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par

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STRATEGIES THERAPEUTIQUES DES CHONDROSARCOMES LARYNGÉS : ETUDE MULTICENTRIQUE DE 45 CAS

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

RESUME

Introduction : Le chondrosarcome laryngé est une tumeur rare, le plus souvent de bas grade qui touche surtout le cartilage cricoïde. Il n'existe pas encore de recommandation sur la prise en charge de ces cancers. Le principal objectif de cette étude est de décrire les caractéristiques de cette pathologie et de comparer les différents traitements réalisés avec leurs résultats fonctionnels et carcinologiques.

Matériel et Méthode : C'est une étude rétrospective, multicentrique sur 10 hôpitaux et cliniques en France. Nous avons isolé dans la base de données d'anatomopathologie de chaque centre l'ensemble des patients suivis pour un chondrosarcome laryngé. Pour chacun, ont été recueillis : le sexe, la date de naissance, les antécédents, l'âge et la clinique au diagnostic, l'imagerie pour le bilan d'extension, la localisation et la taille de la tumeur, la mobilité cordale, le grade, la prise en charge et le devenir. La survie avec larynx en place, fonctionnel et la survie globale ont été réalisée selon la méthode de Kaplan-Meier.

Résultats : 45 patients ont été inclus avec un ratio hommes/femmes de 2,5/1 et une moyenne d'âge au diagnostic de 62 ans. 96% étaient des tumeurs du cartilage cricoïde et 4% du cartilage thyroïde. 44 patients avaient une tumeur de bas grade. Sur les 45 patients, 14 ont eu une laryngectomie totale en première prise en charge et 31 ont eu une chirurgie avec préservation laryngée (chirurgies endoscopiques, thyrotomies médianes, laryngectomies partielles). Dans le groupe préservation laryngée, la survie avec larynx fonctionnel était de 96% à 1 an et de 75% à 5. Le taux de survie globale à 5 ans était de 100% dans ce groupe contre 83% dans le groupe laryngectomie totale première.

Conclusion : Cette étude montre que le traitement conservateur doit être privilégié pour cette pathologie puisqu'il ne diminue pas les chances de survie et permet d'avoir un larynx en place et fonctionnel dans 75% des cas à 5 ans.

Mots clés : chondrosarcome, cancer du larynx, laryngectomie, larynx

ABSTRACT

Introduction: Laryngeal chondrosarcoma is a rare tumor of low grade which mostly affects the cricoid cartilage. There are no official guidelines on how to treat laryngeal chondrosarcoma. Our main objective was to study laryngeal chondrosarcoma's main characteristics, compare different treatment methods and their outcomes.

Materials and methods: This study is a retrospective analysis using the pathology database of 10 French tertiary care centers. The data collected included: gender, date of birth, medical history, age and clinical symptoms at diagnosis, imaging done for extension work-up, primary site and size of the tumor, vocal cord mobility, tumor grade, treatment and outcome.

A Kaplan-Meier survival analysis was performed, first with non-preserved larynx as the outcome, then for overall survival.

Results: 45 patients were enrolled with a 2,5:1 male to female ratio. The mean age at diagnosis was 62 years old. 96% of our patients had cricoid tumors and 4% had thyroid tumors. 44 patients were diagnosed with a low-grade tumor.

Out of our 45 patients: 14 had a total laryngectomy as initial treatment, 31 had at first a laryngeal conservative treatment (endoscopic debulking, median thyrotomy, partial laryngectomy).

When conservative treatment was used, laryngeal functions were preserved at 1 year for 96% and at 5 years for 75% of the patients. Overall survival rate was not modified (100% at 5 years).

Conclusion: These results suggest that laryngeal preservation should be considered as first treatment of choice.

