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Contribution of long-term dysphagia monitoring to first line treatment of head and neck cancer patients

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ABSTRACT

Background: Dysphagia is a serious sequel of head and neck cancer (HNC) and its treatment. This dysfunction is frequent and likely underreported by clinical exam. It seems necessary to assess its global burden during the pre, per and post treatment periods (up to 18 months), regardless of the treatment received.
Methods: This was a prospective cohort study assessing the rate of dysphagia in first-time treated HNC patients, using the deglutition handicap index questionnaire (DHI) and the clinician reporting. Time to occurrence, severity and length of the dysfunction were recorded. The benefit of an evaluation by the patient himself was investigated.
Results: Of 134 evaluable patients: 22 were treated by surgery alone (16.4%), 16 by radiotherapy (RT) alone (11.9%), 3 by chemotherapy (CT) alone (2.2%), 28 by RTCT (20.9%), 31 by induction chemotherapy followed by RTCT (23.1%), 11 by surgery+RT (8.2%) and 23 by surgery+RTCT (17.2%). Patients completed 87.9% of the expected DHI. The dysphagia frequency reported was 92.2% by patient-reporting and 80.9% by clinicians-reporting, whatever the intensity. Self-perceived moderate to severe dysphagia was reported in 69.8% of patients.
Conclusions: Given the strong impact of dysphagia on the quality of life and prognosis of HNC patients, it appears essential to perform screening and systematic monitoring. Using a simple and well accepted questionnaire, such as DHI, which is also well correlated with clinical evaluation, we demonstrated a significant frequency of dysphagia. The use of real-time patient-reported outcomes for its early detection would be an asset, particularly during long-term follow-up.
Registered under ClinicalTrials.gov Identifier no. NCT03068559.

Keywords: Dysphagia, Head-and-neck cancer, Deglutition handicap index, Longitudinal assessment, Deglutition disorders

INTRODUCTION

Swallowing is one of the main functions in which oral, pharyngeal and laryngeal functions cooperate. Tumors in this area, as well as their treatments, can seriously impair the swallowing function, inducing dysphagia, a common complication still badly diagnosed. However, its impact is constant and always negative on the nutritional status, the treatment feasibility and the patients' quality of life.[1]

Many teams have tried to determine prevalence, assessment tools, and dysphagia treatment strategies.[2,3] But few studies were prospective ones and had either a small number of patients or focused on a specific treatment (e.g. intensity modulation radiation therapy, radiochemotherapy). Thus, the duration and evolution of dysphagia irrespective of the treatment administered is not known, although this would greatly facilitate the management of the patient.

For the dysphagia assessment, Kraaijenga et al concluded that there is a need for simple self-evaluation scales compared to professional evaluation ones. The recording of some global indicators of functional status such as weight, dietary changes, nutritional tube dependence, is also advised.[2] Patient–reported measures are commonly applied and provided complementary perspectives.[4]

More recently, Schlinder et al reported a consensus proposition on the management of swallowing difficulties in head and neck patients treated by radiotherapy, that was discussed in the 2013 Milan congress.[5] Six clusters of statements about these difficulties were achieved: 1 and 2/ use of assessment scales: one patient-reported and one operator–reported outcome scale; 3/ taking into account risk factors: research of signs and symptoms of dysphagia consequences (e.g. aspiration); 4/ performing a preventive swallowing dysfunction evaluation (by a nutritionist and a deglutologist). Preventive and therapeutic swallowing exercises are advised and in case of radiation therapy, precautions should be taken (clusters 5 and 6).

The aim of the present prospective study was to assess dysphagia (occurrence, severity, length) in head and neck cancer (HNC), from diagnosis to 18 months after their first line treatment regardless of the treatment. By longitudinal evaluation, we aimed to highlight the contribution of dysphagia early detection and surveillance in the management of a patient treated for HNC.

For this purpose, pursuant to consensus on the dysphagia assessment (compliance with the pre-listed clusters), we used the deglutition handicap index (DHI) questionnaire for dysphagia screening and patient's self-perception (patient-report scale).[6] This was the only questionnaire validated in French evaluating the swallowing function by the patient.[7]

Clinical evaluation according to the common terminology of criteria for adverse events version 4.0 (NCI CTCAE v4.0) issued by the National Cancer Institute and objective measures of swallowing function were also recorded and compared to DHI results (operator-report scale).[8]

METHODS

Study design

This was a prospective, single institution, non-randomized, open study (NCT03068559). It was conducted in accordance with Good Clinical Practice Guidelines and the latest revision of the declaration of Helsinki. The ethics committee approved the study in November 2012. The cancer research center in Nice (France) made the recruitment and the first patient was enrolled in December 2012. Before inclusion, all patients provided written informed consent.

This study was designed to assess dysphagia (rate, severity, length) in the HNC population of patients treated from their 1st line treatment. Patients who met the eligibility criteria were enrolled before the first day of treatment.

The patients were followed up from the first day of treatment, called Day 0, to Day 540. Seven assessments were scheduled after treatment start: Day 30 (1 month), Day 60 (2 months), Day 90 (3 months), Day 180 (6 months), Day 270 (9 months), Day 360 (12 months) and Day 540 (18±1 month). The study flow diagram is presented in Figure 1.

Patient selection criteria

To be enrolled onto the study, patients must have an initial confirmed squamous cell carcinoma of the oral cavity, oropharynx, larynx, nasopharynx or hypopharynx. They must be aged ≥18 and be able to complete questionnaire in French. They must benefit from health insurance. Ineligible patients included: patients treated with prior systemic chemotherapy, radiation therapy or surgery on head and neck area, pregnant or breast-feeding women.

Patient treatment must be validated in a medical multidisciplinary team meeting: surgery, radiotherapy (RT), chemotherapy (CT), radiochemotherapy (RTCT), induction chemotherapy followed by radiochemotherapy (IND+RTCT), surgery followed by radiotherapy (surgery+RT), surgery followed by radiochemotherapy (surgery+RTCT).

The radiation therapy administered was intensity modulated radiation therapy (IMRT) with conventional fractionation. Doses varied from 66 to 70 Gy per treatment modality. Chemotherapy drugs administered were mainly: platin (carboplatin/cisplatin), 5FU, docetaxel. Induction chemotherapy was mainly composed of: platin, docetaxel, 5FU. Chemotherapy combined with radiotherapy consisted mainly of 3 cycles of platin (cisplatin/carboplatin). Cetuximab was used in combination to chemotherapy regimen and for maintenance treatment.

