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## **Routine feasibility of postoperative chemoradiotherapy in head and neck squamous cell carcinoma at high risk of recurrence**

M. Humbert<sup>1,2</sup>, M. De La Losa<sup>1,2</sup>, B. Gery<sup>3</sup>, C. Florescu<sup>3</sup>, J. Thariat<sup>3,4</sup>, A. Rambeau<sup>5\*</sup>

<sup>1</sup> Chirurgie ORL, Centre François Baclesse, Caen, France

<sup>2</sup> Chirurgie ORL, Centre Hospitalier Universitaire, Caen, France

<sup>3</sup> Radiothérapie, Centre François Baclesse, Caen, France

<sup>4</sup> Université de Caen Normandie, France

<sup>5</sup> Oncologie Médicale, Centre François Baclesse, Caen, France

\*Corresponding author:

E-mail: [audrey.rambeau@gmail.com](mailto:audrey.rambeau@gmail.com); [a.rambeau@baclesse.unicancer.fr](mailto:a.rambeau@baclesse.unicancer.fr) (Audrey Rambeau)

Oncologie Médicale, Secteur Orange

Centre François Baclesse

Avenue du Général Harris

14000 Caen

FRANCE

## ABSTRACT

**Objective:** To assess the feasibility in routine practice of postoperative chemoradiotherapy in head and neck squamous cell carcinoma (HNSCC) at high risk of recurrence.

**Method:** A single-center retrospective study recruited all patients receiving postoperative cisplatin chemoradiotherapy for HNSCC at high risk of recurrence. The main endpoints were the rate of complete postoperative chemoradiotherapy and the impact of various clinical factors. Secondary endpoints comprised the impact of completion of therapy on survival and on acute and late toxicity.

**Results:** 106 patients were included. 24.5% showed severe comorbidity. Chemoradiotherapy was complete in 61 patients (57.5%). Radiation therapy was interrupted for >3 days in 16 patients (15.1%). The 3<sup>rd</sup> concomitant cisplatin course could not be implemented in 34 patients (32.1%). Low pre-treatment glomerular filtration rate was significantly associated ( $p=0.003$ ) with treatment interruption; >5% weight-loss during treatment showed suggestive association ( $p=0.026$ ). Completion of treatment was not associated with any significant difference in overall survival ( $p=0.441$ ) or progression-free survival ( $p=0.81$ ). 14.9% of patients showed post-treatment kidney failure; there were 10 cases of osteoradionecrosis (9.4%).

**Conclusion:** The rate of complete postoperative chemoradiotherapy was comparable to that reported in clinical trials, despite frequent comorbidity and poor nutritional status. Early nutritional support is a key factor for treatment under optimal conditions.

**Key-words:** advanced head and neck cancer; postoperative chemoradiotherapy; squamous cell carcinoma; adjuvant treatment; treatment interruption

## **INTRODUCTION**

Adjuvant postoperative radiation therapy has been standard practice in head and neck squamous cell carcinoma (HNSCC) at high risk of recurrence since the 1970s (1). Subsequently, several studies assessed adjuvant chemotherapy in grade III and IV SCC (2,3), and cisplatin associated to radiation therapy was shown to improve results (4). In the early 2000s, phase-III trials by the European Organization for Research and Treatment of Cancer (EORTC) (5) and Radiation Therapy Oncology Group (RTOG) (6) reported overall survival and locoregional control to be improved by 3 concomitant cisplatin courses (D1-D22-D43) at 100 mg/m<sup>2</sup> in HNSCC at high risk of recurrence (7). In 2010, The European Society of Medical Oncology (ESMO) recommended concomitant chemoradiotherapy after grade III-IV HNSCC surgery with microscopically positive margins (R1) and/or extracapsular rupture (8). Interruption of the radiation therapy is mainly due to toxicity (5,6), which is more frequent in case of associated chemotherapy and impairs prognosis, (5,6,9,10).

The main aim of the present study was to assess completion rates for postoperative chemoradiotherapy and the impact of various clinical factors. Secondary aims comprised assessment of the impact of treatment completion on progression-free (PFS) and overall survival (OS), and acute and late toxicity.

## **METHODS**

A single-center retrospective study was performed in the Cancer Center of Caen (France), with approval from the CNIL data protection commission (n°2090357).

