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## Original Paper

# Enhanced Acute Toxicity in Oropharynx Carcinoma Treated with Radiotherapy and Concomitant Cisplatin, 5-Fluorouracil and Mitomycin C

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**The aim of this study was to establish the feasibility of giving concomitant radiotherapy and 3 cycles of chemotherapy with cisplatin (CDDP), 5-fluorouracil (5-FU) and mitomycin C (MMC) in locally advanced inoperable oropharyngeal cancer. From March 1990 to September 1993, 27 male patients (mean age 55 years) were included in this study. 3 patients (11%) were T2N0, 19 (70%) T3 (T3N0: $n = 9$, T3N1: $n = 1$, T3N2: $n = 5$, T3N3: $n = 4$), and 5 (19%) T4 (T4N0: $n = 1$, T4N1: $n = 1$, T4N2: $n = 2$, T4N3: $n = 1$). All patients received conventional radiotherapy delivering 70 Gy in 35 fractions and 52 days, and three cycles of chemotherapy starting on day 1, 21 and 42 with CDDP 20 mg/m$^2$ and 5-FU 400 mg/m$^2$ day 1 to day 4, and MMC 10 mg/m$^2$ day 1. With a mean follow-up of 34 months (17–59), 10 patients (37%) were alive and free of disease. Among the 17 other patients, 8 died of cancer. Crude locoregional control rate was 78%, and probability of local control at 1 and 2 years was 85 and 80%, respectively. One- and 2-year survival rates were 48 and 31%, respectively, for both overall and disease-free survival. Grade 3 or 4 mucositis occurred in 22 patients (81%); enteral feeding was necessary for 63%; mean weight loss was 5.7 kg. Grade >2 thrombocytopenia occurred in 11 patients (41%), grade >2 neutropenia in 8 patients (29%), grade >2 anaemia in 4 patients (15%). Febrile neutropenia or aplasia occurred in 5 patients (19%). 2 patients (7%) died during treatment of haematological or infectious complications related to the treatment. Another patient died 1 month after treatment with grade 4 thrombocytopenia and septicaemia. In conclusion, a high complete response rate has been achieved with this concomitant chemo- and radiotherapy, but with severe digestive and haematological toxicity. Addition of MMC to 5-FU and CDDP might have been responsible for this increased toxicity. This therapeutic combination is therefore not routinely feasible.** 

**Key words: oropharyngeal carcinoma, concomitant chemotherapy and radiotherapy**
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## INTRODUCTION

After radiotherapy alone, prognosis of locally advanced and inoperable head and neck cancer remains poor: local control can be achieved in only 40–50% of patients, and 5-year survival rates range from 10 to 25% [1, 2]. An alternative approach to improve these results is to combine chemotherapy and radiotherapy using one or more drugs that have demonstrated their activity in these tumours [3]. Among the different modalities of combined treatment, concomitant chemo- and radiotherapy has the theoretical advantages of spatial cooperation, additive and supra-additive effects and no delay to radiotherapy [4]. Several studies have demonstrated the feasibility of concomitant treatment with radiotherapy and cisplatin (CDDP) associated with 5-fluorouracil (5-FU), and encouraging results in terms of response rate and local control have been reported with this combination [5, 7]. Mitomycin C (MMC) is an active drug in squamous cell carcinoma; its interaction with radiotherapy is attractive because of its specific action on hypoxic cells [4]. Moreover, in a randomised trial including 120 patients treated with pre-operative, post-operative or exlusive radiotherapy for head and neck cancer, Weissberg demonstrated better local control and disease-free survival with concomitant treatment with MMC and radiotherapy compared with radiotherapy alone [8]. The aim of

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this prospective pilot study was to determine the feasibility of the combination of these three drugs CDDP, 5-FU and MMC, concomitantly delivered with conventional radiotherapy for locally advanced inoperable oropharyngeal cancer.

