Abstract. Background: Achieving locoregional control in high-risk patients with head and neck cancer who are poor candidates for standard continuous-course (chemo) radiotherapy due to advanced age, comorbidities, or very advanced disease is challenging. At our Institution, we have significant experience with a regimen of split-course, accelerated, hypofractionated radiotherapy (SCAHRT) for these patients. Patients and Methods: The SCAHRT regimen consisted of 60-72 Gy in 20-24 fractions separated by several weeks mid-course to allow for toxicity recovery and disease reassessment. It was used for patients with advanced age, significant co-morbidities, anticipated intolerance to definitive (chemo)radiation, and those with oligometastatic disease. Disease-free and overall survival rates were calculated using Kaplan–Meier analysis. Results: Fifty-eight out of 65 patients (89%) completed both courses of treatment. Patients without metastatic or recurrent disease were evaluated for treatment response and survival (n=39). Among this group, total tumor response was 91%, and median locoregional failure-free survival and overall survival were 25.7 and 8.9 months, respectively. Conclusion: In high-risk patients unable to tolerate continuous-course definitive (chemo)radiation, SCAHRT is a safe, well-tolerated and effective method of achieving durable locoregional disease control. In properly selected patients, this regimen is preferable to purely palliative approaches.

Radiation with concurrent systemic therapy is the standard-of-care for non-operative treatment of locally advanced squamous cell head and neck cancer (1, 2). For patients ineligible for systemic therapy, accelerated radiotherapy regimens are also beneficial compared to conventionally fractionated radiation therapy (RT) (3). Large randomized trials and meta-analyses have demonstrated that these intensification strategies increase the rate of tumor control and improve survival, at the cost of increased rates of severe treatment-related toxicity (2-8). However, a small proportion of patients with head and neck cancer are not suitable candidates for aggressive concurrent chemoradiotherapy, accelerated fractionation RT, or even conventional definitive RT, because of poor performance status, medical comorbidities, expected poor tolerance to or compliance with treatment, or a combination of these factors. Patients with oligometastatic but locally advanced disease also represent a therapeutic challenge. In these patients, durable locoregional control (LRC) remains a priority despite the presence of metastases because of the possible substantial morbidity and mortality associated with uncontrolled head and neck disease. This often necessitates aggressive RT with its associated toxicity, despite the palliative intent of therapy.

Deciding on optimal treatment for these compromised patients poses a challenge to surgeons and oncologists alike. While RT is often used palliatively for symptom reduction, there are no consensus guidelines or Level I evidence to direct treatment decisions. Several retrospective studies and prospective single-arm trials have evaluated various regimens of RT for compromised patients with head and neck cancer, including several studies evaluating split-course regimens (9-
However, significant variability in treatment approaches abound, and physicians often struggle to agree on the best therapeutic option for these high-risk patients (10, 12, 16).

At our Institution, in an effort to safely achieve LRC, we have long treated these patients with a planned split-course regimen of accelerated, hypofractionated radiotherapy (SCAHRT). This study reviews our safety and efficacy outcomes with this approach.

Patients and Methods

High-risk patients with head and neck malignancy who underwent SCAHRT between 2002-2010 were identified from our Institutional Review Board-approved head and neck registry, and their electronic medical records were reviewed. Patients were classified as being at high risk for one or more of the following reasons: low performance status, significant comorbidities, anticipated intolerance to definitive (chemo)radiation, and presence of oligometastatic disease. Patients with both newly diagnosed and recurrent cancer of the head and neck were included.

Initially, the regimen consisted of two courses of 30 Gy/10 fractions separated by approximately 3-5 weeks to allow for toxicity recovery. In recent years, the total dose has been increased up to a maximum of two courses of 36 Gy in 12 fractions for those who tolerate the initial course well and have advanced disease. A conventional 3-field approach was used most often earlier in the first half of the study, while intensity modulated radiation therapy exclusively has been used during past 5 years.

All patients were evaluated for safety and toxicity. A subset of patients without metastatic or recurrent disease with technically “curable” disease were also evaluated for efficacy outcomes including response to treatment, LRC, and overall survival. Locoregional tumor response was categorized as complete resolution for patients with no clinical evidence of residual tumor; partial resolution, for patients with a measurable decrease in gross disease; stable disease, for patients who experienced no change in size of gross disease; and progressive disease, for patients with a measured increased in size of disease despite treatment. Patients who experienced measurable disease progression after treatment, including local, regional, or distant failure, were recorded as having failed treatment. Response Evaluation Criteria in Solid Tumors criteria could not be used due to the unavailability of images for patients treated in the earlier years of this series. Patients with a partial response to treatment were not recorded as treatment failures unless the patient demonstrated disease progression after completing treatment.

