Therapeutic Decision Making in Stages III and IV Head and Neck Squamous Cell Carcinoma

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Background: The best treatment for advanced head and neck cancer remains unclear. Proponents of various therapeutic regimens continue to debate this issue with inconclusive and frequently biased data and with carefully selected patients in controlled trials to support their approach. To assess the outcome of patients in a real-world situation, we reviewed a prospectively maintained database of patients with head and neck cancer.

Methods: We reviewed data from 591 consecutive patients with stage III or IV squamous cell carcinoma treated at a university medical center from January 1, 1992, through December 31, 2000, and analyzed survival using the Kaplan-Meier method.

Results: Overall survival was 48%, 40%, and 33% at 2, 3, and 5 years, respectively. We found a significant death rate due to comorbid conditions. The primary tumor was treated surgically (with or without postoperative radiation) in 363 patients, with survival of 55%, 46%, and 38% at 2, 3, and 5 years, respectively. The tumor was treated primarily with radiation therapy (with or without neck dissection) in 193 patients, with survival of 40%, 33%, and 27% at 2, 3, and 5 years, respectively. Overall survival in the surgical group was better than in the radiation group (P = .005, log-rank test). The radiation group was subcategorized into those who underwent radiation because the tumor was so advanced as to be unresectable (n = 86), because they were too unhealthy to undergo radical surgery (n = 23), and because they elected radiation therapy (n = 84). Survival in each of the radiation subgroups at 2, 3, and 5 years was 28%, 20%, and 14%, respectively, in the unresectable group; 34%, 22%, and 11%, respectively, in the unhealthy group; and 57%, 53%, and 46%, respectively, in the elective group. Thus, survival in the elective radiation subgroup exceeded that of the surgical group, although not statistically. We analyzed data regarding T and N stages, age, race, surgical margin status, postoperative radiation therapy, chemotherapy, radiation dose, and tumor site. Multivariate analysis of the surgical group and elective radiation subgroup showed that N stage and age were the strongest predictors of survival and that the method of therapy was not significant. For oropharyngeal cancer, the patients in the elective radiation subgroup did as well as the surgical group. Many patients were noncompliant with portions of therapy, with a resulting reduction in survival.

Conclusions: The data demonstrate the value of analyzing a consecutive series of patients with advanced head and neck cancer. By including patients with comorbidities and those who are noncompliant, we determined a realistic expectation of patient outcomes. By including all patients, the data dramatically show the impact of age, comorbidity, and advanced stage on survival. The survival of patients who underwent elective radiation therapy in combination with neck dissection was similar to that of patients treated with primary tumor surgery. This was particularly true for oropharyngeal tumors. The site and stage-specific data are useful in counseling patients with advanced head and neck cancer regarding treatment choices.
role of chemotherapy added to radiation therapy for head and neck cancer, a meta-analysis of 63 trials of loco-regional treatment with or without chemotherapy demonstrated a survival benefit of only 4% in favor of chemotherapy. The recently completed Intergroup Trial R91-11 used radiation therapy with or without chemotherapy for laryngeal cancer and likewise demonstrated no difference in survival.

These trials have all been performed on patients who were able to participate in a randomized clinical trial, ie, patients who had adequate performance status, were motivated, were likely to comply with therapy, and were carefully monitored during treatment to permit possible early salvage therapy. In addition, many randomized trials analyze only the data from patients who were fully compliant with every step of the treatment. Many patients with advanced head and neck cancer will not and do not complete these trials, therefore distorting the published results.

An analysis of a consecutive case series offers the advantage of including all patients, rather than just idealized, highly compliant patients. Furthermore, if an intent-to-treat analysis (a method initially designed for evaluating randomized trials in which all patients, regardless of complete compliance with therapy, are included) is used, then the data will be useful in decision making regarding treatment. The intent-to-treat analysis, by also including all noncompliant and ill patients, will answer the important question “Is treatment A, despite some patients not completing the recommended therapeutic regimen, better than treatment B, with a similar caveat?” rather than the usual question “Is treatment A better than treatment B?” Stated differently, it is important to know the survival of carefully selected idealized patients with advanced head and neck cancer, but it is more important to know the outcome of all patients, including those who abort or change therapy in midcourse due to noncompliance or other reasons.

