# Randomized Comparison of Neoadjuvant Cisplatin and Fluorouracil Infusion Followed by Radiation Versus Concomitant Treatment in Advanced Head and Neck Cancer

By S.G. Taylor IV, A.K. Murthy, J.-M. Vannetzel, P. Colin, M. Dray, D.D. Caldarelli, S. Shott, E. Vokes, J.L. Showel, J.C. Hutchinson, T.R. Witt, K.L. Griem, W.F. Hartsell, M.S. Kies, B. Mittal, J.-L. Rebischung, D.J. Coupez, J.-L. Desphieux, S. Bobin, and C. LePajolec

***Purpose:*** **To compare two published schedules of cisplatin plus fluorouracil (5-FU) infusion and radiation as either sequential or concomitant treatment for toxicity and efficacy in patients with unresectable head and neck cancer.**

***Patients and Methods:*** **This was a randomized trial between cisplatin 100 mg/m$^2$ over 15 minutes on day 1 plus 5-FU 1.0 g/m$^2$ by continuous infusion on days 1 to 5, repeated every 3 weeks for three cycles, followed by 70 Gy of radiation in 7 to 8 weeks, versus cisplatin 60 mg/m$^2$ over 15 minutes on day 1 plus 5-FU 800 mg/m$^2$ by continuous infusion on days 1 to 5 plus radiation 2 Gy on days 1 to 5, repeated every other week for seven cycles. Unresectable head and neck squamous cancer patients not previously treated with radiation or chemotherapy and with a performance status of 0 to 2 were stratified by tumor (T) and node (N) groupings and performance status and randomized.**

***Results:*** **Two hundred fifteen patients were entered and 214 analyzed, 107 on each arm. After all treatment, overall response rates were different ($P$ = .003), with similar complete response rates, but more partial responses and fewer patients with no change or progression with concomitant treatment. Cox regression analysis for progression-free survival identified concomitant treatment ($P$ = .003), Radiation Therapy Oncology Group (RTOG) stage III grouping ($P$ < .0001), performance status ($P$ = .0002), concomitant treatment ($P$ = .003), and treating institution ($P$ = .006) as significant. The sequential and concomitant treatments showed similar distant failure patterns (10% and 7%, respectively), but divergent regional failure rates (55% and 39%). Severe and worse toxic events were similar between the treatment programs, but radiation-induced mucositis combined with cisplatin-induced water-losing nephropathy, in the concomitant arm only, demanded more supportive care. Survival duration was similar between the treatment arms, but significantly more patients in the sequential arm died of their cancer ($P$ = .011).**

***Conclusion:*** **Concomitant treatment offered improved disease control, predominantly of regional disease, but benefit was dependent on the experience of the treating institution. Translation of this benefit into improved survival is not yet evident, with an excess of deaths from other causes in the concomitant arm.**

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THE INTEGRATION OF chemotherapy into combined modality therapy of head and neck cancer has challenged investigators for three decades. Inoperable head and neck cancer is inadequately treated with radiation alone, with a median survival duration of 12 months or less, and with patients primarily failing to respond regionally. Methods to improve these results must therefore improve regional disease control.

Induction chemotherapy can use full-dose treatment before other therapies. With neoadjuvant therapy, 70% to 90% of patients respond. Measured response rates are consistently higher when chemotherapy is given before other treatment. The reduction in tumor volume should improve oxygenation of residual tumor and thus improve radiation effectiveness.[1] The major concerns of induction chemotherapy are that (1) the chemotherapy may leave a selected subpopulation of tumor cells that are radiation-resistant. Experimental evidence suggests that development of cisplatin resistance can result in radiation resistance.[2,3] (2) Initial chemotherapy may cause accelerated proliferation of surviving tumor cells at the start of radiation; and (3) some patients may refuse further therapy due to false hopes of the durable effects of the chemotherapy or due to fatigue with the prolonged treatment. Investigators from Wayne State have reported high (54%) complete response rates with neoadjuvant cisplatin and fluorouracil (5-FU) infusion.[4] This high response rate has led to wide acceptance of cisplatin and 5-FU infusion as induction therapy. However, randomized trials testing the use of adjuvant chemotherapy have failed to show im-

*From the Departments of Preventative Medicine, Medicine, Therapeutic Radiology, Otolaryngology, and Surgery, Rush University, Northwestern University, and University of Chicago, Chicago, IL; Clinique Hartmann, Seine; and the Polyclinique de Courlancy, Reims, France.*

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*Address reprint requests to Samuel G. Taylor IV, MD, Section of Medical Oncology, Suite 809, Rush Medical Center, 1725 W Harrison St, Chicago, IL 60612.*



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proved disease control or survival. Negative results from prior randomized studies have been explained as due to flawed study design, ineffective chemotherapy, and inadequate patient numbers.[5] Yet, a meta-analysis has not shown any benefit.[6] A recent randomized study in 237 patients has suggested benefit from four cycles of induction cisplatin plus 5-FU chemotherapy.[7]

Combining chemotherapy with radiation is another way to improve regional control in head and neck cancer. Concomitant use of both modalities can take advantage of synergistic interactions that might exist. Tumor cell kill by each modality separately might be increased by conversion of sublethal effects to lethal events with the combination, preventing the development of resistant tumor-cell subpopulations. The concomitant chemotherapy may prevent emergence of a highly proliferative cell fraction during radiation. Several drugs added to radiation individually have caused improved disease control, and usually survival benefit, over that achieved with radiation alone. These include 5-FU,[8] methotrexate,[9] bleomycin,[10] mitomycin,[11] and cisplatin.[12] Used as neoadjuvant therapy, these drugs have failed to show similar benefit, despite often more intense or combination drug therapy, suggesting that the scheduling of treatment may be important. The disadvantages of this approach are concern over increased toxicity, tumor repopulation during the mandated treatment breaks, and compromise in dose or dose-intensity of each modality due to the combined effects on normal tissues. Real benefit is measured as improvement in the therapeutic ratio, the ratio between tumor-cell kill and normal tissue toxicity. Taylor et al[13] reported results of a phase II study of concomitant cisplatin, 5-FU infusion, and radiation, using a split-course fractionation schedule of every-other-week treatment.[13] They were impressed with the durability of disease control, with a median survival duration of 37 months for all patients.