Toxicities were graded retrospectively and were scored according to the Common Terminology Criteria for Adverse Events v3.0 (17). Kaplan–Meier analysis was used to calculate LRC and overall survival (OS). LRC was calculated as the time from the end of treatment to local or regional failure (in patients with a complete response to treatment) or measurable disease progression (in patients with a partial response to treatment). Overall survival was defined as time from biopsy to death. Univariate analysis was performed using Cox proportional hazards regression to identify factors associated with locoregional failure.

Results

Patients’ characteristics. Sixty-five patients (43 men and 22 women) treated with SCAHRT were identified on a retrospective review. Median follow-up for patients overall was 8.5 months. The most common tumors were squamous carcinomas of the oropharynx (40%), hypopharynx (14%), and larynx (12%), followed by small numbers of tumors of other sites and/or histologies (Table I). Fifty-five patients (85%) were previously untreated; 10 patients (15%) presented with recurrent tumors. The majority of patients had stage IV disease. The most common reason (75%) for SCAHRT among patients with stage I-III disease was anticipated intolerance to definitive treatment. The most common reasons for SCAHRT among patients overall were: patient comorbidities (32%), anticipated intolerance to treatment (32%), oligometastatic disease (29%), and low Karnofsky Performance Status (22%). Some patients had more than one documented reason for SCAHRT.

Treatment characteristics. Both courses of treatment were completed in 58 out of 65 (89%) patients. Seven patients did not complete the second course of treatment for the following reasons: one patient developed profound hyponatremia and was discharged to hospice; one patient refused the second course of treatment; one patient developed significant sore throat, dry mouth, and malaise, and decided against a second course of treatment; two patients continued to physically decline after the first course of treatment; and one patient with metastatic disease was asymptomatic at the primary site after the first course of RT and did not receive a second course.

The median number of calendar days from the start of treatment to completion was 14 for both first and second courses of RT. The median number of days between courses was 38 (range=24-263). Four patients had more than 100 days between courses. This was due to patients refusing the second course of treatment and later requiring additional RT for symptomatic progression or because they required additional time to recuperate. These patients were included in the analysis because they were initially planned for the standard split-course approach. Median dose and number of fractions of RT was 33 Gy/11 fractions for the first course and 30 Gy/10 fractions for the second course.

Concurrent chemotherapy was administered to four patients. They were treated with SCAHRT rather than continuous-course RT due to a concern that they would not be able to tolerate continuous-course RT with concurrent systemic therapy given their advanced age. Fifteen patients (23%) underwent surgery prior to SCAHRT. Of these 15 patients, 6 had a complete resection with negative margins.

Toxicity. No grade 4 or 5 radiotherapy toxicities were observed during or after treatment. Twenty-seven (42%) patients required a feeding tube at some point during treatment; 13 patients had a feeding tube at the last follow-up. At 90 days after treatment, one patient had a pain grade 3 or more. One patient experienced diffuse mucosal ulceration/necrosis of the pharyngeal wall and...
pale. 1.5 years after the completion of treatment. She slowly developed progressive dysphagia and required admission for hydration and feeding tube placement (grade 3). At the time, she was disease-free. Unfortunately, she became delirious in the hospital, contracted pneumonia and died several weeks later. Her death was not directly attributable to her treatment. No patient experienced grade 4/5 toxicity directly attributable to RT.

**Survival.** Of the 65 patients in the study, 39 (60%) presented with disease stage I-IVB, without distant metastasis or recurrent disease. These patients were evaluated for treatment response and survival. Of this cohort, 32 patients had a recorded response at follow-up 3 months after treatment. Sixteen (50%) had a complete response, 13 (41%) had a partial response, and three (9%) had stable or progressive disease despite treatment. Overall, 12 patients (31%) subsequently failed after treatment. This included eight (21%) locoregional failures and 4 (17%) distant failures. Median LRC was for 25.7 months, and median overall survival was 8.9 months. Kaplan–Meier curves for LRC and OS are depicted in Figures 1 and 2, respectively. No patient-, tumor-, or treatment-related variables were found to be significantly associated with locoregional failure on Cox proportional hazards regressions analysis (Table II).

**Discussion**

This study presents the outcomes of 65 high-risk patients treated at our Institution with SCAHRT. Our cohort included patients with recurrent disease, oligometastatic disease, as well as patients without metastatic disease who were deemed unable to tolerate a definitive regimen of continuous (chemo)radiation due to reasons such as advanced age, anticipated intolerance to definitive treatment, poor performance status, or comorbidities. Overall, our analysis suggests that SCAHRT is a safe, well-tolerated regimen in a variety of clinical situations involving compromised patients including patients with recurrent disease, prior to surgery, or prior to chemotherapy. Additionally, we found SCAHRT to be effective in achieving LRC among patients without metastatic or recurrent disease. Our findings are similar to previously published reports of split-course regimens (11, 12, 16).

