Carcinomes épidermoïdes du sinus piriforme: évolution des bons répondeurs dans le cadre des protocoles de préservation laryngée par chimiothérapie d'induction

Vourexakis, Zacharias

UNIVERSITÉ DE GENÈVE

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Section de médecine clinique
Département des Neurosciences cliniques

Service d'Oto-rhino-laryngologie et de Chirurgie Cervico-faciale

Thèse préparée sous la direction du Professeur Pavel DULGUEROV

CARCINOMES EPIDERMOIDES DU SINUS PIRIFORME : EVOLUTION DES BONS REPONDEURS DANS LE CADRE DES PROTOCOLES DE PRESERVATION LARYNGEE PAR CHIMIOTHERAPIE D'INDUCTION

Thèse

présentée à la Faculté de Médecine de l'Université de Genève

pour obtenir le grade de Docteur en Médecine

par

Zacharias VOUREXAKIS

de

Athènes (Grèce)

Thèse n° 10708

Genève 2013

UNIVERSITÉ DE GENÈVE

Formulaire à joindre aux exemplaires de la thèse à remettre pour le dépôt légal

THESE

Informations indispensables à dactylographier

Nom et Prénom : VOUREXAKIS Zacharias

Adresse : Service d'ORL-CCF, HUG

Faculté : Médecine Département des Neurosciences Cliniques

Directeur de thèse : Pr Pavel DULGUEROV

Références bibliographiques :

Titre: ''*CARCINOMES EPIDERMOIDES DU SINUS PIRIFORME : EVOLUTION DES BONS REPONDEURS DANS LE CADRE DES PROTOCOLES DE PRESERVATION LARYNGEE PAR CHIMIOTHERAPIE D'INDUCTION*''
Lieu de la publication: Genève

Date de la publication: 2013

Nombre de pages: 62

Résumé :

Il s'agit d'une étude rétrospective sur les carcinomes épidermoïdes du sinus piriforme qui s'intéresse aux résultats oncologiques et fonctionnels des bons répondeurs dans les protocoles de préservation laryngée par chimiothérapie d'induction. Les objectifs secondaires sont l'analyse des récidives et l'efficacité du traitement de rattrapage.

Au total, 42 patients ont été retenus. A 5 ans, la survie sans maladie était à 60% et la survie sans récidive à environ 50%, des résultats très satisfaisants en comparaison aux données de la littérature. La quasi-totalité des échecs carcinologiques a apparu pendant les premiers 4 ans après la fin du traitement et au moins les 2/3 n'étaient pas rattrapables. La fonction des larynx préservés était très satisfaisante au point de vue respiration, phonation et déglutition.

La littérature, notamment les études prospectives randomisées, sont revues afin de mieux comprendre les différentes approches actuellement utilisées dans la préservation laryngée.

Signature du doctorant : Visa du directeur de thèse :

7$%/(#2)#&217(176#

RESUME

Buts de l'étude: Cette étude s'intéresse aux patients avec un carcinome épidermoïde du sinus piriforme traité avec des protocoles de préservation du larynx basés sur la chimiothérapie d'induction. L'objectif principal est d'analyser les résultats oncologiques et fonctionnels des patients qui sont des bons répondeurs à la chimiothérapie d'induction. Les objectifs secondaires sont l'analyse des récidives et l'efficacité du traitement de rattrapage.

Patients et méthodes: Une analyse rétrospective des patients traités à l'Institut Gustave Roussy entre 1999 et 2008 a été effectuée. Seuls les patients répondant aux critères stricts de bonne réponse à la chimiothérapie d'induction ont été retenus pour l'analyse et des données détaillées ont été extraites de leurs fichiers. Après la chimiothérapie d'induction, les patients ont été traités avec une radiothérapie avec ou sans chimiothérapie concomitante. Pour l'évaluation des résultats fonctionnels, des questionnaires ont été adressés aux patients vivants.

Résultats: Au total 42 patients remplissaient les critères d'inclusion et ont été retenus pour l'analyse. Le suivi minimal était de 3 ans. Au moment du diagnostic presque 2/3 des patients présentaient un stade T3 et 71% avaient des métastases ganglionnaires cervicales.

Les résultats oncologiques à 5 ans montrent une survie globale de 60% et une survie sans récidive d'environ 50%. De meilleurs résultats ont été obtenus pour les tumeurs de petite taille (T2) et lors d'absence de métastases ganglionnaires (N0). Il y avait 11 échecs oncologiques (28%), tous locaux et/ou régionaux. Le rattrapage était impossible ou infructueux dans la plupart des cas (64%), spécialement lors de récidive simultanée locale et régionale.

Les résultats fonctionnels du larynx étaient très bons: seulement 1 patient était resté dépendant d'une trachéotomie à la longue terme (2%) et tous les patients ont jugés leur voix au moins adéquate. La très grand majorité (>85%) se nourrissaient exclusivement par voie buccale.

Conclusion: Pour les patients inclus dans un protocole de préservation du larynx par chimiothérapie d'induction, il semble que la réponse à la chimiothérapie d'induction prédit un résultat oncologique relativement favorable et un résultat fonctionnel satisfaisant. Les échecs locorégionaux sont rarement rattrapables.

INTRODUCTION EN FRANÇAIS

Cette thèse s'intéresse aux carcinomes épidermoïdes des sinus piriformes ; l'objectif principal est d'étudier les résultats carcinologiques et fonctionnels chez les bons répondeurs de la préservation laryngée par protocole de chimiothérapie d'induction. Les objectifs secondaires sont l'analyse des récidives et l'efficacité du traitement de rattrapage.

Dans la discussion, les études prospectives randomisées les plus importantes sur la préservation laryngée sont revues, dans le but de mieux cerner les raisons justifiants des stratégies thérapeutiques différentes lorsqu'on tente d'éviter une laryngectomie totale chez les patients atteints d'une tumeur laryngée et hypopharyngée localement avancée.

HYPOPHARYNX : ANATOMIE ET PHYSIOLOGIE

L'hypopharynx est la partie inférieure du pharynx, entre l'oropharynx en haut, l'œsophage en bas et le larynx en avant. L'hypopharynx lui-même est subdivisé en 3 régions (Figure 1): la région retro-crico-aryténoïdienne, la paroi postérieure et deux sinus piriformes. Chaque sinus piriforme a une paroi latérale, un angle (antérieur), une paroi médiale et un fond (apex); il s'abouche en bas à la bouche œsophagienne.

La muqueuse hypopharyngée est constituée d'un épithélium (malpighien, stratifié, non-kératinisant) et d'un chorion. Elle est séparée des muscles constricteurs qui entourent le pharynx par une couche dense de tissu conjonctif, le fascia pharyngo-basilaire (Figure 2).

Le drainage lymphatique de l'hypopharynx est particulièrement riche ; il est bilatéral pour la région retro-crico-aryténoïdienne et la paroi postérieure et à prédominance unilatérale pour les sinus piriformes. Le drainage principal se fait vers les groupes du cou II et III et plus rarement vers les groupes I et V. Le fond des sinus piriformes et la région retro-crico-aryténoïdienne se drainent vers le groupe VI.

Le rôle principal de l'hypopharynx est sa participation aux mécanismes de la déglutition. Les aliments sont propulsés dans les 2 sinus piriformes et entrent par la suite dans l'œsophage.

CANCER DE L'HYPOPHARYNX – GENERALITES

Les cancers des voies aérodigestives supérieures (VADS) représentent environ 3% des nouveaux cas de cancer aux États-Unis (4.5% chez l'homme et 1.9% chez la femme) et sont responsables d'environ 2% des décès dus au cancer.[1, 2]

La fréquence des cancers de l'hypopharynx présente une variabilité géographique considérable et est estimée entre 5-15% des tous les nouveaux cas de cancer des VADS. La France et l'Inde sont deux des pays ou la maladie est plus fréquente. Même dans ces 2 pays il y a des régions où la prévalence est encore plus élevée (Somme, Manche, Calvados, Chennai, …).[3] L'incidence est nettement plus élevée chez les hommes (95%) et l'âge lors du diagnostic est habituellement entre 50 et 70 ans. Concernant la sous-localisation, aux États-Unis et au Canada la majorité des cas touche les sinus piriformes (65-85%), suivie par la paroi postérieure (10-20%) et la région retro-crico-aryténoïdienne (5-15%). A signaler, qu'il y a des pays (comme l'Inde, l'Angleterre et la Suède)[4] où la sous-localisation retro-crico-aryténoïdienne est plus fréquente ;

cette sous-localisation est relativement plus fréquente chez les femmes et peut être associée au syndrome de Plummer-Vinson.

La grande majorité de ces cancers sont des carcinomes épidermoïdes (95%), souvent moyennement ou peu différenciés.

Environ 90% des cancers de l'hypopharynx est lié à la consommation éthylo-tabagique.

La classification des stades utilisée habituellement est celle de l'UICC[5]; pourtant, les stades selon TNM ont une valeur pronostique limitée.[6]

Cliniquement, les cancers de l'hypopharynx peuvent évoluer de façon relativement silencieuse pour des périodes prolongés jusqu'à ce qu'ils soient finalement diagnostiqués. Au moment du diagnostic environ 90% des patients sont en stade III ou IV et presque 20% sont déjà inopérables. Les symptômes d'appel sont d'habitude la dysphagie, la dysphonie, une masse cervicale, la perte pondérale, l'odynophagie, l'otalgie reflexe et l'hémoptysie. Les patients sont fréquemment polymorbides et en mauvais état général.

Le bilan diagnostique est basé sur:

- l'examen clinique,
- la panendoscopie (Figures 3 et 4) et les biopsies,
- le bilan radiologique (qui varie selon les centres et peut comprendre une combinaison des examens suivants: TDM cervico-facial et thoracique, IRM cervico-faciale, PET). (Figure 5)

Par ailleurs une évaluation de médecine interne, un bilan nutritionnel ainsi qu'un bilan dentaire sont souvent indispensables pour la plupart des patients.

Lors du diagnostic initial:

- des métastases ganglionnaires (N+) sont présentes chez 50-80% des patients,
- des métastases à distance (M1) chez 17% des patients et lors de l'autopsie chez 60% des patients.[7]
- 8% des patients présente des tumeurs synchrones.[8]

Le pronostic spécifique à la maladie dépend principalement du stade T et N initial ainsi que de l'état général des patients. Presque les 2/3 des patients vont mourir de leur maladie. Selon une étude américaine[8] des années '80, la survie spécifique à la maladie à 5 ans est environ 33% ; la survie à 5 ans par stade de la maladie est 63% pour le stade I, 58% pour le stade II, 42% pour le stade III et 22% pour le stade IV.

CANCER DE L'HYPOPHARYNX – TRAITEMENT

En règle générale:

- les petites tumeurs sont traitées par chirurgie partielle ou radiothérapie (avec ou sans chimiothérapie) et
- les tumeurs avancées sont traitées par radiochimiothérapie ou par chirurgie radicale (pharyngo-laryngectomie totale, simple ou circulaire) suivie par radiothérapie (avec ou sans chimiothérapie).

Le traitement local et le traitement régional peuvent être parfois dissociés. Une stratégie consiste à enlever une maladie ganglionnaire cervicale avancée par un traitement chirurgical (évidement cervical) suivi d'un traitement de préservation laryngée par radiochimiothérapie pour la tumeur hypopharyngée.[9]

CANCER DE L'HYPOPHARYNX ET LA PRESERVATION LARYNGEE

Pour certains cas localement avancés où une chirurgie partielle n'est plus réalisable, la préservation laryngée peut être tentée par des moyens non-chirurgicaux. Cette préservation laryngée se base sur des combinaisons de radio- et de chimiothérapie. Son efficacité a été étudiée pour la première fois par une série d'études prospectives randomisées dans les années '90.

Le but de cette approche est non seulement la préservation de l'organe anatomique, mais aussi la préservation de sa fonctionnalité (éviction de trachéotomie permanente, alimentation par la voie naturelle et préservation d'une voix fonctionnelle) sans compromettre la survie par rapport au traitement traditionnel de chirurgie radicale. Actuellement et sur la base des études randomisées, on admet que pour des cas bien sélectionnés les combinaisons radio-chimio-thérapeutiques peuvent donner des résultats comparables en termes de survie en préservant en même temps un larynx fonctionnel à une partie des patients chez qui le traitement a été appliqué.

Il y a deux types de traitement non-chirurgical qui sont utilisés:

- la préservation laryngée par radiochimiothérapie concomitante et
- la préservation laryngée par protocole de chimiothérapie d'induction.

Le premier type de traitement est l'approche habituelle aux États-Unis ainsi qu'aux Hôpitaux Universitaires de Genève, alors que le deuxième est l'approche habituelle en France.

Il est difficile de conclure sur la supériorité de l'une ou de l'autre stratégie. Une revue de la littérature est présentée dans la partie 'Discussion' de cette thèse, afin de résumer les données sur les résultats de ces deux approches différentes.

LA PRESERVATION LARYNGEE PAR CHIMIOTHERAPIE D'INDUCTION

Les patients inclus dans un protocole de préservation laryngée par chimiothérapie d'induction, bénéficient initialement d'un certain nombre de cycles de chimiothérapie néoadjuvante (habituellement entre 1 et 4 cycles). Par la suite, une évaluation clinique et radiologique juge la réponse à la chimiothérapie. Les "bons répondeurs" sont sélectionnés pour un traitement de radiothérapie avec ou sans chimiothérapie, réservant la chirurgie pour un rattrapage en cas d'échec. D'autre part, les "non-répondeurs" à la chimiothérapie d'induction sont traités par une chirurgie radicale suivie par radiothérapie, avec ou sans chimiothérapie concomitante (Figure 6).

Cette stratégie de préservation laryngée en termes de survie a été étudié dans des études randomisées au cours des années '90 et 2000. Le but de ces études était de comparer la survie avec l'approche traditionnelle de chirurgie radicale (en général une pharyngolaryngectomie) à la

survie avec l'approche de "tentative de préservation laryngée". Les résultats fonctionnels ont été beaucoup moins étudiés.

LES OBJECTIFS DE CETTE THESE

Cette thèse se focalise sur les bons répondeurs atteints d'un carcinome épidermoïde du sinus piriforme et traités selon le protocole de préservation laryngée par chimiothérapie d'induction.

L'un des deux buts principaux de ce travail est d'étudier le pronostic des patients ayant répondu favorablement à la chimiothérapie d'induction. L'autre but principal est d'étudier la fonction pharyngolaryngée après la fin de la radiothérapie.

Les objectifs secondaires de l'étude sont l'analyse des échecs carcinologiques et l'analyse des possibilités de rattrapage.

La méthodologie de ce travail ne permet pas d'étudier directement si la réponse favorable à la chimiothérapie est un facteur pronostique de survie améliorée. Cette question est abordée dans la discussion par une comparaison des résultats de l'étude aux données de la littérature. Par ailleurs, une revue de la littérature est effectuée afin de mieux comprendre les différents arguments en faveur de chacun des principaux protocoles de préservation laryngée.

SUMMARY

Aim of the study: The present study is interested in patients with pyriform sinus squamous cell carcinoma treated with induction chemotherapy-based larynx preservation protocols. The primary goal is to analyze the oncologic and functional outcomes in good responders of induction chemotherapy. Secondary aims are the analysis of oncologic failures in good responders and the efficacy of salvage treatments.

Methods: A retrospective analysis of patients treated in the Institut Gustave Roussy, between 1999 and 2008 was undertaken. Only patients fulfilling the strict criteria of good response to induction chemotherapy were retained for analysis and detailed data were extracted from their files. For the evaluation of the functional outcome questionnaires were sent to patients who were still alive.

Results: In total 42 patients, fulfilling the inclusion criteria, were retained for analysis. Minimal follow up was 3 years. Almost 2/3 of the patients had T3 disease and 71% had neck nodal metastases. After induction chemotherapy, the good responders were further treated with radiation therapy alone, with or without concurrent chemotherapy.

In terms of survival, the 5-year overall survival was 60% and the 5-year disease-free survival was approximately 50%; both were better for small tumors (T2) and when nodal metastases were absent (N0).

There were 11 oncologic failures (28%), all of them being local and/or regional. Most recurrences (2/3) appeared in the first 3 years after the end of treatment. Salvage treatment was not feasible or unsuccessful in the majority of patients (64%); this was particularly true in cases of simultaneous locoregional failure.

The functional outcome of larynx preservation was very satisfactory: only 1 patient remained permanently dependent on a tracheotomy (2%), all patients judged their voice quality after treatment as sufficient for everyday oral communication, and the vast majority (>85%) have maintained an exclusively oral feeding.

Conclusion: For patients suffering from a pyriform sinus squamous cell carcinoma and treated with an induction chemotherapy-based larynx preservation protocol, responding to induction chemotherapy appears to provide a relatively favorable oncologic outcome and an excellent functional outcome. Locoregional failure of radiation therapy leaves few chances of success to salvage treatments.

