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Pencil Beam Scanning Proton Therapy as Single Vocal Cord Irradiation for Early-Stage Glottic Cancer

Bansi Savla (MD)[1], Jenna Jatczak (CMD)[1], Jason K. Molitoris (MD)[1], Matthew E. Witek (MD)[2], Kimberly Marter (CMD, MS)[1], Mark J. Zakhary (PhD)[1], Junliang Xu (PhD)[1], Grace E. Snow (MD)[3], Elizabeth A. Guardiani (MD)[3], Matthew J. Ferris (MD)[1,*]

[1] *Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland, USA*
[2] *Department of Radiation Medicine, MedStar Georgetown University Hospital, Washington, District of Columbia, USA*
[3] *Department of Otorhinolaryngology, University of Maryland School of Medicine, Baltimore, Maryland, USA*

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ABSTRACT

Purpose: Single vocal cord irradiation (SVCI) is a promising technique to maintain excellent oncologic control and potentially improve upon toxicities for treatment of early-stage glottic squamous cell carcinomas. We sought to investigate whether pencil beam scanning (PBS) proton therapy could improve upon the already favorable dose gradients demonstrated with volumetric modulated arc therapy (VMAT) SVCI.
Patients and Methods: A 64-year-old gentleman was treated in our department with 6X-flattening filter-free VMAT SVCI to 58.08 Gy in 16 fractions for a T1a well-differentiated squamous cell carcinoma of the left true vocal cord and tolerated it well with good local control. Comparative PBS plans were created in Raystation for the Varian ProBeam with clinical target volume (CTVs) generated to mimic the prescription target volume extent of the VMAT planning target volumes when accounting for PBS plan robustness (± 3 mm translational shifts, 3.5% density perturbation). A 3-field single-field optimization plan was selected as dosimetrically preferable. Dosimetric variables were compared.
Results: Several organs at risk doses improved with PBS, including the maximum and mean dose to ipsilateral carotids, maximum and mean dose to contralateral carotid, maximum dose to the spinal cord, maximum and mean dose to inferior constrictor/cricopharyngeus, maximum and mean dose to the uninvolved vocal cord, and mean dose to the thyroid gland. There are tradeoffs in skin dose depending on location relative to the target—with the highest and lowest isodoses extending more into the skin with the VMAT plan but with the moderate isodose lines covering a wider area with the PBS plan, but we deemed it tolerable regardless.
Conclusion: SVCI is a promising strategy for maintaining the oncologic effectiveness of whole-larynx photon radiation while potentially improving upon the historic toxicity profile. The favorable dose distribution with PBS with respect to organs at risk dosimetry for PBS may allow for further improvements upon VMAT SVCI strategies. Clinical implementation of PBS SVCI may be considered.

Introduction

The larynx serves multiple complex functions, including airway protection, communication, and nutrition. Over 5000 early-stage cases are diagnosed per year in the United States, and local control remains excellent around 85% to 95% long term for the most favorable cases.[1-5] The preservation of function is therefore paramount in maintaining the quality of life, and treatment of these cases has focused on maintaining the typically excellent oncologic control while minimizing sequalae of treatment to the maximal extent. Whole-larynx radiation therapy (RT) has long been a standard of care and has been demonstrated to result in improvement in voice compared to pretreatment voice quality.[6,7] Still, whole-larynx RT introduces dose and subsequent post-treatment effects (including edema/fibrosis) to numerous critical structures, and interest remains in reducing target volumes accordingly. Vocal handicap indexes typically remain significantly abnormal in long-term follow-up, particularly in smokers.[7]

Initial efforts were made to improve RT conformality via carotid-sparing intensity-modulated radiation therapy or volumetric-modulated

* Corresponding author.
E-mail address: Matthew.ferris@umm.edu (M.J. Ferris).