Given the potential morbidity and catastrophic consequences of uncontrolled disease in the head and neck, durable LRC is a particularly important outcome in these patients and rivals survival as a worthy goal of care. To evaluate the effectiveness of SCAHRT in achieving durable LRC, we analyzed a subset of 39 previously untreated patients with disease stage I-IVB, excluding patients with distant metastasis or recurrent disease. This subset represented a cohort of patients with locoregionally-confined disease who would otherwise be considered curable if not for their being ineligible for standard chemoradiotherapy.
Median OS among this cohort was 8.9 months, consistent with rates published in similar studies, which ranged from 4-13.3 months (Table III). The median LRC among this cohort was 25.7 months—considerably longer than the median OS in this study, as well as similar studies. Given that the rate of LRC is considerably longer than OS in our study suggests that SCAHRT is an effective means of achieving durable LRC in high-risk patients with compromised expectations of OS.

Figure 1. Locoregional control for patients with stage I to IVB head and neck cancer (N=39).

Figure 2. Overall survival for patients with stage I to IVB head and neck cancer (N=39).
Determining the optimal treatment regimen for patients with locally advanced head and neck cancer who are unable to tolerate definitive (chemo)radiation poses a clinical challenge. A number of published reports describe different palliative treatment regimens that have been used for high-risk patient populations similar to those included in this study (9-16) (Table III). The most important observation made from data in Table III is the heterogeneity with which these patients are approached, from more palliative regimens (e.g. Quad Shot) to more definitive regimens, underscoring the therapeutic challenge these patients present. While differences in patients, tumors, and methods of assessment used in these studies make comparisons between these various treatment regimens difficult, the tumor response rate of 91% in this study compares favorably to those of other published regimens. Our approach therefore offers a more aggressive approach with an opportunity to achieve durable LRC in this high-risk population.

An illustrative example is displayed in Figure 3. The patient was a 91-year-old male with a history of multiply recurrent squamous cell carcinoma of the left hard palate, previously treated with several resections and prior radiotherapy, who presented with recurrent disease at the left skull base. Pre-treatment magnetic resonance imaging revealed a 4.5×4.5×3.8 cm transfacial mass involving the left masticator space, left parapharyngeal space, nasopharynx and pterygomaxillary fissure. Enhancement was seen in trigeminal nerve branches V2 and V3, tracking along the foramen ovale, the foramen rotundum and the vidian canal to abut Meckel's cave. The patient was subsequently treated with two courses of 33 Gy in 11 fractions separated by a 4-week break. Post-treatment magnetic resonance imaging (Figure 3) demonstrated dramatically reduced tumor size with residual non-specific enhancement consistent with treatment effect. At 11 months post-treatment, the patient had not experienced disease progression and was active, living independently, exercising and eating a normal diet. He experienced grade 2 trismus and grade 3 soft tissue necrosis of the left cheek with a non-healing wound that remained stable at 11 months post-treatment.