ABBREVIATIONS

CRT – Chemoradiotherapy = radiation therapy with concomitant chemotherapy

DFS – Disease free survival

DSS – Disease-specific survival

ENT – Ear, nose and throat

EORTC – European Organization for Research and Treatment of Cancer

GETTEC – Groupe d'Etude des Tumeurs Tête et Cou

GORTEC – Groupe Oncologie Radiothérapie Tête et Cou

ICT – induction chemotherapy

IGR – Institut Gustave Roussy

NCDB – American National Cancer Data Base

OS – Overall Survival

PF – Induction chemotherapy with platinum salts (cis- or carbo-platinum) and 5-fluorouracil

RT – Radiation therapy

RTOG – Radiation Therapy Oncology Group

SCC – squamous cell carcinoma

TPF – Induction chemotherapy with taxane and platinum salts and 5-fluorouracil

A) INTRODUCTION

A1) HYPOPHARYNX: ANATOMY AND PHYSIOLOGY

ANATOMY

The pharynx is subdivided in three parts:

- the upper part is called epipharynx or nasopharynx,
- the middle one mesopharynx or oropharynx, and
- the lower part hypopharynx or laryngopharynx.

The limit between the oropharynx and the hypopharynx is the level of the hyoid bone, corresponding to the lowest margin of the C3 vertebra. Caudally, the transition from the hypopharynx to the cervical esophagus is defined by the level of the cricopharyngeus muscle corresponding to the lowest level of the C6 cartilage.

The hypopharynx on its own is subdivided in 3 regions (Figure 1):

- the postcricoid region anteriorly and in the middle,
- the posterior hypopharyngeal wall posteriorly and
- the two pyriform sinuses, one on each side.

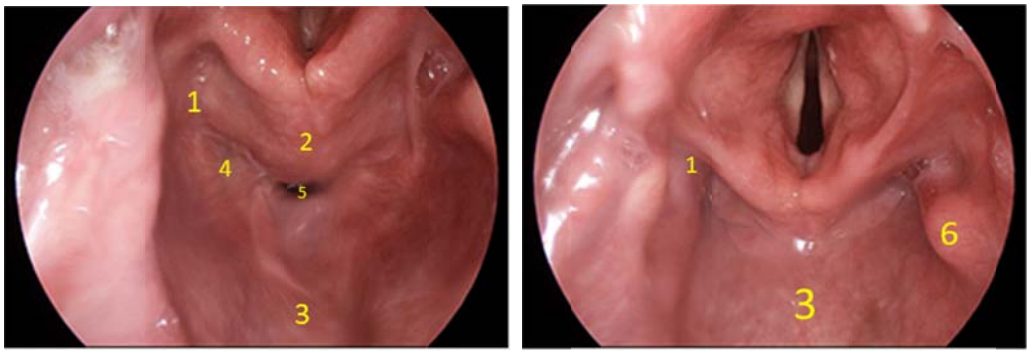
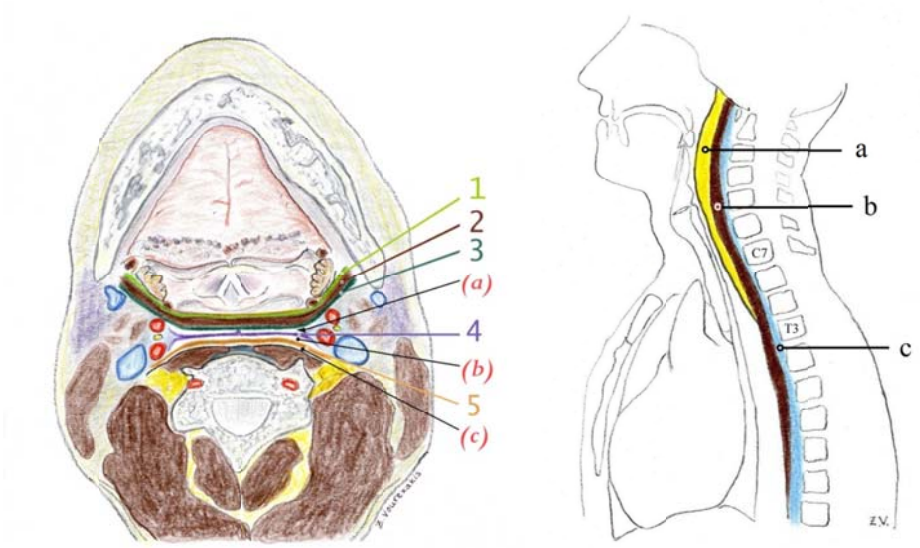


Figure 1: *Endoscopic view of the hypopharynx.*
(1) anterior angle of the pyriform sinus, (2) postcricoid region, (3) posterior hypopharyngeal wall, (4) apex of the pyriform sinus, (5) esophageal inlet, (6) Hyrtl's fold.

The mucosa of the **post-cricoid region** covers the posterior surface of the transverse and oblique arytenoid muscles, the posterior cricoarytenoid muscles and the posterior surface of the cricoid and of the arytenoid cartilages.

The **posterior hypopharyngeal wall** lies on the anterior longitudinal ligament covering the bodies of the 4th, 5th, and 6th cervical vertebrae. Between the hypopharynx and vertebral column lie the buccopharyngeal, the alar and the prevertebral fascias forming the limits of the retropharyngeal space, the danger space and the prevertebral space (Figure 2). The mucosa of the hypopharyngeal walls is surrounded by the inferior pharyngeal constrictor muscle

(thyropharyngeal and cricopharyngeal portion) except at the uppermost part where fibers of the middle pharyngeal constrictor form the muscular envelope. In the midline, between the two bellies of the inferior pharyngeal constrictor (i.e. between the lowest part of the thyropharyngeal muscle and the upper margin of the cricopharyngeus muscle) lies a triangular area of weakness, the so-called Killian's triangle, where Zenker's diverticulum may form.



2a *2b*

Figure 2: 2a) *Drawing of an axial cut of the pharynx: (1)pharyngobasilar fascia, (2) superior pharyngeal constrictor muscle, (3) buccopharyngeal fascia, (4) alar fascia, (5) prevertebral fascia. Deep neck spaces: (a) left and right retropharyngeal space divided by a median raphe, (b) danger space, (c) prevertebral space.* ***2b)*** *Median sagittal cut demonstrating the lower extension of the neck spaces; (a) retropharyngeal space, (b) danger space, and (c) prevertebral space.*

Each **pyriform sinus** has a lateral and a medial (pharyngo-laryngeal) wall joining each other anteriorly, at the pyriform sinus angle. The two walls and the piriform sinus angle converge to the lowermost part of the hypopharynx, the so-called "apex", just above the pharyngoesophageal junction and the esophageal inlet. More specifically:

- the lateral wall of each pyriform sinus lies medially to the thyroid cartilage and the carotid sheath. Its upper third is membranous, corresponding to the cricothyroid membrane, while the lower two thirds are cartilaginous, against the lamina of the thyroid cartilage. The upper laryngeal pedicle with the upper laryngeal nerve raise on the membranous part of the lateral wall of each pyriform sinus a mucosal fold visible in endoscopy, called 'Hyrtl's fold'.
- the medial wall of the pyriform sinus corresponds to the posterior half of the laryngeal vestibule, the aryepiglottic, thyroepiglottic and thyroarytenoid muscles and the lateral part of the cricoid cartilage. Its upper margin forms the so-called aryepiglottic fold. At the level of the vocal cords the angle of the pyriform sinus lies just behind the posterior margin of the paraglottic space.

The hypopharyngeal mucosa consists of non-keratinized squamous stratified epithelium and a chorion. The mucosa is separated from the muscular layer of the constrictors by a thick layer of connective tissue called the pharyngobasilar fascia. A thin layer of connective tissue, called the 'pharyngeal aponeurosis' surrounds the constrictor muscles.

The **arterial supply of the hypopharynx** arises from the posteroinferior laryngeal artery, a branch of the superior laryngeal artery, itself a branch of the superior thyroid artery which arises directly from of the external carotid artery. An additional blood supply is provided from branches of the inferior thyroid artery arising from the thyrocervical trunk of the subclavian artery.[10]

The **venous drainage** is directed through the superior-posterior laryngeal veins towards the internal jugular vein.

The **lymphatic drainage** of the hypopharynx is particularly rich. It is ipsilateral for the pyriform sinuses and bilateral for the postcricoid region and the posterior wall. There is:

- an upper, major pedicle draining to level II (jugulodigastric) and III (supra-omohyoid) lymph nodes and
- an inferior, accessory pedicle draining the pyriform sinus apex and the postcricoid region towards the level VI pretracheal and paratracheal lymph nodes.

The **nerve supply** of the hypopharynx is by sensory and motor branches of the vagus nerve (cranial nerve X). On each side, the sensory innervation of the mucosa is provided by the inner branch of the superior laryngeal nerve and its anastomosis with the inferior laryngeal nerve. The pharyngeal constrictors derive their motor innervation from the pharyngeal branches of the vagus and branches of the recurrent laryngeal nerve.

PHYSIOLOGY

At the level of the oropharynx the pathway for the respiratory and the digestive tract are common while the hypopharynx is the first part of the digestive tract after its separation from the airway. The major role of the hypopharynx is its contribution to swallowing. Food and liquids are forwarded by the tongue base downwards to the hypopharynx. During swallowing the larynx ascends, the epiglottis covers the laryngeal vestibule and hypopharynx is enlarged laterally. Food and liquids slip into the 2 pyriform sinuses and enter the esophagus through the esophageal inlet thanks to the coordinated relaxation of the cricopharyngeus muscle.

The hypopharynx role in phonation is minor, mainly by assisting the oropharynx in the reinforcement of certain harmonics of vowels and giving a low-pitched character to sounds.[10]

A2) HYPOPHARYNGEAL CANCER

EPIDEMIOLOGY

Upper aerodigestive tract cancers (oral cavity, pharynx and larynx) represent 3-3.5% of all new cancer cases in the United States. For 2010, this amounts to almost 50000 new cases, representing 16 new cases per 100000 inhabitants.[2] There is male preponderance with a sex

ratio of 2.4 (incidence of 4.5% in males and 1.9% in females)[2]. In 2010 it was estimated that 2% of all cancer-related deaths in the USA resulted from hypopharyngeal cancers.

Hypopharyngeal cancers have a variable frequency worldwide, representing approximately 5-15% of all upper aerodigestive tract cancers in the USA and Europe. The peak incidence occurs in patients aged 50 to 70 years.[11] Interestingly, high incidence of hypopharyngeal carcinomas are observed in some countries (e.g. France and India)[3, 11] and especially in some regions within the same country (e.g**.** Somme, Manche, Calvados in France, Chennai in India).[3] Other areas with high incidence include Central Europe and Spain while there is low incidence in Israel, Africa, Eastern Asia and Scandinavia. [3, 12]

In the USA and Canada 75% (65-85%) of all hypopharyngeal carcinomas involve the pyriform sinuses, 15% (10-20%) the posterior wall and 10% (5-15%) the postcricoid region. Postcricoid localization is more frequent in India, England, Sweden and Iraq.[4] In endemic regions postcricoid localizations tend to be relatively more frequent in women, with females making up to one third of cases.[11,13]

Hypopharyngeal carcinomas are very lymphophilic tumors, a fact responsible for the observed high rates of nodal metastases (50-80%) at the initial presentationn.[11, 13] Moreover, contrary to other head and neck carcinoma, they often give hematogenous metastasis, mainly to the lungs, but also to the liver, bone, and brain. Distant metastases are diagnosed in almost 17% of patients at presentation and in up to 60% of cases at autopsy.[11] In a large series of hypopharyngeal carcinoma, synchronous second primary cancers were identified in at least 8.3% of 2939 patients.[8]

HISTOLOGY

The vast majority (>95%) of hypopharyngeal cancers arise from the mucosa and are squamous cell carcinomas (SCC). They may be preceded by various precancerous lesions. Invasive carcinomas are usually moderately or poorly differentiated and stain positively for keratin.

Adenocarcinomas represent 0.8% and non-epidermoid carcinomas 2.4% of all hypopharyngeal carcinoma,[14] including basaloid, spindle-cell, small-cell, undifferentiated and minor salivary gland carcinomas. Non-epithelial tumors are very rare and include sarcomas, lymphomas and melanomas.

RISK FACTORS

As for the majority of upper aerodigestive tract carcinomas, alcohol drinking and cigarette smoking are the major risk factors for hypopharyngeal SCC; it is estimated that avoiding both abuses could prevent about 90% of news cases. Compared to laryngeal cancer, the effect of alcohol is stronger and of smoking is weaker in hypopharyngeal SCC.[14]

Another condition that has been specifically correlated to postcricoid carcinoma, mostly in northern European nonsmoker women, is Plummer-Vinson or Paterson-Brown-Kelly syndrome, a triad of iron-deficiency anemia, glossitis and dysphagia due to hypopharyngeal-esophageal webs.[15]

Other less well established correlations include gastroesophageal reflux and nutritional deficits.[13]

STAGING

According to the 7th edition of the UICC TNM Classification of Malignant Tumors[5] published in 2009, hypopharyngeal carcinomas are staged as following.

T-staging

Tis	**in situ carcinoma**
T1	tumor measuring up to 2.0 cm in greatest dimension and limited to one subsite of the hypopharynx
T2	tumor measuring 2,1-4,0 cm in greatest dimension and/or extended to more than one subsites of the hypopharynx or extended to the oropharynx, without laryngeal fixation
T3	tumor measuring more than 4 cm in greatest dimension or vocal cord fixation
T4a	tumor invading the cricoid or the thyroid cartilage or the hyoid bone or the thyroid gland or the strap muscles or the subcutaneous fat or extension to esophagus
T4b	tumor encasing the carotid artery, invading the prevertebral fascia or the mediastinum

N-staging

Nx	**regional lymph node cannot be assessed**
N0	no regional lymph node metastasis
N1	one metastatic lymph node, ipsilateral to the primary tumor, measuring up to 3cm in greatest dimension
N2a	one metastatic lymph node, ipsilateral to the primary tumor, measuring between 3,1 and 6cm in greatest dimension
N2b	more than one metastatic regional lymph nodes, ipsilateral to the primary tumor, measuring up to 6cm in greatest dimension
N2c	at least one metastatic lymph node controlateral the primary tumor and measuring up to 6cm in greatest dimension
N3	at least one metastatic regional lymph node measuring more than 6cm

M-staging

M0	**no distant metastasis**
M1	presence of distant metastasis

Stages

Stage 0	**Tis**	**N0**	**M0**
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	No	M0
	T1, T2, T3	N1	M0
Stage IVa	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVb	T4b	Any N	M0
	Any T	N3	M0
Stage IVc	Any T	Any N	M1

Although the UICC/TNM stage group classification for hypopharyngeal carcinoma creates statistically distinct groups, it is not perform as well as other stage group classifications in predicting disease-specific survival.[6]

CLINICAL PRESENTATION

In contrast to other localizations of upper aerodigestive tract tumors which may present with early manifestations, such as visible lesions of the oral cavity or voice alterations for even small glottic lesions, hypopharyngeal carcinomas may evolve relatively silently or with minor and nonspecific symptoms for prolonged periods before diagnosis. Moreover, many patients tend to seek medical advice with a certain delay even after the appearance of the first symptom. Hence, it is not surprising that most patients present with locally advanced T3 or T4 tumors, almost 90% of cases presenting with advanced stage III or IV tumors and >50% of all cases are already in stage IV. Moreover, almost 1 out of 5 patients (19.5%) presents with an unresectable tumor.[16]

Presenting symptoms may include[16]: dysphagia (53%), neck mass (37%), involuntary weight loss (36%), odynophagia (34%), ipsilateral reflex otalgia (30%) or hemoptysis (6%). Halitosis due to the tumor itself or due to food and saliva stagnation may be present. Tumors extending or not to the larynx may also present with voice hoarseness (39%). Dyspnea is usually a symptom of locally advanced disease.

At the initial consultation patients may be malnourished, with severe co-morbidities such as cardiovascular disease, chronic obstructive pulmonary disease (COPD), liver cirrhosis and peripheral neuropathy; it is estimated that every second patient has associated diseases with at least moderate decompensation, while almost 40% have a significant reduction in performance status[16]. Oral and dental hygiene are usually poor.

A minority of new cases patients may already have distant hematogenous metastases at initial presentation (stage IVc).