## PATIENTS AND METHODS

From March 1990 to September 1993, 27 patients (all male) were treated with concomitant chemo- and radiotherapy for inoperable oropharyngeal carcinoma without distant metastases. Mean age was 55 years (range 34–69). Patients with World Health Organisation performance status higher than 2, older than 70 or who had previously been treated for oropharyngeal cancer were excluded from the study. 8 patients had a history of cardiovascular disease, 1 of pulmonary tuberculosis, 1 of non-insulin-dependent diabetes and 1 of gastroduodenal ulcer.

After a careful complete clinical examination by the surgeon and the radio-oncologist, all patients underwent a panendoscopy of the upper aerodigestive tract with biopsies and a chest X-ray. Tumour staging was determined according to the TNM classification [9]. Blood cell count, ionogram with creatinine determination and a liver test were systematically performed. 3 patients (11%) had a T2N0 tumour, 19 (70%) a T3 tumour (T3N0: $n = 9$, T3N1: $n = 1$, T3N2: $n = 5$, T3N3: $n = 4$), and 5 (19%) a T4 tumour (T4N0): $n = 1$, T4N1: $n = 1$, T4N: $n = 2$, T4N3: $n = 1$). Patients' characteristics are shown in Table 1.

A second oesophageal tumour was diagnosed in 2 patients; another patient had a carcinoma of the vallecula and the hypopharynx simultaneously.

Treatment consisted of concomitant conventional radiotherapy with CDDP, 5-FU and MMC chemotherapy.

Radiotherapy was performed with Cobalt-60 photons in the supine position. Both the primary tumour and the upper neck lymph nodes were included in two parallel opposed lateral fields. Mid-jugular and supraclavicular nodes were treated with an anterior direct field. For each patient, a simulation of all the radiotherapy fields was systematically performed before treatment was started, after production of a thermoformed mask. Total dose was 70 Gy for the primary tumour and the involved neck nodes, and 44–54 Gy for the non-involved nodes, delivered in 5 fractions of 2 Gy per week, one fraction per day. Dose was prescribed according to the recommendations of the International Commission on Radiation Units and measurements report 50. The dose to the spinal cord was 44 Gy. Boost to the posterior neck nodes was given with direct 9 Mev electron beams. 2 patients underwent brachytherapy for boost to the primary tumour, 1 tumour of the soft palate and 1 tumour of the base of tongue.

*Table 1. Patients' characteristics*

| | *n* | % |
|---|---|---|
| Number of patients | 27 | – |
| Median age in years (range) | 55 (34–69) | – |
| Squamous cell carcinoma | | |
| Well differentiated | 3 | 11 |
| Moderately differentiated | 14 | 52 |
| Not differentiated | 2 | 7 |
| Not known | 8 | 30 |
| Second primary tumour | 3 | 11 |
| Tumour location | | |
| Tonsillar region | 10 | 37 |
| Soft palate-uvula | 8 | 30 |
| Base of tongue-epiglottic area | 7 | 26 |
| Posterior wall | 2 | 7 |

Three cycles of chemotherapy at day 1, day 21 and day 42 were delivered concomitantly with radiotherapy. The regimen was CDDP 20 mg/m$^2$/day in a 1 h perfusion, administered 2 h before radiotherapy and 5-FU in continuous infusion at a dose of 400 mg/m$^2$/day from days 1 to 4. MMC 10 mg$^2$/m$^2$/day was given, intratubular, at day 1.

Stomatologist consultation was systematically performed before treatment started; sodium bicarbonate mouth rinsing solution was always prescribed, as well as sucralphate or energetic liquid feeding as soon as mucositis appeared. In case of grade 3 or 4 mucositis, patients were hospitalised for enteral feeding by nasogastric tube.

*Evaluation methods*

During treatment, patients were examined at least weekly to evaluate acute toxicity and tumour regression. After the end of treatment, they were alternately examined by the radio-oncologist and the surgeon every 3 months during the first year, and then every 6 months. Patients with no detectable clinical disease were considered in complete remission. There was no systematic radiographic study included in the response evaluation. Acute reactions and late complications were scored according to the World Health Organisation recommendations [10]. Survival probabilities were calculated by the Kaplan–Meier method [11]. Survival was measured from the beginning of treatment.

