

# Postoperative Adjuvant Chemoradiotherapy in Older Patients With Head and Neck Cancer

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**Background:** In head and neck cancer, the locoregional failure of patients with positive margins, vascular or perineural invasion, and extracapsular spread is high and results in poor survival.

**Objective:** To assess the effect of adjuvant chemoradiotherapy in improving treatment outcomes among older patients with head and neck cancer.

**Methods:** Forty patients undergoing radical surgery (median age, 73.5 years [range, 70-78 years]) were enrolled (35 men and 5 women; Eastern Cooperative Oncology Group performance status, grade 0-2). Disease sites included the oral cavity (10 patients), oropharynx (12 patients), hypopharynx (8 patients), and larynx (10 patients); pathological TNM classifications included T1 N2 (8 patients), T2 N1-2 (12 patients), T3 N0-2 (8 patients), and T4 N0-2 (12 patients), with the following poor prognostic factors: positive margins (6 patients), vascular invasion (14 patients), neural invasion (16 patients), and extracapsular spread (26 patients). All patients were treated with carboplatin (30 mg/m<sup>2</sup> on days 1-5 of weeks 1, 3, and 5) concomitant

with radiotherapy (54.0 Gy to all risk volumes plus 10.0 Gy to high-risk volumes; 5 daily fractions of 1.8 Gy each per week).

**Results:** No grade 4 toxicity was observed. Grade 3 toxicity included mucositis (10 patients), neutropenia (6 patients), dermatitis (2 patients), and thrombocytopenia (1 patient). The radiotherapy dose administered was 52.0 Gy to all risk volumes plus 10.0 Gy to high-risk volumes. Thirty-two patients (80%) received 3 cycles, 6 (15%) received 2 cycles, and 2 (5%) received 1 cycle. Three-year survival was as follows: disease-free survival, 58%; overall survival, 64%; and local control, 79%.

**Conclusions:** Adjuvant chemoradiotherapy may be successful in fit older patients. The results of adjuvant chemoradiotherapy were better than those observed in a comparable group treated with radiotherapy alone and were similar to those observed in a younger group with the same poor prognostic factors treated with adjuvant carboplatin plus radiotherapy.

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**T**RADITIONALLY, radiotherapy is considered a postoperative adjuvant for squamous cell head and neck cancer in certain situations when the risk of disease recurrence above the clavicles exceeds 20%. Several studies<sup>1-4</sup> have reported a positive correlation between local failure and close or positive surgical margins, extent of lymph node involvement in the neck, extracapsular spread, and lower neck lymph node involvement. Tumor infiltration of the nerves and blood vessels on pathological analysis is considered a poor prognostic factor, although this is somewhat controversial.<sup>5</sup> Adjuvant chemotherapy remains experimental and has not improved overall survival, despite the possibility that distant metastases rates may decrease.<sup>6</sup> In locally advanced head and

neck cancer, randomized trials and recent meta-analyses show a significant benefit of chemotherapy concomitant with conventional radiotherapy vs radiotherapy alone.<sup>7-11</sup>

It would be appropriate to test this approach in patients with earlier stage disease that is resectable but at high risk of recurrence. Six randomized trials of concurrent adjuvant chemoradiotherapy in head and neck cancer have been reported.<sup>12-18</sup> Two randomized trials of mitomycin C as a postoperative adjunct to surgery given concomitantly with radiation have shown better locoregional control in combined treatment, with a trend toward improved disease-free survival.<sup>12,13</sup> Twice-daily radiotherapy with or without concurrent cisplatin and fluorouracil was tested in a small trial; no advantage in time to progression or survival was noted for the group

as a whole.<sup>14</sup> In a small group of patients with extracapsular spread, weekly cisplatin concurrent with radiotherapy produced significantly better median survival and 5-year survival than radiotherapy alone.<sup>15</sup>

