Decreased Short- and Long-term Swallowing Problems With Altered Radiotherapy Dosing Used in an Organ-Sparing Protocol for Advanced Pharyngeal Carcinoma

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Objective: To determine the effect of a reduced radiotherapy dose on short- and long-term swallowing problems after organ-sparing treatment.

Design: Prospective case series.

Setting: Tertiary care referral center.

Patients: A consecutive sample of 29 patients with advanced oropharyngeal or hypopharyngeal cancer who were treated with intravenous hydroxyurea and concomitant hyperfractionated, accelerated radiotherapy.

Interventions: Initial experience with 74.4 Gy of radiation demonstrated severe long-term swallowing problems, prompting a dose reduction to 60.0 Gy. Eighteen patients were followed up for this study in the 74.4-Gy group, while 11 were in the 60.0-Gy group.

Main Outcome Measures: Swallowing variables were assessed in both patient groups at 4 months and at 12 months following completion of therapy.

Results: Patient demographics and tumor characteristics were similar in each group, while significant differences were noted in the posttreatment clinical swallowing variables. Persistent severe odynophagia at 4 months (89% [16/18] vs 30% [3/10]) and at 12 months (64% [7/11] vs 11% [1/9]) was greater in the 74.4-Gy group (P = .002). Clinical signs of aspiration were also increased in the 74.4-Gy group, with 81% (13/16) vs 11% (1/9) at 4 months and 60% (6/10) vs 11% (1/9) at 12 months (P<.05). Most striking, however, was the incidence of long-term gastrostomy, with 78% (14/18) of patients receiving 74.4 Gy requiring gastrostomy feedings at 12 months compared with 18% (2/11) in the 60.0-Gy group (P = .002). Local control was unchanged by the altered dosing, with median follow-ups of 43.5 and 24.0 months in the 74.4-Gy and 60.0-Gy groups, respectively.

Conclusion: Decreased radiation doses can maintain disease control and reduce treatment-related long-term swallowing complications.

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The last 2 decades have witnessed significant changes in the treatment of head and neck cancer. Although surgery remains the gold standard for many head and neck cancers, in many centers the treatment approach to advanced disease has undergone a transformation. There has been a shift toward primary chemotherapy and radiotherapy for the treatment of advanced pharyngeal and laryngeal carcinomas, reflecting the organ-preserving benefits of these therapies. Organ-preservation chemotherapy and radiotherapy trials have shown survival similar to standard surgical approaches,1,2 and recent trends have been toward concomitant chemotherapy and radiotherapy regimens.3 However, despite these advances, there have been relatively few reports evaluating function after organ preservation.4-19

Although the functional consequences of the surgical management of head and neck cancer have been well-documented,15-18 the effects of aggressive chemotherapy and radiotherapy have been less well-defined. Radiotherapy alone can produce secondary fibrosis of the pharyngeal muscles and soft tissues, with resultant impairment of pharyngeal contraction and laryngeal elevation.19 Inclusion of salivary glands into the radiation field results in xerostomia and hyposalivation, which further impair mastication and the initiation of the swallowing reflex.20 The addition of chemotherapy, particularly concurrent, to radiotherapy may potentiate the functional adverse effects.

Combinations of chemotherapy with radiotherapy, used in an organ-sparing context, have been shown to produce alterations in pharyngeal transport, increase aspiration rates, cause hypopha-
ryrngeal stenosis, and limit normal pharyngeal function. Among 9 patients with oral and pharyngeal tumors treated in a neoadjuvant study setting, all had reduced swallowing efficiency and 78% had tongue base and laryngeal movement disorders during swallowing. Swallowing deficits following concurrent chemoradiotherapy used to treat 22 patients with oral, oropharyngeal, and hypopharyngeal carcinomas included impaired laryngeal elevation, epiglottic movement, and pharyngeal stripping. A prior investigation of early swallowing abnormalities, using a computerized system for quantitative analysis of specific swallowing variables, following concomitant radiation and intravenous hydroxyurea demonstrated epiglottic dysmotility, impaired laryngeal motion, pharyngeal constrictor dysmotility, and limited bolus transport and clearance, while a long-term follow-up study demonstrated persistence of these findings, with long-term gastrostomy dependence.

Some of the observed changes in organ function may improve over time. Despite early swallowing dysfunction, a study population had marked improvement in dysphagia by 18 months after completion of chemoradiotherapy, with 87% eating normally. However, such improvement is often not the case, particularly compared with preoperative swallowing function. Methods to evaluate the dysfunction have ranged from radiographic swallowing studies to quality-of-life surveys and dysphagia-specific surveys. The validity of questionnaires and self-assessment was noted by Pauloski et al in their study of 132 patients using videofluoroscopy and question-related self-assessment.