Controversies over each of these approaches led to the current randomized study to attempt to identify possible advantages of one of these approaches over the other in advanced, inoperable head and neck cancer. The issue of timing of chemotherapy with other modalities seemed important to understand how best to improve disease control. Both regimens used cisplatin, 5-FU infusion, and radiation, but the dose and schedule were different, with each using a published regimen as either sequential or concomitant therapy. The sequential regimen emphasized giving maximal dosage of chemotherapy before other treatment. The concomitant regimen emphasized only giving radiation during the chemotherapy. There was no comparison to a control group of conventional radiation alone, as such a definitive comparison was felt to be most appropriately performed by a large cooperative group.

## PATIENTS AND METHODS

### *Patient Selection*

Patients with histologically documented squamous cell carcinoma of the head and neck, stages III or IV, considered to be unresectable after evaluation by a surgeon, were eligible if disease was in the following sites: paranasal sinuses, tongue, nasopharynx, or hypopharynx. In addition, stage IV oral cavity and oropharynx lesions, other than tongue, and stage IV larynx cases were eligible. Patients with recurrent head and neck cancer, following prior surgical resection, were also eligible. Other restrictions were as follows: (1) an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better; (2) no evidence of hematogenous metastases by chest x-ray or bone scan if N2 or N3 disease was present; (3) initial leukocyte count of at least 4,000/$\mu$L, serum creatinine less than 1.9 mg/dL, blood urea nitrogen less than 25 mg/dL, bilirubin less than 1.9 mg/dL, and serum transaminase and alkaline phosphatase less than twice normal laboratory limits; (4) informed consent; (5) no prior chemotherapy or radiation therapy to the head and neck area; (6) no prior malignancy outside of the head and neck area, unless a more than 95% chance of cure was anticipated; (7) no coexisting malignancy outside of the head and neck (a second primary tumor within the head and neck was permitted if other eligibility criteria were met for at least one of the lesions); and (8) no other medical or psychiatric condition that would compromise treatment delivery or informed consent.

Patients were stratified into three risk groups defined as (1) T3-4N0 or T1-2N2; (2) T3-4N1-2 or T1-2N3, or recurrence less than 6 cm in size, provided no fixed nodes were present; and (3) T3-4N3 or any TN3 with fixed nodes or recurrence greater than or equal to 6 cm or with fixed nodal disease. Patients were also stratified into two ECOG performance status groups according to status 0 to 1 or 2.

### *Randomization*

Patients were entered and randomized through a central office at the Illinois Cancer Council (ICC). When it became apparent that the accrual goals would be difficult to achieve with the limited participation at the ICC, a separate cooperative venture was organized between Rush University and participating radiation centers in Paris and Reims, France. Restrictions within the ICC prevented inclusion of the French group in the ICC registry, so that a separate randomization was established through the Rush University Medical Oncology Protocol Office using the identical protocol, randomizing by closed-envelope technique within each stratum. This mechanism has allowed both separate and combined analyses.

### *Treatment*

Patients were randomized to receive either sequential or combined chemotherapy and radiation. Sequential treatment began with cisplatin 100 mg/m$^2$ by intravenous infusion over 15 minutes on day 1, and 5-FU 1,000 mg/m$^2$ by intravenous infusion over 24 hours on days 1 to 5 (120 hours), repeated every 3 weeks for three cycles. Dose modification for hematologic toxicity included a delay in ther-

apy until the leukocyte count was greater than 4,000/$\mu$L and platelet count greater than 100,000/$\mu$L. Cisplatin only (not 5-FU) was reduced by 25% for nadir leukocyte and platelet counts between 2,000 and 2,900/$\mu$L and 50,000 and 74,999/$\mu$L, respectively, and by 50% for nadir counts less than 2,000/$\mu$L and 50,000/$\mu$L, respectively. Cisplatin only required reduction by 50% for a serum creatinine level of 2.0 to 2.5 mg/dL. 5-FU only was to be reduced 25% for grade 2 or 3 mucositis. The study allowed patients who became operable following induction chemotherapy to undergo surgery before radiation in the sequential arm only.

Radiation in the sequential arm specified daily fractionation, 5 days per week, of 1.8 to 2.0 Gy to a total dose of 70 Gy. The protocol allowed use of electron boost or interstitial implants to the primary tumor. Implants required a minimal total tumor dose of 74 Gy. Bilateral neck irradiation required a minimal dose of 45 Gy to all noninvolved areas and 74 Gy to involved areas with masses greater than 4-cm. The entire treatment duration for the sequential arm was 16 weeks.