Key words: chondrosarcoma, laryngeal tumor, laryngectomy, larynx

TABLE DES MATIERES

Introduction:

Laryngeal chondrosarcoma is a rare tumor and was first described by Travers in 1816.[1]

It represents 1% [2] of all laryngeal tumors as opposed to squamous cell carcinoma (95,1% of all laryngeal tumors[3]). The primary site of this tumor is the cricoid cartilage (>50%), but it can also be found in the thyroid, arytenoid and epiglottis cartilage.[4]

The etiology of this tumor is unknown. It arises from the hyaline cartilage. In most articles in the literature, the classification used for this tumor is the one described by Evans et al. in 1977[5] which classifies chondrosarcomas into 3 groups: stages 1 and 2, or low grades, are well differentiated tumors with increased cellularity and some binucleated cells ; stage 3 is a high grade tumor, where cellularity is much more important, nuclear abnormalities are more frequent, and mitosis and/or necrosis can be found.[6–8] Low grade chondrosarcomas are most common as observed in the review of Chin et al: out of 426 histological cases reviewed, 91,3% were grade 1 and 2.[4]

Clinically, patients with laryngeal chondrosarcoma can suffer from pain, hoarseness, dysphonia, dyspnea, dysphagia, or a mass in the neck. These symptoms are caused by airway obstruction, cricoarytenoid joint invasion or extra laryngeal growth.[2] Laryngeal chondrosarcoma rarely metastasizes. In a study of 111 cases by Thompson et al.[2] only 1,9% of patients developed metastases (lung, liver and bone being the primary sites). Identification and local extension of the tumor is best assessed by CT scans where “popcorn” calcifications are typically described with cartilage destruction. Diagnosis is confirmed by biopsy, specifying the type and grade of the tumor.

There are no official guidelines on how to treat laryngeal chondrosarcoma. In the literature various surgeries are described, some conservative[9,10] such as endoscopic debulking[11–14] or partial laryngectomy[15,16] others more invasive with total laryngectomy. Chemotherapy and radiotherapy are not initial therapies and only few cases of these treatments are reported in the

literature.[17,18] The literature on laryngeal chondrosarcoma is mainly case reports or small case studies. The largest study to date is the meta analyses of 592 cases by Chin et al.[4], but heterogeneity of data recording, and wide differences in years of publishing limit the results.

The aim of this study was first to describe laryngeal chondrosarcoma's main characteristics, treatments, and outcomes through a multicenter retrospective study. The second aim was to compare the different treatment methods between conservative surgeries and total laryngectomy.

Materials and methods:

- **Center included**

For this retrospective study, data was collected in 10 French tertiary care centers (Tours, Lyon, Nantes, Paris, Caen, Rouen, Poitiers, Angers, Brest, Blois).

- **Patients**

The pathology database was used in each hospital. Medical files of patients with laryngeal chondrosarcoma were then reviewed. Patients who refused all treatments and those lost at close follow up were excluded.

A total of 45 patients were enrolled. All files included dated from 2000 to 2020. (***Figure 1***)

