CONCURRENT PLATINUM-BASED CHEMOTHERAPY AND SIMULTANEOUS MODULATED ACCELERATED RADIATION THERAPY FOR LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE TONGUE BASE

Joshua D. Lawson, MD,1 Kristen Otto, MD,2 Amy Chen, MD,2 Dong M. Shin, MD,3 Lawrence Davis, MD,1 Peter A. S. Johnstone, MD1,3

1 Department of Radiation Oncology, Emory University School of Medicine, Atlanta, Georgia
2 Department of Otolaryngology/Head and Neck Surgery, Emory University School of Medicine, Atlanta, Georgia
3 Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia 30322.

E-mail: peter@radonc.emory.org

Accepted 26 April 2007
Published online 26 July 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20694

Abstract: Background. Randomized data support use of chemotherapy concurrently with radiation in treatment of advanced squamous cell carcinoma (SCC) of the oropharynx. Intensity modulated radiation therapy (IMRT) is increasingly being used to deliver such radiotherapy; no published reports specifically describe results of chemotherapy with IMRT for SCC of the base of tongue (BOT). We present outcomes data using simultaneous modulated accelerated radiation therapy (SMART) combined with platinum-based chemotherapy in treatment of locally advanced SCC of the BOT.

Methods. The records of the Otolaryngology/Head and Neck Surgery Department of Emory University were screened for patients undergoing definitive chemoradiotherapy for SCC of the BOT. Radiation Oncology records were reviewed for dosimetry and prescription data. Hospital and clinic records were reviewed for control and toxicity data. All patients were treated definitively with platinum-based chemotherapy and once-daily RT. Median dose and dose per fraction to sites of gross primary or nodal disease, clinically involved neck, and clinically uninvolved neck were 70.29 Gy (2.13 Gy/fx), 63.03 Gy (1.91 Gy/fx), and 57.75 Gy (1.75 Gy/fx), respectively.

Results. Between January 2003 and August 2005, 34 patients underwent definitive therapy for SCC of the BOT using SMART and chemotherapy. Follow-up was documented in all cases (median, 20.1 months). There have been 3 distant failures and 3 locoregional failures.

Conclusion. With moderate follow-up, chemotherapy and SMART contributes to excellent results, with 24-month actuarial overall survival and local control of 90% and 92%, respectively. Toxicity may be increased, however, with 15% of patients developing esophageal stricture or stenosis.

Keywords: simultaneous modulated accelerated radiation therapy (SMART); chemoradiation; base of tongue (BOT); platinum.
sites, BOT cancers frequently present with bilateral or contralateral adenopathy. Successful resection of these advanced tumors often requires a total glossectomy and total pharyngo-laryngectomy, often with partial mandibulectomy and neck dissection. The inherent morbidity of such procedures, combined with the need to address the bilateral necks, has led to the frequent use of radiotherapy as a curative modality. While radiation alone has shown good control of tumors that are small, superficial, or exophytic, more advanced or infiltrative tumors have poorer responses to conventionally fractionated radiotherapy.

Recently several investigations have evaluated the use of chemotherapy concurrent with radiation therapy in treatment of squamous cell carcinomas of several head and neck sites. Randomized data support use of chemotherapy concurrently with radiation as standard of care in treatment of advanced SCC of the oropharynx. Mature data have shown significant advantages in overall survival, disease-free survival, and locoregional control with the addition of platinum-based chemotherapy to definitive radiation therapy.

Conventional techniques of radiation delivery were used in these trials. This employs 2 opposed lateral radiation fields encompassing the primary tumor as well as the superior areas of lymphatic drainage. These lateral fields are typically matched to a single anteroposterior low neck field treating the inferior bilateral necks and supraclavicular areas. More recently, intensity modulated radiation therapy (IMRT) has been increasingly used in the treatment of head and neck cancers. There are no randomized data comparing conventional radiation delivery with IMRT, but single-institution experience to date has shown no adverse impact on local control and an encouraging ability to reduce radiation toxicities, specifically xerostomia.

