2006

Post-Operative Concurrent Chemoradiation with Mitomycin-C for Advanced Head and Neck Cancer

Amar Rewari

POST-OPERATIVE CONCURRENT CHEMORADIATION WITH MITOMYCIN-C FOR ADVANCED HEAD AND NECK CANCER

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

by

Amar Rewari

2006

POST-OPERATIVE CONCURRENT CHEMORADIATION WITH MITOMYCIN-C FOR ADVANCED HEAD AND NECK CANCER. Amar N. Rewari, Lynn D. Wilson, Yung H. Son, John K. Joe, Douglas A. Ross, Rose J. Papac, Clarence T. Sasaki, James J. Fischer, and Bruce G. Haffty. Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT.

Purpose: Recent prospective randomized trials have shown concurrent chemo-radiation improves local-regional control in post-operative patients with squamous cell carcinomas of the head and neck (SCCHN) using cis-platinum based regimens. This report pools data from three randomized trials performed at Yale that employed mitomycin-C (MC), selecting those patients treated postoperatively, to evaluate the long term benefit of MC in the postoperative setting and to compare these results with other recently published randomized trials.

Methods and Materials: Between 1980 and 1999, a total of 331 SCCHN patients from the three prospective trials were enrolled. Of those patients, 205 were post-operative of which 103 were randomized to receive mitomycin-C and radiation, while 102 received radiation alone or radiation with porfiromycin in the third trial. Patients were treated with daily radiotherapy to a total median dose of 60 Gy over 47 days. Patients who were randomized to MC received 15 milligrams per square meter (mg/M^2) of mitomycin-C on days 5 and 47 (or last day).

Results: The 5-year rate of local-regional control was higher in the MC arms (85.3% vs. 69.9%, $p = .008$). There was no statistically significant difference in overall survival or

distant metastasis. Patients had a lower percentage of high risk factors in both arms of the study, compared to patients of the large prospective trials, including positive margins, 2 or more positive lymph nodes, or oropharynx primary. The gains in local-regional control realized with MC were similar to the improvements in the recently published randomized trials using cis-platinum.

Conclusions: These results confirm significant gains in local-regional control using concurrent chemo-radiotherapy in the postoperative setting for patients with SCCHN. The lack of consensus over a benefit in overall survival and distant metastasis emphasizes the need for further prospective trials in the postoperative management of SCCHN.

ACKNOWLEDGEMENTS

Thank you to my faculty mentor Dr. Bruce Haffty for helping me formulate a hypothesis, supplying me with all the relevant data to conduct a retrospective analysis, and helping me perform a statistical analysis on my findings. It was with his support and encouragement that I have been able to present my work at the American Radium Society Conference in Barcelona, Spain and publish it in The Cancer Journal. Good luck at Robert Wood Johnson School of Medicine. We will surely miss your dedication and commitment to medical student research here at Yale.

Dr. Lynn Wilson also deserves acknowledgment for his help in reviewing all drafts of my paper from abstract to thesis. He has been a strong advocate of all my work as an advisor, future colleague, and friend.

Thank you to the Yale School of Medicine Office of Student Research for providing me with the funding to conduct my research and travel grants to present my findings in Barcelona, Spain.

Finally, thank you to my family and friends for all their continued support.

TABLE OF CONTENTS

I. Introduction……..1

- Historical Data in Support of Post-Operative Radiation…….....1
- Historical Data in Support of Chemo-radiation……..…....4
- Identifying High Risk Factors…….……..6
- Post-Operative Concurrent Chemo-radiation……..…..7
- Yale Data…….….10

II. Statement of Purpose……..12

III. Methods and Materials……..14

- Patient Selection……...14
- Treatment…….15
- Follow-Up……16
- Data Collection and Analysis……...16

IV. Results……...18

- Patients…….18
- Toxicity…….20
- Outcome……21

V. Discussion……...26

VI. References…….32

INTRODUCTION

Head and neck cancers account for nearly 4% of all newly diagnosed cancers every year. (1) In 2000, the estimated number of new cases worldwide was 550,000. (1) At least 40% of patients presenting with squamous cell carcinomas of the head and neck have locally advanced disease, and the associated prognosis remains disappointing. In the USA, the 5-year relative survival rates for the period 1989-1995 did not exceed 45%.

Historical Data in Support of Post-Operative Radiation

Advanced squamous cell carcinomas of the head and neck (SCCHN) have markedly poor outcomes despite decades of effort developing and evaluating various strategies aimed at reducing recurrence and improving survival. Surgical resection followed by postoperative radiation therapy, or radiation therapy alone were the principle modalities employed for patients with advanced head and neck cancer for decades. In 1957, Macomb suggested that the combination of radiation and surgery may be more efficacious than utilizing one initial treatment and reserving the other for salvage therapy. (2) In general, by the 1970's postoperative radiation therapy consisted of 60 Gray (Gy) in 30 fractions and was delivered for the following indications: "surgical resection incomplete, cancer cells close to the margin, surgical margins not clear, nodes positive at multiple levels, cancer through the nodal capsule or midline primary lesion." (3) Despite the prevalence of adjuvant postoperative radiotherapy, no large prospective randomized trials have ever been conducted to compare the treatment to surgery alone for ethical reasons.

Several modern retrospective reviews have been performed that show a benefit to postoperative radiation for SCCHN. Two of the largest of these studies are a Medical College of Virginia review and a Mayo Clinic review. The Medical College of Virginia study reviewed 444 surgical patients from the years 1982 to 1988. (4) The cohort of patients examined was limited to those with advanced disease by selecting for 125 patients who had extra capsular nodal extension (ECE) and/or positive resection margins (PRM). Of these 125 patients, 71 were treated with surgery alone and 54 received surgery and radiation therapy consisting of greater than 50 Gy. Selection of treatment appeared to be more related to physician preference than to the extent of the disease. Patients in both groups were well balanced with respect to T and N stage. In addition, the two groups were comparable with respect to site of primary disease and frequency of ECE/PRM. The three year disease-free survival for the combined treatment group was 45% compared to 25% for the patients who received surgery alone (p=.0001). (4) Local control was assessed with respect to prognostic groups. For patients with ECE the 3 year local control rate was 66% for combined treatment and 31% for surgery alone (p=.03). (4) For patients with PRM, the 3 year local control rate was 49% for the combined treatment and 41% for surgery alone (p=.04). (4) For patients with ECE and PRM, the 3 year local control was 68% for the combined group and 0% for surgery alone (p=.0003). (3) Overall survival was improved for the patients who received post-operative radiotherapy versus those who were observed (3 year survival 72% for combined treatment versus 41% for surgery alone (p=.0003). (4)

In order to account for any potential imbalances in the prognostic factors between the patients who received various treatments the Mayo Clinic group utilized a matched pair analysis based upon known prognostic factors. (5) The matched pair analysis was performed

to pair like patients who received surgery alone versus those who received surgery and postoperative radiotherapy. The database for this matched pair-analysis consisted of 66 consecutive patients with N1 or N2 disease who underwent surgical resection and postoperative radiotherapy between the years of 1974 and 1990. The data base for patients who received surgery alone consisted of a previously published series of 265 patients with N1 or N2 disease. (5) The patients underwent a computer generated matched pair analysis with 56 pairs being found. Patients were matched with respect to age, gender, pathological neck stage, number of metastatically involved nodes (≥ 4), and desmoplastic lymph node pattern.