Objective criteria

The primary outcome event was defined as any patient with a dysphagia detected by DHI questionnaire, called self-perceived dysphagia.[6,7] It is composed of 30 statements on deglutition related aspects in daily life (5 point-rating scale: never (0 point), almost never (1 point), sometimes (2 points), almost always (3 points), always (4 points)). It is subdivided in three domains of 10 items: physical (S) (symptoms related to swallowing), functional (F) (nutritional and respiratory consequences) and emotional (E) (psychosocial consequences), to assess the impact of swallowing problems from a functional, symptomatic, and emotional point of view. The

dysphagia severity referred to cut-off values published by Silbergleit et al in 2012: score <16, no dysphagia; 16<score<34, mild dysphagia; 35<score<62, moderate dysphagia; score ≥63, severe dysphagia.[6] In the case of an exclusive enteral nutrition, the DHI questionnaire was not completed as it was not suitable.

Dysphagia reported by investigator using NCI-CTCAE v4.0 grading (called clinical dysphagia) is a secondary outcome measure.[8] Grade 2 is defined as symptomatic and altered eating/swallowing, grade 3 as severely altered eating/swallowing, tube feeding or parenteral nutrition, grade 4 as life-threatening consequences, intervention indicated. Other secondary outcome measures included: comparison of self-perceived moderate/severe dysphagia (DHI questionnaire, score ≥16) and grade 2 to 4 clinical dysphagia; time of dysphagia occurrence, length of dysphagia, necessity and total length of enteral nutrition (EN); adverse events related to dysphagia and treatment toxicities.

Clinical evaluation and follow-up procedures

The dysphagia evaluation was longitudinal throughout the study with DHI questionnaire completion and with the use of the NCI-CTCAE v4.0 criteria during a medical visit planned in routine practice.[8]

In addition to this, the following assessments were performed at inclusion (before Day 0): full oncologic and nutritional exam (body mass index (BMI), % and speed of weight loss, Detsky index, presence of medical support). Patients' medical history, TN tumor stage, presence of associated complications (aspiration with/without cough, pneumopathy) and total dysphagia risk score (TDRS) were also recorded.[9] TDRS is calculated according to tumor size, neck irradiation, weight loss before treatment, tumor site, and treatment modality (conventional radiotherapy, accelerated radiotherapy, concomitant chemoradiation). Consequently, TDRS was not calculated for patients treated by surgery alone, as the score is not applicable for this population.

At Day 30, Day 60 and Day 90, measurements of patient weight, BMI, Detsky Index, presence of associated complications were recorded. The Day 30 visit also comprised in addition systematic dietitian visit.

During the follow-up period (Day 180, 270, 360 and 540), DHI questionnaire was completed at hospital whenever possible, otherwise it was sent by mail to patients. In case of severe dysphagia detected by the questionnaire (score ≥63), a specific visit by a nutritionist was proposed and if required, by a speech therapist to evaluate the presence of functional causes. The dysphagia outcome severity scale (DOSS) was then completed.[10] Swallowing exercises were performed according to local standards.

Biological exams were performed at investigator discretion in case of malnutrition. Swallowing exercises were explained and performed if needed, per local standards.

Statistics

Qualitative data were presented by using absolute and relative frequency. Quantitative data were presented by using mean, standard deviation, median, range and longitudinal evolution of the mean during treatment. All analyses were made on R.3.2.2 software. Statistical analyzes were performed in the Unité d'Epidemiologie et de Biostatistiques at the Centre Antoine Lacassagne, Nice, France.

RESULTS

In 24 months, 143 patients were included in the study. Of those, 2 withdrew their consent, 2 finally refused to be treated and 5 agreed to participate but were not eligible. Consequently, 134 patients were evaluable for analysis. Among these, there were 38 withdrawals throughout the study due to early death (n=34), withdrawal of consent (n=2) and investigator decision (n=2). Thus, at Day 540, 96 patients remained. Patient flow is summarized in the flow diagram (Figure 1).

On the 134 patients enrolled, 22 were treated by surgery alone (16.4%), 16 by RT alone (11.9%), 3 by CT alone (2.2%), 28 by RTCT (20.9%), 31 by induction chemotherapy followed by RTCT (23.1%), 11 by surgery+RT (8.2%) and 23 by surgery+RTCT (17.2%). Concomitant radiochemotherapy administered in the 3 patients' group weighted for 61.2% of the total population. Baseline characteristics are shown in Table 1.

Almost 27% of patients were over 70 years of age, but distribution was different according to the treatment groups (e.g. 81.8% of patients in the surgery+RT group, 4.4% in the surgery+RTCT group). Patients enrolled had predominantly an oropharyngeal tumor (43.7%). Interestingly, oropharyngeal tumors were more numerous in the following groups: RTCT (57.1%) and surgery+RTCT (65.2%). The p16 status was known for only 2/3 of the patients. The proportions of oral cavity, larynx and hypopharynx tumors were equivalent (from 16.3 to 18.5%).

Small tumors (T1/T2N0-N1 stage) represented 26.1% of the population. More than half of the patients in the surgery alone and RT alone groups had a small N0-N1 tumor. The percentage of large tumors with significant nodal invasion (T3/T4N2/T4N3) was 35.8%, mainly treated by chemotherapy alone or in combination (28.4%).

Of note, the TDRS calculated in 112 patients revealed that the enrolled population presented with more than 82% of risk to dysphagia (intermediate risk 34.8% and high risk 47.3%).