The primary objective of many randomized trials of head and neck cancer is organ preservation, which further complicates the interpretation. However, patients with early T-stage tumors, with their advanced neck disease treated with neck dissection in addition to radiation, were often included. The curative use of radiation therapy in early head and neck primary cancer is not controversial. Since neck dissection is becoming an accepted part of treatment algorithms for patients in organ-preserving protocols, these studies should only include patients with T3 or T4 disease if their goal is to analyze preservation of the organ and not preservation of the neck lymph nodes.

Given all of these problems with data from randomized trials for advanced head and neck cancer, we elected to analyze a consecutive 8-year case series of patients with advanced head and neck cancer to determine the demographics and actual survival of a real set of patients. The therapeutic regimens offered to the patients included surgical resection if possible or full-course radiation therapy to the primary tumor site. The patients, in conjunction with their treating physicians, then selected their treatment course. The patients were divided between those treated with primary site surgery with or without post-operative radiation therapy (surgical group) and those treated with radiation therapy with or without chemotherapy and/or neck dissection, without primary site surgery (radiation group). In addition, for patients who were not treated initially with surgery, we recorded whether that was the result of unresectability, poor health, or an elective decision. This allowed us to perform an intent-to-treat analysis of a consecutive series of patients with advanced head and neck cancer and compare the results.

We further analyzed the data for those patients with advanced T-stage disease and by site. Since all patients treated, and not just those who were eligible for a randomized trial, underwent analysis in this study, we hoped that the results would be helpful in therapeutic decision making for patients with head and neck cancer, in general.

METHODS

We used the head and neck cancer database of the Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati, Cincinnati, Ohio, to retrieve data on all patients with stages III and IV squamous cell carcinoma arising from the mucosa of the upper aerodigestive tract who were treated from January 1, 1992, through December 31, 2000. Only patients with a first occurrence of their primary head and neck cancer were included. We excluded patients with nasopharyngeal cancers and M1 tumors, leaving 591 patients who met these criteria. We retrieved demographic data including age, sex, and race; tumor data including site, stage, and T and N stages; the method of therapy; surgical procedures; radiation dose; and patient outcomes.

In the overall group of 591 patients, the demographic and tumor-related data were analyzed for occurrence. Overall survival and survival by stage were analyzed. The patients were followed up for a median of 38 months. The patients were divided into the surgical and radiation groups. Survival in each of these groups was analyzed and subanalyzed with respect to the demographic and tumor-related data. We compared the survival in these groups using log-rank and Wilcoxon $\chi^2$ analysis. Further comparisons were performed for the main primary tumor sites, particularly for the patients with oropharyngeal cancer, since this was the largest group.

The surgical group included 363 patients, of whom 290 underwent postoperative radiation therapy. Of these 290 patients, 16 also underwent adjunctive chemotherapy. Seventy-three patients did not undergo postoperative radiation therapy. Data concerning why were not prospectively maintained, but results of a medical chart review revealed that 43 of these patients were noncompliant, and in 30, the importance of postoperative radiation was questionable and not clearly recommended (ie, T3 N0 glottic cancer). We therefore included postoperative radiation therapy as a variable in the analysis of the surgical group. The advantage of including patients who did not receive postoperative radiation therapy is that they are representative of how patients actually comply with therapy.

