Oropharyngeal Cancer

6

Suchit H. Patel, Amy J. Xu, Kevin Sine, Nancy Y. Lee, and Pamela Fox

Contents

6.1 Introduction 131
6.2 Simulation, Target Delineation, and Radiation Dose/Fractionation 132
6.3 Patient Positioning, Immobilization, and Treatment Verification 133
6.4 Three-Dimensional (3D) Proton Treatment Planning 133
6.4.1 Passive Scattering (PS) 133
6.5 Pencil Beam Scanning (PBS) 135
6.6 Dosimetry and Toxicity Characteristics 137
Conclusion 139
References 139

6.1 Introduction

Oropharynx tumors (OPC) comprise 24% of all head and neck malignancies, of which the majority arise from the base of the tongue or tonsils [1–4]. Smoking and alcohol use continue to be major risk factors but the prevalence of human papillomavirus (HPV)-associated oropharyngeal cancer has steadily increased by over 200% since the late 1980s [5]. Definitive management involves surgery or radiation therapy (RT) alone for node-negative early-stage tumors or concurrent chemoradiotherapy (CRT) for nodal involvement or locally advanced disease. In surgically

S.H. Patel • A.J. Xu • N.Y. Lee (✉)
Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: leen2@mskcc.org

K. Sine • P. Fox
ProCure Proton Therapy Center, Somerset, NJ, USA

N. Lee et al. (eds.), *Target Volume Delineation and Treatment Planning for Particle Therapy*, Practical Guides in Radiation Oncology,
https://doi.org/10.1007/978-3-319-42478-1_6

managed cases, adjuvant RT or CRT is also often indicated for extracapsular extension or positive surgical margins.

Dosimetry studies dating back nearly 15 years ago have consistently demonstrated the ability of proton RT to reduce the dose to critical structures, including the spinal cord, salivary glands, oral cavity, larynx, mandible, and esophagus [6]. More recent work has focused on the ability of intensity-modulated proton therapy (IMPT) to further enhance the therapeutic ratio by providing homogeneous target coverage with further sparing of normal structures, particularly in locally advanced tumors [7, 8]. Potential reductions in toxicity achieved with proton therapy are of paramount importance in the era of HPV-related OPC in which many young patients are cured of disease and will suffer effects of treatment for decades.

Despite the theoretical benefits of proton dosimetry, experience with proton RT in OPC treatment is limited. Loma Linda University Medical Center reported a 5-year actuarial locoregional control of 84% and grade 3 late toxicity in 11% of patients treated with passively scattered proton fields to deliver concomitant proton boost along with photon treatment during the last 3.5 weeks of treatment [9].

Recent experience with IMPT and more contemporary techniques at M.D. Anderson in which bilateral neck irradiation was pursued for nearly all OPC patients with a three-field technique showed a 2-year PFS of 89% and grade 3 acute mucositis and late dysphagia rates of 58% and 12%, respectively [10].

6.2 Simulation, Target Delineation, and Radiation Dose/Fractionation

CT simulation with intravenous iodinated contrast, when not contraindicated, is crucial to facilitate anatomical delineation. For the purposes of dose calculation, a non-contrast CT needs to be included during simulation as well.

Positron emission tomography (PET) is often helpful for identification of metabolically active gross disease and involved lymph nodes. Large necrotic nodes may not show activity on PET but should be encompassed within high-dose target volumes, especially in HPV-positive cases. Likewise, small nodes that are borderline on PET may represent disease in alcohol- and smoking-related HPV-negative cases and need to be evaluated carefully. Biopsy to show evidence of gross nodal involvement is not always needed in practice, particularly in HPV-related malignancies.

Magnetic resonance imaging (MR) is recommended for accurate delineation of the extent of gross tumor in soft tissue, especially in cases in which artifact from dental amalgam limits evaluation of the tonsils. When possible, MR should be obtained in the treatment position.

PET and MR images should be registered to the planning CT for accurate target delineation. Uncertainties related to image fusion should be considered in the treatment planning process (Chap. 3).

The recommended dosing and fractionation vary:

- For definitive cases, gross tumor volume (GTV), including gross primary tumor and involved regional lymph nodes, should be treated to 70 Gy (RBE). Typically,

an extra CTV margin is used only to outline areas of uncertainty in the extent of the GTV.