Of the 56 patients who received postoperative radiotherapy, the median interval between operation and postoperative radiotherapy was 41 days, the median radiation dose was 56 Gy. The median number of fractions was 30, and the median dose per fraction was 1.8Gy. A majority of these patients had oral cavity and oropharynx lesions (fewer larynx and hypopharynx). The site distribution was well balanced between the treatment groups of surgery alone versus the surgery and postoperative radiotherapy. The Mayo Clinic study demonstrated a statistically significant improvement in survival for the group of patients who received surgery and postoperative radiotherapy compared to surgery alone with respect to death from cancer (2 year overall survival 60% versus 39.4%, $p=0.0182$). (5) Therefore, this matched pair analysis, combined with the results from the Medical College of Virginia, provide support to the use of postoperative radiation for the patients with advanced head and neck malignancies.

During the past few decades there has been considerable debate over whether preoperative radiotherapy might be better than postoperative radiation. A Radiation Therapy

Oncology Group (RTOG) trial was conducted to further examine this question. The RTOG 73-03 trial enrolled 320 patients with Stage III and IV disease of the supraglottic larynx, hypopharynx, oral cavity, and oropharynx and stratified them by gender, T stage, and N stage. (6) Of the total patients, 277 were randomized to preoperative radiotherapy consisting of 50 Gy followed by surgery versus surgical resection followed by postoperative radiotherapy consisting of 60 Gy. The planned therapy was completed for 194 of these patients and the disease site and stage breakdown for the two arms was well-balanced. The overall local-regional control at four years was 48% for the patients who received preoperative irradiation versus 65% for the patients who received postoperative radiation (p=.04). (6) There was a trend toward an overall survival benefit for patients who received 60 Gy postoperative radiation compared to 50 Gy preoperative radiation (p=.10). (6)

Even though postoperative radiation may be better than preoperative radiation or surgery alone, the survival rates still remain low. The poor prognosis of patients with locally advanced HNSCC actually results from two factors. First, local and regional recurrence remains the major obstacle to cure of locally advanced HNSCC. Second, the impact of local-regional failure (LRF) on the treatment outcome is not restricted to progression or recurrence above the clavicles only. Indeed, an analysis of more than 2,500 patients in the Radiation Therapy Oncology Group (RTOG) database who had HNSCC showed a statistically significant increase in the risk of distant metastasis (21% versus 38%) for patients whose local-regional disease was not controlled, as compared with those whose disease was controlled. (7)

Historical Data in Support of Chemo-radiation

Chemotherapy has been added to treatment regimens since the 1970s as a way to improve outcomes. On a biological basis, chemotherapy with cytotoxic drugs has been shown to enhance the response of radiation. The most widely investigated drugs were a combination of platinum derivatives and 5-fluorouracil (5-FU). These drugs act to inhibit repair of lethal and sublethal damage induced by radiotherapy, radiosensitize hypoxic cells, reduce tumor burden, synchronize and redistribute tumor cells into the more sensitive G2-M cell cycle phase, and induce apoptosis. (8) It was because of these *in vitro* effects that chemotherapy was tested in the clinical setting as chemotherapy alone, induction chemotherapy, adjuvant chemotherapy following surgery and/or radiotherapy, and concurrent chemotherapy with radiation. The efficacy of these chemotherapy regimens has been assessed in various meta-analyses with most showing a small benefit in terms of local-regional control. (9-12)

The landmark Intergroup 0034 phase III trial validated the use of sequential chemotherapy and radiation as an effective form of treatment with reduced toxicity. (14,15) All patients in this study had completed surgical resection followed by randomization to radiation alone or chemotherapy followed by radiation. The chemotherapy group received cisplatin and 5-FU every 3 weeks after the completion of surgery. Radiation therapy in both arms consisted of 50-60 Gy using 1.8 to 2Gy fractions per day. Low risk patients were treated to 50-54 Gy and high risk patients were treated to 60 Gy. High risk patients were defined as those with margins less than 5mm, extracapsular extension (ECE), or carcinoma-in-situ at the margins. There was no difference in local control, disease free survival, or overall survival, but there were more distant metastases in the radiation therapy arm alone. At 4 years there were 30% distant metastases in the radiation arm versus 20% in the

sequential chemoradiation arm (p=.02). (14,15) Although there was no overall improvement in local control, sub-group analysis of high risk patients showed a trend toward improvements in local control. (14,15) Patients with high-risk factors have thus been seen as a potential target population for concurrent chemo-radiation, which can be more toxic than sequential therapy.

Identifying High Risk Factors

High risk factors are important prognostic indicators of who is more likely to have local-regional failure and distant metastasis and can alter treatment regimens. It is particularly important to understand high risk patient populations before examining Level 1 evidence in support of concurrent chemo-radiation. RTOG 8503, which tested the value of postoperative chemotherapy and radiation therapy, suggested three risk groupings. (14) Low risk was defined as patients with fewer than two positive nodes, no ECE, and negative surgical margins. Medium risk patients had at least two positive nodes or ECE, but no positive surgical margins. High risk patients had surgical margins that were positive.

Risk assessment by clusters was developed at MD Anderson in the 1990s. Their analysis was designed to clarify which patients needed postoperative radiotherapy, and three main principles emerged. First, the presence of ECE of tumor beyond the capsule of a node in the surgical specimen was an independent variable linked to a significantly increased risk of recurrence. (16) Second, increasing combinations of two or more risk factors (i.e., oral cavity primary, close or positive mucosal margins, nerve invasion, two or more positive lymph nodes, largest node >3 centimeters in diameter, treatment delay >6 weeks, and Zubrod performance status ≥2) were associated with a progressively higher risk of local failure. (16)

Third, a follow-up study by Ang concluded that patients who had no adverse surgical pathologic features or were low-risk did not need postoperative radiotherapy. (17) The 5-year actuarial local-regional control and survival rates achieved with surgery alone in this group were 90% and 83%, respectively. (17)

Post-Operative Concurrent Chemo-Radiation

Having identified head and neck patients with high-risk factors that could benefit from a more aggressive approach of chemo-radiation, a number of smaller trials have been conducted since the 1990s to examine the role of concurrent chemo-radiotherapy in this setting. Bachaud enrolled 83 high risk patients with stage III or IV disease and ECE and randomized them to receive either post-operative radiation or post-operative radiation with weekly Cisplatin chemotherapy at 50 mg/m2 for 7-9 cycles. (18, 19) Despite the small number of patients enrolled, there were statistically significant improvements in local regional control and overall survival (see discussion section). (18, 19) The toxicity was tolerable although more severe than with radiation therapy alone. There was an increase in severe acute toxicity from 18% to 41% with addition of chemotherapy and this primarily consisted of mucositis, weight loss, nausea, and vomiting. (18, 19)

In another prospective trial of 114 patients with advanced squamous cell carcinoma of the head and neck by Smid, mitomycin C and bleomycin were used as the chemotherapeutic agents. Mitomycin-C is a hypoxic cell cytotoxin that has been shown to be synergistically effective with radiation in controlling disease. (20-22) Bleomycin is an antineoplastic antibiotic. This trial showed statistically significant improvements in local regional control and overall survival in the group that received the concurrent chemo-radiation (see discussion

section). (23) Together, these two studies provided suggestive, but not conclusive, evidence that adjuvant concurrent chemo-radiation was more efficacious than post-operative radiation therapy alone.