Concomitant chemotherapy and radiation consisted of seven cycles of cisplatin 60 mg/m$^2$ by intravenous infusion over 15 minutes on day 1, 5-FU 800 mg/m$^2$ by intravenous infusion over 24 hours on days 1 to 5 (120 hours), and radiation 2 Gy on days 1 to 5, delivered every other week. The dosages of cisplatin and 5-FU were to be reduced by 25% for any cycle with a day-1 leukocyte count between 2,500 and 3,499/$\mu$L or a platelet count between 75,000 and 99,999/$\mu$L, by 50% for leukocytes between 2,000 and 2,499/$\mu$L or a platelet count between 75,000 and 99,999/$\mu$L, and by 50% for leukocytes between 2,000 and 2,400/$\mu$L or platelets between 60,000 and 74,999/$\mu$L. All treatment, including radiation, was to be withheld for 1 week for lower counts. Mucositis occurring during the rest week required a 25% dose reduction of 5-FU for the next cycle for grade 2 severity and a 50% dose reduction for grade 3 severity. Mucositis present on day 1 of therapy required a 25% reduction of 5-FU for grade 1, a 50% reduction for grade 2, and all treatment to be withheld for 1 week for grade 3 toxicity. Renal toxicity on day 1 of any cycle required a 50% reduction in the dose of cisplatin for a serum creatinine level between 2.0 and 2.5 mg/dL and a 100% reduction in dose for a creatinine level greater than 2.5 mg/dL, if not correctable with hydration.

Radiation with concomitant chemotherapy required 2.0-Gy fractions only, unless a holiday intervened, in which case 2.5-Gy fractions for 4 days were permitted. Radiation was to only be delivered during concomitant chemotherapy, so that if all chemotherapy was to be withheld for severe myelosuppression or mucositis, the radiation was to be withheld as well. The duration of treatment for the concomitant arm was 13 weeks. With either concomitant or sequential use of radiation therapy, the fields were to be reduced to exclude the spinal cord after 50 Gy.

Surgery was not a specific requirement of the study. The protocol permitted surgical resection in the sequential arm following induction chemotherapy and in both arms following completion of tumoricidal doses of radiation (>66 Gy). The protocol allowed complete investigator discretion as to use of surgery and as to surgical resection of the primary tumor and/or nodal disease. Mention of concern with difficult wound-healing problems with concomitant treatment[13] discouraged use of this modality as a part of treatment of the primary disease. Patients undergoing surgery as a part of the primary treatment on protocol were not scored as treatment failures at that point, independent of the presence of tumor in the specimen, but were monitored for time to failure and death thereafter.

### *Statistical Analysis*

All patients entered on to the study were monitored for treatment-related events and toxicity, response, time to recurrence or progression, time to death, and sites of failure. All entered patients were monitored for survival. Patients known to be disease-free within 1 month of death and/or who underwent autopsy verification of no evidence of disease were censored at time of death as disease-free. Other deaths, even when documented as due to other causes without known recurrence, were counted as recurrence at time of death. Patients who died before or during treatment were omitted from the analyses of disease control. One additional patient, randomized to concomitant treatment, who then refused all therapy, was omitted from the analysis of disease control. For the purpose of analysis, the Radiation Therapy Oncology Group (RTOG) proposed staging system,[14] which divides patients into five stages, appeared to reflect more accurately prognoses than the American Joint Committee (AJC) convention. Response was determined using standardized response criteria.[15] Overall response on the sequential arm was the best response to either chemotherapy or radiation, unless progression occurred during treatment, in which case the overall response was scored as progression. Time to relapse was defined as time from randomization to the date of progression or recurrence. Patients whose disease progressed, whether during or after completion of treatment, were removed from study, treated subsequently at the discretion of the investigators, and monitored for survival. Survival was defined as date of randomization to date of death. The Kaplan and Meier method[16] was used to estimate the progression-free survival duration and survival curves, and the log-rank test[17] was used to compare groups. The Cox proportional hazards model[18] was used to examine the treatment effect on progression-free survival while adjusting for prognostic variables. Variables entered into this Cox regression analysis were performance status, pathology grade, age, and indicator variables representing sex, site, AJC stage, proposed RTOG stage, American (ICC) or French (Paris-Chicago protocol [PCP]) study, and institution. For these subset analyses, a $P$ value less than .01 was accepted as significant to avoid type 1 errors from multiple statistical analyses. Mann-Whitney and $\chi^2$ tests were used to compare treatment groups with respect to toxicity, treatment delays, and patterns of relapse or death. All reported $P$ values are two-sided.

## RESULTS

The trial began as an ICC trial in 1986. By 1988, 40 patients had entered the trial. The trial was expanded to include a second group of investigators as a PCP study with separate randomization in June 1988. It closed to ICC entry in January 1991, with 93 patients entered. PCP entry closed in November 1991, with 122 patients entered. At this preliminary analysis, 214 patients are available for analysis, with 107 randomized to each treatment group. One patient was entered too early for inclusion in this analysis. The median follow-up duration is 30 months, with 30 patients observed for less than 2 years.