For patients receiving radiation therapy to the primary site, the reason for nonsurgical therapy was categorized as tumor unresectability (unresectable subgroup; n = 86), poor health (unhealthy subgroup; n = 23), or elective (elective subgroup; n = 84). Tumors were classified as unresectable because of skull base invasion, prevertebral musculature invasion, or carotid artery involvement requiring arterial resection. Patients were classified as unhealthy if their general health did not permit extensive surgery. This generally included patients with recent myocardial infarctions or severe pulmonary disease before de-
development of their cancer. Although patients in the radiation group did not undergo primary site surgery, they frequently underwent neck dissection, especially if N2 or N3 disease was present.

Among the 193 radiation group patients, 20 received induction and 22 received concomitant chemotherapy. The radiation group was therefore inconsistent in the use of chemotherapy only. Among the 193 radiation group patients, 35 patients received no treatment or radiation group patients, 35 patients underwent neck dissection, especially if N2 or N3 disease was present. The radiation dose was less than 5500 cGy in 39 patients because of non-compliance.

The patient demographics for the 591 patients, including sex, race, and age, are shown in Table 1, with the tumor sites and stages. In addition to 363 surgical group patients and 193 radiation group patients, 35 patients received no treatment or chemotherapy only.

The Kaplan-Meier overall survival for the 591 patients was 48% at 2 years, 40% at 3 years, and 33% at 5 years (Figure 1). When analyzed for Kaplan-Meier disease-specific survival, survival increased to 61% at 2 years, 57% at 3 years, and 53% at 5 years (Figure 1). This finding demonstrates the significant death rate that was not directly attributable to the head and neck cancer.

We analyzed survival by sex, race, and age (Table 2). No statistical difference was found in survival by sex or race. Age was analyzed by dividing the patients into the following 3 groups: younger than 45 years, 45 to 64 years, and 65 years or older. We found a statistically significant poorer survival with increasing age (P<.001, log-rank and Wilcoxon χ² tests).

We also analyzed survival by stage (Table 2). As expected, the patients with stage III disease had statistically better survival than those with stage IV disease (P<.001, log-rank and Wilcoxon χ² tests). The survival of the patients with T4 disease was statistically poorer than that of the patients with T3 disease (P=.002, log-rank χ² test; P<.001, Wilcoxon χ² test). The negative effect of nodal disease is demonstrated by the poor survival in the patients with N2 and N3 disease. The survival of the 89 patients with T4 N0 disease is included to show that this group's survival was only minimally better than that of the T4 group as a whole.
Poor survival is notable, particularly in the T4 and N2 or N3 groups.

**SURGICAL GROUP SURVIVAL**

The Kaplan-Meier overall survival for the 363 surgical group patients was 55% at 2 years, 46% at 3 years, and 38% at 5 years (Figure 2). When analyzed as disease-specific survival, the rates increase to 70% at 2 years, 66% at 3 years, and 60% at 5 years. A significant possible confounding variable within the surgical group was that 73 patients did not undergo postoperative radiation therapy, either electively or because of noncompliance. The survival of the patients who underwent postoperative radiation therapy compared with that of the patients who underwent surgery alone was not significantly different, and this was not used as a further variable in the study (55% for surgery and postoperative radiation therapy at 2 years vs 53% for surgery alone).

Survival was analyzed by sex, race, and age for the surgical group (Table 3). We found no statistical difference in survival by sex or race. A statistically significant poorer survival was found with increasing age (P < .001, log-rank χ² test; P = .006, Wilcoxon χ² test).

Analysis of survival by stage (Table 3) demonstrated that survival was better in the patients with stage III disease compared with patients with stage IV disease (P = .001, log-rank χ² test; P < .001, Wilcoxon χ² test). The survival of the patients with T4 disease was poorer than that of the patients with T3 disease (P = .054, log-rank χ² test; P = .02, Wilcoxon χ² test).

