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*Clinical Study*

# Intensity-Modulated Radiotherapy with a Simultaneous Integrated Boost Combined with Chemotherapy in Stages III-IV Hypopharynx-Larynx Cancer: Treatment Compliance and Clinical Outcomes

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*Objectives.* Retrospective review of our experience using intensity-modulated radiotherapy with simultaneous integrated boost (SIB-IMRT) combined with chemotherapy as the primary treatment of locoregionally advanced larynx and hypopharynx cancers. *Materials and Methods.* Between September 2008 and June 2012, 60 patients (26 with larynx and 34 hypopharynx cancers) were treated. Our policy was to offer SIB-IMRT plus concurrent cisplatin to patients affected by larynx cancer stage T3N0-N1 and NCT with TPF (docetaxel/cisplatin/fluorouracil) followed by SIB-IMRT to patients with larynx cancer stage T2-4N2-3 or hypopharynx cancer T2-4N0-3. SIB-IMRT consisted in a total dose of 70.95 Gy (2.15 Gy/fraction, 5 fractions/week) to the gross primary and nodal disease and differentiated dosages for high risk and low risk nodal regions. *Results.* Complete remission was achieved in 53/60 (88%) of patients. At a median follow up of 31 months (range 9–67), the rate of overall survival and locoregional control with functional larynx at 3 years were 68% and 60%, respectively. T stage (T1–3 versus T4) resulted in being significant for predicting 3-year freedom from relapse (it was 69% and 35%, resp., for T1–T3 and T4 tumors; $P = 0.04$), while site of primary disease (larynx versus hypopharynx) was not significant ($P = 0.35$). *Conclusion.* Our results indicated that combining SIB-IMRT with induction chemotherapy or concurrent chemotherapy is an effective treatment strategy for organ preservation in advanced larynx/hypopharynx cancer.

## 1. Introduction

Squamous cell carcinoma of the larynx is the most common cancer arising in the head and neck region. Conversely, carcinoma of the hypopharynx is the one with the worst prognosis [1]. Definitive radiotherapy administered concomitantly with chemotherapy (CRT) is the current standard of care [1–3] as an alternative to surgery of head-neck squamous cell carcinoma (HNSCC). Nonetheless, the 5-year overall survival remains under 20% for advanced stage hypopharynx cancer and around 40% for nonglottic larynx cancer [2], indicating a strong need to maximize treatment efficacy to improve outcomes. The variation of survival benefit when chemotherapy was administered concomitantly with radiotherapy was 8% at 5 years as compared to radiotherapy alone in the meta-analyses undertaken by the MACH-NC Study Group [4, 5].

The intensification of treatment modality with the aim of increasing locoregional control, through the use of altered fractionation dose of radiotherapy, has also increased acute toxicity [6], making combination therapy less tolerable.

In fact, subsequent meta-analysis including latest HNSCC trials found an overall survival benefit at 12 months when concurrent chemotherapy was added to standard or altered fractionation radiotherapy with significant survival benefit of 3.4% when a nonstandard fractionation dose and, in particular, hyperfractionation were used (8% of absolute improvement in overall survival) [7, 8]. Nevertheless, the MACH-NC meta-analysis reported a high rate of toxicity and a poor compliance, with 25–30% of patients who failed to complete the treatment program [9] or requested a lengthening of the overall radiotherapy cycle with worsening of the expected outcomes [10].

The role of induction chemotherapy (NCT) in this setting was investigated by the three arms RTOG 91-11 randomized trial in which NCT with cisplatin/fluorouracil (PF) was compared to CRT and with RT alone [11]. NCT followed by radiation resulted in being superior to RT alone in terms of disease-free survival and distant failure but resulted in being inferior to concurrent radiochemotherapy in terms of locoregional control. In the context of NCT, efforts have been made to improve the outcome in this subset of patients maximizing locoregional treatment with combination of RT plus concurrent chemotherapy, but data are controversial. The results from the PARADIGM randomized phase 3 trial reported comparable survivals between aggressive approaches with NCT plus CRT versus upfront CRT [12], reflecting an uncertain role for the intensification of locoregional treatment with CRT after NCT.