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arc therapy (VMAT).[8] While carotid dose can be modestly mitigated (depending on patient anatomy) with this approach compared to 2 to 4 beam 3D conformal radiation therapy, the majority of the glottic and supraglottic larynx still typically receives the prescription dose, absent use of a simultaneous integrated boost technique. Transoral laser microsurgery is increasingly utilized for the treatment of early-stage glottic tumors, and with reports of excellent local control despite the very focused nature of the technique,[9] there has been increasing interest in the RT community for consideration of single vocal cord irradiation (SVCI). Single vocal cord irradiation is an emerging technique developed to target principally the involved cord, therefore minimizing dose to noninvolved laryngeal structures, particularly on the contralateral side. Theoretically, this would blend (or improve upon) the favorable voice quality of RT while maintaining oncologic outcomes and improving post-treatment swallowing function. Early results have been favorable, though the technique is far from widely adopted.[10,11]

Intensity-modulated proton therapy with pencil beam scanning (PBS) has increasingly been used in the management of head and neck cancers to reduce integral doses to normal organs at risk (OARs). As planning and clinical experience with PBS improve, initial hesitancy for the use of PBS in the larynx due to target motion and air within the target is waning, and usage of PBS for laryngeal cases is likely increasing accordingly. One initial report describes whole larynx (with simultaneous integrated boost technique) treatment of early-stage glottic lesions with proton beam therapy with excellent oncologic control and tolerability, but currently, there is no report describing the use of PBS for SVCI in the management of early-stage glottic cancers.[12] We theorized PBS may improve upon the dosimetry achievable with a high-quality VMAT SVCI plan.

In this technical report of a novel approach to treating early-stage glottic cancer, we evaluated the following: (1) the feasibility of using PBS for SVCI and (2) a dosimetric comparison of PBS versus traditional VMAT for SVCI.

Materials and methods

Patient

The clinical details and the treatment plan of a patient with T1aN0 glottic cancer (Figure 1) who had been treated with VMAT SVCI at the University of Maryland Medical Center were utilized in our present study. Our study was approved by our institutional review board.

Computed tomography simulation and target delineation

The patient underwent computed tomography (CT) simulation with IV contrast at University of Maryland Medical Center with the Siemens Somatom Go Open Pro scanner. During the scan, the patient was instructed not to swallow during CT imaging. The CT image was taken with 1 mm-thick slices. The patient underwent a 4D respiratory CT with 10 phases, which was used to assess for tumor motion. The patient was immobilized with a 5-point custom-made aquaplast mask to allow for reproducibility.

The gross target volume was contoured with the aid of an endoscopic examination. The internal gross target volume was created by combining the gross target volume over the 10 phases of the 4DCT, to account for breathing. The planning target volume (PTV) was generated by expanding the internal gross target volume by 5 mm superiorly and inferiorly and 3 mm radially. The patient was instructed not to swallow during treatment. Image guidance was performed with kVs aligned to the cervical spine and a cone beam computed tomography aligned to the thyroid cartilage with each fraction. Vision RT was utilized for