To assess these results further, two large phase III multi-center trials were conducted by the RTOG and European Oncology Radiation Therapy Commission (EORTC) to evaluate the role of high dose concomitant chemo-radiation (chemotherapy given every 3 weeks) in the post-operative setting. The EORTC trial #22931 enrolled 334 patients from 1994-2000 with specific criteria for inclusion related to high risk factors: stage III or IV disease, oral and oropharynx primary with lymph nodes at levels IV or V, vascular embolisms, perineural disease, ECE, or positive margins. The primary endpoints of the study were disease free survival, local regional control, and overall survival. Patients were randomized to receive either post-operative radiation to 66 Gy in 33 fractions over 6.5 weeks or chemo-radiation using the same radiation schedule combined with three courses of cisplatin 100 mg/m2 on days 1, 22, and 43. After 5 years, patients had a statistically significant improvement on all endpoints. Local regional control improved from 69% to 82% with concurrent therapy (p=.007), disease free survival improved from 36% to 47% (p=.04), and overall survival increased from 40% to 53% (p=.02). (24) Objective acute mucositis and late toxicity were not significantly increased in patients who received concurrent therapy. (24)

The RTOG 95-01 study similarly compared concurrent chemo-radiation with cisplatin to post-operative radiation therapy alone. This trial consisted of 459 patients from 1995-2000 and included those individuals with high risk factors of two or more positive lymph nodes, positive surgical margins, or ECE. The end-points were similar to the EORTC study (i.e., disease free survival, local regional control, and overall survival.) The patients

were randomized to receive either post-operative radiation to 60 Gy in 30 fractions over 6 Gy fractions with or without a 0.6 Gy boost over 3 days or chemo-radiation using the same radiation therapy schedule combined with three courses of cisplatin 100mg/m2 on days 1, 22, and 43. At 3 years the arm receiving concurrent chemo-radiation showed significant improvements with respect to local regional control (82% versus 72%, p=.01) and disease free survival (54% versus 45%, p=.04). (25) Overall survival, however, did not show statistically significant improvement with the addition of chemotherapy (64% versus 57%, p=.19). (25) With regard to toxicity, the addition of chemotherapy resulted in a substantially greater incidence of severe acute side effects in this trial. Grade 3 or higher toxicity was observed in 34% of patients treated by radiotherapy alone, but more than doubled to 77% in the patients treated with concurrent therapy. (25) Severe late toxicity was not significantly different between the treatments.

There is no clear explanation for the difference between overall-survival outcomes between the RTOG and EORTC trials, although differing patient eligibility criteria and risk stratification most likely were the main contributors. The eligibility criteria common to both trials were ECE and positive margins. In addition, RTOG included patients with two or more positive lymph nodes, while EORTC included patients with stage III/IV disease, enlarged lymph nodes at level IV/V, oropharynx or oral cavity primary, vascular embolisms, and perineural invasion. The distribution of these criteria across the two studies leads to some interesting observations. First, 94% of the cases in the RTOG trial had N2 or N3 disease as compared with only 57% in the EORTC trial. Second, there were a greater number of patients with oropharynx primary, a poor prognostic indicator (see “Identifying Risk Factors” section above), in the RTOG group than in the EORTC study. Finally, there was a greater

proportion of patients with positive margins in the chemo-radiation arm than in the radiation arm of the RTOG trial (27% versus 19%), while the EORTC trial showed the reverse with more patients with positive margins in the radiation arm than the chemo-radiation arm (34% versus 31%). In contrast, the dose levels delivered in each trial were similar (i.e., analyses of compliance indicate that most cases received at least 60 Gy in either trial.) (8) Thus, differences in outcomes most likely represented differences in the risk factors of the patient populations in the two trials and will be examined in further detail in the discussion section.

Yale Data

Our institution conducted three separate prospective clinical trials from 1980 to 1999 testing concurrent chemo-radiation with mitomycin-C in patients with head and neck cancers. (26-29) As mentioned earlier, mitomycin-C is a hypoxic cell cytotoxin that has been shown to be synergistically effective with radiation in controlling disease. All three trials did not limit inclusion to patients receiving postoperative radiation, but also included patients who were being treated with primary radiation. The first trial randomized patients to radiation alone or radiation with mitomycin-C and showed improvements in local-regional control for those who received the combined modality treatment. (28) The second trial randomized patients to radiation alone or radiation with mitomycin-C and dicumarol. (26) Dicumarol was added because laboratory studies suggested it enhanced the hypoxic cytotoxicity of mitomycin. (29-31) In the clinical setting, however, the trial did not show any added benefit for dicumarol beyond those already documented with the combined therapy of radiation and mitomycin-C. (27) The third trial had drug treatment in both arms and randomized patients to either radiation with mitomycin-C or radiation with porfiromycin. (26) Porfiromycin is a

methylated derivative of mitomycin-C and was shown in laboratory studies to have even greater differential hypoxic cell cytotoxicity than mitomycin-C. (32-37) In the clinical setting, however, porfiromycin did not significantly improve local-regional control and only added to increased toxicity.

STATEMENT OF PURPOSE

The EORTC and RTOG 95-01 recently published phase III trials in the New England Journal of Medicine that evaluated the role of concurrent chemo-radiation with cisplatin and 5-flourouracil for patients with advanced squamous cell carcinoma of the head and neck in the post-operative setting. Both trials showed an improvement in local-regional control for patients who received concurrent chemo-radiation, however, they differed in their survival outcomes. While the EORTC did show a statistically significant improvement in overall survival, the RTOG study did not. It was speculated that this difference was due to eligibility criteria and risk stratification of the patients in the two trials.

Yale has large data sets from three separate randomized trials that used mitomycin-C as a chemotherapeutic agent for patients receiving concurrent chemo-radiation for advanced head and neck cancer. All three trials included patients treated in both the postoperative setting as well as with primary radiation. However, management strategy (i.e. primary radiotherapy versus postoperative) was a major stratifying variable, allowing separate analysis of postoperative patients. Given the differing outcomes from the EORTC and RTOG trials, there is a unique opportunity to use the Yale data to shed further light on the role of post-operative concurrent chemo-radiation.

This thesis pools data from the mitomycin-C trials, limiting the analysis to those squamous cell carcinoma of the head and neck patients who received therapy postoperatively, and examines the role of chemo-radiation (mitomycin-C) with respect to overall survival and local-regional control. In addition, I documented high-risk factors such as positive margins, multiple positive lymph nodes, and oral cavity/oropharynx primary to

compare eligibility criteria and risk stratification with the recent RTOG, EORTC and other postoperative trials. I also conducted a sub-set analysis of these high-risk factors to see if any was an independent prognosticator for local regional failure, distant metastases, or reductions in overall survival.

My hypothesis is that we will see improvements in local-regional control in the post-operative patients who are treated with concurrent chemo-radiation, since we saw similar results for all patients who were treated with this treatment in the three separate trials. I do not anticipate seeing a survival benefit, since this was not observed in the trials. I anticipate the two arms of our study to be well-balanced with respect to high-risk factors since our patients were risk-stratified in the individual trials. However, I do not know how our patient population will compare to the EORTC and RTOG, nor do I know if any of our risk factors will be seen as an independent prognosticator for local-regional failure, distant metastases, or reductions in survival.