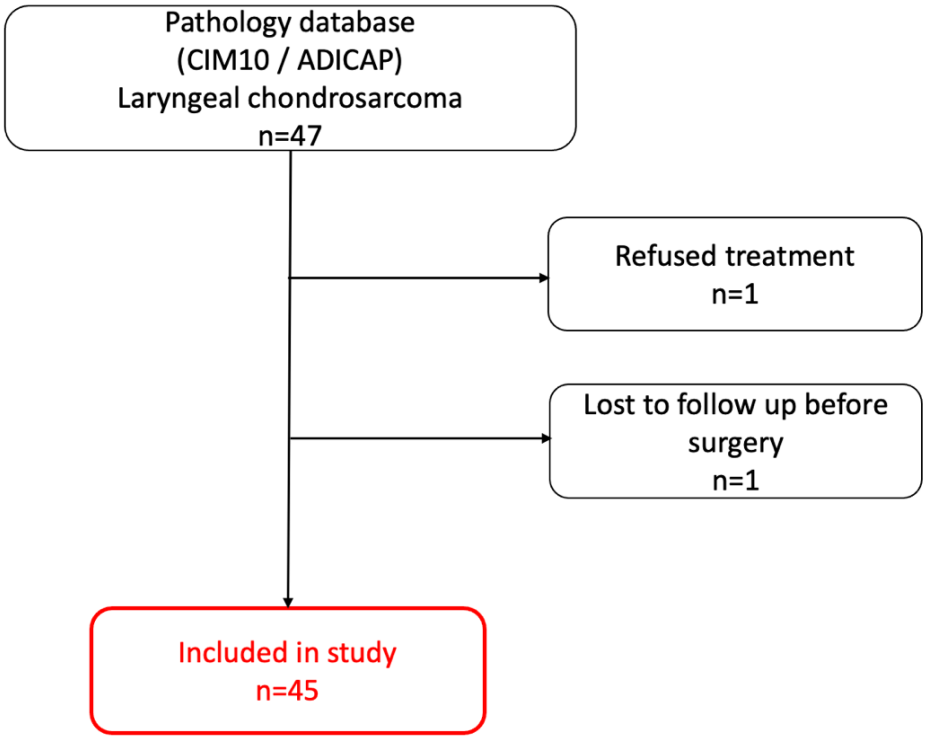

Figure 1. Flow chart

This study was approved by the ethics committee in human research of Tours (n° 2021003).

- **Data collected**

The data collected included: gender, date of birth, medical history, age and clinical symptoms at diagnosis, imaging done for extension work-up, primary site and size of the tumor, vocal cord mobility, tumor grade, treatment and outcome. For each surgery performed we noted average length of hospital stay, complications observed (hematoma, infection, emphysema, dyspnea, fistula…), whether a nasogastric tube or a tracheotomy had been necessary and if so, for how long.

- **Primary and secondary endpoints**

The first aim was to study presenting symptoms, clinical characteristics and treatment outcomes of patients with laryngeal chondrosarcoma. Different types of surgeries were analyzed separately to compare the outcome of patients treated by total laryngectomy and of those treated by a more conservative approach (endoscopy, median thyrotomy and partial laryngectomy). The second aim was to find a correlation between patient criteria and the type of treatment chosen.

- **Data analyses**

All statistical analyses were performed using Microsoft Excel v16.59 and the software R v3.6.2. First, characteristics of the participants, functional and oncological results after different treatment options were described according to their nature by sample size and percentages or by mean and standard deviation. Then, data were compared between patients with initial total laryngectomy versus those with laryngeal conservative surgery, using t-test or Wilcoxon test for numeric variables and Chi2 or Fisher tests for categorical variables, according to the conditions of use of each test. The results with $p \leq 0.05$ were considered as statistically significant. Two Kaplan-Meier survival analysis were performed, one to assess the overall survival rate in both groups and one with non-preserved larynx as the outcome, in order to show laryngeal preservation through time.

Results:

- **Clinical and pathologic features:** ***(Figure 2; Table 1)***

A total of 45 patients were enrolled: 32 males and 13 females, who ranged in age from 40 to 87 years old. The mean age at diagnosis was 62 years old (male, 61; female, 64). Patients' clinical symptoms at diagnosis included: pain (n=1), hoarseness or dysphonia (n=33), a mass lesion

(n=2), dyspnea (n=20) or dysphagia (n=2). Some patients had more than one symptom at presentation, on the other hand 4 were discovered accidently. Ninety-six percent of our patients had cricoid tumors and 4% had thyroid tumors. Forty-four patients were diagnosed with a low-grade tumor (stage 1 or 2), 1 patient was diagnosed with a high-grade tumor and 1 patient had a tumor transformation from low-grade to high-grade during follow up. At diagnosis, based on CT scanner, 13% had a tumor measuring over 4cm, 53% had a tumor measuring between 2 and 4cm, 7% had a tumor of less than 2cm and 27% did not have any size description in their medical files.

Out of our 45 patients: 14 had a total laryngectomy as initial treatment, 31 had at first a laryngeal conservative treatment.