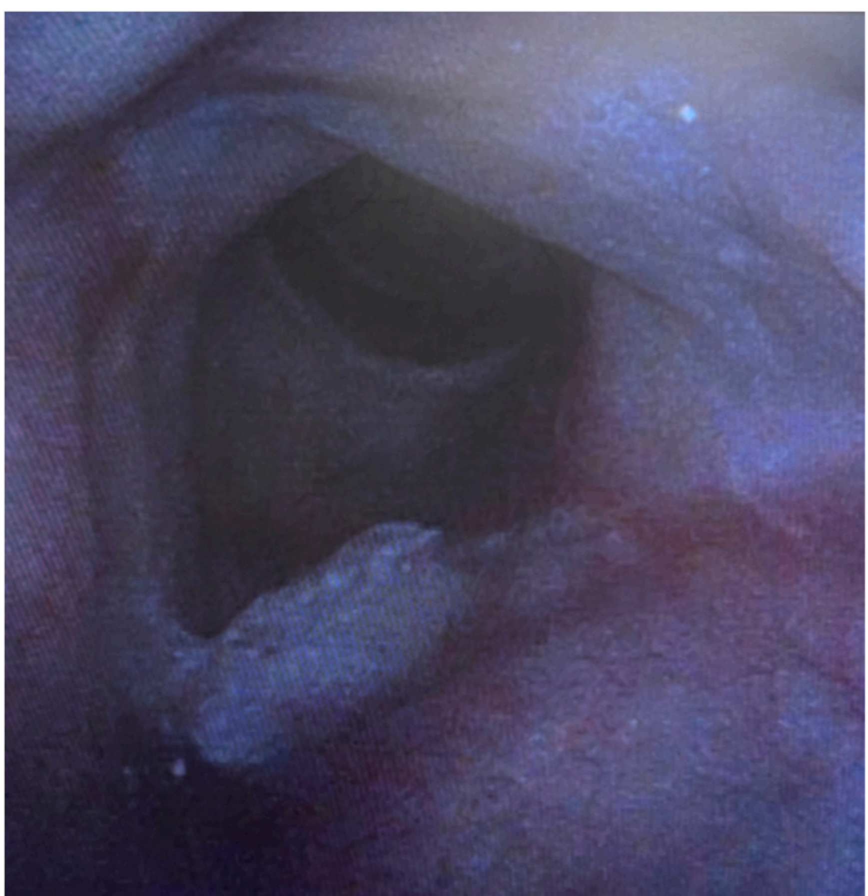

Figure 1. Flexible fiberoptic laryngoscope view of the treated lesion at initial presentation.

optical surface monitoring around the laryngeal prominence. The beam was held if intrafractional motion exceeded 3 mm or 3° for more than 2 seconds. The OARs included ipsilateral and contralateral carotid, contralateral arytenoid, cricoid cartilage, inferior constrictor/cricopharyngeus, laryngeal cartilage, spinal cord, thyroid gland, uninvolved vocal cord, and skin. Organ at risk goals are to be listed in the Table.

Treatment planning and plan evaluation

All calculations for the VMAT plan were performed for 6X-flattening filter free MV photons. The linear accelerator used was the Varian Edge with the high-definition multileaf collimitors. Volumetric-modulated arc therapy treatment plans were calculated in the Raystation treatment planning system. The prescription dose was 58.08 Gy in 16 fractions to the PTV. This fractionation was adopted from the favorable results demonstrated in the Al-Magmani et al SVCI experience.[13] Two full arcs and 2 noncoplanar partial arcs (90°-181° and 270°-179°) with 10° couch kicks were utilized, and 95% of the PTV received 99% of the prescribed dose, with a 114% hotspot (Figure 2A).

Comparative PBS plans were created in Raystation for Maryland Proton Treatment Center's Varian ProBeam with CTVs generated to mimic the prescription target volume extent of the VMAT PTVs when accounting for the PBS plan robustness (± 3 mm translational shifts). We also accounted for 3.5% density perturbation in the PBS robustness analysis. Several beam angles were investigated to optimize conformal coverage while minimizing hot spots and dose to OARs. Two 2-field single-field optimization plans were attempted (Figure 2B and C), but ultimately a 3-field single-field optimization plan incorporating beam angles from both of the 2-field plans was selected as dosimetrically preferable (Figure 2D). A 3 cm range shifter was utilized to provide an adequate surface dose. The 3-field plan allowed for superior conformality around the target, particularly with respect to the distal edge, which is adjacent to the airway. This 3-field plan was also thought to be likely the most robust with respect to likely minor positional changes. It also helped to spread out the skin dose, minimizing the extent of higher isodose lines extending toward the skin surface, which would help keep the skin dose tolerable and most similar to the VMAT plan. The OARs were pushed to as low as achievable while maintaining target volume coverage and appropriate robustness; 97% of the clinical target volume (CTV) received 99% of the prescribed dose, with a 113% hotspot. For the robustness evaluation, 95% of the CTV received 95% of the dose in the worst-case scenario.

Results

The patient was a 64-year-old gentleman with a history of occasional (less than monthly) cigar use and 1 to 2 mixed alcoholic drinks per day with a stage I, T1aN0M0 well-differentiated squamous cell carcinoma occupying the entirety of the left true vocal cord, with the bulk of the lesion involving the anterior two thirds and extending to the

