Stereotactic body radiotherapy as primary treatment for elderly and medically inoperable patients with head and neck cancer

Emile Gogineni DO1 | Zaker Rana MD1 | Prashant Vempati MD12 | Jessie Karten BS1 | Anurag Sharma MS1 | Peter Taylor MS1 | Lucio Pereira MD2 | Douglas Frank MD2 | Doru Paul MD3 | Nagashree Seetharamu MD3 | Maged Ghaly MD1

1Department of Radiation Medicine, Northwell Health, Lake Success, New York
2Department of Otolaryngology, Northwell Health, Lake Success, New York
3Department of Medical Oncology, Northwell Health, Lake Success, New York

Correspondence
Maged Ghaly, MD, Department of Radiation Medicine, Northwell Health, 450 Lakeville Road, Lake Success, NY 11042, USA.
Email: mghaly@northwell.edu

Abstract
Background: Patients with head and neck cancer (HNC) who are not candidates for definitive treatment represent an increasing challenge, with limited data to guide management. Conventional local therapies such as surgery and chemoradiation can significantly impact quality of life (QoL). There has been limited data published using stereotactic body radiotherapy (SBRT) as primary treatment in previously unirradiated patients. We hypothesize that SBRT provides high rates of control while limiting toxicity.

Methods: A total of 66 medically unfit previously unirradiated patients with HNC were treated with SBRT, consisting of 35-40 Gy to gross tumor volume and 30 Gy to clinical target volume in five fractions.

Results: Median age was 80 years. Local control (LC) and overall survival (OS) at 1 year were 73% and 64%. Two patients experienced grade 3 toxicity.

Conclusion: SBRT shows acceptable outcomes with relatively low toxicity in previously unirradiated patients with HNC who are medically unfit for conventional treatment. SBRT may provide an aggressive local therapy with high rates of LC and OS while maintaining QoL.

KEYWORDS
head and neck cancer, quality of life, radiosurgery, SABR, SBRT, stereotactic

1 | INTRODUCTION

The annual incidence of elderly patients with head and neck cancer (HNC) continues to rise, with expected rates of over 30 000 by the year 2030.1 The association between age and clinical outcomes for patients with HNC is a controversial topic.2,3 However, the correlation between age and an increasing incidence of medical comorbidities in patients with cancer has been sufficiently supported.4 The prevalence of multiple comorbid conditions in patients with HNC is high, and it has been shown to decrease overall survival (OS).5 This population of patients is often excluded from randomized trials that shape management because of both their age and high incidence of disqualifying medical conditions.6,7 Even retrospective data and subset analyses from prospective trials are limited for elderly patients, and consequently evidence-based guidelines are lacking.8 Thus, they
represent a challenge to clinicians as they search for a balance between the desire for curative treatment while limiting toxicity that would affect quality of life (QoL).

Elderly patients often present with locally advanced disease but with less neck involvement, suggesting additional benefit to achieving local control (LC) in this population. Although surgical resection is a viable treatment for patients with HNC, the elderly are at increased risk for the toxicities associated with this modality. A meta-analysis published in 2009 showed improved survival with the use of chemotherapy; however, this benefit was not seen in patients >70 years old.

Thus, radiation alone is often the only option for elderly patients who present with locally advanced HNC. Elderly patients with HNC and good functional status have shown the ability to tolerate radiation; however, 7 weeks of daily treatment with high expected rates of toxicity may not be ideal for patients with multiple comorbidities and social issues who have limited expected survival. Stereotactic body radiotherapy (SBRT) is an advanced radiation planning and delivery technique that uses high doses of radiation per day with a limited number of fractions. It has been a well-established option for treatment of early-stage inoperable lung cancers in the elderly population. Although the most common use of SBRT for HNC is in the setting of re-irradiation as evidenced by multiple prospective trials, several studies have retrospectively addressed its use as primary treatment, albeit limited by small patient numbers.

We hypothesize that SBRT provides high rates of LC while minimizing toxicity in patients who are unfit for conventional definitive treatment modalities.

2 | PATIENTS AND METHODS

Approval was obtained from the Institutional Review Board (IRB #15-089). The informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization were waived, given that this was a retrospective chart review and the fact that no Protected Health Information (PHI) was reported.

Between August 2011 and June 2018, 66 previously unirradiated patients with HNC were treated with a course of SBRT ± systemic therapy. Eligible patients included those with biologically proven primary invasive cancer involving any subsite of the head/neck. Patients included in this analysis had follow up of at least 6 months or until their time of death if this was less than 6 months. All patients were deemed on a case-by-case basis to be unable to tolerate conventional definitive treatment modalities such as surgery and chemoradiation by our multidisciplinary head and neck tumor board. Common reasons for this decision were age, medical comorbidities, and bulk of disease. Patients were then informed that they did not qualify for standard modalities of curative treatment and were offered SBRT as an alternative. It was explained that the goal was not to cure their disease but instead to optimize palliation, with an aim of preventing further progression locally that could potentially cause debilitating symptoms. All patients signed consent indicating an understanding of this intention.