### Table III. Overview of studies of radiation for high-risk patients with head and neck squamous cell carcinoma.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Fractionation scheme</th>
<th>No. of patients</th>
<th>Median age, years</th>
<th>Overall disease response</th>
<th>≥Grade 3 toxicity</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corry, et al. (11)</td>
<td>14 Gy/4 fractions bid over 2 days. Repeat q4w up to 42 Gy/12 fractions</td>
<td>30</td>
<td>73</td>
<td>53%</td>
<td>Mucositis 0%</td>
<td>5.7 Months</td>
</tr>
<tr>
<td>Porceddu, et al. (15)</td>
<td>30 Gy/5 fractions, 2 fractions/week. 6 Gy boost for good responders</td>
<td>35</td>
<td>68</td>
<td>80%</td>
<td>Mucositis 26%; dysphagia 11%; dermatitis 11%</td>
<td>6.1 Months</td>
</tr>
<tr>
<td>Minatel, et al. (13)</td>
<td>50 Gy/20 fractions with 2-week mid RT break. Concurrent bleomycin</td>
<td>58</td>
<td>67</td>
<td>69%</td>
<td>Mucositis 46%; dysphagia 3.4%</td>
<td>7 Months</td>
</tr>
<tr>
<td>Mohanti, et al. (14)</td>
<td>20 Gy/5 fractions. Further RT up to 70 Gy in patients with response after 4 weeks</td>
<td>352</td>
<td>55</td>
<td>37% (PR only)</td>
<td>N/A</td>
<td>6.6 Months</td>
</tr>
<tr>
<td>Agarwal, et al. (9)</td>
<td>Boost of 10 Gy/4 fractions in good responders</td>
<td>110</td>
<td>55</td>
<td>73%</td>
<td>Dermatitis 14%, mucositis 66%; dermatitis 3%; dysphagia 9%</td>
<td>1-Year PFS: 55%</td>
</tr>
<tr>
<td>Kancherla, et al. (12)</td>
<td>40 Gy/10 fractions, 2-week mid RT break</td>
<td>33</td>
<td>76</td>
<td>72%</td>
<td>Mucositis 6%, dermatitis 3%; dysphagia 9%</td>
<td>9 Months</td>
</tr>
<tr>
<td>Stevens, et al. (16)</td>
<td>50 Gy/20 fractions, 2-week mid RT break</td>
<td>148</td>
<td>71</td>
<td>82%</td>
<td>Not assessed</td>
<td>5.2 Months</td>
</tr>
<tr>
<td>Chen, et al. (10)</td>
<td>3.7 Gy/fractions bid ×2 days. Repeat q2-3w up to 44.4 Gy</td>
<td>60</td>
<td>70</td>
<td>77%</td>
<td>9% Grade 3</td>
<td>4 Months</td>
</tr>
<tr>
<td>Current study</td>
<td>60-72 Gy/20-24 fractions, 4- to 6-week mid RT break</td>
<td>65</td>
<td>71</td>
<td>91%</td>
<td>Nograde 4/5 toxicities; 42% feeding tube use</td>
<td>8.5 Months</td>
</tr>
</tbody>
</table>

*aOverall disease response comprises rates of complete response (CR) and partial response (PR) unless noted. bid: Twice a day, PFS: progression-free survival, RT: radiotherapy.*
The toxicity profile of this regimen also compares favorably with similar studies of split-course radiation (Table III). Twenty-seven patients (42%) required a feeding tube at some point during treatment, and 13 patients (20%) were using a feeding tube at the last follow-up. No other significant toxicities were observed. Perhaps the best measure of tolerability, 58 out of 65 patients (89%) completed both courses of treatment. With the more recent implementation of intensity-modulated radiation therapy and the resultant decrease in skin and mucosal toxicity in general, this regimen is even easier to deliver without substantial morbidity.

Recently, the use of stereotactic body RT has been increasingly used in the re-irradiation setting in head and neck cancer. After early-phase studies demonstrated that doses of 40-50 Gy in five fractions delivered to a limited treatment volume were safe, a significant corpus of published data is emerging which catalogs treatment of hundreds of patients with this approach. While some articles describe a 15-20% risk of severe, life-threatening complications, most demonstrate surprisingly favorable toxicity profiles and fairly promising control rates. Some are now considering the use of stereotactic body RT in high-risk patients who have never been irradiated, similarly to our cohort. It certainly is a novel treatment paradigm worth considering as an alternative to SCAHRT (18).

This study has a number of limitations. It is retrospective, the sample size is limited, and some patients had limited follow-up information. The treatment regimen changed over the years, with intensification of total radiation dose, which may have impacted outcomes. However, as no patient experienced grade 4/5 toxicity and most grade 3 toxicities were well managed with a feeding tube, we believe the high-dose regimen to be safe and would likely only lead to improved local disease control. Another challenge of the study was that it comprised a heterogeneous patient population. However, this lends to the clinical relevance in that our findings apply to a broad spectrum of high-risk patients encountered in clinical practice. Our ability to analyze the LRC and OS of our non-metastatic, non-recurrent disease cohort also helped provide more detail on the data.

Conclusion

For patients with high-risk, locally advanced head and neck cancer who are not candidates for standard continuous course RT or chemoradiotherapy, SCAHRT is a safe and effective treatment regimen that offers the potential for long-term, durable LRC in addition to effective palliation. For these high-risk patients, this regimen may have advantages over purely palliative approaches by providing more durable LRC than standard palliative treatment regimens. Comparative studies are needed to better define optimal treatment strategies for this unique and heterogeneous patient population.
References


5. Horiot J-C, Bontemps P, van den Bogaert W, Le Fur R, van den Weijngaert D, Bolla M, Bernier J, Lusinchi A, Stuschke M, Lopez-Torrecilla J, Begg AC, Pierart M and Collette L: Accelerated fractionation (af) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: Results of the eortc 22851 randomized trial. Radiotherapy and Oncology 44(2): 111-121, 1997.


Received December 18, 2015
Revised January 21, 2016
Accepted January 28, 2016