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RESEARCH ARTICLE

THE ROLE OF CONCURRENT RADIO-CHEMOTHERAPY IN THE MANAGEMENT OF LOCALLY ADVANCED INOPERATEABLE SQUAMOUS CELL CARCINOMAS OF THE LARYNX

R. Ousalm, Y. Amine, O. El Kadiri, T. Igarramane, M. Saadoune, S. Laatittioui, S. Barkiche, N. Oumghar, M. Derfaoui, A. El Omrani and M. Khouchani

1. Radiation Oncology Department. Oncology and Hematology Hospital; Mohammed VI University Hospital. Marrakech.

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Abstract

To investigate the role of concomitantchemo radiotherapy in the management of inoperable squamous cell carcinomas of the larynx, we conducted a retrospective study of 50 cases collected over a 10-year period from January 2012 to December 2021. The study considered various clinical, radiological, endoscopic, therapeutic, and prognostic aspects of this condition. The mean age of the patients was 62.12 years, with a male-to-female ratio of 1.567. The diagnostic approach was consistent, based on clinical, endoscopic, radiological, and histological data. Therapeutic management involved induction chemotherapy in 76% of patients, combined with local treatment using chemo radiothera py. Laryngeal cancer is a common malignancy of the upper aero digestive tract, primarily affecting older men and associated with alcohol and tobacco use. It is often diagnosed at advanced stages. The diagnostic process relies on a multimodal approach: clinical, endoscopi c, radiological,and histological. Total laryngectomy, although curative, causes significant functional and psychological impacts. Larynx-preserving strategies have emerged as key approaches, offering good oncological outcomes but with notable acute and late toxicities. Hence the importance of holding a multidisciplinary consultation meeting.

Introduction:-

Laryngeal cancer is a common condition of the upper aero digestive tract, primarily linked to risk factors such as smoking and alcohol abuse; it predominantly affects older men. It poses a significant public health challenge due to its functional impact and its effects on patients' quality of life.In Morocco, this cancer ranks 16th, with 1,213 new cases in 2020, accounting for 2% of all cancers; it is most often diagnosed at a late stage. [3]The diagnosis is based primarily on direct laryngoscopy and histopathological examination. Radiological imaging is of great value in assessing disease spread and guiding treatment decisions.

Corresponding Author: R. Ousalm
Address: Radiation Oncology Department. Oncology and Hematology Hospital; Mohammed VI University Hospital. Marrakech.

The standard treatment for locally advanced squamous cell carcinoma of the larynx—total laryngectomy—while curative, results in permanent loss of vocal function and significant psychological and social consequences. Given these limitations and contraindications, larynx-preserving strategies have emerged as a promising therapeutic alternative, aiming to maintain laryngeal function while preserving oncological efficacy. Several therapeutic strategies are used for laryngeal preservation in locally advanced, inoperable cancers: induction chemotherapy followed by radiation therapy, concomitantchemo radiation, and finally the sequential approach combining induction chemotherapy followed by concomitantchemo radiation (CCR).Among these strategies, concomitantchemo radiotherapy (CCRT) plays a central role, combining the cytotoxic effects of radiation therapy and chemotherapy to optimize oncological and functional outcomes. This approach offers satisfactory local control for locally advanced tumors while avoiding disfiguring surgery. [2] However, its use is associated with significant acute and delayed toxicity, requiring careful patient selection and multidisciplinary care.

Materials and Methods:-

This is a retrospective, descriptive study analyzing the profiles of patients with locally advanced squamous cell carcinoma of the larynx treated with larynx-preserving strategies (induction chemotherapy followed by concomitant chemo radiotherapy or concomitant chemo radiotherapy alone), focusing on morbidity and mortality.The study was conducted in the Department of Oncology and Radiation Oncology at Mohammed VI University Hospital, covering a 10-year period (2012–2021). Among the 370 cases of laryngeal cancer, 50 patients meeting the inclusion criteria (histologically confirmed laryngeal cancer, inoperable cases, complete records) were selected. Patients who had undergone laryngectomy, those with metastatic disease, or those with incomplete records were excluded. Data were collected from patient records and radiotherapy records using a standardized data collection form covering epidemiological, clinical, Para clinical, therapeutic, and follow-up aspects. Ethical considerations included patient confidentiality and data protection, ensuring compliance with informed consent.

Results:-

The average age of the patients was 62.16 years, ranging from 32 to 92 years. The most affected age group was between 45 and 80 years, accounting for 64% of the total, with a sex ratio of 15.67. Regarding medical history: 82% of patients were smokers. Of these, 79% were still active smokers at the time of the initial consultation. 28% of patients were alcoholics, with evidence of alcohol-tobacco intoxication in 20% of patients. And 10% of patients were cannabis users. Meanwhile, 16% of patients had occupational exposure to carcinogens. No patient was known to have another cancer in the ENT region, nor had any received prior cervical radiation therapy.The time elapsed between symptom onset and the initial consultation ranged from 1 month to 1 year. It exceeded 6 months in 60% of cases. This finding explains the advanced stage of the disease at the time of diagnosis.
Dysphonia was the primary presenting symptom, present in 92% of cases.

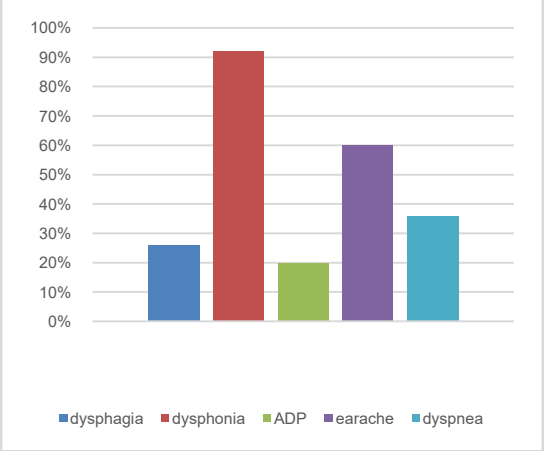

Fig.1:the main clinical signs in our series.

The initial clinical examination revealed impaired general condition in 20% of patients. One-third of the patients were malnourished, while half had a normal BMI.

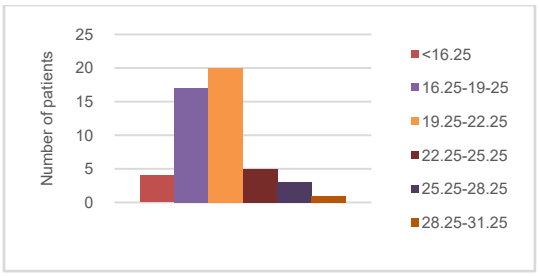

Fig.2:distribution of cases by BMI

Following an otolaryngological examination: laryngeal mobility was preserved, and there were no signs of invasion of the base of the tongue. On indirect laryngoscopy, involvement of all three laryngeal levels was present in 54% of cases.