WORKUP

As for all upper aerodigestive tract tumors, detailed clinical ENT examination is the first and crucial step for tumor workup; it is based on direct and indirect examination with mirrors or endoscopes (rigid telescopes or flexible fiberoptic endoscopes). It should be focused in the following aspects:

- the physician should describe the lesion's macroscopic characteristics and its local extension. Fiberoptic transnasal flexible endoscopes allow the patient to make a Valsalva maneuver during the physical examination which may be helpful in a better appreciation of the local extension. Positive pressure on the pharyngeal lumen dilates the pharynx and the pyriform sinuses hence allowing a better evaluation of the lower extension of the tumor and the differentiation between a posterior wall and a postcricoid area tumor;
- at this stage special attention should be given in the evaluation of vocal cords mobility which is a prognostic factor taken into consideration in staging and therapeutic decision-making;
- saliva and food stagnation in the pyriform sinuses and aspiration problems indicating a disordered swallowing mechanism, should be identified;
- neck palpation should detect metastatic cervical lymph nodes, allow the description of their characteristics and detect signs of extralaryngeal and extranodular spread;
- at this stage of initial evaluation it is crucial to look for synchronous tumors, since for certain localizations (oral cavity, posterior surface of the soft palate …) clinical examination may be superior to panendoscopy and could guide biopsy localization.

Rigid endoscopy of the pharyngo-laryngeal region under general anesthesia allows biopsies which are mandatory to confirm the diagnosis (Figure 3). Moreover it provides a better examination of the pyriform sinuses, the posterior wall, and the postcricoid region. A detailed mapping of the tumor with precise delimitation of its margins is necessary, on both the horizontal plane (anterior angle, lateral and medial wall of the pyriform sinuses, posterior pharyngeal wall and postcricoid region) and the vertical plane (evaluation of tumor's lower extension towards the esophageal inlet) (Figure 4).

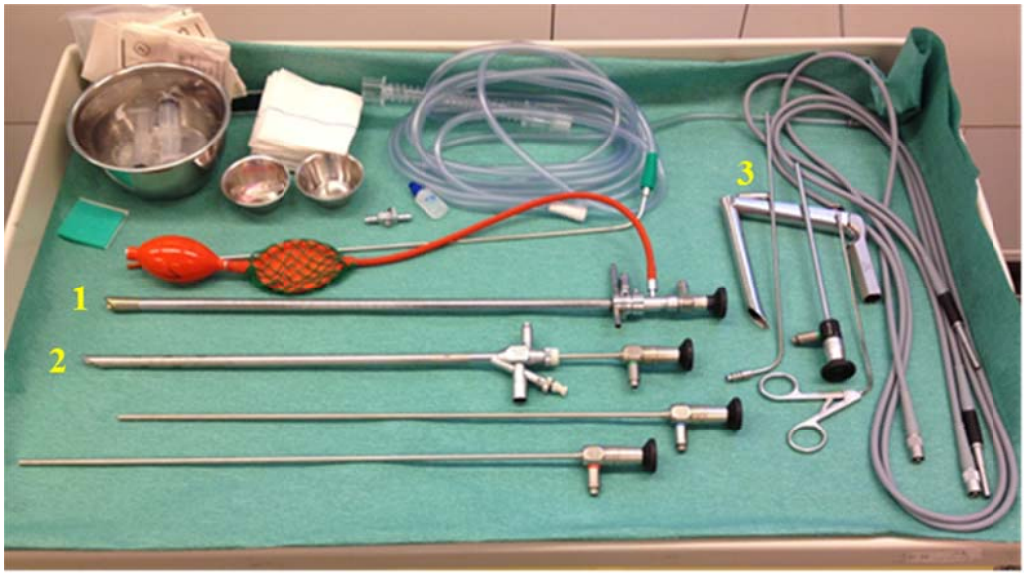


Figure 3: *Material used for a rigid endoscopy under general anesthesia, in the University Hospitals of Geneva. The rigid esophagoscope (1) is associated to a pneumatic system (in orange) to dilate the esophageal lumen during inspection. The rigid bronchoscope (2) appears right under the esophagoscope and can be used with 0°, 30° and 90° telescopes. A pharynsgoscope (3) with a short 0° telescope and a biopsy forceps appears on the right.*

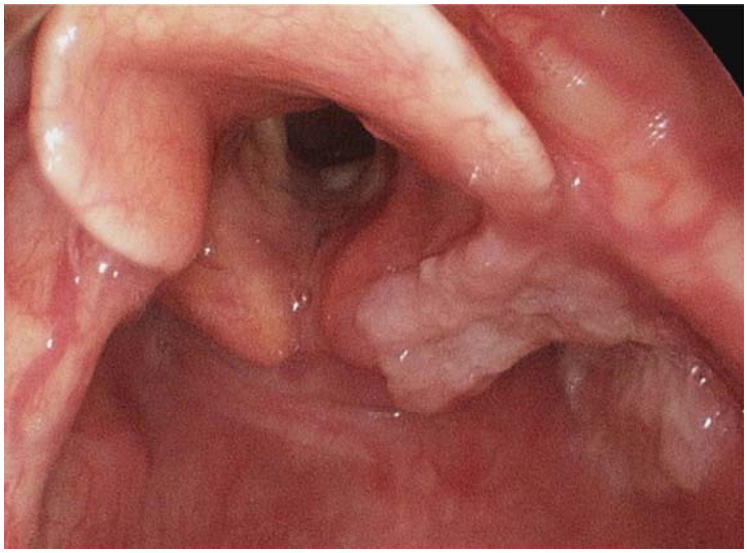


Figure 4: *An endoscopic view of a right pyriform sinus SCC occupying the anterior angle and both medial and lateral walls; the mucosa of the postcricoid region, the apex of the pyriform sinus and the esophageal inlet were macroscopically intact. This picture was taken under general anesthesia with a Macintosh laryngoscope blade and a 0° telescope. The vocal cords were mobile.*

Endoscopic examination of the esophagus and often of the tracheobronchial tree is also part of the initial workup for patients with positive history of smoking and alcohol drinking as the entire mucosa of the upper aerodigestive tract, the esophagus and the tracheobronchial tree is

exposed to increased risk of carcinogenesis. This exposition explains cases with simultaneous second primary tumors. The interest of this approach consists in its potential of detecting precancerous lesions or small subclinical carcinomas which are not detected by imaging, allowing biopsies and consequently early treatment with improved prognosis. Endoscopic examination may be performed with rigid endoscopes, under general anesthesia, at the same time as the rigid pharyngolaryngoscopy; in that case the examination is the called rigid 'panendoscopy'. Alternatively, the examination of the esophagus and the tracheobronchial tree may be performed with flexible endoscopes by trained otolaryngologists, gastroenterologists or pneumologists.

Imaging is a mandatory part of the tumor work-up:

- ***CT-scan of the head and neck*** region with contrast injection and a simultaneous Valsalva maneuver is a crucial examination for tumor staging and therapeutic decision-making (Figure 5). It allows for the assessment of local tumor extension, of regional disease (cervical lymph node metastasis) and of the relations between the tumor and vital structures (carotid artery …). Cartilaginous invasion should also be assessed by imaging as it would be an indication for radical surgery.
- ***MRI*** is more sensible than CT-scan for the evaluation of soft tissue extension and probably less sensible for cortical bone erosion. Laryngeal mobility during the exam seems to be an obstacle in acquiring quality images but its use is of increasing interest, although it doesn't make part of the routine work-up in all centers. Its superiority to CT-scan for delimitating soft tissue extension renders MRI even more interesting for posterior pharyngeal wall carcinomas work-up,
- hypopharyngeal squamous cell carcinomas tend to give hematogenous metastasis more often than other head and neck carcinomas. Pulmonary metastases are the most frequent site of secondary localizations; hence, ***chest CT-scan*** makes nowadays part of the initial work-up in most centers,
- for the same reason there is increasing interest in the role of ***Positron-Emission Tomography*** (PET) in the work-up. Combined or not to CT-scan or MRI (PET-CT or PET-MRI) it may detect metastasis other on distant localizations such as lungs, liver, and bone. It is considered to be highly sensitive but not specific since increased metabolism due to inflammation or tumor proliferation are difficult to differentiate.

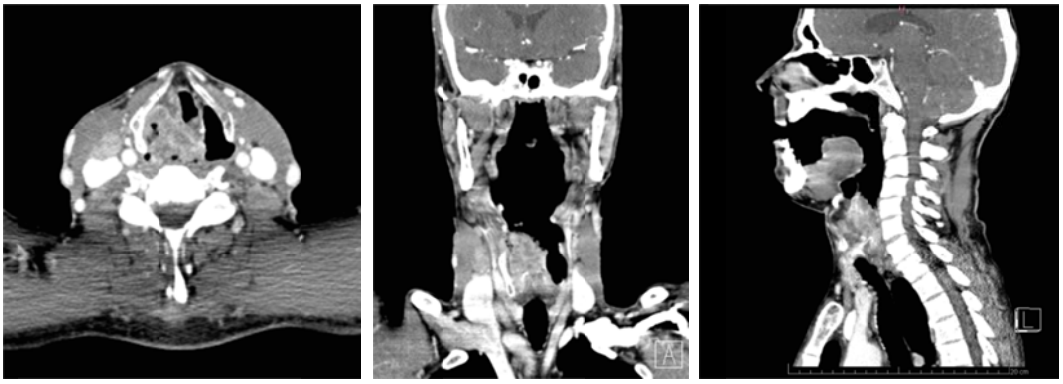


Figure 5: *An axial, coronal and sagittal CT-scan of a male patient presenting a hypopharyngeal SCC centered on the right piriform sinus and the postcricoid region.*

Apart from the staging-related work-up, patients with hypopharyngeal squamous cell carcinoma should have an ***internal medicine work-up***; performance status, nutritional status, vitamin deficiencies, cardio-pulmonary, hepatic and renal function as well as any other comorbidities should be assessed. The main indication of this evaluation is related to the need to include chemotherapy in the treatment regimen of the majority of hypopharyngeal cancer patients. Moreover, alcohol and nicotine addiction should be evaluated and included in the therapeutic approach.

Finally, as almost all patients will need to receive radiotherapy as exclusive or postoperative adjuvant treatment, a ***dental examination*** should be included in the initial workup.

PROGNOSTIC FACTORS AND PROGNOSIS

A retrospective population-based study of 595 patients treated for hypopharyngeal cancer in Ontario, Canada in the '90s (January 1990 – December 1999) shows that the main prognostic factors correlated to disease-specific survival (DSS) are: regional nodal status (N), tumor local extension (T), and performance status.[17]

As patients with hypopharyngeal SCC tend to have multiple comorbidities, prognosis is not only influenced by cancer but also by other factors compromising the overall survival (OS). The major factors influencing survival are listed below in order of importance:

- regional nodal status (N),
- alcohol consumption,
- tumor local extension (T),
- performance status,
- age,
- comorbidities.

The sub-localization within the hypopharynx does not influence the prognosis.

Directly after treatment with curative intent 1 out of 5 patients had residual disease. Most treatment failures appeared in the first year and half of first failures included distant metastases. Less than half of all patients were disease-free in 3 years while almost 2/3 of all patients diagnosed with a hypopharyngeal cancer would die of the disease.

In a survey based on almost 3000 patients diagnosed with hypopharyngeal SCC in the '80s (1980-1985 and 1990-1992) in the USA, the overall 5-year DSS was 33,4%.[8] More specifically, the 5-years DSS were:[8] 63.1% for stage I, 57.6% for stage II, 41.8% for stage III, and 22% for stage IV.

Moreover, the long-term results of the EORTC 24981 prospective randomized study comparing surgery followed by radiation therapy to an induction chemotherapy preservation protocol, show that after a 10 ½ year median follow-up the survival rates for patients with T2-T4 pyriform sinus SCC (for inclusion criteria see paragraph C1) were about 10%.[18]

HIGHLIGHTS

Hypopharyngeal SCC present certain particularities compared to the other localizations of uppers aerodigestive tract tumors:

- they are often diagnosed in more advanced stages, in part because they may remain asymptomatic at the initial stages and in part because patients tend to underestimate the initial often nonspecific symptoms;
- patients often have significant comorbidities and a reduced performance status;
- there is an increased risk of distant metastases;
- the overall prognosis remains poor.

A3) TREATMENT OF PYRIFORM SINUS SCC

GENERAL PRINCIPLES

The two main treatment modalities for hypopharyngeal SCC are surgery and radiation therapy. These two may be associated to each other and are both used with curative intent.

Chemotherapy has a more limited role in the treatment of upper aerodigestive tract SCC; in everyday clinical practice it is never administered as a main, single-modality treatment with curative intent. However, due to the locoregional aggressiveness of hypopharyngeal tumors and their metastatic potential, it is often used in association with radiation therapy. It may also be used as induction chemotherapy in laryngeal preservation protocols.

The **surgical treatment** of a pyriform sinus SCC depends on the localization and the local extension of the tumor and may consist of a partial pharyngectomy (associated or not with total laryngectomy) or a total pharyngolaryngectomy. In all cases surgery should be followed by postoperative radiation therapy, with or without concomitant chemotherapy.

Tumor surgery of the hypopharynx should always be associated with neck treatment. Even in patients with cN0 nodal status, prophylactic treatment of neck levels II, III, IV, ipsilateral VI and retropharyngeal nodes should be considered. In some cases neck dissection may be the sole surgical treatment [9] prior to primary tumor chemoradiation; this strategy is discussed below.

Radiation therapy (RT) on the other hand, may be used as a main treatment modality or as a postoperative adjuvant treatment, combined or not to chemotherapy, for both the primary tumor and the neck lymph nodes. As it is the case with all SCC of the upper aerodigestive tract, the smaller a tumor is, the more efficient RT is.

Chemotherapy (CT), as already mentioned, is not currently used as a single-modality treatment with curative intent. More specifically chemotherapy me be administered:

- as concomitant treatment to radiation therapy (CRT), where its role is limited to the potentialization of the latter;
- as neoadjuvant treatment (ICT) with 3 different goals: 1) to render an inoperable primary tumor or an inoperable neck accessible to surgery, 2) to halt progression of a rapidly growing tumor before definite treatment is administered, 3) as first step of a laryngeal preservation protocol, which is the main subject of this thesis and is going to be discussed in details in the following sections.
- as palliative treatment in patients for whom no curative treatment is available. In such cases it is associated to other palliative measures and its goal is quality of life improvement and life prolongation.

CHOICE OF TREATMENT MODALITY

There is no universal consensus on what is considered to be the best treatment modality for all different localizations and stages of hypopharyngeal SCC. Moreover, physicians' expertise and patients-related criteria are taken into consideration and influence the choice of treatment modalities.

There are though some principles that are more or less widely accepted:

- since hypopharyngeal SCC are highly lymphophilic tumors, the treatment planning should always take into consideration lymph nodes treatment, no matter the clinical stage of the primary tumor (T) or the neck (N);
- as hypopharyngeal SCC are locally and regionally aggressive tumors, radiation therapy is almost invariably administered to all patients, either as a full-dose treatment or as an adjuvant postoperative treatment;
- there is an increased potential of hypopharyngeal tumors for hematogenous, distant metastases with a dramatic impact in the overall survival. Local treatments as surgery and radiation therapy do not seem to be sufficient in cases with an increased metastatic risk and the role of chemotherapy is under investigation. The indications of chemotherapy concomitant to radiation therapy include T3 and T4 tumors, N2 or N3 nodal disease as well as histological signs of poor prognosis such as positive surgical margins, extracapsular nodal spread and perineural invasion.

The main principles and outlines (2012) of the treatment strategy for pyriform sinus SCC in the Institute Gustave Roussy (IGR), where the present study was made, are resumed as follows:

- **T1/2 N0/1**: exclusive RT or partial surgery with neck dissection followed by RT, the choice depending on tumor macroscopic characteristics and localization;
- **T1/2 N2**: CRT;
- **T2N0/1** with contraindications to partial surgery and **T3** tumors: larynx preservation protocol or total pharyngolaryngectomy followed by RT or CRT;
- **T4a**: total pharyngo-laryngectomy followed by CRT if preservation is contraindicated;
- **N3 disease**: neoadjuvant chemotherapy, followed by neck dissection (+/-tumor surgery) followed by CRT.

Criteria as patient's characteristics, comorbidities and contraindications to chemotherapy and laryngeal preservation are also taken into consideration.

A4) LARYNX PRESERVATION PROTOCOLS

INTRODUCTION

Until the '70s the standard treatment of locally advanced laryngeal and hypopharyngeal SCC was radical surgery while the alternative would be exclusive radiation therapy with preservation of surgery as salvage treatment. By the beginning of '80s a promising role of chemotherapy seemed to emerge from the association of cisplatin to 5-fluorouracil. Since no survival benefit from the introduction of chemotherapy could be demonstrated, research focused on its potential in improving the quality of life. For laryngeal and hypopharyngeal SCC this could be achieved by attempting larynx preservation.[19]

The 'Veterans Affairs' trial for locally advanced laryngeal SCC in 1991[20] and the 'EORTC 24891'[21] trial for locally advanced pyriform sinus SCC in 1996, were the first randomized prospective trials to show that a nonsurgical treatment protocol including induction chemotherapy (ICT) followed by RT in good responders or followed by surgery and RT in non-

responders could attempt larynx preservation without compromising survival when compared to a protocol of initial surgery followed by radiation therapy.

