there is of course associated morbidity in terms of cosmesis, speech rehabilitation[33] and shoulder function. Again therefore, the challenge is to use these flaps in the appropriate patients and one can imagine a risk calculator of sorts which could be developed to predict those patients most at risk of fistula formation.

No discussion of flaps would be complete without brief mention of free flaps (typically either radial forearm or anterior lateral thigh). These can normally be raised by a second operative team simultaneously to the ablative procedure and are especially useful for larger defects or for 360 degree reconstruction. Using a free flap however does increase operation time and requires extra equipment and expertise. Sometimes the donor vessels have also been irradiated which compromises success leading some centres to advocate their use in primary laryngectomy but rely on pedicled flaps for salvage laryngectomy.

POST-LARYNGECTOMY REHABILITATION

However safe and effective a modern total laryngectomy may be, there is however no escaping the fact that it remains a hugely invasive procedure with profound implications for the life of the patient beyond simple survival statistics. Indeed, rehabilitation is perhaps more accurately described as adjusting to and coping with the stoma. Fortunately, alongside the advances in reconstruction there are also advances in rehabilitation. The modern laryngectomee benefits from HMEs, speech protheses and a plethora of further adjuncts (including a swimming snorkel) allowing them a far fuller life than previously possible. Much of the literature surrounding rehabilitation focuses on the airway and speech which we have not investigated in this thesis. Chapter 15 however deals with the perhaps under-reported difficulties many laryngectomy patients have with swallowing.

The saying "eat to live or live to eat" should also be mentioned. Due to changes in airflow, whilst the olfactory sense organ has been unaffected by treatment, patients following laryngectomy invariably have a much reduced enjoyment in eating. As touched upon in the introduction, there are however techniques to try and improve airflow to the nose and therefore improve smell.

FIGURE : The laryngectomy snorkel, www.thelarysnorkelstore.com

RADIOTHERAPY

Clearly, organ preserving therapies have undergone the most significant improvements over the years. Modern radiotherapy benefits from huge advances in computers and linear accelerators allowing more precisely delivered doses and sparing surrounding tissues. Simple external beam has been improved with 3D conformational radiotherapy, intensity modulated radiotherapy and most recently volumetric modulated arc therapy[34]. There is also research in using heavy ions therapy in particular settings. All-in-all radiotherapy over the years has gradually replaced many operative strategies and is now a proven treatment modality for all but the largest tumors.

There are however several caveats and areas of further research. One of course is that organ preserving does not necessarily mean function preserving. Indeed, in chapter 9 we report that of the 114 patients with T3/T4 laryngeal cancers in the Swiss cohort treated initially with an organ sparing approach, 11/114 (10%) had permanent tracheotomies, 2/114 (2%) had a functional laryngectomy and 33/114 (29%) had salvage laryngectomies.

Could this be improved by better intensity modulation? Could better pre-operative risk profiling allow for dose de-escalation in certain settings and perhaps escalation in others? Efforts are indeed underway in this direction[35], one such effort being the reduction in elective neck radiotherapy for smaller tumours. One can imagine a future where even fairly large tumours under the TNM staging would be classed as low risk for neck metastases and therefore no elective neck radiotherapy would be performed.

Another exciting area of research is adaptive "real time" dose painting[36]. With repeated anatomical and potentially functional scanning, there is the possibility again of dose de-escalation or escalation depending on how radio-responsive a tumour is. Some patients may even start their radiotherapy only to be counselled for an early stop in favour of a laryngectomy. In this regard, a recent systematic review suggested that functional imaging performed at 2-3 weeks after treatment initiation was optimal in predicting loco-regional failure and overall survival[37].

Again, as with surgery, there has also been an improvement in the recognition and treatment of radiotherapy side-effects. Though not described in this thesis, efforts are underway to profile patients at particular risk of functional loss or conditions such as chondro-necrosis who may well be better treated with surgery than radiotherapy.

CHEMOTHERAPY

Platinum based chemotherapy has been shown to increase the effectiveness of radiotherapy for loco-regional disease and can be used as a palliative agent in the setting of distant metastases. It does however increase the toxicity of treatment considerably.

Again, not mentioned in this thesis, but an area of active research in the University Medical Center, Utrecht, is whether dosing patients according to their metres squared is the way to strike the best balance between effectiveness and toxicity. Indeed, following on from the skeletal muscle mass research described in chapter 7, we are now investigating whether skeletal muscle mass is a better parameter for dosing than metres squared. Several studies in different types of cancers have shown that low skeletal muscle mass leads to significant risk for chemotherapy-related toxicities and dose limiting toxicities. An explanation for the relationship between low skeletal muscle mass and toxicity might be that hydrophilic drugs, including platinum-based chemotherapeutic agents, mainly distribute in the lean body mass of which skeletal muscle mass is the largest contributor. Therefore, it could be that currently we are overdosing low muscle mass patients, potentially meaning they cannot finish their chemotherapy, and conversely, underdosing higher muscle mass patients who might have tolerated higher doses.