METHODS AND MATERIALS

Patient Selection

All three clinical trials were conducted at Yale University following patient presentations at multidisciplinary head and neck tumor board conferences. The trials were conducted by faculty members from the department of Therapeutic Radiology, and sections of Medical Oncology, and Otolaryngology. Patients were all clinically staged and classified according to the American Joint Commission/Tumor Node Metastasis system at the times of their enrollment in the trials and I have restaged them according to 2002 guidelines. (38) Eligible patients had histologically proven squamous cell carcinoma within one of the following anatomic locations: oral cavity, oropharynx, larynx, hypopharynx, paranasal sinus, or unknown primary. For the most part, patients had Stage III or IV carcinoma, however patients with Stage I and II were also considered if they were deemed to be high-risk by the tumor board which based decisions on unfavorable pathological findings, level of node involvement, and site of primary. Patients in the postoperative as well as primary radiation groups were eligible for the trials, but were stratified by management strategy (primary RT, postoperative high risk, postoperative low risk). In the current analysis I included only those patients who received radiotherapy in the postoperative setting. Patient selection criteria included: age between 20-80 years, no distant metastases, no prior radiation, no history of malignancy within five years, no history of chemotherapy within three years, and no history of peptic ulcer, esophageal varices, or bleeding disorders. Patients had to be able to tolerate chemotherapy by having the following tests within specified Karnofsky limits: hematocrit, white cell count, platelet count, prothrombin/partial thromboplastin time, total bilirubin,

blood urea nitrogen level, creatinine level, calcium, phosphate, AST, and ALT. All three prospective trials were approved by the Yale University institutional review board and all patients gave written informed consent.

Those who met the eligibility criteria were then randomized by a biased coin method in which balance between the treatment groups was forced with respect to primary site and extent of disease. Patients were randomized at the time of consultation with the radiation oncologist. Patients in trial 1, conducted from 1980 to 1986, were randomized to either radiation alone or radiation with mitomycin-C. Patients in trial 2, conducted from 1986 to 1992, were randomized to radiation alone versus radiation with mitomycin-C and dicumarol. Patients in trial 3, conducted from 1992 and 1999, were randomized to either mitomycin-C or porfiromycin.

Treatment

Radiation therapy was planned by the radiation oncologists and physicists and administered by the therapists using 4-6 MeV linear accelerators with standard fractionation schedules of 1.8 to 2.0 Gy per day, 5 days a week. Radiation was administered using standard bilateral or three field arrangements to encompass the primary site and regional lymph nodes. The total dose of radiation was at the discretion of the radiation oncologist. Patients treated postoperatively were required to receive a minimum dose of 54 Gy, but generally received 60 Gy or more in the later years of the trials, receiving a median dose of 60 Gy over a 47 day period. There was no difference between the drug-treatment arms and the no-drug arms with respect to total dose and duration.

Patients randomized to receive mitomycin-C received the drug intravenously at a dose of 15 milligrams per square meter (mg/M^2) on the fifth day of the radiation course by their medical oncologist. Patients scheduled to receive 60 Gy or more received a second dose of mitomycin on day 47 or day 50. The second dose of mitomycin was reduced or eliminated if grade 3 or 4 hematologic toxicity occurred. In the second trial, patients who received mitomycin-C also received 300 mg of dicumarol on the day before mitomycin-C and 200 mg on the day after mitomycin. In the third trial, patients who were not in the mitomycin-C arm received a dose of porfiromycin at 40 mg/M^2 intravenously on day 5 and a second dose on day 47.

Follow-up

Patients were evaluated weekly by the radiation oncologist during the radiation course. After the radiotherapy was complete, patients were evaluated on 1-3 month intervals for the first 2 to 3 years, and on 6 to 12 month intervals thereafter. Tumor response, adverse effects, and patient status were recorded by the radiation oncologist.

Data Collection and Analysis

I reviewed the charts of all the patients enrolled in the three trials and documented a number of characteristics including: primary site of tumor, stage, radiation dose given, type of neck dissection (e.g., radical, modified, none, ipislateral, bilateral, etc.), number of lymph nodes sampled, number of lymph nodes with pathologic presence of disease, extra-capsular extension, pathologic findings of surgical resection margins, type of primary surgery, evidence of recurrence, and location of recurrence.

Patients with biopsy or clinically diagnosed recurrences at the primary site and/or the regional lymph nodes were labeled as local-regional relapses. Patients with clinical or radiological evidence of metastatic disease were labeled as distant relapses. Local-regional recurrence free survival (local-regional control) was recorded as the time from randomization to the time of a local-regional relapse. Overall survival was recorded as the time from randomization to the time of death.

Comparison of variable and control groups was analyzed for statistical significance with the chi square test for all categorical variables, and the t-test for all continuous variables. Overall survival and local-regional recurrence free survival were calculated using the Kaplan-Meier method. (39) Statistical comparisons between the treatment arms were made using the log-rank test. (40) These statistical tests were performed jointly by me and my faculty mentor. In addition, a subset analysis of all high risk factors and their impact on local-regional control, distant metastases, and overall survival were conducted.

RESULTS

Patients

One hundred twenty patients were enrolled in the first trial from 1980 to 1986, 83 patients were enrolled in the second trial from 1986 to 1992, and 128 patients were enrolled in the third trial from 1992 to 1999. Of the 331 total patients enrolled in the three trials only 316 were available for analysis. Of these 316 patients, 205 were treated postoperatively and are the subject of this analysis. Previously published data show no effect of dicumarol. (27) We have therefore included patients treated with mitomycin-C and dicumarol in the arm with those just treated with mitomycin-C. Previously published reports show no benefit to porfiromycin. (26) We have therefore included the patients in the third trial who received porfiromycin in the control arm. Thus of the 205 post-operative patients, 102 patients were randomized to the Mitomycin-C/radiotherapy group and 103 were randomized to the control arm. Retrospective record reviews were performed on these sub-groups, recording high risk factors such as margin status and number of positive lymph nodes. Table 1 lists the characteristics of these patients. The table shows that both arms of our study were well-balanced with respect to all patient variables.

Table 1. Characteristics of Patients and Tumors

Characteristic	Radiotherapy N = 103	Combined Therapy N = 102	Total N = 205
Sex -- no. (%)			
Male	82 (80)	21 (85)	103
Female	21 (20)	15 (15)	102
Race -- no. (%)			
White	72 (78)	82 (92)	154
Black	16 (17)	7 (8)	23
Asian	1 (1)	0 (0)	1
Other	3 (3)	0 (0)	3
Age -- no. (%)			
< 60	77 (75)	82 (80)	159
> 60	26 (25)	20 (20)	46
Primary Site -- no. (%)			
Oral Cavity	34 (33)	31 (31)	65
Oropharynx	23 (22)	25 (25)	48
Hypopharynx	15 (15)	16 (15)	31
Larynx	18 (17)	23 (23)	41
Nasopharynx	1 (1)	0 (0)	1
Paranasal Sinus	11 (11)	5 (5)	16
Unknown Primary	1 (1)	1 (1)	2
Tumor Stage -- no. (%)			
0	2 (2)	0 (0)	2
1	11 (12)	10 (11)	21
2	25 (27)	34 (36)	59
3	37 (40)	24 (25)	61
4	17 (19)	27 (28)	44
Nodal Stage -- no. (%)			
0	41 (43)	43 (45)	84
1	18 (19)	23 (24)	41
2	32 (33)	24 (25)	56
3	5 (5)	6 (6)	11
AJC Stage -- no. (%)			
I	6 (7)	3 (3)	9
II	14 (15)	13 (14)	27
III	30 (33)	31 (33)	61
IV	42 (46)	47 (49)	89
Resection Margins -- no. (%)			
Negative	60 (58)	53 (53)	113
Positive	25 (24)	30 (30)	55
Unknown	18 (17)	17 (17)	35
Lymph Node Status -- no. (%)			
0-1 Positive	55 (54)	41 (44)	96
>1 Positive	32 (32)	38 (40)	70
Unknown	14 (14)	15 (16)	29

Toxicity

As anticipated, the major toxicities in the mitomycin-C group were hematological, consisting of leukopenia and thrombocytopenia. There were more mild, moderate, and severe hematologic toxicities in the patients treated with mitomycin-C. No hematologically related treatment deaths occurred in any trial. Non-hematological toxicities included mucositis and epidermitis and were not significantly different between the mitomycin-C and the control arms. The hematological and non-hematological toxicities are outlined in Tables 2 and 3.

