Oral Cavity Tumors

5

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Contents

5.1 Introduction

Oral cavity and pharynx cancers account for 2.9% of all cancers in the United States. The most common sites of oral cavity cancer are the oral tongue and floor of the mouth. There are over 45,000 new cases of oral cavity and pharynx cancers diagnosed each year, with over 8500 deaths annually [1]. Known risk factors for oral cavity cancer include tobacco and alcohol use, infection with human papillomavirus, and chewing of betel nut leaves. Oral cavity cancers are often initially managed surgically, followed by radiation ± chemotherapy. Locoregionally advanced oral cavity cancers are treated with a combination of surgery and

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RT ± chemotherapy, due to the high risk of local recurrence compared to other head and neck squamous cell carcinoma sites [2]. Risk factors for recurrence of oral cavity cancers include the presence of extracapsular nodal spread, positive resection margins, N2 or N3 nodal disease, perineural invasion, and vascular invasion [3, 4].

Oral cavity cancers are often grouped with oropharyngeal cancers; therefore, there are no published clinical studies evaluating proton therapy in oral cavity cancers alone. There are few published clinical studies assessing the role of protons for oropharyngeal cancers, which demonstrated improved locoregional control [5, 6]. The efficacy and toxicity of protons in oropharyngeal cancers are currently being further evaluated in a clinical trial setting, with patients randomized to IMRT or IMPT [7]. A previous study of IMPT in oral cavity cancers demonstrated a 2-year rate of local control of 91% and 2-year locoregional progression-free survival of 84% [6]. Incidence of late Grade 3 toxicity has not been known to increase significantly despite the higher doses administered via proton therapy, with xerostomia and mucositis being the most commonly observed adverse events [6, 7].

The RTOG 8502 regimen of photon radiotherapy has been shown to be effective for the treatment of advanced head and neck cancers. The regimen is colloquially referred to as "Quad Shot" and consists of 3.7 Gy fractions delivered twice daily over 2 consecutive days for 4 week intervals, for a total of three cycles [8]. A recent study of the RTOG8502 regimen as a hypofractionated proton radiotherapy regimen has also been shown to demonstrate a favorable palliative response in patients with incurable recurrent metastatic malignancies of the head and neck and is used at our institution for the treatment of appropriate oral cavity cancers (unpublished data).

Tumors with lower risk of lymph node metastasis (retromolar trigone, hard palate, gingiva) should be treated to the tumor bed with consideration of ipsilateral lymph nodes. For tumors with higher risk of lymph node metastasis (buccal mucosa), coverage of bilateral cervical lymph nodes should be considered. Tumors with high risk of spread to surrounding musculature and glands (oral tongue, floor of mouth) should include bilateral neck coverage and consideration for lymph node coverage in the radiation fields.

Proton therapy allows for delivery of higher radiation doses to the oral cavity with lower exposure to surrounding critical structures and without evidence of worsening toxicity. "The anterior location of oral cavity tumors along with the high risk of local recurrence offers a potential opportunity to improve outcomes with proton dose escalation, although this remains to be explored."

5.2 Simulation, Target Delineation, and Radiation Dose/Fractionation

CT can be used for initial determination of soft tissue and bony involvement (including the pterygopalatine fossa, mandible, and hard palate). Dental panoramas can determine mandibular involvement if CT cannot be obtained. For the purposes of dose calculation, a non-contrast CT needs to be employed in planning proton therapy.

MRI is critical for determination of perineural spread and primary tumor delineation, particularly if dental artifacts complicate CT visualization.

PET imaging is superior to CT and MRI in detection of occult nodal metastasis, although it is limited in the detection of small metastasis.

The patient should be supine with the neck in slight hyperextension for simulation. A five-point mask should be used for immobilization of the head, neck, and shoulders. A bite block can be used for oral tongue cancers to decrease dose to the superior or inferior oral cavity, as appropriate. Custom bite blocks can be fabricated to immobilize the oral tongue laterally in order to reduce unnecessary dose (Fig. 5.1).

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).

Radiation dosing and fractionation varies depending on the clinical scenario (Tables 5.1, 5.2, 5.3, and 5.4).