Survival was analyzed with respect to the margin of resection of the primary cancer (Table 3). The margins were classified as clear in 219 patients, close in 41 patients, and involved in 82 patients. In 21 patients, the status of the margins was not clearly stated. Survival was only minimally improved in patients with clear margins (P = .07, log-rank χ² test; P = .06, Wilcoxon χ² test).
**Table 4. Tumor Site and Stage for Radiation Subgroups**

<table>
<thead>
<tr>
<th>Radiation Subgroups, No. (%) of Patients</th>
<th>Unresectable (n = 86)</th>
<th>Elective (n = 84)</th>
<th>Unhealthy (n = 23)</th>
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</thead>
<tbody>
<tr>
<td>Tumor site</td>
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<td></td>
</tr>
<tr>
<td>Oropharynx</td>
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<tr>
<td>Larynx</td>
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<td>10 (43)</td>
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<tr>
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<td>16 (19)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Glottic</td>
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<td>9 (11)</td>
<td>7 (30)</td>
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<tr>
<td>Hypopharynx</td>
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<td>2 (9)</td>
</tr>
<tr>
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<td>0</td>
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</tr>
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<td>9 (39)</td>
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<td>N3</td>
<td>16 (19)</td>
<td>11 (13)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*Percentages have been rounded and may not sum to 100. Subgroups are described in the “Radiation Subgroups” subsection of the “Results” section.

**RADIATION GROUP SURVIVAL**

The Kaplan-Meier overall survival for the 193 radiation group patients was 40% at 2 years, 33% at 3 years, and 27% at 5 years (Figure 2). Analysis of survival by sex, race, and age for the radiation group (Table 3) showed no difference in survival by sex. Statistical analysis demonstrated that African American patients had poorer survival than white patients ($P = .01$, log-rank $\chi^2$ test; $P = .03$, Wilcoxon $\chi^2$ test); however, of the 60 African American patients in the radiation group, 34 had unresectable disease and had a 2-year survival of only 19%. The poorer survival in the African American patients was therefore the result of later presentation of disease in a less socioeconomically prosperous group rather than a true racial difference. Older patients had poorer survival than younger patients, although this difference was not decisively statistically significant ($P = .16$, log-rank $\chi^2$ test; $P = .053$, Wilcoxon $\chi^2$ test).

Analysis of survival by stage (Table 3) showed that survival was better in the patients with stage III disease compared with the patients with stage IV disease ($P < .001$, log-rank and Wilcoxon $\chi^2$ tests). The survival of the patients with T4 disease was poorer than that of the patients with T3 disease, although this was not statistically significant ($P = .25$, log-rank $\chi^2$ test; $P = .24$, Wilcoxon $\chi^2$ test).

Of the 193 radiation group patients, 42 also received chemotherapy. There was no difference in survival between those who received chemotherapy and those who did not. Thirty-nine patients received less than 5500 cGy of radiation therapy. The patients whose radiation dose was greater than or equal to 5500 cGy had statistically better survival than those who received a smaller dose ($P < .001$, log-rank $\chi^2$ test; $P < .001$, Wilcoxon $\chi^2$ test) (Table 3).

**RADIATION SUBGROUPS**

The 193 patients who received primary radiation therapy were divided into the following 3 treatment subgroups: unresectable (86 patients), elective (84 patients), and unhealthy (23 patients). The number of patients in each of these subgroups by site and stage are shown in Table 4. As expected, the unresectable subgroup had a high percentage of patients with T4 or advanced neck disease.

We calculated survival for each of these subgroups using the Kaplan-Meier method, as shown in Figure 3 and Table 5. Also included in Table 5 is the disease-specific survival of each of the subgroups. Table 6 shows the survival of each of the subgroups with respect to stage. The survival of each of the 3 subgroups was statistically significantly different from that of the others ($P < .001$, log-rank and Wilcoxon $\chi^2$ tests).

Because of the earlier finding that age was statistically significant, we analyzed the elective subgroup by age. The 2-year survival in those aged 20 to 44 years was 74% compared with only 50% in those aged 45 to 64 years and 60% in those 65 years or older. However, only 13 patients were among those aged 20 to 44 years.