In the 2000s, randomized prospective trials focused in the definition of the optimal preservation protocol. The two options that have prevailed nowadays are:

- **concurrent chemoradiotherapy** which is the dominant preservation protocol in the USA. The total dose of radiotherapy is typically administered over a 7-week period and associates 3-dimensional conformal radiation therapy (in a 5 days/week schedule) to 3 cycles of cisplatin in treatment days 1,22, and 43. Both primary tumor and lymph nodes are treated. Different radiotherapy modalities, such as intensity-modulated radiation therapy or accelerated and hyperfractionated schemes have also been tried but none of them has become the universally accepted gold standard.
- **induction chemotherapy** followed in good responders by radiation therapy and by surgery and radiation therapy in non-responders. This is the dominant preservation protocol in France. The basic idea of this approach is to use neoadjuvant chemotherapy in order to select patients who can be cured by radiation therapy. Patients with inadequate response to induction chemotherapy are considered to have fewer chances to respond to radiation therapy and are treated with radical surgery followed by radiotherapy.

Radiation therapy alone seems to be less efficient in terms of laryngeal preservation than the previous 2 approaches.

In regard to the 2 dominant protocols, so far there are no randomized prospective trials comparing concurrent chemoradiotherapy to induction chemotherapy-based preservation using taxanes, platinum salts and 5-fluorouracil, which is nowadays the neoadjuvant regimen of choice. A review of the evidence-based data supporting each of these two different approaches is performed in the discussion chapter of this thesis.

AIMS

The primary aim of larynx preservation is to spare the larynx and prevent a permanent tracheostomy by avoiding radical surgery without compromising survival. Increasing emphasis is given to the functional aspect of the preservation; not only the larynx should be spared but it should also remain functional. Ideally, after the end of the treatment, patients should be able to breathe through the normal airway, have a functional voice and continue to eat exclusively by mouth. On the contrary, severe laryngeal dyspnea and/or aspiration problems necessitating a tracheotomy, insufficient oral feeding necessitating a feeding tube or a gastrostomy, as well as loss of functional voice for everyday needs would be at least a partial failure of the larynx preservation strategy.

INDICATIONS & DESCRIPTION

Schematically, larynx preservation protocols are considered in cases of laryngeal and hypopharyngeal SCC where partial surgery is not indicated but total pharyngolaryngectomy is not mandatory.

For hypopharyngeal SCC, laryngeal preservation is typically attempted in cases of:

- T3 lesions,
- big T2 lesions if partial surgery is contraindicated (postcricoid or interarytenoid extension, poor general health, reduced pulmonary reserves, …) and
- lesions staged T4a due to soft tissue invasion (strap muscles, thyroid gland, esophagus) without cartilage involvement.

At the IGR in Villejuif, where the study of the present thesis was carried out, patients included in a larynx-preservation protocol are initially treated with 3 cycles of ICT. The response is evaluated just prior to the 3rd cycle (Figure 6). Two principle parameters are taken into account at the evaluation of tumor response: 1) tumor volume regression and 2) remobilization of the arytenoids.

The evaluation of tumor's regression is based on endoscopic examination under general anesthesia and on CT-scan findings while arytenoids remobilization is evaluated by clinical examination.

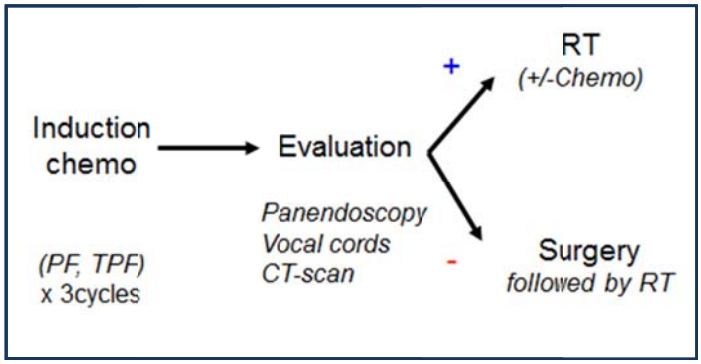


Figure 6: *A paradigm of larynx preservation protocol with induction chemotherapy, as applied at the IGR. Response to ICT is evaluated just before the 3rd cycle. The various randomized prospective trials have used different criteria (volume reduction, vocal cord mobility, and metastatic nodes response), different means of evaluation (imaging, clinical examination, direct laryngoscopy under general anesthesia) and a different timing pattern of evaluation.*

A patient with hypopharyngeal SCC is considered to be a 'good responder' to induction chemotherapy and hence a good candidate for radiation therapy (+/- chemotherapy) if there is ≥80% regression of the tumor's volume and both arytenoids move normally. Neck may be treated separately by neck dissection prior to radiation therapy in case of significant persistent disease after chemotherapy.

Patients with an inadequate (according to the above-mentioned criteria) response to induction chemotherapy are treated with radical surgical of the primary tumor associated to neck dissection and postoperative radiation therapy, provided that the tumor remains operable.

Neoadjuvant chemotherapy regimens have traditionally associated platinum salts, preferably cisplatinum (CDDP), and 5-fluoro-uracil (5FU), hence the abbreviation PF (Platinum-Fluorouracil). In the 90's 'PF' was the standard regimen of larynx preservation. Later-on,

randomized prospective clinical trials (GORTEC 2000-01[22] and TAX 324[23], see paragraph C2) have demonstrated increased efficacy and improved prognosis while associating PF to taxanes (TPF). Thus, TPF is currently considered the first-choice regimen of neoadjuvant chemotherapy in larynx preservation protocols.

CONTRAINDICATIONS

Patients with a pyriform sinus SCC should be carefully selected according to the above mentioned indications before an attempt of larynx preservation. But even for patients fulfilling the inclusion criteria there are cases that should probably be excluded from such an attempt.

It is nowadays clear that radiotherapy alone is less efficient in terms of laryngeal preservation than concomitant chemoradiotherapy; hence patients with medical contraindications for a cisplatin-based chemotherapy should not be included in a concomitant chemoradiotherapy protocol. Similarly, patients who could not tolerate a TPF chemotherapy regimen should reasonably be excluded from any attempt of induction chemotherapy larynx preservation protocol.

Moreover, indications of larynx preservation are based on randomized prospective studies of the last 2 decades. For patients dissimilar to those included in these studies, no conclusions can be made for the oncological and functional outcomes of such an approach. Hence, hypopharyngeal tumors with extension to the valleculae or base of tongue and cases of continuity between the primary hypopharyngeal lesion and nodal metastases should not be treated with a larynx preservation approach.

As already mentioned, the aim of preservation is not limited to sparing an anatomical structure (larynx) but also aims to preserve pharyngo-laryngeal functions (natural breathing, eating and speaking). If these functions are already compromised before treatment, it would be irrational to risk a jeopardized oncological outcome in order to preserve a non-functional larynx. Therefore, the presence of tracheotomy, history of recurrent aspiration pneumonia and partial or total enteral feeding (nasogastric tube or gastrostomy) should be taken into consideration and be considered as relative contraindications for a preservation attitude.

Finally, for induction chemotherapy preservation protocols it should be mentioned that in some hospitals like the IGR significant attention is given to the restored mobility of a previously hypomobile arytenoid as a measure of response to induction chemotherapy. Hence, in cases of candidates for larynx preservation presenting normal arytenoid mobility before treatment, response to induction chemotherapy would be hard to evaluate and direct chemoradiation therapy should be tried.

THE GOOD RESPONDER OF THE INDUCTION CHEMOTHERAPY PROTOCOLS

Selecting good responders for radiation therapy is the central idea of larynx preservation protocols with neoadjuvant chemotherapy. This selection aims to achieve a better oncological and functional outcome.

It is speculated that patients responding favorably to chemotherapy are more likely than non-responders to be cured by radiation therapy. In other words, it is considered that there is a

probable association between 'chemosensitivity' and 'radiosensitivity' of the tumor, allowing selection of patients with increased chances for complete remission when treated with radiation therapy. However, it is noteworthy that results from randomized trials show that lack of chemosensitivity of a tumor is (at least) not a perfect predictor of poor outcome of treatment with radiation therapy. In the RTOG 91-11 study[24], a minority of patients refusing surgery, after inadequate response to induction chemotherapy, have obtained complete and durable disease control with nonsurgical treatment.

Concerning response criteria different protocols were used in the major randomized trials in regard to the parameters evaluated, the means used for and the timing of the evaluation:

- all trials have taken into consideration primary tumor's volume reduction, some of them nodal response and some others vocal cord mobility,
- some trials evaluated response to induction chemotherapy after every cycle, some others only prior to the last cycle while others after the completion of the 3rd cycle.

Moreover, the inclusion criteria of the major randomized trials were not homogenous. Consequently, it is clear that it is difficult to establish an optimal protocol of evaluation of response to induction chemotherapy.

At the IGR, a major criterion of selection is arytenoid mobility as a key element of favorable outcome in terms of functionality and overall survival. Only patients presenting (before any treatment) impaired vocal cord mobility are considered as optimal candidates for induction chemotherapy larynx preservation (as remobilization could be used as a criterion of response) while candidates for preservation with normal pre-treatment vocal cord mobility are treated with direct chemoradiation.

Moreover, it is speculated that irradiating a larynx with reduced mobility would probably fix permanently the hypomobile or immobile vocal cords with long-term sequels in the functional outcome (respiration, swallowing) and the overall survival (risk of increased morbidity and mortality due to aspiration-related pulmonary infections); hence patients with impaired vocal cord mobility after induction chemotherapy are oriented towards treatment with total laryngectomy.

B) STUDY

B1) INTRODUCTION

Survival rates of patients with hypopharyngeal squamous cell carcinoma (SCC) are based on statistics concerning patients treated with different modalities (surgery, radiation therapy, concurrent chemoradiation, or induction chemotherapy-based preservation protocols) but little is published on the survival rates of good responders of induction chemotherapy protocols. The outcome of previous studies on larynx preservation has been oriented towards the preservation rates. It would be interesting to know what the prognosis is for a patient responding favorably to induction chemotherapy, stated differently the question is whether a good response to induction chemotherapy predicts an improved survival.

On the other hand, the main idea of larynx preservation protocols is not limited to sparing the larynx as an anatomical structure but also to sparing a functional organ allowing physiological swallowing, phonation and respiration. It's of great interest to see if induction chemotherapy-based larynx preservation can provide an improved rate of pharyngo-laryngeal functions' preservation.

The present study targets patients with pyriform sinus SCC, treated with induction chemotherapy-based larynx preservation protocols. The focus was exclusively on patients fulfilling all the criteria of good response who have additionally completed their treatment by definite radiation therapy (+/- concomitant chemotherapy) as scheduled.

B2) OBJECTIVES

The primary endpoints of this study are the oncological and functional outcomes in the specific subgroup of the so-called good responders of induction chemotherapy, who are supposed to be the most favorable candidates for a positive outcome of radiation therapy. Hence the primary end points are:

- the oncological outcomes tin terms of overall and recurrence-free survival rates,
- the functional outcomes, referring to respiration, voice and swallowing performance after treatment.

The secondary endpoints of this study are:

- the analysis of treatment failures and
- the possibilities of salvage therapy.

B3) MATERIAL AND METHODS

The study was carried out in a reference cancer center in France, the Institut Gustave Roussy (IGR) in Villejuif.

The data base of the tumor board of the Head and Neck Department (where decisions on the treatment are taken for all head and neck cancer cases) was used for searching patients potentially eligible in the study; the list of those treated between 1999 and 2008 for pyriform sinus SCC was screened for patients initially treated with chemotherapy.

The criteria of inclusion in the study were the following:

- primary tumor arising from the pyriform sinus,
- histology of squamous cell carcinoma,
- minimum follow-up of 3 years after the end of treatment (radiation therapy),
- tumor accessible to surgery before the induction chemotherapy,
- induction chemotherapy as part of a larynx preservation protocol,
- induction chemotherapy was the first treatment to be given for the disease,
- good response to induction chemotherapy, i.e. tumor volume regression and remobilization of the previous immobile arytenoid(s),
- tumor remaining accessible to surgery after induction chemotherapy,
- induction chemotherapy followed for good responders by radiation therapy (+/- concomitant chemotherapy),
- treatment plan completed exactly as initially scheduled,
- treatment and regular follow-up at the IGR.

Exclusion criteria included the following:

- history of a previous head and neck cancer,
- recent history of any other cancer,
- synchronous tumors,
- metastatic disease,
- chemotherapy initially given with a palliative intent,
- any treatment for the same disease prior to induction chemotherapy, including neck dissection,
- tumor not accessible to surgical resection before the induction chemotherapy (chemotherapy aiming to render tumor accessible to surgery),
- radiation therapy given after an insufficient response to induction chemotherapy (for example in case of patients refusing surgery),
- radiation therapy interrupted or administered in a suboptimal way, different than the initial treatment plan,
- treatment done elsewhere after the decision at the tumor board of the IGR,
- patient lost of follow-up from the IGR.

A detailed review of the medical files of all patients retained in the study was performed. Data collected included patients' characteristics, staging, details on treatment modalities and evolution of the disease.

The main parameters calculated in the evaluation of the oncological outcome were the overall survival (OS) and the disease-free survival (DFS):

- the OS refers to patients remaining alive after a given period of time from the end of radiation therapy, and is calculated as a percentage of all patients included in the study,
- the DFS refers to patients remaining alive with no recurrence of the disease during a given follow-up period after the end of radiation therapy. It is also calculated as a percentage taking into consideration all patients included in the study.

OS and DFS rates could be precisely calculated for the first 3 years after the end of treatment, as all patients included in this study were followed for at least 3 years. The Kaplan-Meier estimator was used to calculate the survival rates in the long run.

Additional parameters which were analyzed included patterns of treatment failure (local, regional, locoregional, or distant), the time elapsed from the end of the treatment to failure, possibilities of salvage therapy, and appearance of metachronous tumors.

Analysis of the functional outcome was based on the degree of preservation of normal pharyngo-laryngeal functions. The following table resumes the parameters evaluated (Table 1).

Function	Function related parameters
Breathing	- presence of tracheotomy - duration of tracheotomy (permanent, temporary)
Speaking	- voice alteration (subjective) - sufficiency of voice for everyday life needs (subjective)
Swallowing	- nutritional pathway (oral, enteral, combined) - food consistence (normal, mixed, semiliquid, liquid) - aspiration problems

Table 1: *Parameters taken into consideration in the evaluation of the functional outcome of larynx preservation.*

In order to evaluate the functional outcome, self-administered questionnaires were sent to all patients who were still alive when the present study was carried out (2012). Each questionnaire contained 10 questions in total, divided in 3 parts (see F, Annexes 1 and 2):

- 4 concerning breathing and history of tracheotomy,
- 2 concerning voice quality, and
- 4 concerning swallowing difficulties, meals consistence, aspiration problems and the need of feeding tube or gastrostomy.

The same information was searched in the files of all patients included in the study. For patients already deceased, data could be analyzed only when sufficient documentation was available in the medical records. For those who were still alive and had answered the questionnaire, a comparison was made between the answers given and the data provided from patients' records in order to confirm the accuracy of the provided information.

STATISTICAL ANALYSIS

The comparison of the treatment subgroups in terms of T-stage, N-stage and disease stage was made with the Fischer exact and $\chi 2$ tests. The Kaplan-Meier method was used to estimate OS and DFS rates as a function of time after the end of treatment. The Mantel-Cox test (logrank test) was used for the comparison of the survival curves, when this was possible. For all calculations the 'MedCalc' statistical software was used.

B4) RESULTS

COHORT DESCRIPTION

Between 1999 and 2008, a total of 724 patients were treated in the IGR for hypopharyngeal SCC. The primary tumor was originating from the pyriform sinus region in 559 cases (77%). An almost equal number of pyriform sinus patients were initially treated with surgery (222) and chemotherapy (200), while a minority (109) was directly treated by radiation therapy (Figure 7). Among the 200 patients initially treated with chemotherapy, only 161 were treated with curative intent while for the remaining 39 patients treatment was palliative.