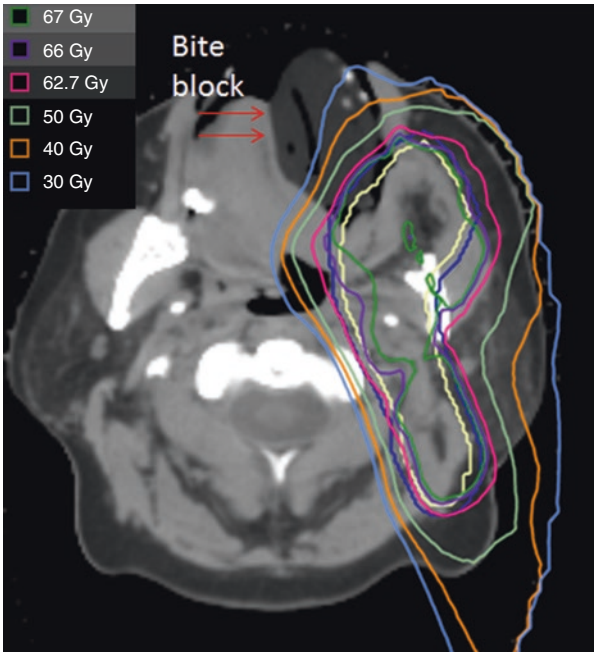

Fig. 5.1 Uniform scanning plan demonstrating use of a custom mouth guard to offset the ipsilateral tongue to minimize the dose to the oral tongue. Bite block indicated by *red arrows* above

Table 5.1 Recommended target volumes and radiation doses for definitive treatment of oral cavity cancers

Volume	Target	Dose
GTV	Gross disease, involved nerves, and regional lymph nodes	70 Gy (RBE)
High-risk clinical tumor volume (CTV_{70})	Include margin of 5 mm if there is uncertainty of gross disease extent	70 Gy (RBE)
High-risk clinical tumor volume ($CTV_{59.4}$)	Include up to a 10 mm margin for positive nodes and high-risk ipsilateral or contralateral nodes	59.4 Gy (RBE)
Low-risk clinical tumor volume (CTV_{54})	Include ipsilateral and contralateral nodes at low-risk for subclinical disease	54 Gy (RBE)

Table 5.2 Recommended target volumes and radiation doses for adjuvant treatment of oral cavity cancers

Volume	Target	Dose
High-risk clinical tumor volume (CTV_{66})	Include preoperative target volume and regions of extracapsular nodal extension, soft tissue invasion, bone invasion, and positive margins	66 Gy (RBE)
High-risk clinical tumor volume (CTV_{60})	Include preoperative tumor volume and nodal disease, operative bed, and ipsilateral or contralateral nodes at high risk for subclinical disease	60 Gy (RBE)
Low-risk clinical tumor volume (CTV_{54})	Include uninvolved ipsilateral and contralateral lymph nodes at low risk for subclinical disease	54 Gy (RBE)

Table 5.3 Site-specific recommendations for clinical target delineation of oral cavity cancers

Tumor site	Stage	Clinical treatment volume
Oral tongue, floor of the mouth	T1—T4N0	Include tumor bed, base of the tongue, and entire oral tongue. Consider including the alveolar ridge for floor of the mouth lesions. Treat both sides of the neck, even for well-lateralized T1—T2N0 lesions if depth of invasion is >4 mm; inclusion in low- or high-risk CTV is up to physician discretion. Ipsilateral and/or contralateral levels I–IV can be considered
	T1—T4N1-3	Include tumor bed, base of the tongue, and entire oral tongue. Consider including the alveolar ridge for floor of the mouth lesions. Treat both sides of the neck; inclusion in low- or high-risk CTV is up to physician discretion. Ipsilateral and/or contralateral levels I–IV can be considered
Buccal mucosa	T1—T4N0	Target volume for the inner cheek should be generous and include the preoperative tumor bed, entire buccal mucosa, and ipsilateral lymph nodes. Extend coverage posteriorly to retromolar trigone and superiorly to near the inferior orbital rim. If well-lateralized, the tumor can be treated at ipsilateral levels I–IV alone. Otherwise, bilateral cervical lymph node coverage can be considered
	T1—T4N1-3	Target volume for the inner cheek should be generous and include the preoperative tumor bed, entire buccal mucosa, and ipsilateral lymph nodes. Extend coverage posteriorly to retromolar trigone and superiorly to near the inferior orbital rim. Ipsilateral levels I–IV should be treated within the neck. Treatment of contralateral neck can be considered depending on pathologic findings and discussions with the surgeon
Retromolar trigone, hard palate, gingiva	T1—T4N0	Include the preoperative target volume and postoperative tumor bed. Ipsilateral levels I–IV can be considered for all cases, with treatment of contralateral neck at physician discretion. Hard palate tumors are generally minor salivary gland tumors; "Chap. 8" can be used for treatment guidelines for coverage of lymph node regions
	T1—T4N1-3	Include the preoperative target volume and postoperative tumor bed. Treat the ipsilateral levels I–IV for all cases, and consider treatment of the contralateral neck. Hard palate tumors are generally minor salivary gland tumors; "Chap. 8: Major Salivary Glands" can be used for treatment guidelines for coverage of lymph node regions