All patients were treated with SBRT consisting of 35-40 Gy to gross tumor volume (GTV) in five fractions delivered biweekly. GTV was defined as gross tumor seen on imaging studies and/or clinical examinations. In patients with gross disease in the lateral neck, ipsilateral neck nodal levels II-IV were included as a clinical target volume (CTV). In patients with gross disease in the nasopharynx, lateral retropharyngeal nodes were included as a CTV. Using dose-painting techniques, 30 Gy was prescribed to the CTV in these patients. Planning target volume (PTV) primary and PTV nodal were created by expanding the GTV and CTV with 2-mm margins, respectively. Patients were simulated with standard immobilization using a thermoplastic head and neck mask. Simulation CT without IV contrast was obtained with a 2-mm slice thickness, and magnetic resonance imaging (MRI) and/or positron emission tomography (PET) images were fused at the discretion of the treating physician. Daily cone-beam CT and kilovoltage (kV) imaging were used in order to account for interfractional variations. An example of a treatment plan dose wash is depicted in Figure 1.

Administration of concurrent systemic therapy was at the discretion of medical oncologists and was captured for all patients who received it.

All constraints for organs at risk (OARs) are listed in Table 1. The prioritized OAR constraints were dependent on the site treatment: the cranial nerve foramen and skull base bony structures were prioritized in patients receiving radiation to skull base. In patients receiving radiation to the aerodigestive tract, special attention was paid to the laryngeal cartilage and mandible. With lateral neck radiation, the brachial plexus and carotid arteries were prioritized.

The validated short geriatric 8 (G8) questionnaires were collected at baseline, at 1 month, and at 2-3 months posttreatment in order to evaluate health-related QoL.

Local failure was defined as an increase in size and/or avidity on follow-up imaging within the PTV identified by the reading radiologist. Regional failure was defined as new findings seen on follow-up imaging concerning
for progression outside of the PTV but within the head/neck. Distant failure was defined as new findings seen on follow-up imaging concerning for progression outside of the head/neck. All concerning imaging findings were confirmed pathologically via biopsy when feasible. In cases where imaging showed concern for progression but biopsy was not deemed safe, failure was determined by multidisciplinary tumor board consensus.

Survival and local, regional, and distant control (each measured from completion of SBRT) were estimated by using the Kaplan-Meier method with SPSS Version 21 (SPSS, Chicago, Illinois). Toxicities were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4). Univariate and multivariate analyses were performed using Cox regression analysis.

### RESULTS

Baseline patient characteristics and treatment details are outlined in Table 2. A total of 66 patients were included for analysis with a median follow-up of 15 months (range: 3-88 months). Median age was 80 years (range: 47-99) and 61% were male. Median Karnofsky performance status (KPS) was 70 (range: 50-80). Median Charlson comorbidity index score was 12% (range: 0%-21%). Median G8 score was 10 at baseline, 9.5 at 1 month follow-up, and 9.5 at 2-3 month follow-up. Treated sites included oral cavity (35%), lateral neck (17%), parotid (9%), larynx (8%), hypopharynx (6%), and thyroid (6%). 67% were squamous cell carcinoma and 9% were melanoma. T-classification was T1 in 10%, T2 in 37%, T3 in 16%, and T4 in 37%. N-classification was N0 in 40%, N1 in 18%, N2 in 40%, and N3 in 2%. Only one patient had HPV+ oropharyngeal disease.

All patients completed SBRT, with a median PTV volume and V90% of 82 cc and 94%, respectively. 33 patients (50%) received 35 Gy and 33 patients (50%) received 40 Gy to the PTV primary.

34 patients (52%) received concurrent systemic therapy of immunotherapy, cetuximab, and/or chemotherapy. Of the six patients who received concurrent chemotherapy alone, regimens included carboplatin/paclitaxel (n = 3), cisplatin (n = 2), and cyclophosphamide/cisplatin/doxorubicin (n = 1). 20 patients (30%) received
cetuximab alone. Of the four patients (6%) who received a combination of chemotherapy and cetuximab, chemotherapy regimens included carboplatin/paclitaxel (n = 3) and cisplatin (n = 1). Two patients (3%) received nivolumab immunotherapy concurrent with SBRT. Dosing of systemic therapy was adjusted for patients with poor performance status who were felt to be unable to tolerate full doses and was administered at the discretion of medical oncologists after approval from multidisciplinary tumor board.