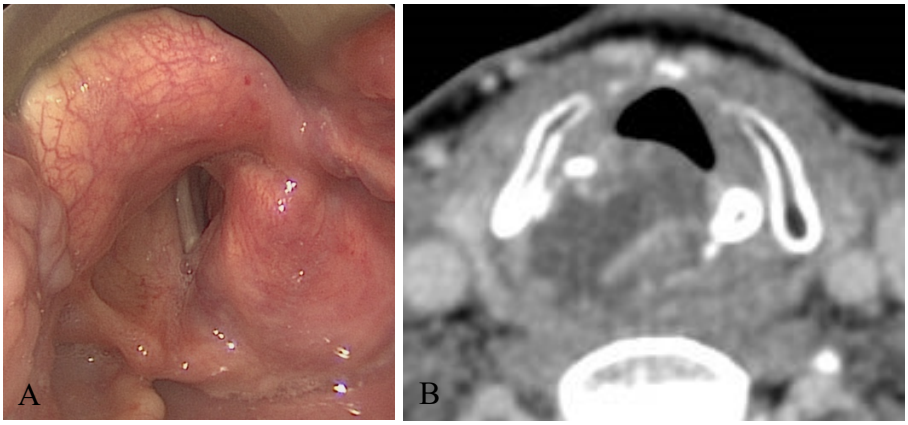

Figure 2. A 52-year-old female presenting with dysphonia and dyspnea. She had a cricoid chondrosarcoma. Median thyrotomy was performed as initial treatment.
A: endoscopic view before biopsy; B: CT scanner before surgery

Table 1. Patients and tumor characteristics

Characteristics	N	%
Gender		
M	32	71%
F	13	29%
Primary site		
Cricoid	43	96%
Thyroid	2	4%
Grade*		
Low	44	98%
High	1	2%
Size		
Unknown	12	27%
<2cm	3	7%
2-4cm	24	53%
>4cm	6	13%
Presentation**		
Pain	1	2%
Hoarseness or dysphonia	33	73%
Neck mass	2	4%
Dyspnea	20	44%
Dysphagia	2	4%
Asymptomatic	4	9%

F: Female; M: Male
*: Low: grade I and II; High: grade III
**: some patients had more than one presentation at diagnosis

- **Treatment and outcomes:**
    - **Patients with conservative treatment (n=31):**

After diagnosis, 19 patients were treated by endoscopic debulking, 9 had a median thyrotomy and 3 had partial laryngectomy. Twenty-three had additional surgery through follow up for tumor recurrence, with a mean of 2,6 surgeries per patient. A total of 51 endoscopic debulking,

21 median thyrotomies, 8 partial laryngectomies and 2 tracheotomies were performed. Thirteen had finally secondary total laryngectomy.

However, laryngeal functions were preserved (no total laryngectomy, no definitive tracheotomy and no gastrostomy)) at 1 year for 96% and at 5 years for more than 75% of these patients. (***Figure 3***)

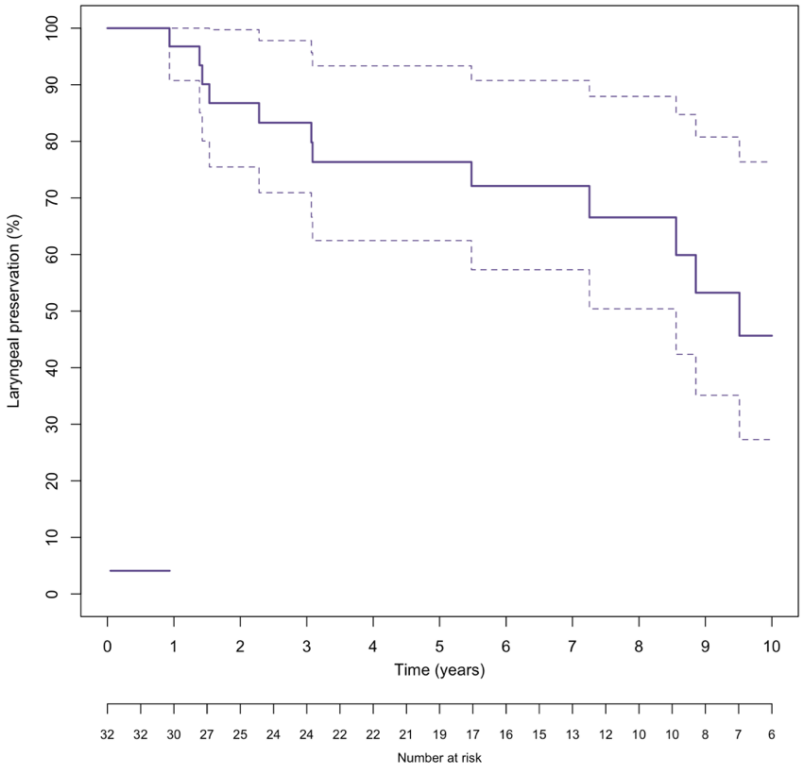

Figure 3. Laryngeal preservation, over a 10-year period, for 31 patients with a conservative treatment of laryngeal chondrosarcoma
Full line is the laryngeal preservation survival and doted lines are the error limits