Table 2. Hematologic Toxicity

	Radiotherapy	Combined Therapy	Total
Hemoglobin			
Normal (>11)	93	89	182
Mild (9.5-11)	7	10	17
Moderate (8-9.5)	3	3	6
Leukopenia			
Normal (>4000)	69	34	103
Mild (3000-4000)	19	30	49
Moderate (2000-3000)	10	24	34
Severe (1000-2000)	4	13	17
Life-threatening (<1000)	1	1	2
Thrombocytopenia			
Normal (>100,000)	90	66	156
Mild (75,000-100,000)	7	13	20
Moderate (50,000-75,000)	4	15	19
Severe (25,000-50,000)	1	6	7
Life-threatening (<25,000)	1	2	3

Table 3. Non-hematologic Toxicity			
	Radiotherapy	Combined Therapy	Total
Mucositis			
Normal	16	17	33
Mild	20	28	48
Moderate	47	28	75
Severe	17	25	42
Not Recorded	3	4	7
Epidermitis			
Normal	43	31	74
Mild	27	30	57
Moderate	19	28	47
Severe	11	11	22
Not Recorded	3	2	5
Nausea/Vomiting			
Normal	97	92	189
Mild	0	6	6
Moderate	3	3	6
Not Recorded	3	1	4

Outcome

The 5-year rate of local-regional control for patients in the radiotherapy group was 69.9% with 31 of 103 patients failing. The 5-year rate of local-regional control was 85.3% in the mitomycin-C group, with 15 of 102 patients failing. (p=0.008). Figure 1 summarizes local-regional control rates in both arms at 10 years (p=0.017; mantel & haenszel chi square = 5.69).

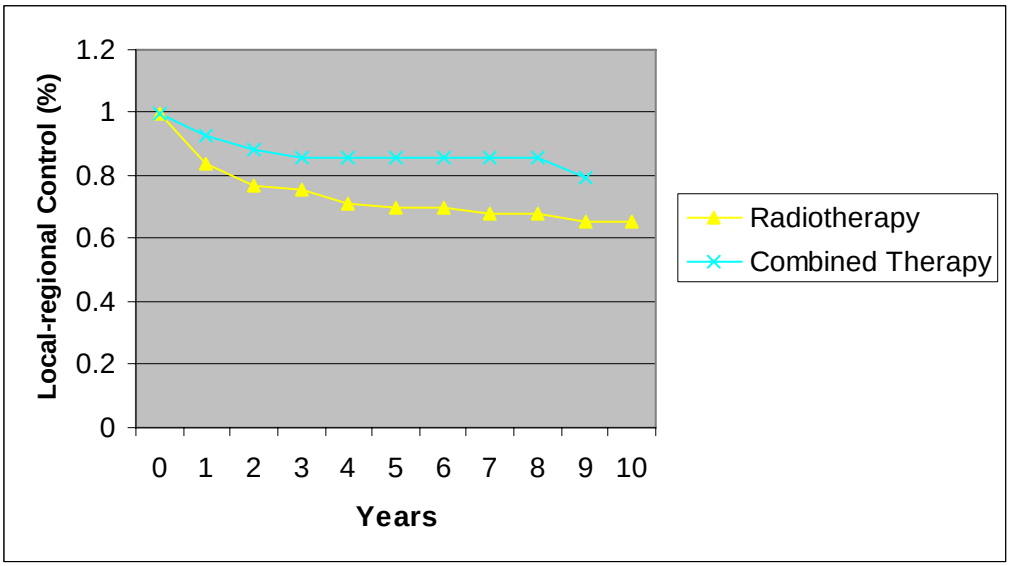

Figure 1. Rates of Local-Regional Control
Patients assigned to receive concurrent chemotherapy and radiotherapy had a higher rate of local-regional control than patients assigned to receive radiotherapy alone. (p = .017, mantel & haenszel chi square = 5.69)

Distant recurrence rates and overall survival rates were not within 95% confidence for statistical significance. The 5-year rate of distant metastasis was 22.3% in the radiotherapy group and 19.0% in the mitomycin-C group (p=0.558). The 5-year overall survival rate for patients in the radiotherapy group was 51.0% and 49.4% in the mitomycin-C group (p>0.50). Figure 2 summarizes overall survival rates for the two arms (p>0.50). Seventy six patients in the radiotherapy group and 81 patients in the mitomycin-C group died within 5 years from any cause out of 205 patients treated with radiation postoperatively

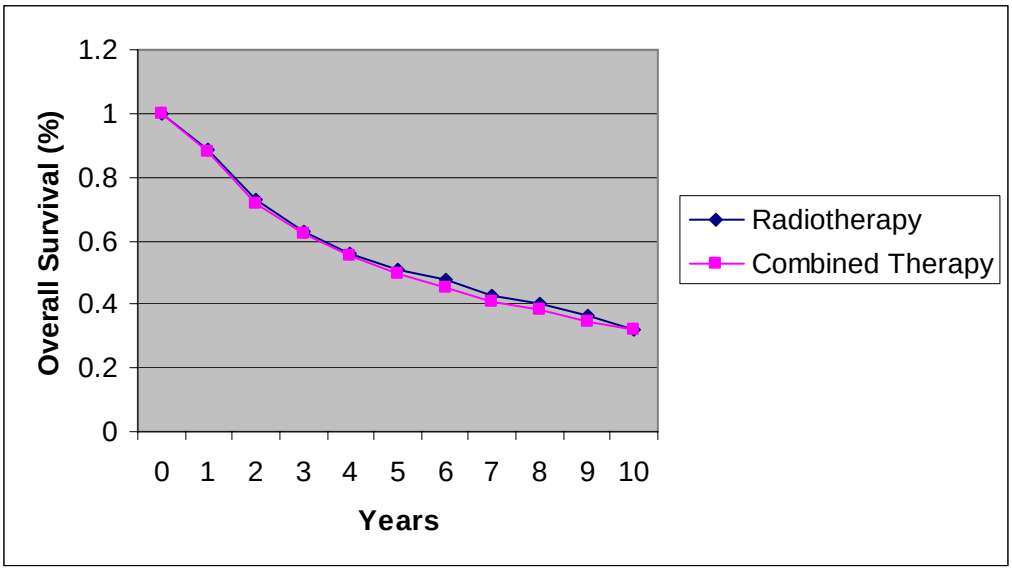

Figure 2. Rates of Overall Survival
Overall Survival did not differ significantly between groups.
($p > 0.50$, mantel & haenszel chi square = 0.289)

A subset analysis was performed evaluating local-regional control for those patients who had high-risk factors of two or more positive lymph nodes or positive margins. Node positive patients that were randomized to receive mitomycin-C had a local-regional control rate of 83.2% at 5 years compared to 64.4% in the control group ($p=.096$). Although this is not statistically significant with 95% confidence, it is within 90% confidence and shows a trend toward a potential benefit. The sampling of patients with positive margins was also not statistically significant. Local-regional control was seen in 82.0% of mitomycin-C treated patients and 70.1% of control patients at 5 years ($p>0.50$). The initial trials were underpowered to perform a subset analysis of high-risk factor patients.