Subsequently, the TAX 324 trial comparing two NCT regimens followed by CRT found that docetaxel/cisplatin/fluorouracil-(TPF-) based NCT was superior to PF in terms of survival and progression-free survival [13]. Other studies showed a better outcome with TPF-based NCT in respect to PF regimen [14, 15] and especially in patients with advanced larynx and hypopharynx carcinomas [16]. In this context, sequential chemoradiotherapy with TPF-based NCT may be considered as an alternative to concurrent radio-chemotherapy for markedly advanced cancers of larynx and hypopharynx.

Radiotherapy of HNSCC causes relevant acute and late toxicities, but modern techniques like intensity-modulated radiotherapy (IMRT) have shown to significantly reduce long-term effects [6, 17–19], becoming the reference technique in clinical practice. IMRT allows to achieve a high conformability, high dose gradient, and ability to deliver higher doses sparing normal tissues and limiting toxicity to organs at risk while maintaining treatment effects. In the context of IMRT, the adoption of a simultaneous integrated boost (SIB) allows to reach a moderate hypofractionation scheme 2.15 Gy per fraction to the gross-tumor planning target volume (PTV), with the aim of enhancing locoregional control without compromising safety and treatment compliance. The purpose of this study was to retrospectively review our experience on locoregionally advanced cases of the larynx-hypopharynx cancer using SIB-IMRT combined with concurrent or sequential chemotherapy, depending upon the site and stage of the disease.

## 2. Patients and Methods

We evaluated the efficacy and toxicity of combining a SIB-IMRT schedule with two different chemotherapy combination strategies depending upon disease location and stage in patients with locally advanced larynx and hypopharynx cancers. It is our institutional policy to offer an organ preservation treatment program to all patients with larynx/hypopharynx cancer requiring total laryngectomy, including T4 stages.

Inclusion criteria require patients with a histologically proven untreated larynx or hypopharynx invasive squamous cell carcinoma, stage III or IV according to the American Joint Committee of cancer staging (AJCCS) seventh edition [20], no distant metastases or previous head and neck cancers, and Karnofsky performance status greater than or equal to 70. An additional inclusion criterion requires a serum creatinine level below 120 $\mu$mol/L or a creatinine clearance level higher than 60 mL/min. Response to NCT was evaluated with clinical examination after 2 cycles of chemotherapy; patients presenting disease progression underwent salvage surgery. All remaining patients were treated with radiation after NCT.

Between September 2008 and June 2012, 60 patients completed the chemoradiotherapy schedule. All patients were evaluated by the "Head and Neck Committee" (i.e., a surgeon, an oncologist, and a radiotherapist) at the Aviano National Cancer Institute. All patients were staged with contrast-enhanced head and neck CT scan and 52 patients had also FDG-PET-CT scan examination. Patients affected by larynx cancer stage T3N0-N1 received SIB-IMRT plus cisplatin (IMRT-CCT) on days 1–21 and on day 42 of radiotherapy. Patients with larynx cancer stage T2-4N2-3 or hypopharynx cancer T2-4N0-3 received upfront NCT with three cycles of TPF (docetaxlel 75 mg/m$^2$ day 1, cisplatin 100 mg/m$^2$ day 1, and 5 FU 1000 mg/m$^2$ day 1–5) or PF in the cases of patients unfit for taxane administration, followed by SIB-IMRT (NCT-IMRT). SIB-IMRT was scheduled to start three weeks after the end of chemotherapy.

Radiotherapy for all patients was delivered using a seven or nine-beam SIB-IMRT technique and was carried out either at a 6 MV-linear accelerator or tomotherapy unit. Patients received a prescription dose of 7095 cGy in 33 fractions, at 2.15 Gy each, to the gross primary and nodal tumor (PTV 1), 6270 cGy at 1,90 Gy per fraction to the high risk nodal region (PTV 2), and 5670 cGy at 1,70 Gy per fraction to the low risk nodal region (PTV 3). All patients were treated with IMRT to bilateral necks.

The gross target volume (GTV) was defined as the initial extent of gross tumor and involved lymph nodes, based on clinical examination and imaging at presentation. High-risk subclinical disease included nodal GTV plus a margin for microscopic spread while low risk subclinical disease included uninvolved nodal drainage areas based on the tumor size and site. Margins of 5 mm were added to the GTV to

generate the PTV 1 and to the subclinical high risk and low risk volumes to define the PTV 2 and PTV 3 for prophylactic radiotherapy. Our treatment plan aimed to deliver more than 95% of the prescribed dose to 95% of the PTV. The maximum, minimum, and mean doses were analyzed for PTVs. The volume receiving less than 95% of the prescribed dose and the volume receiving more than 105% of the prescribed dose were evaluated for dose homogeneity and target coverage. Spinal cord, parotid glands, submandibular glands, carotids, thyroid gland, and skin were routinely contoured and evaluated in the dose-volume histograms.