- Both the primary tumor site and the involved levels of the ipsilateral neck (levels II–IV) should be treated to 60 Gy (RBE). In postoperative cases, areas of surgical margin positivity or extracapsular extension can be treated to 66 Gy (RBE). Lateral retropharyngeal nodes (up to the level of the first cervical vertebra) are usually included in this target, and level Ib is not included unless there is involvement or tumor extension into the oral cavity.
- A low-risk clinical tumor volume can be treated to 50–54 Gy (RBE) that includes the uninvolved and nonsurgically violated ipsilateral neck.
- For HPV-positive disease, lower subclinical dosing may be considered, such as 54 Gy and 45 Gy to the high-risk and low-risk clinical target volumes, respectively.

Target volumes should be expanded according to institutional standards, typically by 3–5 mm, to create a planning target volume (PTV) to account for setup variation and range uncertainties.

Consultation with a medical oncologist regarding concurrent radiosensitizing chemotherapy should be considered, especially for large primary tumors, margin positivity, extensive nodal involvement, and/or suspected or confirmed extracapsular extension.

6.3 Patient Positioning, Immobilization, and Treatment Verification

Simulation and treatment should be conducted in the supine position with a 5-point mask for optimal immobilization of the head, neck, and shoulders.

Setup accuracy should be ascertained with daily orthogonal X-ray imaging or volumetric imaging, if available, to confirm setup accuracy.

When in-room 3D imaging (e.g., cone beam CT) is not available, weekly verification CT scans with the patient in treatment position are recommended during the course of treatment to assess for potential changes in anatomy (i.e., due to weight loss, tumor shrinkage, etc.) and resultant changes in the accuracy of the dose distribution. This is especially relevant for HPV-positive nodal disease, in which large necrotic nodes shrink early in the course of treatment. Replanning should be considered to reduce errors in true dosimetry in this setting.

6.4 Three-Dimensional (3D) Proton Treatment Planning

6.4.1 Passive Scattering (PS)

Generally, two or three field plans are used for ipsilateral coverage of the primary or postoperative site and regional nodes. Fields should be arranged for short depths and homogeneous coverage, which is often best achieved by anterior oblique and superior oblique beams. For large targets that are well lateralized (i.e., large primary

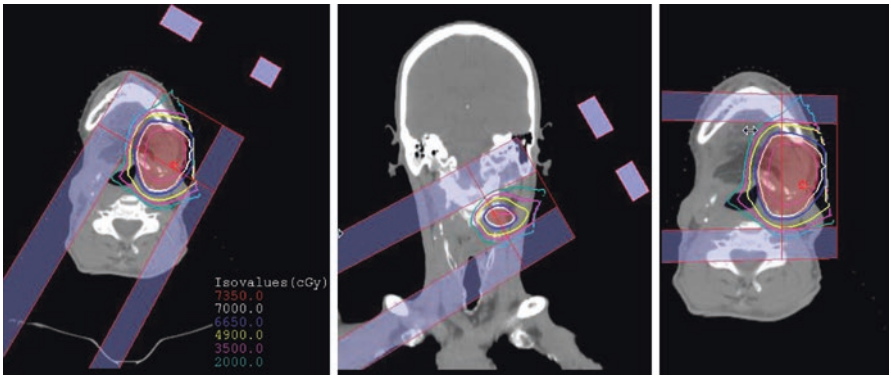

Fig. 6.1 A sample passive scattering proton plan for a patient with cT2N1 squamous cell carcinoma of the left base of tongue treated with chemoradiation followed by total glossectomy for a recurrence who then presented with a left lateral oropharyngeal wall recurrence. A three-beam passive scattering technique was utilized with a left lateral (*left panel*), left superior oblique (*center*), and an anterior oblique (*right*) beam

tumor or postoperative reconstruction), a lateral beam may also offer dosimetric advantages (Fig. 6.1).

It is not optimal to overlap the distal edge of more than two beams, and in particular, any critical organs at risk should not receive distal range out dose from more than one beam to avoid hotspots where true dose may be uncertain.

Dental artifacts can be addressed by contouring the high atomic number material and correcting for the density. Treatment planning systems should allow for manual corrections that can be determined based upon the material. If the material is not known, conservative estimates using gold or amalgam can be substituted. Additionally, the artifacts must be contoured and forced to the appropriate densities or stopping powers.