- Hospitalization stay:

Mean hospitalization stay was of 2 days for endoscopic debulking, 11 days for median thyrotomy and 17 days for partial laryngectomy. (***Figure 4***) Length of hospital stay varied whether a temporary tracheotomy and a feeding tube were necessary or not after surgery, and if patients suffered from post-operative complications.

- Complications:

There were few complications with endoscopic surgeries: 4 patients had post-operative dyspnea on laryngeal oedema. Only two of these patients had a temporary tracheotomy. Oral feeding was authorized immediately after endoscopic surgery.

Patients treated by median thyrotomy: 3 had post-operative dyspnea, 2 had emphysema and 2 presented swallowing dysfunction with aspiration. Oral feeding was authorized at a median of 2,5 days after surgery. Eleven patients treated by median thyrotomy had a temporary tracheotomy.

Patients who had partial laryngectomy: 1 had post-operative dyspnea, 2 had emphysema and 2 had swallowing dysfunction. Oral feeding was started at a median of 9 days after surgery. Six of the patients treated by partial laryngectomy had a temporary tracheotomy.

Overall, in this conservative group, 13 patients needed a secondary total laryngectomy, 12 lived with persistent disease, 5 were without disease at last follow up and 1 died of another cause. None of the patients treated by laryngeal conservative surgery died of disease nor developed any metastasis. No adjuvant treatment was performed. The overall survival rate at 5 years for the conservative group was of 100%.

- **Patients treated by initial total laryngectomy (n=14):**

Patients who underwent total laryngectomy had a mean hospital stay of 24 days with a standard deviation of 22 days (***Figure 4***).

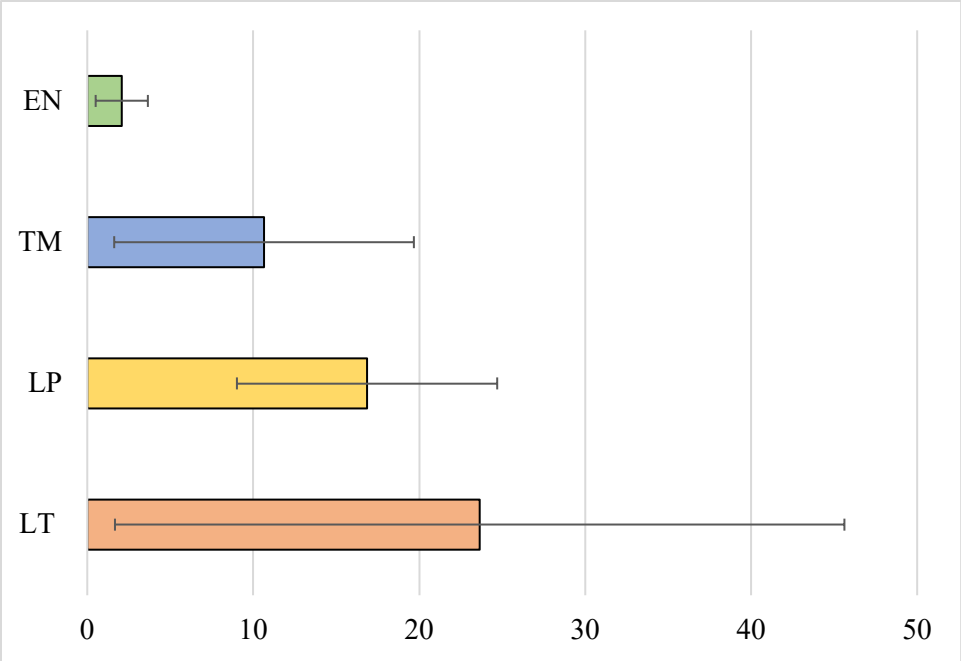

Figure 4. Mean hospitalization stays with standard deviation (in days) for the different surgeries performed for laryngeal chondrosarcoma treatment
Colored bar is the mean stay and the error bar represents the standard deviation
EN=Endoscopic treatment TM=medial thyrotomy LP= Partial Laryngectomy LT= initial Total Laryngectomy

Many differences were noted between patients' hospital stay after total laryngectomy depending on whether they had post-operative complications or not, such as hematoma (n=2), dyspnea (n=1), pharyngostoma (n=4).

