Adverse Events Associated With Concurrent Chemoradiation Therapy in Patients With Head and Neck Cancer

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Objective: To assess toxicities, functional outcomes, and health-related quality of life associated with concurrent chemoradiation therapy (CRT) in patients with head and neck cancer.

Design: Prospective and retrospective outcomes study.

Setting: Tertiary care institution.

Patients: Participants in the longitudinal Outcomes Assessment Project whose head and neck cancer was treated with CRT between February 1, 2000, and March 1, 2007 (n=104).

Interventions: Patients prospectively provided functional and health-related quality of life information, including data from the 1-year and most current follow-up visits. Medical records were reviewed to determine toxicity and survival rates.

Main Outcome Measures: Well-defined acute and late toxicities; functional outcomes (diet, dentition, tracheostomies); head and neck cancer-specific, general health, and depression outcomes; and survival rates.

Results: Most patients had oropharyngeal or laryngeal tumors (87.5%) and advanced-stage disease (75.0%). Approximately one-half had hematologic toxicities and toxicity-related treatment delays. Approximately one-quarter had neurotoxicities and/or ototoxicities, moist desquamation, pneumonia, nausea and vomiting requiring hospitalization or intravenous fluids, dehydration or malnutrition requiring hospitalization, and mild or moderate fever. Although patients receiving the current intensity-modulated radiation therapy (IMRT) protocol using the Pinnacle3 planning system had more toxicity-related treatment delays, they had fewer toxicities and better functional and health-related quality of life outcomes compared with those receiving conventional lateral opposing-field radiation or the initial IMRT protocol using the Best nomos PEACOCK planning system.

Conclusions: Patients receiving CRT experience a substantial number of treatment-related adverse events, primarily affecting oropharyngeal and laryngeal function, with improvement noted for the current IMRT protocol. Improving dental prosthetic rehabilitation and including evaluations with speech and swallowing pathologists before and during treatment may enhance patient outcomes.

Meta-analyses that have compared trials with currently accepted chemotherapy and radiation protocols have shown a significant survival benefit with the use of concurrent CRT compared with radiation alone. Although neoadjuvant therapy showed a survival benefit over radiation alone in the Radiation Therapy Oncology Group 91-11 randomized trial, concurrent CRT showed the highest laryngectomy-free survival rate, locoregional control rate, and lowest distant metastasis rate. Concurrent CRT using platinum-based agents has therefore emerged as the current nonsurgical treatment of choice in many medical centers.

Most studies addressing these cancer treatments focus on oncologic outcomes as the primary end point of interest. Rates of treatment adverse effects are inconsistently reported, with one major reason being the difficulty of accurately capturing this information. Determining the incidence of acute adverse effects such as mucositis, skin desquamation, treatment delay, and hematologic toxicity from clinical records is often difficult. Determining the incidence of late adverse events such as dysphagia and dependency on gastric tubes or tracheostomies often requires close follow-up for a long period.

The purpose of the present study was to present a comprehensive accounting of the treatment effects of CRT for head and neck cancer at our institution. Toxicities, self-reported health-related quality of life, functional outcomes, survival rates, and cause of death data are presented. The incidence of these adverse events was broken down by type of radiation and chemotherapy protocol to determine whether more current protocols resulted in better outcomes.

**METHODS**

Patients were eligible for this study if they had a primary head and neck carcinoma that was diagnosed between January 1, 2000, and February 28, 2007, if they received definitive, concurrent CRT at the University of Iowa, and if they were enrolled in this institution’s head and neck cancer Outcomes Assessment Project, a longitudinal study that is conducted with University of Iowa Investigational Review Board approval. During the time frame of this study, the Outcomes Assessment Project had an accrual rate of 76.1%; 11.6% of patients refused to participate, and 12.3% were missed during busy clinical settings in which numerous patients are being seen, sometimes for a short length of time, with limited resources to capture them all.