Our efforts have been to develop an organ-sparing protocol that is reliable, simple, and effective to treat advanced pharyngeal carcinomas without excessive adverse effects. Because of the significant toxicities in initial trials of concomitant hydroxyurea and radiotherapy, we modulated the radiation dose to try to reduce the toxicities of this therapy. The objective of this investigation was to evaluate the effect of a reduced radiotherapy dose, administered in combination with infusional chemotherapy, on the short- and long-term swallowing toxicities in patients with advanced-stage nonlaryngeal head and neck carcinoma who were treated with concomitant intravenous hydroxyurea and hyperfractionated, accelerated external radiotherapy.

A phase I-II clinical trial of parenteral hydroxyurea and external beam radiotherapy was approved by the Albert Einstein Cancer Center Review Committee and the Montefiore Medical Center Institutional Review Board and initiated in 1995. Preliminary results of this trial were previously reported. Following determination of the safety of infusional hydroxyurea in combination with hyperfractionated radiotherapy, 40 patients with stage III or IV carcinoma of the oral cavity or oropharynx or stage II, III, or IV carcinoma of the hypopharynx were entered into the phase II component of the study. Twenty-four of these patients were treated with 74.4 Gy of radiation, while 16 subsequently were treated at a reduced radiotherapy dose of 60.0 Gy. All patients received 0.313 mg/m² per minute of hydroxyurea as a continuous infusion during their radiotherapy. The group of patients presented in this study is composed of 18 patients from the 74.4-Gy phase and 11 patients from the 60.0-Gy phase of the treatment protocol. The other patients were excluded from this data analysis because of insufficient follow-up (5 patients) or a lack of evaluable swallowing data (early death, refusal to participate, or local failure [6 patients]). The demographics of these patients are presented in Table 1 and are similar in both groups, except for the longer follow-up for the earlier cohort of patients treated at the higher dose of radiotherapy.

No patient had a medical history of neurologic disease, gastroenterologic dysfunction, other head and neck cancer, surgery, or radiotherapy to the head and neck region. No patient was taking medication that might affect swallowing function or had previously undergone swallowing therapy. Before treatment, all patients were eating orally; however, in this study most patients underwent pretreatment gastrostomy tube placement, based on the initial patients’ experience of severe swallowing dysfunction following the initiation of the concomitant intravenous hydroxyurea and hyperfractionated accelerated external radiotherapy protocol. The mucositis scores, weight change, and pretreatment symptom and alimentation details for the patients are presented in Table 2.

Analysis of clinical swallowing variables was assessed during routine posttreatment visits. The patients also underwent...
planned radiographic swallowing evaluation with a standard modified barium swallow under the guidance of a trained speech and swallowing pathologist. Prior reports of these patients have described ubiquitous radiograph changes that have not practically separated clinical groups within the treatment cohort. Therefore, because initial analysis of radiographic studies in both treatment groups in the present study recapitulated these published findings, these data were not included in the present report. The importance of the clinical factors in these patients, with regard to medical management and symptom control, prompted an analysis of clinical swallowing variables in this study. Inconsistent swallowing therapy was applied in both groups and was not associated with the differences reported herein. Clinical signs of aspiration or penetration were defined as choking or coughing after the ingestion of food substances, assessed similarly to a clinical bedside swallowing evaluation performed by a speech and swallowing pathologist.

STATISTICAL ANALYSIS

Data were analyzed using Statistica 6.1 (StatSoft Inc, Tulsa, Okla), a commercially available statistics software program. Data evaluation included chi-square analysis, t test, Kaplan-Meier analysis, and log-rank analysis.

RESULTS

The 2 groups evaluated in this study were similar with respect to demographic data, as demonstrated in Table 1. The inclusion of the 2 patients in the 74.4-Gy group who had oral cavity primary tumors was allowed because of significant involvement of the oropharyngeal structures as well, and the patient with stage II disease had a pyriform sinus primary tumor that was large and would have required a total laryngectomy for surgical management. The toxicity analysis findings for the latter patient were identical to the remainder of the group and did not bias the data in any particular direction. The pretreatment swallowing symptoms among the 2 groups were abnormal in many of the patients but were not significantly different between the 2 groups in frequency or severity (Table 2). Table 2 also details 2 of the standard toxicity items reported for nonsurgical trials, mucositis and weight loss. Although the mucositis scores were similar at the completion of therapy, they were significantly less in the 60.0-Gy patients at 4 months (P = .006) and approached significance at 12 months following therapy (P = .07). This suggests that the initial toxicity is unchanged by the altered radiation dose but that the chronic toxicities are reduced. In addition, and perhaps most important, the overall survival was not compromised in the patients treated with the lower radiation dose of 60.0 Gy (Figure 1).