Two recent randomized trials have investigated concurrent cisplatin and radiotherapy in an adjuvant setting vs conventional postoperative radiotherapy: the European Organisation for Research and Treatment of Cancer trial reported 3-year locoregional control results (83% vs 64%, respectively), time to treatment progression (66% vs 44%), disease-free survival (59% vs 41%), and overall survival (65% vs 49%), which were all statistically significantly better in patients receiving combination treatment.<sup>16</sup> The Eastern Cooperative Oncology Group (ECOG)/Intergroup trial reported a 2-year disease-free survival advantage (54% vs 42.5%) in the chemoradiotherapy group, with a trend toward better overall survival (63% vs 56.6%).<sup>17</sup>

The problem of cancer management in older persons will become increasingly important. Underestimation of life expectancy in older patients and the perception that radical treatment will be poorly tolerated often lead to the prescription of less than adequate therapy. Adjuvant chemoradiotherapy may improve treatment outcomes but may be associated with significant early and late adverse effects, and applicability to older persons is not well established. This study assesses treatment toxicity, patient compliance, and clinical results in patients 70 years and older who were treated with concomitant adjuvant chemoradiotherapy.

## METHODS

### PATIENTS

Between September 15, 1996, and March 15, 2001, eligible patients were enrolled in a prospective trial of conventional radiotherapy plus concomitant carboplatin in the postoperative setting. All patients had histologically confirmed squamous cell carcinoma of 1 or more of the following sites: oral cavity, oropharynx, hypopharynx, and larynx. Primary surgery was performed with curative intent in lesions classified as T3-T4, any N M0 (except T3 N0 of the larynx, with sufficient safety margins), or any T N2-3 M0.

To target patients at high risk for recurrence, eligibility included 1 or more of the following pathological criteria: final margins positive for invasive disease, any node with extracapsular extension, extensive perineural invasion of a single major nerve trunk or of more than 3 smaller nerve branches, or vascular invasion. Eligible patients had an ECOG performance status of grade 0 to 2 and were 70 years or older. Patients with a history of malignancy, gross residual disease following surgery, or previous chemotherapy or radiotherapy were excluded.

Eligibility criteria included *adequate bone marrow reserve* (hemoglobin, >9 g/dL; platelet count, >100 × 10<sup>3</sup>/μL; and granulocyte count, >1.5 × 10<sup>3</sup>/μL), *adequate renal function* (serum creatinine, ≤2.0 mg/dL [≤177 μmol/L]; and serum urea nitrogen, ≥40 mg/dL [≥14.3 mmol/L]), and *adequate liver function* (bilirubin, <2.0 mg/dL [≤34 μmol/L]; prothrombin and activated partial thromboplastin times ≤1.5 times the normal range; and aspartate aminotransferase and alanine aminotransferase elevated to >3 times the normal range). A complete medical history was taken and physical examination performed be-

fore treatment, including height, weight, and ECOG performance status. Staging procedures of primary lesions consisted of computed tomography of the primary lesion and the neck, endoscopy with biopsy, and chest x-ray. Magnetic resonance imaging was recommended for treatment planning, but not for staging.

All patients were given pretreatment dietary counseling, reinforced weekly. Dietary supplements were available to all patients who were unable to consume adequate calories for maintenance (determined from record of weight change and history). A feeding tube was placed when and if needed, following our institutional protocol. Pretreatment placement of a percutaneous endoscopic gastrostomy tube was not required.

Written informed consent was obtained from all patients at the start of therapy. Patient management was provided by a multidisciplinary team, including head and neck surgeons and medical, radiation, and nurse oncologists. All patients underwent a pretreatment dental evaluation, with appropriate care. Patients were observed by a multidisciplinary team weekly while receiving treatment and immediately afterward, then every 2 months for the first year, every 3 months for the second and third years, and every 6 months thereafter.

### CHEMOTHERAPY

Carboplatin was delivered concurrently with radiotherapy beginning on day 1 of radiation therapy (always on a Monday). Carboplatin was administered intravenously for 15 minutes, 45 to 60 minutes before irradiation. A dosage of 30 mg/m<sup>2</sup> on days 1 through 5 of weeks 1, 3, and 5 was administered.

### RADIOTHERAPY

Radiotherapy was delivered 4 to 6 weeks after surgery, as soon as adequate healing allowed it. Delay longer than 6 weeks was considered a major protocol violation, and the patient was excluded from the trial. To increase treatment accuracy, the patient's head was immobilized with a thermoplastic mask. Orthogonal laser beams were used to assess treatment position reproducibility.