All patients receiving postoperative chemoradiotherapy for HNSCC at high risk of recurrence between 2007 and 2016 were included. Surgery was required to have been curative. Patients with history of neck irradiation were excluded.

Criteria for high recurrence risk comprised: lymph-node with capsule rupture, positive margins,  $\geq 3$  positive lymph nodes, perineural invasion and vascular or lymphatic embolism. Screening used the chemotherapy prescription software.

3D conformational radiation therapy used photons and electron beams between 2007 and 2013, or intensity modulation (IMRT) with integrated boost by 6MV photon beam as of 2011. Radiation was delivered in 5 fractions per week at 2 Gy per fraction. Concomitant chemotherapy used cisplatin at 100 mg/m<sup>2</sup> every 3 weeks (D1-D22-D43) associated to hyperhydration and prophylactic antiemetics.

Treatment was considered complete for 3 chemotherapy courses and full radiation dose without  $\geq 3$  days' interruption. Malnutrition was defined by body-mass index (BMI)  $< 18$  kg/m<sup>2</sup> or  $> 5\%$  body-weight loss. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) (12). Comorbidity was considered severe for scores  $\geq 3$  on any item of the Cumulative Illness Rating Scale (CIRS).

Quantitative variables were reported as median [range], and qualitative variables as number and percentage. The Fisher exact test was used to compare categorical variables and Kruskal-Wallis test for continuous variables continues. PFS and OS were estimated following Kaplan-Meier and compared on log-rank test (13). The significance threshold was set at  $p < 0.05$ ;  $p$ -values  $< 0.005$  were considered suggestive [16].

## **RESULTS**

### **Population data**

106 of the 163 patients receiving concomitant cisplatin chemoradiotherapy between 2007 and 2016 were retrospectively included (Figure 1).

There was male predominance: sex ratio 5.6. Median age was 58 years (range, 22-72 years). Table 1 shows clinical characteristics. 27 patients (25.4%) showed malnutrition at diagnosis, 12 of whom received pre-treatment enteral feeding. 26 patients (24.5%) had severe comorbidity: cardiac pathology (n=7), lower-limb arteriopathy obliterans (n=7), high blood pressure (n=5), neurologic pathology (n=3), chronic lymphoid leukemia (n=3), or type-2 diabetes (n=3). 61 patients (67%) were active smokers and/or with active alcohol abuse.

## **Treatment**

Surgery mostly consisted in: oropharyngectomy + neck dissection (n=18), exclusive neck dissection (n=18), interruptive pelvimandibulectomy + neck dissection (n=14), pharyngolaryngectomy + neck dissection (n=14), and partial glossectomy + neck dissection (n=9). Surgery included reconstruction in 34 cases (32%): free flap, n=16; local flap, n=15. Mean interval between surgery and chemoradiotherapy was 8.6 weeks (95% confidence interval (CI), [8.4-9.2]), and was >6 weeks in 96 cases (90.6%). Prognostic factors for chemoradiotherapy comprised: extracapsular rupture (n=80, 75.5%),  $\geq 3$  positive lymph nodes (n=57, 53.8%), R1 margins (n=29, 27.4%), perineural invasion (n=13, 12.3%), vascular embolism (n=8, 7.5%), or lymphatic embolism (n=5, 4.7%).

Scheduled radiation dose was 70 Gy (n=89, 84.8%), 66 Gy (n=11, 10.4%), 62 Gy (n=1), or 60 Gy (n=5, 4.8%). Radiation therapy was conformational in 57 cases (53.8%) and IMRT in 49 (46.2%)

## **Feasibility and acute tolerance of chemoradiotherapy**

Adjuvant treatment was complete in 61 cases (57.5%). Low creatinine clearance was significantly associated with incomplete treatment (p=0,003); >5% body-weight loss during treatment showed suggestive association (p=0.026). (Table 2).

Radiation therapy was interrupted for more than 3 days in 16 patients: grade 3 cutaneomucosal toxicity (n=5), lung infection (n=3), severe weight-loss (n=5), general health deterioration (n=2). Seven patients showed radiodermatitis and 18 showed grade-3 radiomucositis.