The main differences in the treatments were in clinical swallowing function. The alteration observed in the clinical signs of aspiration or penetration was significant following reduction of the radiotherapy dose to 60.0 Gy. The results are depicted in Figure 2, and the reduced aspiration or penetration was present throughout the study, with significant differences in all categories. The posttreatment differences at 4 months for liquids, puree, and solids were 81% (13/16) vs 11% (1/9) (P < .001), 69% (11/16) vs 11% (1/9) (P = .004), and 69% (11/16) vs 25% (2/8) (P = .03), respectively, for the 74.4-Gy vs 60.0-Gy patients. At 12 months, the differences were equally marked for liquids, puree, and solids, showing clinical aspiration or penetration in these bolus groups of 60% (6/10) vs 11% (1/9) (P = .04), 60% (6/10) vs 11% (1/9) (P = .03), and 60% (6/10) vs 0% (0/8) (P = .007), respectively, in the 74.4-Gy vs 60.0-Gy groups. Additional significant findings included a reduction in severe odynophagia in the 60.0-Gy group (Figure 3). Again, this was significant at the 4-month (P = .002) and 12-month (P = .02) posttreatment intervals.

One of the critical quality-of-life issues for these patients is the presence of a gastrostomy tube and the ability to eat orally. This was most altered in the 60.0-Gy group, reducing the overall prevalence of gastrostomy tubes from 78% (14/18) following 74.4 Gy to 18% (2/11) following 60.0 Gy of radiation (P = .002, log-rank test). In addition, the median time to tube removal was cut in half from 10 months to 5 months, and the Kaplan-Meier curve depicting removal of the tubes is shown in Figure 4. Most patients within the study resumed some form of oral alimentation, albeit recreational rather than nutritive in many of the 74.4-Gy patients, and the data are presented in Table 3. As was the case in previous reports, hypopharyngeal narrowing was present in nearly one third of the patients in both groups (74.4 Gy...
most reports have documented significant impairment in swallowing function, in particular, has shown mixed results, but quality-of-life issues will best determine which treatment alternatives. Therefore, critical assessment of the long-term disease control equivalent to their time-tested surgical algorithm and radiotherapy protocols achieve survival and amelioration of treatment outcomes. Many organ-sparing chemoradiation and radiotherapy protocols achieve survival and disease control equivalent to their time-tested surgical alternatives. Therefore, critical assessment of the long-term quality-of-life issues will best determine which treatment is optimal, based on function. The assessment of swallowing function, in particular, has shown mixed results, but most reports have documented significant impairment in swallowing variables. A follow-up to the Veterans Affairs protocol study describing swallowing dysfunction in surgical and nonsurgical groups found that the alterations could take up to 2 years to improve, and a similar prevalence of dysfunction was present in both groups. Alterations described following chemotherapy and radiotherapy have included decreased laryngeal elevation, decreased epiglottic movement, pharyngeal stasis, and pharyngeal constrictor dysmotility, and an overall reduction in swallowing efficiency. In addition to these radiographic abnormalities, clinical functional consequences have been noted, including aspiration and prolonged gastrostomy tube dependence as was the case with the higher radiation dosing schedule in the present study.