A variation of IMRT, simultaneous modulated accelerated radiation therapy (SMART), treats primary tumor, malignant adenopathy, and at-risk nodal areas with daily fractionation using differing fraction sizes for gross tumor versus at-risk areas. This technique of simultaneous boosting typically delivers single-fraction daily dose to gross disease in excess of 2.1 Gy. We have been using SMART since the beginning of 2003, and present clinical results from its implementation with concurrent platinum-based chemotherapy in a homogeneous population of patients with locally advanced SCC of the BOT.

MATERIALS AND METHODS

After Institutional Review Board approval was granted, the records of the Otolaryngology/Head and Neck Surgery Department of Emory University were screened for patients undergoing definitive chemoradiotherapy for SCC of the BOT. Radiation Oncology records for reviewed for dosimetry and prescription data. Hospital and Clinic records of patients receiving follow-up care were reviewed for control and toxicity data.

Patients. Between January 2003 and August 2005, 34 patients underwent definitive therapy for SCC of the BOT using SMART and chemotherapy. Excluded from this analysis are all patients with any surgical intervention beyond biopsy prior to initiation of chemoradiotherapy (n = 2), all patients treated palliatively (prescribed radiotherapy dose of <60 Gy) (n = 2), and all patients receiving radiation monotherapy (n = 1). Patients receiving neck dissection following chemoradiation, whether as part of the initial plan or as salvage, are included. Pretreatment evaluation for all patients included a thorough history and physical examination with flexible fiberoptic laryngoscopy, complete blood counts, liver function tests, chest X-ray, and CT scan of the neck. Positron emission tomography (PET) was obtained whenever possible. Staging determinations were made according to the 6th edition of American Joint Committee on Cancer staging criteria. Treatment modality was determined by a joint conference with representatives from Head and Neck Surgery, Radiation Oncology, Medical Oncology, Oral Surgery, Oral Pathology, and Diagnostic Radiology. Each patient had a percutaneous endoscopic gastrostomy (PEG) tube placed prior to initiation of therapy. The patient characteristics and stage at presentation are presented in Tables 1 and 2. No patient had known metastatic disease at presentation.

Chemotherapy. All 34 patients received platinum-based chemotherapy. Twenty-one patients received high-dose cisplatin, 7 patients received weekly paclitaxel and carboplatin, and 6 patients received at least 1 dose of high-dose cisplatin and then switched to weekly paclitaxel and carboplatin or single-agent carboplatin.

In detail, high-dose cisplatin 100 mg/m^2 was administered on the same day or the day after initiation of radiation therapy, and repeated every 3 weeks (days 1, 22, and 43). For high-dose cisplatin, all patients received premedication of antie-
metics with intravenous saline (0.9%) hydration with mannitol 12.5 g before and after cisplatin infusion. The weekly paclitaxel and carboplatin consisted of 60 mg/m² and area under the curve (AUC) of 2, respectively (duration, 7 weeks), and the first dose was given on the same day or the day after starting radiation therapy. Six patients were started with high-dose cisplatin and then switched to weekly paclitaxel and carboplatin (1 patient for 5 weeks and 1 patient for 4 weeks). One of the 6 patients received only low-dose carboplatin (AUC = 2) weekly (duration, 5 weeks), and 1 patient received a moderate dose of carboplatin (AUC = 7). The last 2 patients received high-dose cisplatin for (100 mg/m²), 2-doses (days 1 and 22) and developed tinnitus and mild hearing loss and 1 patient did not receive any further chemotherapy. The other patient was administered carboplatin alone (AUC = 6) for 1 dose. Ninety-five percent of the planned doses of chemotherapy were delivered to all patients.