To identify the surgical bed and high-risk anatomical areas, computed tomographic scan was used, with a 1-cm interval between slices. Thirty-nine patients (97%) were treated with a cobalt Co 60 unit using a source with an axial distance of 80 cm, and the remainder with a 6-megavoltage photon linear accelerator. Irradiation techniques varied depending on the location of the primary tumor. In most cases, the surgical bed and upper neck lymphatics were irradiated with wide lateral and parallel opposed isocentric fields. The lower neck, supraclavicular areas, and stoma were treated through a single anterior field. All fields were treated each day. However, other field arrangements were occasionally used (single anterior field, single lateral field, and anterior and posterior wedge pair).

A dose of 54.0 Gy was delivered to anatomical regions at risk of subclinical microscopic disease, while 64.8 Gy was given for positive margins or extracapsular nodal extension. When lateral portals were used, treatment was given with a shrinking field technique: the dose to the spinal cord was limited to 41.4 Gy. The dose given to the posterior cervical field, on one or both sides of the neck, was boosted with 6 to 10 megaelectron volts through a lateral portal. When a single field was used, usually 80% of the dose was delivered with 12 to 16 megaelectron volts and 20% with cobalt Co 60 or 4 to 6 megavoltage of photons.

All patients were treated with 5 daily fractions of 1.8 Gy each per week. The dose was specified and calculated at mid plane along the central axis for lateral opposed beams or at the

point of intersection of the central axis of the beams for other techniques. In patients who were treated with an anterior lower neck field, the dose was specified at a depth of 3 cm. All treatment plans were reviewed in a biweekly planning session attended by the head and neck radiation oncology staff to ensure uniformity of treatment techniques and compliance with protocol guidelines.

### TOXICITY EVALUATION

For the predominantly radiation-related toxicity of mucositis, pharyngeal, and skin toxicity, the Radiation Therapy Oncology Group grading system was used (available at: <http://www.rtog.org/members/toxicity/main.html>). Toxicity was assessed at least once weekly during therapy, every 2 months during the first year, and every 3 months in the second and third years after therapy. Assessment included medical history and physical examination, blood counts, urinalysis, and blood chemistry. If grade 3 or 4 chemotherapy-related toxicity<sup>19</sup> occurred (not including radiation-related toxicity), all chemotherapy was withheld until toxicity had improved by at least 2 grades. Subsequent dosages required a 25% dose reduction. Radiotherapy was not interrupted for chemotherapy-related toxicity, unless the physician in charge deemed it in the patient's best interest for radiotherapy to be delayed. If chemotherapy was delayed for more than 2 weeks, radiotherapy was completed without any further chemotherapy. Delayed doses of chemotherapy were not administered after completion of radiotherapy.

### QUALITY OF LIFE AND STATISTICAL EVALUATION

Time to progression was measured as the time from the first day of therapy until death from the disease or the appearance of new lesions. Survival was measured from the date of entry into the study until death from any cause. Time to progression and survival time were summarized using Kaplan-Meier product-limit curves. The prospective quality-of-life evaluation included the Functional Assessment of Cancer Therapy head and neck version.<sup>18</sup> Patients were assessed before treatment, during treatment, and at 2-month intervals after treatment for 1 year.

## RESULTS

### PATIENT CHARACTERISTICS

Forty patients entered the study (**Table 1**). The median age was 73.5 years (range, 70-78 years). Thirty-five patients (88%) were male. Twenty-six patients had an ECOG performance status of grade 0 (65%), 12 patients (30%) had a grade of 1, and 2 patients (5%) had a grade of 2. The primary sites were as follows: oral cavity (10 patients [25%]), oropharynx (12 patients [30%]), hypopharynx (8 patients [20%]), and larynx (10 patients [25%]). The pathological TNM classifications were as follows: T1 N2 (8 patients [20%]), T2 N1-2 (12 patients [30%]), T3 N0-2 (8 patients [20%]), and T4 N0-2 (12 patients [30%]).

The most frequent poor prognostic factor was extracapsular disease, reported in 26 patients, followed by neural invasion (16 patients), vascular invasion (14 patients), and positive margins (6 patients). Some patients had 2 or more poor prognostic factors.