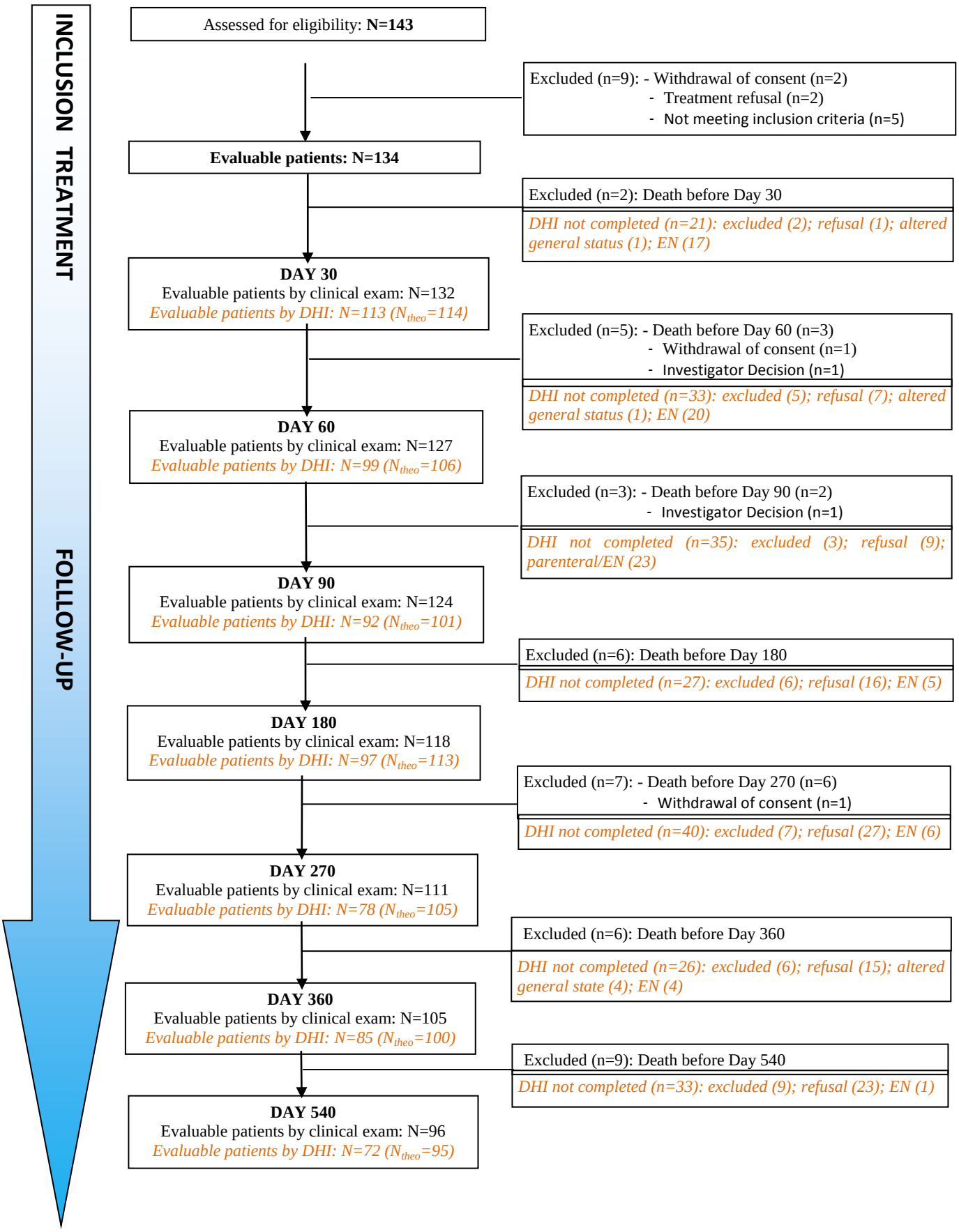

Figure 1: Flow diagram showing number of subjects in each stage of the study and DHI questionnaire completion.
Footnotes: DHI: DHI Questionnaire; EN: Enteral Nutrition ; N_{theo} : Theoretical evaluable patients by DHI.

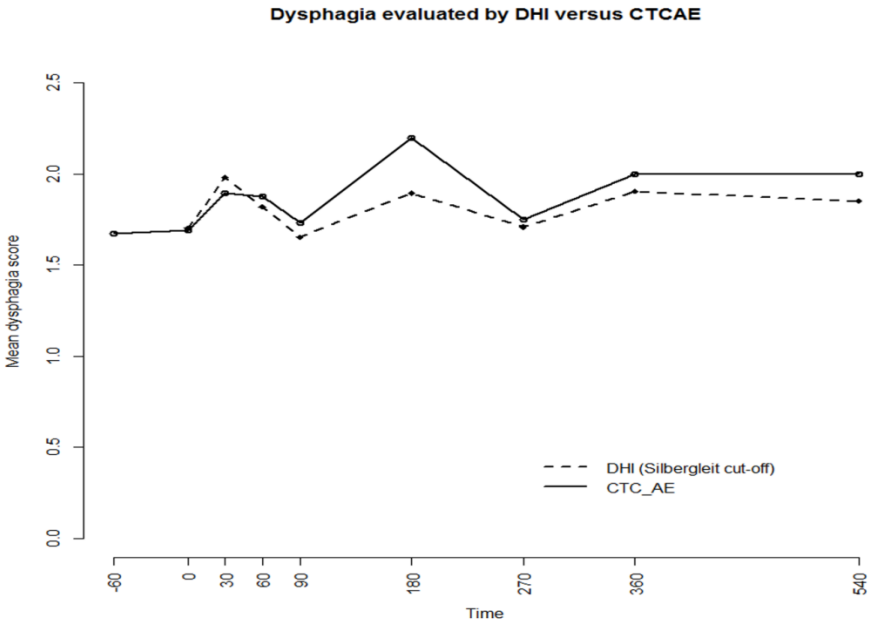

Figure 2: Comparison of self-perceived dysphagia by DHI and clinical dysphagia diagnosed graded by NCI-CTCAE v4.0.

