An Intergroup Phase III Comparison of Standard Radiation Therapy and Two Schedules of Concurrent Chemoradiotherapy in Patients With Unresectable Squamous Cell Head and Neck Cancer

By David J. Adelstein, Yi Li, George L. Adams, Henry Wagner, Jr, Julie A. Kish, John F. Ensley, David E. Schuller, and Arlene A. Forastiere

Purpose: **The Head and Neck Intergroup conducted a phase III randomized trial to test the benefit of adding chemotherapy to radiation in patients with unresectable squamous cell head and neck cancer.**

Patients and Methods: **Eligible patients were randomly assigned between arm A (the control), single daily fractionated radiation (70 Gy at 2 Gy/d); arm B, identical radiation therapy with concurrent bolus cisplatin, given on days 1, 22, and 43; and arm C, a split course of single daily fractionated radiation and three cycles of concurrent infusional fluorouracil and bolus cisplatin chemotherapy, 30 Gy given with the first cycle and 30 to 40 Gy given with the third cycle. Surgical resection was encouraged if possible after the second chemotherapy cycle on arm C and, if necessary, as salvage therapy on all three treatment arms. Survival data were compared between each experimental arm and the control arm using a one-sided log-rank test.**

Results: **Between 1992 and 1999, 295 patients were entered on this trial. This did not meet the accrual goal of 362 patients and resulted in premature study closure. Grade 3 or worse toxicity occurred in 52% of patients enrolled in arm A, compared with 89% enrolled in arm B ($P < .0001$) and 77% enrolled in arm C ($P < .001$). With a median follow-up of 41 months, the 3-year projected overall survival for patients enrolled in arm A is 23%, compared with 37% for arm B ($P = .014$) and 27% for arm C (P = not significant).**

Conclusion: **The addition of concurrent high-dose, single-agent cisplatin to conventional single daily fractionated radiation significantly improves survival, although it also increases toxicity. The loss of efficacy resulting from split-course radiation was not offset by either multiagent chemotherapy or the possibility of midcourse surgery.**

J Clin Oncol 21:92-98.

THE ADJECTIVE unresectable, when applied to a squamous cell head and neck cancer, implies extensive disease with a poor prognosis. Radiation therapy has been the standard of care for such patients, although the overall survival after radiation has, in general, been less than 25%.[1-3] A number of efforts have been made to improve these disappointing results, including altered radiation therapy fractionation schedules[4-6] and the use of systemic chemotherapy in conjunction with radiation.[2] Although both induction chemotherapy schedules[7] and alternating radiation and chemotherapy treatment schedules[8,9] have been explored for this patient population, it is the concurrent chemoradiotherapeutic schedules that have produced the greatest interest.[10] Between 1982 and 1987, the Head and Neck Intergroup conducted a phase III randomized trial comparing radiation therapy alone with radiation and concurrent weekly cisplatin given at a dose of 20 mg/m^2/wk.[11] Although the response rate was greater in patients treated with the concurrent regimen, the median survival was only 13 months and did not differ between the two treatment arms. The study was considered a negative trial, and this concurrent weekly cisplatin chemoradiotherapeutic regimen was not adopted as a treatment standard.

In 1987, the Radiation Therapy Oncology Group (RTOG) first reported results from a phase II trial testing radiation and concurrent high-dose cisplatin (100 mg/m^2 given every 3 weeks during radiation therapy). A complete response rate of 71% and a 4-year survival of 34% were reported in a cohort of 124 patients.[12]

A phase II trial from the Eastern Cooperative Oncology Group (ECOG), first reported in 1991, explored a cisplatin and fluorouracil chemotherapy regimen given concurrently with radiation therapy in unresectable patients. In this study, the radiation therapy course was split after 30 Gy to allow for the possibility of midcourse surgery in patients rendered resectable by the induction chemoradiotherapy. In a 52-patient cohort, the complete response rate was 77%, with a projected 4-year survival of 49%.[13]

The promising results of these two pilot studies formed the basis for a second-generation trial in unresectable patients, initiated in 1992 by the Head and Neck Intergroup. This study compared a control arm of standard radiation therapy, with the RTOG regimen using concurrent radiation and high-dose cisplatin every 3 weeks, with a third arm using the ECOG regimen of cisplatin and fluorouracil, concurrent split-course radiation, and midcourse surgery if possible. ECOG and the Southwest Oncology Group (SWOG) participated in this study.