Table 5.4 Recommended dose constraints for organs at risk in bilateral cases

Organ at risk	Recommended dose constraint
Oral cavity (excluding PTV)	Mean dose <10 Gy (RBE)
Larynx	Mean dose <20 Gy (RBE)
Ipsilateral parotid gland (for non-parotid cases)	Mean dose <26 Gy (RBE) (ideally lower)
Ipsilateral submandibular gland (for non-submandibular cases)	Mean dose <39 Gy (RBE)
Contralateral submandibular and parotid glands	Mean dose 0 Gy (RBE)
Esophagus	Max dose < Rx dose Mean dose ≤ 40 Gy (RBE) V60 ≤ 17% (ideally lower)
Brachial plexus	No hot spots
Brainstem	0.05 cc < 60 Gy (RBE) Max surface dose ≤64 Gy (RBE)
Optic nerves and optic chiasm	0.05 cc < 60 Gy (RBE)
Spinal cord	1.0 cc < 50 Gy (RBE) Surface max ≤64 Gy (RBE)

5.3 Patient Positioning, Immobilization, and Treatment Verification

CT simulation should be performed using a slice thickness of 3 mm or less. Intravenous contrast should be used for target delineation, particularly for cervical lymph node detection. The CT should span from the top of the head to the carina, with the isocenter just superior to the arytenoids.

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

In-room CT imaging (i.e., cone beam CT) is ideally used for treatment verification. When in-room 3D imaging is not available, verification CT scans with the patient in treatment position are recommended during the course of treatment to assess for potential changes in anatomy such as weight loss, tumor shrinkage, and potential changes in the accuracy of the dose distribution. Currently at our center, we generally rescan every other week for definitive cases and once during treatment for postoperative cases, though there are exceptions depending on the clinical scenario.

5.4 Three-Dimensional (3D) Proton Treatment Planning

5.4.1 Passive Scattering (PS)

Three field plans are typically utilized (two to four beams) in planning oral cavity cases. With all proton planning, care must be taken not to overlap the distal end of more than two beams and no more than one beam ranging out into an organ at risk (OAR). With proton planning, air gap between the compensator

and patient surface is also an important consideration. Minimizing the air gap reduces penumbra and scatter while increasing conformality. When using smaller air gaps, be mindful of collisions between the compensator and the patient or treatment table.

Worst and best case scenarios should be evaluated with relevant range uncertainties (2.5%*range + 2 mm), based on physical and biological uncertainties.

With proton planning, artifacts, dental hardware, surgical clips, and other foreign materials must be contoured and assigned the proper forced densities in order to ensure accurate beam calculation.

Special care should be taken to avoid beams traversing through dental hardware and air cavities that can change during the course of treatment (Fig. 5.2).

While planning with uniform scanning (US) or passive scattering (PS), compensators should be created with the dental filling at a lower electron density. This will maintain a smoother compensator with less ridges and pylons. After the compensator is calculated, apply appropriate forced density, and evaluate the beam coverage and OARs.

If it is necessary for the beam path to treat through the fillings, there will be a cold spot distal to the filling. This effect can be minimized by using multiple beam angles.

Patching field technique can be used to keep the parotid dose and other OARs below tolerance. Patched fields are two orthogonal beams in which the distal 50% isodose line of one beam is abutting the 50% lateral penumbra line of the other

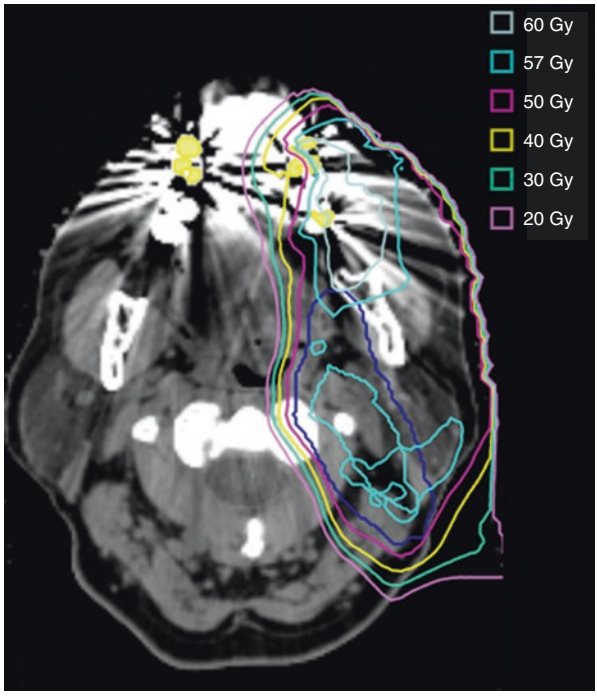

Fig. 5.2 Example of a uniform scanning plan demonstrating contouring of a dental filling artifact

beam. When possible, use a minimum of two patched pairs to minimize the hot spots along the patch lines. Maintain a 15–20% hot spot at the match line to allow for over and under range uncertainties (Fig. 5.3).