**Radiation Therapy.** Prior to initiation of treatment, contrast-enhanced CT simulation was performed in all cases. All patients were simulated and treated supine, immobilized by a thermoplastic head mask affixed to the treatment couch. PET images were used for treatment planning in 28 (82%) patients; these images were fused to simulation CT images for contouring. Gross tumor volumes (GTV) were established from these fused images and correlated with physical examination findings. Typical expansion to clinical target volume (CTV) and planning target volume (PTV) added margins of 1 to 1.5 cm, with modifications in areas adjacent to critical normal structures. Neck volume contours were generated using the technique of Chao et al., until publication of the joint European Organization for Research and Treatment of Cancer and Radiation Therapy Oncology Group (EORTC/RTOG) recommendations, when the latter was adopted. Critical normal tissues contoured included spinal cord, brainstem, bilateral parotid glands, bilateral submandibular glands, vocal cords, and in some cases, optic apparatus and/or cochlea. A margin of 0.5 cm was added to the contoured spinal cord; no margin was added to any other critical normal structure. All contours were approved prior to treatment planning by the radiation oncologist concerned.

Treatment planning was performed using Eclipse treatment planning software (Varian Medical Systems, Palo Alto, CA) by 1 of 2 certified medical dosimetrists (CMD), each with extensive experience in treatment planning for head and neck cancers. SMART was used in all cases. All patients were treated using 6 MV photons, using 7 radiation fields with gantry angles of 0, 46, 107, 158, 204, 255, and 313 degrees. All patients were treated with 5 daily fractions per week, to a median (range) of 33 fractions (31–35 fractions). Inhomogeneity corrections were not used. SMART was delivered on a Varian linear accelerator (Varian Medical Systems, Palo Alto, CA). After September 2005, each accelerator was equipped with an on-board imaging (OBI) unit and dedicated software. This system consists of an X-ray tube (model G242, 0.4 and 0.8 mm focal spots, 14° anode angle, 800 kJ/h, Varian Medical Systems, Salt Lake City, UT) and amorphous-silicon imaging panel (model PaxScan 4030CB, Varian Medical Systems, Salt Lake City, UT) attached to the gantry of the linear accelerator with Exact robotic arms (Varian Medical Systems, Baden, Switzerland). Use of this system allows daily orthogonal kV images to be obtained, with shifts made to verify isocenter alignment to digitally reconstructed radiographs (DRRs) obtained at CT simulation.

In these 34 patients treated definitively with concurrent platinum-based chemotherapy and

| **Table 1. Patient characteristics.** |
|-------------------------------|------------------|
| **Factor**                   | **No. (%)**     |
| **Sex**                      |                  |
| Male                         | 23 (68)         |
| Female                       | 11 (32)         |
| **Smoking history**          |                  |
| Yes                          | 24 (71)         |
| No                           | 10 (29)         |
| **Age, y**                   |                  |
| Mean (range)                 | 61 (34–76)      |
| **AJCC stage**               |                  |
| I                            | 0 (0)           |
| II                           | 2 (6)           |
| III                          | 3 (9)           |
| IV                           | 29 (85)         |

**Note:** Values represent number of patients (%) except otherwise stated.

| **Table 2. T and N classification for 34 patients.** |
|----------------------------------|------------------|
| **T classification**             | **N0** | **N1** | **N2a** | **N2b** | **N2c** | **N3** |
| T1                               | 0      | 0      | 3       | 6       | 1       | 0      |
| T2                               | 2      | 2      | 0       | 4       | 1       | 1      |
| T3                               | 0      | 1      | 0       | 2       | 1       | 0      |
| T4                               | 1      | 1      | 0       | 2       | 4       | 2      |
uniform radiation therapy for locally advanced BOT SCC, mean (median, range) total dose to gross disease was 70.14 Gy (70.29 Gy, 69.30–70.4 Gy). Mean (median, range) dose per fraction to gross disease was 2.13 Gy/fx (2.13 Gy/fx, 2.10–2.20 Gy/fx). Mean (median, range) dose to the remainder of the clinically involved neck was 61.05 Gy (63.03 Gy, 54.4–63.03 Gy). Mean (median, range) dose per fraction to the remainder of the clinically involved neck was 1.85 Gy/fx (1.91 Gy/fx, 1.7–1.95 Gy/fx). The mean dose to the remainder of the clinically uninvolved neck was 58.34 Gy (57.75 Gy, 54.4–63.03 Gy). Mean dose per fraction to the remainder of the clinically uninvolved neck was 1.77 Gy/fx (1.75 Gy/fx, 1.7–1.91 Gy/fx).