72 patients (68.8%) received all 3 cisplatin courses, including 3 with dose reduction at the last course; 27 received 2 courses (25.5%), and 7 only 1. Reasons for interruption comprised: acute kidney

failure (n=16), hepatotoxicity (n=17), general health deterioration (n=4), infection (n=3), severe mucositis (n=3), and ototoxicity (n=2). Five patients showed chemotherapy-induced grade 3-4 vomiting (4.7%). Two showed febrile neutropenia. Patients with initial malnutrition received significantly fewer courses (p=0.001), as did those with low glomerular filtration rate (p=0.001). Enteral feeding during treatment showed suggestive association with incomplete chemotherapy (p=0.022).

37 patients had unscheduled hospital admission (34.9%): acute kidney failure (n=16), enteral feeding (n=5), sepsis (n=6), pain secondary to mucositis (n=5), vomiting (n=3), or other (n=2).

### **Survival**

42 patients died during follow-up, including 23 from disease progression. Five-year OS was 58.9%. Median OS was 84.9 months (Figure 2).

32 patients showed recurrence (30.2%). Median PFS was 12.6 months [range, 1.7-89.4 months]. Five-year recurrence-free survival was 62.7%. Recurrence locations were locoregional only (n=8), metastatic only (n=16), or locoregional and metastatic (n=5). Five patients had a metachronous head and neck secondary location.

Complete chemoradiotherapy was not significantly associated with improved survival (p=0.81 for PFS and p=0.441 for OS). Likewise, non-interruption of radiation therapy was not associated with better PFS or OS (p=0.2872 and p=0.244, respectively), and nor was administration of all 3 chemotherapy courses (p=0.196 and p=0.707, respectively).

### **Late toxicity**

Post-treatment kidney function data were available for 87 patients. Glomerular filtration rate was <60 mL/min in 13 patients, including 3 with <30 mL/min. Risk of chronic kidney failure showed a suggestive relation to age (p=0.019).

Nineteen of the 36 patients (52.8%) requiring enteral feeding during treatment recovered exclusively oral feeding within 3 months; 10 (9.4%) were never withdrawn from enteral feeding.

There were 10 cases of osteoradionecrosis (9.4%). Primary sites comprised oral cavity (n=6), oropharynx (n=3) and oral cavity + oropharynx (n=1). Median post-treatment interval to onset was 14 months [range, 1.4-71.5 months]. Osteoradionecrosis was significantly associated with radiation dose ( $p=0.021$ ) and suggestively associated with pre-treatment malnutrition ( $p=0.021$ ).

## DISCUSSION

The present study assessed the feasibility of postoperative chemoradiotherapy in locally advanced HNSCC displaying negative prognostic features. Treatment was performed as scheduled in 57.5% of cases. All 3 cisplatin courses were administered in 68%. The study population was older than the EORTC and RTOC cohorts (7): median age, 58 years versus respectively 53 and 54 years. Primary sites were mostly oral cavity and oropharynx or, less often, larynx. Tumor stages and rates of R1 margins, capsule rupture and perineural invasion were comparable. Almost a quarter of patients had at least 1 severe comorbidity and would have been excluded from most therapeutic trials. 67% of patients were active smokers and/or alcohol abusers. Even so, treatment was complete in 57.5% of cases. Bernier (5) reported a completion rate of 49%, and a study of exclusive chemoradiotherapy reported 58.9% (14). The only significant risk factor for treatment interruption was low pre-treatment glomerular filtration rate ( $p=0.003$ ), although there was a suggestive relation to >5% weight-loss during treatment ( $p=0.026$ ). Almost one-third of patients required unscheduled hospital admission, mainly for cisplatin nephrotoxicity or radiomucositis-related symptoms.

Kidney function is critical for treatment. One-third of interruptions of chemotherapy directly implicated nephrotoxicity, which also accounted for half of the unscheduled admissions. Factors for cisplatin nephrotoxicity according to Motwani comprise age, dose, high blood pressure and hypoalbuminemia (15). HNSCC requires high cisplatin doses of 100 mg/m<sup>2</sup> in patients who are often malnourished and thus at high risk of toxicity. In the present study, malnutrition was a factor for incomplete chemotherapy; missing retrospective data prevented analysis of blood pressure and hypoalbuminemia.