From the Cleveland Clinic Foundation, Cleveland; Arthur G. James Cancer Hospital, Columbus, OH; Dana-Farber Cancer Institute, Boston, MA; Fairview University Medical Center (University of Minnesota), Minneapolis, MN; H. Lee Moffitt Cancer Center, Tampa, FL; Henry Ford Hospital, and Karmanos Cancer Institute, Wayne State University, Detroit, MI; and Johns Hopkins University, Baltimore, MD.

Submitted January 2, 2002; accepted September 18, 2002.

This study was conducted by the Eastern Cooperative Oncology Group (Robert L. Comis, MD, Chair) and supported in part by Public Health Service grants nos. CA23318, CA66636, CA21115, CA04919, CA73590, CA58416, VA14028, CA04920, and CA16116 from the National Cancer Institute, National Institutes of Health, and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Address reprint requests to David J. Adelstein, MD, The Cleveland Clinic Foundation, Department of Hematology and Medical Oncology, Desk R35, 9500 Euclid Ave, Cleveland, OH 44195; email: adelstd@ccf.org.

0732-183X/03/2101-92/$20.00

DOI: 10.1200/JCO.2003.01.008

One of the major obstacles to the study of patients with unresectable head and neck cancer is the definition of unresectability.[14] The anatomic criteria for unresectability are not standard and vary from surgeon to surgeon and institution to institution. Additional patient factors including age, performance status, and the willingness to accept surgical morbidity also affect resectability. This makes interpretation of the literature difficult. In the first-generation Head and Neck Intergroup trial, careful anatomic definitions of unresectability were used.[11] These same definitions were again used by the ECOG pilot study[13] and were also chosen for this clinical trial. Although some of these patients might have been amenable to surgery, particularly at major medical centers, the population studied is nonetheless well defined and clearly has advanced disease. The use of these kinds of careful definitions ensures some degree of uniformity and interpretability for these trials.

PATIENTS AND METHODS

Eligibility for this clinical trial required a histologically confirmed diagnosis of squamous cell or undifferentiated carcinoma of the head and neck, excluding primaries originating in the nasopharynx, paranasal sinus, or parotid gland. Using the American Joint Committee on Cancer 1988 staging system,[15] stage III or IV disease was necessary, with no evidence of distant hematogenous metastases. A careful evaluation for resection was required from the responsible surgeon, and criteria for unresectability were carefully defined for individual primary site as follows: (1) hypopharynx: the tumor must extend across the midline of the posterior pharyngeal wall or be fixed to the cervical spine; (2) larynx: there must be either direct extension into surrounding muscle or skin or greater than 3 cm of subglottic extension; (3) oral cavity: the lesion must be so extensive that a functional reconstruction was not possible; (4) base of tongue: the tumor must extend into the root of tongue, or the patient must refuse a recommended total glossectomy; and (5) tonsil: the tumor must extend into the pterygoid region as manifested by clinical trismus or demonstrated radiographically, or there must be extension of tumor across the midline of the pharyngeal wall or directly into soft tissue of the neck.

In addition, patients with neck lymph node metastases fixed to the carotid artery, the mastoid, the base of skull, or the cervical spine were also considered unresectable. Medical unsuitability for resection was not sufficient for patient eligibility. Similarly, patient refusal of a surgical procedure, except in the case of a recommended total glossectomy, was not considered a reason for unresectability. A tumor map and a clear statement regarding the reason for unresectability were required from the responsible investigator and were reviewed by the study chairmen (D.J.A. and G.L.A.) in every case.

Eligibility also required an ECOG performance status of 0 or 1, with adequate hematologic, renal, and hepatic function, and normal serum calcium. Patient availability and compliance with adequate long-term follow-up was required, as was a pretreatment assessment by the investigator that the patient could withstand intensive multimodality treatment. Both measurable and evaluable disease were acceptable for patient entry.

Prior treatment of any kind for this cancer rendered a patient ineligible for this study. Any prior head and neck or lung cancer, or any other previous malignancy from which the patient had not been disease-free for more than 5 years (except a resected basal or squamous cell skin cancer or a cervical cancer in situ) also excluded patient entry. Patients with an unknown primary site but with squamous cell cancer involving neck nodes were not eligible. Pregnant or lactating women were not eligible.