**Table 1. Characteristics in 40 Patients\***

Characteristic	Value
Age, median (range), y	73.5 (70-78)
Sex	
Male	35 (88)
Female	5 (13)
ECOG performance status	
0	26 (65)
1	12 (30)
2	2 (5)
Site of disease	
Oral cavity	10 (25)
Oropharynx	12 (30)
Hypopharynx	8 (20)
Larynx	10 (25)
Pathological TNM classification	
T1 N2	8 (20)
T2 N1-2	12 (30)
T3 N0-2	8 (20)
T4 N0-2	12 (30)
Poor prognostic factors, No.	
Positive margins	6
Vascular invasion	14
Neural invasion	16
Extracapsular disease	26

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

\*Data are given as number (percentage) unless otherwise indicated.

**Table 2. Toxicity Among Patients**

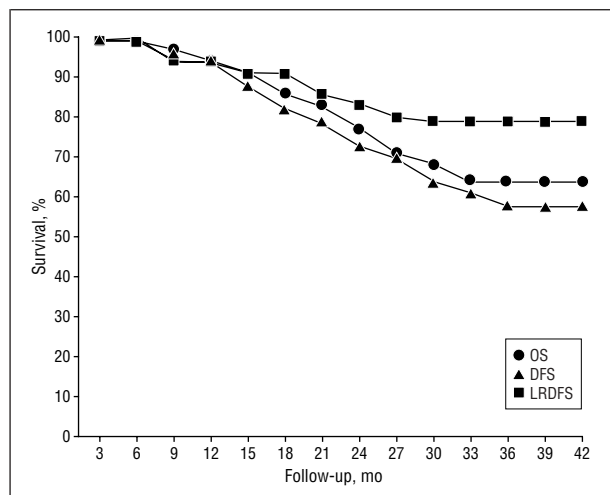
Toxic Reaction	Toxicity Grade, No. (%)*		
	1	2	3
Neutropenia	12 (30)	8 (20)	6 (15)
Anemia	12 (30)	6 (15)	0
Thrombocytopenia	8 (20)	4 (10)	1 (3)
Nausea or vomiting	6 (15)	3 (8)	0
Mucositis	10 (25)	16 (40)	10 (25)
Dermatitis	8 (20)	6 (15)	2 (5)
Peripheral neuropathy	6 (15)	3 (8)	0

\*No grade 4 toxicity was observed.

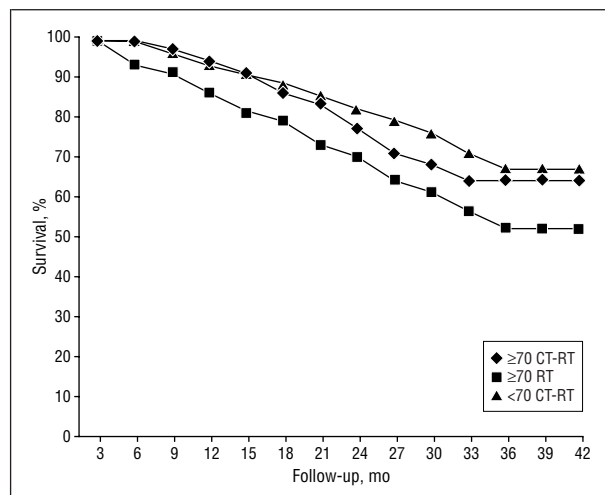
### TOXICITY

All patients were evaluated for toxicity, which is reported in **Table 2**. No grade 4 toxicity was observed. Of the 40 patients, 10 (25%) developed grade 3 mucositis, which was the most frequent toxic reaction. Grade 3 neutropenia and thrombocytopenia were observed in 6 patients (15%) and 1 patient (3%), respectively. Grade 3 dermatitis was observed in 2 patients (5%). Patients with grade 3 mucositis required a median of 2 weeks after radiotherapy for clinical recovery. Other toxic reactions included xerostomia in 22 patients (55%). All immediate toxic reactions were managed on an outpatient basis. No patient required hospitalization for adverse events.