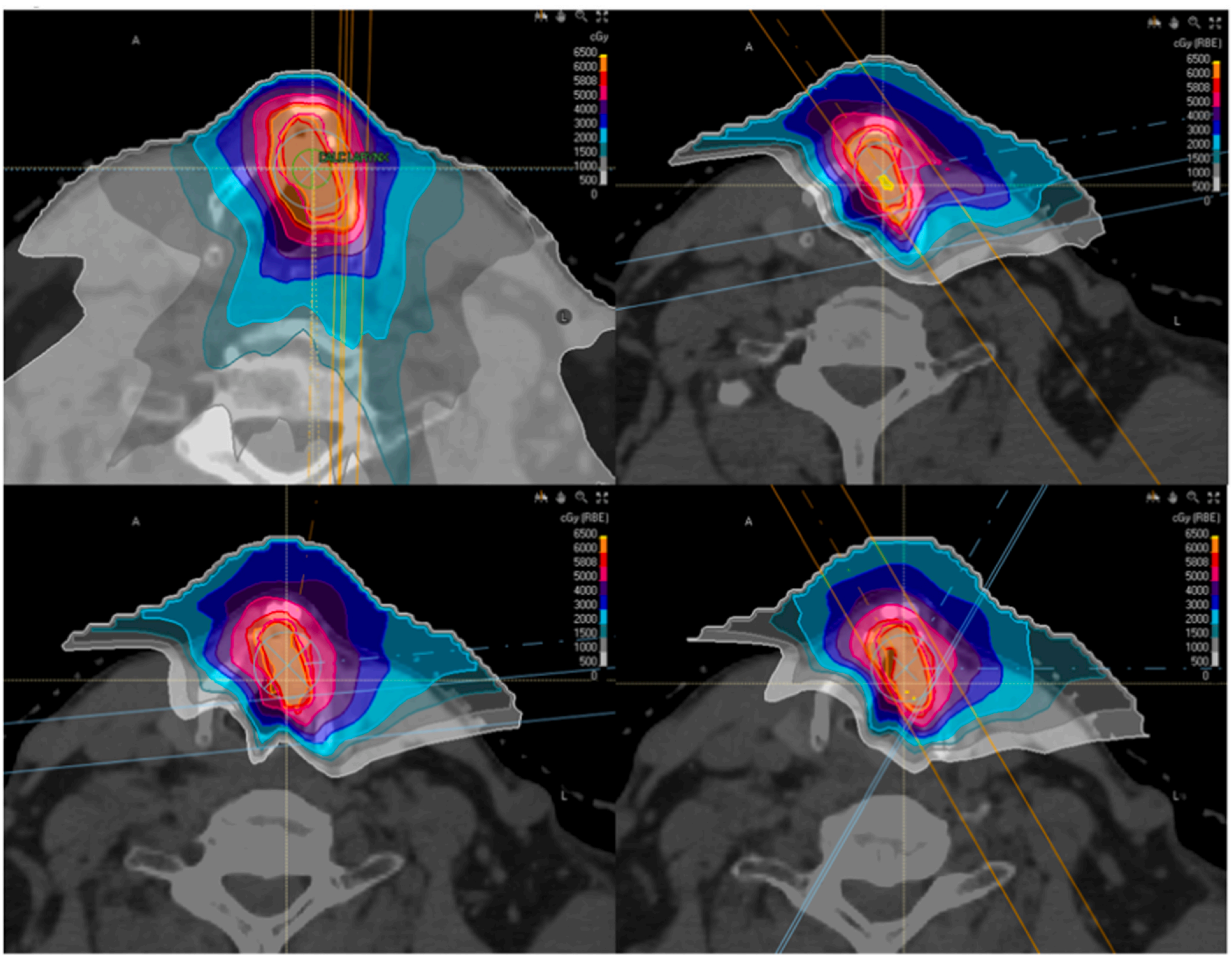

Figure 2. A (upper left): Volumetric modulated arc therapy plan (6 MV flattening filter-free beam). B (upper right): Unused 2-field pencil beam scanning (PBS) plan. C (lower left): Another unused 2-field PBS plan. D (lower right): The preferred 3-field single-field optimization PBS plan.

Table
Clinical goal comparison between PBS and VMAT plans.

Structure	Coverage metric	VMAT	PBS	Clinical importance
GTV	V99% ≥ 100%	100%	99.7%	None
CTV	V100% ≥ 95%	100	97.1	None
CTV	V95% ≥ 95%	100	98.9	None
Arytenoid (contralateral)	0.03 cm^3 ≤ 31.3 Gy	21.7 Gy	22.8 Gy	None
Carotid (contralateral)	Mean ≤ 15.2 Gy	4.9	0.15	Low
Carotid (contralateral)	0.03 cm^3 ≤ 31.3 Gy	9.6	1.1	Low
Carotid (ipsilateral)	Mean ≤ 15.2 Gy	12.5	2.2	Moderate
Carotid (ipsilateral)	0.03 cm^3 ≤ 31.3 Gy	25.8	7.5	Moderate
Inferior constrictor/cricopharyngeus	Mean ≤ 20 Gy	17.4	2.4	High
Inferior constrictor/cricopharyngeus	0.03 cm^3 ≤ 31.3 Gy	30.0	14.7	High
Spinal cord	0.03 cm^3 ≤ 35 Gy	13.0	0.0	Moderate
Thyroid	Mean ≤ 20.8	8.4	4.3	Low
Vocal cord (contralateral)	Mean ≤ 50.05 Gy	36.3	24.8	Moderate
Vocal cord (contralateral)	0.03 cm^3 ≤ 56.3 Gy	53.3	43.7	Moderate