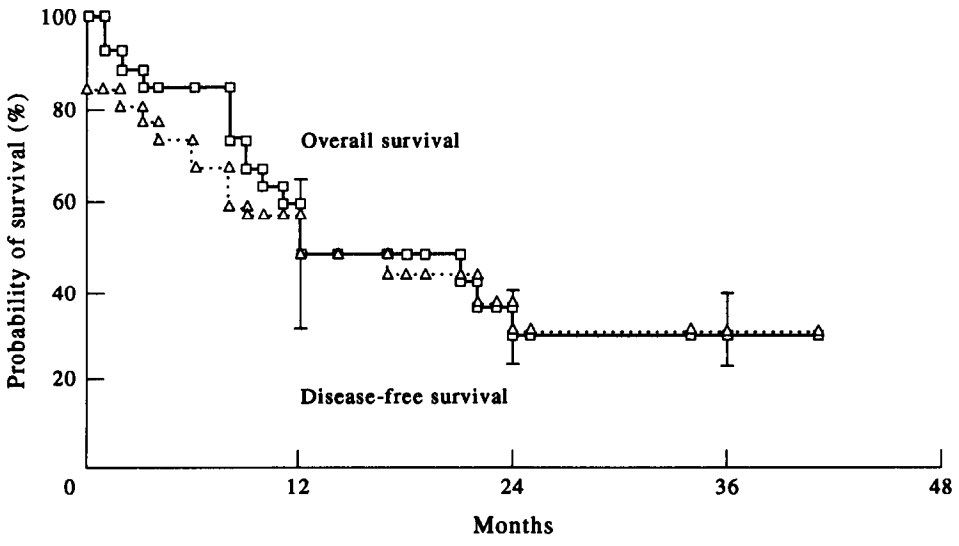
## RESULTS

*Treatment results*

In February 1995, with a mean follow-up of 34 months (range 17–59), 10 patients (37%) were alive with no evidence of disease; 8 patients died of cancer, 3 of treatment-related toxicity, and 6 of intercurrent disease. Among cancer-related deaths, there were 4 locoregional relapses and 4 distant lung metastases. Of the 4 patients for whom local control was not achieved, 3 had a tonsillar region tumour (T3N2M0, T3N3M0, T4N3M0), and the other had a base of tongue tumour T4N2M0. Local control was achieved for 2 of the 3 patients who died of treatment-related toxicity. Among the 6 patients who died of intercurrent disease, 5 were in complete remission. The mean time to death was 16 months (range 8–24) from the beginning of treatment for these 6 patients. The last patient committed suicide during treatment, but was considered to be in complete remission. Local control was thus achieved in 21 of 27 (78%) of the patients. Probability of local control at 1 and 2 years was, respectively, 85 and 80%. Local control rate was 60% for tumours of the tonsillar region (6/10), 71% for tumours of the base of tongue (5 of 7), and 100% for tumours of soft palate (8 of 8) and posterior wall (2 of 2). One- and 2-year survival rates were 48 and 31%, respectively for both overall and disease-free survival, the difference between the two curves being observed only in the first year (Figure 1).

*Treatment toxicity (Table 2)*

22 patients (81%) developed grade 3 or 4 mucositis; mean weight loss was 5.7 kg (9.6% of initial body weight). A feeding




| | | | | |
|---|---|---|---|---|
| Variance | – | 0.009 | 0.001 | 0.001 |
| Patients at risk: | | | | |
| Overall survival | 27 | 16 | 6 | 2 |
| Disease-free survival | 27 | 15 | 6 | 2 |

**Figure 1. Overall and disease-free survival of the 27 patients.**

*Table 2. Toxicity related to the treatment*

| Toxicity | Grade 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Mucosal | 1 | 0 | 4 | 4 | 18 |
| Cutaneous | 3 | 6 | 15 | 3 | 0 |
| Thrombocytopenia | 14 | 1 | 1 | 6 | 5 |
| Neutropenia | 10 | 3 | 6 | 6 | 2 |
| Anaemia | 9 | 9 | 5 | 3 | 1 |
| Infections | 18 | 1 | 6 | 0 | 2 |

tube was necessary for 17 patients (63%). Grade >2 thrombocytopenia occurred in 11 patients (41%), grade >2 neutropenia in 8 patients (30%), and grade >2 anaemia in 4 patients (15%). A febrile hypoplasia or aplasia occurred in 5 patients (19%) during treatment. No pulmonary toxicity was observed.