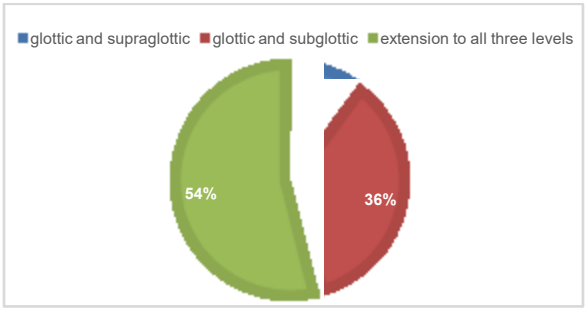

Fig.3:data from indirect laryngoscopy.

The tumor growth pattern was nodular in 68% of cases, infiltrative in 12%, and ulcerative in 20%.72% of patients had a tracheostomy at the time of diagnosis (across all settings), representing 36 patients.And 28% of patients had cervical lymphadenopathy on initial clinical examination.The primary imaging modality was cervical computed tomography, which was ordered for all patients.

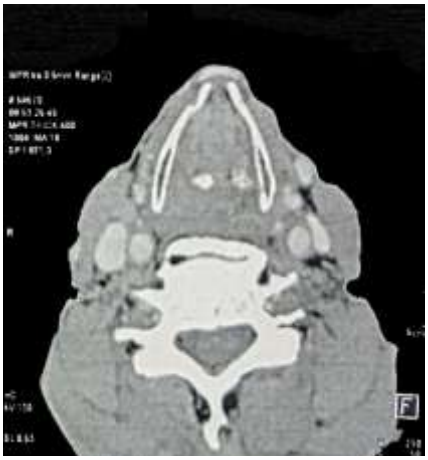

Fig.4: Axial-view cervical CT scan with contrast enhancement of a patient being treated for locally invasive laryngeal carcinoma.

On cervical CT scans, the tumor size was between 20 and 40 mm in 68% of cases. Involvement of the arytenoid cartilage was present in 68% of cases.

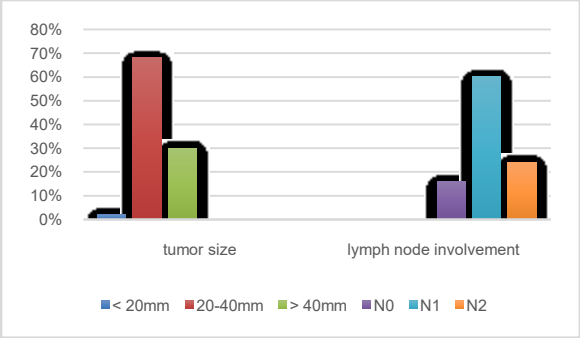

Fig.5: The results of the cervical CT scan.

Lymph node involvement (N1) was present in 60% of patients.

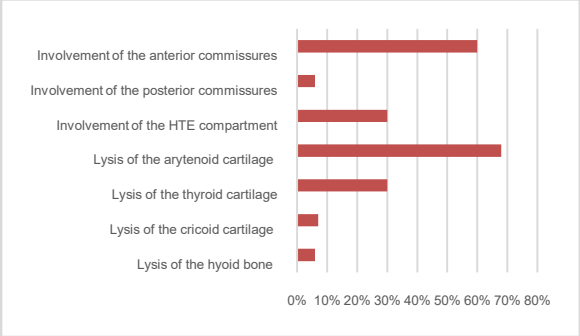

Fig.6: Results of the cervical CT scan.

All patients underwent direct laryngoscopy. Vocal cord mobility was impaired in 88% of the patients.

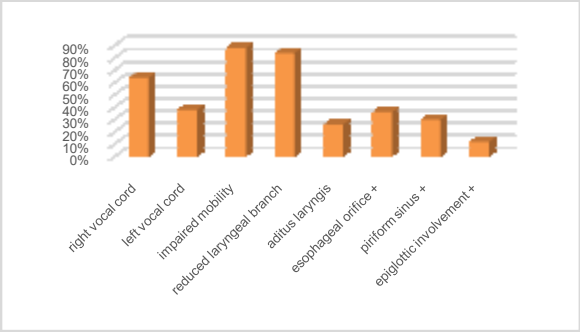

Fig.7: Results of direct laryngoscopy.

The diagnosis was confirmed histologically. Squamous cell carcinoma was detected in all patients, with moderately differentiated features in 86% of cases. As part of the loco regional staging evaluation, a pan-endoscopy was performed in 60% of patients and revealed no other associated sites.As part of the assessment for distant metastasis, a thoracoabdominal CT scan was ordered for all patients, and it did not reveal any secondary sites.
Overall, the tumor was classified as T4N0M0 in 36% of cases.

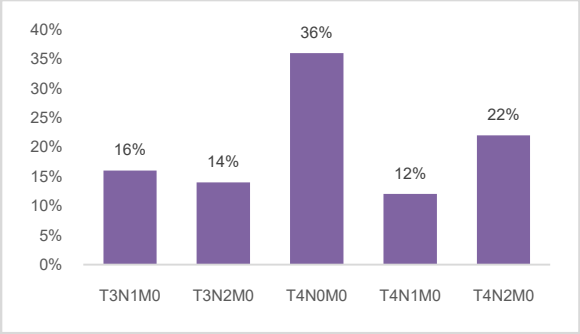

Fig.8: TNM classification.

In order to select an appropriate treatment strategy, all cases were presented at a multidisciplinary team meeting attended by an intensive care physician, a radiologist, an otolaryngologist, and a radiation oncologist. The cases included in our study were inoperable due to the locally advanced nature of the tumor, the patient's refusal of total laryngectomy, or the tumor's inoperability (patients with multiple tumors).

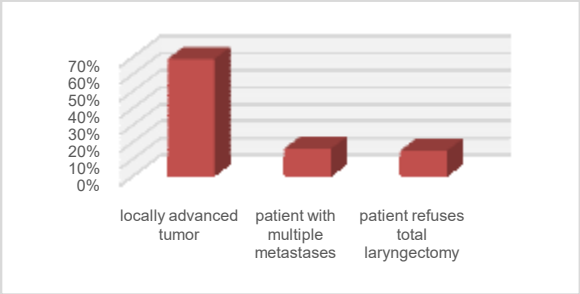

Fig.9: Breakdown of cases by reason for inoperability.

Treatment was based on induction chemotherapy followed by concomitant chemo radiotherapy (CCRT) in 76% of cases. Meanwhile, 24% received CCRT from the outset. The choice of chemotherapy regimen was based on age, underlying conditions, the patient's general condition, and laboratory results.
5-FU-CDDP was the chemotherapy regimen used in 74% of patients.

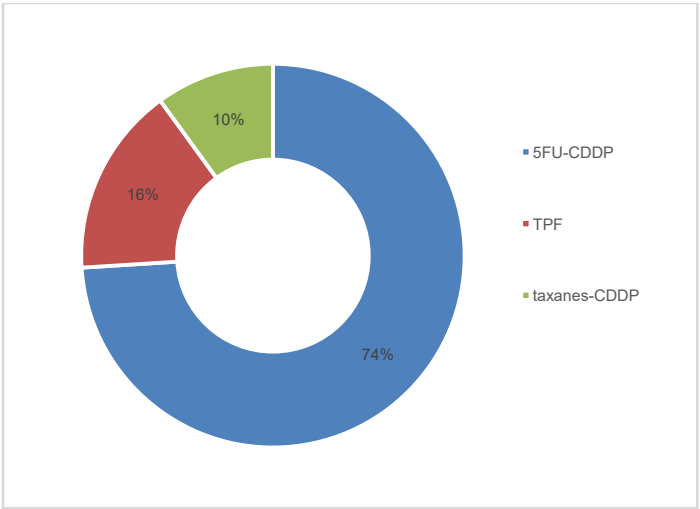

Fig.10: Distribution of patients by type of induction chemotherapy regimen.