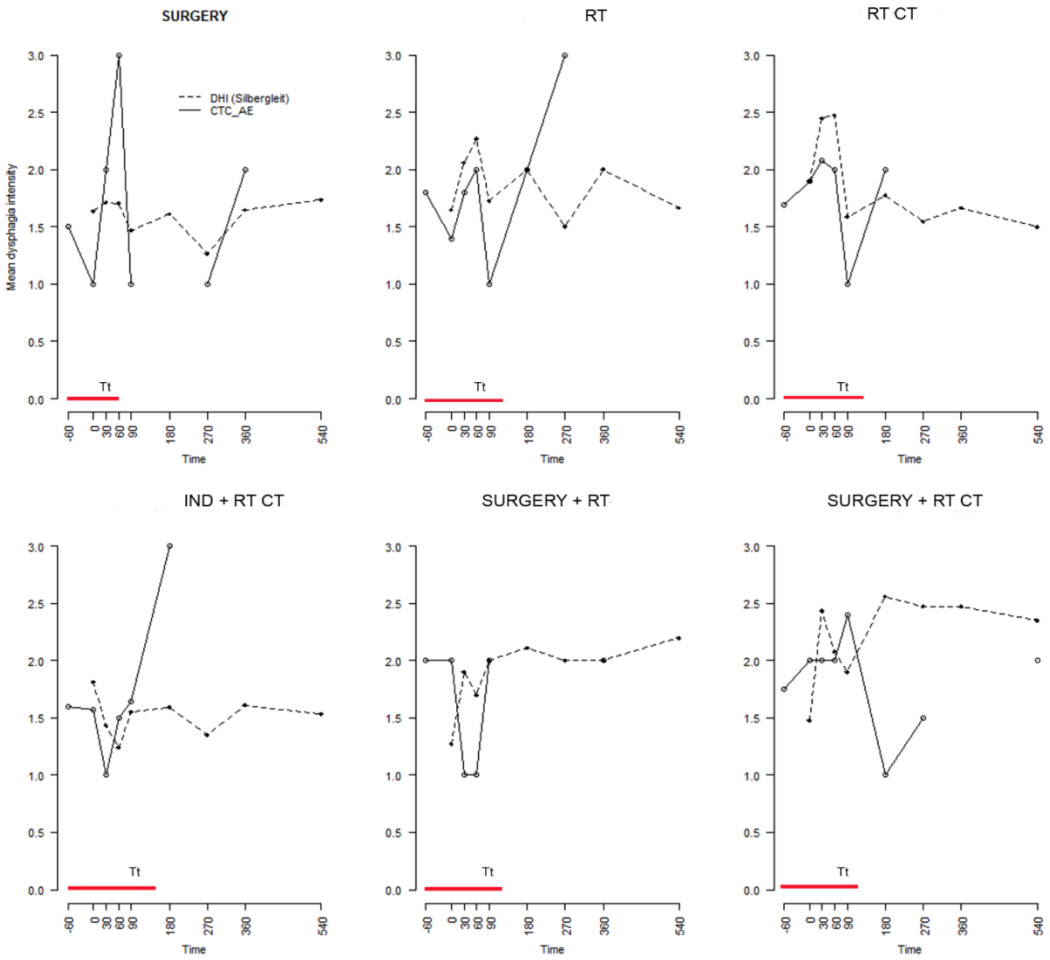

Figure 3: Comparison of self-perceived dysphagia (DHI-reported) and clinical dysphagia graded by NCI-CTCAE v4.0 by treatment groups.

Table 1: Baseline patient characteristics by treatment group (n=134).

Characteristics	Treatment groups (No. patients (%))							
	Surgery (N=22, 16.4%)	**RT** (N=16, 11.9%)	**CT** (N=3, 2.2%)	**RTCT** (N=28, 20.9%)	**IND+ RTCT** (N=31, 23.1%)	**Surgery +RT** (N=11, 8.2%)	**Surgery +RTCT** (N=23, 17.2%)	**Total** N=134
Age (years)								
≤70	14 (63.6)	9 (56.2)	2 (66.7)	20 (71.4)	29 (93.5)	2 (18.2)	22 (95.6)	98 (73.1)
>70	8 (36.4)	7 (43.8)	1 (33.3)	8 (28.6)	2 (6.5)	9 (81.8)	1 (4.4)	36 (26.8)
Primary tumor location								
Oral cavity	11 (50.0)	4 (25.0)	0 (0.0)	2 (7.1)	0 (0.0)	3 (27.3)	5 (21.7)	25 (18.5)
Larynx	5 (22.7)	5 (31.2)	0 (0.0)	6 (21.4)	5 (16.1)	3 (27.3)	1 (4.4)	25 (18.5)
Hypopharynx	0 (0.0)	2 (12.5)	3 (100.0)	3 (10.7)	11 (35.5)	1 (9.1)	2 (8.7)	22 (16.3)
Oropharynx	6 (27.3)	4 (25.0)	0 (0.0)	16 (57.1)	14 (45.2)	4 (36.4)	15 (65.2)	59 (43.7)
HPV Status p16+/known	3/4	3/3	0/0	4/7	3/8	2/4	6/14	21/40 (52.5)
Nasopharynx	0 (0.0)	1 (6.3)	0 (0.0)	1 (3.6)	1 (3.2)	0 (0.0)	0 (0.0)	3 (2.2)
Tumor stage (TN)								
T1 / T2N0-N1	14 (63.6)	9 (56.2)	0 (0.0)	4 (14.3)	2 (6.5)	3 (27.3)	3 (13.0)	35 (26.1)
T3 / T4N0	1 (4.5)	1 (6.3)	0 (0.0)	4 (14.3)	7 (22.6)	2 (18.2)	4 (17.4)	19 (14.2)
T1 / T2N2 / T1N3	3 (13.6)	2 (12.5)	0 (0.0)	7 (25.0)	3 (9.7)	1 (9.1)	9 (39.1)	25 (18.5)
T3 / T4N2 / T4N3	3 (13.6)	3 (18.7)	3 (100.0)	11 (39.3)	19 (61.3)	4 (36.4)	5 (21.7)	48 (35.8)
T3 / T4N1	1 (4.5)	0 (0.0)	0 (0.0)	2 (7.1)	0 (0.0)	1 (9.1)	2 (8.7)	6 (4.5)
TxNx	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Total dysphagia risk score (N=112)								
Low-risk (TDRS 0-9)	NA	11 (68.7)	0 (0.0)	1 (3.6)	3 (9.7)	4 (36.4)	1 (4.4)	20 (17.8)
Intermediate risk (10-18)		1 (18.7)	2 (66.7)	11 (39.3)	9 (29.0)	6 (54.5)	10 (43.5)	39 (34.8)
High risk (>18)		4 (12.5)	1 (33.3)	16 (57.1)	19 (61.3)	1 (9.1)	12 (52.2)	53 (47.3)
Associated complications								
Aspiration with cough	1 (4.5)	2 (12.5)	1 (33.3)	6 (21.4)	3 (9.7)	0 (0.0)	1 (4.4)	14 (10.4)
Aspiration without cough	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)
No aspiration	21 (95.5)	14 (87.5)	2 (66.7)	20 (71.4)	28 (90.3)	11 (100.0)	22 (95.6)	118 (88.1)
Nutritional status (Detsky index)								
A: No malnutrition	16 (72.7)	7 (43.8)	1 (33.3)	19 (67.8)	20 (64.5)	5 (45.4)	17 (73.9)	85 (63.4)
B: Mild malnutrition	3 (13.6)	2 (12.5)	1 (33.3)	1 (3.6)	5 (16.1)	2 (18.2)	1 (4.4)	16 (11.9)
C: Moderate malnutrition	3 (13.6)	3 (18.7)	0 (0.0)	5 (17.8)	1 (3.2)	3 (27.3)	5 (21.7)	20 (14.2)
D: Severe malnutrition	0 (0.0)	4 (25.0)	1 (33.3)	3 (10.7)	5 (16.1)	1 (9.1)	0 (0.0)	14 (10.4)
Enteral nutrition support								
Yes	0 (0.0)	1 (6.3)	1 (33.3)	7 (25.0)	5 (16.1)	0 (0.0)	1 (4.4)	15 (11.2)
No	22 (100.0)	15 (93.7)	2 (67.6)	21 (75.0)	26 (83.7)	11 (100.0)	22 (95.6)	119 (88.8)

TDRS: Total Dysphagia Risk Score; No.: Number; RT: Radiotherapy; CT: Chemotherapy; RTCT: Radiochemotherapy; IND: induction chemotherapy; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events.