Follow-up. Each patient was seen at least weekly during the course of radiation treatment. Follow-up information was available for all patients. Each patient was seen 1 month following completion of treatment and then every 1 to 3 months by the treating surgeon, medical oncologist, or radiation oncologist. A thorough physical exam was performed at each follow-up visit. Follow-up CT imaging was obtained 1 to 2 months following treatment. Follow-up PET scans were performed when clinically indicated. The mean (median, range) duration of follow-up was 22.2 months (20.1, 3.6–42.8 months).

Statistical Methods. Twenty-four-month actuarial local progression-free survival, regional progression-free survival, distant metastases-free survival, and overall survival were determined using the method of Kaplan and Meier, using STATA version 9.2 (College Station, TX). Planned neck dissection following chemoradiotherapy showing the presence of residual viable tumor cells was not scored as regional failure as this was considered completion of the planned curative therapy. Failure was defined as biopsy-proven recurrent disease or imaging results inconsistent with any other explanation besides disease recurrence or metastasis. Follow-up durations are calculated from the date of diagnosis.

RESULTS

Response to Treatment. Each patient was able to complete the prescribed course of therapy. Of the 34 patients treated, all but 1 (97%) received a complete response (CR) from chemoradiotherapy. One patient had persistent local disease and is considered to have had local failure at time 0. This patient was treated for stage T4N2c disease; she received 69.96 Gy at 2.12 Gy/fx to her primary tumor and 56.1 Gy at 1.7 Gy/fx to her bilateral necks given with 3 cycles of cisplatin chemotherapy. She was not a surgical candidate following chemoradiotherapy and elected hospice care 3.6 months after completion of treatment.

Neck Dissections. Following chemoradiotherapy, unilateral neck dissections were performed in 5 patients, with another 2 patients receiving bilateral neck dissections. For these 7 patients, T classification at presentation was as follows: T1, 1 patient; T2, 1 patient; T3, 1 patient; and T4, 4 patients. Nodal classification at presentation was as follows: N2b, 2 patients; N2c, 3 patients; and N3, 2 patients. Of 9 necks dissected, viable tumor remained in 2 (22%). One of these patients (originally N2c) has continued to remain without evidence of disease; the other patient (originally N3) subsequently had failure in the dissected neck, as described later. There were additionally 2 distant failures in this group of patients, the details of which are provided later.

Locoregional Control. At last follow-up, 29 patients remain without evidence of recurrent or metastatic disease. Actuarial local control and regional (neck) control are presented in Figure 1. At 24 months, estimated local and regional control are 92% and 97%, respectively.

There were 3 locoregional failures, 2 local and 1 regional. These occurred at 0, 7.1, and 11.8 months of follow-up. The patient with failure at time 0 is described above. Another of these patients was treated for stage T2N3 disease; he received 70.4 Gy at 2.2 Gy/fx to his primary tumor and 54.4 Gy at 1.7 Gy/fx to his bilateral necks with 1 cycle of cisplatin and 2 cycles of carboplatin chemotherapy. CT scan 5 weeks following chemoradiotherapy showed no residual adenopathy, so neck dissection was not performed. This patient was found to have recurrent disease in the BOT as well as metastatic disease to the lungs at 7.1 months of follow-up. He began salvage chemotherapy and elected hospice care 18.2 months after diagnosis.