Table 1 lists patient characteristics. Five patients were ineligible according to the protocol terms. In the sequential group, one patient had T3N0 laryngeal carcinoma and

**Table 1. Sequential Versus Concomitant Chemotherapy and Radiation in Head and Neck Cancer: Patient Characteristics**

| Characteristic | Sequential (n = 107) | Concomitant (n = 107) |
|---|---|---|
| Ineligible | 2 | 3 |
| Randomization group (%) | | |
| ICC | 44 | 43 |
| PCP | 56 | 57 |
| Age, years | | |
| Median | 55 | 60 |
| Range | 23-74 | 32-79 |
| % Female | 21 | 11 |
| Performance status (%) | | |
| 0 | 30 | 30 |
| 1 | 63 | 62 |
| 2 | 7 | 8 |
| Disease site (%) | | |
| Sinus | 1 | 1 |
| Oral cavity | 10 | 7 |
| Tongue | 20 | 27 |
| Oropharynx | 17 | 29 |
| Nasopharynx | 8 | 4 |
| Hypopharynx | 33 | 22 |
| Larynx | 11 | 10 |
| Tumor differentiation (%) | | |
| Well | 40 | 41 |
| Moderately well | 33 | 40 |
| Poor | 24 | 20 |
| Anaplastic | 2 | 0 |
| Disease stage (AJC/UICC) | | |
| III | 18 | 13 |
| IV | 78 | 83 |
| Recurrent | 5 | 4 |
| Disease stage (RTOG proposed) (%) | | |
| III (T3-4N0, T1-2N2) | 33 | 26 |
| IV (T1-3N3, T3-4N1) | 38 | 35 |
| V (T4N2-3) | 24 | 36 |
| Recurrent | 5 | 4 |

one patient had a positive bone scan, in retrospect. In the concomitant group, one patient had a positive esophageal biopsy as a second primary tumor outside of the head and neck area, one patient had liver function tests above the protocol limits, and one had received prior limited neck radiation for a laryngeal primary tumor. This last patient had a stomal recurrence following prior laryngectomy. She received full-dose retreatment despite the prior radiation. These patients were a small minority of the total and were included in the overall analyses.

Some chance imbalances in the patient distribution occurred. Stratification variables included performance status and disease extent. Performance status was well balanced. However, stage was not, despite central, blinded randomization, with an excess of early cases in the sequential arm and advanced cases in the concomitant arm. In addition, the randomization process assigned somewhat younger and slightly more female patients to the sequential arm. Nasopharynx and hypopharynx predominated in the sequential arm, and oropharynx in the concomitant arm. The analysis of results used a Cox regression analysis to correct for potential bias in interpretation due to chance imbalances between the treatment groups.

*Response*

Clinical response to the induction chemotherapy in the sequential group included 23% complete responses, 58% partial, 14% no change, and 5% disease progression. Table 2 lists the best response to all treatment by clinical assessment. Overall response rates were significantly different between the two regimens ($P = .006$). While complete response rates were similar (50% and 52%, respectively), more patients in the concomitant arm had a partial response and more patients in the sequential group had no change or progression.

Biopsy confirmation of response was not a protocol requirement. However, 54 patients underwent either biopsy or surgery after treatment that allowed histologic assessment of response. Histologic confirmation of complete response was usual in both treatment groups, with only one patient tested in each group having residual tumor found on biopsy. Histologically positive biopsies from partial responders tended to be fewer with concomitant treatment: four biopsies positive of 14 (29%) in the

**Table 2. Response to Therapy**

| Response Data | Sequential | Concomitant |
|---|---|---|
| % Response to induction chemotherapy | | |
| Complete response | 23 | |
| Partial response | 58 | |
| No change | 14 | |
| Progression | 5 | |
| % Response to chemotherapy and radiation | | |
| Complete response | 50 | 52 |
| Partial response | 28 | 41 |
| No change or progression | 18 | 4 |
| Not assessable | 4 | 3 |
| % Histologically negative | | |
| Complete response (n = 27) | 94 | 90 |
| Partial response (n = 25) | 36 | 71 |
| No change (n = 2) | 0 | ND |
| % Complete response based on stage (proposed RTOG divisions) | | |
| III (T3-4N0, T1-2N2) | 57 | 57 |
| IV (T1-2N3, T3N1-3, T4N1) | 51 | 59 |
| V (T4N2-3) + recurrent | 42 | 43 |

Abbreviation: ND, not determined.

**Table 3. Dose Delivery of Combined Modality Treatment**

| | Sequential | Concomitant |
|---|---|---|
| % Ideal dose | | |
| Cisplatin | | |
| Median | 97 | 88 |
| Range | 32-112 | 0-105 |
| 5-FU | | |
| Median | 97 | 79 |
| Range | 13-112 | 0-104 |
| % of patients receiving radiation (Gy) | | |
| 0 | 12 | 2 |
| < 65 | 11 | 17 |
| 65-75 | 75 | 80 |
| > 75 | 3 | 1 |
| % of patients with radiation therapy delays (weeks) | | |
| 0 | 22 | 36 |
| 1 | 24 | 27 |
| 2 | 20 | 11 |
| 3 | 10 | 9 |
| > 3 | 8 | 13 |
| Not assessable or unknown | 15 | 4 |

concomitant group, compared with seven of 11 (64%) in the sequential group ($P$ = .08).

Complete response rates by disease stage, using the RTOG staging divisions, were similar between treatment arms (Table 2).

*Dose Delivery*

Table 3 lists treatment delivery parameters. More modifications in chemotherapy dose were required for the concomitant treatment, leading to a reduction in the median percentage of ideal dose actually delivered for both cisplatin and 5-FU. However, the total radiation dose delivered was similar between the two groups, with 78% of patients in the sequential arm and 81% of those in the concomitant arm able to receive a therapeutic dose level defined as a dose of 65 Gy or greater. However, a significant minority of patients in the sequential arm received no radiation due to untoward events during the induction treatment or patient refusal. Only two patients (one sudden death before treatment and one patient who refused all treatment after randomization) received no radiation in the concomitant group.

Patients assigned to receive concomitant treatment were more likely than those assigned to receive sequential treatment to have less than 1-week treatment delays, but there was no statistically significant difference with respect to treatment delays ($P$ = .23). Table 3 lists the frequency of treatment delays, based on duration of time for delivery of the radiation therapy.