Regarding associated complications, only 10.4% of patients had aspiration with cough before treatment start. Concerning nutritional status, 34 patients (25.4%) had moderate to severe malnutrition and only 15 (11.2%) had an enteral nutrition support before treatment. Enteral nutrition support was set up during and after treatment in 90 patients (67.2%).

Self-perceived dysphagia (patients' reporting)

The primary outcome related to the DHI questionnaire, which was well accepted by patients. It has been completed in 71.2% of cases (763/1072). If we consider patients withdrawn during the study, notably due to early death and legitimate reasons for not completing the questionnaire (enteral nutrition and altered general status), the rate of questionnaire completion increased to 87.9%.

Table 2: Self-perceived dysphagia according to the DHI questionnaire by treatment group (N=134).

Characteristics	Treatment groups							
	Surgery (N=22, 16.4%)	**RT** (N=16, 11.9%)	**CT** (N=3, 2.2%)	**RTCT** (N=28, 20.9%)	**IND + RTCT** (N=31, 23.1%)	**Surgery +RT** (N=11, 8.2%)	**Surgery + RTCT** (N=23, 17.2%)	**Total** N=134
Self-perceived dysphagia severity	135 (76.7)	96 (75.0)	7 (12.5)	134 (59.8)	190 (76.6)	69 (78.4)	132 (71.7)	763 (71.2)
Score 0-15 (no dysphagia)	82 (60.7)	46 (47.9)	5 (71.4)	57 (42.5)	131 (68.9)	30 (43.5)	32 (24.2)	383 (50.2)
Score 16-34 (mild dysphagia)	28 (20.7)	22 (22.9)	1 (14.3)	35 (26.1)	29 (15.3)	22 (31.9)	55 (41.7)	192 (25.2)
Score 35-62 (moderate dysphagia)	22 (16.3)	22 (22.9)	0 (0.0)	37 (27.6)	21 (11.1)	15 (21.7)	31 (23.5)	148 (19.4)
At D360	23.5%	41.7%	NA	25.0%	22.2%	42.9%	42.1%	
At D540	26.7%	33.3%	NA	0.0%	13.3%	60%	35.3%	
Score ≥63 (severe dysphagia)	3 (2.2)	6 (6.2)	1 (14.3)	5 (3.7)	9 (4.7)	2 (2.9)	14 (10.6)	40 (5.2)
Time of dysphagia occurrence (score ≥16)	53	50	2	77	59	39	100	380 (49.8)
Pre-treatment	9 (17.0)	8 (16.0)	1 (50.0)	15 (19.5)	15 (48.4)	3 (7.7)	9 (9.0)	60 (15.8)
Day 30	9 (17.0)	11 (22.0)	0 (0.0)	20 (26.0)	8 (13.6)	8 (20.5)	12 (12.0)	68 (17.9)
Day 60	8 (15.1)	7 (14.0)	0 (0.0)	14 (18.2)	5 (8.5)	5 (12.8)	10 (10.0)	49 (12.9)
Day 90	5 (9.4)	6 (12.0)	0 (0.0)	9 (11.7)	9 (15.2)	6 (15.4)	7 (7.0)	42 (11.1)
Day 180	7 (13.2)	6 (12.0)	1 (50.0)	7 (9.1)	9 (15.2)	6 (15.4)	14 (14.0)	50 (13.2)
Day 270	3 (5.7)	3 (6.0)	NA	4 (5.2)	3 (5.1)	4 (10.2)	17 (17.0)	34 (8.9)
Day 360	6 (11.3)	6 (12.0)	NA	5 (6.5)	6 (10.2)	4 (10.2)	16 (16.0)	43 (11.3)
Day 540	6 (11.3)	3 (6.0)	NA	3 (3.9)	4 (6.8)	3 (7.7)	15 (15.0)	34 (8.9)
No. of patients with perceived dysphagia (max. score recorded per patient)	(N (%)) 18 (81.8)	(N (%)) 14 (87.5)	(N (%)) 2 (66.7)	(N (%)) 26 (96.3)	(N (%)) 22 (71.0)	(N (%)) 11 (100.0)	(N (%)) 23 (100.0)	(N (%)) 116 (86.6)
During the pretreatment period	9 (40.9)	8 (57.1)	1 (50.0)	15 (57.7)	15 (68.2)	3 (27.3)	9 (39.1)	60 (51.7)
Score 16-34 (mild dysphagia)	4 (44.4)	5 (35.7)	0 (0.0)	8 (53.3)	7 (46.7)	3 (100.0)	7 (77.8)	34 (56.7)
Score 35-62 (moderate dysphagia)	5 (55.6)	3 (21.4)	0 (0.0)	7 (46.7)	7 (46.7)	0 (0.0)	2 (22.2)	24 (40.0)
Score ≥63 (severe dysphagia)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	2 (3.3)
After Day 0	15 (68.2)	14 (100.0)	1 (50.0)	24 (92.3)	19 (86.4)	11 (100.0)	23 (100.0)	107 (92.2)
Score 16-34 (mild dysphagia)	7 (46.7)	6 (42.8)	1 (50.0)	4 (16.7)	8 (42.1)	3 (27.3)	4 (17.4)	33 (30.8)
Score 35-62 (moderate dysphagia)	7 (46.7)	4 (28.6)	0 (0.0)	15 (62.5)	6 (31.6)	6 (54.5)	12 (52.2)	50 (46.7)
Score ≥63 (severe dysphagia)	1 (6.7)	4 (28.6)	0 (0.0)	5 (20.8)	5 (26.3)	2 (18.2)	7 (30.4)	24 (22.4)
Swallowing dysfunction evaluation (DOSS)								
No. of evaluations	3	5	0	6	5	1	10	30
No. of patients	1	4	0	6	2	1	7	21

At baseline, 60 out of the 134 evaluable patients reported tumor-induced dysphagia (44.8%). There was no dysphagia reported in nasopharynx cancer patients and very little dysphagia development noted in the surgery alone group. Eighteen patients (13.4%) never reported dysphagia. Moderate to severe self-perceived dysphagia was reported by 188 DHI in 81 patients (60.4%) throughout the study.