Across the time frame of this study, patients received 3 different types of radiation: conventional radiation delivered as lateral opposing fields, IMRT using the “first-generation” PEACOCK planning system (Best nomos, Pittsburgh, Pennsylvania), and IMRT using the more current Pinnacle’ planning system (Phillips Healthcare, Andover, Massachusetts). Most patients received either the conventional dosage or a weekly regimen of chemotherapy at the discretion of the medical oncologist. The conventional regimen consisted of 1 dose (100 mg/m²) of cisplatin or of carboplatin with fluorouracil every 3 weeks for a total of 3 treatments, and the weekly regimen consisted of 1 dose (20-30 mg/m²) of cisplatin (with or without fluorouracil) or of carboplatin with paclitaxel every week for a total of 6 to 7 treatments. Six patients received other regimens.

Data regarding the case mix characteristics and patients’ self-reported health-related quality of life were gathered prospectively. Medical records were reviewed to collect information about patient demographic characteristics, disease and treatment characteristics, and adverse events. Toxicities were recorded as present or not present at any point in the patients’ treatment and follow-up. Dentition, type of diet, and adverse clinical outcomes, such as the presence of a tracheostomy and the use of enteral feedings, were identified at patients’ 12-month visits and at a subsequent visit representing the last recorded follow-up. “Most current” outcomes presented in this article represent the patients’ last follow-up visit, which was their 12-month visit if they did not have a later one.

The acute and late toxicity data included degree of mucositis (as defined by the Radiation Therapy Oncology Group grading criteria); toxicity-related treatment delays; hospital admission for severe mucositis, dehydration or malnutrition, or fever; nausea or vomiting requiring hospitalization or administration of outpatient intravenous fluids; the presence of hematologic toxicities, neurotoxicities, or otoxicities; the incidence of trismus, moist desquamation, pneumonia, osteoradionecrosis, or renal impairment; fever with or without neutropenia; and treatment-related death. A list of these toxicities and the criteria for determining their clinical significance is given in Table 1.

**Table 1**

Patients’ dentition was categorized as functionally dentate ($\geq 12$ teeth per ridge), partially dentate ($<12$ teeth per ridge), or edentulous (no teeth). Diet was categorized as full (completely unrestricted), slightly restricted (relatively full, with a few restrictions), soft, liquid, minimal oral intake (could take food orally but required tube feedings for support), or no oral intake.

The health-related quality of life outcomes were collected from these patients prospectively during their enrollment in the Outcomes Assessment Project. Patients completed validated surveys about their general health, head and neck cancer-specific quality of life, and depressive symptoms at various time points. The present study included data that patients provided at diagnosis, at 1 year, and at their last available follow-up visit (as many as 8 years after diagnosis).

The 30-item Head and Neck Cancer Inventory was used to measure head and neck cancer-specific outcomes for eating, speech, aesthetics, and social disruption (pain, socializing with friends and family, employment). The multiple items in each of these 4 domains measure frequency and severity using a 5-point scale; then domain scores are normalized to a scale of 0 to 100, with higher scores representing better functioning. Cutoff scores of these 4 domains measure frequency and severity: very low (10-20), low (21-30), moderate (31-60), and high (61-100) categories. The Medical Outcomes Study 36-item Short-Form Health Survey was used to measure self-perceived general physical and mental health in 8 separate domains. These scores are normalized to a range of 0 to 100, with higher scores representing better functioning, and are then transformed to norm-based z scores derived from the general population. Two summary scores representing overall physical and mental health can be calculated from these domain scores, permitting an easy and understandable interpretation of general health outcomes. Symptoms of depression were measured using the Beck Depression Inventory. Total scores derived from this standardized, 21-item instrument range from 0 to 63, with higher scores representing a larger (worse) number of depressive symptoms. Based on published norms, these scores can be categorized into normal (0-9), mild (10-20), moderate (21-30), and severe ($\geq 31$) levels of depressive symptoms.

Descriptive statistics were used to demonstrate the incidence of adverse events in this group of patients receiving CRT. Actuarial survival analyses were performed using data obtained from this institution's cancer registry to determine observed survival rates (death from all causes) and disease-specific survival rates (death with cancer). The Wilcoxon (Gehan) test was used to determine significant differences across treatment groups.