This study was conducted under the auspices of ECOG and SWOG and was approved by the individual institutional review boards of all participating institutions. Written informed consent was required from all patients before the start of any therapy.

The pretreatment staging evaluation included a medical history, physical examination, chest radiograph, and electrocardiogram. An examination under anesthesia was recommended to include direct laryngoscopy, bronchoscopy, esophagoscopy, and nasopharyngoscopy when appropriate. A complete blood cell count and serum chemistries including creatinine, magnesium, calcium, blood urea nitrogen, bilirubin, alkaline phosphatase, AST, ALT, and albumin were obtained. All patients underwent a pretreatment dental evaluation, with appropriate care, and a pretreatment audiogram. Computed tomographic scans or magnetic resonance imaging of the involved head and neck region were performed when indicated.

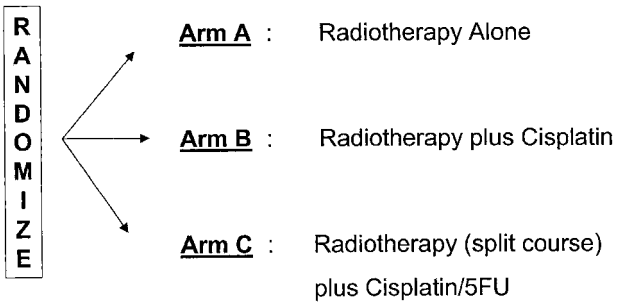

Fig 1. Treatment schema.

On study entry, eligible patients, stratified by primary site, tumor extent (T1 to T3 *v* T4), and nodal status (N0 *v* N1 *v* N2/3) were randomly assigned to one of three treatment arms (Fig 1). Arm A consisted of radiation therapy administered to a total dose of 70 Gy given in single, daily, 2-Gy fractions. The radiation was given as a continuous course with no split. Arm B consisted of identical radiation therapy, with concurrent single-agent cisplatin, 100 mg/m^2 intravenously on days 1, 22, and 43 of the radiation. Arm C chemoradiotherapy (Fig 2) consisted of three courses of a 4-day continuous infusion of fluorouracil, 1,000 mg/m^2/d, with a cisplatin bolus injection of 75 mg/m^2 on day 1, given every 4 weeks. Concurrent radiation therapy, at a rate of 2 Gy/d, was split between the first chemotherapy course (30 Gy) and the third chemotherapy course (30 to 40 Gy). A total dose of 60 to 70 Gy was therefore given, depending on the response. The radiation therapy break was planned to allow for the possibility of surgical resection in those patients rendered resectable after the first two courses of chemotherapy and the first 30 Gy of radiation. Patients who had achieved a complete response after this induction or who remained unresectable proceeded, without surgery, to complete chemoradiotherapy.

The aim of the radiation treatment was to include the gross primary tumor with a generous margin (generally 2 cm), as well as the entire neck and supraclavicular fossae. Field reductions at approximately 40 to 44 Gy were suggested to exclude the spinal cord from the large photon fields. At a total dose of 44 Gy, only the primary tumor and clinically or radiographically involved nodes were treated with a margin of 1 cm. For those patients undergoing resection on arm C, the entire operative field and incisions were to be included in the second phase of treatment. Suggested radiation therapy portals were provided to all investigators. A megavoltage source, either cobalt 60 or linear accelerator with energy of 6 MV or less, was required. Electron beams of suitable energy could be used in the final portion of treatment to boost the primary tumor site or grossly involved lymph nodes. Opposed lateral fields were recommended, although in selected cases, anterior-posterior minimantle fields encompassing the primary tumor and upper and lower necks could be used. Each field was to be treated each treatment day, 5 d/wk. A single anterior supraclavicular field was to be treated to a dose of 50 Gy unless gross disease was initially present in this region. Treatment for such disease was then to be boosted to the total dose of 70 Gy.