Table 1: the chemotherapy drugs used.

Medications	Dosage	Duration
Cisplatin	100 mg/m^2	D1-D2-D3 D1=D21
5-Fluorouracil	1000 mg/m^2	D1-D2-D3-D4-D5 D1=D21
Docetaxel	75-100 mg/m^2	D1 D1=D21

74% of patients received three courses of induction chemotherapy.

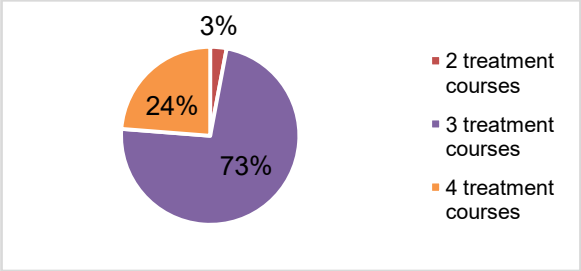

Fig.11: Distribution of patients by number of induction chemotherapy cycles.

An evaluation CT scan of the neck was ordered for all patients. And 51% showed a tumor reduction of more than 50%.

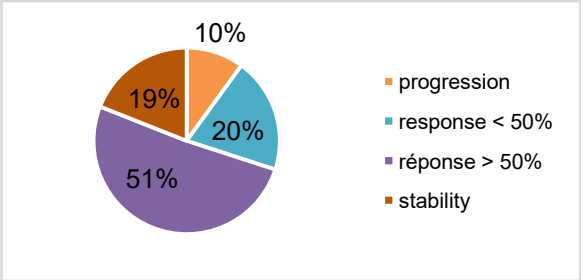

Fig.12: Distribution of patients based on their response to induction chemotherapy.

The side effects associated with chemotherapy were as follows: they were primarily gastrointestinal in nature.

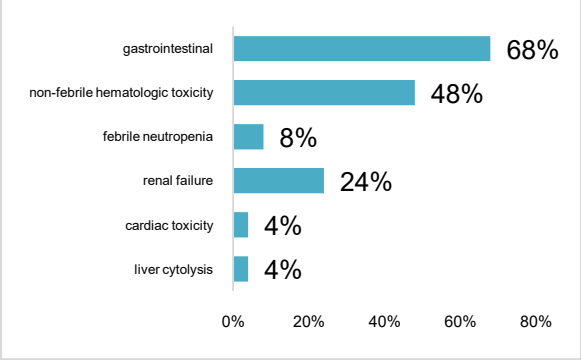

Fig.13: Distribution of patients based on the toxicities of induction chemotherapy.

Total laryngectomy was discussed with all patients who did not achieve a response of more than 50% to induction chemotherapy; however, our study included patients who were inoperable or who refused radical treatment.This study involved a series of 50 cases, all of whom received radiation therapy combined with concomitant chemotherapy. This therapeutic approach involves a non-radiation phase followed by a radiation phase. During the first phase, a consultation should be scheduled to explain the radiation therapy regimen, its principles, and the crucial role of concomitant chemotherapy in radio sensitization. Explain to the patient the benefits of the five-point thermoformed mask throughout the treatment period. A consultation with a psychiatrist may be necessary for patients with claustrophobia. Oral care is routinely performed before treatment begins, ideally involving the placement of a fluoride mouth guard, to prevent complications.

The nutritionist's opinion is also sought to prevent any complications related to patient malnutrition. All patients underwent a technical phase, the preparation stage of which is essential for selecting a comfortable and reproducible position for the radiation therapy sessions. The use of immobilization devices, primarily the five-point thermoformed mask, is necessary to reproduce the same position. Next, every patient scheduled for radiation therapy must undergo a dosimetric CT scan in the treatment position, which will serve as the basis for virtual treatment planning.In our study, the dosimetric CT scan is performed with 3-mm slice thickness, covering the cortex to the carina, and without contrast injection. The images are then transmitted to the treatment planning workstations. It also allows for better visualization of the tumor and its extensions, enabling more accurate delineation of the target volumes. Three types of target volumes must be defined: The gross tumor volume (GTV) corresponds to the tumor and lymph node volume visualized by clinical, endoscopic, and radiological data.

Fig14: A patient being treated for squamous cell carcinoma of the larynx during her dosimetric CT scan.

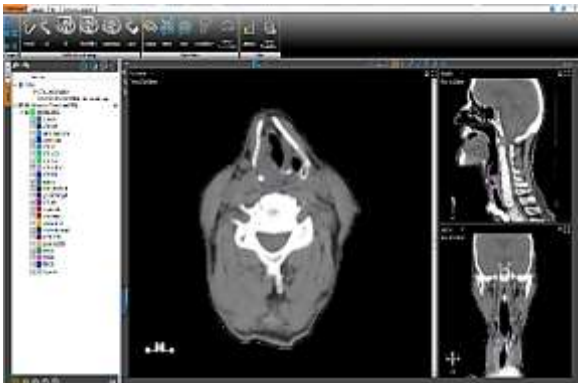

Fig15: GTVt delineation for squamous cell carcinoma of the larynx.

The microscopic tumor volume (CTV) corresponds to microscopic tumor and lymph node spread. It includes a margin around the GTV and takes into account the natural history of the cancer. It is used to describe three risk levels: High-risk CTV corresponds to the GTVt and GTVn with a 5-mm margin. Intermediate-risk CTV corresponds to the high-risk CTV plus microscopic extensions and lymph node areas above and below the GTVn. Low-risk CTV corresponds to the intermediate-risk CTV plus prophylactic lymph node areas.

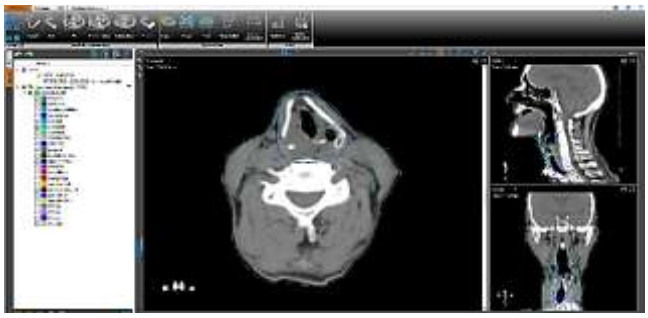

Fig16: Delineation of the CTVt and CTVn for squamous cell carcinoma of the larynx.

The planned treatment volume (PTV) is obtained by adding a 5-mm margin around the CTV to account for positioning errors and the physiological movement of adjacent organs. Thus, in total, three dose levels were treated: the PTVHR, which received 70 Gy; the PTVRI, which received 60–66 Gy; and the PTVBR, which received 50–54 Gy. The treatmentwasadministeredin 35 fractions of 2 Gy each.