**COMPARISON OF THE SURGICAL AND RADIATION GROUPS**

We found differences in the tumor sites between the surgical and radiation groups, with a large number of patients with oral cavity cancer being treated surgically. We therefore performed site-specific analyses. When we compared the Kaplan-Meier survival of the surgical and radiation groups, the surgical group had statistically better survival ($P = .005$, log-rank $\chi^2$ test; $P = .003$, Wilcoxon $\chi^2$ test). The radiation subgroups, however, had statistically different survival, with that of the elective group being much better than that of the unresectable or the unhealthy group. When the survival of the elective group
was compared with that of the surgical group, the elective group had a better survival, although this difference was not statistically significant ($P = .22$, log-rank $\chi^2$ test; $P = .22$, Wilcoxon $\chi^2$ test).

Since the survival of the elective subgroup may have been comparable to that of the surgical group because T3 and T4 tumors resulted in worse outcomes in either group, we compared the survival of the patients with T3 and T4 disease in the surgical group and elective subgroup. The curves cross, and we found no statistical difference ($P = .75$, log-rank $\chi^2$ test; $P = .55$, Wilcoxon $\chi^2$ test).

**OROPHARYNGEAL CANCER**

Oropharyngeal cancers constituted 35% of the tumors treated and therefore the best subgroup for comparison. In addition, they were relatively evenly divided between the surgery and radiation groups (surgery group, 93 patients; radiation group, 101 patients). The tumor stages for oropharyngeal cancer are shown in Table 7. Although we found differences in individual T stages, ie, the radiation group had more T4 and N3 disease and the surgery group had more T3 disease, the overall distribution of advanced T-stage tumors was similar.

The overall survival of the patients with advanced oropharyngeal cancer was 49% at 2 years, 44% at 3 years, and 34% at 5 years. The survival of the patients in the surgical group was 56% at 2 years, 52% at 3 years, and 41% at 5 years. The survival of the patients in the radiation group was 48% at 2 years, 39% at 3 years, and 30% at 5 years. Survival of the surgical group appeared better than that of the radiation group; however, the radiation group included the unresectable and unhealthy subgroups, and the difference in survival was not significant ($P = .25$, log-rank $\chi^2$ test; $P = .38$, Wilcoxon $\chi^2$ test).

Analysis of the radiation subgroups shows a large difference in survival between the elective subgroup and the unresectable or unhealthy subgroups ($P < .001$ log-rank and Wilcoxon $\chi^2$ tests) (Table 8). When we compared the surgical group with the elective subgroup, the elective subgroup had better survival; however, the difference was not statistically significant ($P = .19$, log-rank $\chi^2$ test; $P = .17$, Wilcoxon $\chi^2$ test).

As many of these patients were treated with neck dissection, some of those with stage III or IV disease in the radiation group may have survived because they under-
went radiation therapy for a small primary tumor and then a neck dissection. We therefore specifically compared patients in the surgical and radiation groups and the elective subgroup with T3 and T4 disease. Although the radiation group had the poorest survival, we found no difference in survival between the patients with T3 and T4 disease in the elective subgroup and the surgical group (P = .20, log-rank \( \chi^2 \) test; \( P = .17 \), Wilcoxon \( \chi^2 \) test) (Table 8).

Of the 163 patients with laryngeal cancer, 101 had supraglottic and 62 had glottic disease. Surgery was the more common method of treatment, with 108 patients undergoing total laryngectomy or supraglottic laryngectomy and 43 undergoing radiation therapy. The tumor stages for the patients with laryngeal cancer are shown in Table 9.

The overall survival of the patients with advanced laryngeal cancer was 58% at 2 years, 47% at 3 years, and 39% at 5 years. The survival of the patients in the surgical group was 66% at 2 years, 53% at 3 years, and 44% at 5 years. The survival of the patients in the radiation group was 43% at 2 years, 39% at 3 years, and 39% at 5 years. Survival in the surgical group was better than in the radiation group; however, the radiation group included the unresectable and unhealthy subgroups (\( P = .11 \), log-rank \( \chi^2 \) test; \( P = .04 \), Wilcoxon \( \chi^2 \) test).