Another area of contention, ever since the original Veteran's Administration paper[38], revolves around the use of induction chemotherapy versus concomitant chemotherapy. The original paper used induction chemotherapy to identify responders and non-responders. The latter group were then laryngectomised, whilst the former underwent radiotherapy. Whilst later work, in particularly by the EORTC group[39] showed concomitant chemoradiotherapy to be as effective as induction chemotherapy followed by radiotherapy, there seems an inherent logic in trying to identify responders early. Rather like the discussion above about identifying radio-responsive tumours, if better markers could be found for chemo-sensitive tumours, it would save some patients a needless chemo-radiotherapy and conversely perhaps move some patients from surgery towards organ preserving treatment.

IMMUNOTHERAPY

Immunotherapy has demonstrated exceptional results in melanoma but has only recently been used in head & neck oncology as part of a curative treatment program. In current clinical practice it is exclusively reserved for the palliative setting in laryngeal cancer. This may change however and then many of the same questions would have to be answered as with chemotherapy. Would immunotherapy be its own single treatment modality or would be it be used as a neo-adjuvant/adjuvant treatment alongside surgery or radiotherapy? How could responders be identified? Indeed, the whole treatment protocol would need to be researched and designed bearing in mind such phenomena as the well-recognised potential increase in tumour size at the beginning of treatment ("pseudo-progression"). Alongside the known checkpoint inhibitors there are a myriad of other ways the immune system could be modulated including tumour vaccination and activated T-cell therapy. Huge advances are no doubt on the horizon.

FOLLOW UP/SURVEILLANCE

There are many reasons to follow-up laryngectomy patients[40]. In the immediate post-operative setting there are often issues around speech, swallow and stoma care. Alongside the medical focus, patients need help and support with rebuilding their lives. Cancer nurse specialists and patient clubs are invaluable if sometimes unseen resources for patients.

The surgeon's role should also be to holistically care for their patient, though often follow-up appointments are very brief and almost entirely focused on whether there is residual or recurrent cancer. This cancer surveillance is a form of secondary cancer screening and should fulfil all the principles of primary cancer screening as described above. Many country's guidelines recommend frequent follow-up in the first few years post-laryngectomy and then less frequent routine follow-up for a total of 5 years.

There are several observations immediately worth making. Firstly, that the symptomatic patient should not wait for their routine follow-up but should contact their team immediately. Conversely, there is the question of whether an asymptomatic patient who has already exhausted all curative treatment options (for example post-salvage laryngectomy) need to be routinely followed-up at all[41]. In a sense, patients who would only receive treatment for symptom-relieve need only present to their team when they have symptoms.

It is however also clear that the risk factors for laryngeal cancer overlap considerably with other cancer types (notably lung[42]) and thus that follow-up has three roles:

1. General medical care / psycho-social support
2. Secondary screening for residual or recurrent cancer
3. Primary screening for second primary cancer

Given individual patient differences in their need for the above 3 follow-up purposes, the one-size fits all approach to follow-up protocols should be regarded as a guideline rather than best practice.

There is also debate as to the role of routine imaging. Clearly the response evaluation scan performed after organ sparing treatment is crucial but differences of opinion exist as to whether further routine scans should be performed and whether this would reduce the need for clinical follow-up. This is especially true when dealing with distant recurrence and second primary tumours at distant sites. Though not included in this thesis, unpublished work performed in Zurich looked at routine use of PET-CT at 3 months, 9 months and 18 months post organ sparing treatment for T3/T4 laryngeal cancer and found that whilst it reduced time to detection of recurrence, it did not improve disease specific or overall survival.

CLOSING COMMENTS

Over the past 50 years, we have moved from a situation where patients would most likely die of loco-regional disease to one where people live far longer and often die of distant metastases, second primary tumours or other co-morbidities. This is in large part due to improvements in treatment, but it may also be that the type of laryngeal cancer we see today is different from the type seen before. Rather like the situation with HPV and oropharyngeal cancer, it may be that an, as yet, undiscovered factor is driving today's laryngeal cancer and that this is different from previously. Clearly, smoking habits have changed over the last 50 years along with the constituents of cigarettes as well. Perhaps vaping will lead to an epidemic of new type of laryngeal cancer in years to come.

Whatever its explanation, the improvements in survival were previously substantial but seem to have stalled in the last 20 years, at least in the USA[43]. Speaking as a surgeon, there is the suspicion that the pendulum may have swung too far away from total laryngectomy towards organ preserving therapies and that survival has suffered as a result.

This thought however focuses perhaps too narrowly on survival and fails to appreciate the very significant impact a total laryngectomy has on a patient. These impacts are somewhat difficult to measure and whilst "meten is weten" not everything measurable is important and not everything important is measurable! Survival, whilst easily measured, needs to be complemented by other outcome measures to allow us to really evaluate whether today's advanced laryngeal patients are doing "better" than 20 years ago. Indeed, looking back at this thesis and thinking of the personal stories of the patients aggregated herein makes me somewhat embarrassed at the lack of these subtler outcome measures.