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study are shown in Table 2. Almost three-fourths were men, and the mean age was 55.7 years. Most had oropharyngeal tumors (69.3%) and presented with stage IV disease (75.0%). During the study period, the most prevalent form of radiation therapy was IMRT; 51.9% of patients received IMRT with the initial PEACOCK delivery system and 33.7% with the current Pinnacle protocol. The remaining patients (14.4%) received radiation therapy in the form of lateral opposing fields. Virtually all patients in the lateral–opposing-fields group received conventional chemotherapy (93.3%), whereas the percentage getting weekly concurrent chemotherapy rose from 25.9% for those getting the initial IMRT protocol to 60.0% of those getting the current IMRT protocol (data not shown).

Information about completion of chemotherapy was available for 92 of these 104 patients (88.5%). Almost half (48.9%) did not receive their planned number of chemotherapy cycles (data not shown). When broken down by type of chemotherapy, the percentages receiving less than the planned number of cycles was 45.5% (25 of 55) in the conventional chemotherapy group, 59.4% (19 of 32) in the weekly chemotherapy group, and 20.0% (1 of 5) in the “other” chemotherapy regimen group.
TOXICITIES

High-grade mucositis was the most prevalent acute toxicity and was present in virtually all patients, whereas mucositis severe enough to necessitate hospital admission was present in 9.6% (Table 3). Approximately half of all patients experienced hematologic toxicities (59.6%) and toxicity-related treatment delays (46.2%), whereas approximately one-quarter experienced moist desquamation (28.8%), neurotoxicity and/or ototoxicity (26.9%), nausea or vomiting requiring hospitalization or outpatient intravenous fluids (26.9%), dehydration or malnutrition requiring hospitalization (26.0%), pneumonia (25.0%), and mild or moderate fever (23.1%). The less prevalent toxicities included elevated creatinine level (19.2%), a fever severe enough to require hospital admission (18.3%), trismus (7.7%), and osteoradionecrosis (3.8%). Last, 2 of the 104 patients (1.9%) died within 2 months of the start of treatment.

Nine patients (8.7%) did not have any of the toxicities listed in Table 3, whereas the remaining 95 patients (91.3%) had a mean of 3.2 toxicities each (range, 1–7). When broken down by type of radiation therapy, patients getting lateral opposing-field radiation had a mean of 3.9 toxicities compared with 3.1 for both the initial IMRT and the current IMRT protocols. There was a general trend toward decreasing incidence of toxicities as the type of radiation therapy advanced from lateral opposing fields to initial IMRT and then to current IMRT. The major exceptions to this pattern were toxicity-related treatment delays, the incidence of which rose from 40.0% to 54.3%; severe fevers requiring hospitalization, which rose from 13.3% to 22.9%; and mild or moderate fevers, which rose from 20.0% to 25.7%, respectively, between the lateral–opposing-field period and the adoption of current IMRT protocols.

The most severe level of mucositis, experienced by almost 70% of all patients during the course of their treatment, was patchy or confluent mucositis (data not shown). Comparing the incidence of severe mucositis across the different types of radiation therapy is difficult, however, given that the percentage of patients whose mucositis grade was not noted in their medical records differed substantially across the 3 treatment groups.

Hematologic toxicities and neurologic and/or ototoxicities were the 2 groups that demonstrated substantial differences based on type of chemotherapy (data not shown). Hematologic toxicities were present in 65.1% of the conventional group compared with 48.6% in the weekly group, and neurologic and/or ototoxicities were present in 33.3% of the conventional group compared with 14.3% in the weekly group.

FUNCTIONAL OUTCOMES

One-quarter of the patients received no foods orally or a minimum oral intake diet at the most recent follow-up visit, having increased to 25.6% from 6.4% at diagnosis (Table 4). Type of diet was evaluated by dental status to determine whether the increase in edentulous patients (14.1% at diagnosis to 39.7% at the most recent follow-up) appeared to be a major influence on dietary restrictions. At the most recent follow-up visit, 33.8% of patients (14 of 26) with restricted diets (soft foods only through no oral intake) were edentulous, whereas 32.7% of patients (17 of 52) with unrestricted diets were also edentulous.