The elective subgroup included only 25 patients with laryngeal cancer. Their survival was 43% at 2, 3, and 5 years. This survival was poorer than that of the surgical group, but owing to the limited numbers was not statistically significant (\( P = .36 \), log-rank \( \chi^2 \) test; \( P = .30 \), Wilcoxon \( \chi^2 \) test). The survival of the surgical and radiation groups and elective subgroup is shown in Table 10, with additional information for specific stages. The stage-specific survival of the surgical group and elective subgroup is similar, but limited numbers prevent any firm conclusions.

### HYPOPHARYNGEAL CANCER

Seventy-five patients had hypopharyngeal cancer. Surgery was the most common method of treatment, with 43 patients undergoing surgery and 27 undergoing radiation. Very advanced stages predominated, with 56 of the 70 treated patients having T3 or T4 disease and 40 having N2 or N3 disease.

The overall survival of the patients with hypopharyngeal cancer was 39% at 2 years, 31% at 3 years, and 23% at 5 years. The survival of the patients in the surgical group was 53% at 2 years, 41% at 3 years, and 34% at 5 years. The survival of the patients in the radiation group was 20% at 2 years, 15% at 3 years, and 10% at 5 years. Survival in the surgical group was significantly better than in the radiation group (\( P = .003 \), log-rank \( \chi^2 \) test; \( P = .003 \), Wilcoxon \( \chi^2 \) test) (Table 10). The 27 radiation group patients included only 5 who underwent elective radiation therapy. The group mostly consisted of the 20 patients in the unresectable subgroup, with 2 in the unhealthy subgroup, all of whom had very poor survival. The 5 elective subgroup patients had good survival, but no comparisons could be made with this limited cohort.

### MULTIVARIATE ANALYSIS

To determine which factors were most significant in predicting patient survival, a multivariate analysis was conducted on all 356 patients who underwent curative therapy. The factors analyzed were American Joint Committee on Cancer site and stage, T and N stages, treat-
ment group (surgical vs radiation), and age (20-44 vs 45-64 vs ≥65 years). The most significantly predictive factors of survival were age, treatment group, T stage, and site. We then performed an analysis using these 4 most predictive factors. The treatment group was most significant (P < .001), followed by age (P = .003), site (P = .008), and T stage (P = .01).

To verify that the poor survival of the radiation group was due to the inclusion of the unresectable and unhealthy subgroups, we performed a multivariate analysis of the radiation group. The factors analyzed were site, stage, and T and N stages, treatment subgroup (unresectable vs elective vs unhealthy), age, radiation treatment dose (≥5500 vs <5500 cGy), and whether chemotherapy was administered. The most significantly predictive factors of survival were site, treatment subgroup, radiation dose, and N stage. An analysis was then performed using these 4 most predictive factors. The treatment subgroup was most significant (P < .001), followed by radiation dose (P < .001), site (P < .001), and N stage (P = .02).

Given the significant difference in survival between the patients in the elective subgroup and those in the unhealthy and unresectable subgroups, a separate multivariate analysis was performed of the surgical group and elective subgroup. The factors analyzed were site, stage, T and N stages, treatment group (surgical vs elective), and age. The most significantly predictive factors of survival were age, T and N stages, and site. Although treatment group was not significant, we included it in the further analysis, along with these 4 most predictive factors. The N stage was most significant (P = .001), followed by age (P = .002), T stage (P = .003), and site (P = .07). We found no significant difference in survival due to treatment group (P = .75).

To determine which factors were most predictive of survival within the surgical group, we performed an analysis using site, stage, T and N stages, age, tumor margins, and administration of postoperative radiation therapy. The most significantly predictive factors were N and T stages, site, and age. We then performed an analysis using these 4 most predictive factors. Patient age was most significant (P < .001), followed by N stage (P < .001). Site (P = .07) and T stage (P = .09) were less significant.

