

# Efficacy of Adjuvant Chemotherapy for Patients With Resectable Head and Neck Cancer: A Subset Analysis of the Head and Neck Contracts Program

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To evaluate the efficacy of adjuvant chemotherapy for patients with advanced head and neck squamous cancer, the Head and Neck Contracts Program conducted a three-arm study comparing standard surgery and radiation, induction chemotherapy (cisplatin and bleomycin) plus standard therapy, and induction chemotherapy plus standard therapy followed by maintenance cisplatin for 6 months. As previously reported, this trial of 462 patients demonstrated no significant difference in disease-free survival or survival, but a significantly lower metastatic rate in the maintenance arm. To determine whether particular subgroups may have benefited from adjuvant therapy, we evaluated results based on primary site, and tumor (T) and node (N) stage. Of the 192 patients with oral cavity cancer, those on the maintenance arm had a significantly improved 3-year disease-free survival (67%) compared with the standard arm (49%) or induction arm (44%) (overall  $P = .05$ ). For hypopharyngeal and laryngeal cancers there was no marked overall benefit. For the 106 patients with T<sub>1</sub> plus T<sub>2</sub>

disease, there was marginal improvement in disease-free survival for the maintenance group (72%) compared with the standard group (47%) or induction group (43%) (overall  $P = .09$ ). There was no advantage for patients with T<sub>3</sub> and T<sub>4</sub> disease. There was superior disease-free survival for patients with N<sub>1</sub> disease on the maintenance arm (70%) compared with the standard arm (42%) ( $P = .024$ ). The same was true for disease-free survival in 109 patients with N<sub>2</sub> disease: standard (52%), induction (30%), maintenance (84%) (overall  $P < .001$ ). There was no benefit for N<sub>3</sub> disease. A significant survival advantage with maintenance chemotherapy was only seen for N<sub>2</sub> disease (overall  $P = .04$ ). Since head and neck cancer patients are a heterogeneous group, there may be particular sites and stages for which adjuvant chemotherapy would be advantageous, and subset analysis can help indicate directions for new trials.

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**A**PPROXIMATELY 46,000 new cases of squamous cancer of the head and neck were diagnosed in 1988.<sup>1</sup> The majority of these patients presented with advanced disease, stage

III or IV, and despite optimal treatment with surgery and/or radiation, less than half will be cured.<sup>2</sup> In an attempt to improve outcome, chemotherapy has been added to combined modality programs—as induction treatment before standard therapy, concurrently with radiation therapy, and as adjuvant therapy following definitive primary treatment.<sup>3-5</sup>

The earliest use of chemotherapy in the primary treatment program was as a radiosensitizer, predominantly in patients with unresectable disease. Despite encouraging pilot data, most randomized trials have been negative. Only single-agent bleomycin, fluorouracil (5-FU), and mitomycin have been demonstrated to improve outcome compared with radiation alone.<sup>4,6,7</sup> The gain, however, has been modest. In recent years, chemotherapy has been evaluated in an induction or pretreatment role before primary treatment. Overall response rates approximate 70%, with 20% complete responses. At least eight randomized trials have evaluated the use of induction chemotherapy, some including adjuvant chemotherapy as well.<sup>5</sup> None have demonstrated benefit, and two studies have actually shown de-

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creased survival in patients who received induction chemotherapy when compared with controls.<sup>8,9</sup> Adjuvant or maintenance chemotherapy following standard treatment for head and neck cancer has rarely been tested alone in randomized studies. It has been added to trials of induction chemotherapy, so that the individual contribution of adjuvant chemotherapy is difficult to assess.

In 1987, we reported the results of the Head and Neck Contracts Study in which induction and maintenance chemotherapy were tested in patients with advanced head and neck cancer.<sup>10</sup> We found no significant difference in survival between the groups; the 5-year estimated disease-free survival for those rendered free of tumor at surgery was 64% for patients randomized to the maintenance arm, compared with 55% for the standard arm, and 49% for the induction arm. Time to distant metastasis as the first site of relapse was significantly longer for those on the maintenance arm, and the frequency of distant metastases as the first site of relapse was significantly lower for the maintenance arm. We concluded from this trial that one cycle of induction chemotherapy had no impact on outcome, and that maintenance chemotherapy, while reducing distant metastases, did not improve survival significantly.

One possible reason that efficacy of adjuvant chemotherapy has not been demonstrated is the heterogeneity of this disease with survival differences dependent on site and stage. There may be particular subgroups of patients who would benefit from adjuvant chemotherapy, but when combined in large trials, that improvement is obscured. To investigate this possibility, we evaluated outcome for subsets of patients from the Head and Neck Contracts Program based on primary site, tumor (T) status, and node (N) status. The goal of our effort was to generate new hypotheses to be tested in future clinical trials.