Median oral feeding was started at 9,5 days after surgery.

After initial total laryngectomy, 9 patients were without disease at last follow up, 2 patients died of surgery complications and 1 patient died of another cause (2 were lost at close follow up). Only 1 of these patients received adjuvant radiation therapy. The overall survival rate at 5 years for the patients treated by total laryngectomy was of 83%.

- **Type of surgery (conservative versus total laryngectomy) according to patient characteristics *(Table 2)***

In this study there was a 2.5/1 male to female ratio. There was no significant difference ($p>0.05$) between sex and therapeutic approaches.

Mean age at diagnosis was of 59.6 for patients treated with a conservative approach and 66.9 for those treated with total laryngectomy. There was a significant difference ($p=0.038$) when we compared age at diagnosis for these two groups.

Out of the clinical symptoms at diagnosis, presence of dyspnea was especially studied as it could be associated with a more advanced tumor. No significance was found ($p>0.05$) between dyspnea and surgery approach.

Tumors were separated into four groups depending on their greatest dimension in centimeters (cm): <2cm; 2-4cm; ≥4cm; size unknown at diagnosis. None of the tumors measuring less then 2cm had initial total laryngectomy. However, this parameter was not significantly correlated with the type of surgery ($p>0.05$).

When comparing cricoarytenoid joint extension, when tumor had progressed to both joints, total laryngectomy was always performed initially (n=3) and when both joints were intact (n=14) laryngeal preservation surgery was most common (n=11) ($p\leq0.05$).

Results show a trend in the type of surgery performed depending on the hospital center of care. Five out of 6 patients in Center 5, as well as 4 out of 6 patients in Center 3 had initial total laryngectomy. Whereas, in Centers 1 and 2, all the patients (respectfully 11 and 6) had initial laryngeal preservation. However, these differences were not significant. ($p>0.05$)

Table 2. Type of surgery according to patient characteristics

Criteria	initial LT (N=14)	CT (N=31)	Test	P*
Gender				
F	5 (35,7%)	8 (25,8%)	Fisher	0,5024
M	9 (64,3%)	23 (74,2%)		
Mean age at diagnostic (standard deviation)	66,9 (11,3)	59,6 (10,4)	T-test	0,0384
Symptoms at diagnostic				
Dyspnea	6 (42,9%)	15 (48,4%)	Chi2	0,9828
Size				
<2cm	0 (0%)	3 (14,3%)	Fisher	0,517
2-4cm	10 (83,3%)	14 (66,7%)		
>4cm	2 (16,7%)	4 (19%)		
Local extension**				
0	3 (21,4%)	11 (35,5%)	Fisher	0,05
unilateral	8 (57,1%)	20 (64,5%)		
bilateral	3 (21,4%)	0 (0%)		
Location of hospital				
center 1	0 (0%)	11 (35,5%)		
center 2	0 (0%)	6 (19,4%)		
center 3	4 (28,6%)	2 (6,5%)		
center 4	1 (7,1%)	5 (16,1%)		
center 5	5 (35,7%)	1 (3,2%)		
center 6	1 (7,1%)	3 (9,7%)		
center 7	1 (7,1%)	1 (3,2%)		
center 8	1 (7,1%)	1 (3,2%)		
center 9	1 (7,1%)	0 (0%)		
center 10	0 (0%)	1 (3,2%)		

LT: Total Laryngectomy CT: Conservative treatment
*: $p \leq 0,05$ is considered significant
**: extension to the cricoarytenoid joint none, uni or bilateral

Discussion:

Patients treated by laryngeal preservation surgeries, especially cancer debulking by endoscopy or median thyrotomy, have shorter hospitalization stay, fewer complications and earlier oral feeding than those treated by total laryngectomy. Overall survival rate is not modified by these techniques. Finally, these surgeries allow patients to keep a functional larynx at 5 years in 75% of the cases. These results suggest that laryngeal preservation should be considered as the first treatment of choice for tumors of stages I and II.