At 12 months, LC was 73%, with median time to local failure of 28.3 months (see Table 3). 21 patients developed in-field failures and 4 patients had marginal failures. Regional and distant control rates at 12 months were 73% and 76%, respectively. Of the patients with at least 24 months follow-up (n = 13), LC was 69%. No chronic grade ≥ 3 toxicities were noted in these patients.

No demographic variables had a significant effect on control rate or survival using univariate and multivariate analysis, including age, gender, race, KPS, smoking, alcohol, stage, dose, time elapsed during SBRT, PTV dose and volume, and use of concurrent systemic therapy.

Two patients (3%) experienced grade 3 (G3) acute toxicity, which included one G3 dysphagia and one G3 anorexia. No grade 4 (G4) or 5 (G5) toxicities were recorded and no patient experienced chronic G3+ toxicity.

4 DISCUSSION

We believe this to be the largest series of primary SBRT for HNC published to date. It shows promising results, with high rates of LC (73%) and OS (64%) at 12 months.

Low toxicity rates (3% G3, no G4+) and a lack of significant change in G8s from baseline to follow-up (10 to 9.5) suggest that patients tolerated treatment well without negatively affecting their functional status. This is in contrast to surgery and/or definitive chemoradiation, which in the elderly population are associated with poor treatment compliance and high rates of morbidity.30,31

An ideal therapy for this patient population involves a short course of treatment, which achieves high rates of LC without subjecting patients to toxicity. Although the majority of studies evaluating HNC patients who are not fit for definitive treatment aim for symptom palliation, our primary intention in the use of SBRT was to provide LC in order to prevent further progression, which could potentially result in debilitating symptoms and a reduction in QoL.23 There have been several similar primary SBRT series published in early-stage asymptomatic patients who were treated in order to provide LC, as opposed to symptom palliation (see Table 4).19-21,23-25

A small study from the University of Colorado by Amini et al reported on 3 patients who received primary SBRT, all of whom had LC of disease without G3+ toxicity at last follow-up.25 Siddiqui et al published data on 44 patients with HNC treated with SBRT at the Henry Ford Health System, 10 of whom had not received prior radiation. At 12 months, rates of LC and OS were 83% and 70% for these 10 patients. Although there were several G3 and G4 toxicities reported for the entire patient

### Table 2 Patient characteristics and treatment details (n = 66)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>80 (47-99)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (61)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (39)</td>
</tr>
<tr>
<td>Median KPS (range)</td>
<td>70 (50-80)</td>
</tr>
<tr>
<td>Median Charles comorbidity index score (range)</td>
<td>12% (0-21)</td>
</tr>
<tr>
<td>Median G8 score</td>
<td>10</td>
</tr>
<tr>
<td>Sites treated with SBRT</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>23 (35)</td>
</tr>
<tr>
<td>Lateral neck/occult nodal</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Parotid</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Larynx</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (20)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>44 (67)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (20)</td>
</tr>
<tr>
<td>PTV dose</td>
<td></td>
</tr>
<tr>
<td>35 Gy</td>
<td>33 (50)</td>
</tr>
<tr>
<td>40 Gy</td>
<td>33 (50)</td>
</tr>
<tr>
<td>Median PTV volume</td>
<td>82 cc</td>
</tr>
<tr>
<td>Concurrent systemic therapy with SBRT</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>34 (52)</td>
</tr>
<tr>
<td>Chemotherapyb</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>20 (30)</td>
</tr>
<tr>
<td>Chemotherapyb + cetuximab</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

Abbreviations: KPS, Karnofsky performance status; PTV, planning target volume; SBRT, stereotactic body radiotherapy.

aOther sites treated included oropharynx, skin, maxillary sinus, nasopharynx, nasal cavity, and orbit.

bChemotherapy regimen was modified for patients with poor performance status.
cohort, only two of the primary SBRT patients experienced G3 toxicity, including pain and cataract, with no G4+ toxicities. A series by Vargo et al from the University of Pittsburgh Medical Center included 10 patients treated with SBRT, 20-44 Gy in 1-5 fractions. LC and OS were 69% and 64%, and two patients reported G3 toxicity, including dysphagia and mucositis.

A study from Japan by Kawaguchi et al evaluated 14 elderly patients treated with SBRT, 35-42 Gy in 3-5 fractions. No patients had distant metastatic disease and only one had nodal involvement. With median follow-up of 36 months, crude rates of LC and OS were 71% and 79%, with one patient experiencing G3 osteoradionecrosis. A series from Canada by Khan et al reported on 21 patients treated with SBRT, 35-48 Gy in 5-6 fractions. 16 of these patients were treated with primary SBRT in the de novo setting without a history of previous radiation. The rates of LC and OS at 12 months for this cohort were 87% and 60%, respectively, and toxicity was not reported.