#### METHODS

Between 1978 and 1982, the National Cancer Institute supported the Head and Neck Contracts Program, a multi-institutional trial of induction and adjuvant chemotherapy in head and neck cancer. Four hundred sixty-two patients with stages II (pyriform sinus), III, and IV (oral cavity, hypopharynx, and larynx) resectable head and neck squamous cancers were stratified by institution, primary site, and stage and randomized to (1) surgery and postoperative radiotherapy, (2) induction chemotherapy with one cycle of cisplatin (100

mg/m<sup>2</sup>) and bleomycin (15 mg/m<sup>2</sup> × 5 days), followed by standard therapy, or (3) induction chemotherapy, standard therapy, and maintenance chemotherapy with monthly cisplatin (80 mg/m<sup>2</sup>) for 6 months.

Forty-five percent of patients randomized to maintenance chemotherapy did not receive the required treatment because of strict toxicity guidelines, patient refusal, disease recurrence, or death. Patients were analyzed in the group to which they were randomized even if they did not complete the entire treatment program,<sup>11</sup> with the exception of one patient randomized to receive standard therapy but who received induction chemotherapy and was placed in the latter group for analysis. Disease-free survival was calculated from the time of surgery to first recurrence for patients with negative margins at surgery. This excluded 32 of the 443 assessable patients who were not rendered disease-free at surgery. Survival was determined for all 443 assessable patients from study entry until death from any cause or date last seen. For subset analysis, disease-free survival and survival were analyzed by arm for each site, T stage, and N stage. The Cox life-table regression model was used to determine the relative importance of these variables simultaneously on disease-free survival.<sup>12</sup> The Kaplan-Meier method was used to estimate disease-free survival and survival.<sup>13</sup> All the curves were compared with one another using the log-rank test.<sup>14</sup> All *P* values in this report are of the two-sided type.

#### RESULTS

One hundred ninety-two patients with oral cavity cancer entered the trial. The three arms were comparable with regard to patient characteristics (Table 1). Patients were predominantly men with a median age of 56 to 57 years and a mean Karnofsky performance status of 88 to 89. Slightly more patients had stage IV disease on the induction arm. There was an overall difference in disease-free survival among the three groups (overall *P* = .05), with the maintenance arm superior to both the standard (*P* = .11) and induction (*P* = .015) arms (Fig 1). The 3-year disease-free survival rates were 67% for the maintenance group, 49% for the standard group, and 44% for the induction group. There was no difference in survival. For the 148 patients with laryngeal cancer, the patient characteristics among the three arms were similar. For this subgroup there was no significant difference in disease-free survival (overall *P* = .39, Fig 2) or survival between the three arms. The 71 patients with hypopharyngeal cancer (predominantly pyriform sinus) were evenly distributed with regard to patient characteristics between the three arms, although the maintenance arm had fewer patients with stage IV disease, and the induction arm had more patients with stage II disease. The



Table 1. Patient Characteristics by Subgroups

Characteristics	Site								
	Oral Cavity			Laryngeal			Hypopharyngeal		
Arm	S	I	M	S	I	M	S	I	M
No. patients	69	62	61	50	50	48	24	24	23
Median age (yrs)	56	56	57	56	57	57	58	54	57
Male sex (%)	91	82	89	88	82	85	83	88	91
Mean performance status	88	88	89	88	86	86	88	88	84
Stage (%)									
II	—	—	—	—	—	—	12	17	13
III	43	31	44	56	50	50	17	12	26
IV	57	69	56	44	50	50	71	71	61

Abbreviations: S, standard; I, induction chemotherapy; M, maintenance chemotherapy.

3-year disease-free survival was 46% for the standard arm, 25% for the induction arm, and 70% for the maintenance arm (overall  $P = .11$ , Fig 3). The maintenance arm was superior to the induction arm ( $P = .027$ ), but much less so when compared with the standard arm ( $P = .15$ ). There was no difference in survival.

Outcome in squamous cancers of the head and neck is related to stage as defined by the American Joint Committee on Cancer.<sup>15</sup> One hundred six patients had less extensive local disease ( $T_1$  plus  $T_2$ ), and the three arms were comparable

with regard to age, sex, and performance status. Disease-free survival was 47% for the standard group, 43% for the induction group, and 72% for the maintenance group. This was of marginal significance (overall  $P = .09$ , Fig 4). The maintenance arm was superior to either the induction ( $P = .045$ ) or standard ( $P = .064$ ) arm. There was no significant impact on survival. For the 305 patients with more bulky or extensive disease ( $T_3$  and  $T_4$ ), the three arms had similar patient characteristics. Delivery of maintenance chemotherapy had no advantage over standard therapy