Aggressive hydration and antiemetic therapy was used with all cisplatin administration. The use of colony-stimulating factors was explicitly discour-

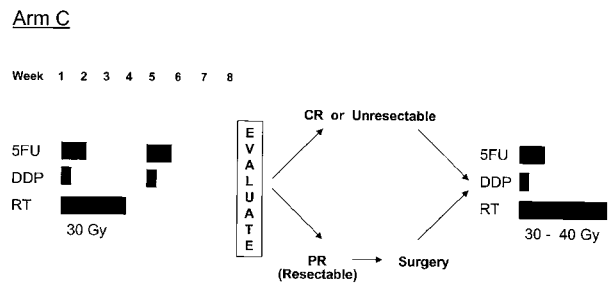

Fig 2. Detail of treatment schema for arm C. 5 FU, fluorouracil; DDP, cisplatin; RT, radiation therapy, CR, complete response; PR, partial response.

aged. Dose modifications for the cisplatin administration for patients enrolled in arm B were defined for nadir or treatment day leukopenia or thrombocytopenia as well as for any nephrotoxicity, neurotoxicity, or ototoxicity. For patients enrolled on arm C, dose modifications were not made. Instead, subsequent courses of chemotherapy were not given in the face of residual mucositis or myelosuppression. If mucositis or myelosuppression required a delay of more than 3 weeks, the next chemotherapy cycle was deleted.

Except for the defined treatment break for patients enrolled on arm C, interruptions in radiation therapy were not planned. Completion of the radiation therapy in the allotted time period was encouraged. It was anticipated that radiation therapy would continue despite the development of significant mucositis and or myelosuppression, particularly in the concurrent treatment regimens.

Definitions of response were conventional. Patients enrolled on arms A and B completed all of their planned treatment before any assessment of response. Patients enrolled on arm C were evaluated for possible resection 3 weeks after completing the second cycle of chemotherapy and again for response after completing all treatment. Those arm C patients believed to have achieved a clinical complete response after the second cycle of chemotherapy, and those patients believed to have continued evidence of unresectable disease at this time, proceeded to receive the third course of concurrent chemoradiotherapy beginning on or about day 56. Surgical resection was recommended for those patients who had achieved a partial response and were now considered resectable. The final course of chemoradiotherapy could then begin 2 to 6 weeks postoperatively, depending on patient recovery. Progressive disease at this first evaluation point mandated removal from trial. Patients enrolled on arm C received a total radiation dose of 70 Gy except for those who underwent surgical resection and were found to have no residual viable tumor. A total dose of 60 Gy was recommended in that situation.

The extent of midcourse surgery for arm C patients was defined on the basis of the residual disease present, not the original tumor, and resection was only to be performed if it was believed to be potentially curative; that is, if tumor-free margins and a functional reconstruction were possible. The possibility that previously unresectable patients might undergo successful tumor resection after chemoradiotherapy was recognized and considered acceptable. An appropriate neck dissection was recommended on the basis of initial disease extent.

At the completion of all planned therapy, any patients with residual disease, irrespective of treatment arm, could be considered for salvage surgical resection. The results of this salvage surgery would not impact response assessment, however. Elective neck dissection was also suggested for those patients with initial N2 or greater neck disease who had achieved a complete response at the primary site. After the completion of all therapy, patients were followed at regular and frequent intervals. It was recommended that any suspected recurrences be biopsied.

The major end point of the study was overall survival. Additional end points included disease-specific survival (failure being defined as death from disease) and complete response rate, with secondary end points being toxicity (using common toxicity criteria) and recurrence patterns. Survival was calculated from the date of patient registration.

The original accrual goal for this study was 462 patients, which was identified as necessary to detect an increase of 50% in median survival between the control arm (radiation therapy alone) and either of the two experimental arms, with 80% power using a two-sided log-rank test, two planned interim analyses, and each treatment comparison with a type I error of 0.025 to preserve an overall type I error of 0.05 for the trial. An accrual rate of 84 patients/yr was projected. Because of slow accrual, in 1997, at the time of the first interim analysis, the ECOG Data Monitoring Committee agreed to reduce the accrual goal to 362 patients. Because the questions being asked were naturally one-sided, the design was changed to perform a one-sided test. If the original design was modified to use a one-sided test, the type I error for each treatment comparison would be 0.0125. However, a less rigorous type I error for each comparison of 0.025 was deemed to be acceptable and was adopted. Interim analyses were scheduled at 128 and 170 deaths and were performed at 117 and 165 deaths. Criteria for early stopping were not met at these times. The study, however, was closed in December 1999 because of increasingly slow accrual. Fisher's exact tests were used to analyze the response rates.[16] The Kruskal-Wallis exact test was also performed to compare ordinal categorical variables across treatment arms.[17] Survival data were analyzed using the Kaplan-Meier method[18] and the significance tested by log-rank tests.[19] One-sided tests were used to compare the two experimental arms with the control (radiation therapy) arm. The comparison between the two experimental arms, however, was not planned and was believed to require a two-sided log-rank test. The results were analyzed as of January 2001.