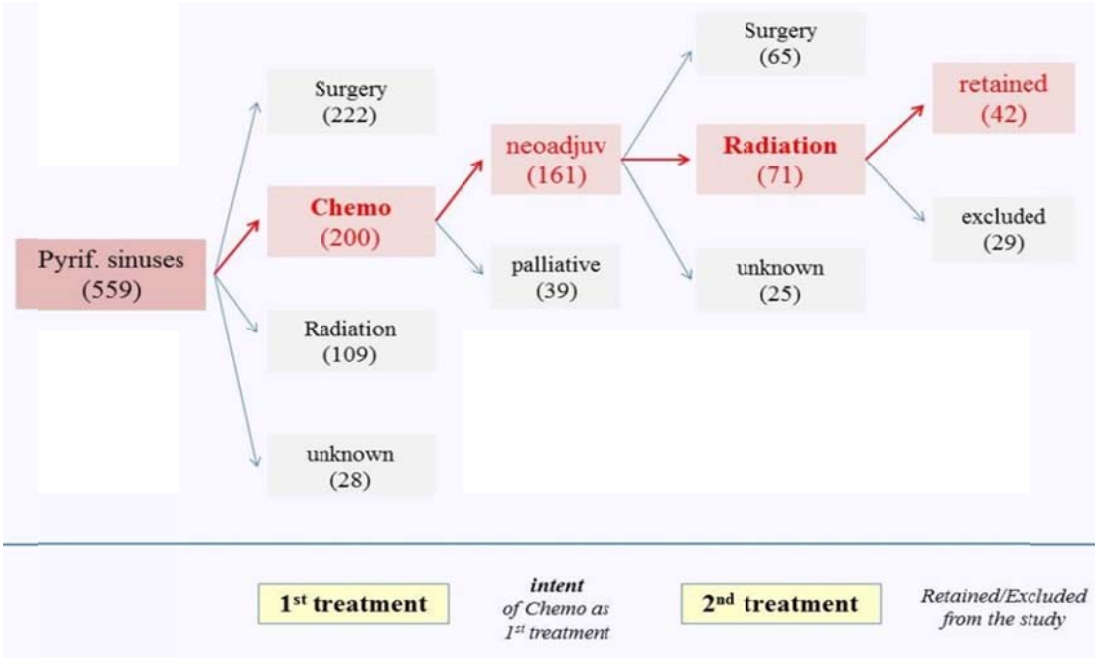


Figure 7: *flow diagram of the 559 patients treated for pyriform sinus SCC in the IGR between 1999 and 2008, aiming to identify those treated with an induction chemotherapy-based larynx preservation protocol (Pyrif.=Pyriform, Chemo=chemotherapy, Radiation=Radiation therapy, neoadjuv=neoadjuvant).*

The initial chemotherapy treatment was followed by radiation therapy (+/- concomitant chemotherapy) in 71 cases. In this group of 71 patients, only 42 were good responders, fulfilling the inclusion criteria and were thus being retained for this study.

The reasons, for which the remaining 29 patients could not be included, are the following:

- inoperable tumors for which induction chemotherapy was meant to render them operable (so, there was no larynx preservation intent),
- patients with inadequate response to induction chemotherapy ('bad responders') who had refused surgery and were finally treated with radiation therapy,
- tumors inoperable after induction chemotherapy for which radiation therapy was the only remaining therapeutic option,
- treatment interruption before the completion of the scheduled radiation scheme,

- history of other primary malignancies,
- patients with more than one tumor (synchronous second primary tumors),
- loss from follow-up from the IGR (in most of these cases a part of the treatment and the follow-up was done in another institution).

CHARACTERISTICS OF INCLUDED PATIENTS

The mean age of the 42 patients retained was 57,7 years (56,6 y for the RT group vs 58,9 y for the RCT group), ranging from 42 to 72 years.

The sex ratio was 10:1 (38♂:4♀).

The vast majority (93%) of the patients retained had a positive history of tobacco consumption and only 20% of patients did not report regular alcohol drinking.

Concerning TNM staging (Table 2):

- T3 was the most frequent tumor stage (64%),
- 76% of all patients had locally advanced tumors (32 were T3 or T4a),
- 7% had disease stage II (3/42), 48% stage III (20/42) and 45% stage IV (19/42),
- nodal stages were represented by 29% N0 (12/42), 38% N1/N2a (16/42) and 33% N2bc/N3 (14/42) patients.

In terms of histology, detailed data were available for 37 patients: 65% of them (24/37) had well differentiated SCC, 24% moderately (9/37) and 11% poorly differentiated (5/37) SCC.

Staging

	T1	T2	T3	T4a		
N0		3	8	1	12	29%
N1		2	10	1	13	38%
N2a		1	2		3	
N2b		2	3	1	6	33%
N2c			4		4	
N3		2		2	4	
	-	10	27	5	42	
			64%			

Table 2: *Summary of the T and N stage for the included patients (all patients were M0).*

TREATMENT MODALITIES

Induction chemotherapy regimens were administered as following (Table 3):

- 20 patients have received induction chemotherapy with PF (platinum salt+5FU),
- 20 patients have received induction chemotherapy with TPF (docetaxel+PF),
- 1 patient has received induction chemotherapy with TP (taxane+platinum salt), and

- in one case the regimen was not clearly mentioned in the patient's records.

	RT	CRT	
PF	**14**	**6**	**20**
TPF	**6**	**14**	**20**
TP	1	0	1
?	0	1	1
	21	21	42

Table 3: *Cross tabulation of induction chemotherapy regimen (PF: platinum+fluorouracil, TPF: taxane+PF) by main treatment modality (RT: radiation therapy alone, CRT: radiation therapy with concomitant chemotherapy).*

Following a satisfactory response of induction chemotherapy (good responders):

- 21 patients were treated with exclusive radiation therapy (preceded by PF in 14 cases, by TPF in 6 cases and TP in 1 case) and
- 21 patients were treated with radiation therapy and concomitant chemotherapy (preceded by PF in 6 cases, TPF in 14 cases and an unknown agent in 1 case); for concomitant chemotherapy cisplatin was given in 6 cases, carboplatin in 7 cases, cetuximab in 6 cases, and an unknown agent in 2 cases (Table 3).

Interestingly, PF-based induction chemotherapy followed by radiation therapy alone was the dominant regimen in the first half of the study period, while TPF followed by CRT dominated the second half (Table 4a+b).

	99	2000	2001	2002	2003	2004	2005	2006	2007	2008	Tot
PF/RT	1	5	3	1	3	0	1	0	0	0	*14*
TPF/RT	0	0	0	1	0	0	0	1	1	3	*6*
PF/RCT	0	0	2	1	0	1	2	0	0	0	*6*
TPF/RCT	0	0	0	0	0	0	0	4	4	6	*14*
Autres	0	0	0	0	1	0	0	1	0	0	*2*
PF	1	5	5	2	3	1	3	0	0	0	*20*
TPF	0	0	0	1	0	0	0	5	5	9	*20*
RT	1	5	3	2	3	0	1	2	1	3	*21*
RCT	0	0	2	1	1	1	2	4	4	6	*21*
											42

Table 4a

	99	2000	2001	2002	2003	2004	2005	2006	2007	2008	Tot
PF/RT	13 : 14					0	1	0	0	0	*14*
TPF/RT	0	0	0	1	0	0	0	1	1	3	*6*
PF/RCT	0	0	2	1	0	1	2	0	0	0	*6*
TPF/RCT	0	0	0	0	0	0	0	14 : 14			*14*
Autres	0	0	0	0	1	0	0	1	0	0	*2*
PF	20 : 20							0	0	0	*20*
TPF	0	0	0	1	0	0	0	19 : 20			*20*
RT	14 : 21					1	1	2	1	3	*21*
RCT	0	0	2	1	1	1	16 : 21				*21*
											42

Table 4b

Table 4: *a) Treatment modalities according to year of treatment, in detail.*
b) Treatment modalities according to year of treatment, with summing of the dominant treatment modality.

FOLLOW-UP PERIOD

All 42 patients included in the study were followed for at least 3 years or until they were deceased and almost 80% of them (33/42) were followed for at least 5 years or until they were deceased. As TPF and CRT started being used in the latest years of the period studied, the follow-up period of patients treated with these regimens is inevitably shorter compared to patients treated with TP followed by RT.

ONCOLOGIC OUTCOME

Survival (OS, DFS)

The 3-year overall survival was 74% (31/42), which means that a quarter of all patients (11/42) were dead within the first 3 years after the end of radiation therapy. The 5-year overall survival was estimated to be around 60% (SE≈0.08) (Figure 8).

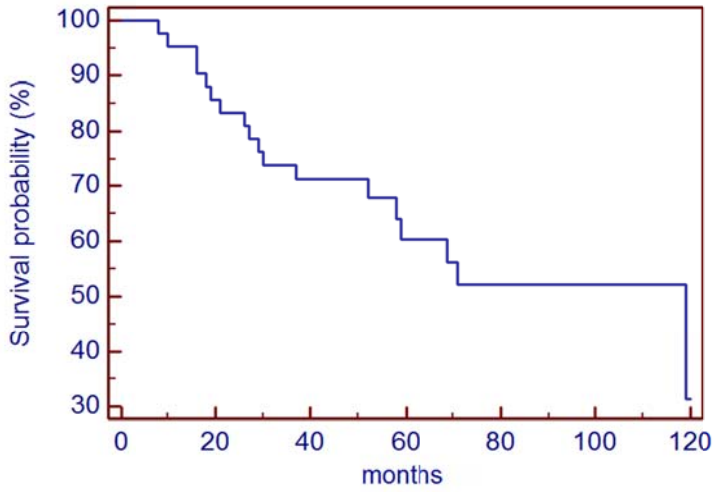


Figure 8: *Overall survival probability for all 42 patients included in the study.*

Concerning the disease-free survival, the 3-year DFS for all 42 patients was 65% (27/42), while the 5-year DFS was estimated to be slightly more than 50% (SE≈0.08). This means that barely more than half of all patients were still alive with no recurrence during the 5 years following the end of radiation therapy (Figure 9).

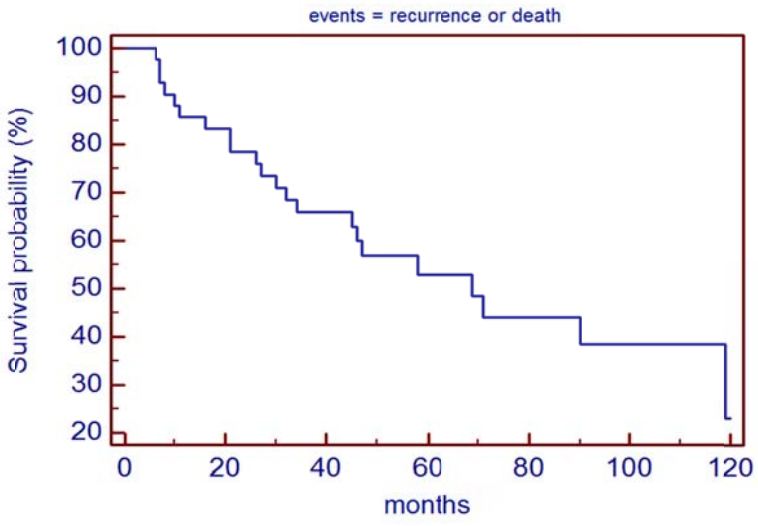


Figure 9: *Disease-free survival probabilty for all 42 patients included in the study.*

Calculating the DFS for the 10 T2 tumors, separately from the 32 T3/T4a tumors (Figure 10) shows a 3-year DFS of 100% (10/10) for the T2 versus 56% (18/32) for the T3/T4a stages, and a 5-year DFS of approximately 80% versus 40%, respectively (p>0.05).

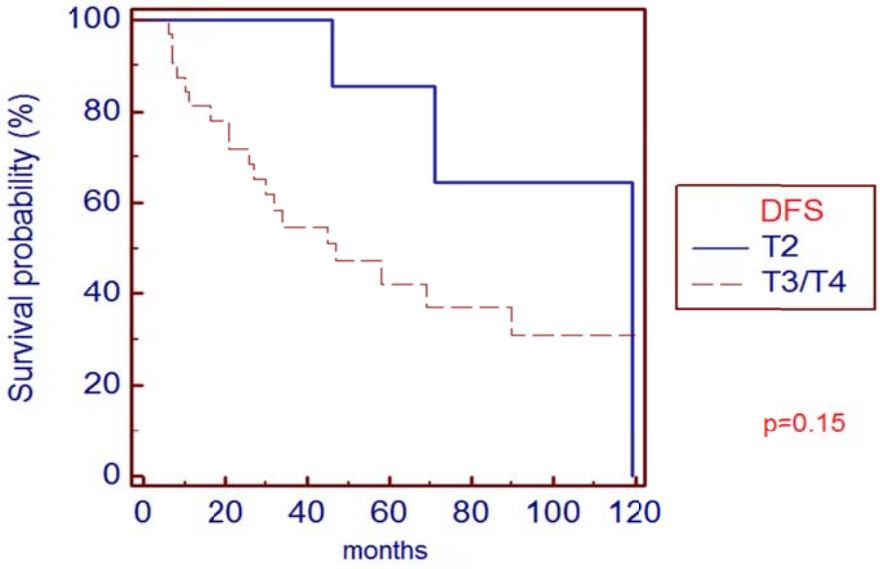


Figure 10: *Disease-free survival probability for the 10 T2 and 32 T3/T4a patients; the difference in the DFS probability is not statistically significant (p=0.15, HR=2.14, 95%CI 0.89 to5.18)*

Similarly, if we examine the DFS separately for the 12 N0 tumors and the 30 N+ ones (Figures 11, 12) we notice that:

- the 3-year DFS is calculated to be 83% (10/12) for the N0 versus 57% (17/30) for the N+,
- the 5-year DFS is estimated to be approximately 80% versus 40%, respectively (p<0.05). Interestingly, these two groups had no significant difference in terms of OS (p=0.12).

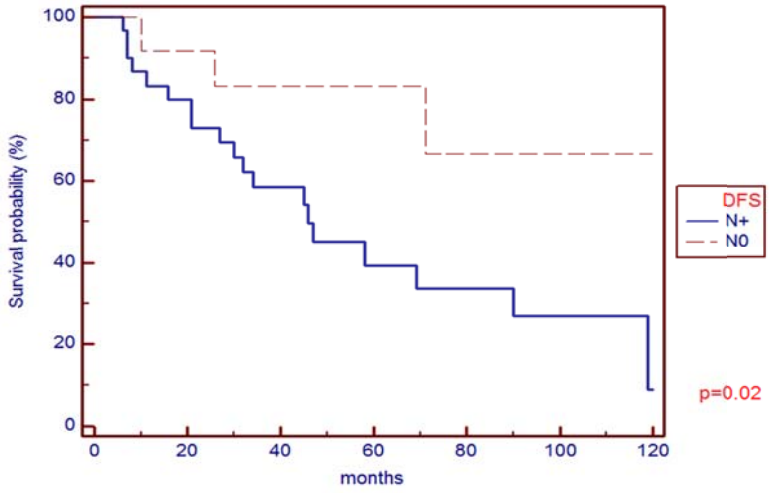


Figure 11: *Disease-free survival probability for the 12 N0 and the 30 N+ patients; there is a statistically significant difference in the DFS probability between N0 and N+ patients (p=0.02, HR=0.27, 95%CI 0.11 to 0.63).*

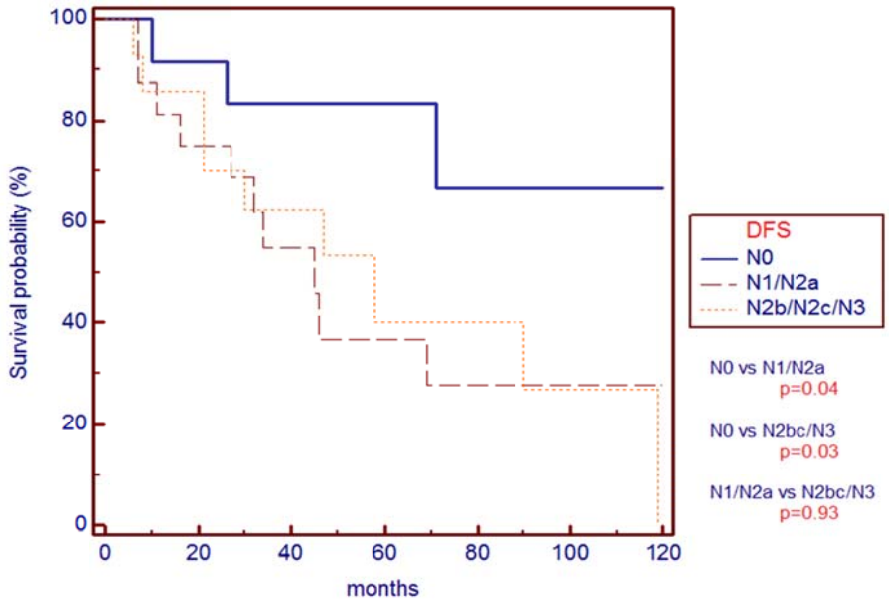


Figure 12: *Disease-free survival probability for the 12 N0, 16 N1/N2a and 14 N2bc/N3 patients. Interestingly, there is no statistically significant difference in the DFS probability among patients with a single homolateral nodal metastasis (N1/N2a) and those with more advanced (N2bc/N3) neck disease (p=0.93, HR=0.96, 95%CI 0.40 to 2.32).*

Treatment failures

One of the secondary objectives of this study was to analyze treatment failures; as such were considered local, regional and locoregional recurrences as well as metastatic failures in patients initially considered as M0.