The effect of concurrent therapy on swallowing dysfunction has been evaluated in several studies and found to have significant consequences. Newman et al described 47 patients following an intra-arterial cisplatin and concomitant radiation (RADPLAT) regimen and noted eating and weight changes to be maximal at 6 months, finding that the function of the patient at 6 months often predicted his or her swallowing function, ie, oral or gastrostomy, at 12 and 18 months. They did not identify a significant degradation in function in late follow-up. Another description of these patients by Murry et al as-sessed quality of life and swallowing function by survey. They found that, of those who improved with regard to swallowing function, the improvement was noted soon after therapy completion. This is in contrast to the Veterans Affairs protocol study describing quality of life and swallowing function by survey. They found that, of those who improved with regard to swallowing function, the improvement was noted soon after therapy completion. This is in contrast to the Veterans Affairs protocol study describing quality of life and swallowing function by survey. They found that, of those who improved with regard to swallowing function, the improvement was noted soon after therapy completion. This is in contrast to the Veterans Affairs protocol study describing quality of life and swallowing function by survey. They found that, of those who improved with regard to swallowing function, the improvement was noted soon after therapy completion. This is in contrast to the Veterans Affairs protocol study describing quality of life and swallowing function by survey. They found that, of those who improved with regard to swallowing function, the improvement was noted soon after therapy completion. This is in contrast to the Veterans Affairs protocol study describing quality of life and swallowing function by survey. They found that, of those who improved with regard to swallowing function, the improvement was noted soon after therapy completion. This is in contrast to the Veterans Affairs protocol study describing quality of life and swallowing function by survey. They found that, of those who improved with regard to swallowing function, the improvement was noted soon after therapy completion. This is in contrast to the Veterans Affairs protocol study describing quality of life and swallowing function by survey. They found that, of those who improved with regard to swallowing function, the improvement was noted soon after therapy completion.
alterations, we questioned the effect of time on these alterations. The long-term effects, greater than 1 year following therapy, consisted of the same abnormalities present in the early (<4 months) and late (>12 months) periods. The changes were ubiquitous, affecting 100% of these patients. Although the patients in that study recovered some swallowing ability, 60% required gastrostomy tube feedings at the late follow-up to maintain their nutritional status.

Additional studies evaluating the long-term effects on swallowing have shown similar results. List and colleagues, treating with cisplatin, 5-fluorouracil, oral hydroxyurea, and hyperfractionated radiation, evaluated 64 patients by a quality-of-life survey and determined that "in no area, however, was patients' functioning at 12 months clinically better than that before treatment." In fact, one third of their patients continued with late swallowing dysfunction. Another study by Eisbruch and associates, using concurrent gemcitabine and radiation, demonstrated that their patients had persistent problems 6 to 12 months following therapy, noted high aspiration and pneumonia rates, and did not show a marked improvement over time. The long-term swallowing problems in our 74.4-Gy group are similar to those noted by these research groups. The modest reduction in radiation dose in our study produced a significant decrease in the long-term complications, which is particularly important because both aforementioned trials used cell cycle modulating agents to potentiate radiotherapy.

The clinical factors described in the present study (aspiration, chronic pain, weight loss, and mucositis) are those most often cited in reports assessing toxicities in the patients with head and neck cancer. Our patients' weight loss and mucositis scores are consistent with the other aggressive chemotherapy and radiation therapy trials cited in this article. Our patients in both radiation groups had similar mucositis scores at the completion of therapy, but the scores were significantly different at 4 months. This suggests that the chronic toxicities were reduced in the 60.0-Gy group, as the mucositis resolved more rapidly. Also, there was persistent mucositis in the 74.4-Gy group 12 months following therapy, unlike the 60.0-Gy group, in whom all mucosal inflammation had resolved. Mirroring this, the trend toward less severe weight loss was present in the 60.0-Gy group, supporting the concept of reduced chronic toxicity. The onset of oral intake is another functional indicator. Although the 2 treatment groups showed similar ultimate rates of oral intake, the 74.4-Gy patients took longer to achieve their intake. Patients took as long as 5 years to recover some liquid intake in the high-dose group, compared with a maximum of 10 months in the low-dose group. This difference lacked statistical significance in this study \( (P = .17) \), but few would argue the clinical significance of such a difference and its daily effect on patients' lives.

Although mucositis and weight loss provide evidence of the adverse effects of chemotherapy and radiotherapy, clinical aspiration or penetration, odynophagia, and gastrostomy tubes are less ambiguous. All 3 of these factors showed a statistically significant improvement in the patients treated with the lowered radiation dose of 60.0 Gy. The decrease in the incidence of odynophagia documented in the 60.0-Gy patients has a potentially significant effect on the quality of life of these patients, because chronic pharyngeal pain is a frequent complaint among those treated with chemotherapy and radiotherapy for head and neck cancer. In addition, the clinical evidence of aspiration or penetration was marked in the patients receiving 74.4 Gy at the 4- and 12-month follow-ups. This is comparable to the 65% and 62% of patients who had aspiration in the early and late follow-ups described by Eisbruch et al. A similar high aspiration rate of 89% was documented by Lazarus et al following chemotherapy and radiotherapy. Therefore, the reduction in our 60.0-Gy patients to less than 25% is significant compared with published data as well.