We then analyzed the oropharyngeal group using the following factors: T and N stages, treatment group (surgical vs radiation), and age. Age was the most predictive factor (P = .002), followed by N stage (P = .06). Treatment group and T stage were not significantly predictive.

**COMMENT**

This study verifies the limited survival we can currently obtain for patients with advanced head and neck cancer. These findings are consistent with previous data. Analysis of the National Cancer Data Base showed a 5-year disease-specific survival of 57%, and in that study, most patients had stage I and II disease. In this study, the 5-year disease-specific survival was a comparable 53%. However, our actual 5-year Kaplan-Meier survival was only 33%. This clearly highlights the high frequency of death due to intercurrent disease in patients with head and neck cancer.

This high rate of deaths due to noncancer causes will remain a major problem in treating head and neck cancer. Regardless of new treatments that are discovered, the noncancer death rate will remain high and limit our ability to significantly increase long-term survival for these patients. Throughout this study, therefore, the major statistic presented was survival rather than disease-free survival. Survival is also the most important issue for patients selecting treatment for head and neck cancer. Unfortunately, the survival statistics presented herein accurately represent what becomes of patients with advanced head and neck cancer, i.e., a significant rate of deaths due to cancer, a significant rate of deaths due to comorbid factors, and survival of a limited group.

The demographics of the disease are a major part of the poor cure rates. The patients present at an advanced age and with multiple comorbidities, at times making them so unhealthy that surgery is not considered. As seen in the multivariate analysis, age was a very important predictor of survival. This was not because the cancers necessarily behaved worse in the elderly, but in large part was due to the comorbidities present in the older population. The combination of the patient’s age and health therefore must be considered in formulating an individual patient’s treatment plan.

A comparison of the surgical and radiation groups showed better survival in the surgical group. However, the radiation group contained the patients in the unhealthy and unresectable subgroups who had poorer survival. The patients who underwent elective radiation did as well as or better than those who opted for surgery. These patients were generally similar with regard to age and stage; however, we found differences in site, and the site-specific analysis was therefore important.

The multivariate analysis showed that the treatment group was an important prognosticator; however, this was due to the poor survival of the unhealthy and unresectable subgroups. Age, site, and T stage were the most predictive factors. For the patients in the radiation group, compliance with radiation dosing was very important. When we compared the elective subgroup with the surgical group, the method of treatment was insignificant, whereas the important variables in predicting survival were N stage, age, and T stage.

The data were analyzed by site, with the greatest attention given to the patients with oropharyngeal cancer. These patients receiving elective radiation therapy did as well as or better than those who opted for surgery. This remained true for patients with advanced T stages. Multivariate analysis confirmed that the method of treatment was an insignificant predictor of survival and that age and N stage were most important. Others have reported on the responsiveness of oropharyngeal cancers to radiation therapy and advocate its routine use rather than surgery. These data support the use of radiation therapy (with or without chemotherapy and/or neck dissection) as the primary treatment for oropharyngeal cancer.
The outcomes of patients with laryngeal cancer in the surgery group were comparable to those of patients in the VA Laryngeal Cancer Study. The outcomes of the patients in the radiation group were not as good, even in the elective subgroup. Only 25 of these patients were in the elective subgroup, 5 of whom had N3 disease and all of whom died of cancer. Other than confirming that radiation therapy regimens are acceptable for laryngeal cancer, no new conclusions can be drawn.

The hypopharyngeal data tend to support surgery as first-line treatment. Among the patients with hypopharyngeal cancer, the surgical group had much better survival rates than the radiation group. However, the radiation group had only 5 patients who underwent elective radiation therapy. The patients with unresectable disease had very poor survival. These data show the importance of carefully selecting patients for surgery for hypopharyngeal cancer. When aggressive surgery is performed, and the cancer is resectable, at least a reasonable cure rate can be achieved, even in a group of patients with advanced T stages.