There were 3 toxic deaths, 2 during treatment and 1 a month after the end of treatment. 1 patient had a T2N0M0 tonsillar region limited tumour, another patient a T3N0M0 tumour of the base of tongue reaching the tonsillar region, and the last patient a T3N2M0 tumour of the tonsillar region, the base of tongue and the ipsilateral wall. The cause of death was in all cases infections and associated with aplasia for 2 patients, grade 4 thrombocytopenia for the patient who died after the end of treatment, and renal failure in 2 patients.

*Compliance to radiotherapy*

24 patients (89%) completed the radiotherapy planned dose. 1 patient died of intercurrent disease during radiotherapy, and 2 other patients died of treatment-related toxicity. Mean tumour delivered dose was 68 Gy (±7 Gy); mean duration of treatment was 49 days (±7 days); a treatment break of more than 7 days was necessary for 4 patients (mean duration: 14 days; range 1–12 weeks).

*Compliance to chemotherapy*

Sixty-six courses of chemotherapy were delivered, which represents an average of 2.4 cycles per patient. Of the patients, 90% were given three or two courses of chemotherapy. Reasons for not delivering chemotherapy were thrombocytopenia for 5 patients, mucositis and performance status deterioration for 2 patients, extravenous administration of chemotherapy for 1 patient and infectious disease for 4 patients. MMC administration at each cycle of chemotherapy was possible for 8 of 15 patients who have been given three cycles (53%), and for 5 of 9 patients who have been given two cycles (56%). 2 patients did not receive MMC. The limiting factor of MMC administration was thrombocytopenia. All except 2 patients were given the full planned dose of CDDP and 5-FU at each course; chemotherapy was stopped on day 2 of the third cycle because of febrile syndrome for 1 patient, and at day 3 of the third cycle for the other patient. Only 30% of the patients (8/27) received the treatment as it was initially planned.

## DISCUSSION

After conventional external beam radiotherapy at a dose of 70 Gy concomitantly associated with three cycles of chemotherapy with CDDP, 5-FU and MMC in locally advanced oropharyngeal cancer, locoregional control was achieved in 78% of the patients. However, it was at the expense of an excessive toxicity, particularly mucosal and haematological, with a toxic death rate of 11%.

The efficacy of chemotherapy in locally advanced non-

metastatic head and neck cancer has been evaluated according to different modalities: induction or neoadjuvant chemotherapy, adjuvant chemotherapy and concomitant chemo- and radiotherapy. Regimens with CDDP alone or in combination with 5-FU are the most commonly used [12].