Out of 42 patients included in our study the oncologic outcome could be judged as 'successful' or 'failure ' in 39 cases. In 3 cases the situation was not clear:

- in one case, 1½ year after the end of RT a patient presented a laryngeal cancer contralateral to the initial pyriform sinus carcinoma, hence considered as a metachronous tumor and treated by total laryngectomy without signs of local recurrence of the initial hypopharyngeal tumor,
- in a second case, a patient deceased 26 months after the end of radiation therapy was presenting a pharyngostoma in the last months of his life, suspect for local recurrence but repetitive biopsies were negative,
- in a third case, a patient known for alcoholic liver cirrhosis developed a fulminant liver failure and imaging prior to his death revealed multiple pulmonary and retroperitoneal metastases as well as a liver localization of unclear origin - a primary hepatocellular carcinoma or metastasis of the pyriform sinus tumor.

As these cases could not be clearly categorized as 'treatment failures', the following calculations do not take these 3 patients into consideration and the percentages refer to the remaining 39 patients, instead of the 42 initially treated and included in the study.

In total, there were 11 cases considered as treatment failures (28%) (Table 5); in 10 of them recurrence was diagnosed between 6 months and 4 years after the end of radiation therapy while in 1 patient 'recurrence' was diagnosed more than 7 years after the end of treatment!

More precisely there were: 5 cases of isolated local recurrence (45% of all failures), 2 cases of isolated nodal recurrence (18% of all failures), and 4 cases of locoregional failure (36% of all failures). One case of locoregional failure concerned a patient having had positive biopsies in the same pyriform sinus 7 years after the initial treatment. Thus, the vast majority of oncologic failures (9/11) presented with primary tumor recurrence (with or without neck recurrence). While most failures concerned patients treated with RT it should be taken into consideration that patients treated with RT in this study were in general followed for longer periods than those treated with the more recently introduced CRT (Table 4b).

	Failure level	Initial stage	Interval between end of RT & recurrence (mois)	Type of induction CT	Type of definite treatment
1	T	T2	46	TPF	RT
2		T3	34	PF	RT
3		T3	47	PF	RT
4		T3	11	PF	RT
5		T3	45	TPF	RT
6	N	N1	32	TPF	RT
7		N1	7	TPF	CRT
8	T + N	T3 N1	7	TPF	RT
9		T3 N2c	6	PF	CRT
10		T4 N3	21	PF	CRT
11		T4 N3	90	PF	RT

Table 5: *Detailed characteristics of treatment failures.*

A careful look at the table allows the following observations:

- there were no cases of isolated metastases without prior local, regional or locoregional failure, although some of the deceased patients after local, regional or locoregional failure presented distant metastases in the last stages of their disease,
- there were no cases initially considered N0 who have subsequently presented a nodal failure,
- both of the 2 isolated nodal recurrences (and 3/6 of all nodal failures) concerned patients with a unique homolateral metastatic lymph node up to 3cm (N1),
- most cases of locoregional failure (3/4) concerned patients with advanced disease (T3/T4a and N2c/N3 tumors) and only 1 case concerned a stage III patient,

- the 2 cases of treatment failure of T4a tumors (out of 5 T4a tumors initially included in the study population) were simultaneous recurrences on the pyriform sinus and the lymph nodes (=locoregional failures).

In total, there was a 23% failure rate (9/39) localized in the pyriform sinus, either as an isolated local recurrence either as a locoregional failure. As expected, bigger primary tumors tended to present an increased local failure rate than smaller ones: 10% for T2 (1/10) versus 22% for T3 (6/27) versus 40% for T4a (2/5) tumors.

Concerning nodal failures, there were 6 recurrences in total (2 isolated local and 4 locoregional) out of 30 patients initially staged N+ (20%). The rate of nodal failure for the 42-patient study population was 14% (6/42). It is surprising to observe that half of nodal failures (3/6) concerned patients initially staged N1. Patients with nodal stage N1 had more nodal failures than logically expected: 23% nodal failures were observed in N1 patients (3/13) versus 0% in N0, 8% in N2 and 50% in N3, which means that there were more failures for N1 than for N2 patients! If we regroup patients with different nodal stages to 3 groups, those with no clinical lymph node metastases (N0), those with a single ipsilateral nodal metastasis up to 6 cm (N1/N2a) and those with more advanced neck disease (N2b/N2c/N3) we conclude that the only subgroup with significantly lower regional failure rate is the one of the N0 patients (0/12), while regional failure rates for the N1/N2a and the N2b/N2c/N3 subgroups were 19% (3/16) and 21% (3/14), respectively.

Failure rate was almost equal between patients having received induction chemotherapy with PF (6/20) and TPF (5/20), while more failures concerned patients having been previously treated with exclusive RT (8/21) than with concomitant CRT (3/21). These observations should be interpreted with caution, as the small number of patients in each subgroup precludes any comparison. Moreover, patients treated with exclusive RT were followed for longer periods than those treated with concomitant CRT.

Salvage treatment

After local, regional, or locoregional failure was confirmed by biopsies, salvage treatment was attempted in 8 out of 11 patients. For the remaining 3 patients palliative chemotherapy was proposed (all 3 of the latter presented locoregional failures, one patient was initially staged T3N1 while the 2 others were staged T4aN3) (Table 6).

In total, 6 total pharyngo-laryngectomies were performed and were associated to neck dissection in 3 cases and re-irradiation in 1 case. All 5 isolated local recurrences were treated by total pharyngo-laryngectomy (with neck dissection in 2 cases and with re-irradiation in 1 case), while only 1 out of 4 locoregional failures was still considered operable. The 2 isolated nodal recurrences were treated with neck dissection followed by (new) radiation therapy.

Level of failure	Initial TNM staging	interval RT & failure (months)	Salvage treatment modality	No recurrence since salvage treatment (months)	Efficient salvage Tx
T only	T2	46	TPL + reRT	67	√
	T3	34	TPL	49	√
	T3	47	TPL	44	√
	T3	11	TPL+nd		X
	T3	45	TPL+nd		X
N only	N1	32	nd + reRT	14	√
	N1	7	nd + reRT		X
T + N	T3 N1	7	CT		X
	T3 N2c	6	TPL+nd		X
	T4 N3	21	CT		X
	T4 N3	90	CT	(?)	(?)
			in red = surgery		0% TN 60%T ≤50%N

Table 6: *Details on the treatment offered to the 11 patients with recurrences as well as the results of the treatment. (nd = neck dissection, reRT= reirradiation, TPL = total pharyngolaryngectomy, X = definite failure of salvage treatment)*

Salvage treatment of oncologic failures was not possible or definitely inefficient in 7 out of 11 patients (64%), including:

- 40% of the isolated local failures (2/5),
- 50% of the isolated nodal failures (1/2),
- 50% of the salvage total pharyngo-laryngectomies (3/6),
- 100% of the locoregional failures (4/4),
- 100% of the failures of radiation therapy with concomitant chemotherapy (3/3).

Metachronous tumors

Metachronous tumors refer to those developed at least 6 months after the diagnosis of the first tumor. Metachronous aerodigestive tumors were identified in the follow-up of 6 patients, corresponding to a 14% of the initially 42 patients treated.

In terms of localizations: 3 of them (7%) concerned ENT localizations (oral cavity, oropharynx, larynx) and 3 of them were pulmonary tumors.

ENT metachronous tumors were identified between 1½ and 8½ years after the end of radiation therapy while pulmonary metachronous tumors were diagnosed after 3 to 4½ years of follow-up. The prevalence was equal between PF and TPF subgroups (3/20) but higher in the RCT than the RT subgroup (4/21 versus 2/21).

There were 2 more cases of metachronous tumors localized outside the airways and the gastrointestinal tract, rendering the total number of metachronous tumors to 8 (19%):

- one of them concerned a patient who was found to have a liver tumor with concomitant pulmonary and retroperitoneal metastasis and could represent either a

primary liver carcinoma or a metastatic localization of the primary hypopharyngeal carcinoma,

- the second case concerned a case of prostatic carcinoma discovered 9 years after the end of the larynx preservation protocol.

FUNCTIONAL OUTCOME

As already discussed, the aim of laryngeal preservation is not only to cure patients and spare their larynx but also to preserve the pharyngolaryngeal functions. Hence, the functional outcome is the second primary endpoint of this study. Self-administered questionnaires were sent to all patients who were not known to be dead when the present study was carried out. Moreover, information about the functional outcome was searched in the files of all patients included in the study. The three functions (breathing, voice production and swallowing) are analyzed separately.

Airway

Information concerning breathing and airway patency were available for all 42 patients included in the study. Only 3 patients (7%) have needed a tracheotomy in some stage of the disease;

- two of them were transitory and the patients have been weaned from their cannula during the follow-up,
- only 1 patient (2%) needed to keep tracheotomy in the long term.

Voice

Voice alterations could be evaluated only in the 15 patients who have replied to the 2 related questions of the questionnaire, as no useful data could be obtained from the revision of the medical records of the remaining 27 patients. The questionnaire focused on patients' subjective perception of voice quality. It was based on 2 simple questions concerning voice adequacy before and in the long term after the end of treatment (>3 years).

All 15 patients judged that after at least 3 years after the end of treatment their voice quality was satisfactory or at least sufficient for needs in everyday life. Two third of the patients (10/15) considered that their voice was not altered from treatment, while 20% (3/15) found their voice deteriorated and 13% (2/15) judged it as improved compared to the voice quality just prior to the induction chemotherapy.

Swallowing

At least three years after the end of treatment, all patients having returned the questionnaires (17/17) were fed exclusively by mouth, although a quarter of them (4/16) had been partially or totally dependent from a feeding tube in the past. When taking into consideration data from medical files in addition to the answers obtained from the questionnaires, exclusive oral feeding was possible in the last documented follow-up for 85% of patients for which data was available (29/34), the remaining 15% mainly corresponding to

patients with progressive disease, previously fed orally but necessitating enteral feeding in the last period of their lives.

For patients being fed exclusively by mouth, meal texture was described (when this information was available) as:

- 'normal' for 2/3 of them (18/28),
- 'in small pieces/mashed/blended' for the remaining 1/3 of them (9/28) while
- one patient (1/28) was fed exclusively by liquids and semiliquids.

Persisting but minor aspiration problems were encountered by 36% of 25 patients fed exclusively by mouth (9/25). Despite aspiration problems it is noteworthy that no functional laryngectomies had to be performed in our study population.

C) DISCUSSION

C1) RADICAL SURGERY VERSUS LARYNX PRESERVATION

Small hypopharyngeal tumors (T1 and small T2) may be treated either with partial pharyngectomy or with radiation therapy, both treatments achieving satisfactory oncological outcome while preserving the pharyngo-laryngeal functions.

For more advanced tumors, when partial surgery is no longer possible and total pharyngolaryngectomy seems to be the only surgical option, larynx preservation by nonsurgical means could be a promising alternative. Nonsurgical approaches should provide at least the same survival rates while preventing permanent tracheotomy and preserving the pharyngo-laryngeal functions.

The comparison of the oncologic outcome of a larynx preservation approach versus a direct surgical approach for locally advanced laryngeal and hypopharyngeal tumors has been the object of three major prospective randomized trials in the 90's (Table 7). Two of them were focused on laryngeal carcinomas and the 3rd one on hypopharyngeal localizations:

- the first and most influential of the three studies is the landmark US study of the **Department of Veterans Affairs Laryngeal Cancer Study Group**, published in 1991.[20] It compares surgery followed by radiation therapy to larynx preservation with induction chemotherapy followed by radiation therapy for good responders and surgery for non-responders, in cases with advanced laryngeal carcinoma. In total 332 patients were enrolled in the study and the induction chemotherapy group had received cisplatin and fluorouracil. The study concludes that the 2-year OS was equivalent for the two groups (68%) while the patterns of failure were different.
- the **European EORTC 24891** 'Head and Neck Cancer Cooperative Group' study for larynx preservation in pyriform sinus cancer was published by J.L. Lefebvre et al. in 1996.[21] It included 194 patients and compared surgery followed by radiation therapy to larynx preservation by induction chemotherapy (cisplatin, fluorouracil) followed by radiation therapy for good responders. It concludes in equivalent survival rates between the 2 groups. Locoregional failures were also equivalent, whereas there were more metastatic failures in the surgery group.
- the French study of the **GETTEC group**, concerning T3 laryngeal carcinomas, was published by J.M. Richard et al. in 1998.[25] Similarly to the previous trials, surgery followed by radiation therapy (32 patients) was compared to cisplatin-fluorouracil induction chemotherapy followed by radiation therapy for good responders (36 patients). In this study, in contrast to the previous-ones, survival rates (OS and DFS) are significantly better in the surgery arm. This trial was interrupted prematurely as the majority of the patients refused surgery.

Study	Year	Localization	# patients	Endpoint	Conclusion
VA	1991	Larynx	332	OS	Surgery +RT = ICT
EORTC 24891	1996	Pyriform sinus	194	OS	Surgery + RT = ICT
GETTEC	1998	Larynx	68	OS & DFS	Surgery + RT > ICT
Pignon et al.	2000	Larynx + Pyriform sinus	594	Meta-analysis	Surgery + RT > ICT (p=0.10)

Table 7: *Characteristics of the 3 major randomized trials for locally advanced laryngeal and hypopharyngeal SCC. They have all compared radical surgery followed by RT to ICT-based laryngeal preservation, in terms of survival. On the bottom line, the meta-analysis of these 3 studies.*
(DFS = disease-free survival, ICT = induction chemotherapy, OS = overall survival, RT = radiation therapy)

In 2000, **Pignon et al.**[26] published a meta-analysis based on the 3 previous randomized trials; in total 594 were retained and the median follow-up was 5.7 years. There was an overall non-significant trend (p=0.10) in favor of the surgery arm with an absolute negative effect that reduced the 5-year OS from 45% in the surgery arm to 39% in the ICT arm. Local failures were twice more frequent in the ICT arm and only a portion of them could be treated successfully with salvage surgery. In all 3 studies, 39% of patients in the ICT arm were alive at 5 years and 61% dead; 59% of those alive at 5 years (23% of those initially included in the ICT arm) had their larynx preserved and 41% had already had salvage laryngectomy (16% of those initially included in the ICT arm). Among the 3 trials there was significant heterogeneity (p=0,04) and interestingly there was some evidence that the effect of IC was negative for laryngeal tumors (hazard ratio 1.4) but may have been beneficial for hypopharyngeal tumors (hazard ratio 0.9). This observation could be due to the difference in response criteria between the hypopharynx EORTC trial (complete response needed) and the 2 larynx trials (partial or complete response needed).

The previous evidence allowed larynx preservation to become more and more popular in the treatment of advanced laryngeal and hypopharyngeal tumors. However, an interesting public debate started in 2006, challenging the efficacy of CRT in terms of survival, in the treatment of laryngeal cancers:

- Hoffman et al. published in 2006 a report[27] based on data from the American National Cancer Data Base (158426 cases of laryngeal SCC, treated between 1985 and 2001) and observed that in the previous 2 decades survival from laryngeal cancer had decreased, paralleling the increased use of nonsurgical treatment modalities. The authors speculated that the decrease in survival could be related to changes in the management of laryngeal cancers.
- A year later, Chen et al.[28] published another analysis based on the American National Cancer Data Base (7019 patients included in the analysis) comparing treatment strategies. Survival for stage IV laryngeal cancers was better for patients treated with total laryngectomy while it was equivalent for stage III laryngeal cancers. For both stage III and IV survival was worse for patients treated with radiation therapy alone.
- The above-mentioned data from the American National Cancer Data Base, as analyzed in the previous 2 publications, inspired an editorial by Olsen in Head and Neck[29], focusing on the relationship between the increase of nonsurgical treatment modalities and the decrease of survival in patients with larynx cancer in the USA. Olsen tried to

explain the decrease in survival by the following observations and speculations: 1)patients treated during this timeframe in the US were probably inappropriately chosen for CRT, since they differed from the VA trial inclusion criteria, 2) many patients (about 45%) included in the VA and another chemoradiation randomized trial (RTOG 91-11[30]) could have probably been candidates for partial laryngeal surgery which provides excellent results for T1-T3 tumors.

The authors of the VA and RTOG 91-11 trials replied to Olsen's editorial and gave their own interpretation for the NCDB data for increasing mortality from laryngeal cancer in the US.

The first author of the VA trial, G. Wolf, commented [31] that:

- a major decrease in survival concerned the period 1985-90, prior the publication of the results of the VA and RTOG 91-11 trials,
- between 1990-1996 there was an improvement in the survival from supraglottic T3N+ and T4N0 tumors,
- the decreased survival concerned mainly (60%) supraglottic T1 and T2 tumors which would not be candidates for CRT anyway,
- for T3 tumors the only significantly inferior results in terms of survival concerned RT-alone treated patients and not CRT and laryngectomy/RT treated patients, which provided better and equivalent results,
- during this period in the US there was not only an increase in the proportion of patients treated by CRT but also an important increase in those treated by partial surgery,
- only 12% of the VA trial were eligible for partial surgery (and had bad results anyway),
- salvage surgery should be performed in a early and timely fashion to obtain equivalent results to the VA trial.

Thus, G. Wolf attributed the increased mortality to failures of RT as monotherapy, to failures in the treatment of small tumors not interesting laryngeal preservation protocols, to probable failures of inappropriately performed partial surgery and to probable delays in salvage surgery.