The final patient with locoregional failure presented with stage T4N3 disease; he received 70.29 Gy at 2.13 Gy/fx to his primary tumor and 63.03 Gy at 1.91 Gy/fx to his bilateral necks given with weekly carboplatin and paclitaxel chemotherapy. Eight weeks after completion of chemoradiotherapy, he received a unilateral neck dissec-
tion, at which time 3 of 16 lymph nodes were found to harbor viable tumor cells. He was followed closely and developed recurrent disease in the dissected neck at 11.8 months of follow-up. This was not resectable due to encasement of the carotid and he was treated with salvage chemotherapy alone. At last follow-up he remained alive, without evidence of BOT recurrence, and on salvage chemotherapy with C-225 and cisplatin.

Distant Failure. Actuarial distant metastasis-free survival is presented in Figure 2. There were 3 distant failures. One patient developed both locoregional and distant failure, as described above. Another patient developed distant failure alone at 12 months of follow-up. This patient was treated for stage T4N2c disease; 8 weeks following chemoradiotherapy, he received a unilateral neck dissection which showed no viable tumor. One month later, his contralateral neck was dissected, which again showed no viable tumor. At 12 months follow-up, he was found to have a right lower lobe abnormality; right lower lobectomy revealed SCC without malignant adenopathy. Metastatic disease could not be excluded, so he is considered as having distant failure for the purposes of this analysis despite some uncertainty as to whether this was truly distant failure or in fact a second primary tumor. This patient began salvage chemotherapy and remains without evidence of local failure or further distant metastases. The third patient with distant failure was treated for stage T4N3 disease. Unilateral neck dissection was performed 8 weeks following chemoradiotherapy, showing no viable tumor. At 14.5 months of follow-up, he developed pulmonary metastases and began salvage chemotherapy.

Treatment Toxicities. Toxicities were graded according to the RTOG radiation morbidity scoring criteria. Acute toxicities were acceptable; every patient was able to complete the prescribed course of radiotherapy. Treatment breaks were required in only 2 patients. One patient missed 4 separate days because of nausea; another patient missed 1 day because of machine malfunction. Nearly all patients developed grade 1/2 mucous membrane, salivary gland, and esophageal toxicity acutely. The most frequent grade 3 toxicity was leukopenia. Late toxicities were also largely acceptable, with 18 (53%) patients having grade 1 and 10 (29%) having grade 2 salivary gland toxicity. Five patients (15%) developed late grade 3 esophageal toxicity. Dilation was attempted in all 5 and was successful in 4. One of these patients remains completely PEG-reliant; the others have had PEG tube removed at a mean (range) of 7.9 (6–12.2) months. Frequency of acute and late toxicities is presented in Table 3.

Prior to initiation of treatment, each patient had a PEG tube placed. At completion of therapy, PEG tube removal occurred when a patient was

**FIGURE 1.** Actuarial local progression–free survival (A) and regional progression–free survival (B).

**FIGURE 2.** Actuarial distant metastasis–free survival.
able to maintain his or her weight for at least 2 weeks without any use of the tube. Mean (range) time from diagnosis until PEG tube removal was 5.9 (2.1–15.1) months. At last follow-up, 3 patients remained PEG tube reliant. One patient was discharged to hospice with her PEG tube in place shortly after completion of chemoradiotherapy with substantial residual disease. Another patient is able to take nutrition orally but is not able to maintain her weight without supplementation through her PEG tube. The final PEG-reliant patient developed esophageal stricture following chemoradiotherapy. This patient has had multiple attempts at dilation without success and he remains completely PEG-dependant. The probability of retaining a PEG tube in place is presented in Figure 3.

Overall Survival. A total of 3 patients have died, each of disease-specific causes as described above. Overall survival is presented in Figure 4.

DISCUSSION

Oropharyngeal cancers in general represent a treatment challenge, often progressing to advanced stage at time of presentation. Cancers of the BOT represent further specific challenges as surgical treatment is often quite morbid. Though patients with negative margins treated with postoperative radiotherapy have good local control, the rate of complications in patients treated with surgery has been found to be significantly higher than in patients treated with radiation followed by neck dissection.32,33 Given the similar outcomes results for surgery compared with radiation with neck dissection and the substantial morbidities of surgery, many physicians and patients opt against surgery for treatment of most SCCs of the BOT.