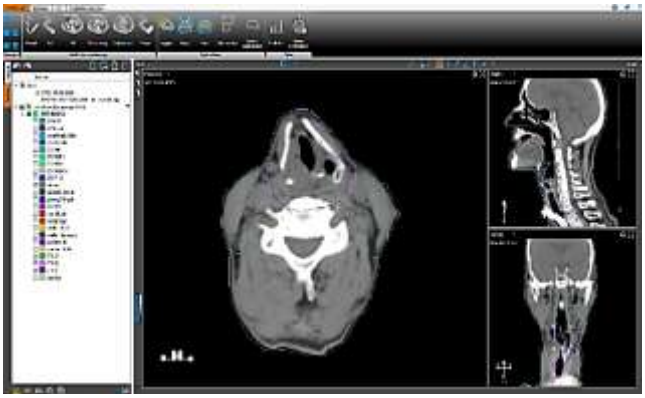

Fig17: PTV delineation for squamous cell carcinoma of the larynx.

The dosimetry scan also helps identify organs at risk. These are defined based on the irradiated area. They consist of all the healthy organs surrounding the tumor. This information is crucial for protecting these organs and documenting the dose received by each one.

Fig18: Identification of risk areas for squamous cell carcinoma of the larynx.

Treatment planning in radiation therapy is a very important step in ensuring uniform dose distribution across the PTV and better protection of at-risk organs.

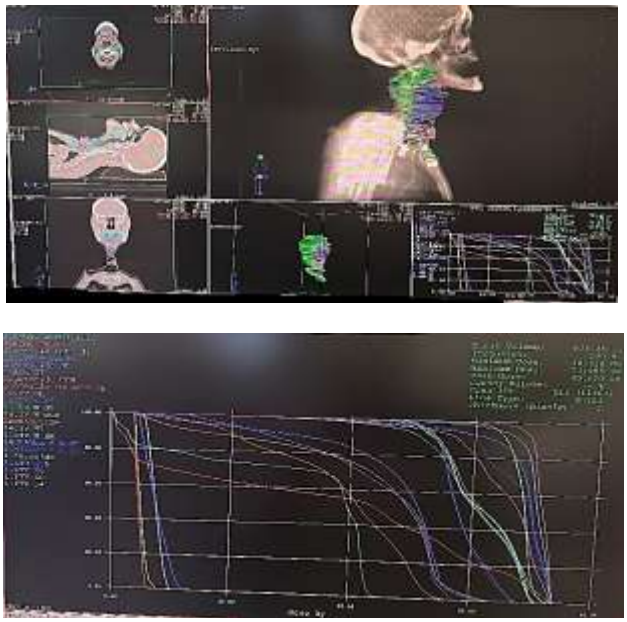

Fig19: Dosimetry overview for squamous cell carcinoma of the larynx.

All of our patients were treated using the RC3D technique over a period of 7–8 weeks.
To ensure accurate delivery of radiation therapy, positional verification was performed using CBCT in all patients on days 1, 2, and 3, followed by weekly checks and at each change in the treatment plan.All patients received cisplatin-based chemotherapy at a dose of 100 mg/m² over a three-day period (Day 1 = Day 21).The occurrence of acute toxicity and the smooth progress of treatment were also monitored during weekly medical consultations. Acute toxicities were dominated by radiation mucositis in 54% of cases and radiation dermatitis in 50% of cases. Topical creams and mouthwash preparations are prescribed during the first consultation to prevent and delay the onset of side effects. Side effects were then managed according to their grade. During follow-up consultations, nutritional status was systematically assessed. Fifty-six percent of patients experienced nutritional issues, while nasogastric tube feeding was required in 32% of cases. Sixty-four percent maintained oral feeding with the initiation of a high-protein diet.

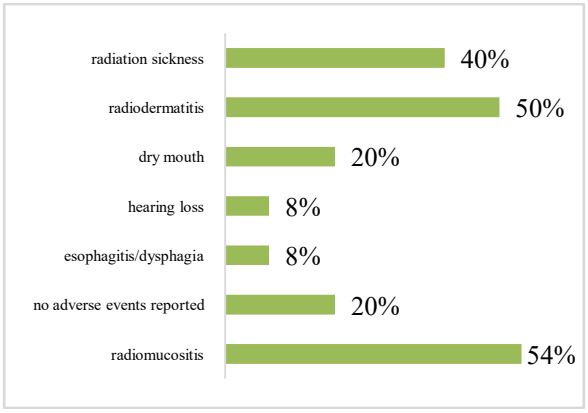

Fig20: distribution of patients based on acute toxicities.

At the end of treatment, follow-up visits were scheduled to assess the response to treatment as well as the occurrence of late toxicities. The most common late toxicity was chronic radiation mucositis, which occurred in 18% of cases.

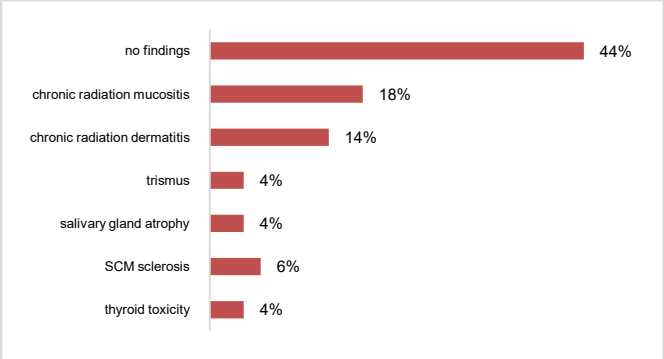

Fig21: distribution of patients based on chronic toxicities.

The assessment of treatment response was multimodal, combining clinical, endoscopic, histological, and radiological evaluations. At the time of our study, the progress of our patients was monitored as follows:

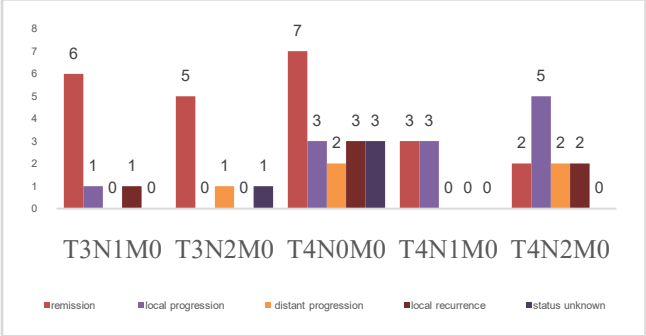

Fig22: patient outcomes in our center based on the initial TNM classification.

Discussion:

Laryngeal cancer accounts for 3.5% of all cancers diagnosed worldwide each year [14]. In Morocco, according to the Greater Casablanca registry of cancer (2018–2021), it represents 1.3% of all recorded cancers. It primarily affects individuals aged 45–70, with an increasing incidence rate among younger individuals due to early alcohol and tobacco use. Laryngeal cancer remains predominantly a male cancer, despite the rising incidence rate among women due to alcohol and tobacco use. The sexe ratio is 4 [1].