Large tumors that respond early in the treatment course should be managed with adaptive replanning to avoid off target dosimetry.

For cases requiring only unilateral treatment, passive scattering can achieve optimal coverage of the ipsilateral primary and neck and should allow minimal dose to the contralateral neck with excellent sparing of the contralateral salivary glands, oral cavity, larynx, brainstem, and spinal cord (Fig. 6.2).

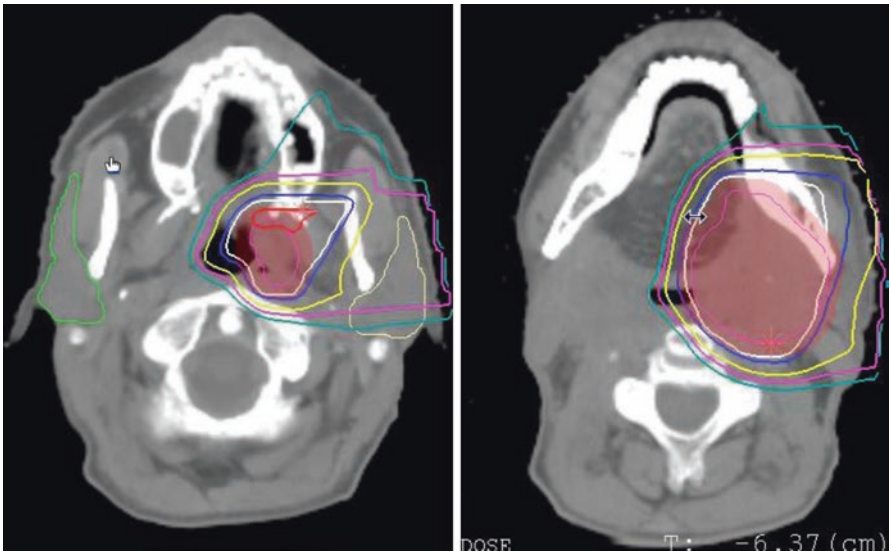

Fig. 6.2 Dose distribution for the patient in Fig. 6.1. Note the complete sparing of the contralateral submandibular and parotid glands, as well as considerable sparing of the contralateral oral cavity. Isodose lines are color-coded same as in Fig. 6.1

6.5 Pencil Beam Scanning (PBS)

Unlike other sites of the head and neck in which the skin is part of the target, for definitive cases of OPC, PBS can provide conformal plans that can better spare the skin due to greater control over the proximal dose distribution. This can be achieved through the use of explicit avoidance structures where appropriate.

While the same two to four beam arrangement that is used with PS can be used with PBS, the use of PBS allows for careful delivery of radiation to the contralateral neck while still sparing critical organs (Figs. 6.3 and 6.4).

OPC cases needing bilateral neck irradiation typically utilize bilateral oblique beams and a single midline opposing beam. Addition of extra fields does not seem to confer an advantage as it does for IMRT [11].

Care should be taken to ensure that all artifact and dental hardware are accurately contoured and proper mass density/electron density is applied prior to calculation. Use beams that avoid going through hardware, though in OPC, this is sometimes not possible.