*Toxicity*

Table 4 lists the distribution of common toxicity events in each treatment arm. It also includes vascular events (cerebral, myocardial infarction, sudden death, and other arterial occlusions), as these have occurred with some regularity with cisplatin/5-FU treatment. The toxic events listed are those that occurred during the entire treatment (chemotherapy and radiation). The frequency of skin and mucous membrane toxicities was similar between the two groups, occurring predominantly during radiation in both groups. Relatively little mucositis and practically no skin toxicity was reported during induction chemotherapy in the sequential arm.

No overt differences occurred in grade 4 or 5 toxic events between the two treatments. Lethal events listed as vascular toxicity included two sudden deaths and one stroke in the sequential arm and one arterial occlusion, one sudden death, and three strokes in the concomitant arm. Other lethal events not included in Table 4 were one laryngeal edema, one respiratory failure, and one gastrointestinal bleed in the sequential group (seven events in all), and one gastrointestinal bleed, one cerebral dementia (thought to be possibly related to cisplatin), two patients with progressive cachexia, and one patient with

**Table 4. Acute Toxicity of Sequential and Concomitant Chemotherapy and Radiation: Worst Toxicity Level as Percent of Patients**

| | Grade | | | | | |
|---|---|---|---|---|---|---|
| Toxicity | 0 | 1 | 2 | 3 | 4 | 5 |
| Mucositis | | | | | | |
| Sequential | 16 | 12 | 33 | 35 | 3 | — |
| Concomitant | 19 | 16 | 23 | 36 | 5 | — |
| Skin | | | | | | |
| Sequential | 71 | 13 | 11 | 4 | 0 | — |
| Concomitant | 70 | 14 | 9 | 7 | 0 | — |
| Leukopenia | | | | | | |
| Sequential | 52 | 19 | 17 | 8 | 3 | 1 |
| Concomitant | 11 | 14 | 42 | 31 | 2 | 1 |
| Thrombocytopenia | | | | | | |
| Sequential | 65 | 26 | 3 | 3 | 3 | 0 |
| Concomitant | 33 | 38 | 18 | 9 | 3 | 0 |
| Emesis | | | | | | |
| Sequential | 43 | 35 | 18 | 3 | 1 | — |
| Concomitant | 38 | 28 | 20 | 14 | 0 | — |
| Renal | | | | | | |
| Sequential | 59 | 22 | 18 | 1 | 1 | 0 |
| Concomitant | 65 | 18 | 15 | 1 | 0 | 0 |
| Vascular | | | | | | |
| Sequential | 96 | 0 | 1 | 0 | 0 | 3 |
| Concomitant | 95 | 0 | 0 | 2 | 1 | 5 |
| Weight loss | | | | | | |
| Sequential | 46 | 14 | 13 | 14 | — | — |
| Concomitant | 22 | 31 | 33 | 14 | — | — |

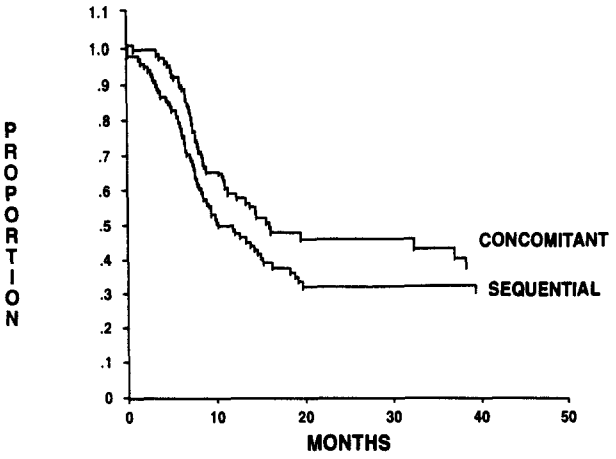


**Fig 1. Kaplan-Meier progression-free survival curves for time to progression or recurrence based on assigned treatment arm.**

severe alcoholic intoxication and dehydration (11 events in all). An additional two patients died in the concomitant arm before any therapy was given: one of sudden death the same day he was enrolled in the study, and one who refused all therapy after randomization.

The distribution of grade 1 to 3 toxicities was notably different between treatment groups. Leukopenia ($P$ = .001) and thrombocytopenia ($P$ = .040) of a degree not considered life-threatening were more frequent in the concomitant arm. Weight loss was also more likely to occur and be more severe in the concomitant treatment group ($P$ = .02). The median weight loss was 5.8% with sequential treatment and 9.3% with concomitant therapy. Eighty-eight percent of patients receiving concomitant therapy had a loss of more than 5% of their starting weight at some point during therapy, compared with 44% of sequentially treated patients. As mentioned earlier, two patients given concomitant therapy died of progressive cachexia and a third of alcoholic intoxication and dehydration. The possible contribution of cisplatin treatment in any of these events is unclear.

Renal toxicity only included toxicities reflected by elevations of serum creatinine and/or blood urea nitrogen. These were similar between the two treatments. However, virtually all patients developed water-losing nephropathy, with prominent sodium, potassium, and magnesium wasting. This toxicity was not quantitated, but contributed to the marked weight fluctuations commonly observed during therapy.

*Disease Control*

Figure 1 shows the Kaplan-Meier disease-free survival curve for the two treatment programs. Patients who died of non–treatment-related causes, who had been evaluated and found to be without evidence of tumor recurrence within 1 month of death, were censored at time of death. No statistically significant difference exists between treatments in this uncorrected life-table analysis ($P$ = .10).