The incidences of posttreatment adverse outcomes are shown in Table 5. The most recent follow-up visit, a

Table 3. Incidence of Treatment-Related Adverse Events by Type of Radiation Therapy in Patients With Head and Neck Cancer Treated With Chemoradiation

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Patients (N=104)</th>
<th>Lateral Opposing Fields (n=15)</th>
<th>IMRT, Initial Protocol (n=54)</th>
<th>IMRT, Current Protocol (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositisb</td>
<td>96 (92.3)</td>
<td>12 (100)b</td>
<td>52 (98.1)b</td>
<td>33 (97.1)b</td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>62 (59.6)</td>
<td>11 (73.3)</td>
<td>33 (61.1)</td>
<td>18 (51.4)</td>
</tr>
<tr>
<td>Toxicity-related treatment delay</td>
<td>48 (46.2)</td>
<td>6 (40.0)</td>
<td>23 (42.6)</td>
<td>19 (54.3)</td>
</tr>
<tr>
<td>Moist desquamation</td>
<td>30 (28.8)</td>
<td>5 (33.3)</td>
<td>16 (29.6)</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>Neurotoxicity and/or ototoxicity</td>
<td>28 (26.9)</td>
<td>4 (26.7)</td>
<td>16 (29.6)</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td>Severe nausea or vomiting</td>
<td>28 (26.9)</td>
<td>5 (33.3)</td>
<td>14 (25.9)</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>Severe dehydration or malnutrition</td>
<td>27 (26.0)</td>
<td>5 (33.3)</td>
<td>12 (22.2)</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>26 (25.0)</td>
<td>5 (33.3)</td>
<td>14 (25.9)</td>
<td>7 (20.0)</td>
</tr>
<tr>
<td>Mild or moderate fever</td>
<td>24 (23.1)</td>
<td>3 (20.0)</td>
<td>12 (22.2)</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>Elevated creatinine level</td>
<td>20 (19.2)</td>
<td>4 (26.7)</td>
<td>9 (16.7)</td>
<td>7 (20.0)</td>
</tr>
<tr>
<td>Severe fever</td>
<td>19 (18.3)</td>
<td>2 (13.3)</td>
<td>9 (16.7)</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td>Acute severe mucositis</td>
<td>10 (9.6)</td>
<td>3 (20.0)</td>
<td>5 (9.3)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Trismus</td>
<td>8 (7.7)</td>
<td>2 (13.3)</td>
<td>4 (7.4)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>4 (3.8)</td>
<td>2 (13.3)</td>
<td>1 (1.9)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Treatment-related death</td>
<td>2 (1.9)</td>
<td>0</td>
<td>2 (3.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: IMRT, intensity-modulated radiation therapy.

a The initial protocol used the PEACOCK planning system (Best nomos, Pittsburgh, Pennsylvania), and the current protocol uses the Pinnacle planning system (Phillips Healthcare, Andover, Massachusetts).

b Mucositis during treatment was unknown for 6 of the cases (1 undergoing current IMRT, 2 undergoing the previous IMRT protocol, and 3 undergoing lateral opposing fields), so the denominator for calculating percentages is the number of cases with known mucositis status during treatment.
mean of 3.1 years after diagnosis for these patients, represents their last follow-up visit, whether it was their 12-month visit or a subsequent one. More than one-quarter (26.4%) depended on enteral feedings, 13.8% depended on a tracheostomy, and 16.9% reported intermediate or high levels of pain at their most recent follow-up visit. Data from the subset of patients with both a 12-month and a later follow-up visit (mean, 3.4 years after diagnosis) were also analyzed to determine whether there was any improvement or deterioration across these years. The results indicated that the percentage of patients who had a gastric tube remained virtually unchanged after 1 year but that the percentage who had a tracheostomy increased from 6.4% at 1 year posttreatment to 14.1% at the recent follow-up visit. Of the 6 patients who received a tracheostomy after their 12-month follow-up visit, 1 experienced a recurrence between the 12-month and most recent follow-up visit, 2 had a recurrence before their 12-month follow-up, and 3 have not had a recurrence.