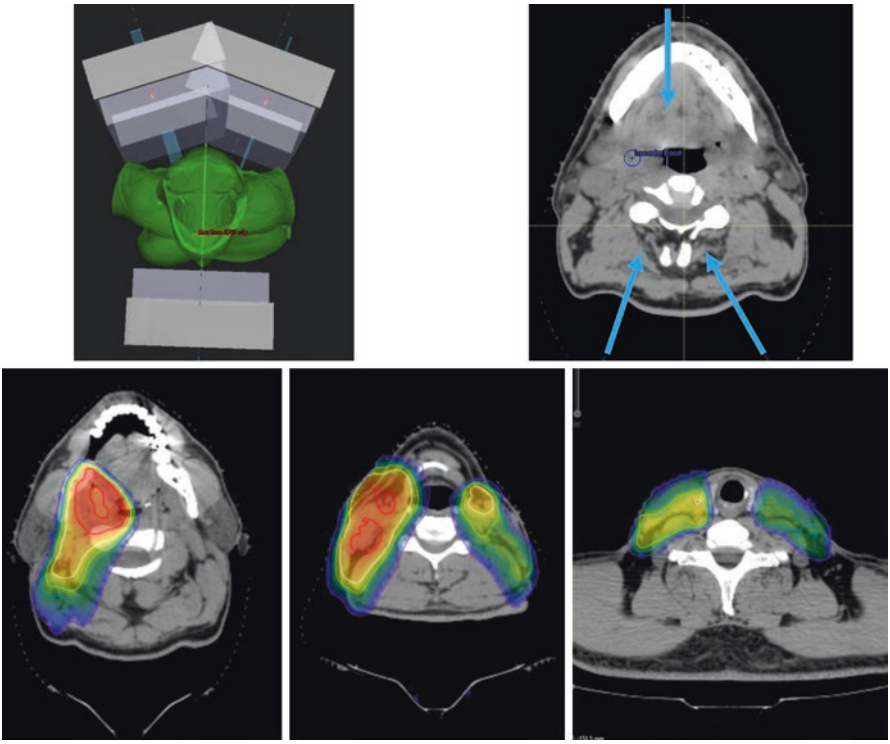

Fig. 6.3 An IMPT beam arrangement for a patient with cT2N2b SCC of the right tonsil to obtain bilateral neck treatment, utilizing bilateral posterior oblique beams and a single anterior midline beam (*upper panels*) to obtain conformal coverage of targets while sparing the larynx and oral cavity (*lower panels*). Color wash spans 40–75 Gy, and isodose lines highlight 40 Gy (*violet*), 50 Gy (*blue*), 54 Gy (*green*), 60 Gy (*yellow*), and 70 Gy (*red*)

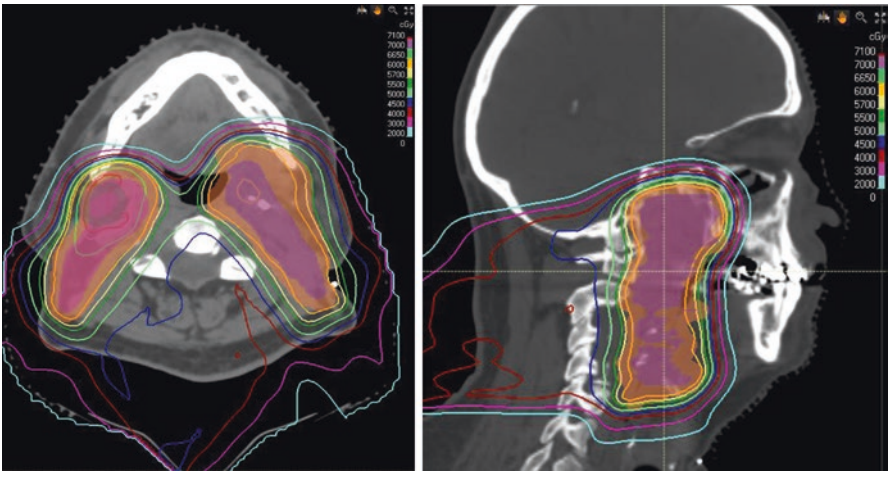

Fig. 6.4 Dose distribution for a patient with HPV-positive, pT2N2b squamous cell of left tonsil, treated with postoperative chemoradiation with proton therapy following transoral robotic resection and neck dissection. Note sparing of the anterior oral cavity, even with bilateral neck treatment

Table 6.1 OPC dose constraints guidelines at MSKCC

OAR	Constraint	Dose
Oral cavity	Mean dose	35–40 Gy
Spinal cord	Dose to 0.1 cc	<50 Gy RBE[a]
	Surface max	64 Gy RBE[b]
Brainstem	Dose to 0.05 cc	< 60 Gy RBE[a]
	Core max	53 Gy RBE
	Surface max	64 Gy RBE[b]
Cochlea[c]	Max dose	<50 Gy RBE
Parotid	Mean dose	25 Gy RBE ALARA
Larynx	Mean dose	<35 Gy RBE

[a]For plans with prescription dose ≤60 Gy RBE
[b]Isodose line may touch structure surface
[c]If ipsilateral hearing is absent, contralateral cochlea constraint is <35 Gy RBE

For the majority of cases in which bilateral neck irradiation is needed, single field optimization (SFUD) or multi-field optimization IMPT or rarely, a mix of the two techniques can be used in order to meet currently recommended dose constraints. Sample constraints are noted in Table 6.1 for OPC planning that are typically employed at MSKCC, but each center should establish their own set of dose constraints based on their clinical experience.