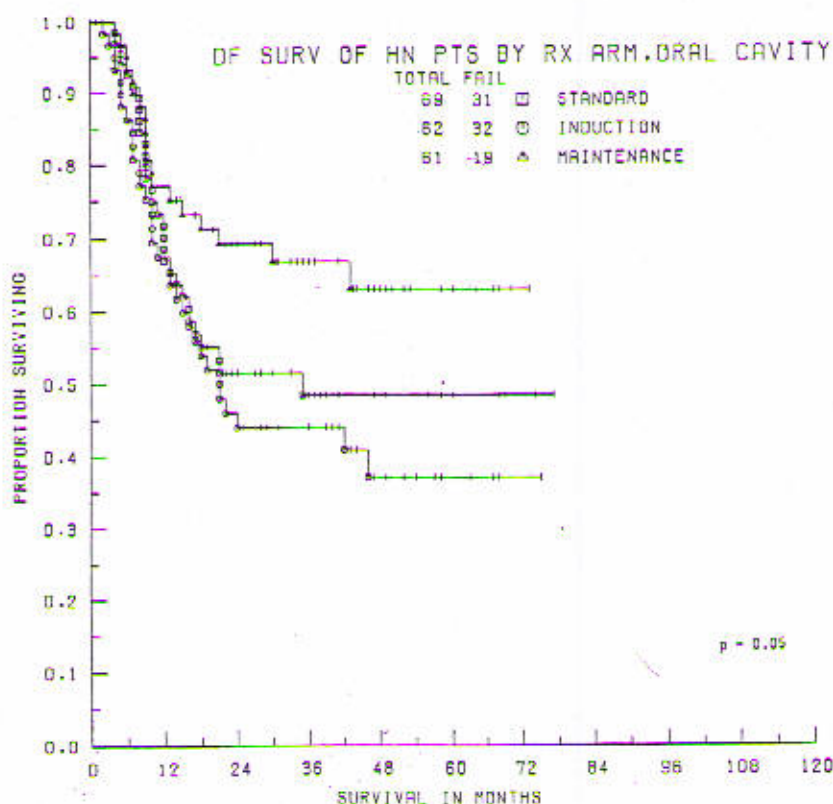


Fig 1. Disease-free survival time according to treatment group for 192 patients with oral cavity cancer. Outcome is superior for the maintenance arm compared with the standard and induction arms (overall  $P = .05$ ).



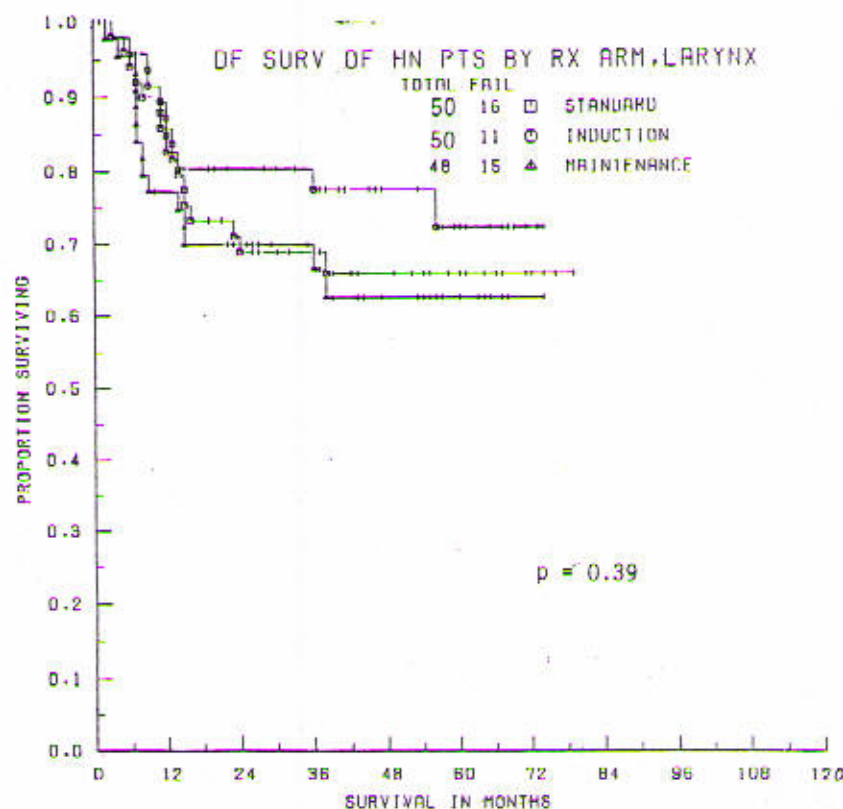


Fig 2. Disease-free survival time according to treatment group for 148 patients with laryngeal primaries (overall  $P = .39$ ).

with regard to disease-free survival (overall  $P = .68$ ) or survival.