If we analyze DHI scores equal or superior to 35 found at long-term (Day 360, 12 months and Day 540, 18 months) on total completed questionnaires, results varies between treatment group: self-perceived dysphagia is more frequent in RT group and surgery +RT(CT) groups. Results per treatment group are described in Table 2. All the results expressed in number of patients having had dysphagia (DHI-reported or clinician-reported) refer to the maximum grade reached by the patients.

During the treatment and the first follow-up period (D0 to Day 270 -9 months-), 107 patients reported dysphagia (79.8%) among whom 69% concerned moderate or severe deglutition handicap.

Clinical dysphagia (clinicians' reporting)

Regarding secondary outcomes, dysphagia was reported in 84 patients (62.7%), of whom 73 were grade 2 to 4 (54.5%). Grade 3 or 4 dysphagia was mostly found in RTCT and surgery+RTCT groups. Table 3 summarizes

the results by treatment groups. Pre-treatment dysphagia was present in 42 patients (31.3%). In addition, nearly 50 patients (37.3%) experienced dysphagia during and after treatment, with a maximum grade ≥2 in 3 quarters of cases. Grade 1 dysphagia was reported in the majority (43.4% of total events), followed by grade 2 (37.5%), 3 (17.1%) and 4 (2.0%). At Day 270, Day 360 and Day 540, dysphagia events were rarely reported by standard medical practice.

Table 3: Dysphagia according to NCI-CTCAE by treatment group (N=134).

Characteristics	Treatment groups							
	Surgery (N=22, 16.4%)	**RT** (N=16, 11.9%)	**CT** (N=3, 2.2%)	**RTCT** (N=28, 20.9%)	**IND+ RTCT** (N=31, 23.1%)	**Surgery +RT** (N=11, 8.2%)	**Surgery +RTCT** (N=23, 17.2%)	**Total** N=134
Dysphagia grade	12	20	1	39	38	13	29	152
Grade 1	6 (50.0)	9 (45.0)	1 (100.0)	15 (38.5)	20 (52.6)	6 (46.1)	9 (31.0)	66 (43.4)
Grade 2	5 (41.7)	8 (40.0)	0 (0.0)	15 (38.5)	11 (28.9)	5 (38.5)	13 (44.8)	57 (37.5)
Grade 3	1 (8.3)	3 (15.0)	0 (0.0)	8 (20.5)	7 (18.4)	1 (7.7)	6 (20.7)	26 (17.1)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	1 (7.7)	1 (3.4)	3 (2.0)
Time of dysphagia occurrence								
Pre-treatment	6 (50.0)	5 (25.0)	0 (0.0)	13 (46.4)	12 (38.7)	2 (15.4)	4 (17.4)	42 (31.3)
Day 30	1 (8.3)	5 (25.0)	0 (0.0)	10 (25.6)	5 (13.2)	1 (7.7)	2 (6.9)	24 (15.8)
Day 60	1 (8.3)	5 (25.0)	1 (100.0)	12 (30.8)	1 (2.6)	2 (18.2)	8 (27.6)	30 (19.7)
Day 90	1 (8.3)	1 (5.0)	0 (0.0)	2 (5.2)	4 (10.5)	1 (7.7)	6 (20.7)	15 (9.9)
Day 180	1 (8.3)	2 (10.0)	0 (0.0)	1 (2.6)	14 (36.8)	5 (38.5)	6 (20.7)	29 (19.1)
Day 270	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.6)	2 (5.3)	1 (7.7)	0 (0.0)	5 (3.3)
Day 360	1 (8.3)	1 (5.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.9)	4 (2.6)
Day 540	1 (8.3)	0 (0.0)	NA	0 (0.0)	0 (0.0)	1 (7.7)	1 (3.4)	3 (2.0)
No. of patients with dysphagia (max grade per patient)	n (%) 9 (40.9)	n (%) 12 (75.0)	n (%) 1 (33.3)	n (%) 19 (67.6)	n (%) 21 (67.8)	n (%) 7 (63.6)	n (%) 15 (65.2)	n (%) 84 (62.7)
During the pretreatment period	6 (66.7)	5 (41.7)	0 (0.0)	13 (68.4)	12 (57.1)	2 (28.6)	4 (26.7)	42 (50.0)
Grade 1	3 (33.3)	2 (16.7)	0 (0.0)	5 (26.3)	7 (33.3)	0 (0.0)	1 (6.7)	18 (21.4)
Grade 2	3 (33.3)	2 (16.7)	0 (0.0)	7 (36.8)	3 (14.3)	2 (28.6)	2 (13.3)	19 (22.6)
Grade 3	0 (0.0)	1 (8.3)	0 (0.0)	1 (5.3)	2 (9.5)	0 (0.0)	0 (0.0)	4 (4.8)
After day 0	3 (13.6)	12 (75.0)	1 (33.3)	19 (67.9)	16 (76.2)	5 (71.4)	12 (80.0)	68 (80.9)
Grade 1	2 (66.7)	4 (33.3)	1 (100.0)	3 (15.8)	6 (37.5)	1 (20.0)	1 (8.3)	18 (26.5)
Grade 2	1 (33.3)	5 (41.7)	0 (0.0)	8 (42.1)	5 (31.2)	3 (60.0)	5 (41.7)	27 (39.7)
Grade 3	0 (0.0)	3 (25.0)	0 (0.0)	7 (36.8)	5 (31.2)	0 (0.0)	5 (41.7)	20 (29.4)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (20.0)	1 (8.3)	3 (4.4)
No. patients with enteral nutrition support set up after day 0	20 (90.9)	4 (25.0)	1 (33.3)	22 (78.6)	15 (48.4)	8 (72.7)	20 (86.9)	90 (67.2)

Comparisons of moderate to severe self-perceived dysphagia and clinical dysphagia

The comparison of grade 2 to 4 clinical dysphagia and moderate/severe self-perceived dysphagia demonstrates that complaint of dysphagia in patients was easily reported by the questionnaire, even during long-term follow-up. Indeed, the presence of dysphagia was detected more often by this way than by a clinical visit at distance from the end of the initial treatment.