Modeling work has also suggested that reducing the spot size for PBS may translate into further dosimetric advantages in reducing normal tissue exposure, in particular that of the sublingual glands [12].

6.6 Dosimetry and Toxicity Characteristics

In case-matched control analysis of comparing the dosimetry of IMRT and IMPT plans for OPC patients undergoing definitive RT or CRT at MDACC, IMPT allowed for reduced dose to several critical structures when compared to IMRT plans generated on the same target volumes, particularly those related to acute oral toxicity and nausea (Table 6.2). Comparing these to additional matched patients that underwent IMRT treatment further corroborated this dosimetric benefit [7]. Similar studies have been reported elsewhere as well, specifically for OPC patients, with significant reduction in parotid, sublingual gland, and oral cavity dose [8].

Prospective OPC patients undergoing IMPT at MDACC experienced relatively favorable acute toxicities, with grade 3 dermatitis of 46%, mucositis in 58%, and dysphagia of 24%. Late grade 3 dysphagia was 12%. Median weight loss was 7.4%. One of 50 patients developed oropharyngeal mucosal ulceration 16 months after treatment completion, with stabilization of the ulcer and improvement in symptoms after hyperbaric oxygen therapy [10]. Furthermore, retrospective cohort and case-matched analyses of toxicity suggest lower rates of xerostomia, weight loss, taste and appetite changes, and reduced need for gastrostomy tubes with proton therapy for OPC, though patient-reported outcomes apparently do not reflect this fully [13, 14].

Table 6.2 Dosimetric comparison of mean dose to critical structures for 25 patients [7]

Structure	IMPT plan for IMPT-treated patients (Gy ± SD)	IMRT plan for IMPT-treated patients (Gy ± SD)	*P* value	IMRT plan for matched cohort of IMRT-treated patients (Gy ± SD)	*P* value
Anterior oral cavity	8.3 ± 5.9	31.0 ± 7.2	<0.001	30.5 ± 7.9	<0.001
Posterior oral cavity	40.5 ± 15.3	54.3 ± 8.1	<0.001	50.6 ± 8.0	0.011
Esophagus	20.9 ± 12.2	33.6 ± 14.4	0.002	18.6 ± 9.7	0.543
Inferior PC	32.8 ± 10.7	45.6 ± 10.4	<0.001	28.8 ± 15.8	0.068
Middle PC	48.2 ± 17.8	57.0 ± 14.4	0.046	54.6 ± 9.4	0.543
Superior PC	55.3 ± 13.0	58.1 ± 11.0	0.305	58.0 ± 11.3	0.511
Brainstem	7.7 ± 3.7	14.4 ± 6.4	<0.001	18.6 ± 8.8	<0.001
Cerebellum	12.6 ± 4.3	18.8 ± 4.8	<0.001	18.9 ± 7.6	<0.001
Area postrema	14.6 ± 9.0	24.5 ± 7.2	<0.001	30.7 ± 6.5	<0.001

The first two columns show the dose for IMRT and IMPT plans for the same cohort, and the rightmost column shows the mean dose for the case-matched cohort. Only selected rows shown for clarity

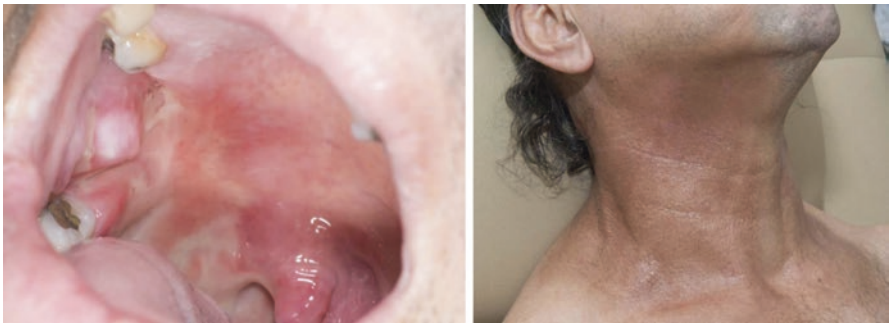

Fig. 6.5 Minimal oral cavity mucositis (*left*) and dermatitis (*right*) 1 week after completing definitive chemoradiation for the patient treated with IMPT to the bilateral neck from Fig. 6.3

While no randomized data exist to demonstrate the reduced toxicities that have been reported in case series with PBS, the anecdotal and single institution data seem promising, and patients do well with carefully planned treatment (Fig. 6.5).