During radiotherapy, all patients were evaluated at least once a week and then followed up every 2 to 3 months for the first year and then every 3 to 4 months for the second year; after 2 years, patients were followed every 6 months. Two months after radiotherapy, all patients received a clinical examination plus computed tomography scan and a positron emission tomography-computed tomography (PET-CT) was scheduled after 4 to 6 months or when clinically indicated. The present protocol did not include planned neck dissection; it was our treatment policy to perform neck dissection on patients who had persistent nodal disease, after cytohistological confirmation.

Overall survival analysis (OS) was computed from the date of diagnosis to the date of death (all causes) or to the last follow-up. Locoregional control (LRC) with functional larynx was computed for all patients from the end of radiotherapy to the date of locoregional relapse or laryngectomy. Freedom from relapse (FFR) was computed to the date of relapse; patients who died without evidence of relapse or treatment related death were censored for calculating FFR. Survival analysis was conducted by the Kaplan-Meier method [21], and the differences between sites of cancer were assessed by log-rank test. Results were considered statistically significant for values of $P \leq 0.05$ (two-tailed test). Primary endpoints were overall survival and locoregional control at 36 months; secondary endpoints were disease free survival, larynx preservation rate, toxicity, and treatment compliance, as well as any adverse treatment event.

## 3. Results

Eight women and 52 men were included in the analysis. Median age was 62 years old, with a 40–81-year range. Up to October 2013, the median follow up for all patients was 31 months (9–67-month range). Table 1 shows patient characteristics. Of the 60 patients, 26 had cancer of the larynx and 34 had cancer of the hypopharynx. There were 29 (48%) patients with stage III and 31 (52%) patients with stage IV. Eleven patients (18%) were classified as stage T4 and 27 (45%) as N2-N3 stage.

Concerning the IMRT-CCT group, 12/15 patients completed the planned 3 cycles of concomitant cisplatin, while two patients received only two cycles due to grades 3-4 mucositis. In the NCT-IMRT group, 40/45 patients received TPF-NCT. The remaining 5 patients were managed with PF because of age >80 years or for relevant concomitant comorbidity. The most common grades 2 to 3 toxicity attributed to NCT was neutropenia (grades 2 and 3 in 31% and 25% of patients, resp.).

Table 1: Clinical characteristics of 60 patients with hypopharyngeal-laryngeal cancer.

| Characteristics | *N* (%) |
|---|---|
| Site | |
| Hypopharynx | 34 (56.7) |
| Larynx | 26 (43.3) |
| Age (years) | |
| Median (range) | 63 (40–85) |
| Gender | |
| Male | 52 (86.7) |
| Female | 8 (13.3) |
| Histological grading | |
| G2 | 31 (51.7) |
| G3 | 29 (48.3) |
| T stage | |
| T2 | 8 (13.3) |
| 7T3 | 41 (68.3) |
| T4 | 11 (18.3) |
| N stage | |
| N0 | 20 (33.3) |
| N1 | 13 (21.7) |
| N2 | 25 (41.7) |
| N3 | 2 (3.3) |
| Tumor stage | |
| III | 29 (48.3) |
| IV | 31 (51.7) |
| Type of treatment | |
| NCT-IMRT[1] | 45 (75.0) |
| IMRT-CCT[2] | 15 (25.0) |

[1]NCT-IMRT: induction chemotherapy followed by IMRT. [2]IMRT-CCT: IMRT with concurrent administration of cisplatin.

Table 2 describes clinical outcomes in terms or treatment response and pattern of recurrence. Of the 60 patients, 53 (88.3%) achieved a complete response at the completion of radiotherapy. Among the 7 patients who presented residual disease, 3 were salvaged with laryngectomy and were alive and disease free at time of analysis, while the remaining 4 patients were deemed not operable and died of the disease. Seventeen patients had disease recurrence (28%); 15 were locoregional and 2 (4%) were distant. Concerning pattern of locoregional failure, 4 patients had regional recurrence, 3 patients had local recurrence, and 8 patients had both local and regional recurrence. Out of the 15 locoregional recurrences 14/15 resulted in being suitable for salvage surgery which consisted in laryngectomy in 7 cases (Table 2). Six patients developed a second primary cancer: three lung cancers, two intestinal carcinomas, and one esophageal cancer; in three patients, it was the cause of death.