The most significant effect of this dose alteration was in the area of gastrostomy tube persistence. Our practice is to continue with gastrostomy tube feedings until the patient is able to maintain his or her weight for 1 month without using the tube for supplemental feeding. Therefore, this also implies the ability to swallow effectively without aspiration. Few studies have included the rates of gastrostomy tube persistence among their data; however, the radiation dose groups in this study serve as an internal control. The ability to remove the gastrostomy tubes in the patients treated with the lowered radiation dose is significant in terms of the absolute numbers of patients who had their tubes removed (4 of 18 in the 74.4-Gy group and 9 of 11 in the 60.0-Gy group) and the time at which their tubes were removed. The high incidence of tube persistence in the 74.4-Gy patients, despite the high rates of oral intake, is indicative of the recreational nature of the oral intake in many of these patients. The same is true for the 2 patients who kept their tubes in the 60.0-Gy group. The removal of the gastrostomy tube is perhaps the most important and reliable indicator of adequate oral intake in these patients, and it has a tremendous effect on their quality of life. Survival was not compromised by the decrease in radiation dose, and this study demonstrates the potential effect of altering a single treatment variable without compromising survival.

Hypopharyngeal narrowing continues to be an issue. There were 4 patients in the low-dose group who had symptomatic hypopharyngeal narrowing, compared with 6 in the high-dose group. The difference, however, is in the presence of complete hypopharyngeal stricture, a finding not observed in the 60.0-Gy group but present in 3 of the patients in the 74.4-Gy group. The development of a subtotal stricture may be managed by dilation, as was the case in these patients. Complete stenosis, on the other hand, requires some form of significant reconstruction, and often this can only be performed at the expense of the larynx because the stricture has been in the postcricoid region extending to above the arytenoids. Many of the dilations in the patients with subtotal stricture have been managed by retrograde dilation through their gastrostomy stomas. This has the advantage of avoiding the inadvertent creation of a second lumen or hypopharyngeal perforation. The prevalence of hypopharyngeal narrowing is similar in the present study to that described by Eisbruch and colleagues, who noted stricture rates of 35% and 46% in their early and late groups, respectively.

There are several potential limitations of this study. Although the study demonstrated statistically signifi-
cant improvement in swallowing function in the 60.0-Gy patients, the sample size is small and the tumor types are homogeneous. Although this is an advantage with respect to clarity of effect, it may prevent generalized conclusions regarding such an effect. In addition, intravenous hydroxyurea is not part of any other head and neck treatment protocol. Indeed, such dose changes may not have the same effect when using other chemotherapeutics that may potentiate radiation to a lesser degree. However, cell cycle agents, such as hydroxyurea, are becoming increasingly useful for their ability to arrest the cell in a radiosensitive state, potentiating radiation-related cell death. The effects demonstrated in this study may also be pertinent for other such drugs. Last, no “objective” swallowing assessment was included, except for gastrostomy tube status. Earlier studies showed that all patients had similar radiographic alterations and these findings were not predictive of functional recovery. Therefore, because the same radiographic changes were seen in the 60.0-Gy group, this was not included in the present analysis. Radiographic changes are not always clinically important, and it is still debated which objective assessment is most appropriate, including modified barium swallow, fiberoptic endoscopic swallowing evaluations, or dysphagia-related questionnaires. Because the ultimate objective assessment is the presence or absence of a gastrostomy tube, it seems appropriate to use this as an end point. As was the case in our group treated with 74.4 Gy, swallowing of various food consistencies is often present, but this may be more of a recreational or quality-of-life effect rather than a nutritional one.

CONCLUSIONS

As we continue to search for novel, and often nonsurgical, methods to treat advanced head and neck cancer, we must not ignore the functional consequences of our therapy. In the rush to accept organ-sparing treatment protocols, functional status has often been de-emphasized. The recent focus on quality-of-life measurement and assessment of swallowing by many authors is critical to the appropriate evaluation of these therapies. Adequate longitudinal functional follow-up of these patients is also important. Traditional toxicity assessment often considers late effects to be 3 months following therapy. Our group, and others, has demonstrated the need to assess long-term functional toxicities at 6 and 12 months after therapy. The present study evaluated a treatment protocol that had 1 variable altered because of unacceptable chronic swallowing toxicities and found that a reduction in radiation dose resulted in a dramatic decrease in long-term swallowing problems, while maintaining the same level of disease control and survival. Such considerations should become the standard when evaluating organ-sparing protocols, as a spared organ is not always a functional one.

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