Abbreviations: PBS, pencil beam scanning; VMAT, volumetric modulated arc therapy; GTV, gross target volume; CTV, clinical target volume.

anterior commissure without extension onto the contralateral cord (Figure 1). The patient had a pretreatment diagnostic CT of the neck/chest that showed no regional or distant involvement. After establishing care in our multidisciplinary head and neck clinic, he elected to undergo VMAT SVCI treatment as described above. He tolerated treatment well with minimal on-treatment or post-treatment side effects (grade 1 radiation dermatitis only), ongoing laryngeal control, and no chronic side effects.

A comparison of clinical goals (dose-volume parameters utilized for plan quality for SVCI at our institution) between the clinically utilized VMAT plan and the preferred PBS plan (Figure 2D) is displayed in the Table. Here, we include our estimate as to the clinical importance of the difference in each dosimetry parameter between VMAT and PBS plans. Figure 3 demonstrates the differential dose between the 2 plans. Several OAR doses improved with PBS, including the maximum and mean dose to ipsilateral carotids, maximum and mean dose to contralateral carotid, maximum dose to the spinal cord, maximum and mean dose to inferior constrictor/cricopharyngeus, maximum and mean dose to the uninvolved vocal cord, and mean dose to the thyroid gland. There are tradeoffs in skin dose depending on location relative to the target—with the highest and lowest isodoses extending more into the skin with the VMAT plan but with the moderate isodose lines covering a wider area with the PBS plan, but we deemed it tolerable regardless.

Discussion

Intensity-modulated proton therapy with PBS has gained favor for many disease sites, particularly for head and neck cancers, yielding significant dosimetric advantages. More robust clinical data will continue to emerge, but early experiences suggest that PBS may be