Concerning functional outcome and organ preservation, laryngectomy was performed in 14/60 patients (23%), in 13 cases for salvage and in 1 case because of radionecrosis at 8 months after radiotherapy.

Table 2: Distribution of patients, response, and relapses after chemoradiotherapy of 60 patients according to site.

| | Total *N* (%) | Hypopharynx *N* (%) | Larynx *N* (%) | Notes |
|---|---|---|---|---|
| Response | 60 (100) | 34 (56.5) | 26 (43.5) | |
| Complete response | 53 (88.3) | 30 (88.2) | 23 (88.5) | |
| Residual disease | 7 (11.7) | 4 (11.8) | 3 (11.5) | 3/7 patients underwent salvage surgery (all laryngectomies) |
| Relapse | | | | |
| Locoregional relapse | 15 (28.3) | 8 (26.7) | 7 (30.4) | 14/15 patients underwent salvage surgery (7 laryngectomies) |
| Distant metastasis | 2 (3.8) | 2 (6.7) | — | |

Overall, the goal of obtaining the organ preservation with functional larynx without major complications (i.e., PEG tube dependence, persistent grade 2 or 3 dysphagia, pharyngoesophageal stenosis requiring dilatation or permanent tracheostomy) was reached in 43/60 patients (71.6%). The rate of LRC with functional larynx at 2- and 3-years for all patients was 63% and 60%, respectively.

There were no significant differences in toxicity between the IMRT-CCT and NCT-IMRT groups as measured by the frequency of mucositis, feeding tube placement or PEG, and percent weight loss (>10% in 12% of the patients). Odds ratio is 0.55 (95% CI 0.21–17.43), $P = 0.55$.

Concerning patients compliance to SIB-IMRT, all patients completed the radiation program, with 6 patients (10%) requiring a treatment suspension due to toxicity. The causes of radiation suspension were mucosal toxicity, dysphagia, severe sore throat, and weight loss.

Grades 3-4 acute radiation toxicity were registered in 4 cases (6.6%); 1 patient developed sepsis which required hospitalization, 1 patient had significant deterioration of a preexisting liver disease, 1 patient died of myocardial infarction three weeks after the end of radiotherapy, and 1 patient underwent total laryngectomy for radiation necrosis. Concerning late effects, 62% of the patients developed grade ≥2 acute salivary toxicity, though with a partial recovery over time manifesting as objective improvement of late xerostomia-related symptoms.

OS and FFR at 3-years were 68% and 58%, respectively (Figures 1 and 2). We stratified FFR according to the site of disease (larynx versus hypopharynx) and stage (T1–3 versus T4) (Figures 3 and 4). T stage (T1–3 versus T4) resulted in being significant for predicting 3-year freedom from relapse (it was 69% and 35%, resp., for T1–T3 and T4 tumors; $P = 0.04$), while disease site (larynx versus hypopharynx) was not significant for this endpoint ($P = 0.35$).

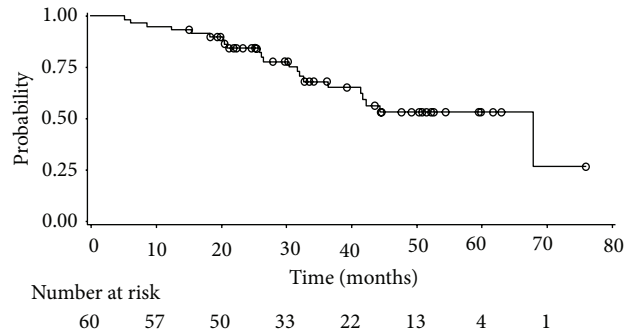


Figure 1: Overall survival of 60 patients with hypopharyngeal-laryngeal cancer.

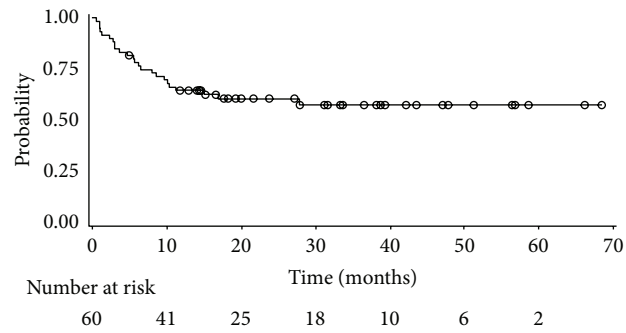


Figure 2: Freedom from relapse of 60 patients with hypopharyngeal-laryngeal cancer.