Subset analysis was also performed by arm for patients with nodal involvement. Within each subgroup, the arms were evenly balanced for sex, age, and performance status. Of the 97 patients with  $N_1$  disease, there was an overall statistically significant difference in disease-free survival among the three arms (overall  $P = .05$ , Fig 5), with the maintenance arm at 70% superior to the standard arm at 42% ( $P = .024$ ). Among the 109 patients with  $N_2$  disease, the maintenance arm had superior disease-free survival (overall  $P < .001$ , Fig 6). The maintenance arm (84%) was superior to either the induction (30%) ( $P < .001$ ) or standard (52%) ( $P = .015$ ) arm. If patients had more extensive nodal involvement,  $N_3$ , chemotherapy had no influence on outcome (overall  $P = .77$ ). Only in patients with  $N_2$  disease was there a significantly better survival for the maintenance arm (overall  $P = .04$ , Fig 7).

The effects on disease-free survival of nodal status and site of the primary were evaluated simultaneously using the life-table regression model of Cox.<sup>12</sup> After accounting for treatment

and site in the model, the importance of nodal status as a predictor of disease-free survival remained ( $P < .001$ ). Similarly the site of the primary was an important predictor after accounting for treatment and nodal status ( $P = .008$ ). Thus, both factors have an independent and important impact on disease-free survival.

#### DISCUSSION

Adjuvant chemotherapy following primary treatment has not been studied extensively in head and neck cancer. However, animal models support this approach.<sup>16</sup> In designing an adjuvant program in head and neck cancer, one would want to select a group of patients with a high likelihood of having either residual microscopic disease following primary treatment or micrometastatic disease. Thus, most adjuvant trials include patients with advanced, resectable disease. Second, chemotherapy should be given early following primary treatment, and it should be intensive to avoid the development of drug resistance. Third, only effective drugs should be used. No trial to date has met these criteria, but there



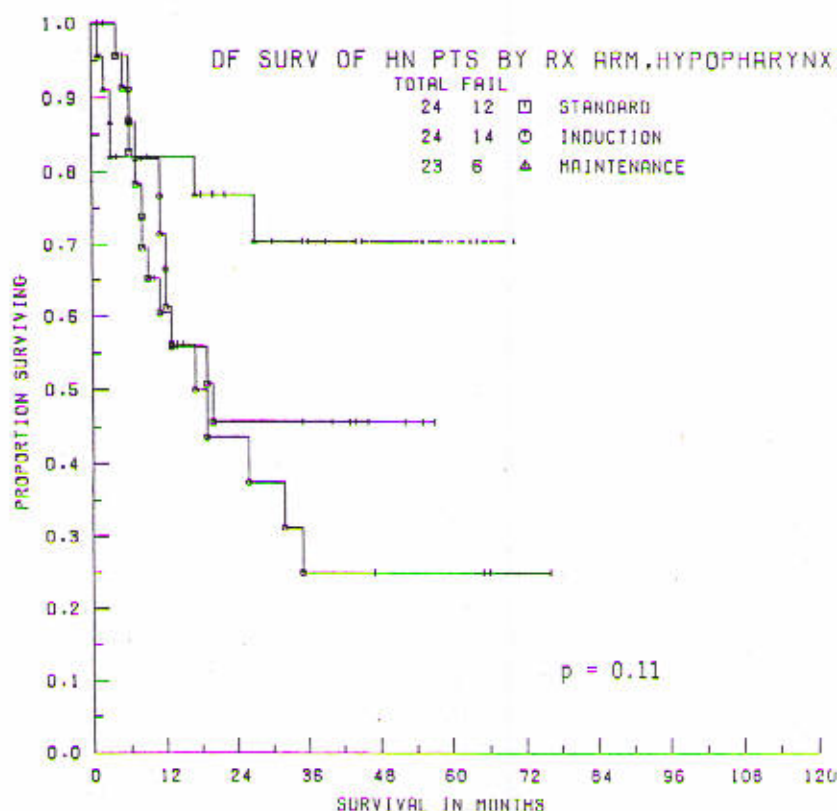


Fig 3. Disease-free survival time according to treatment group for 71 patients with hypopharyngeal primaries (overall  $P = .11$ ).

are some suggestive benefits of adjuvant chemotherapy for head and neck cancer that cannot be ignored.