When outcomes at the most recent follow-up visit were broken down by type of radiation therapy, the lateral–opposing fields treatment group had the largest percentage of patients with tracheostomies (30.8%); 14.3% who underwent the initial IMRT protocol and 3.2% who underwent the current IMRT protocol had tracheostomies. The lateral–opposing fields treatment group also had the largest percentage of patients requiring enteral feedings (53.8%), which were required by 31.0% of the initial IMRT protocol and 6.5% of the current IMRT protocol.

HEALTH-RELATED QUALITY OF LIFE OUTCOMES

Patients treated with concurrent CRT generally had good quality of life in the head and neck cancer–specific areas of speech, aesthetics, and social disruption (Table 6), with mean scores ranging from 72.7 to 81.1, representing “high” functioning. However, only 23.6% of patients reported scores in the high-functioning range for eating, which is representative of essentially normal functioning. Patients’ physical health appeared to be relatively normal, given that approximately 25% of their physical health scores were in the lowest and the highest categories, representing the quartile groupings of the age-matched general population. Their mental health, however, was poorer than that of the general population, with 42.9% of the patients’ scores falling into the general populations’ lowest quartile. Despite these low scores, only 4.4% of this patient sample was experiencing moderate or severe depression.

SURVIVAL

The 5-year survival rates for all patients were 66.2% when death from all causes was the end point (observed) and 74.0% when death with cancer was the end point (disease-specific) (Figure 1). The survival rate was higher for the subset of patients with oropharyngeal cancer, who had 71.7% observed survival and 79.3% disease-specific survival at 5 years (Figure 2). Patients who received lateral–opposing-fields radiation had the lowest 5-year observed survival at 53.3% (Figure 3), although the difference was not statistically significant (P = .45).

Overall, 33 patients (31.7%) from this cohort of 104 have died. Two patients died within 7 weeks of treatment initiation; 7 additional patients died within 12 months of diagnosis (3 with cancer present, 1 with no cancer, and 3 with unknown cancer status). The remaining 24 patients died 12 or more months after diagnosis (16 with cancer present, 1 with no cancer, and 7 with unknown cancer status).
The present investigation of adverse events associated with CRT includes a well-delineated set of toxicities and adverse outcomes captured across a broad follow-up period. The results were then examined with respect to the progressive change in treatment modalities during the 7-year study period to provide contemporary conclusions about these outcomes. The intent was to comprehensively evaluate the outcome of patients receiving CRT at the University of Iowa in terms of toxicity, functional outcomes, health-related quality of life, and survival.

Approximately half the patients in this study experienced a toxicity-related delay in either chemotherapy or radiation therapy. Previous studies have demonstrated that unplanned prolongations of radiation therapy are associated with significantly decreased locoregional control and survival rates owing to accelerated repopulation.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Mean HRQOL Scores</th>
<th>High (70-100)</th>
<th>Intermediate (31-69)</th>
<th>Low (0-30)</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eating</td>
<td>49.4</td>
<td>23.6</td>
<td>57.0</td>
<td>19.4</td>
<td>72</td>
</tr>
<tr>
<td>Speech</td>
<td>72.7</td>
<td>68.4</td>
<td>23.7</td>
<td>7.9</td>
<td>76</td>
</tr>
<tr>
<td>Aesthetics</td>
<td>81.1</td>
<td>82.6</td>
<td>6.7</td>
<td>10.7</td>
<td>75</td>
</tr>
<tr>
<td>Social disruption</td>
<td>77.4</td>
<td>67.5</td>
<td>28.6</td>
<td>3.9</td>
<td>77</td>
</tr>
</tbody>
</table>

Health Quarters Derived From Age-Matched General Population Norms

| Physical health     | 28.6              | 30.0          | 12.8                 | 28.6       | 70             |
| Mental health       | 42.9              | 22.8          | 21.4                 | 12.9       | 70             |