## 4. Discussion

The association of conventional fractionation radiotherapy with concomitant cisplatin based chemotherapy is considered the reference therapy for locally advanced HNSCC, and this is particularly relevant to cancers of the oropharynx with a 5-year absolute benefit of +8.4% [22].

Latest therapeutic strategies indicate that the use of NCT followed by radiotherapy is a reasonable modality of treatment in patients with bulky lymph nodes to reduce the rate of distant metastases and for cancer of the hypopharynx, with an expected benefit at 5 years of +3.3% [22]. Furthermore, recently updated results of RTOG 91-11 trial in advanced larynx cancer showed that clinical outcomes in terms of laryngectomy-free survival between the PF-based NCT and concomitant chemotherapy arms resulted in being similar [23]. However, it should be noted that trials using TPF as neoadjuvant chemotherapy were not included in the recently updated meta-analysis of chemotherapy in head and neck cancer.

The addition of Taxanes to PF (TPF) when compared to the induction of only two drugs (PF) in TAX 324 study provided a survival benefit for cancer of the larynx [13]. The GORTEC study evaluated the induction with TPF compared to PF followed by radiotherapy in patients with tumors of the

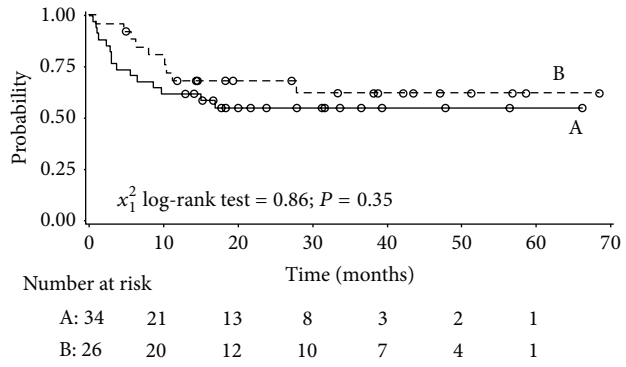


Figure 3: Freedom from relapse of 60 patients with hypopharyngeal-laryngeal cancer by site (A = hypopharyngeal versus B = laryngeal cancer).

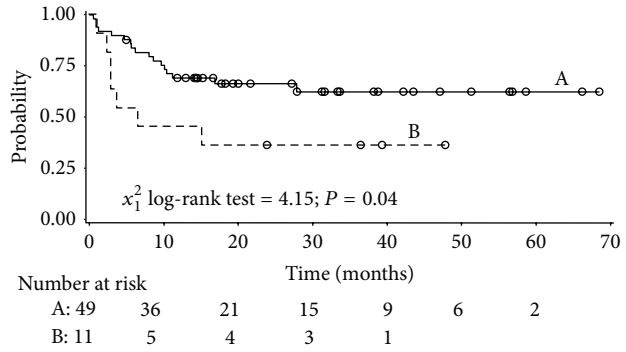


Figure 4: Freedom from relapse of 60 patients with hypopharyngeal-laryngeal cancer by stage (A = T2-T3 versus B = T4).

larynx or hypopharynx for larynx preservation. Preliminary results have shown higher rates of conservation of the larynx with TPF, probably related to the better response rate with TPF (80% against 59% for PF). Based on this result, the TPF schedule is actually considered the standard NCT regimen.

Most studies, investigating the effectiveness of CRT in terms of overall survival, cause specific survival, and organ preservation rate for HNSCC, considered inhomogeneous cohorts of patients with regards to site of disease (in major series of definitive CRT for HNSCC, the tumors were mostly oropharyngeal cancers, and only a limited number were larynx-hypopharynx cancers). The tumor site is recognized as an important prognostic factor for HNSCC; thus, reported clinical results could be biased in spite of the better outcome of oropharyngeal cancer compared to patients with unfavorable sites (larynx-hypopharynx). The report on the survival of cancers of the upper respiratory tract published by AIRTUM 2011 for Northeast Italy (where our Institute is located) reported an overall survival of 62% and 54% at 3 and 5 years, respectively, without distinction of site [24]. During the last ASTRO meeting, Olson et al. [25] presented their data on 25-year survival of 1775 patients affected with HNSCC cancer, diagnosed in British Caledonia between 1986 and 1990. The 5-year survival for hypopharynx cancer was below 20% and for nonglottic larynx cancer approximately 40% [26]. This confirms that survival rates for unselected patients is significantly lower than the published data from cohorts of patients treated in controlled multicenter studies; therefore, it is representative of a patient population object of a careful selection. In our study, we focused on the effectiveness of primary radiation with SIB-IMRT associated with chemotherapy for organ preservation in a subset of consecutive patients with operable locally advanced cancer of the larynx-hypopharynx managed by a mono institutional equip and consistently treated in accordance with shared guidelines.