In the treatment of real patients with advanced head and neck cancer, compliance remains a major problem. These patients frequently have psychological issues that limit their compliance with therapy. Our study design, which controlled the prospective data we obtained, was not aimed at study compliance. However, many areas of noncompliance occurred, including incomplete courses of radiation therapy or inadequate postoperative radiation. Additional factors that could have been studied include radiation treatment breaks, noncompliance with recommendations for postradiation neck dissection, additional information on why patients did not comply with postoperative radiation therapy, noncompliance with recommended nutritional regimens, and smoking after the diagnosis. To obtain these data, we would need to perform a retrospective medical chart review and would therefore add additional biases; however, the data as they stand highlight the major problem posed by compliance. For patients in randomized trials, selection criteria necessitate that they will be compliant with treatment. Often, if patients become noncompliant, their results are considered nonevaluable and are eliminated from the data evaluation. In this study, we included all patients, because when discussing treatment options we never know which patients will comply with the regimen.

Although chemotherapy was used in some of these patients, this use was not routine. More aggressive application of chemotherapy may have increased response, but also may have just increased patient noncompliance. Although randomized trials support chemotherapy concomitantly with radiation therapy to improve cure of head and neck cancer, patient motivation and compliance must be considered in routine clinical application.

Despite age, comorbidities, and noncompliance, patients with advanced cancer can obtain long-lasting cures, even in the unresectable and unhealthy groups. The 28% 2-year survival in the unresectable group compares favorably with the 2-year survival rate reported in the recent randomized trial of unresectable head and neck cancer.

An important part of regimens that use radiation therapy as the primary modality is to consider neck dissection. In the patients treated primarily with radiation therapy, only 2 neck failures were seen, both in patients who refused neck dissection. For patients with N2 or N3 neck disease who are treated primarily with radiation therapy, we continue to recommend neck dissection 4 to 6 weeks after the completion of radiation therapy.

Furthermore, although much is written about the importance of salvage surgery in patients treated primarily with radiation therapy, salvage surgery was of minimal importance in this study. Most patients in whom radiation therapy failed had large tumors (T3 or T4) that persisted and were unresectable, or the patient refused surgery owing to the expected morbidities. Salvage surgery at the primary site was therefore attempted only 10 times, and only 2 of those patients were rendered disease free.

Given that neck dissection can be added to radiation therapy and yield good cure rates in patients with advanced nodal disease, and that the difficult cancers to control without primary site surgery are large tumors, future randomized trials for advanced head and neck cancer where the aim is organ preservation should concentrate on T3 and T4 tumors rather than include all stage III and IV tumors.

Although randomized trials are important, particularly as we continue to evaluate new treatment regimens with chemotherapy and new agents for head and neck cancer, the data presented herein are, in our opinion, critically important. Randomized trials fail to address a large subsection of patients afflicted with head and neck cancer, namely the sick, elderly, and poorly compliant. By analyzing the results of randomized trials in conjunction with large sequential patient series, the true course of head and neck cancer can be evaluated and may be useful in aiding patients and physicians in selecting treatment for head and neck cancer. Surgery continues to have a role in the primary treatment of advanced head and neck cancer and, in many instances, yields the best chance of cure. Of course, surgery remains vitally important in treating advanced neck disease. Radiation therapy as a primary form of treatment was demonstrated to be a truly viable option, even with advanced primary site disease, especially of the oropharynx.

The treatment of patients with advanced head and neck cancer needs to be individualized, with mortality due to cancer and noncancer causes considered when formulating a treatment plan. The morbidity of surgery, radiation therapy, and chemotherapy needs to be considered by the patient, as does later quality of life. The most important issue to the patient will always be survival. The specific survival data presented herein will allow physicians to counsel patients faced with the difficult choice of how best to treat their advanced head and neck cancer.
REFERENCES


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