Our rate of local-regional control for all post-operative patients compares similarly with the results from the EORTC trial and the RTOG (95-01) trial which both showed a statistically significant benefit. (24,25) The EORTC rate of local-regional relapse at 5 years was 31% with radiotherapy and 18% with combined radiotherapy and platinum ($p=.007$).

The RTOG (95-01) rate of local-regional relapse at 45 months was 30% with radiotherapy and 19% with combined radiotherapy and platinum (p=.01). The RTOG (95-01) trial did not show any significant benefits in terms overall survival or distant metastasis. The EORTC trial did show a 5 year overall survival benefit with 53% in the combined therapy group and 40% in the radiotherapy group (p=.02). Other randomized trials of patients treated with concurrent chemo-radiotherapy showed similar gains in local-regional control. The trial by Bauchaud et al, employing cis-platinum demonstrated a 15% improvement in local-regional control, and the trial by Smid et al, employing Mitomycin and Bleomycin demonstrated a 17% improvement in local-regional control. (18-19,23) The comparisons between our outcomes and those of other concurrent chemo-radiation trials are summarized in Table 4.

Table 4. Comparable Analysis of Outcomes

	n	LRC (%)	p	Overall Survival (%)	p
Bauchaud et al.	**83**		**0.05**		**<0.01**
RT		55		13	
RT+cis-Platinum		70		30	
Smid et al	**114**		**0.037**		**0.036**
RT		69		64	
RT+MC+Bleomycin		86		74	
EORTC	**334**		**0.007**		**0.04**
RT		69		40	
RT+cis-Platinum		82		53	
RTOG 95-01	**416**		**0.01**		**0.19**
RT		72		41	
RT+cis-Platinum		82		49	
Yale Mitomycin Trial	**205**		**0.008**		**>0.05**
RT		70		51	
RT+MC		85		49	

The Bauchaud, Smid, and EORTC trials all showed improvements in LRC and overall survival, while our study mirrors RTOG (95-01) in only showing significant benefits in LRC.

High risk factors, including positive margins, oropharynx primary, and two or greater positive lymph nodes from our trial compared to those factors from the EORTC and RTOG (95-01) trials are summarized in Table 5. The patient population of our trial was most similar to the EORTC trial, except we even had fewer numbers of positive margins, oropharynx primary, and two or more positive lymph nodes than their study.

Table 5. Patient Stratification by High-Risk Factors

	Radiotherapy (%)	Combined Therapy (%)
RTOG Trial		
Oropharynx	37	48
Positive Margins	29	17
2 or more LN	81	83
EORTC Trial		
Oropharynx	28	32
Positive Margins	26	31
2 or more LN	56	53
Yale Mitomycin Trial		
Oropharynx	22	25
Positive Margins	24	30
2 or more LN	32	40

DISCUSSION

Advanced squamous cell carcinomas of the head and neck have markedly poor outcomes despite decades of effort developing and evaluating various strategies aimed at reducing recurrence and improving survival. Surgical resection followed by postoperative radiation therapy, or radiation therapy alone were the principle modalities employed for patients with advanced head and neck cancer for decades. Post-operative radiation therapy was shown to have clear benefits compared to surgery alone by the Mayo Clinic and Medical College of Virginia which used retrospective and matched-pair analysis. (4,5) Post-operative radiation therapy was also shown to be superior to pre-operative radiation therapy in terms of local-regional control for the head and neck. (6) However even with the administration of post-operative radiation therapy, advanced head and neck carcinomas continued to have survival rates between 30-40%. (6) Chemotherapy was added in an effort to improve outcomes. The landmark Intergroup 0034 trial looked at postoperative chemotherapy followed by radiotherapy, compared to post-operative radiotherapy alone, concluding no survival benefit for those treated with chemotherapy. (14) The chemotherapy was tolerable, did not restrict the adequate delivery of post-operative radiation, and slightly, but significantly decreased distant metastasis. (14) Consequently, post-operative chemotherapy was instituted in treatment regimens of squamous cell carcinoma of the head and neck, but outcomes continued to remain dismal. (15)

Platinum derived analogs and specifically cis-diamminoplatinum [II] (cisplatin) are the agents most often delivered concomitantly with radiation in the treatment of locally advanced squamous cell carcinomas of the head and neck. Cisplatin induces radiation

sensitization under oxic and hypoxic conditions, enhances formation of toxic platinum intermediates in the presence of radiation induced free radicals, and a radiation-induced increase in cellular platinum uptake. (41-45) Platinum derived compounds thus represent reference agents to combine radiotherapy in head and neck cancer patients since they are potentially strong radiosensitizers and active chemotherapeutic compounds to treat squamous cell carcinomas. Also, mucositis is generally not a dose-limiting toxicity for platin drugs, facilitating their combination with radiation. (46)

Concurrent chemo-radiation with cisplatin in the post-operative setting has been investigated in three prospective randomized clinical trials providing strong evidence supporting concurrent chemotherapy for the enhancement of local-regional control. (18,19,24,15) Other endpoints remain in conflict: The EORTC study and Bauchaud's study showed improvement in overall survival and median time to progression, but the RTOG (95-01) did not. (18,19,24,25) These differences have been speculated to be the result of differing patient eligibility criteria resulting in more high-risk patients enrolled in the RTOG study. The RTOG (95-01) had more patients with two or more dissected lymph nodes and oropharynx primary sites than EORTC, which previous studies have shown to be high risk factors in terms of survival, disease progression, and local control. As compared to the Bachaud study, and the RTOG 95-01 and EORTC trials that used cisplatin, our study utilized mitomycin-C as the agent for concurrent chemo-radiation. Mitomycin along with Bleomycin was also used in the study by Smid et al. (23)

Theoretically, one of the causes of failure of radiation therapy to control squamous cell carcinoma of the head and neck is the existence within the tumors of viable hypoxic cells of decreased radiosensitivity. (47,48) There is abundant evidence in the literature supporting

the existence of hypoxic tumor cells that are relatively resistant to radiation. (49,50) Mitomycin is a natural-occuring prototype of the quinone bioreductive alkylating agent class. The drug and its analogs act as a bi-functional akylating agent that forms DNA to DNA and DNA to protein crosslinks when activated to the alkylating species; under hypoxic conditions, a greater number of DNA crosslinks occur for a given dose of mitomycin than occurs in oxygenated cells. (21) *In vitro* and *in vivo* studies at Yale's Therapeutic Radiology Department laboratories have shown that mitomycin is preferentially cytotoxic for hypoxic cells compared with well-oxygenated cells. The drug is not a classic radiation sensitizer, but is rather independently cytotoxic. (51) It was on the basis of these laboratory findings that the prospective randomized trials described in this report were designed in an effort to improve outcome in patients with squamous cell carcinoma of the head and neck being treated with radiation therapy. The rationale for the treatment used was that radiation therapy, which is most effective against well-oxygenated cells, used in combination with mitomycin, which is selectively cytotoxic to hypoxic cells, would theoretically result in an enhanced therapeutic ratio. (52)

Our results demonstrate a statistically significant 15% local-regional control improvement at both 5 and 10 years, for those receiving combined modality therapy. These results are also consistent with the study by Smid et al, who demonstrated a 17% improvement in local-regional control. Smid also showed a small but significant improvement in survival using Mitomycin-C. Overall survival and distant metastasis rates were not significantly improved with the combination in our studies. While all of these studies using concurrent chemo-radiation in the postoperative setting appear to show similar 15-20% improvements in local-regional control, the survival benefits are clearly conflicting.