Two nonrandomized trials of adjuvant chemotherapy for high-risk patients have demonstrated improved outcome. Huang et al administered six cycles of bleomycin, methotrexate, vinblastine, and chloroethyl cyclohexyl nitrosourea (lomustine; CCNU) to 20 patients with stages III and IV squamous cancers whose primary treatment was either radiotherapy or surgery and postoperative radiotherapy.<sup>17</sup> Survival and disease-free survival for this group were superior to that for 24 concurrently treated patients who declined chemotherapy. Johnson et al treated 50 patients with extracapsular spread of disease, as noted in the resection specimen, with 18 courses of methotrexate, 5FU, and leucovorin.<sup>18</sup> At approximately 2 years, eight patients died of unrelated causes, and 66% of the remaining patients were disease-free. In their previous experience with patients who had extracapsular spread, survival was only 38%.

There are at least six randomized trials of

adjuvant chemotherapy in patients with advanced, resectable head and neck cancer (Table 2).<sup>10,19-25</sup> In most of these trials, induction chemotherapy or chemotherapy concurrent with radiation was given as well. Rentschler et al randomized 60 patients to surgery and postoperative radiotherapy versus methotrexate in escalating doses administered weekly for four doses before surgery and following surgery, and for eight doses after radiation therapy.<sup>19</sup> At a median follow-up of 43 months, there was no significant difference in disease-free survival or survival at 55%.

Taylor et al reported on 95 patients randomized to standard therapy consisting of surgery and/or radiation or to induction chemotherapy with methotrexate followed by standard therapy followed by methotrexate every 3 months for 1 year.<sup>20</sup> The authors found poor compliance to the adjuvant chemotherapy because of severe mucositis, and after the first 35 patients had entered the study, the regimen was shortened and intensified to cisplatin and doxorubicin for four cycles. A quarter of the patients refused this chemother-



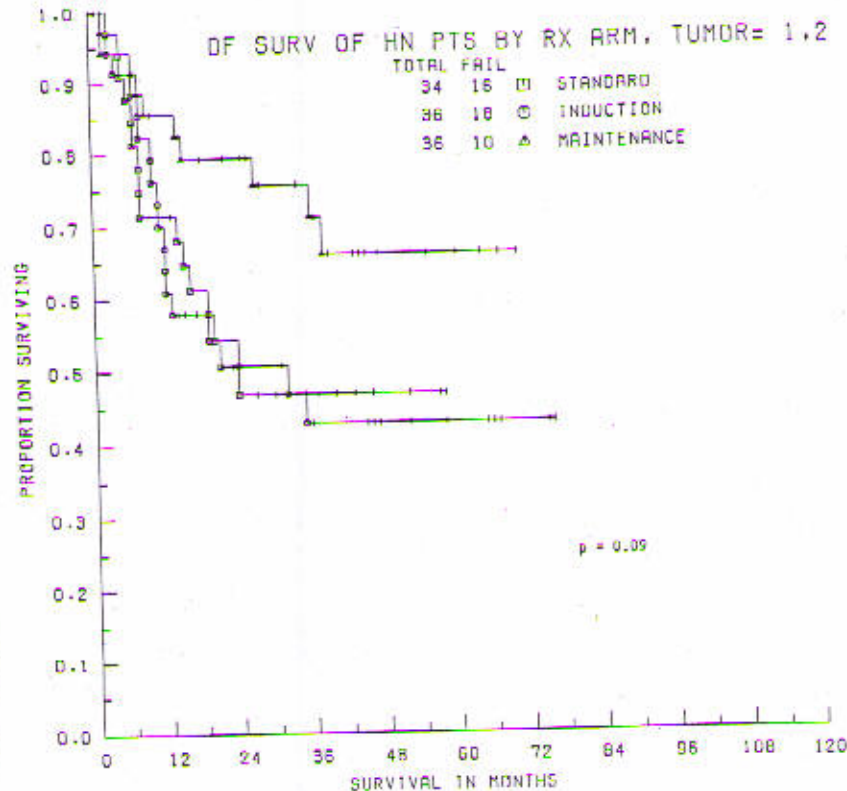


Fig 4. Disease-free survival time according to treatment group for 106 patients with  $T_1$  and  $T_2$  tumors. Outcome is better for the maintenance arm compared with the standard and induction arms (overall  $P = .09$ ).

apy as well. At a median follow-up of four years, there was no significant difference between the chemotherapy and control groups.

Holoye et al randomized 83 patients with advanced head and neck cancer to standard therapy or to standard therapy plus two cycles of chemotherapy (cyclophosphamide, methotrexate, 5-FU, and bleomycin) before treatment.<sup>21,22</sup> If patients responded to induction chemotherapy, two cycles of adjuvant chemotherapy were given after primary treatment. Poor compliance led to eventual discontinuation of postoperative chemotherapy. At 2 years, survival was 43% in the control group and 31% in the chemotherapy group.