European (16) and American (17) nutrition Societies recommend close dietary monitoring and oral supplementation to prevent interruption of radiotherapy in HNSCC. Enteral feeding is

recommended in case of high mucositis risk, but intensive nutritional treatment is not necessary (18). In the present study, severe weight-loss and enteral feeding were associated with interruption of chemotherapy. Despite a pre-treatment malnutrition rate of 25.4%, only half of these patients had enteral feeding. Preventing weight-loss during treatment is essential to avoid interruption. Patients with large pharyngeal, oral or supraglottic tumor show a malnutrition risk of 85%, compared to 7% for glottic primaries (19). Therefore, advanced T or N oral or oropharyngeal primary may indicate preventive gastrostomy to avoid malnutrition and dehydration in case of high toxicity risk.

The present retrospective design precluded reliable analysis of late toxicity such as ototoxicity or neurotoxicity. Analysis of causes of death was likewise unable to implicate disease progression. Mortality due to cisplatin toxicity could not be assessed, which was a limitation in the study of late toxicity.

Parson et al. (20) stressed the role of treatment duration: each week of interruption of radiation therapy is associated with 10-12% loss of local control (21,22). Interruption of radiation therapy plays a major role in tumor progression (23–25). Several studies showed that intervals of more than 6 weeks between surgery and initiation of radiation therapy are associated with poorer locoregional control (25,26). Baine et al. reported poorer survival in case of failure to complete concomitant chemotherapy (14). These prognostic factors did not emerge in the present study. The median interval between surgery and initiation of adjuvant therapy was 8.6 weeks, due to the high rates of reconstruction (27) (32%) and of severe comorbidity (24.5%) delaying cicatrization. Nevertheless, 5-year OS and PFS were 58.9% and 30% respectively, comparable to literature reports (5,7,28).

## **CONCLUSION**

The present rate of complete postoperative chemoradiotherapy was comparable to that in previous therapeutic trials. Concomitant cisplatin therapy is feasible as a routine attitude, despite comorbidities. Early nutritional support is a key to preventing weight loss and dehydration and unscheduled hospital admission, enabling chemoradiotherapy to be conducted under optimal conditions.

**Figure 1:** Inclusions flowchart.

**Figure 2:** Progression-free (PFS) and overall survival (OS) according to Kaplan-Meier with 95% confidence intervals

	n (%)
<b>Age</b>	
18-69 years	104 (88.1%)
≥ 70 years	2 (1.9%)
<b>Gender</b>	
male	90 (84.9%)
Female	16 (15.1%)
<b>Performance status (WHO)</b>	
0	47 (44.3%)
1	56 (52.8%)
2	3 (2.8%)
<b>Smoking</b>	
Active	59 (55.7%)
Ex	33 (31.1%)
Never	14 (13.2%)
<b>Alcohol abuse</b>	
Active	49 (46.2%)
Ex	27 (25.5%)
Never	30 (28.3%)
<b>Primary location</b>	
Oral cavity	39 (36.8%)
Oropharynx	30 (28.3%)
Hypopharynx	12 (11.3%)
Larynx	5 (4.7%)
Lymphadenopathy of unknown primary	18 (17.0%)
Multiple	2 (1.9%)
<b>T stage</b>	
T1-2	39 (36.8%)
T3-4	48 (45.3%)
Tx	16 (15.1%)
NA	3
<b>N stage</b>	
N0-1	31 (29.2%)
N2-3	75 (70.8%)
NA	1

**Table 1:** Patient data at diagnosis

WHO: World Health Organization, NA: not available

	Complete treatment	Incomplete treatment	p
Gender (% male)	88.4%	79.5%	0.100
Mean age (years)	55	58	0.239
Severe comorbidity (%)	25%	23.3%	1
Malnutrition at diagnosis (%)	23.3%	29.5%	0.504
Pre-treatment enteral feeding (%)	11.7%	7.1%	0.519
<b>Weight-loss &gt; 5%*</b>	<b>45%</b>	<b>69.7%</b>	<b>0.026</b>
Enteral feeding*	28.3%	52.3%	0.161
<b>Mean creatinine clearance</b>	<b>89.3 mL/min</b>	<b>86.3 mL/min</b>	<b>0.003</b>
Mean scheduled radiation dose	69.0 Gy	69.0 Gy	0.105
IMRT (%)	46.7%	43.2%	0.842
Active smoking (%)	65%	45.4%	0.071
Active alcohol abuse (%)	51.7%	40.9%	0.323