Because of the imbalance in the distribution of patient characteristics and the inclusion of two separate study populations (ICC and PCP patients), Cox regression analysis was performed to assess significant prognostic variables associated with disease control. Variables put into the initial model included age, performance status, pathologic grade, and indicator variables representing study location (ICC or PCP), institution, sex, disease site, and stage (both RTOG proposed system and AJC stage). RTOG stage, performance status, and treatment at institution 1 were highly significant in the final model obtained by stepwise elimination, while disease site was of borderline significance. Including these variables resulted in a significant difference ($P$ = .003) in favor of concomitant therapy in disease-free survival when the indicator variable representing treatment type was added to the final model. The $P$ values for the variables in this model are listed in Table 5.

Table 6 lists the failure patterns for three significant prognostic variables. Patients with oropharyngeal and tongue lesions appeared to benefit most from concomitant treatment, whereas other disease sites showed smaller differences. However, in the final proportional hazards model, these differences were erased. Hypopharynx and larynx sites tended to have the better outcomes in the Cox regression analysis, but the $P$ values were only at a borderline level of significance for multiple comparisons ($P$ = .03 and .04, respectively). While the institution where the patient was treated was a significant variable in the final model, no significant difference occurred in results between the ICC and PCP studies ($P$ = .32 by log-rank analysis and .70 by Cox regression analysis), justifying the pooling of the separately randomized patients from the ICC and PCP studies in the overall analysis.

Because of the divergence in range of results between

**Table 5. Significant Prognostic Variables on Disease-Free Survival by Cox Regression Analysis**

| Prognostic Variable | Favorable Category* | $P$ |
|---|---|---|
| RTOG stage | Stage III | < .0001 |
| Performance status | 0 > 1 > 2 | .0002 |
| Treatment | Concomitant | .003 |
| Institution | Institution 1 | .006 |

*The category within each prognostic grouping that gave the best outcome.

**Table 6. Failure Pattern Based on Significant Prognostic Variables**

| Variable | Sequential | | Concomitant | |
|---|---|---|---|---|
| | No. | % Failures | No. | % Failures |
| Performance status | | | | |
| 0 | 31 | 35 | 30 | 43 |
| 1 | 64 | 75 | 58 | 55 |
| 2 | 5 | 100 | 8 | 63 |
| RTOG stage groupings | | | | |
| III (T3-4N0, T1-2N2) | 33 | 52 | 24 | 33 |
| IV (T1-2N3, T3N1-2, T4N1) | 38 | 61 | 34 | 50 |
| V (T4N2-3) + recurrent | 29 | 83 | 38 | 66 |
| Institution | | | | |
| 1 | 30 | 67 | 17 | 35 |
| 2 | 13 | 54 | 22 | 64 |
| 3* | 8 | 75 | 7 | 71 |
| 4 | 12 | 75 | 6 | 67 |
| 5 | 37 | 59 | 42 | 48 |

*Eight institutions from ICC each entering ≤ 4 patients.

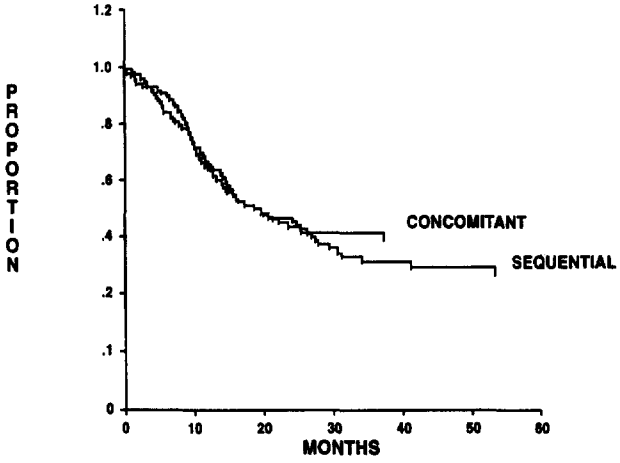


**Fig 2. Kaplan-Meier survival curves for deaths due to all causes based on assigned treatment arm.**

institutions for patients treated with concomitant therapy, we examined dose delivery of the treatment. By Cox proportional hazards regression, neither the percentage of ideal dose actually delivered for 5-FU or cisplatin, nor the number of cycles received was significantly related to outcome, and institution 1 remained significant when these variables were included in a proportional hazards model. Institution 1 was the only institution to have had extensive prior experience with the concomitant treatment arm and this experience may have been important in some, as yet, undetermined way.

Sites of failure included primary tumor site, regional neck disease, and distant metastases. The percentage of patients who developed distant metastases was low in each treatment group (Table 7). The overall pattern of recurrence did not appear to differ between the two treatment groups overall.

**Table 7. Sites of Failure**

| | Percent Failures | |
|---|---|---|
| | Sequential (n = 100) | Concomitant (n = 94) |
| Site | | |
| Tumor only | 25 | 21 |
| Node only | 13 | 3 |
| Metastasis only | 8 | 7 |
| Tumor and node | 15 | 15 |
| Tumor or node plus metastasis | 2 | 0 |
| Unknown* | 1 | 5 |
| Total regional recurrences | 55 | 39 |
| Total distant failures | 10 | 7 |

*Patients who died without verified recurrence but not having undergone reevaluation within 1 month of death.