There now exist randomized data supporting the addition of chemotherapy to radiotherapy in treatment of cancers of the oropharynx.10,17 In this trial, patients were randomized to receive either 70 Gy radiotherapy alone or identical radiotherapy combined with carboplatin (70 mg/m²/day for 4 days) and 5-fluorouracil (600 mg/m²/day continuous infusion for 4 days) chemotherapy starting on days 1, 22, and 43 of radiotherapy. Five-year data are now available showing a statistically significant advantage for the chemoradiotherapy arm in locoregional control (48% vs. 25%) and overall survival (22% vs. 16%). Radiotherapy in this trial was delivered via opposed lateral cervical fields matched to a single anteroposterior supraclavicular field.

**Table 3.** Frequency of acute and late toxicities.

<table>
<thead>
<tr>
<th>Frequency by grade of toxicity</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>16</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>12</td>
<td>19</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>11</td>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pharynx/Eosophagus</td>
<td>13</td>
<td>19</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Larynx</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper GI</td>
<td>3</td>
<td>18</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>WBC</td>
<td>4</td>
<td>10</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hct/Hgb</td>
<td>13</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| Late                          |     |     |     |     |
| Eosophagus                    | 13  | 3   | 6   | 0   |
| Larynx                        | 6   | 0   | 0   | 0   |
| Mucous membrane               | 4   | 0   | 0   | 0   |
| Salivary gland                | 18  | 10  | 0   | 0   |
| Skin                          | 3   | 0   | 0   | 0   |
| Subcutaneous tissue           | 3   | 5   | 0   | 0   |

Abbreviations: WBC, white blood cells; Hct/Hgb, hematocrit/hemoglobin.

**FIGURE 3.** Probability of percutaneous endoscopic gastrostomy tube remaining in place, from time of diagnosis.
Recently IMRT has been increasingly used in the treatment for cancer of various head and neck sites. There are no randomized data comparing IMRT with conventional radiotherapy techniques, but multiple single-institution experiences have been published. The largest single-institution experience with IMRT for oropharyngeal cancers was published in 2006. This was a report on a heterogeneous group of 50 patients treated with 1 of 3 IMRT techniques, 86% of which were also treated with concurrent platinum-based chemotherapy. Nearly half (46%) of these patients' primary tumors were in the BOT; 4% were treated postoperatively. With 18-month median follow-up, estimated 2-year local progression-free, regional progression-free, distant metastases-free, and overall survival were 98, 88, 84, and 98%, respectively. Toxicities were acceptable in this study, with 6% of patients developing esophageal strictures.

To our knowledge, this is the first report on chemoradiotherapy with IMRT specific to the BOT. We have treated a homogeneous population of patients with locally advanced SCC of the BOT with uniform radiation techniques and platinum-based chemotherapy. This cohort of patients presented with advanced disease, with 71% stage N2b or greater. Twenty-nine (85%) of the patients in this investigation presented with stage IV disease. Despite the advanced stage at presentation, nearly all (97%) of these patients received a clinical CR from chemoradiotherapy. With median follow-up of 20.1 months, we have found 24-month actuarial local progression-free, regional progression-free, distant metastasis-free, and overall survival to be 92, 97, 90, and 90%, respectively. There have been no marginal failures to date.

These results compare favorably with the reported Memorial Sloan-Kettering Cancer Center (MSKCC) experience. Comparisons require caution, however, as our patient populations and treatments differed somewhat. Patients with primary BOT tumors make up just 46% of the MSKCC report. Additionally, 14% of the MSKCC patients were treated with radiotherapy alone, and 4% were treated postoperatively.

Comparisons with the prospective, multi-institutional French 9401 trial require further caution. Primary tumor location was the BOT in 38% of patients in this trial. Additionally, T and N classifications differ; 85% of patients treated on the French trial had T3 or T4 disease, compared with only 41% in the current report. However, the patients in the current report were less likely to have N0 disease (10% vs. 24%) and more likely to have N2 disease (71% vs. 42%).