Table 2: Incidence rates of laryngeal cancer by sex for the period 2018–2021 (GCRC)[1]

	Men	**Women**	**both genders**
Incidents	265	23	288
Frequency[a]%	2.7	0.2	1.3
Gross incidence/100000	2.9	0.2	1.6
Standardized incidence rate among the Moroccan population/100000	2.9	0.2	1.5

standardized incidence rate for the global population/100000	2.8	0.2	1.4
Cumulative incidence among people aged 0–64%	0.15	0.01	0.08
Cumulative incidence among people aged 0–74	0.35	0.03	0.18
Cumulative risk, ages 0–64%	0.15	0.01	0.08
Cumulative risk, ages 0–74%	0.35	0.03	0.18

a: the proportion calculated based on the total number of recorded cases, broken down by sex

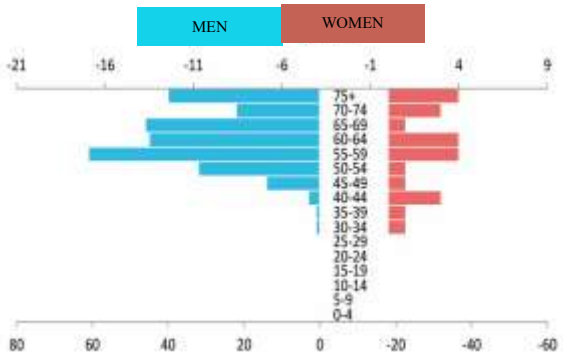

Fig23: Distribution of laryngeal cancer cases by sex and age for the period 2018–2021 (GCRC)[1].

Although laryngeal cancer is a multifactorial disease influenced by various factors (environmental, occupational, dietary, genetic, etc.), the combination of tobacco and alcohol is objectively the primary risk factor. Tobacco smoke contains more than 30 carcinogenic substances, including polycyclic aromatic hydrocarbons and nitrosamines [4]. The association with laryngeal cancer has been confirmed by several studies worldwide. In his study of 162 cases of laryngeal cancer, Franceshi concluded that 95% were chronic smokers, compared to 85.3% in Bouallali's study [5,6]. The synergistic effect of the alcohol-tobacco combination has been known since the work of Rothman and Keller in the 1970s. In that study, while the relative risk (RR) was 1 among "non-drinkers, non-smokers," it rose to 2.33 among "heavy smokers, non-drinkers," to 2.43 among "heavy drinkers, non-smokers," and to 15.5 among "heavy drinkers, heavy smokers" [7].

The risk of developing upper aero digestive tract cancer linked to marijuana use (the active ingredient being THC: Tetrahydrocannabinol (THC) is proportional to the dose, frequency, and duration of exposure [7]. It is commonly noted that patients treated for cancer of the upper aero digestive tract often have poor dental health [8]. A study in China suggested that such poor oral health could constitute an independent risk factor for cancers of the head and neck, particularly the larynx [8]. In contrast to oropharyngeal cancers, the viral role in laryngeal cancer is minor; it is primarily HPV. There is no solid evidence establishing a causal link between these cancers and adenoviruses, cytomegaloviruses, or human herpesvirus 6 (HHV-6). However, certain viruses, particularly those in the human papillomavirus (HPV) family, are suspected of being involved [9]. A retrospective epidemiological study, including 292 patients with aero digestive tract carcinoma and 1,568 controls, revealed that laryngeal papillomatosis is associated with HPV infection, although the risk of malignant transformation remains low and appears to be more closely linked to concomitant smoking [10].

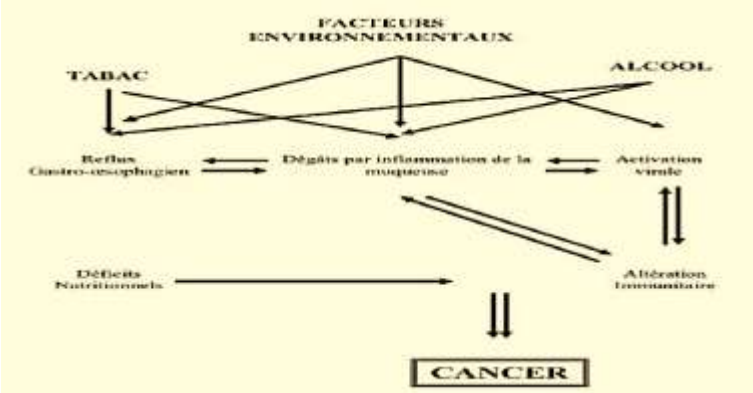

Fig24: diagram explaining laryngeal carcinogenesis.

The time to consultation refers to the period between the onset of the first symptoms and the date of the first visit to a doctor. This time varies considerably, generally being shorter in developed countries than in developing countries, where it can span several years. H. Teppo noted in his study conducted in Finland that diagnostic delays exceeding 12 months constituted an independent and statistically significant determinant of a worsened prognosis [11].

Table3:A look at our series in light of another series.

Study	Country	Consultation period longer than 6 months
DJOMOU [12]	Cameron	85.5%
SADEK [13]	Morocco	74%
KATILE [14]	Mali	65%
ADAMA [15]	Senegal	47.9%
EL ACHKAR [16]	France	33%
Notre série	Morocco	60%

The clinical presentation of laryngeal cancer is primarily characterized by the triad of dysphonia, dyspnea, and dysphagia; the timing of these symptoms depends on the initial anatomical site. Dysphonia appears early in the case of glottic carcinoma, but manifests later in supra-glottic or subglottic carcinomas. Dysphagia, or simple discomfort in the pharynx, is generally associated with supraglottic carcinomas, whereas odynophagia is often linked to involvement of the epiglottis, hypopharynx, or base of the tongue. Hemoptysis reported by patients, although rare, generally involves hemoptytic sputum and may occur due to ulceration and bleeding from an exophytic tumor, which often triggers testing for tuberculosis in our setting and consequently leads to a delayed diagnosis. Upper airway obstruction is often the reason for presentation to the emergency department, requiring a tracheotomy. A neck mass almost always indicates metastatic cervical lymphadenopathy and may also result from direct tumor spread into cervical tissues. It is therefore crucial to inform the public that even a mild symptom, such as persistent hoarseness lasting more than three weeks, dysphagia, or cervical lymphadenopathy—especially in individuals who consume alcohol and tobacco—should prompt an immediate consultation with an ENT specialist.

The ENT examination is a critical step in diagnosing a laryngeal lesion. In addition to the importance of the ENT examination for diagnosing laryngeal cancer, it is important to emphasize the oral health status as part of the pre-treatment evaluation, and to plan for any necessary dental care and screen for associated lesions (precancerous lesions: e.g., leukoplakia). The general examination should focus on assessing the patient's overall condition,

nutritional status, and associated comorbidities; alcohol and tobacco use; the local, regional, and systemic spread of the cancer; and, although rare, the search for signs of metastatic spread. At the end of the examination, dated and signed charts summarizing these findings are prepared to optimize treatment indications and modalities and to serve as a reference for evaluating treatment response. Mirror laryngoscopy is a simple method for indirectly examining part of the larynx and the mobility of the vocal cords; currently, this technique is being replaced by nasofibroscopy, which improves image quality through magnification and on-screen display, in addition to offering the ability to record the procedure. Direct laryngoscopy, whether rigid or flexible using a fiber-optic system, with or without general anesthesia, allows for the examination of the various segments of the larynx and hypopharynx, providing a comprehensive macroscopic and functional assessment of lesions. In tumor pathology, direct laryngoscopy is particularly important for the diagnosis of laryngeal cancer: it allows for the description of the tumor's appearance, its location, and its endoluminal extensions into the larynx, hypopharynx, base of the tongue, and even the esophageal orifice; its impact on the mobility of the vocal cords and epiglottis, and, most importantly, to perform a biopsy to confirm malignancy and determine the histological type.