An alternative to SBRT for palliative treatment of HNC is the “QUAD SHOT” approach. QUAD SHOT, as proven in RTOG 8502, is a regimen that consists of 3.7 Gy twice-daily fractions given over 2 consecutive days per cycle with a rest period of 2-4 weeks between the three prescribed cycles for a total dose of 44.4 Gy. Although this regimen is well tolerated with G3+ toxicity rates of ~5%, it has shown median times to progression of 3-5 months, providing little durability in LC. Additionally, more than half of these patients require repeated courses of simulation and treatment, an inconvenience for patients who often face social and medical hurdles and have low expected survival rates, as evidenced by RTOG 8502’s median survival of <6 months.

Other palliative hypofractionated schema have been attempted, including the “Hypo trial” and the “Christie scheme” among others; however, these have yielded lower rates of control and/or higher rates of toxicity (G3 + 15-65%) when compared with the data presented herein. Proton therapy represents an evolving portion of the field with exciting potential for all sites. Although retrospective studies have shown promise for the use of proton therapy in HNC, its use has been restricted to the setting of re-irradiation, with limited data published on primary treatment for HNC with protons.

Immunotherapy continues to be an evolving portion of the field, showing improved OS rates when compared with standard of care systemic therapy for recurrent and metastatic HNC in multiple randomized trials, including KEYNOTE-040 and Checkmate 141. Although immunotherapy as monotherapy may not be an ideal option for control of local disease with median progression-free survival rates of 2-3 months, its combination with SBRT is the subject of many ongoing clinical trials, such as KEYSTROKE, which randomizes patients with recurrent HNC to SBRT ± pembrolizumab (NCT03546582).

These results highlight the benefits of using primary SBRT for elderly patients with HNC who are not candidates for conventional definitive treatment: short treatment time, low toxicity, and high rates of LC without adversely affecting QoL.

**TABLE 3** Outcomes

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Median follow-up (range)</th>
<th>Local control at 12 mo</th>
<th>Regional control at 12 mo</th>
<th>Distant control at 12 mo</th>
<th>Overall survival at 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>15 mo (3–88)</td>
<td>73%</td>
<td>73%</td>
<td>76%</td>
<td>64%</td>
</tr>
</tbody>
</table>

**TABLE 4** Summary of data for primary SBRT in elderly patients

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Dose</th>
<th>LC</th>
<th>OS</th>
<th>G3 toxicitiesa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amini et al22</td>
<td>3</td>
<td>25-36 Gy/5 fx</td>
<td>Crude 100%</td>
<td>12 mo 33%</td>
<td>0 G3</td>
</tr>
<tr>
<td>Siddiqui et al16</td>
<td>10</td>
<td>18-48 Gy/1-8 fx</td>
<td>12 mo 83%</td>
<td>12 mo 70%</td>
<td>1 G3 pain</td>
</tr>
<tr>
<td>Vargo et al17</td>
<td>10</td>
<td>20-44 Gy/1-5 fx</td>
<td>12 mo 69%</td>
<td>12 mo 64%</td>
<td>1 G3 dysphagia</td>
</tr>
<tr>
<td>Kawaguchi et al18</td>
<td>14</td>
<td>35-42 Gy/3-5 fx</td>
<td>Crude 71%</td>
<td>Crude 79%</td>
<td>1 G3 osteonecrosis</td>
</tr>
<tr>
<td>Khan et al21</td>
<td>16</td>
<td>35-48 Gy/5-6 fx</td>
<td>12 mo 87%</td>
<td>12 mo 60%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Present study</td>
<td>66</td>
<td>35-40 Gy/5 fx</td>
<td>12 mo 73%</td>
<td>12 mo 64%</td>
<td>1 G3 dysphagia</td>
</tr>
</tbody>
</table>

Abbreviations: fx, fractions; G3, grade 3; Gy, gray; LC, local control; OS, overall survival; SBRT, stereotactic body radiotherapy.

*aNo grade ≥ 4 toxicities have been documented in patients receiving primary SBRT for cancers of head and neck from the abovementioned studies.*
REFERENCES

29. Potel L, Lycke M, Boterberg T, et al. G-8 indicates overall and quality-adjusted survival in older head and neck cancer...

How to cite this article: Gogineni E, Rana Z, Vempati P, et al. Stereotactic body radiotherapy as primary treatment for elderly and medically inoperable patients with head and neck cancer. *Head & Neck*. 2020;42:2880-2886. [https://doi.org/10.1002/hed.26342](https://doi.org/10.1002/hed.26342)