Table 1. Study Population

	Arm			
	A	B	C	Total
Patients entered	102	97	96	295
Ineligible	6	10	6	22
No data	1	0	1	2
Analyzable	95	87	89	271

RESULTS

Between March 1992 and December 1999, 295 patients were entered on this study. SWOG entered 149 patients, and ECOG entered 146 patients. The study was administered and analyzed by ECOG.

Table 1 identifies the eligible and analyzable patients on each treatment arm. A total of 271 of the 295 patients were considered analyzable (ie, eligible with adequate data submitted). Among the reasons for ineligibility were resectability of the cancer in eight patients, metastatic disease in three patients, poor performance status in two patients, and an elevated calcium level in two patients. Among the 271 analyzable patients, two patients on each arm never received the assigned treatment for a number of miscellaneous reasons.

The clinical characteristics of the 271 analyzable patients are presented in Table 2. No differences were identified between the treatment arms in age, sex, race, performance status, and primary tumor site or tumor differentiation. Table 3 details the staging of the three treatment arms. Among the entire analyzable population, 96.3% of patients had stage IV disease, and 85% of all

Table 2. Clinical Characteristics

	Arm		
	A (n = 95)	B (n = 87)	C (n = 89)
Age (years)			
Mean (range)	56.7 (33-38)	56.8 (25-80)	57.8 (27-78)
Sex			
Male	86 (90.5%)	76 (87.4%)	76 (85.4%)
Female	9 (9.5%)	11 (12.6%)	13 (14.6%)
Race			
White	61 (64.2%)	53 (60.9%)	55 (61.8%)
African American	24 (25.3%)	28 (32.2%)	26 (29.2%)
Other	10 (10.5%)	6 (6.9%)	8 (9.0%)
Performance status			
0	32 (33.7%)	27 (31.0%)	32 (36.0%)
1	63 (66.3%)	60 (69.0%)	57 (64.0%)
Primary tumor site			
Oral cavity	16 (16.8%)	11 (12.7%)	9 (10.2%)
Oropharynx	52 (54.7%)	52 (59.8%)	56 (62.9%)
Hypopharynx	19 (20.0%)	17 (19.5%)	14 (15.7%)
Larynx	8 (8.5%)	7 (8.0%)	10 (11.2%)
Tumor differentiation			
Well differentiated	10 (11.8%)	13 (16.5%)	13 (16.9%)
Moderately well differentiated	48 (56.5%)	37 (46.8%)	41 (53.3%)
Poorly differentiated	27 (31.8%)	28 (35.4%)	22 (28.6%)
Undifferentiated	0	1 (1.2%)	1 (1.3%)

Table 3. Staging

Arm	T1	T2	T3	T4	Total
A					
N0			4	11	15
N1	1			10	11
N2		4	6	36	46
N3	1	2	3	17	23
Total		2	6	13	74
B*					
N0			1	13	14
N1		1		7	8
N2		2	8	27	37
N3	2	6	3	16	27
Total	2	9	12	63	
C					
N0			2	11	13
N1			1	9	10
N2		4	7	39	50
N3	3	4	2	7	16
Total	3	8	12	66	

*Staging incomplete in one patient on arm B.

patients had T4 or N3 tumors. No statistically significant staging differences were identified between the treatment arms.

Grade 3 and greater toxicity is detailed in Table 4. Data are available for 287 patients, including some of those patients considered ineligible. When significant, *P* values for comparisons between the treatment arms are provided. Nausea and vomiting were significantly worse for patients enrolled on arm B, the high-dose cisplatin arm. Not surprisingly, myelosuppression was worse for patients enrolled on the arms containing chemotherapy. When all grade 3, 4, and 5 toxicities are combined, arm B seemed most toxic. Both arms B and C proved more toxic than arm A. Toxic death, defined as death resulting from treatment within 30 days of treatment completion, was uncommon on this study.