Evolution over time is presented in Figure 2: a parallel evolution of the intensity of the dysphagia perceived by the patients and those diagnosed by the clinician throughout the study was observed. To note, there are 2 local maximum at Day 30 and Day 180. The first one represents acute toxicity of the treatment. The second one, occurring approximately 3 months after the end of the treatments, could be due to late adverse events. Details of dysphagia evolution by treatment group are presented in Figure 3.

Table 4: Clinical dysphagia length and time of occurrence (n=134).

Characteristics	Treatment groups							
	Surgery (N=22, 16.4%)	**RT** (N=16, 11.9%)	**CT** (N=3, 2.2%)	**RTCT** (N=28, 20.9%)	**IND + RTCT** (N=31, 23.1%)	**Surgery + RT** (N=11, 8.2%)	**Surgery + RTCT** (N=23, 17.2%)	**Total** N=134
Length of clinical dysphagia (days)								
Mean (SD)	243.8 (190.0)	96.7 (97.0)	36	145.4 (110.0)	124.6 (100.0)	117.9 (71.0)	129.3 (130.0)	135.9 (120.5)
Median (range)	180 (54-580)	57 (3-270)	36 (36-36)	140 (28-380)	99 (7-380)	110 (35-230)	78 (7-510)	102 (3-579)
Length of clinical dysphagia occurrence after Day 0 (days)								
Mean (SD)	203.6 (210.0)	84.9 (98.0)	36	96.1 (96.0)	87.0 (88.0)	101.3 (65.0)	128.7 (130)	107.4 (115.1)
Median (range)	120 (24-530)	56 (3-270)	36 (36-36)	56 (15-310)	53 (3-290)	86 (35-230)	64 (7-510)	59.0 (3-530)
Time of clinical dysphagia occurrence after Day 0 (days)								
Mean (SD)	69.7 (82)	26.3 (14)	131.0	20.0 (13.0)	79.6 (59.0)	159.0 (190.0)	59.7 (22.0)	67.4 (79.0)
Median (range)	32.0 (13-160)	24.0 (7-50)	130.0 (130-130)	23.0 (0-36)	97.0 (0-160)	91.0 (27-500)	58.0 (34-100)	42.0 (0-496)
Length of enteral nutrition support throughout the study (days)								
Mean (SD)	59.1 (75)	133.5 (100)	100	147.4 (120)	161.5 (150)	63.7 (45)	207.2 (180)	133.4 (136.6)
Median (range)	28 (5-270)	96 (60-280)	100 (100-100)	110 (11-430)	110 (14-570)	58 (7-140)	140 (6-520)	91 (5-574)

Time of occurrence, length of clinical dysphagia

Results are presented in Table 4. The mean time (SD) and median (range) of dysphagia occurrence after Day 0 were respectively 67.4 (79.0) days and 42 (0-496) days. The mean length (SD) of dysphagia was 135.9 (120.5) days and the median (range) were 102 (3-579) days. If we consider clinical dysphagia reported after the first day of treatment, the mean (SD) length was 107.4 (115) days, with a median of 59 days, illustrating treatment-induced dysphagia.

Results by treatment groups

All results are presented by treatment groups in Tables 1 to 4, allowing direct comparisons. Details are also provided in the supplemental materials part.

The patients' baseline characteristics, particularly nutritional status and the need for enteral support are of interest in estimating the impact of initial dysphagia (Table 1). In Tables 2 and 3, the numbers of patients suffering from moderate or severe dysphagia (patient-reported or clinician-reported) are presented. Enteral nutrition support instituted during and after treatment is also presented. Table 4 summarized results on time of occurrence and length of clinical dysphagia. The delays in initiation and the duration of enteral nutrition after the beginning of treatment make possible to quickly evaluate the impact of treatment-induced dysphagia. These are also presented in this table. To note, only 3 patients were treated by chemotherapy alone. The results of this group are presented in Tables but no comment is given in the text due to the size of the series.

DISCUSSION

This is a data analysis obtained from a prospective, longitudinal study of 134 never treated HNC patients in a single institution. Baseline characteristics were consistent with the literature (tumor stage and site distribution).

Patients were at high risk of dysphagia. In 18 months follow-up, we observed a high DHI completion rate (87.9%). Tumor-induced dysphagia was reported by patient in nearly 45% of case at baseline. During the treatment and the first 9 months, almost 80% of patients perceived dysphagia, among whom 69% relates to moderate or severe deglutition handicap. The intensity of perceived dysphagia has a parallel evolution over time to that diagnosed by the clinician. Two local maximum were observed at day 30 (treatment acute toxicity) and day 180 (treatment late toxicity).

A single prospective and two retrospective studies were conducted on dysphagia evaluation on a population comprising all tumor stages and sites.[11-13] This complication is under-diagnosed and often not treated properly, due to a lack of a uniform "gold standard" evaluation. In our cohort, clinical dysphagia (physician-reported) was present in almost 63% of patients. However, it has been demonstrated that clinical toxicities are under-estimated due to the subjective nature of this symptom.[2,14-16] Indeed, when we analyze self-perceived dysphagia, the frequency increases to 86.6%. The overall percentage of dysphagia in the HNC population demonstrates the importance of a multidisciplinary management of this symptom within an institution. In intensive non-surgical regimen, the reported frequency varied from 30 to 50%.[17-19] Yet, these results are related to long term events only. Likewise, the multivariate analyses performed in 2010 on 8000 head and neck cancer patients demonstrated that 40% of patients, regardless the treatment administered, had a post treatment dysphagia.[20]

Initial dysphagia should be investigated, as the patients who cannot swallow adequately before treatment are at greater risk for chronic swallowing dysfunction after treatment.[21-24] It is then essential to distinguish tumor-induced dysphagia due to an obstruction through a tumor volume or to a tissue infiltration inducing pain and/or trismus, and treatment-associated dysphagia.

In the literature, whenever swallowing function is systematically investigated by videofluoroscopy, at least one abnormality is always found at diagnosis.[12, 25, 26] So Pauloski et al suggested that the presence of tumor is sufficient to disrupt normal swallowing function.[25] Moreover, on his retrospective study of 236 patients, Nguyen concluded that the location (hypopharynx> oropharynx>larynx>oral cavity) and the locally advanced stages (T3/T4, N2/N3) are at risk of severe dysphagia.[12] On the other hand, two of these teams have also collected the self-perceived dysphagia complaint in pretreatment period and reported a 41% frequency on 330 patients and 32.7% on 55 patients.[25,26] This lower result might be related to the Functional Oral Intake Scale (FOIS) chosen, which is limited to a 7-point ordinal scale regarding oral intake only. In our cohort, the patient-perceived dysphagia investigated by the DHI before treatment, reached to a frequency of 44.8%, significantly higher than that found by our clinician's report (31.3%).