This is likely due to different patient populations, varying co-morbidities and other selection biases in patient accrual to these studies.

Table 5 presents data re-stratifying our patients according to high-risk factors such as positive margins, two or more dissected lymph nodes, and oropharynx primary site comparing outcomes of those patients with such risk factors to the RTOG 95-01 and EORTC trials. The argument had been made that the EORTC showed an improvement in overall survival because the EORTC had a smaller percentage of patients with 2 high-risk factors: oropharynx primary sites and 2 or more lymph nodes, while the RTOG (95-01) had a lower percentage of patients with positive margins. By the same argument, since the percentage of our patients with oropharynx primary sites, positive margins, and 2 or more lymph nodes was even smaller than the EORTC, we should have seen similar improvements in overall survival to the EORTC. However, our outcomes parallel those of RTOG (95-01), not EORTC, and provide evidence that eligibility criteria alone cannot justify the difference in overall survival and other possible confounding variables should be studied**.**

The aggressive approach of concurrent chemo-radiation does not provide benefits without a cost. There is a significant increase in acute and late toxicity (grade 3 or higher), including hematologic, in the RTOG trial, which was not present in the EORTC study. Mitomycin-c also showed increased grade 3 and 4 toxicities in our study. Although there were no deaths related to the toxicity, the treatment might need to be reserved for patients who are only deemed high enough risk to deserve it. There is a growing body of evidence demonstrating that treatment can be tailored, with more aggressive regimens being more appropriate for more aggressive tumors and less aggressive regimens being more appropriate

for less aggressive tumors. The issue of triaging head and neck patients with respect to high risk factors has been advocated in many recent publications and editorials. (53-55)

Previous studies by the RTOG 8503 and MD Anderson, which were described in the introduction, have shed some light on the potential high risk factors and their influence on patient outcomes. The issue is far from clear, however, and further identification is still considered necessary to accurately triage patients. Recently, the data from EORTC and RTOG 95-01 has been reanalyzed by pooling the two trials and using a collaborative comparative analysis of selection criteria, clinical and pathologic risk factors, and treatment outcomes. Patients who were eligible for both trials, namely ECE and positive margins, showed statistically significant improvements in local-regional control, disease free survival and overall survival. (56) Patients who had two or more histopathologically positive lymph nodes did not appear to benefit from the addition of chemotherapy on any of the endpoints.

A subset analysis of the high risk factors from this report, showed most of our initial trials had not been constructed with the power to adequately evaluate risk factors independently. However, we did observe improvements in local-regional control (within 90% confidence) for those patients who had two or more positive lymph nodes and were treated with mitomycin-c. This potential trend toward local control could provide some rationale in favor of concurrent chemo-radiation in patients with multiple positive lymph nodes, which was not observed in the other two trials.

In the future, more trials should be done to assess the benefit of different concurrent schedules (daily or weekly), alternative cytotoxic agents (e.g., taxane), or drugs designed to counteract a growth promoting signal (e.g., an anti-epidermal growth factor receptor [EGFR] drug.) (53) Song and colleagues' recent review of the role of EGFR targeted therapies in

combination with radiation therapy for head and neck cancer illustrates the potential appeal of such approaches. (57) Bonner et.al. recently published a phase III trial in the New England Journal of Medicine showing that patients with SCCHN who received cetuximab, a monoclonal antibody against the ligand-binding domain of EGFR, demonstrated an overall survival benefit without added toxicity. With current improvements in local-regional control more intensive analysis should be given to controlling distant metastases and more trials employing induction chemotherapy followed by surgery and adjuvant concurrent chemo-radiation might also be examined. Of course, such treatment regimens once again heighten the potential for severe toxicities and their risk needs to be balanced against therapeutic gains. Finally, from a radio-therapeutic standpoint, altering fractionation with concurrent chemo-radiation is still being actively investigated.

In conclusion, mitomycin-C when used concurrently with radiation in post-operative patients with advanced squamous cell carcinoma of the head and neck, offers significant improvement in local-regional control. The acceptable toxicity profile, as well as the significant gains observed justify its consideration as an adjunct to radiation therapy in the postoperative setting.

REFERENCES

1. Parkin DM, Muir CS, Whelan Sl, Gao YT, Ferlay J, Powell J. 1992. *Cancer incidence in five continents, vol. 6*. Lyon: IARC.
2. MacComb, W.a.F.G. 1960. Planned combination of surgery and radiation in treatment of advanced primary head and neck cancer. *American Journal Roentgenol*. 77:397-415.
3. Barkley, H.T., Jr. 1972. Management of cervical lymph node metastases in squamous cell carcinoma of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx. *Am J Surg*. 124:462-467.
4. Huang DT, Johnson CR, Schmidt-Ullrich R et.al. 1992. Postoperative radiotherapy in head and neck carcinoma with extracapsular lymph node extension and/or positive resection margins: a comparative study. *Int J Radiat Oncol Biol Phys.* 23:737-742.
5. Lundahl RE, Foote RL, Bonner JA, et al. 1998. Combined neck dissection and postoperative radiation therapy in the management of the high-risk neck: a matched-pair analysis. *Int J Radiat Oncol Biol Phys.* 40:529-534.
6. Kramer S, Gelber RD, Snow JB, et al. 1987. Combined radiation therapy and surgery in the management of advanced head and neck cancer: final report of study 73-03 of the Radiation Therapy Oncology Group. *Head Neck Surg.* 10:19-30.
7. Leibel SA, Scott CB, Mohiuddin M et al. 1991. The effect of local-regional control on distant metastatic dissemination in carcinoma of the head and neck: results of an analysis from the RTOG Head and Neck Database. *Int J Radiat Oncol Biol Phys*. 21:549–556.
8. Bernier J, Cooper JS. 2005. Chemoradiation after surgery for high-risk head and neck cancer patients: how strong is the evidence? *The Oncologist*. 10:215-224.

9. Stell PM, Rawson NS. 1990. Adjuvant chemotherapy in head and neck cancer. *Br J Cancer.* 61:779–787.

10. Munro AJ. 1995. An overview of randomized controlled trials of adjuvant chemotherapy in head and neck cancer. *Br J Cancer*. 71:83–91.

11. El-Sayed S, Nelson N. 1996. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. A meta-analysis of prospective and randomized trials. *J Clin Oncol*. 14:838–847.

12. Pignon JP, Bourhis J, Domenge C et al. 2000. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACHNC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet*. 355:949–955.

13. Browman GP, Hodson DI, Mackenzie RJ et al. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: a systematic review of the published literature with subgroup analysis. Head Neck 2001;23:579–589.

14. Laramore GE, Scott CB, al-Sarraf M, et al. 1992. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034. *Int J Radiat Oncol Biol Phys.* 23:705-713.

15. Hong WK. 1992. Adjuvant chemotherapy for resectable squamous cell carcinoma of the head and neck. Report on Intergroup Study 0034. *Int J Radiat Oncol Biol Phys*. 23:885-886.

16. Peters LJ, Goepfert H, Ang KK et al. 1993. Evaluation of the dose for post-operative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys*. 26:3–11.