Level of Depressive Symptom Severity

| Depression         | 7.4               | 23.5          | 2.9                  | 1.5        | 68             |

Abbreviations: HNC, head and neck cancer; HRQOL, health-related quality of life.

a Percentages in the columns underneath represent row percentages.

b The 4 levels were determined using cutoff scores that represent quartiles of the 1998 general population reference values for men and women aged 55-64 years.
lation by tumor stem cells\textsuperscript{33,34}. Another study\textsuperscript{35} showed that one-third of patients in clinical trials evaluating concurrent CRT for head and neck carcinomas do not receive the planned number of chemotherapy cycles. That percentage was higher in the present study, with 48.9% of patients not receiving their planned number of chemotherapy cycles.

Oropharyngeal mucositis and hematologic toxicity were the 2 most prevalent toxicities in this study. Much has been written about mucositis in this patient population as a primary cause of pain, inadequate nutrition or hydration, psychological distress, and treatment delay, as well as increased costs owing to longer hospital stays.\textsuperscript{36} A 2003 study showed that ulcerative mucositis was responsible for increased costs owing to longer hospital stays.\textsuperscript{36} A 2003 study showed that ulcerative mucositis was responsible for unplanned radiation therapy modifications in 11% of patients,\textsuperscript{37} whereas a 2006 study showed that breaks in radiation therapy were caused by moderate and severe mucositis in 15.8% and 46.8% of patients, respectively.\textsuperscript{38}

The present study's 80% rate falls in the upper end of a range from 22.5% to 81.0%, representing previously published results of retrospective, single-institute studies of patients receiving IMRT with concurrent chemotherapy.\textsuperscript{5,14,15,39,40} The large difference in these findings is most likely owing to inconsistent documentation and reporting methods in the medical record. Even in the present study, 14 patients were missing information about the presence of mucositis (n=6) or its grade (n=8).

Because many of the toxicities examined in this study can be associated with severity of mucositis, much work has been done to identify radioprotectant medication to prevent mucositis in patients undergoing CRT. Although no well-accepted medication has yet been found, the rate of severe mucositis requiring hospitalization has declined as the radiation protocols have advanced from lateral opposing fields (20.0%) to the initial IMRT protocol (9.3%) and then the current IMRT protocol (5.7%).

Clinically significant hematologic toxicity was present in 59.6% of these patients. Chemotherapy is usually considered to have more of an effect on hematopoiesis than radiation therapy, and these toxicities differed substantially by type of chemotherapy in the present study, from 65.1% in the conventional group to 48.6% in the weekly group. The smaller differences seen in the incidence of hematologic toxicity for the various types of radiation therapy are likely owing to the fact that conventional chemotherapy was more prevalent with lateral-opposing-fields radiation therapy (93.3%) than with the initial IMRT (66.7%) or the current IMRT (37.1%) protocols. This finding suggests that weekly chemotherapy protocols will result in reduced rates of hematologic toxicities and their related treatment delays.

Of the 6 toxicities that were present in approximately one-quarter of these patients, neurotoxicities and/or ototoxicities may not be generally as disruptive but may result in worse long-term outcomes. The results of this study showed only a slight decrease in neurotoxicity and ototoxicity as a function of type of radiation therapy, from 26.7% with lateral opposing fields to 22.9% with current IMRT. However, certain neurotoxicities are also a well-known adverse effect of platinum-based chemotherapy.\textsuperscript{41,42} As with hematologic toxicities, neurotoxicities and ototoxicities also differed substantially by type of chemotherapy and were present in 33.3% of the conventional group compared with 14.3% in the lower-dose weekly group.