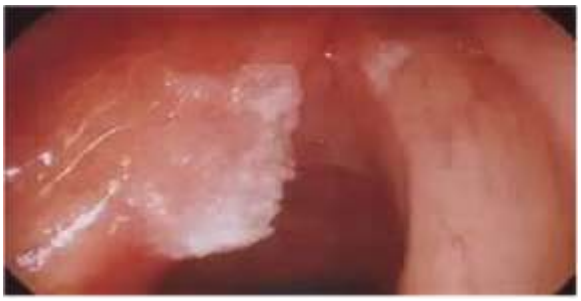

Fig25: appearance of a budding tumor on nasofibroscopy.

From a pathological standpoint, squamous cell carcinoma remains the most common histological type among laryngeal cancers. It accounts for 95 to 98% of cases [17,18]. Other histological types are rare or even exceptional, and their management tends to be quite specific.

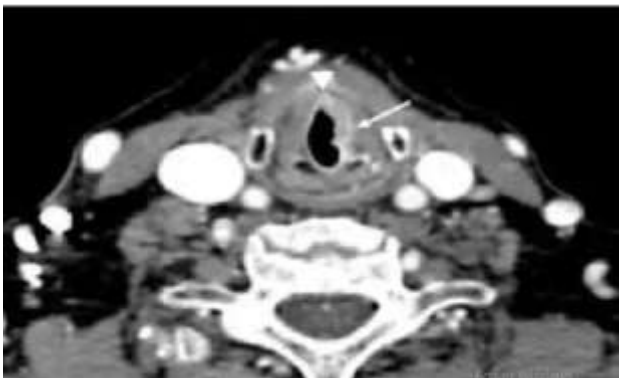

Fig26: Axial CT scan of the neck, with contrast, centered on the glottis, showing thickening of the left vocal cord.

From a radiological perspective, CT scanning remains the gold standard for evaluating the larynx, particularly in cases of neoplastic disease. It provides details on: the tumor's location, size, and its intraluminal and parietal extensions not visualized by endoscopy (Para laryngeal spaces, superior thyroid fossa, cartilages, soft tissues, lower parts of the subglottic region, etc.), Regional lymph node involvement: size, number, bilateral distribution, and the affected lymph node regions to determine the TNM classification. Although the sensitivity of computed tomography remains moderate for the evaluation of laryngeal cartilages (51–71%), invasion of the ventricular bands (59%), and extra-laryngeal tissues (46%), it retains good sensitivity for the evaluation of the pre-epiglottic space (82%), the glottic-subglottic region (74%), and the glottis, with a specificity approaching 80–90%. Computed tomography (CT) is essential for evaluating the therapeutic response (induction chemotherapy or radiation therapy) in addition to

endoscopic findings and during post-treatment follow-up to detect loco regional recurrences and potential complications such as narrowing of the upper aero digestive tract, the presence of fistulas, and other functional problems.

Table4:Distribution according to the extent of tumor spread in laryngeal cancer.

The study	One story	Two stories	Three stories
ACHKARSeries[19]		61%	
KATILESeries[15]	4%	60%	37%
LAAREJSeries[20]	8%	52%	40%
SLIMANISeries[21]	24.5%	33%	42.5%

The use of MRI to assess the extent of tumors of the larynx and hypopharynx is fairly limited. Its disadvantages compared to multi-detector helical CT include long scan times that can cause swallowing artifacts, lower spatial resolution, and imaging focused on a specific area rather than the entire upper aero digestive tract. It is therefore recommended only as a second-line option in specific situations. However, MRI proves useful for detailing the cartilaginous extension of a laryngeal tumor or tumor spread into the depth of the vocal cord. As part of the regional staging workup, pan-endoscopy is an important examination in the evaluation of squamous cell carcinomas of the upper aero digestive tract; it involves exploration of the various compartments of the pharynx for loco regional lesion assessment and, above all, the detection of other cancers of the upper aero digestive tract, although its use is no longer routine in the absence of symptoms. And as part of the assessment for distant metastasis, a thoracoabdominal CT scan is routinely performed to search for secondary sites, particularly in the lungs and liver. The use of PET-CT in assessing the spread of laryngeal cancer remains limited due to the unavailability of the test as a routine procedure, but it remains valuable for follow-up in cases of suspected tumor or lymph node recurrence. An assessment of local-regional and distant spread allowed the tumor to be classified according to the TNM classification. According to the Greater Casablanca registry, laryngeal cancer is classified as stage IV in more than 60% of cases.

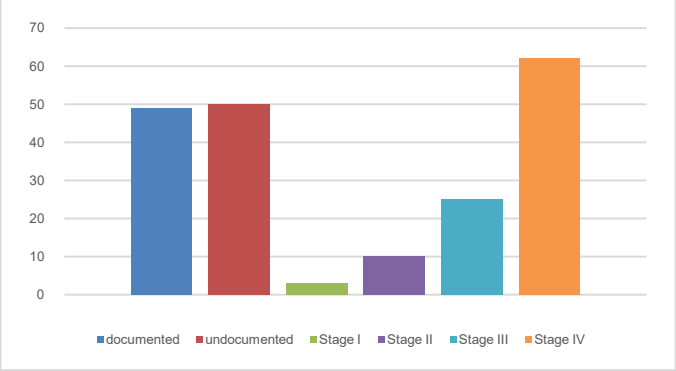

Fig27: Distribution of laryngeal cancer cases by stage at the time of diagnosis.

In terms of treatment, the history of laryngeal preservation has been marked by gradual advances in the management of laryngeal cancers, driven by the desire to preserve laryngeal function while ensuring effective cancer control. At the beginning of the 20th century, total laryngectomy, introduced by Theodor Billroth in 1873, was the standard of care for locally advanced laryngeal tumors. Although effective, this radical approach resulted in permanent loss of laryngeal function, prompting the search for less mutilating alternatives. The first attempts at laryngeal preservation emerged with partial surgery (or conservative surgery), introduced in the 1950s. These techniques, such as supraglottic laryngectomy and vertical laryngectomy, allowed for the selective removal of the tumor while preserving a functional portion of the larynx. However, their use remained limited to early-stage tumors (T1, T2). In the 1970s and 1980s, the emergence of radiation therapy as an effective treatment modality transformed the management of laryngeal tumors.