The role of surgery in these patients was left to investigator discretion and was not specified in the study. All patients were considered initially unresectable. The protocol allowed surgery following induction chemotherapy in the sequential treatment arm only. Only four patients had surgery at that time. Surgery was also performed to resect suspected residual disease following completion of radiation in either arm, to resect recurrence, and to repair complications of treatment (osteoradionecrosis or incompetent larynx). A total of 17 patients (16%) in the sequential arm had surgery that included resection of the primary tumor, compared with 11 patients (10%) in the concomitant arm. Three additional patients (3%) had resections limited to the neck in the sequential arm, compared with eight (7%) in the concomitant arm. Of the 20 patients undergoing surgical procedures in the sequential group, seven (35%) remain alive at 20 to 71 months of follow-up. Eight (44%) of 18 patients undergoing surgical procedures in the concomitant arm are alive at 17 to 69 months.

*Survival*

Figure 2 shows the survival results for the two treatment groups. No overall survival benefit is apparent for either regimen. Causes of death are listed in Table 8. Significantly more patients in the sequential group died of their cancer than in the concomitant group ($P = .011$). This is true despite including in the concomitant group five patients who died without confirmed recurrence and one patient who refused all treatment after randomization.

**Table 8. Causes of Death**

| Cause of Death | No. of Patients | |
|---|---|---|
| | Sequential | Concomitant |
| Death with disease | 59* | 44† |
| Death during treatment | 6 | 11 |
| Death from other causes | | |
| Vascular/cardiac | 3 | 4‡ |
| Trauma | 1 | 2 |
| Bleeding | 1 | 3 |
| Second primary | 1 | 1 |
| Pulmonary | 0 | 4 |
| Total | 7 | 15 |

*Includes 1 patient who died without verified recurrence.

†Includes 5 patients who died without verified recurrence and 1 who refused any treatment.

‡Includes 1 sudden death before treatment.

Causes of death other than cancer included a wide variety of events. However, only one patient in each group has died of a second malignancy while remaining disease-free from the treated head and neck primary tumor.

## DISCUSSION

This trial suggests, with a direct comparison, that simultaneous administration of chemotherapy with radiation leads to better tumor control over sequential administration of the same drugs with radiation. The results indicate that this improvement is primarily due to improved regional control, as the incidence of distant metastases was similar and quite low in both groups of patients (10% sequential *v* 7% concomitant). Having the greatest impact on disease control within the radiation field would suggest that the simultaneous administration of chemotherapy had some direct sensitization or antiproliferative effect with the radiation.

This study is, by no means, unique in this observation. In a smaller, single-institution study, Adelstein et al[19] observed the same effect. Merlano et al[20] and the South of England Co-operative Oncology Group (SECOG)[21] have separately shown that an alternating schedule of chemotherapy and radiation is superior to sequential administration of the same treatments. Recently, Merlano et al[22] have also confirmed that this alternating schedule is better than uninterrupted radiation alone.

An alternative explanation for the benefit found in this trial with the concomitant program could be the greater amount of chemotherapy delivered in the concomitant arm, rather than the importance of giving the chemotherapy with radiation. The dose-intensity of the concomitant arm was 30 mg/m$^2$/wk for cisplatin and 2.0 g/m$^2$/wk for 5-FU, compared with 33 mg/m$^2$/wk and 1.67 g/m$^2$/wk, respectively, with neoadjuvant therapy. The total dose to be delivered was 420 mg/m$^2$ cisplatin and 28 g/m$^2$ 5-FU for concomitant treatment, compared with 300 mg/m$^2$ and 15 g/m$^2$ respectively, in the sequential arm. However, the radiation was more dose-intense in the sequential arm (9.0 to 10 Gy/wk) compared with the concomitant arm (5.0 Gy/wk). The entire length of treatment was 16 weeks for sequential therapy and 13 weeks for concomitant therapy. The design of this trial did not attempt to make dose delivery equivalent. Each regimen was an established program administered at recommended dosage.

It seems unlikely that chemotherapy dose-intensity would explain the different results, based on prior treatment experience. Investigators have administered bleomycin, cisplatin, and methotrexate, for example, in very dose-intense schedules as neoadjuvant therapy without benefit,[23,24] but low dose-intense schedules have shown benefit when administered concomitantly with radiation.[9,10]

In contrast, the reduced dose-intensity of the radiation in the concomitant treatment has concerned radiation oncologists. Radiation is the primary modality of disease control in these patients and interruption of radiation may lead to a proliferative advantage in surviving tumor cells that only huge doses of radiation can overcome.[25,26] While this argument is relevant to radiation alone, it appears less relevant to programs combining chemotherapy and radiation, as witnessed by the improved regional control observed in this study. Investigators in the first randomized trial with 5-FU and radiation concluded that combined treatment was superior, despite more treatment breaks and the reduced total dose of radiation delivered, and suggested that future trials needed to incorporate planned treatment breaks.[27] Merlano et al[22] have also shown that 60 Gy delivered in 8 weeks with chemotherapy added in an alternating schedule, interrupting the radiation, is better than 70 Gy delivered in 7 weeks without interruptions. It may be advantageous to administer chemotherapy during radiation, despite treatment breaks, for the very reason most radiation oncologists are reluctant to do it—accelerated proliferation, which may make surviving tumor cells more sensitive to chemotherapy.

The low incidence of distant metastases in both groups is noteworthy. Some studies have suggested that the one positive effect of adjuvant chemotherapy is the reduction in incidence of distant metastases.[28] The current trial indicates that it is also possible to gain excellent distant disease prevention with concomitant treatment regimens, without the need for additional adjuvant therapy.