Ervin et al treated 144 patients with advanced head and neck cancer with two cycles of induction chemotherapy (cisplatin, bleomycin, methotrexate, and leucovorin [PBM]) followed by surgery and/or radiation therapy.<sup>23</sup> Following chemotherapy, surgery, and radiation, patients rendered disease-free were randomized to receive no further treatment or three cycles of adjuvant chemotherapy with PBM. Although 144 patients

entered the trial, only 46 entered the randomized adjuvant study, and of those 26 randomized to chemotherapy, only 10 received all three courses of treatment. The estimated failure-free survival at 3 years for the 26 patients on the adjuvant chemotherapy arm was 88%, compared with 57% for the 20 patients in the control group ( $P = .03$ ). An updated analysis reported a 2-year failure-free survival of 84% for the chemotherapy arm and 61% for the control arm ( $P = .14$ ).<sup>24</sup>

Szipirglas et al randomized 95 patients with anterior tongue or floor of mouth cancer to standard treatment, adjuvant immunotherapy, or adjuvant chemotherapy for 2 years with methotrexate and bleomycin.<sup>25</sup> Although adjuvant chemotherapy delayed time to recurrence, there was no difference in recurrence-free survival or survival between the three arms. Subset analysis demonstrated a significant survival advantage for the chemotherapy group in patients with  $T_1$ - $T_2$ ,  $N_0$  disease, while there was no advantage for patients with more advanced disease.

Why have we failed to prove benefit from adjuvant chemotherapy for head and neck can-



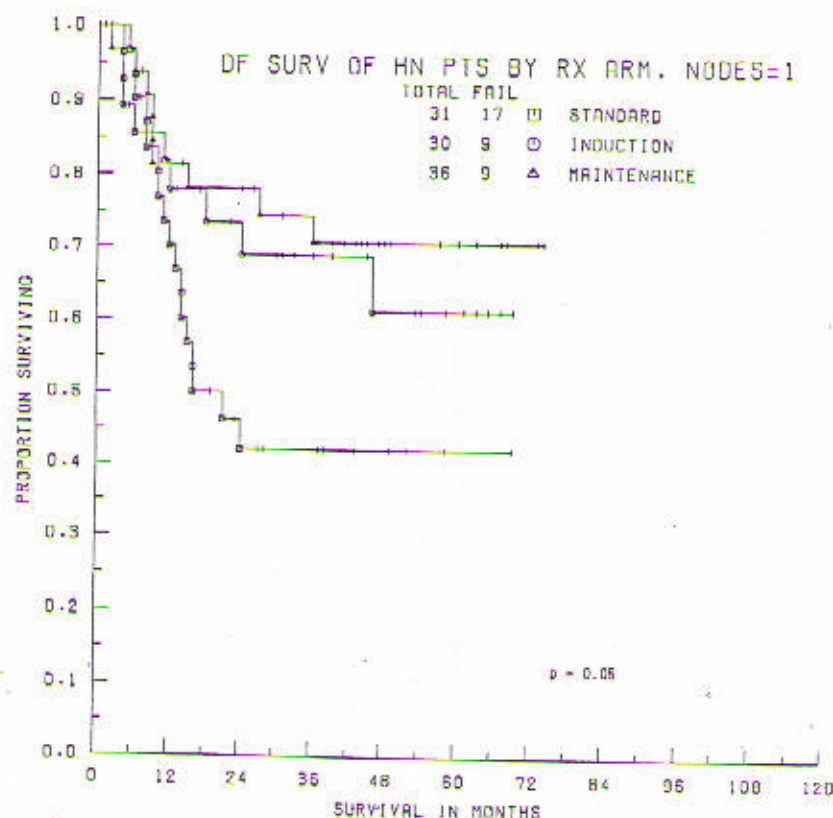


Fig 5. Disease-free survival according to treatment group for 97 patients with disease, demonstrating a trend toward better outcome for the maintenance arm compared with the standard arm (overall  $P = .05$ ).

cer? Perhaps the concept does not work. Squamous cancers of the head and neck have a low growth fraction, and the majority of remaining cells may not be sensitive to chemotherapy. Tumors may possess biochemical resistance, particularly if patients have previously been exposed to induction chemotherapy. Following primary treatment, vascularity to the tumor bed may be diminished, compromising chemotherapy delivery.