The main author of the RTOG 91-11 trial, A. Forestiere made the following remarks[32]:

- the analysis of Hoffman et al. was retrospective and consequently it had many limitations such as the absence of treatment details, the lack of sufficiently detailed information for the N stage and the neck management,
- the decreased survival on the data from the NCDB mainly concerned stage I and II supraglottic and not glottic SCC, as well as T3 tumors treated by RT alone,
- cartilage-invasion cases were excluded from the RTOG 91-11 trial,
- even if the expertise was available, very few patients in the RTOG 91-11 trial could have had partial surgery,
- in the RTOG 91-11 study the increased failure rate for fixed arytenoids concerned only the RT-alone (44.1%) and the IC (49.4%) arms but not the CRT arm (28.5%).

To summarize we could say that:

- larynx preservation is addressed to intermediate size and advanced tumors who cannot be treated by external partial surgery but for which total pharyngo-laryngectomy is not mandatory,
- candidates for larynx preservation should be patients fulfilling the inclusion criteria applied on the clinical trials,
- for a selected population of patients suffering from advanced laryngeal and hypopharyngeal carcinomas, larynx preservation by concomitant CRT or IC is nowadays considered to be more or less equivalent to radical surgery followed by RT in terms of survival; it should be reminded though, that randomized trials for advanced, high-risk resected head and neck cancers have shown an advantage of concurrent postoperative CRT in comparison to postoperative RT alone,[33, 34]
- only exclusive RT was systematically found to be significantly inferior in terms of preservation rates compared to surgery, concurrent CRT, and ICT-based protocols,
- improved preservation rates could probably be achieved from modifications in the ICT and the post-induction treatment (see below).

C2) LARYNX PRESERVATION PROTOCOLS : REVIEW

When partial surgery was not indicated, the main treatment modalities for larynx preservation have traditionally been:

- radiation therapy alone (RT),
- radiation therapy with concomitant chemotherapy (CRT),
- induction chemotherapy (ICT) followed, in case of major response, by radiation therapy +/- concomitant chemotherapy, otherwise followed by surgery and radiation therapy +/- concomitant chemotherapy.

Table 8 summarizes some of the main trials interested in comparing the alternative treatment modalities for larynx preservation.

Article	Year	Localization	# patients	Endpoint	Conclusion
RTOG 91-11	2003[30]	Larynx	518	Lx preservation	CRT > ICT or RT
	2012[35]			LFS	CRT = ICT > RT
Prades et al. [36]	2010	Pyriform sinus	71	Lx preservation Survival	CRT > ICT CRT = ICT
GORTEC2000-01 [22]	2009	Larynx + Hypopharynx	213	Lx preservation	TPF > PF
TAX 324 [23]	2009	Larynx + Hypopharynx Subgroup analysis	166 (out of 501)	OS, DFS	TPF > PF
EORTC 24954[37]	2009	Larynx + Hypopharynx	450	Survival with functional Lx	Altern. = Sequential
Hitt et al. [38]	2009	Head & Neck	439	Time to failure	ICT/CRT > CRT
Bonner et al. [39]	2010	Head & Neck	424	5years OS	RT+ctx > RT
TREMPLIN [40]	2013	Larynx + Hypopharynx	153	3-months Lx preservation	ICT+RT+cisplat = ICT+ RT+ctx

Table 8: *Characteristics of the major prospective randomized trials, comparing different treatment modalities of larynx preservation for locally advanced laryngeal and hypopharyngeal SCC.*
(Lx=Larynx, LFS=laryngectomy-free survival, OS=overall survival, DFS=disease-free survival, CRT=concomitant chemoradiotherapy, ICT=induction chemotherapy, RT=radiation therapy alone, cisplat=cisplatin, ctx=cetuximab)

A key-study, comparing the 3 previously mentioned treatment modalities to each other is the **RTOG 91-11** study[30], published by Forastiere et al. in 2003. This study focused on advanced laryngeal SCC and analyzed data from 518 patients who were randomized in 3 arms: 173 in the RT arm, 172 in the CRT arm and 173 in the ICT arm. Induction chemotherapy patients had received cisplatin and fluorouracil (PF) while patients in the CRT arm had received cisplatin concurrently to RT. The paper concludes that OS rates are similar in all 3 groups while locoregional control and laryngeal preservation rate at 2 years are significantly higher after radiotherapy with concurrent cisplatin (88% versus 75% for the induction chemotherapy group and 70% for the radiotherapy alone group). Both chemotherapy-based regimens had a better DFS than radiotherapy alone due to reduced metastatic failures. Moreover, ICT followed by RT had no advantage compared to RT alone in terms of laryngeal preservation and survival.

Similar were the conclusions of the **Prades et al.**[36] prospective randomized phase III trial for T3N0 pyriform sinus carcinomas. In total 71 patients were enrolled in the trial which concluded that in terms of laryngeal preservation, radiotherapy with concurrent cisplatin (CRT) is superior to induction chemotherapy (cisplatin + fluorouracil). Survival rates (OS, DFS) did not differ significantly between the 2 groups.

Despite these 2 studies concluding that concurrent CRT is the most efficient nonsurgical approach in succeeding laryngeal preservation, there are many specialists believing in the superiority of the ICT-based approach. It is of great interest to see and understand how these different approaches are justified.

While the initial RTOG 91-11 paper is a key-trial providing the basis for present larynx preservation by concomitant CRT, this landmark-study was heavily criticized. The main reason is that the initial primary endpoint in the study protocol was laryngectomy-free survival and not laryngeal preservation which was the primary endpoint cited in the article. Physicians criticizing the methodology speculated that a high number of unexpected deaths in the concomitant CRT arm were considered as unrelated to cancer or treatment and were excluded from the data analysis, which would not have been the case if 'overall-survival with larynx in place' was the endpoint.

In 2012, nine years after the initial publication, the **long term results of the RTOG 91-11** were published by Forestiere et al.[35] This time, with a median follow-up of 10.8 years, the primary end-point was laryngectomy-free survival. The paper concluded that the ICT and the concomitant CRT arms were equivalent in terms of laryngectomy-free survival and both were significantly superior (more patients alive with larynx preserved) to RT alone. Hence the 'reputation' of larynx preservation by ICT (followed by RT in good responders) seems to have been restored in the RTOG 91-11 study. The OS did not differ significantly among the 3 groups. Moreover, this time it was clearly mentioned that more unexpected deaths (considered in the 2003 article to be unrelated to laryngeal cancer and treatment) were detected in the concomitant chemoradiotherapy group.

Laryngeal preservation by ICT protocols is further supported by evidence of improved outcomes from adding taxanes to the previously tested cisplatin and 5-fluorouracil ICT regimens

(i.e. PF evolving to TPF) and encouraging results from modifications in the post-induction regimens in good responders (RT + cisplatin, RT + cetuximab).

The **GORTEC 2000-01 trial**, published by Pointreau et al. in 2009,[22] compared two different ICT regimens for laryngeal and hypopharyngeal SCC: PF versus PF+docetaxel (TPF). In both arms ICT was followed by RT (+/- CT) for good responders or by surgery and RT (+/- CT) for non-responders. The 3-year preservation rate was significantly higher for the TPF arm while the OS and DFS were not statistically significantly different. In other words, the conclusion was that TPF-based regimens could preserve more larynxes than PF, without compromising survival.

The results of the GORTEC 2000-01 trial were further supported by subgroup analysis of the **TAX 324 trial** for patients with resectable laryngeal and hypopharyngeal carcinomas, which was published by Posner et al. in 2009.[23] The trial had enrolled a total of 501 patients with head and neck SCC, including 166 patients suffering from advanced hypopharynx or larynx SCC. It compared the oncological outcome of IC with TPF (90 patients) versus IC with PF (76 patients), both followed by concomitant CRT for good responders. The subgroup analysis concluded that without compromising overall survival, operable patients treated with TPF-based IC had significantly higher laryngectomy-free survival and DFS compared to the PF arm. The long term results of this trial were published in 2011 confirming at 5 years' the statistically significant benefit in survival (OS and DFS) for patients with locally advanced head and neck SCC treated with IC with TPF. [41]

It is possible that optimization of IC-based protocols of laryngeal preservation could also be achieved by optimization of the post-induction treatment of good responders.

A randomized phase III trial was presented by **Hitt et al.** in the 2009 ASCO annual meeting[38]. The trial enrolled 439 patients and compared induction chemotherapy (PF or TPF) followed by chemoradiotherapy versus direct CRT as first-line treatment of unresectable locally advanced head and neck SCC. It concluded that IC followed by CRT significantly increases time to treatment failure and locoregional control rates. This specific trial was not designated to operable hypopharyngeal or laryngeal SCC as all the previously mentioned ones, but shows the potential of an improved oncological outcome when ICT is followed by CRT.

Similarly, **Bonner et al**.[39] published in 2010, the 5-year survival data from a phase III randomized trial comparing RT alone (213 patients) versus RT + cetuximab (211 patients), for locoregionally advanced head and neck (not only laryngeal and hypopharyngeal) cancer. The article concludes in an improved 5-year OS rate for patients treated with RT + cetuximab.

The randomized phase II **TREMPLIN study**[40] compares two different modalities of sequential chemoradiotherapy in the treatment of previously untreated patients with stage III-IV laryngeal and hypopharyngeal SCC who were candidates for total laryngectomy. All 153 enrolled patients were initially treated with 3 cycles of TPF induction chemotherapy. Those with a response<50% had surgery while good responders were randomized in 2 arms (116 patients): RT and cisplatin and RT and cetuximab. Although local failures were more often in the cetuximab arm, salvage surgery was feasible only in this arm, resulting in a similar ultimate local control. Hence, OS and larynx functional preservation (18 months after treatment) as well as larynx preservation were

similar in the two arms, toxicity was substantial for both arms, and compliance was higher in the cetuximab arm.

C3) EVIDENCE-BASED DATA ANALYSIS

Among the key studies in organ preservation, those interested in hypopharyngeal localizations were those made in Europe and more specifically the EORTC 24891 trial (exclusively focused on hypopharynx SCC), the GORTEC 2000-01 and TREMPLIN trials (equally interested in laryngeal and hypopharyngeal tumors), as well as the study published in 2010 by Prades et al. (pyriform sinus). On the contrary, two of the major larynx preservation trials who were carried out in the USA, the VA laryngeal cancer study group trial and the RTOG 91-11, as well as the French GETTEC trial, have been exclusively interested in laryngeal tumors.

Concerning the ICT trials, it is still unclear whether the role of ICT is limited in patient selection or if ICT has a therapeutic effect. There have been studies, like the one published by Urba et al.[42], that were designed so that the decision for definite treatment was made after a single cycle of ICT (in order to avoid delays in treatment and compromises in treatment's intensity and efficacy), judging that ICT offers little therapeutic advantage beyond selecting patients. On the other hand this attitude could compromise benefits of ICT on distant metastases, most major randomized trials (Veterans, EORTC 24891, GETTEC, RTOG 91-11, GORTEC) being based on a 3-cycle ICT.

Nevertheless, it should be reminded that lack of response to ICT is not a perfect predictor of poor outcome of nonsurgical management, as shown by data from patients from the RTOG 91-11 study who had refused surgery after poor response to ICT and had subsequently durable disease control by RT.

Concerning the key randomized trials, there was an undeniable and significant heterogeneity in the different *protocols for response evaluation*, during (or right after) the induction chemotherapy and the different criteria of good response determining the further orientation of the patients towards radiation therapy or surgery. In particular:

- In the US trials (VA and the RTOG 91-11) the evaluation and the decision for the definite treatment modality was made between the 2nd and 3rd cycle. In the VA trial, the decision was based on clinical criteria (tumor volume reduction on clinical examination) and negative biopsies after the 3rd cycle, while the RTOG 91-11 trial introduced an additional CT-scan evaluation.
- In the GORTEC 2000-01 trial the decision was made 3-5 weeks after the completion of all 3 cycles of ICT; it was also based on clinical and imaging (CT-scan or MRI) evaluation.
- Finally, the EORTC 24891 trial evaluated the response after every single cycle; definite surgery could be decided already after the first cycle while definite radiation therapy could be decided only after the 2nd or 3rd cycle.
- Concerning the criteria of response, the two major US studies (VA and RTOG 91-11) focused in the regression of the tumor volume while the European ones (EORTC 24891, GORTEC 2000-01) also considered recovery of vocal cord mobility. Tumor volume was calculated as the sum of the product of the longest dimension of the tumor and its perpendicular.

- In the US studies, a tumor regression ≥50% would be sufficient for a 'good responder' while in the (prematurely interrupted) GETTEC study for laryngeal tumors a good response required tumor regression ≥80% and return of vocal cord mobility to normal.
- The two US studies (VA and RTOG 91-11) would irradiate patients with complete or partial regression of the tumor (after 2 cycles of IC), provided that there was no progression in the nodal status. The EORTC 24891 required complete response of the primary tumor and normal cord mobility prior to definite radiation therapy while the GORTEC 2000-01 would irradiate patients with partial tumor regression provided that vocal cord mobility had returned to normal.

Concerning the nodal status, inclusion criteria were not uniform; the VA, RTOG 91-11 and GORTEC 2000-01 trials had no inclusion restrictions for nodal metastases while the EORTC 24891 had excluded N2c and inoperable N3 tumors. Moreover, criteria for attitude's adjustment differed concerning lymph nodes response to ICT. The US studies required regression or at least zero progression in the lymph node status, the EORTC 24891 did not exclude patients requiring neck dissection prior to IC (if the physician judged that it was necessary) while in the GORTEC 2000-01 trial, neck dissection would be performed only in cases of residual disease after the completion of definite radiation therapy. It is noteworthy that in total, 73% (435/594) of all patients included in the VA, GETTEC and EORTC studies had N0 or N1 disease!

Overall, the above mentioned key-studies differed in the inclusion criteria, the end points, the regimens and the response criteria. Despite these difficulties, we could try to summarize **the current knowledge on laryngeal preservation** in the following statements:

- all the 'key' trials on larynx preservation have enrolled previously untreated patients requiring total laryngectomy, with operable tumors at the first attempt of treatment,
- most studies were focused on laryngeal SCC and few on hypopharyngeal tumors,
- laryngeal preservation has been accepted as an alternative to total laryngectomy in carefully selected patients,
- most studies have focused on survival rates and laryngeal preservation but little is known about pharyngo-laryngeal function in preserved larynxes,
- in the randomized trials available so far, no nonsurgical approach has provided a superior survival effect than total laryngectomy followed by postoperative radiation therapy,
- radiotherapy alone is inferior to CRT and ICT-based preservation protocols, in terms of laryngeal preservation and laryngectomy free survival,
- PF-based ICT followed by RT has a slight and non-statistically significant reduced 5-years OS rate when compared to radical surgery followed by RT,
- TPF-based ICT protocols are superior to PF protocols in terms of laryngeal preservation,
- there are no clinical trials comparing direct CRT to TPF-based ICT followed by RT,
- the most effective post-induction regimen is still under investigation (RT versus RT+cisplatin versus RT+cetuximab versus newer regimens).

Trials on larynx preservation conducted in the near future should, among other, compare regimens with the most effective arms of the RTOG 91-11 (concurrent cisplatin and radiation

therapy), the GORTEC 2000-01 (TPF followed by radiation therapy) and the TREMPLIN (TPF followed by concomitant cisplatin or cetuximab and radiation therapy), in order to determine the most effective post-induction regimen.

Concerning the ICT-based larynx preservation protocols:

- precise criteria of good response are still to be defined,
- the importance of the evaluation of vocal cord mobility is to be clarified, as for the moment it appears as a decisive criterion only in the European studies,
- there is increasing interest in the potential role of newer techniques, such as the positron-emission tomography (PET), in the evaluation of response to ICT,
- identification of molecular predictors of tumor chemo- and radio-sensibility would be of particular interest.

It seems widely accepted that further improvements in survival could be difficult to achieve by improvements in surgical techniques. Hopes for more efficient cancer treatment should probably rely on newer knowledge and better understanding of cancer biology, as well as on the development of personalized medicine.

C4) NEW KNOWLEDGE ACQUIRED FROM THE PRESENT STUDY

The present study on larynx preservation for pyriform sinus SCC focused exclusively on good responders of induction chemotherapy, attempting to investigate:

- the prognosis, once a favorable response to induction chemotherapy is obtained or in other words what outcome could be expected from radiation therapy, when treating the theoretically optimal candidates selected with neoadjuvant chemotherapy,
- the functional outcome in patients for which larynx preservation was achieved.

The **prognosis of patients with chemosensible pyriform sinus tumors** when candidates for ICT-based larynx preservation protocol was assessed: ¾ of these patients are still alive 3 years after the end of treatment and 60% after 5 years (OS). Moreover, 2/3 of them are alive without recurrence during the first 3 years and a bit more than half of them during the first 5 years (DFS). Similar results are difficult to extract from the published data in the randomized prospective studies because in the population of good responders are inevitably included non-responders to ICT who have refused surgery (although they were treated by RT, they do not represent patients with chemosensible tumors).