Radiotherapy alone became an alternative for early-stage tumors, allowing surgery to be avoided in many cases. Locally advanced tumors (T3, selected T4) remained problematic, however, until the introduction of combination therapies.The 1990s marked a major milestone with the development of induction chemotherapy followed by radiation therapy. The PIVOT study of the Veterans Affairs Laryngeal Cancer Study (Veterans Affairs Laryngeal Cancer Study), published in 1991, demonstrated that induction chemotherapy with cisplatin and 5-FU, followed by radiation therapy, could offer survival rates comparable to total laryngectomy while preserving laryngeal function in approximately 64% of cases. This protocol paved the way for wider adoption of non-surgical approaches. In the 2000s, concomitant chemo radiation gradually replaced induction chemotherapy for locally advanced tumors, becoming the standard of care. It has shown higher laryngeal preservation rates, although often associated with increased toxicity. More recently, advances in immunotherapy (anti-PD-1, anti-PD-L1) and precision radiation therapy (IMRT) offer new prospects for laryngeal preservation by targeting tumors more specifically while minimizing side effects. These developments reflect an ongoing trend toward personalized treatments focused on patients' quality of life while maintaining oncological efficacy. The laryngeal preservation strategy aims to maintain the function and anatomy of the larynx in patients with cancerous lesions.

The primary goal is to enable normal swallowing and speech, while avoiding partial or total laryngectomy, which could compromise the patient's quality of life. To achieve this goal, several approaches can be employed: Radiation therapy targets tumors while sparing surrounding healthy tissue. Chemotherapy is used in conjunction with radiation therapy to help reduce tumor size. These two therapeutic methods can be combined in three ways: induction chemotherapy followed by concomitant chemo radiation, concomitant chemo radiation from the outset, or chemotherapy followed by conventional radiation therapy. After treatment, rehabilitation interventions may be implemented to improve voice and swallowing. In summary, the laryngeal preservation strategy is based on a multidisciplinary approach aimed at effectively treating cancer while preserving the organ with as much function as possible.Following the results of early American and European studies that sought to preserve the larynx using induction chemotherapy based on platinum salts and fluorouracil, the three-cycle PF regimen has thus become a standard alternative to radical surgery, particularly for patients without medical contraindications.

The role of this initial chemotherapy is to reduce tumor and lymph node volume, treat micro metastatic disease early, and, above all, test chemo responsiveness in vivo. Studies exploring the addition of taxanes, such as docetaxel, have demonstrated improved disease control and survival compared to the PF regimen alone. Consequently, the TPF regimen (Docetaxel, Cisplatin, 5-Fluorouracil) has become the standard of care for induction chemotherapy in advanced laryngeal and/or hypo pharyngeal cancers, followed by radiation therapy alone, as confirmed by the GORTEC 2000-01 trial [22]. However, it is crucial to manage the toxicity of this intensified regimen, especially in patients in poor general condition and with comorbidities, so as not to delay radiotherapy, which remains the cornerstone of this therapeutic strategy. Other regimens are possible if triple therapy is contraindicated or growth factors are unavailable: PF (cisplatin-5-fluorouracil) or TP (docetaxel-cisplatin)

Table 5: Response to radiotherapy alone versus induction chemotherapy followed by radiotherapy [23].

Randomized trials of induction chemotherapy versus concomitant chemo-radiation.

Study	N	Site	Treatment	Response to chemotherapy	LP	OS
[illegible]	547	Larynx	(1) IC → RT	65% (CR + PR)	71% at 5Y	58% at 5Y
			(2) CCRT	NA	64% at 5Y	55% at 5Y
			(3) RT	NA	64% at 2Y	54% at 5Y
[illegible]	428	Larynx, Hypopharynx	(1) IC → RT	69% (CR + PR)	40% at 2Y	42% at 5Y
			(2) Alternating CCRT	NA	45% at 2Y	44% at 5Y

N: number of patients, LP = larynx preservation, OS: overall survival, CCRT: concurrent chemotherapy and radiation therapy, RT: radiation therapy, IC, induction chemotherapy, NA: not applicable, CR: complete response, PR: partial response, Y: years.

The benefit of induction chemotherapy followed by RT has been demonstrated in various trials evaluating the concomitant administration of chemotherapy with RT, as well as induction chemotherapy followed by concomitant

chemo radiotherapy. Regarding concomitant chemotherapy: This involves administering systemic chemotherapy at the same time as RT from the outset to improve the likelihood of disease control and laryngeal preservation. Although this combination is more effective for disease control and organ preservation in eligible patients, the Radiation Therapy Oncology Group (RTOG) 91-11 trial showed a higher unexplained mortality rate in the RCC-only arm compared to induction chemotherapy followed by radiotherapy; furthermore, the RTOG 91-11 group had better overall survival with equivalent laryngectomy-free survival (LFS).The superiority of concomitant chemotherapy is also supported by updated individual patient data from the Meta-Analysis of Chemotherapy in Head and Neck Cancers (MACH-NC). Based on 3,216 patients with laryngeal cancer, concomitant chemotherapy improves survival compared to neoadjuvant systemic therapy. This robust benefit (HR 0.8; 95% CI 0.71–0.96) raises questions about the protocols used in neoadjuvant therapy, given that the majority of studies opted for PF rather than the standard treatment, which is TPF. Thus, concomitant chemotherapy may be offered to carefully selected patients with locally advanced, resectable stage III and IVA laryngeal cancer using a cisplatin-based regimen at a dose of 100 mg/m² every 21 days.

Sequential chemotherapy allows for a reduction in metastases due to Cl and improved loco regional control provided by concomitant chemotherapy. Unfortunately, the majority of studies (TAX324; Tremplin; ...) have failed to demonstrate the benefit of this treatment modality, regardless of the concomitant protocol administered: carboplatin, cetuximab, or CF. Furthermore, it appears that the patients who might benefit most from sequential therapy are those with large tumors (large T3 and selected T4) and/or advanced lymph node disease with a high risk of distant metastases, provided they opt for the TAX324 trial protocol with TPF as induction therapy and concomitant carboplatin, with three-year survival rates reaching 60% to 80%. Furthermore, a Phase III trial, named DeCide, is currently underway in the United States to further explore this issue. This trial compares RCC treatment using taxane, 5-FU, and hydroxyurea, with or without TPF-based induction chemotherapy [24]. The final results of this study are still pending.

Table 6: Studies supporting the use of carboplatin in patients eligible for cisplatin.

Study	Results
LOKICH J ET AL[25]	Approval of carboplatin as an alternative to cisplatin in cases where cisplatin is contraindicated, given its proven lower nephrotoxicity
HAMAUCHI S ET AL[26]	A 70% remission rate (small retrospective study)
WILKINS AC ET AL[27]	Identical results between the two groups (cisplatin and carboplatin)
VLACICH G ET AL[28]	Weekly carboplatin yielded satisfactory results, with a 3-year survival rate of 82%

External beam radiation therapy is recognized by the French National Authority for Health (HAS) as a first-line curative treatment, equivalent to surgery, and can be used alone or in combination with chemotherapy. It is the cornerstone of laryngeal preservation. Initially, radiation therapy demonstrated its effectiveness in treating localized laryngeal cancer, but the introduction of chemotherapy as a sensitizing treatment and then as induction therapy expanded its indications to include locally advanced stages. Advances in techniques have seen three-dimensional conformal radiotherapy give way to intensity-modulated radiotherapy (IMRT), offering better anatomical targeting of the volume to be irradiated while protecting healthy tissues [29] [30] [31]. This method is now the standard for treating cancers of the upper aero digestive tract. However, it requires more preparation time and more sophisticated equipment than conventional three-dimensional radiotherapy [32]. In the laryngopreservation protocol, conformal radiotherapy is administered in 2 or 3 courses depending on the risk level, which determines the dose to be administered, ranging from 70 Gy for the high-risk volume to 50 Gy for the prophylactic volume.