A complete response was identified in 27.4% of the arm A patients, 40.2% of the arm B patients, and 49.4% of the arm C patients. The difference between arms A and C was statistically significant ($P = .002$) but was only marginally significant between arms A and B ($P = .07$). It must be noted, however, that the complete response rate for arm C included patients undergoing midcourse surgical resection.

With a median follow-up of 41 months for patients who are alive, the 3-year projected overall survival for the control arm, arm A, is 23% with a median survival of 12.6 months. The survival of patients enrolled on arm B proved significantly better than control, with a 3-year projection of 37%, a median of 19.1 months, and a *P* value of .014. Arm C produced results that were midway between arms A and B and were not statistically different than either. The 3-year projected survival was 27%, with a median survival of 13.8 months (Fig 3).

Similar results were seen for disease-specific survival rates. Of the 201 deaths, 134 deaths were due to disease (55 of 77 patients enrolled on arm A, 37 of 59 on arm B, and 42 of 65 on arm C). For arm A, the 3-year projected disease-specific survival was 33%, for arm B it was 51%, and for arm C it was 41%. Again, projected disease-specific survival for patients enrolled on arm B was significantly better than for those on arm A ($P = .01$). Projected disease-specific survival for patients enrolled on arm C was not significantly different than either of the other two treatment arms (Fig 4).

A site of first recurrence was identified when possible. No differences could be identified among the three treatment arms. Specifically, it did not seem that chemotherapy affected the likelihood of distant recurrence when compared with radiation therapy alone. Distant metastases were the first site of recurrence in 17.9% of arm A patients, 21.8% of arm B patients, and 19.1% of arm C patients; the differences were statistically insignificant.

Compliance with the treatment regimen, as measured by treatment completion, was possible in 65 of the arm C patients (73%), 74 of the arm B patients (85.1%), and 88 of the arm A patients (92.6%; arm A *v* C, $P < .001$; arm B *v* C, $P = 0.05$). If those patients not completing treatment are excluded, the treatment duration, as displayed in Table 5, was close to that prescribed by the protocol. Note that almost 7 additional weeks were required to complete treatment for arm C patients when compared with patients on arms A and B, an observation resulting from the planned midcourse treatment break for possible surgery in patients enrolled on arm C.

This potential for surgical resection was the rationale for the split course of radiation therapy for patients enrolled on arm C. When surgical results, however, were analyzed, little difference in the rate of surgical resection was observed among the three treatment arms (Table 6). Ultimately, 21% of all patients underwent surgery; neck dissection alone was performed in 56% of the surgical cases.

DISCUSSION

This multi-institutional Intergroup trial demonstrates the superiority of concurrent single-agent cisplatin chemoradiotherapy over radiation therapy alone in patients with advanced unresectable squamous cell head and neck cancer. Survival and disease-specific survival were statistically better in well-defined and well-matched

Table 4. Toxicity (grade 3-5)

	Arm			*P*		
	A (N = 98)	B (N = 95)	C (N = 94)	A versus B	A versus C	B versus C
Nausea/vomiting	6	15	8	.03		
Mucositis/dysphagia	32	43	44	.08	.06	
Leukopenia	1	40	29	< .001	< .001	< .001
Thrombocytopenia	0	3	3			
Anemia	0	17	18	< .001	< .001	
Renal	1	8	0	.01		.01
Skin	13	7	2		.005	
All grade 3-5	51	85	72	< .0001	< .001	.02
Feeding tube	39	49	48			
Toxic death	2	4	2			