Calculating survival rates in regard to **N stage**, it seems that disease-free survival is better only for patients with N0 disease ($p<0.05$). Even the presence of a single metastatic lymph node seems sufficient to influence negatively prognosis as much as the presence of multiple ones (figure 12).

The **functional outcome** for the population studied is absolutely satisfactory; the great majority of patients have managed to preserve pharyngo-laryngeal functions in a significant degree showing the validity of the effort of laryngeal preservation (=preservation of a functional larynx).

Analysis of oncologic **treatment failures** shows that almost all of them (10/11) are diagnosed within the first 4 years but only 2/3 of them within the first 3 years. Hence studies following patients for short periods may fail to identify 'late' recurrences. Surprisingly none of the patients analyzed in this series has presented an isolated metastatic failure (=locoregional control with metastatic failure).

This study was not designed to investigate whether a good response to ICT is a predictor of improved survival, apart from being predictor of increased chances for larynx preservation. In order to judge if there is a **survival benefit for good responders**, their survival should ideally be compared to the survival of non-responders. Furthermore, the final outcome might depend on the post-induction definite treatment modalities. Unfortunately, no randomized trial has addressed this question.

As such a control group does not exist in the present study, an alternative would be to compare the survival of good responders treated with definite RT (+/-CT) to the survival rates of the traditionally accepted most efficient treatment available, i.e. immediate radical surgery followed by radiation therapy. The EORTC 24891 phase III trial (see paragraph C1) had included 194 pyriform sinus patients randomized in 2 arms; 94 were treated with immediate surgery followed by RT and 100 were treated with a PF-based laryngeal preservation protocol[21]. The staging comparison of the 42 patients of the present study and patients in the EORTC 24891 trial is shown in Table 9 while the survival rates are shown in Table 10.

Disease stage	Present study (42 good responders)	EORTC 24891 (194 patients)	
		Surgery (94 pts)	ICT (100 pts)
Stage II	7%	6%	7%
Stage III	48%	54%	59%
Stage IV	45%	39%	34%

Table 9: *Distribution of patients in terms of disease-stage in the two studies. (ICT=induction chemotherapy)*

The 42 patients of the present study seem to have equivalent or slightly more advanced disease stages compared to patients of the EORTC 24891 trial (Table 9).

Survival rates	Good responders in present study (42 pts)	EORTC 24891	
		Surgery (94 pts)	ICT (100 pts)
5yOS	60%	33%	38%
5yDFS	50%	26%	32%

Table 10: *Survival rates of good responders (present study) compared to survival rates of patients treated either with immediate surgery either with a PF-based larynx preservation protocol (EORTC 24891 trial). (5yOS=overall survival 5 years after the end of treatment, 5yDFS=disease-free survival 5 years after the end of treatment)*

Although statistical comparison of the survival curves of the 2 studies was not possible, the 5-year OS and 5-year DFS seem to be clearly higher in the good responders' population:

- compared to patients treated with immediate surgery in the EORTC trial,
- compared to patients treated with a laryngeal preservation protocol (good and bad responders together) in the EORTC trial.

This observation may suggest an improved oncologic outcome for patients responding to ICT, which could be attributed either to patients' selection for radiation therapy or to a therapeutic effect of chemotherapy [24]. It is unknown if any survival benefit would concern good responders if they were finally treated with surgery. No matter what the exact effect of ICT is, it is reasonable to speculate that if there was a way to predict radiosensibility of a tumor, substantial improvements could be achieved in terms of survival by choosing to irradiate the good candidates.

C5) LIMITATIONS OF THE PRESENT STUDY

The main limitations of the present study are presented below:

a) The total **number of patients** included in the study: although in a 10-year period a significant number of patients (=559) were treated for pyriform sinus SCC in the IGR, only 42 patients (8%) fulfilled the inclusion criteria and could be retained for analysis. Undoubtedly, ICT-based larynx preservation protocols concerned a minority of all patients treated for pyriform sinus SCC in this period (Figure 7). A multicenter collaboration would be necessary in order to recruit more patients.

b) The **different treatment modalities**: patients included were treated either with radiation therapy alone either with radiation therapy with concomitant chemotherapy. Moreover, in the majority of cases the regimens of neoadjuvant chemotherapy were based either on TP either on TPF. As already mentioned the 4 therapeutic subgroups were equivalent in terms of staging but comparisons between them are not possible due to the small number of patients weakening the power of statistical tests.

c) The **absence of a control group**: for the main objectives of this study (description of the oncological and functional outcome, analysis of treatment failures and results of salvage treatment) no control group was necessary. Nevertheless, this would be mandatory before making any definite conclusions on potential survival benefits for good responders.

d) **Retrospective study**: apart from the heterogeneity of the population treated, especially concerning treatment modalities, the retrospective character of the study limited the data available for the analysis of the functional outcome. In cases of poor documentation in the medical files, pharyngolaryngeal functions of deceased patients could not be evaluated.

e) Interpretation of the **results concerning voice evaluation** should be made with caution as they reflect the opinion of a third (15/42) of all patients included in the study and more

precisely of those who were still alive and did fine in terms of oncological outcome of treatment when the study was carried out.

D) SUMMARY AND CONCLUSIONS

The present study of patients with pyriform sinus SCC treated with induction chemotherapy-based larynx preservation protocols focusing on the good responders of induction chemotherapy shows a 5-year OS of approximately 60% and a 5-year DFS of 50%.

Survival rates were influenced by:

- nodal stage, with 5-years DFS being significantly different (p=0.02) between N0 (80%) and N+ (40%) patients,
- local extension, with 5-year DFS being 80% for small tumors (T2) versus 40% for locally advances tumors (T3 and T4a), although this comparison showed a trend with no statistical significance (p=0.15).

The 11 **oncologic failures** (28%) observed in the study population included 5 local, 2 regional (nodal) and 4 simultaneous local and regional failures. Surprisingly, there were no cases of isolated distant metastases. Two thirds (7/11) of the oncologic failures appeared within the first 3 years after the end of radiation therapy.

Salvage treatment was attempted by means of surgery with or without re-irradiation. The attempt was definitively unsuccessful in 64% of oncologic failures (7/11); this was particularly true in cases of simultaneous locoregional failure as all these patients finally died due to disease progression.

The **functional outcome** of larynx preservation was satisfactory:

- only 3/42 patients (7%) have needed a tracheotomy; 2 tracheotomies were transitory and only 1 was permanent (2%),
- all patients judged their voice quality as at least sufficient for everyday oral communication,
- the vast majority of patients (>85%) could maintain in the long-term an exclusively oral feeding, with 2/3 of them being able to eat normal consistencies.

In conclusion, responding to induction chemotherapy appears to provide a favorable oncologic outcome with satisfactory pharyngolaryngeal function. Locoregional failure of radiation therapy, in good ICT responders, leaves relatively low chances of success to salvage treatments.

E) CONTRIBUTION OF THE AUTHOR AND ACKNOWLEDGEMENTS

The author of this thesis is responsible for:

- the idea and the design of the study,
- the data collection,
- the development of the questionnaire,
- the analysis and interpretation of the results,
- the review of the literature.

During the period in which the author worked at the *Institut Gustave Roussy* he had the opportunity to deepen his understanding of pyriform sinus SCC and induction chemotherapy-based larynx preservation protocols thanks to fruitful discussions with **Dr François Janot**, head of the department of Head and Neck Surgery and **Dr Anne-Marie Le Ridant**, surgeon in the same department. They are thanked for their guidance and useful advice during the realization of this study.

The author is thankful to **Pr Pavel Dulguerov** for his help, comments and corrections in the preparation of the present thesis manuscript.

F) ANNEXES

Annex 1: Questionnaire for the evaluation of the functional outcome, sent to patients previously followed for at least 3 years after the end of radiation therapy; the first 2 parts were dedicated to breathing and voice.

Respiration

1. Au début de votre traitement (de chimiothérapie et de radiothérapie) étiez-vous déjà porteur d'une trachéotomie pour respirer ?
   - ☐ Oui
   - ☐ Non

2. Au cours de votre traitement (de chimiothérapie et de radiothérapie) avez-vous bénéficié d'une trachéotomie pour respirer ?
   - ☐ Oui
   - ☐ Non

3. A un moment donné après la fin de votre traitement (de chimiothérapie et de radiothérapie) avez-vous eu une trachéotomie afin de pouvoir respirer ?
   - ☐ Oui
   - ☐ Non

Si la réponse à cette dernière question est oui, combien de temps après la fin du traitement l'opération de la trachéotomie a-t-elle eu lieu ?

Environ
... ans et ... mois après la fin du traitement

4. Si à un moment donné après la fin du traitement vous vous êtes trouvés avec une trachéotomie, combien de temps êtes-vous restés avec la trachéotomie ?
   - ☐ J'ai toujours la trachéotomie
   - ☐ Elle a été enlevée environ ... ans et ... mois après qu'elle a été mise en place

Voix

5. Juste avant le début du traitement (de chimiothérapie et de radiothérapie) est-ce que votre voix était compréhensible pour les besoins de la vie quotidienne ?
   - ☐ Oui, je n'avais pas de problème majeur de voix
   - ☐ Ma voix était altérée et la communication avec les autres était plus difficile que d'habitude
   - ☐ Non, pratiquement je n'avais plus de voix

6. Est que votre voix actuelle est satisfaisante pour les besoins de votre vie quotidienne ?
   - ☐ Oui, je n'ai pas de problème majeur de voix
   - ☐ Ma voix est altérée, pourtant j'arrive à communiquer avec les autres en parlant
   - ☐ Je ne parle pratiquement plus et je dois écrire ce que je veux dire aux autres

Annex 2: The third part of the questionnaire for the functional outcome was dedicated to swallowing.

Alimentation

7. Actuellement vous êtes alimentés ...	☐ Exclusivement par la bouche ☐ Exclusivement par sonde nasogastrique ou gastrostomie ☐ En partie par sonde et en partie par la bouche
8. Si vous êtes alimentés (exclusivement ou partiellement) par la bouche quelle est la consistance des vos repas ?	☐ Normale, je peux manger toutes les consistances sans problème ☐ Surtout mixée, hachée ou semi-liquide ☐ Exclusivement liquide
9. Si pendant ou après la fin de votre traitement (de chimiothérapie et de radiothérapie) vous avez eu une sonde nasogastrique ou une gastrostomie, combien de temps après la fin du traitement avez-vous pu vous en sevrer en récupérant une alimentation exclusivement par la bouche ?	☐ Je n'ai jamais eu de sonde d'alimentation ☐ Je suis toujours alimenté (exclusivement ou en partie) par sonde ☐ Je me suis sevré de la sonde environ ... ans et ... mois après la fin de la radiochimiothérapie
10. Pendant ou après la fin de votre traitement (de chimiothérapie et de radiothérapie) avez-vous eu de problème de fausses routes (=avaler de travers) à la déglutition entrainant des problèmes de pneumonies ?	☐ Oui, mon médecin m'avait parlé des fausses routes ayant provoqués des pneumonies ☐ Non, je n'ai jamais eu de vrai problème de fausses routes

G) REFERENCES

1. Muir C, Weiland L. Upper aerodigestive tract cancers. Cancer 1995;75:147-53.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
3. Curado MP, Edwards B, Shin HR, et al. Cancer Incidence in Five Continents. Volume IX. In: IARC Sci Publ; 2007.
4. Cancer de l'hypopharynx (Accessed 01.05.2013, at http://www.france-cancer.net/netscope.php?i=2&titre=Cancer+de+l\%27hypopharynx+.)
5. Sobin LH, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. 7th ed: Wiley-Blackwell; 2009.
6. Hall SF, Groome PA, Irish J, O'Sullivan B. TNM-based stage groupings in head and neck cancer: application in cancer of the hypopharynx. Head Neck 2009;31:1-8.
7. Spector JG, Sessions DG, Haughey BH, et al. Delayed regional metastases, distant metastases, and second primary malignancies in squamous cell carcinomas of the larynx and hypopharynx. Laryngoscope 2001;111:1079-87.
8. Hoffman HT, Karnell LH, Shah JP, et al. Hypopharyngeal cancer patient care evaluation. Laryngoscope 1997;107:1005-17.
9. Allal AS, Dulguerov P, Bieri S, Lehmann W, Kurtz JM. A conservation approach to pharyngeal carcinoma with advanced neck disease: optimizing neck management. Head Neck 1999;21:217-22.
10. Dehesdin D CO. Anatomie du pharynx. Encycl Méd Chir Oto-Rhino-Laryngologie 1998:20-491-A-10.
11. Lefebvre JL, Chevalier D. Hypopharynx cancer. Oto-Rhino-Laryngologie Encycl Méd Chir 2004:274-89.
12. Popescu CR, Bertesteanu SV, Mirea D, Grigore R, lonescu D, Popescu B. The epidemiology of hypopharynx and cervical esophagus cancer. J Med Life 2010;3:396-401.
13. Hypopharyngeal Cancer. Emedicine - WebMD LLC., 2011. (Accessed 2012, at http://emedicine.medscape.com/article/1375268-overview.)
14. Barnes L, Tse LLY, Hunt JL, et al. Tumors of the Hypopharynx, Larynx and Trachea: Introduction. In: Barnes L, Eveson JW, Reichart PA, Sidransky D, eds. WHO Classification of Tumours: Pathology and Genetics, Head and Neck Tumours. Lyon: IARC Press; 2005:114.
15. Wahlberg PC, Andersson KE, Biorklund AT, Moller TR. Carcinoma of the hypopharynx: analysis of incidence and survival in Sweden over a 30-year period. Head Neck 1998;20:714-9.
16. Hall SF, Groome PA, Irish J, O'Sullivan B. The natural history of patients with squamous cell carcinoma of the hypopharynx. Laryngoscope 2008;118:1362-71.
17. Hall SF, Groome PA, Irish J, O'Sullivan B. Towards further understanding of prognostic factors for head and neck cancer patients: the example of hypopharyngeal cancer. Laryngoscope 2009;119:696-702.
18. Lefebvre JL, Andry G, Chevalier D, et al. Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. Ann Oncol 2012;23:2708-14.
19. Lefebvre JL, Calais G. La preservation laryngee, etat de la question. Cancer Radiother 2005;9:37-41.
20. Group DoVALCS. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991;324:1685-90.

21. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890-9.
22. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009;101:498-506.
23. Posner MR, Norris CM, Wirth LJ, et al. Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324: survival, surgery, and organ preservation. Ann Oncol 2009;20:921-7.
24. Pfister DG, Ridge JA. Induction chemotherapy for larynx preservation: patient selection or therapeutic effect? J Clin Oncol 2006;24:540-3.
25. Richard JM, Sancho-Garnier H, Pessey JJ, et al. Randomized trial of induction chemotherapy in larynx carcinoma. Oral Oncol 1998;34:224-8.
26. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-55.
27. Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. Laryngoscope 2006;116:1-13.
28. Chen AY, Halpern M. Factors predictive of survival in advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg 2007;133:1270-6.
29. Olsen KD. Reexamining the treatment of advanced laryngeal cancer. Head Neck 2010;32:1-7.
30. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091-8.
31. Wolf GT. Reexamining the treatment of advanced laryngeal cancer: the VA laryngeal cancer study revisited. Head Neck 2010;32:7-14.
32. Forastiere AA. Larynx preservation and survival trends: should there be concern? Head Neck 2010;32:14-7.
33. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-44.
34. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945-52.
35. Forastiere AA, Zhang Q, Weber RS, et al. Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients With Locally Advanced Larynx Cancer. J Clin Oncol 2012.
36. Prades JM, Lallemant B, Garrel R, et al. Randomized phase III trial comparing induction chemotherapy followed by radiotherapy to concomitant chemoradiotherapy for laryngeal preservation in T3M0 pyriform sinus carcinoma. Acta Otolaryngol 2010;130:150-5.
37. Lefebvre JL, Rolland F, Tesselaar M, et al. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. J Natl Cancer Inst 2009;101:142-52.
38. Hitt R, Grau JJ, Lopez-Pousa A, et al. Final results of a randomized phase III trial comparing induction chemotherapy with cisplatin/5-FU or docetaxel/cisplatin/5-FU follow by

chemoradiotherapy (CRT) versus CRT alone as first-line treatment of unresectable locally advanced head and neck cancer (LAHNC). J Clin Oncol 2009;27:6009.
39. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21-8.
40. Lefebvre JL, Pointreau Y, Rolland F, et al. Induction Chemotherapy Followed by Either Chemoradiotherapy or Bioradiotherapy for Larynx Preservation: The TREMPLIN Randomized Phase II Study. J Clin Oncol 2013.
41. Lorch JH, Goloubeva O, Haddad RI, et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. Lancet Oncol 2011;12:153-9.
42. Urba S, Wolf G, Eisbruch A, et al. Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. J Clin Oncol 2006;24:593-8.