The incidence of moist desquamation, a grade 3 toxicity that involves bleeding induced by minor trauma, decreased as radiation therapy progressed, from 33.3% with lateral opposing fields to 29.6% with the initial IMRT protocol to 25.7% with the current IMRT protocol. This finding is in agreement with a previous study which indicated that more current IMRT plans that contour the skin as a sensitive structure were associated with less toxicity than earlier IMRT plans that used multiple tangential fields or that did not block the skin as a sensitive structure.\textsuperscript{17}

Patients receiving CRT are immunosuppressed and are at an increased risk for pneumonia or sepsis from aspiration of even small amounts.\textsuperscript{43} The incidence of pneumonia, a surrogate measure for aspiration and poor swallowing function, was 25.0% in the present study. Pneumonia has been cited in previous articles as a frequent cause of death for patients who died during the treatment period, and it was the cause of death for 2 patients in this study who died within 8 weeks of the initiation of treatment. The incidence of pneumonia declined from 33.3% in the lateral–opposing-fields group to 20.0% in the current IMRT protocol group.

Functional and health-related quality of life outcomes indicated that poor oral function remained a persistent problem for this patient population, with many of these patients reporting poor eating function and 25.0% requiring enteral feedings at the most current follow-up visit, which occurred a mean of 3.4 years after diagnosis. Lack of insurance reimbursement for oral rehabilitation is one possible reason for this finding, and affordable dentures are one means of improving these patients' eating outcomes. Another avenue for enhancing their health-related quality of life is through the guidance of a multidisciplinary team approach that focuses on improved oral intake, nutrition, and swallowing function that is initiated before treatment. The current protocol at the University of Iowa in-

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Type of Radiation & Year, % of Patients & No. of Patients \\
\hline
LOF & Initial IMRT & Current IMRT \\
\hline
Initial IMRT & 94.3 & 90.7 & 82.1 & 83.3 & 66.7 & 73.3 & 53.3 & 79.5 & 77.2 & 69.8 & 54 \nCurrent IMRT & 84.3 & 90.7 & 82.1 & 83.3 & 66.7 & 73.3 & 53.3 & 79.5 & 77.2 & 69.8 & 54 \n\hline
\end{tabular}
\caption{Observed survival by type of radiation therapy for patients whose head and neck cancer was managed with chemoradiation (n=104). IMRT indicates intensity-modulated radiation therapy; LOF, lateral opposing fields.}
\end{table}
involves consultation with a speech and swallowing pathologist for an evaluation before treatment and swallowing therapy during treatment.

Chemo radiation therapy appears to yield good survival rates. The 5-year rates for all patients were 66.2% for observed survival and 74.0% for disease-specific survival. These rates were even higher (71.7% and 79.5%, respectively) for patients with oropharyngeal tumors.

Because information about toxicities was collected retrospectively, this study was limited by incomplete documentation of certain data that at times made it difficult to determine the presence or severity of these toxicities. Because of demonstrated inconsistencies in physicians’ reporting of chemotherapy-related adverse effects, several standardized methods for reporting these toxicities have been developed. One such example is the most current form of the Common Toxicity Criteria 2.0, which covers 260 toxicities spanning 27 organ systems, 30 of which are specifically related to head and neck cancer. The Common Toxicity Criteria has been adopted by major organizations such as the European Organisation for the Research and Treatment of Cancer, which should help to improve the consistency of reporting.

Regardless of this limitation, the results of the present study indicated that patients receiving CRT experience a substantial burden of treatment-related adverse events. It is difficult to completely separate the effects of chemotherapy vs radiation therapy on development of these adverse events. However, patients who received the current IMRT protocol were less likely to experience a treatment-related toxicity or a long-term need for tracheostomies or enteral feedings. They were somewhat more likely, however, to experience a toxicity-related delay in treatment, possibly owing to a higher incidence of fever among patients who received weekly chemotherapy or simply owing to the fact that they had more opportunities to have a delay in chemotherapy administration. Continued efforts to reduce the incidence of these toxicities would not only lessen patients’ short-term pain and discomfort but would also potentially increase the duration of their long-term survival.

It is evident that a significant number of problems related to CRT center around oropharyngeal and laryngeal function. Dental prosthetic rehabilitation for many of these patients is not optimal, which has a detrimental effect on returning to an unlimited oral diet. Pneumonia during and after treatment resulting from laryngeal incompetence is a life-threatening event in this patient population. Early identification of aspiration before initiating treatment and frequent evaluation with speech and swallowing pathologists throughout treatment may decrease this risk.

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