Thus, clinical dysphagia and patients' perception did not always concur at this stage of disease: quite always present with instrumental measures or underestimated by the clinician. We can understand that patients with lower stage tumors were less likely to complain about swallowing problems than patients with higher stage tumors. In addition, the patients with oral cavity lesion were less likely to perceive swallowing disorders than those with tumors of the pharynx. These differences in dysphagia perception per tumor site highlight the multidimensional nature of swallowing perception.

However, this discordance is not found per and post treatment phase, during which patients with dysphagia complaints also demonstrate impaired swallowing function on videofluoroscopy.[13]

Regarding dysphagia occurrence after treatment start, we noted 50.7% of dysphagia by clinicians' rating and 79.8% by patients' reporting. If we analyze these figures per treatment group, the results are heterogeneous.

Concerning treatment, the surgical excision, especially of the tongue base or of the pharyngeal or laryngeal structures, causes swallowing disorders with a high aspiration risk. Moreover, the reconstruction techniques, with denervated free flaps, do not insure the function maintenance.[27] Tumor site, T-stage and resection area have given heterogeneous results on the functional impairment frequency. In our study, we found 68.2% of self-perceived dysphagia vs. 13.6% of dysphagia reported by clinicians, all tumor sites combined.

Rogers et al describe 23% of patient-reported long-term swallowing disorders in his oral cavity and oropharyngeal population only.[28] Our population is too small to present significant results per tumor sites, but we found similar long-term dysphagia frequency. The swallowing dysfunction after surgery is obviously important for the patients' quality of life, which can account for this difference.

Likewise, for patients treated by both surgery and radiotherapy, dysphagia frequency varies greatly according to the method of measurement and the type of population: 52% (by University of Washington quality of life questionnaire -UW-QOL-) *vs.* 100% in our cohort by DHI, and 20.7% *vs.* 45.4% reported by clinicians.[9,28] Actually, the interpretation of these results is hazardous and has to be carefully taken into account due to the very low number of patients enrolled in our study (i.e. 11 patients).

Radiotherapy, during its course, is responsible for oral mucositis and xerostomia. Russi et al explained also that the inflammatory edema of the anatomic structures could also lead to a poor synchronization between pharyngeal contraction actions, the opening of the upper esophageal sphincter and larynx closure, with risk of silent aspiration.[19] The doses received by the pharyngeal constrictors, the larynx, crico–pharyngeal and/or the upper esophageal sphincter are strongly correlated with the swallowing disorders.[29] The literature on IMRT suggests that limiting the radiation dose to certain structures may result in favorable swallowing outcomes.[30] In their groups of patients treated by IMRT (RT and surgery+RT), all the patients reported dysphagia after Day 0. The latter was diagnosed clinically in 75% and 71% of cases (RT and surgery+RT respectively), which is compatible with our results (75% of clinical dysphagia and 100% of self-perceived dysphagia by DHI).

Today, radiotherapy is potentialized by a systemic therapy (i.e. chemotherapy or immunotherapy). This combination became the gold standard for the advanced stage tumors which are the most common ones. However, this combination is also the source of a significant dysphagia in both acute and late phases, which has been investigated extensively in studies looking for predictive factors and treatment strategy.[19] Jiang et al have demonstrated that a hypopharyngeal tumor site and the existence of pretreatment dysphagia, are factors of late dysphagia worsening.[31] Moreover, Gluck et al has stressed the importance of considering the toxicities of lower grade (NCI-CTCAE Grades 1 and 2) to have an adequate estimation of the dysphagia burden.[15]

In previous papers, the estimated prevalence of dysphagia during and after chemoradiotherapy/radiotherapy varies from 43% to 64% by instrumental measure.[17,20,32,33] In our study, the frequencies reported were 92.3% (RTCT) to 100% in the RT group by patient-reporting and 67.9% (RTCT) to 75% (RT) by clinicians-reporting, whatever the intensity. Patients treated with chemoradiation had more than 2.5-times-greater odds of dysphagia than those treated with surgery alone.[20]

In the population treated by (chemo)radiotherapy of Wilson et al., self-perceived swallowing has deteriorated significantly post treatment ($p<0.001$).[34] Long-term swallowing outcomes are a key factor of functional success after treatment. They depend on treatment: aspiration, fibrosis, stricture, pneumonia, xerostomia. For example, Kreeft et al noted aspiration rates more than 1-year post surgery ranging from 12% to 50%.[35]

The study of Feng et al using both observer-rated and patient-reported dysphagia has demonstrated an early significant worsening after therapy, followed by a gradual improvement over the next 12 months with a subsequent stabilization during the second year.[36] Wilson et al. have also demonstrated a little improvement from 3 to 12 months, as shown in our results, probably due to the symptoms improvement by the tumor size reduction.[34] Finally, our results showed that radiotherapy is the treatment factor influencing the most significantly the occurrence and duration of clinical dysphagia.

CONCLUSION

Dysphagia associated with HNC is currently not managed homogeneously despite existing consensus. This is mainly due to insufficient detection and evaluation, as well as an incomplete knowledge of its causes, its risk factors, and its evolution.

In total, the heterogeneous nature of studies regarding design, inclusion criteria, treatment modality, and dysphagia assessment makes it difficult to obtain a clear insight in the prevalence and severity of treatment-related dysphagia. Most studies dealing with dysphagia are retrospective studies or conducted on a small number of patients. Few studies focus on the overall management of dysphagia. Given its strong impact on the quality of life and prognosis of these patients (increased risk of complications, reduced response to treatments, and malnutrition), it appears essential to perform screening

and systematic monitoring. In addition, a successful pretreatment swallowing is a positive predictor for most patients to achieve safe, successful post-treatment swallowing

Using a simple and well accepted questionnaire, such as DHI, which is also well correlated with clinical evaluation, we demonstrated a significant rate of dysphagia and the contribution of its long-term monitoring on treatment.

From a clinical point of view, a better knowledge of dysphagia, its mechanisms, incidence, severity, duration, and evolution involve a better monitoring. The use of real-time collection of patient-reported outcomes for early detection of dysphagia would be an asset for the current approach and for long-term follow-up. As a surrogate factor of nutritional status, dysphagia better management could lead to maintenance or improvement of patient nutritional status and thus treatment compliance. Moreover, this good knowledge could also guide physicians to modulate the intensity of treatment according to the prognosis.

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