Our results in terms of survival and functional outcome were satisfactory: the 3-year overall survival resulted in being 68%, with a locoregional control with functional larynx rate of 60% at 3 years. These data resulted comparable with the literature series of IMRT-CCT; Studer et al. [27] reported the results of 123 patients with hypopharynx and larynx cancer treated with IMRT and concurrent chemotherapy with a 3-year survival of 86% and 74% of patients achieving locoregional control with functional laryngopharynx. In another series [28] of patients treated with IMRT and concurrent cisplatin at Memorial Sloan-Kettering Cancer Center, the overall survival rate at two years was 63% with 89% patients who were laryngectomy free. In this study, the advantage was also pointed out in terms of late complications from the adoption of IMRT technique, due to the dose minimization to the esophagus/inferior constrictor musculature, thus, decreasing this late complication [28]. Our results in terms of compliance to SIB-IMRT were fairly good, with 6.6% of the patients reporting severe acute toxicity and all patients completing the radiation program.

Functional outcome of definitive CRT had been compared to total laryngectomy with voice restoration technique in a recent prospective study conducted by the Royal Marsden Hospital Head and Neck Unit and The Institute of Cancer Research showing that patients with locally advanced laryngeal-pharyngeal cancers who receive radical CRT had significantly better voice and good functional outcomes during the 12 months following treatment, when compared with patients who underwent surgery [29]. Our functional outcomes corroborate the effectiveness of CRT as primary treatment for operable larynx-hyphopharynx cancer for organ preservation, keeping surgery as salvage therapy. Therefore, our study confirms that approximately 7 out of 10 patients may benefit from chemoradiotherapy, despite the locally advanced laryngeal-hypopharyngeal lesions. In addition, in these patients, development of acute and late toxicities due to the use of a moderate hypofractionation of the dose through a SIB-IMRT technique was well tolerated. It has been demonstrated that locally advanced head and neck carcinoma has benefited from altered radiotherapy fractionation regimens with a higher total dose in the setting of radiation alone [30]. The Radiation Therapy Oncology Group RTOG 9003 study [6] showed that hyperfractionation or accelerated fractionation with concomitant boost allows to reach a higher locoregional control when compared to conventional fractionation (54.5% versus 46.0% at 2 years). In our previous experience employing IMRT-SIB technique in treatment of nasopharyngeal cancer, we established that

the dose of 215 cGy fraction associated with chemotherapy was well tolerated; further dose increase caused an unacceptable acute and/or late toxicity [31]. In the present study, the association IMRT-concurrent chemotherapy produced acute and chronic toxicities comparable to those produced by NCT-IMRT, and only one patient treated with NCT-IMRT underwent radical laryngectomy for necrosis of the cricothyroid cartilage.

The present study has several limitations with the major among them being its retrospective nature and the adoption of CRT limited to T3-N0-1 larynx cancer, which prevents the comparison between the sequential regimen and CRT for more advanced disease. The main strength of our analysis was the wide use of FDG-PET-CT scans for staging (86% of patients). Also we believe that the homogeneities in the clinical personnel managing the patients account for reducing bias related to patients selection and treatment. The rationale of NCT-IMRT has been to reduce the risk of distant failure in patients with more advanced disease.

In conclusion, in agreement with recent studies, our results showed that three agent NCT-IMRT can have a role in the setting of organ preservation in patients with poor prognostic factor as hypopharynx cancer and markedly advanced disease. Intensification of IMRT with a moderate hypofractionation scheme resulted in being feasible and effective both in association with chemotherapy and part of NCT-IMRT strategies for patients affected with laryngeal and hypopharyngeal cancers, stages III and IV.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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