Before starting treatment, 3 patients had a percutaneous endoscopic gastrostomy tube and 2 had a nasogastric tube. Six patients (15%) chose to undergo nasogastric tube placement in anticipation of severe dysphagia. No percutaneous endoscopic gastrostomy tube placement was required



**Figure 1.** Overall survival (OS), disease-free survival (DFS), and locoregional disease-free survival (LRDFS) among patients in this study.



**Figure 2.** Overall survival of patients 70 years or older treated with adjuvant chemoradiotherapy ( $\geq 70$  CT-RT) or radiotherapy alone ( $\geq 70$  RT) and overall survival of patients younger than 70 years treated with adjuvant chemoradiotherapy ( $< 70$  CT-RT).

**Table 3. Characteristics of Patients 70 Years and Older vs Younger Than 70 Years Treated With Adjuvant Chemoradiotherapy\***

Characteristic	Age, y	
	$\geq 70$	$< 70$
Age, median, y	73.5	58
Sex		
Male	35 (88)	33 (83)
Female	5 (13)	7 (18)
ECOG performance status	0	0
Site of disease		
Oral cavity	10 (25)	12 (30)
Oropharynx	12 (30)	10 (25)
Hypopharynx	8 (20)	10 (25)
Larynx	10 (25)	8 (20)
Pathological TNM classification		
T1 N2	8 (20)	6 (15)
T2 N1-2	12 (30)	11 (28)
T3 N0-2	8 (20)	10 (25)
T4 N0-2	12 (30)	13 (33)
Poor prognostic factors, No.		
Positive margins	6	7
Vascular invasion	14	12
Neural invasion	16	18
Extracapsular disease	26	25

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

\*Data are given as number (percentage) unless otherwise indicated.

during treatment. No patient was completely dependent on percutaneous endoscopic gastrostomy or nasogastric tube feeding more than 3 months after treatment.

Long-term or chronic adverse effects, noted after 3 months from the start of treatment, were seen in a few patients. There was 1 case of moderate osteoradionecrosis in an oral cavity lesion; response to medical treatment was complete. Clinical hypothyroidism after treatment was noted in 3 patients.

### CLINICAL OUTCOME

Because of toxicity, only 110 (92%) of the scheduled 120 courses were administered; 32 patients (80%)

received all 3 courses, 6 (15%) received 2 courses, and 2 (5%) received only 1 course. The median chemotherapy delay was 3 days (range, 0-14 days). The radiotherapy dose was 52.0 Gy to all risk volumes plus 10.0 Gy to high-risk volumes, and the median radiation delay was 0 days (range, 0-7 days). The median carboplatin dose intensity was 79.72 mg/m<sup>2</sup> per week; the relative dose intensity was 0.89. After a median follow-up of 2.5 years (range, 1.5-6.0 years), the 3-year local control was 79%, 3-year disease-free survival was 58%, and 3-year overall survival was 64% (**Figure 1**).

We compared results between patients 70 years or older treated with radiotherapy alone vs patients younger than 70 years treated with radiotherapy and concomitant carboplatin (45 mg/m<sup>2</sup> on days 1-5 of weeks 1, 3, 5, and 7), based on previous study results and following a previous protocol<sup>20</sup> (**Table 3**). A computer program matched patients by ECOG performance status, site of disease, pathological TNM classification, and poor prognostic factors. Clinical outcomes in the patients 70 years or older treated with radiotherapy alone were: 3-year overall survival, 52%; 3-year disease-free survival, 41%; and 3-year local control, 64%; these results were inferior to those reported in this study (**Figure 2**). The results observed in the younger group of patients, treated with the combination therapy, were comparable to those reported in this study: 3-year overall survival, 67%; 3-year disease-free survival, 60%; and 3-year local control, 81%.

### QUALITY OF LIFE

Despite adverse effects, there was little change in patients' emotional or social well-being as a result of combination therapy, as evaluated by the Functional Assessment of Cancer Therapy. The overall quality-of-life score declined during treatment from 85.7 to 81.4, but had fully recovered by 12 months (score, 87.1); there were no significant differences between pretreatment and in-treatment values (**Table 4**).