**Table 2:** Clinical factors and treatment completion

IMRT: Intensity Modulated Radiation Therapy

\* during treatment

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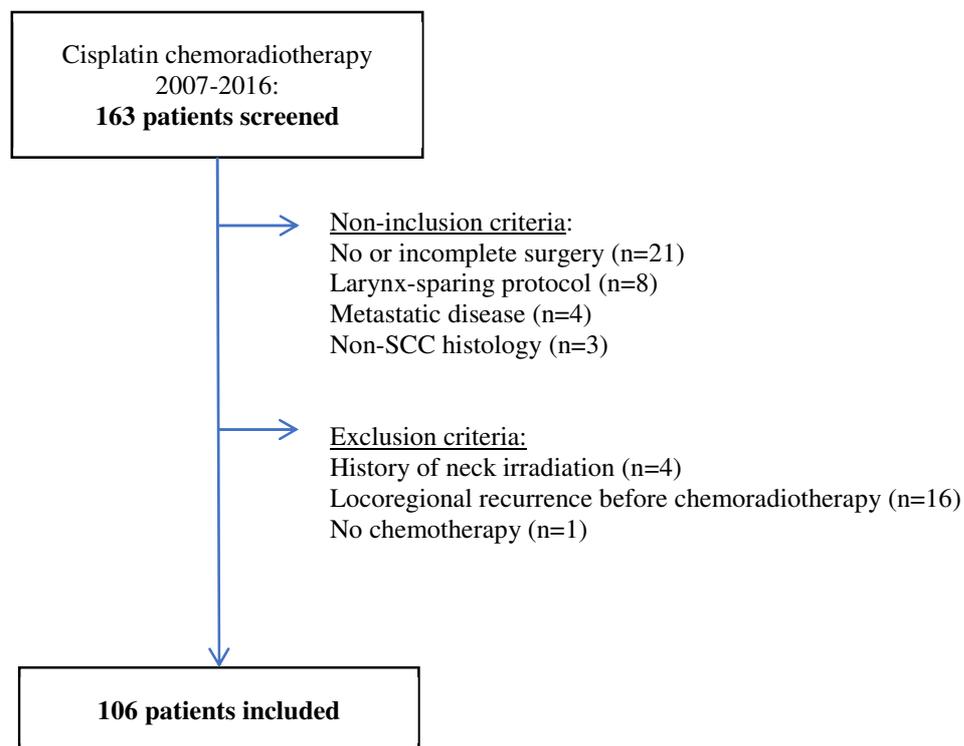
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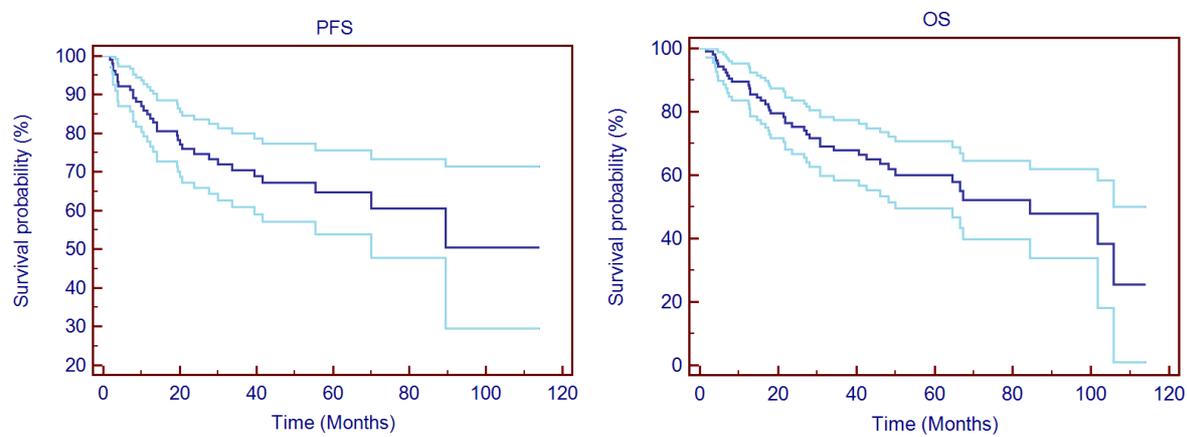
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**Figure 1:** Inclusions flowchart



**Figure 2:** Progression-free (PFS) and overall survival (OS) according to Kaplan-Meier with 95% confidence intervals