- **Demographics**

Laryngeal chondrosarcoma has a male predominancy in this study with a male to female ratio of 2,5/1 which is close to what is found in the literature: 3/1.[2–4,19] The mean age at diagnosis was of 62 years old in this review as well as in previous studies.[3,4,20] Presenting symptoms at diagnosis are usually hoarseness and dyspnea.[2,4,19,20]

- **Histology**

Laryngeal chondrosarcoma most commonly affects the cricoid cartilage, while thyroid epiglottis and arytenoid chondrosarcoma are rarer.[2,4,19–21] In this study we used the classification described by Lichtenstein et al.[22] and modified by Evans et al.[5,23] However, even though this classification is of common use, it should be known that it has never been officially validated for head and neck chondrosarcomas. Furthermore, grading of chondrosarcoma can be difficult, especially differentiating stage I and II since different stages can be found in the same tumor. Nevertheless, it can be said that low grade (I and II) chondrosarcomas are most frequent in the larynx, they represent more than 90% of the cases found in the literature.[2,4] In this study, the two patients with high grade chondrosarcoma were treated by total laryngectomy. This is consistent with previous studies.[2,21]

- **Therapy and Outcomes**

Laryngeal chondrosarcoma rarely metastasizes, in our study only 1 (2%) patient had lung metastases. In the literature the risk of developing a metastatic disease is 1,9%.[2]

Death from laryngeal chondrosarcoma is uncommon, mostly patients suffer from surgery complications such as pharyngostoma, hematoma, infection, swallowing dysfunction. In this study none of our patients died from the disease but 2 patients died of initial total laryngectomy complications.

In this study, we found trends that could explain treatment choice depending on patient and tumor characteristics. Extension to the cricoarytenoid-joints seems to have an impact on the choice of radical surgery ($p \leq 0,05$). This is probably due to the need of a definitive tracheotomy for these patients. Location of care of patients seems to influence the treatment plan, even though no trend was found significant by lack of inclusion.

- **Limitations**

All files included were from 2000-2020 and computerized. This range in time inclusion limits the bias of medical advances (surgery, imaging). The follow up for each patient varied depending on the date of diagnosis, this heterogeneity limits our laryngeal preservation analysis.

This study included hospitals and clinics throughout France, giving a good overview of the diverse methods of laryngeal chondrosarcoma patient care.

With 45 patients included, this is one of the largest cohorts [2–4] on laryngeal chondrosarcoma. However, a wider inclusion is needed to further evaluate patient characteristics impact on treatment plan. The variation of treatment choice in the different city centers indicate that a recommendation is needed to decrease these factors and increase the number of laryngeal

preservations when possible. A decisional tree is suggested to help surgeons decide the ideal treatment for each patient. ***(Figure 5)***