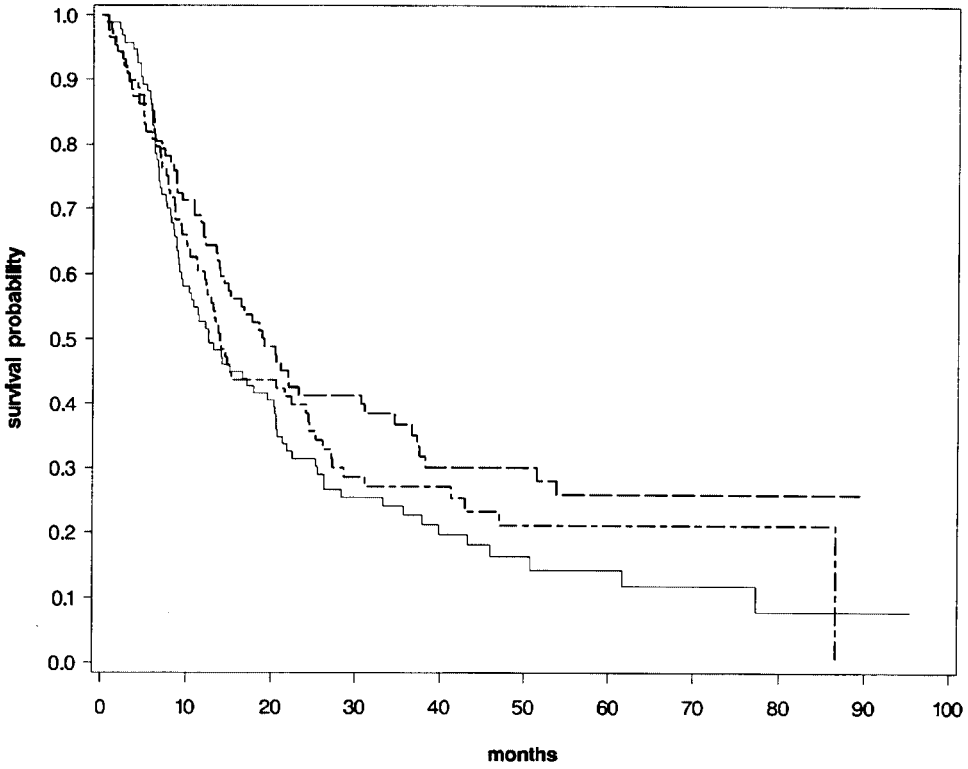

Fig 3. Kaplan-Meier projected overall survival. Arms A, B, and C. A = ———; Arm B = — — —; Arm C = —·—·.

patient cohorts. The results reported for the radiation therapy alone control arm are identical to those seen in the previous Intergroup unresectable cancer study in a similarly defined patient population,[11] further confirming the validity of these observations. Not surprisingly, toxicity was greater when chemotherapy was added to the radiation treatment. Toxicity was, however, quite manageable, particularly for a cooperative group setting. These data would strongly support the adoption of concurrent single-agent cisplatin and radiation as a standard of care for patients considered inappropriate for surgical resection due to disease extent.

The role of systemic chemotherapy in the definitive management of patients with squamous head and neck cancer has undergone intensive investigation during the last 30 years. Despite surprising chemosensitivity to drugs such as cisplatin and fluorouracil,[20-22] extensive phase III testing of induction chemotherapy schedules has failed to demonstrate any reproduc-