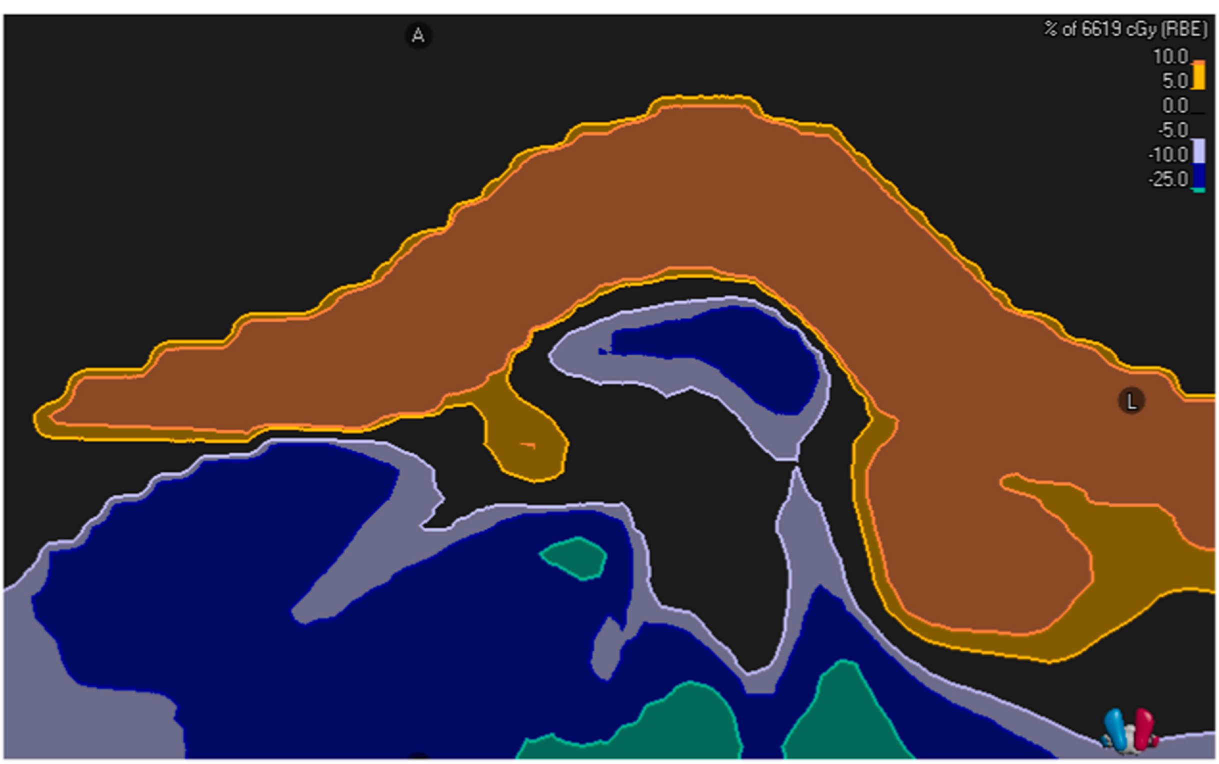

Figure 3. Comparison of pencil beam scanning versus volumetric modulated arc therapy dose distributions. Red and gold colors are areas increased dose with pencil beam scanning plan (+25% removed since all outside body, as is the majority of the +10% except in the posterolateral portion of the neck). Blue and green colors are increased dose for the volumetric modulated arc therapy plan, including the green patch in vicinity of the right arytenoid.

effectively utilized for laryngeal cases (despite air inherent to the larynx and laryngeal movement with swallowing) similar to other head and neck primary sites.[12]

Many studies have reported an increased risk of carotid injury and stroke because of radiation vasculopathy, which is believed to be both time and dose-dependent.[14,15] Beyond exposure to the high-dose region, though, even the more modest doses used in Hodgkin lymphoma seem to contribute to vascular disease over the long term.[16,17] VMAT techniques have shown promise in reducing unnecessary doses to carotid arteries, but in our PBS plan for this typical T1a case, we found an improvement with PBS versus VMAT in contralateral carotid mean (15 vs 490 cGy) and max dose (110 vs 959 cGy), and ipsilateral carotid mean (223 vs 1253 cGy) and max dose (755 vs 2588 cGy). While it is unclear the extent of clinical benefit this yields, we demonstrate that the notable improvements in carotid dosimetry possible with VMAT SVCI are perhaps enhanced by PBS. The clinical advantages of any SVCI approach compared to a 3D conformal radiation therapy whole-larynx approach are probably significant with respect to decreasing the likelihood of a vascular event post treatment, and the SVCI dose metrics are considerably superior to even a typical carotid-sparing VMAT whole-larynx plan. So both SVCI approaches, either VMAT or PBS, are probably valid ways to decrease carotid risk, though the PBS plan does make the dose reduction more dramatic and perhaps more clinically significant. The advantages over VMAT are at the low and low-moderate dose levels, which are perhaps less likely to drive toxicity compared to the higher dose levels. Still, the general consensus is growing that less dose to vascular structures is likely better, with ample data from the thoracic radiation realm suggesting this.

Max dose to the spinal cord was also significantly decreased with the use of PBS versus VMAT (0 vs 1295 cGy). While the spinal cord dose with the VMAT plan is well below accepted tolerance, the potential advantage of virtually no dose to the spinal cord is that it allows for flexibility and reduced overlap of dose if a second head and neck cancer were to develop, particularly in younger patients who are at a higher risk of developing secondary, or metachronous second malignancies.

Important sequelae of laryngeal RT that could significantly affect patient quality of life include swallow function and voice quality. Aspiration pneumonia because of RT-induced dysphagia is common yet often unrecognized by clinicians and under-reported by patients and can lead to devastating outcomes. Dose to the cricopharyngeus muscle in the treatment of head and neck cancers has been predictive of death from aspiration pneumonia due to impaired swallow function.[18] In our report, the cricopharyngeus muscle received significantly lower mean (243 vs 1742 cGy) and max (1473 vs 2997 cGy) doses with PBS compared to VMAT.