The combination of surgery and radiotherapy is commonly used in the management of squamous cell carcinoma of the head and neck. Postoperative radiotherapy in patients at risk for local recurrence is widely accepted as being effective in improving locoregional control. Recent data have shown that, even in patients who received high dosages of conventionally fractionated postoperative radiotherapy, there are subgroups of patients (with positive margins, multiple risk factors, and advanced neck disease) who still have unacceptable recurrence rates, ranging from 36% to 47%.<sup>1-4</sup> There is evidence that concomitant chemoradiotherapy can improve locoregional control and disease-free and overall survival.<sup>16,17</sup> Authors have stressed that advanced age is not in itself a criterion for excluding patients from standard treatment with radiotherapy, chemotherapy, or surgery.<sup>21</sup> In head and neck cancer, age is not an independent negative prognostic factor. Because older patients are often excluded from prospective trials, information regarding the feasibility and results of new aggressive therapeutic approaches in this subpopulation are lacking.

We chose to administer carboplatin with conventional radiotherapy because this drug has a good tolerability and compliance among older cancer patients. A previous study<sup>22</sup> among locally advanced head and neck cancer patients showed that carboplatin plus conventional radiotherapy provides better clinical outcomes than radiotherapy alone.

In another study,<sup>20</sup> the feasibility of treatment with carboplatin (45 mg/m<sup>2</sup> on days 1-5 of weeks 1, 3, 5, and 7) concomitant with radiotherapy in an adjuvant setting was demonstrated in a younger group of head and neck cancer patients undergoing radical surgery. The regimen investigated in this trial was well tolerated, with no grade 4 toxicity and with an acceptable level of grade 3 toxicity. Late effects were rare and were not clinically relevant. The chemotherapy compliance was good; most patients (80%) received the full course of chemotherapy, and the carboplatin relative dose intensity was 0.89. A previous pharmacokinetic study<sup>23</sup> showed that, with this carboplatin schedule, platinum accumulation occurs during the fifth or seventh week of treatment. In the older patient group studied herein, our dosage reduction (from 45 to 30 mg/m<sup>2</sup>) and the exclusion of a seventh treatment week probably explain the good results of this schedule.

In a previous study, Pignon et al<sup>24</sup> assessed early and late toxicity according to age in 1307 patients, 12% of whom were 70 years or older. No differences in the occurrence of objective early mucosal reactions were noted among the various age groups. Allal and colleagues<sup>25</sup> have recently reported that aggressive accelerated radiotherapy schedules are feasible in geriatric patients. The results of the present study confirm previously established beliefs that adjuvant chemoradiotherapy can be successfully applied in older patients who are "fit" to receive such treatment. The role of the combination therapy in the postoperative setting can only be validated by phase III trials. A comparison of the results herein with those

**Table 4. Quality of Life (QOL) Before, During, and 1 Year After Chemoradiotherapy\***

Measure	Before	During	1 Year After
QOL domain scores			
Emotional	15.8 ± 4.5	16.7 ± 3.5	16.7 ± 3.5
Social	23.1 ± 4.4	21.4 ± 5.4	23.1 ± 4.4
Functional	18.4 ± 6.7	15.1 ± 6.7	15.9 ± 7.1
Physical	23.1 ± 5.5	17.9 ± 5.4	21.8 ± 5.5
Overall QOL score	85.7 ± 17.5	81.4 ± 15.7	87.1 ± 18.1

\*Data are given as mean ± SD.

of the group 70 years or older treated with radiotherapy alone suggests that superior results are obtained with chemoradiotherapy compared with radiotherapy alone in this age group. No statistical tests were performed on this comparison in terms of any end points, because the tacit implication would be that the 2 patient groups were similar. Without the randomization process to ensure mean comparability between the 2 patient groups, it would be necessary to evaluate bone marrow, renal, and hepatic functions in the other patients to determine their potential eligibility in our protocol. Unfortunately, such data were not available.

No comprehensive geriatric assessment was performed in our series. However, this has proved to be effective for clinical assessment of aging in randomized controlled studies in the general geriatric population.<sup>26</sup> Prospective clinical trials with measures of comprehensive geriatric assessment, quality of life, and economic factors are needed among older head and neck cancer patients.

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