Toxicity of treatment is a major concern, especially

with concomitant therapy. Severe mucositis, the major toxicity concern with concomitant 5-FU and radiation, was comparable in frequency between sequential and concomitant treatments. Less well quantified was toxicity related to cisplatin-induced nephropathy. Glomerular damage, evidenced by increased serum creatinine, was uncommon, despite the study not requiring an initial creatinine clearance measurement. However, weight loss was significantly more common with concomitant treatment, and dehydration appeared to be a major contributing cause, as weight fluctuations were often profound. A water-losing nephropathy induced by cisplatin appeared to be responsible for this morbidity. This nephropathy was aggravated by radiation-induced mucositis that reduced oral fluid intake with concomitant treatment. The worst mucositis with the sequential therapy occurred with radiation, 6 to 9 weeks after the last cisplatin treatment, when the renal tubular toxicity would have resolved. However, patients often were not sensitive to their dehydrated status, until symptomatic orthostatic hypotension occurred, due to the marked diuresis they experienced and because dehydration can occur despite apparently adequate fluid intake. Other symptoms of dehydration were weakness and fatigue, and persistent nausea, anorexia, and vomiting. All of these symptoms could be dramatically corrected by vigorous rehydration.

Grade 4 to 5 toxicity directly attributable to chemotherapy was uncommon with either treatment. Grade 4 to 5 vascular events, during therapy, occurred in 3% of patients assigned to sequential treatment and 5% of concomitant patients. Reports have described vascular events occurring with 5-FU administration[29] and vascular spasm does occur with this treatment. While most of such events in this study did not occur during the time of actual chemotherapy administration, only seven additional vascular/cardiac deaths (3%) occurred in the entire follow-up period.

One patient died of laryngeal edema shortly after the first neoadjuvant treatment. Investigators at Rush Memorial have described increased tumor swelling with cisplatin administration, which may be life-threatening with head and neck cancers.[30] This case emphasizes the importance of (1) substituting pharmacologic for osmotic diuretics such as mannitol in these situations due to the potential for third-space expansion with osmotic diuretics, (2) the use of high-dose methotrexate and repeated diuretics during postcisplatin hydration, and (3) close observation in high-risk patients.

The number of deaths due to cancer were less in the concomitant group, while the overall survival was similar. It is possible that some residual toxicity with concomitant treatment caused more noncancer deaths in this group. With the singular exception of the patient who died suddenly at home before beginning concomitant therapy, it is impossible to exclude an unidentified toxicity as a contributing cause of death in cancer free individuals. No increase in nonlethal late effects has been identified in the concomitant group. However, some swallowing or other dysfunction from treatment or from prior tumor destruction of the normal swallowing mechanism could possibly have contributed to these noncancer deaths. Prospective monitoring of swallowing and laryngeal function may be helpful in the future.

While no overall difference in outcome occurred between the American ICC and French PCP studies, institutional differences were statistically significant in the Cox regression analysis. Institution 1 was a statistically significant variable in the final model ($P = .006$). This institution was the site of the initial phase II study with the concomitant treatment regimen. The second best disease control results with concomitant treatment occurred at institution 5, which entered the most patients into this arm. This observation suggests experience with this regimen may be important for optimal results. However, attempts to explain these differences between institutions by dose delivery of the chemotherapy and radiation failed to identify any significant trends.

One striking difference between the sequential and concomitant treatment results was outcome based on clinical assessment of response. While the percentage of patients who achieved a clinically complete response was similar between the treatments, more patients in the concomitant arm had a partial response, while fewer had stable disease or progression ($P = .002$). A high percentage of those partial responders to concomitant therapy who underwent a biopsy were histologically clear (71%), in contrast to only 36% of patients who underwent a biopsy and were partial responders to sequential treatment. The subsequent disease control of such partial responders to concomitant therapy was also better than that of partial responders to sequential therapy. This observation was consistent with the durable disease control in clinically assessed partial responders in the phase II study.[13] The lack of association between clinical assessment and pathologic findings following treatment with this regimen has been reported in lung cancer.[31] Residual mass lesions that may be sterile appear to be a feature of concomitant, but not necessarily sequential, therapy. Realization of this observation dictates continued treatment of patients who might appear to be responding poorly to therapy as tumor sterilization

is possible. Failure to achieve a clinically complete response to sequential therapy, on the other hand, is a poor prognostic sign.

Moderately advanced cancers had the greatest treatment differences between concomitant and sequential therapy. Concomitant treatment significantly improved regional control. This observation has encouraged us to pursue concomitant treatment in operable patients, who would require major ablative procedures and still need radiation therapy. The durability of disease control found with concomitant treatment suggested that this regimen may reasonably be examined as an option to surgery in head and neck cancers independent of site. Such a role has been advocated for neoadjuvant chemotherapy in laryngeal cancers[32] and other disease sites,[33] but the less frequent occurrence of disease progression during therapy, the ability to offer this treatment to all such patients rather than to complete responders only,[33] and the better disease control achieved with concomitant treatment would seem to make this approach a better alternative to surgery.

In conclusion, concomitant treatment required more supportive care and physician experience to deliver, with more frequent weight loss and with moderate hematologic toxicity. Given these reservations, it achieved improved disease control over sequential treatment, primarily due to better regional disease control without an increase in distant relapse or in second primary tumors. While survival with respect to cancer was improved, overall survival was similar between treatments, indicating the difficulties in managing this patient population. Nevertheless, reducing the risk for regional recurrence in head and neck cancer seems a worthwhile achievement in these patients. A more complete survival analysis will require additional follow-up.

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