17. Ang KK, Trotti A, Brown BW et al. 2001. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head and neck cancer. *Int J Radiat Oncol Biol Phys*. 36:1147-1153.

18. Bachaud JM, David JM, Boussin G et al. 1991. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced squamous cell carcinoma of the head and neck: preliminary report of a randomized trial. *Int J Radiat Oncol Biol Phys*. 20:243-246.

19. Bachaud JM, Cohen-Jonathan E, Alzieu C et al. 1996. Combined operative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Radiat Oncol Biol Phys.* 36:999-1004.

20. Sartorelli AC. 1988. Therapeutic attack of hypoxic cells of solid tumors: presidential address. *Cancer Res*. 48:775-778.

21. Sartorelli AC, Hodnick WF, Belcourt MF, et al. 1994. Mitomycin C: a prototype bioreductive agent. *Oncol Res*. 6:501-508.

22. Rockwell S, Hughes CS. 1994. Effects of mitomycin C and porfiromycin on exponentially growing and plateau phase cultures. *Cell Prolif*. 27:153-163.

23. Smid L, Budihna M, Zakotnik B et al. 2003. Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head and neck carcinoma. *Int J Radiat Oncol Biol Phys* 56:1055-1062.

24. Bernier J, Domenge C, Ozsahin M, et al. 2004. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 350:1945-1952.

25. Cooper JS, Pajak TF, Forastiere AA, et al. 2004. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 350:1937-1944.

26. Haffty BG, Wilson LD, Son YH, et al. 2005. Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: Final results of a randomized clinical trial. *Int J Radiat Oncol Biol Phys*. 61:119-128.

27. Haffty BG, Son YH, Papac R, et al. 1997. Chemotherapy as an adjunct to radiation in the treatment of squamous cell carcinoma of the head and neck: results of the Yale Mitomycin Randomized Trials. *J Clin Oncol*. 15:268-276.

28. Weissberg JB, Son YH, Papac RJ, et al. 1989. Randomized clinical trial of mitomycin C as an adjunct to radiotherapy in head and neck cancer. *Int J Radiat Oncol Biol Phys*. 17:3-9.

29. Haffty BG, Son YH, Sasaki CT, et al. 1993. Mitomycin C as an adjunct to postoperative radiation therapy in squamous cell carcinoma of the head and neck: results from two randomized clinical trials. *Int J Radiat Oncol Biol Phys*. 27:241-250.

30. Keyes SR, Rockwell S, Sartorelli AC. 1984. Enhancement of mitomycin C cytotoxicity to hypoxic tumor cells by dicoumarol in vivo and in vitro. *Cancer Res*. 45:5638-5643.

31. Rockwell S, Keyes SR, Sartorelli AC. 1989. Modulation of the antineoplastic efficacy of mitomycin C by dicoumarol in vivo. *Cancer Chemoter Pharmacol*. 24:349-353.

32. Rockwell S, Keyes SR, Sartorelli AC. 1988. Preclinical studies of porfiromycin as an adjunct ot radiotherapy. *Radiat Res*. 116:100-113.

33. Keyes SR, Loomis R, DiGiovanna MP, et al. 1991. Cytotoxicity and DNA crosslinks produced by mitomycin analogs in aerobic and hypoxic EMT6 cells. *Cancer Commun*. 3:351-356.

34. Rockwell S, Hughes CS. 1994. Effects of mitomycin C and porfiromycin on exponentially gorwing and plateau phase cultures. *Cell Prolif*. 27:153-163.

35. Rockwell S, Hughes CS, Keyes SR, et al. 1993. Porfiromycin as an adjunct to radioteraphy in young an old mice. *Exp Gerontol*. 28:281-293.

36. Rockwell S, Kim SY. 1995. Cytotoxic potential of monoalkylation products between mitomycins and DNA: Studies of decarbamoyl mitomycin C in wild-type and repair-deficient cell lines. *Oncol Res*. 7:39-47.

37. Keyes SR, Rockwell S, Kennedy KA, et al. 1991. Distribution of porfiromycin in EMT6 sollid tumors and normal tissues of BALB/c mice. *J Natl Cancer Inst*. 83:632-637.

38. American Joint Committee on Cancer: Cancer Staging Manual. New York: Springer-Verlag; 2002.

39. Kaplan EL, Meier PL. 1958. Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association.* 53:457-481.

40. Mantel N. 1966. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep.* 50:163-170.

41. Dewitt L. 1987. Combined treatment of radiation and cis-diamminedichloroplatinum (II): a review of experimental and clinical data. *Int J Radiat Oncol Biol Phys*. 13:403-26.

42. Begg AC. Cisplatin and radiation: interaction probabilities and therapeutic possibilities. *Int J Radiat Oncol Biol Phys*. 19:1183-9.

43. Creagan ET, Fountain KS, Frytak S, DeSanto LW, Earle JD. 1981. Concomitant radiation therapy and cis-diamminedichloroplatinum (II) in patients with advanced head and neck cancer. *Med Pediatr Oncol*. 9:119-20.

44. Denham JW, Abbott RL. 1991. Concurrent cisplatin, infusional 5-flourouracil, and conventionally fractionated radiation therapy in head and neck cancer: dose limiting mucosal toxicity. *J Clin Oncol*. 9:458-63.

45. Leipzig B. 1983. Cisplatin sensitization to radiotherapy of squamous cell carcinomas of the head and neck. *Am J Surg*. 146:462-5.

46. Bernier J, Pfister DG, Cooper JS. 2005. Adjuvant chemo- and radiotherapy for poor prognosis head and neck squamous cell carcinomas. *Critical Reviews in Oncology/Hematology*. 56:353-364.

47. Vikram B, Strong EW, Shah J, et al. 1980. Elective postoperative radiation therapy in stages III and IV epidermoid carcinoma of the head and neck. *Am J Surg.* 140:580-584.

48. Pinto LHJ, Canary PCV, Araujo CMM, et al. 1991. Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stages III and IV oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 21:557-562.

49. Rockwell S, Moulder JE. 1990. Hypoxlc fractions of human tumors xenografted into omce: A review. *Int J Radiat Oncol Biol Phys* 19:197-202.

50. Moore JN, Hasleton PS, Buckley CH. 1985. Tumour cords in 52 human bronchial and cervical carcinomas: Inferences for their cellular kinetics and radiobiology. *Br J Cancer* 51:407-413.

51. Pajak TF, Laramore GE, Mardial VA, et al. 1991. Elapsed treatment days – A critical item for radiotherapy quality control review in head and neck trials: RTOG report. *Int J Radiat Oncol Biol Phys*. 20:13-20.

52. Boring C, Squires T, Tong T, et al. 1994. Cancer Statistics. *CA Cancer J Clin*. 44:-26.

53. Cooper JS and Bernier J. 2005. Rationale for Triage in the Postoperative Management of Head and Neck Cancers. *Oncology*. 19:1011-1017.

54. Adelstein DJ. 2005. Review of "Rationale for Triage in the Postoperative Management of Head and Neck Cancers. *Oncology.* 19:1018,1023.

55. Laramore GE. 2005. Review of "Rationale for Triage in the Postoperative Management of Head and Neck Cancers. *Oncology.* 19:1023-1024.

56. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. 2005. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head & Neck*. 843-850.

57. Song J, Chen C, Raben D. 2004. Emerging role of EGFR targeted therapies and radiation in head and neck cancer. *Oncology*. 18:1757-1777.

58. Bonner JA, Hariri PM, Giralt J, et al. 2006. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 6:567-78.