The sequence of administration of chemotherapy and radiotherapy seems to influence local control and maybe survival, as has been suggested by Merlano, who compared, in a randomised study, four cycles of neoadjuvant chemotherapy with vinblastine, methotrexate and bleomycin followed by conventional radiotherapy with the same chemotherapy regimen administered alternately with radiotherapy [13]. Although results were poor in the two groups, complete response rate and survival were higher in the alternating chemo- and radiotherapy group [13]. Concomitant administration of chemo- and radiotherapy is therefore an interesting concept that presents the advantages of spatial cooperation, additive and supra-additive effect, and no delay to radiotherapy which can avoid the acquisition of induced chemoresistance [4]. The first randomised trials that compared concomitant chemo- and radiotherapy with radiotherapy alone reported an increased toxicity rate in the chemo- and radiotherapy group, but some reported an improvement in local control and disease-free survival, with drugs such as 5-FU [14], bleomycin [15] or MMC [8]; the same conclusions have been drawn from two other randomised trials that compared post-operative concomitant chemo- and radiotherapy with CDDP or MMC to postoperative radiotherapy alone [16, 17]. In order to improve these promising results, pilot studies have tested the feasibility of concomitant radiopolychemotherapy [4]. In spite of an increased toxicity rate, encouraging results in terms of locoregional and survival have been published. With CDDP/5-FU combination, Taylor and coworkers reported a complete response rate of 55% and a median survival at 37 months for 53 patients [6]; these results have been confirmed by another pilot study, with a complete response rate of 77%, a 4-year survival rate of 49% and a median survival of 37 months [5]. Higher than an 80% complete response rate and a 2-year survival rate of 40% have been achieved with 5-FU/MMC combination in non-nasopharyngeal advanced head and neck cancers [18]; with the same drugs, Dobrowski and coworkers reported, in 70 patients, an overall survival rate of 61%, and respective median survival for T2, T3 and T4 tumours of 28, 26 and 9 months later [19].

Although several randomised studies have demonstrated the superiority of concomitant chemo- and radiotherapy over sequential treatment [20] or neoadjuvant chemotherapy [21] on local control, no phase III trial has yet evaluated concomitant radiopolychemotherapy compared with radiotherapy alone; encouraging phase II results justify phase III trials in unresectable head and neck tumours. However, several questions concerning the optimal chemotherapy regimen, as well as the modalities of radiotherapy, remain unsolved.

The role of platinum compounds and especially of CDDP is well established because of its radiosensitising properties demonstrated *in vitro* [4, 22] and *in vivo* [23, 24]; however, whether the addition of 5-FU to CDDP leads to an improvement in therapeutic index is still unproven. Complete response rates, using CDDP alone, ranging from 67 to 95%, are comparable with those reported with a CDDP/5-FU combination, as well as 2-year survival rates around 55% [23, 25, 26]; toxicity is nevertheless lower with CDDP (<1%) than with the CDDP/5-FU (4–9%) [6, 20, 21]. The addition of MMC to these two drugs does not seem feasible because of the induced high toxicity rate, as reported here. Optimal chemotherapy administration is still not clearly established: continuous infusion, bolus, injection frequency. It seems that, for CDDP, continuous infusion is more effective than bolus administration [24].

Debate is still ongoing over conventional, hyperfractionated or accelerated radiotherapy. Encouraging results have been reported in terms of local control and diminution of late sequelae with hyperfractionated or accelerated radiotherapy [27]. In oropharyngeal cancers, base of tongue tumours excepted, a better local control and an improvement in disease-free survival has been achieved after hyperfractionation in comparison with conventional radiotherapy, as reported in the EORTC 22791 randomised trial [28]. Promising results, in terms of local control and survival, in comparison with historical series of patients treated with conventional radiotherapy, have also been reported after hyperfractionated and accelerated radiotherapy [29]. Ongoing phase III trials should determine if conventional radiotherapy still remains the standard treatment modality in head and neck cancers. Combining, therefore, accelerated or hyperfractionated radiotherapy with chemotherapy, which has been demonstrated to improve the response rate without improving survival [2], is another interesting approach in locally advanced head and neck cancers. Several phase II trials have already illustrated the feasibility of concomitant treatment with CDDP/5-FU and hyperfractionated or accelerated radiotherapy, with complete response rates ranging from 71 to 92% [30, 31]. Larger series with longer follow-up are needed to confirm the possible gain of this combined treatment over radiotherapy alone.

In conclusion, this concomitant chemo- and radiotherapy with CDDP, 5-FU and MMC is not to be recommended because of the excessive observed toxicity rate. There was a 11% incidence of treatment-related mortality, and there was no improvement in survival. However, the encouraging local control rate and the promising results reported in the literature justify the development of phase III trials comparing concomitant radiopolychemotherapy with conventional radiotherapy in stages III and IV head and neck cancers. Phase I and II trials are also needed to determine the optimal combined regimen.

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