It may be that adjuvant chemotherapy will be beneficial, but the concept has not been tested adequately. Optimal regimens have not been used. Many trials, designed several years ago, delivered single-agent chemotherapy and were not particularly intensive. In almost every study, investigators reported poor tolerance or compliance to adjuvant chemotherapy, limiting the number of cycles delivered. Another factor may be the heterogeneity of this disease with survival differences dependent on site and stage. There may be particular subgroups who would benefit from adjuvant chemotherapy, but when combined with other subgroups in whom adjuvant

chemotherapy is not particularly beneficial, advantage may not be obvious. Subset analysis from the Head and Neck Contracts study suggests this. Patients with oral cavity cancer have an improvement in disease-free survival from maintenance chemotherapy, whereas patients with laryngeal primaries had no benefit. Because of this heterogeneity, we may be too conservative to detect larger differences between groups that are realistic to expect. When analyzing the data based on stage of disease, we found that relapse-free interval was improved by adjuvant chemotherapy in patients with less extensive tumors ( $T_1$  and  $T_2$ ), but not in those with more bulky disease ( $T_3$  and  $T_4$ ). The same was true for extensive nodal disease. Those with less extensive nodal disease had improved disease-free survival with adjuvant chemotherapy, whereas those with extensive nodal disease did not. Perhaps we have selected the wrong group to test adjuvant chemotherapy. Our findings would suggest that adjuvant chemotherapy may be more effective in patients with less extensive disease.

To place these conclusions in their proper



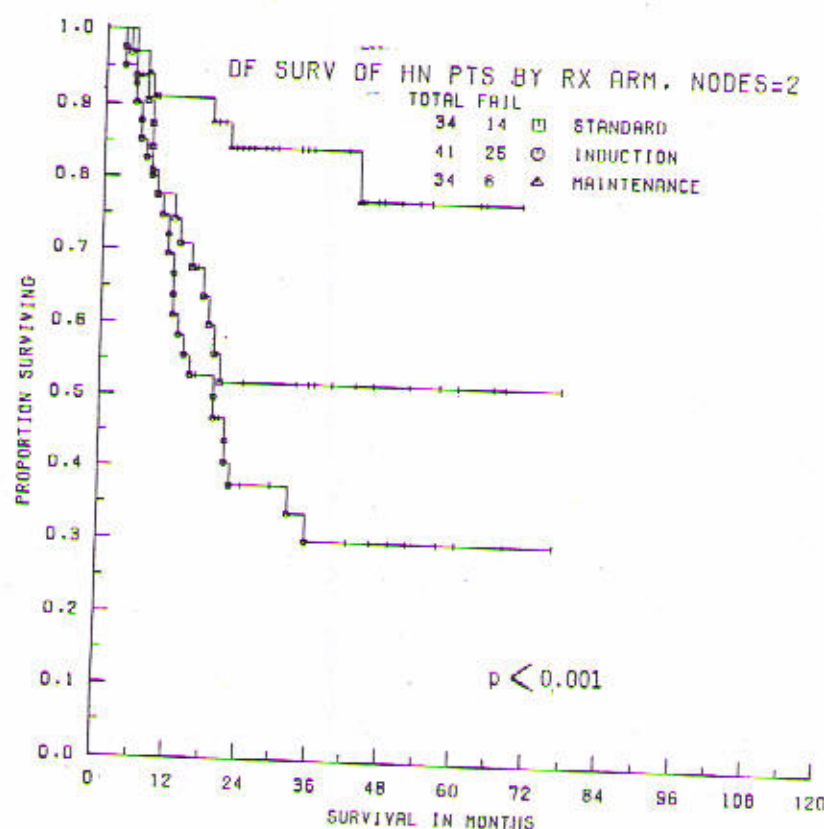


Fig 6. Disease-free survival time according to treatment group for 109 patients with N<sub>2</sub> disease, demonstrating a superior outcome for those on the maintenance arm compared with the induction and standard arms (overall  $P < .001$ ).

perspective, some statistical issues that underlie this (and any) retrospective analysis should be acknowledged. First, the conclusions should be viewed in the spirit of hypothesis generation as opposed to hypothesis testing, because the hypotheses examined were post hoc and not specified before the start of the study. Moreover, the hypotheses were based on the analysis of several subgroups of patients within the entire study population. New studies should be designed that formally test prospectively the findings presented in this report. One reason for conducting a new study is that many statistical tests were performed on these data, and thus our conclusions may have been influenced by the "multiple comparisons" problem.<sup>26-28</sup> When data in the same study are examined in a number of different subgroups, a certain number of false-positive findings are bound to arise. As the number of tests increases, so does the probability of a false-positive result. While there are a number of statistical procedures to adjust the  $P$  value and maintain an overall experiment-wide false-positive rate at a specified level,<sup>26,27</sup> their

use is frequently limited in practice by statistical assumptions that make it difficult to specify the precise degree of adjustment.

Another statistical reason that these findings should be tested prospectively is that the statistical power required to detect a specified treatment difference is affected by the sample size. A simple significance test may fail to reject the standard null hypothesis of equality in treatment efficacy between two treatments, although the true difference may be considerable.<sup>29</sup> In Fig 3, we observed an equivocal result for the effect of maintenance therapy in patients with a hypopharyngeal primary. A prospective study could be designed to have enough patients to insure that, with greater than 80% power, a specified treatment difference would be detected at the two-sided  $P = .05$  level. Thus, trials with more prolonged follow-up are necessary to detect modest differences that are important from a broader public health perspective.