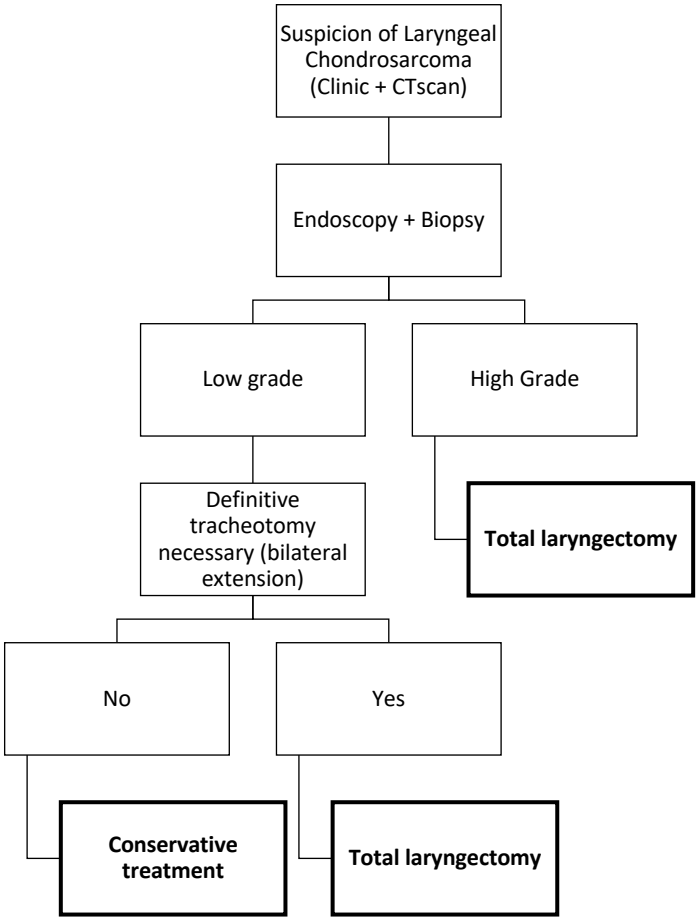

Figure 5. Decisional treatment tree for laryngeal chondrosarcoma

Conclusion:

Laryngeal chondrosarcoma is a rare cancer that mainly affects the cricoid cartilage. It is in more than 95% of the cases a low-grade tumor with exceptional regional or distant metastases and a good long term survival rate. The treatment is surgical. Laryngeal preservation surgeries (even without free margins) for this cancer should be prioritized since as shown in our study they do not reduce survival rate and enable to keep a functional larynx at 5 years in 75% of the cases.

Conflict of interest:

The authors declare that there are no conflicts of interest to disclose.

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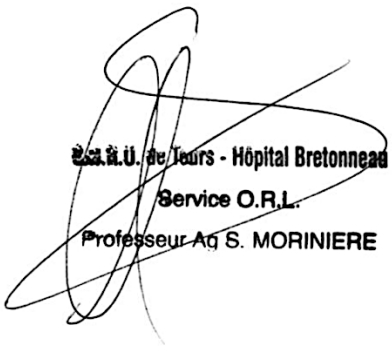
Vu, le Directeur de Thèse



Vu, le Doyen
De la Faculté de Médecine de Tours
Tours, le

Schleich Marianne
32 pages – 2 tableaux – 5 figures

Résumé :

Introduction : Le chondrosarcome laryngé est une tumeur rare, le plus souvent de bas grade qui touche surtout le cartilage cricoïde. Il n'existe pas encore de recommandation sur la prise en charge de ces cancers. Le principal objectif de cette étude est de décrire les caractéristiques de cette pathologie et de comparer les différents traitements réalisés avec leurs résultats fonctionnels et carcinologiques.
Matériel et Méthode : C'est une étude rétrospective, multicentrique sur 10 hôpitaux et cliniques en France. Nous avons isolé dans la base de données d'anatomopathologie de chaque centre l'ensemble des patients suivis pour un chondrosarcome laryngé. Pour chacun, ont été recueillis : le sexe, la date de naissance, les antécédents, l'âge et la clinique au diagnostic, l'imagerie pour le bilan d'extension, la localisation et la taille de la tumeur, la mobilité cordale, le grade, la prise en charge et le devenir. La survie avec larynx en place et fonctionnel et la survie globale ont été réalisée selon la méthode de Kaplan-Meier.
Résultats : 45 patients ont été inclus avec un ratio hommes/femmes de 2,5/1 et une moyenne d'âge au diagnostic de 62 ans. 96% étaient des tumeurs du cartilage cricoïde et 4% du cartilage thyroïde. 44 patients avaient une tumeur de bas grade. Sur les 45 patients, 14 ont eu une laryngectomie totale en première prise en charge et 31 ont eu une chirurgie avec préservation laryngée (chirurgies endoscopiques, thyrotomies médianes, laryngectomies partielles). Dans le groupe préservation laryngée, la survie avec larynx fonctionnel était de 96% à 1 an et de 75% à 5. Le taux de survie globale à 5 ans était de 100% dans ce groupe contre 83% dans le groupe laryngectomie totale première.
Conclusion : Cette étude montre que le traitement conservateur doit être privilégié pour cette pathologie puisqu'il ne diminue pas les chances de survie et permet d'avoir un larynx en place et fonctionnel dans 75% des cas à 5 ans.

Mots clés : chondrosarcome, cancer du larynx, laryngectomie, larynx

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