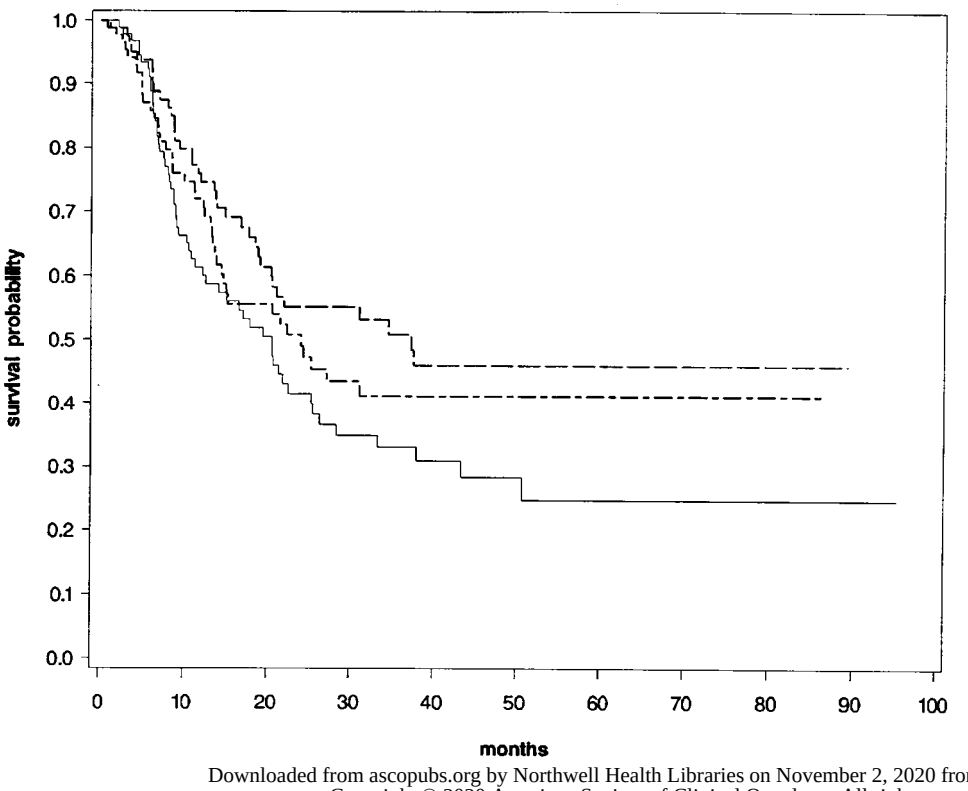

Fig 4. Kaplan-Meier projected disease-specific survival. Arms A, B, and C. A = ———; Arm B = — — —; Arm C =—·—·.

Table 5. Mean Treatment Duration (days)*

	Arm		
	A	B	C
Per protocol	47	47	82
Actual (range)	52.1 (46-77)	52.5 (46-91)	98.9 (80-163)

*In patients completing treatment.

ible survival benefit.[7,23] Concurrent chemotherapy and radiation, however, has been a more consistently successful treatment, and a survival benefit from the addition of such single agents as fluorouracil,[24,25] bleomycin,[26] mitomycin C,[27] and cisplatin[28,29] has been observed. Recently, several single- and multi-institutional trials have reported both a survival and locoregional control benefit from more aggressive concurrent radiation and multiagent chemotherapy regimens.[30-33] Significant toxicity has also resulted from these aggressive treatment regimens, raising concern that these approaches may not be appropriate in the community. This study was conducted by the cooperative groups in a number of community hospitals. The toxicity was manageable and the benefit clear.

Table 6. Surgery

	Arm		
	A (n = 95)	B (n = 87)	C (n = 89)
Midcourse			
Primary and neck			4
Neck only			10
Salvage			
Primary site only	2	—	—
Primary and neck	4	10	4
Neck only	12	11	2
Total	18	21	20

The question, however, is why the multiagent chemotherapy regimen was not more successful than the single-agent cisplatin arm. Several observations are apparent. First, arm C used a split-course radiation therapy schedule to allow for the possibility of midcourse surgery in patients rendered resectable after initial chemoradiotherapy. It is well recognized that this is a suboptimal way to deliver radiation,[34,35] and the limited number of patients undergoing surgical resection demonstrates the failure of this treatment strategy. In contrast to previous studies of this regimen,[13,36] only 14 of the 89 arm C patients (16%) underwent midcourse surgical resection, and in 10 of these 14 (71%), surgery consisted of a neck dissection alone. The result was the use of a suboptimal split-course radiotherapy regimen without the benefit of any major increase in the number of surgical resections. The complexity of the multiagent split-course schedule also caused difficulty, and failure to complete the planned therapy was more common in patients enrolled on this treatment arm. Thus, the failure of arm C to improve on the results obtained with single-agent cisplatin may reflect a design flaw in the treatment schedule that might have obscured any potential benefit from more aggressive chemotherapy. The concept of salvage surgery, however, even in patients initially deemed unresectable, is a viable one. Twenty patients underwent salvage resection of the primary tumor site; another 25 patients underwent a neck dissection, suggesting the importance of ongoing surgical involvement in the management of these patients.

In conclusion, concurrent chemotherapy and radiation can be safely administered with acceptable toxicity in a multi-institutional, cooperative oncology group trial. The addition of concurrent high-dose, single-agent cisplatin to conventional single daily fraction radiation therapy significantly improves survival. Further investigation of this approach is indicated.

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