Improvement in disease-free survival has not been translated into improved survival in these trials. Demonstrating a survival advantage from



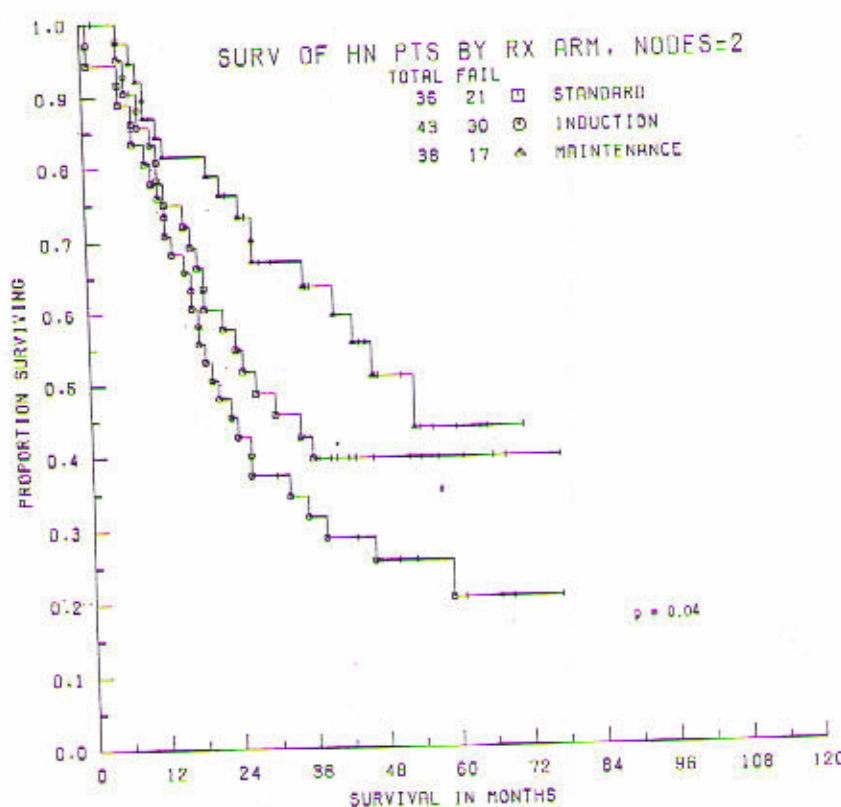


Fig 7. Survival time of 117 patients with N<sub>2</sub> disease by treatment group demonstrating better outcome for patients on the maintenance arm (overall  $P = .04$ ).

any combined modality approach is difficult in this population in which there is a significant death rate from second primaries and other medical problems.<sup>30,31</sup> In the trial by Rentschler et al<sup>19</sup> for example, almost half the patient deaths were unrelated to the primary cancer.

Future attacks on head and neck cancer may include definitions of biologic characteristics and growth regulatory mechanisms of squamous cancers. DNA content,<sup>32</sup> presence of keratin,<sup>33</sup> and C1q binding activity<sup>34</sup> may prove to be predictive of recurrence rate, so that those patients can be

selected who most need combined modality therapy. Finally, use of subgroup analyses may help us to design more focused trials in which large treatment differences in particular categories of patients may be more likely to occur. With these early leads, we should not abandon the concept of adjuvant chemotherapy in head and neck cancer.

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Table 2. Randomized Trials of Adjuvant Chemotherapy for Head and Neck Cancer

Investigators	No. Patients	Adjuvant Chemotherapy	% Disease-Free Survival (years)		% Survival (years)	
			Control	Chemotherapy	Control	Chemotherapy
Rentschler et al <sup>19</sup>	60	Mtx	59 (3)*	66	55 (3)	55
Taylor et al <sup>20</sup>	95	Mtx or CP, Adria	37 (3)*	50	41 (3)	41
Holoye et al <sup>21</sup> , Kun et al <sup>22</sup>	83	Bleo, cyclo Mtx, 5FU	64 (2)	59	43 (2)	31
Ervin et al <sup>23</sup> , Clark et al <sup>24</sup>	46	CP, bleo, Mtx	61 (2)	84	—	—
Szpirglas et al <sup>25</sup>	95	Mtx, bleo	47 (2)	52	58 (4)	58

Abbreviations: Mtx, methotrexate; CP, cisplatin; Adria, Adriamycin, doxorubicin (Adria-laboratories, Columbus, OH); bleo, bleomycin; cyclo, cyclophosphamide; 5FU, fluorouracil.

\*Estimated from published curves.



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