Alongside survival, what this thesis does focus on is PCF formation and management. PCFs are a very common and potentially extremely severe complication of total laryngectomy associated with increased costs and poorer overall survival. The chapters reflect the ever evolving management strategies, particularly for the ycN0 patients and the appreciation of low skeletal muscle mass as a risk factor. This latter measure is now being used to drive further research at the UMC Utrecht, both in terms of chemotherapy dosing and the use of pectoralis major interposition flaps.

All this said, I cannot help but feel that the future of advanced laryngeal cancer therapy lies in biological therapies whatever the further refinements/improvements to the anatomically driven but biologically non-specific modalities of surgery and radiotherapy. Whilst for example checkpoint inhibitors are widespread in melanoma or lung cancers, they are only belatedly finding their place in head & neck cancers, and then only in the palliative setting. This will no doubt change in the coming years.

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HNSCC	Head and Neck squamous cell carcinoma
AJCC	American Joint Committee on Cancer
SCC	Squamous cell carcinoma
LSCC	Laryngeal squamous cell carcinoma
HPV	Human papilloma virus
EGFR	Epithelial growth factor receptor
RT	radiotherapy
CRT	chemoradiotherapy
TNM	Tumor, node, (distant) metastasis
CHP	cricohyoidopexy
CHEP	cricohyoidoepiglottopexy
3DCRT	3-dimensional conformal radiation therapy
IMRT	intensity modulated radiation therapy
VMAT	volumetric modulated arc therapy

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This dissertation had no well-defined beginning, and I hope that despite a defined end-point, I can continue to research and publish in this area in the years to come. In total, it spans 10 years of clinical work spread across 3 countries with too many kind and helpful colleagues to mention all by name.

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Finally, I would like to acknowledge the patients whose human stories lie behind the cold statistics and analyses contained herein. It is a privilege and forever humbling to be involved in their care. As I looked through the data, I would frequently pause to either remember of reimagine those difficult moments, and I hope in some small way that this research helps to improve patient care in the future.

ABOUT THE AUTHOR

Thomas Pézier was born the third of four children to French parents in London. During his school years he was a keen sportsman captaining several school teams and singing with the school choir in several of London's foremost concert halls and Glynbourne Opera house. He was also an award winning pianist at the national level and passed his Royal Guildhall of Music & Drama recital certificate with honours. His undergraduate studies were in French & Philosophy at Magdalen College, Oxford University, winning the John Doncaster prize for Modern Languages and writing an extended paper on "Supernatural liaisons in medieval French texts". He was also vice-captain of the college boat club and represented Oxford university boat, ski and water polo clubs (half blue).

Shortly before graduation, Thomas realized that he wanted to study medicine and enrolled in a master's program at the London School of Hygiene & Tropical Medicine. During this year he was able to perform "wet work" at the Medical Research Councils Human Biochemical Genetics unit based at the Galton Laboratories resulting in a thesis "Genetic susceptibility to neural tube defects: a detailed analysis of the CYP26A1 (P450RAI) gene". Still a keen oarsman, he represented the University of London Boat Club at Henley Royal Regatta in 2000.

Thomas was then able to secure an NHS scholarship for a fast track 4 year graduate medical degree at St. George's Hospital Medical School, University of London, during which time he did electives in Ghana and California. Alongside his studies, he continued to row and was also part of the 2003 St. George's cross channel swim team.

Graduating as a doctor in 2004, Thomas moved to the Netherlands to live with his partner and worked as an assistant in cardio-thoracic surgery in the Leiden University Medical Center for 8 months. Returning to London in 2005 he joined the standard NHS training program completing rotations in general medicine, general surgery, trauma & orthopaedics, plastics, ENT and oral & maxillofacial surgery, becoming a member by examination of the Royal College of Surgeons of England in 2010.

Thomas then moved to Switzerland, spending $2^1/_2$ years at the Unispital Zurich under Prof.Dr. Rüdi Probst and a year at the Luzerner KantonsSpital under Prof.Dr. Thomas Linder. He past his ENT specialist exams (in German!), becoming an ENT specialist in 2014 before going to Geneva for a fellowship in sialendoscopy under Prof.Dr. Francis Marchal. Returning to the Ostschweiz, he went into private practice together with Dr. Peter Brändle.

A year later, Thomas, now with his wife and 2 young boys, was on the move again, this time for a Head & Neck fellowship split between the Netherlands Cancer Institute in Amsterdam and the University Medical Center, Utrecht under Prof. Michiel van den Brekel and Prof. Remco de Bree respectively. During this time, the idea and motivation for this PhD crystallized.

Thomas currently lives in Laren and commutes to his work as a Consultant ENT / Head & Neck and Thyroid surgeon at Bart's Health NHS Trust, the UK's largest hospital trust. He still enjoys sport, music and languages but enjoys time with his young family most of all.