Our locoregional control and distant metastasis-free survival are encouraging for all patients except those presenting with stage N3 disease. Displayed in Figure 5 is distant metastasis-free survival by nodal stage. Patients with stage N0-N2a disease are grouped together, as are patients with stage N2b-N2c. Patients with stage N3 disease represent the final curve. Of the 3 patients presenting with N3 disease, each had treatment failure. One failed regionally, one developed distant metastases, and the final patient developed both local and distant failure. Two of these 3 patients have died, with the patient remaining on salvage chemotherapy at last follow-up. No patient in this report was treated with neoadjuvant chemotherapy. Current investigations are aimed at determining the value of induction chemotherapy in patients with advanced head and neck cancers; our small experience indicates a need for improved regional and distant control in patients with very advanced (N3) nodal disease.

Whether induction chemotherapy will offer this improvement remains to be seen.

We have additionally compared outcomes for patients receiving different chemotherapeutic regimens. Figure 6 displays the failure-free survival for all patients receiving 3 cycles of cisplatin (n = 21) versus any other chemotherapy (n = 13). These curves demonstrate a remarkably different outcome for the patients receiving any departure from 3 cycles of cisplatin chemotherapy. The reasons for variations in chemotherapy were described above.

Acute toxicities in our experience were acceptable. We have specifically noted a low incidence of
grade 3 mucosis (10%). This compares favorably with the 71% grade 3/4 mucosis seen on the French 9401 trial and the 38% grade 3 mucosis noted in the MSKCC experience. There are several possible explanations for this difference. First, both our results and those of the MSKCC are retrospective and therefore likely underestimate the true occurrence of toxicities. Second, our report focuses exclusively on patients treated for primary BOT tumors. This may partially explain our relatively high incidence of late esophageal toxicity despite the low incidence of acute mucositis.

While acute toxicities were acceptable, there may be an increase in late esophageal toxicity associated with our treatment technique. Contrary to the MSKCC experience,\(^\text{21}\) we have noticed an increase in late esophageal morbidity, with 15% of these patients suffering esophageal stricture or stenosis. Stage at presentation for the 5 patients developing this toxicity was as follows: T1N2b, T2N0, T2N1, T3N2c, and T4N2b. Cervical esophageal stricture developed in 3 patients, with 2 patients developing complete stenosis. Dilatation was successful in 4 of these 5 patients, with 1 patient remaining PEG reliant at last follow-up. We do not have typically contoured the esophagus or the supraglottic larynx at the time of treatment planning, but experience from our institution as well as others has shown esophageal V\(_{50}\) or V\(_{60}\) to be predictive of this toxicity.\(^\text{34,35}\) Given the mid-line location of the BOT as well as its proximity to the upper esophagus, constraining the cervical esophagus may not always be feasible. Still, we have subsequently begun to contour the esophagus from the level of the cricopharyngeus superiorly to the lowest CT slice with neck volumes contoured inferiorly and have attempted to limit this volume to less than 60 Gy.\(^\text{34}\)

**CONCLUSION**

Our results show excellent 3-year actuarial locoregional control, distant metastasis-free survival, and overall survival with SMART and platinum-based chemotherapy. These results were obtained in a homogeneous population of patients with locally advanced SCC of the BOT. Treatment was relatively well tolerated, but late esophageal toxicity may be increased with this form of therapy. Attempts to minimize such toxicity should be made when using this highly effective treatment regimen.

**Acknowledgments.** Dr. Johnstone and Dr. Shin are Georgia Cancer Coalition Distinguished Cancer Scholars, supported in part by the Georgia Cancer Coalition, and by NCMHD grant 5P60 MD000525 (P.A.S.J.), NIH U01 CA101244 (D.M.S.), and NIH R01 CA112643 (D.M.S.).

**REFERENCES**