Ongoing trials will further help to define the role of proton RT in the treatment of OPC. An observational study at Mayo Clinic is open to evaluate local control at 2 years, as well as quality of life measures, of mucosal sparing proton beam therapy after resection of favorable risk OPC (NCT02736786). Another observational cohort study is ongoing at MDACC to evaluate functional patient-reported outcomes following low-risk OPC treated with either definitive transoral resection or definitive IMPT (NCT02663583). Lastly, a multi-institutional randomized phase II/

III trial is ongoing to evaluate severe toxicity following IMRT vs. IMPT for locally advanced OPC (NCT01893307).

Conclusion

Reported data on the use of proton RT for patients with OPC are promising in delivering safe and effective treatment while limiting normal tissue exposure with potentially significant quality of life improvements (e.g., in reduction of mucositis, nausea, and long-term xerostomia). As technological advances with IMPT continue to grow (i.e., routine use of small spot sizes), additional benefits may be gained yet, though ongoing prospective randomized trials are ongoing to further outline the role of proton RT.

References

1. Cohan DM, Popat S, Kaplan SE, Rigual N, Loree T, Hicks WL Jr. Oropharyngeal cancer: current understanding and management. Curr Opin Otolaryngol Head Neck Surg. 2009;17(2):88–94.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
3. Gunn GB, Debnam JM, Fuller CD, et al. The impact of radiographic retropharyngeal adenopathy in oropharyngeal cancer. Cancer. 2013;119(17):3162–9.
4. Viens LJ, Henley SJ, Watson M, et al. Human papillomavirus-associated cancers—United States, 2008–2012. MMWR Morb Mortal Wkly Rep. 2016;65(26):661–6.
5. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294–301.
6. Cozzi L, Fogliata A, Lomax A, Bolsi A. A treatment planning comparison of 3D conformal therapy, intensity modulated photon therapy and proton therapy for treatment of advanced head and neck tumours. Radiother Oncol. 2001;61(3):287–97.
7. Holliday EB, Kocak-Uzel E, Feng L, et al. Dosimetric advantages of intensity-modulated proton therapy for oropharyngeal cancer compared with intensity-modulated radiation: a case-matched control analysis. Med Dosim. 2016;41:189–94.
8. van de Water TA, Lomax AJ, Bijl HP, et al. Potential benefits of scanned intensity-modulated proton therapy versus advanced photon therapy with regard to sparing of the salivary glands in oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2011;79(4):1216–24.
9. Slater JD, Yonemoto LT, Mantik DW, et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. Int J Radiat Oncol Biol Phys. 2005;62(2):494–500.
10. Gunn GB, Blanchard P, Garden AS, et al. Clinical outcomes and patterns of disease recurrence after intensity modulated proton therapy for oropharyngeal squamous carcinoma. Int J Radiat Oncol Biol Phys. 2016;95(1):360–7.
11. Steneker M, Lomax A, Schneider U. Intensity modulated photon and proton therapy for the treatment of head and neck tumors. Radiother Oncol. 2006;80(2):263–7.
12. van de Water TA, Lomax AJ, Bijl HP, Schilstra C, Hug EB, Langendijk JA. Using a reduced spot size for intensity-modulated proton therapy potentially improves salivary gland-sparing in oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2012;82(2):e313–9.
13. Blanchard P, Garden AS, Gunn GB, et al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer—a case matched analysis. Radiother Oncol. 2016;120(1):48–55.
14. Sio TT, Lin HK, Shi Q, et al. Intensity modulated proton therapy versus intensity modulated photon radiation therapy for oropharyngeal cancer: first comparative results of patient-reported outcomes. Int J Radiat Oncol Biol Phys. 2016;95(4):1107–14.