Dosimetry is the result of treatment planning, and its validation must meet clearly defined objectives: for target volumes, 100% of the PTV must receive at least 95% of the prescribed dose (no under dosing); and to avoid

overdosing, the maximum dose must not exceed 107% of the prescribed dose. And for organs at risk: the treatment plan must adhere to the maximum permissible doses for each organ (maximum dose, average dose, and/or dose per volume). Despite the key role of radiation therapy in laryngeal preservation strategies, it is associated with significant acute and late toxicity. Acute toxicities are predictable and reversible and occur during or after treatment; they mainly include radiation mucositis, which causes dysphagia and odynophagia, leading to malnutrition, dehydration with metabolic disorders, and radiation dermatitis, which remains common despite new techniques due to the proximity of the target volumes (larynx and lymph node regions) to the skin. The use of concomitant chemotherapy introduces additional toxicity, hence the importance of proper management through prevention and early treatment to avoid the potential need to discontinue therapy. In the long term, late toxicities—such as fibrosis, swallowing difficulties, persistent laryngeal edema, cartilage necrosis, xerostomia, and hypothyroidism—can lead to lasting functional complications and impair quality of life and the ability to fully preserve laryngeal function.While new radiation therapy techniques (IMRT, ARC therapy, etc.) offer the advantage of allowing compliance with dosimetric constraints for organs at risk and thereby minimizing the severity and frequency of toxicities, knowledge of the anatomy and natural history of cancer is necessary to avoid compromising oncological outcomes.

Table 7: Acute toxicity, RTOG scale according to Cox et al. [33].

ranks	0	1	2	3	4
Skin	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous membrane	No change over baseline	Injection/may experience mild pain not requiring analgesic	Patchy mucositis that may produce an inflammatory serosanguinous discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Salivary gland	No change over baseline	Mild mouth dryness/slightly thickened saliva/may have slightly altered taste such as metallic taste/these changes not reflected in alteration in baseline feeding behavior,	Moderate to complete dryness/thick, sticky saliva/markedly altered taste		Acute salivary gland necrosis

		such as increased use of liquids with meals			
Pharynx & esophagus	No change over baseline	Mild dysphagia or odynophagial may require topical anesthetic or non-narcotic analgesics/may require soft diet	Moderate dysphagia or odynophagialmay require narcotic analgesics/may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment baseline) requiring N-G feeding tube, iv. fluids or hyperalimentation	omplete obstruction, ulceration, perforation, fistula
Larynx	No change over baseline	Mild or intermittent hoarseness/ cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

Table 8: late-onset toxicity, RTOG/EORTEC scale according to COX et al. [33].

ranks	**0**	**1**	**2**	**3**	**4**
Skin	NONE	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Market atrophy; gross telangiectasia	Ulceration
Mucous membrane	NONE	Slight atrophy and dryness	Moderate atrophy and telangiectas	Marked atrophy with	Ulceration

			ia; little mucous	complete dryness	
Salivary gland	NONE	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
esophagus	NONE	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required	Necrosis /Perforation Fistula
Larynx	NONE	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis

The GETTEC study, although limited to 68 participants, showed less favorable results, focusing solely on T3 tumors [34]. In France, the majority of tumors were glottic or transglottic with fixed mobility, whereas in the United States, two-thirds were supraglottic. Furthermore, a meta-analysis conducted at the Gustave Roussy Institute involving 602 The study of patients revealed 5-year survival rates of 45% for surgery and 39% for induction chemotherapy, with no statistically significant difference. However, 58% of survivors retained a functional larynx (i.e., 23% of patients in the chemotherapy group) [35].

Table 9: Overall 5-year survival in our study in light of other studies.

Study	Country	Year	Number of cases	5-year survival
STENSON ET AL[19]	United States	2015	161	64%
FULLER ET AL [36]	United States	2016	166	67%
WOLF G, FORASTIERE A, ANG K, ET AL [37]	United States	1999	332	45%
SU ET AL [38]	China	2020	366	51%

VETERANS [37]	United States	1991	332	53%
EORTEC [39]	EUROPE	1998	194	38%
OUR SERIES	Morocco	2024	50	71.4%

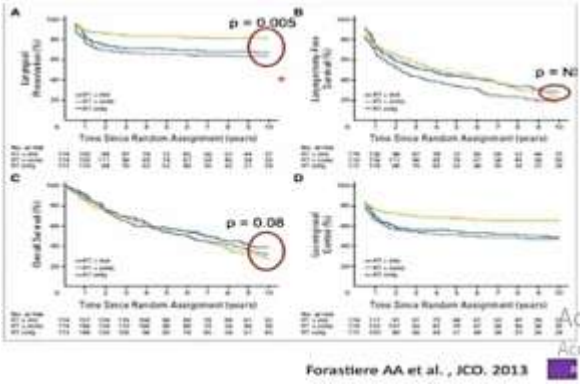

Fig28: Survival curve and laryngeal preservation rate from the RTOG study[40].

The updated RTOG91-11 study, which compared three non-surgical laryngeal prostatectomy (LP) strategies in 520 patients with locally advanced laryngeal cancer, showed, after a follow-up of 10.8 years, no significant difference in overall survival, but showed superiority of concomitantchemoradiotherapy (CRT) in laryngeal preservation and locoregional disease control compared to CRT and radiotherapy alone. However, unexplained mortality was noted in the CRT arm (30.8%) versus 20.8% in CRT and 16.9% in radiotherapy alone [40].

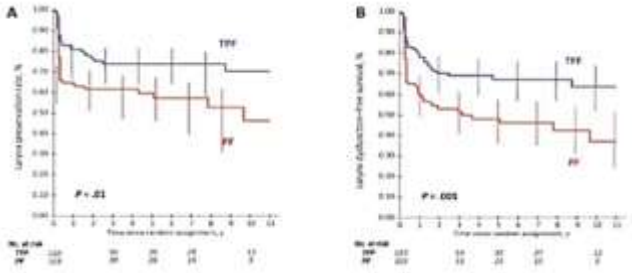

Fig 29: Comparison of laryngeal preservation rates and recurrence-free survival between the two protocols (TPF and PF) in the GORTEC 2000-01 studies [40].

Conclusion:-

Laryngeal preservation strategies involve three main options: induction chemotherapy (IPC), which selects responsive patients to avoid total laryngectomy; concomitantchemotherapy-radiotherapy (CCR), which offers better laryngeal preservation rates using cisplatin or cetuximab in combination with radiotherapy; and the sequential approach, combining both strategies to improve progression-free survival, particularly in patients with large tumors or advanced N status. Follow-up includes regular clinical examinations and imaging to assess response or detect recurrence. Treatment decisions depend on tumor stage, patient status, and available resources, aiming to preserve laryngeal function without compromising overall survival. Current research is exploring less toxic protocols, targeted therapies (anti-EGFR, mTOR inhibitors), and immunotherapy, with the potential to reduce reliance on radiotherapy in the future.

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