In addition to the excellent local control with SVCI, toxicities are low, and voice quality significantly improves with time and may be better than for whole-larynx RT.[13,19] While whole-larynx RT typically improves voice compared to pretreatment, post-treatment vocal handicap indexes are still typically significantly altered from normal function, particularly for ongoing smokers.[7] A firmer answer on outcomes, both patient-reported quality of life and oncologic, compared to whole-larynx radiation, will hopefully be established by the ongoing multi-institutional VOCAL trial, which aims to randomize 155 patients to SVCI versus whole-larynx RT for T1 glottic cancers.[20] Our report demonstrated that the contralateral vocal cord received lower mean (2480 vs 3632 cGy) and max (4372 vs 5326 cGy) doses with PBS compared to VMAT. Perhaps this difference could lead to even less post-treatment vocal cord edema with corresponding benefits for vocal quality. We do believe the combination of lowered cricopharyngeus dose and lowered contralateral cord dose probably would have the potential to yield clinically significant benefits.

Finally, hypothyroidism occurs in 18% of early-stage patients, and this risk would also be expected to be minimized with the use of the beam angles of our PBS SVCI approach.[7]

PBS is more prone to density and positional changes in the beam path, though swallowing is ultimately a low percentage of the beam-on time, and encouraging patients to swallow between beams is an effective strategy.[21] While surface monitoring and beam holds are one strategy we utilize for VMAT SVCI cases, it is also feasible to treat SVCI cases with meticulous cone beam computed tomography acquisition and review; 3 mm radial and 5 mm craniocaudal margins on the CTV are appropriate. (These VMAT PTV margins can be readily replicated in the PBS planning process.)[22] This is only one case, and subtle anatomy differences between patients are to be expected, though this is a fairly prototypical case, and the beam arrangements utilized would be anticipated to be feasible broadly given the similarity of target volumes between patients if the disease is limited to just 1 cord.

Limitations include, principally, that the patient was not treated with PBS SVCI so a clinical outcome following such a treatment is not yet available. Additionally, even VMAT SVCI, though increasing in use, remains somewhat controversial, so the exact merits of SVCI using any approach remain to be cemented. Techniques for treating early-stage glottic larynx cases now vary widely, and many approaches are considered acceptable. While local control has historically been excellent, particularly with the rise of altered fractionation, and vocal quality typically improves with treatment and may be superior to surgical approaches, patients, particularly elderly patients in our experience, are still often quite affected by acute and occasionally chronic side effects and may benefit from an approach, such as PBS SVCI, which minimizes dose to uninvolved laryngeal substructures to the maximal extent. Thus, we thought this potential approach worthy of reporting conceptually prior to clinical implementation, given that it is a novel modality (PBS) being used for a treatment concept still being established (SVCI), for a condition (early-stage glottic larynx cancer) with historically excellent oncologic results and tolerable clinical profile for many patients.

In summary, dosimetrically, PBS SVCI holds the potential to improve even further upon the dose gradients offered by VMAT SVCI, and with careful planning, robustness evaluation, and meticulous treatment delivery, it may be a viable strategy worthy of further investigation.

Conclusion

Single vocal cord irradiation is a promising strategy for maintaining the oncologic effectiveness of whole-larynx photon radiation while potentially improving upon the historic toxicity profile. The favorable dose distribution with PBS with respect to OAR dosimetry for PBS may allow for further improvements upon VMAT SVCI strategies. Clinical implementation of PBS SVCI may be considered.

Author contribution

Bansi Savla: Conceptualization, Data curation, Investigation, Methodology, Writing (Original draft). Jenna Jatczak: Conceptualization, Data Curation, Investigation, Methodology, Writing (Original draft). Jason K. Molitoris: Conceptualization, Methodology, Writing (Original draft). Matthew E. Witek: Conceptualization, Methodology, Writing (Original draft). Kimberly Marter: Methodology, Writing (Original draft). Mark J. Zakhary: Methodology, Writing (Original draft). Junliang Xu: Methodology, Writing (Original draft). Grace E. Snow: Methodology, Writing (Original draft). Elizabeth A. Guardiani: Methodology, Writing (Original draft). Matthew J. Ferris: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing (Original draft, Revision).

Declaration of Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Matthew J. Ferris, MD, reports a relationship with Maryland Proton Treatment Center that includes employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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