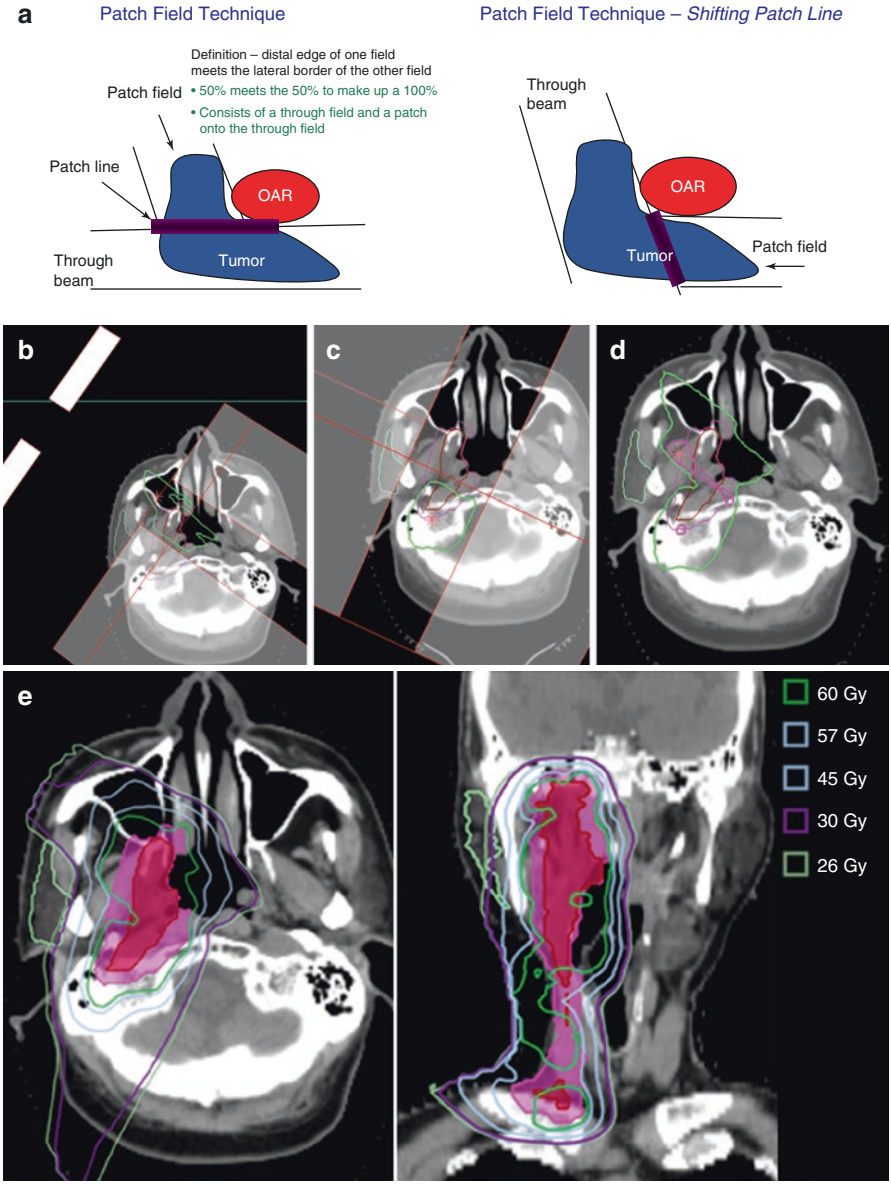

Fig. 5.3 Passive scattering plan illustrating a patch technique to avoid the parotid gland, for the treatment of a recurrent squamous cell carcinoma of the right lateral oral tongue, status post right partial glossectomy and radical resection of the right tonsil and right base of the tongue. (**a**) Illustrates the patch field technique; (**b**) demonstrates a through beam; (**c**) is the patch field abutting the 50% lateral isodose line of (**b**); (**d**) demonstrates the patch pair isodose distribution. The through beam plus patch field yields one patch pair; the 15% hot spot is represented by the *purple line*; (**e**) is the composite plan with isodose distribution of all fields

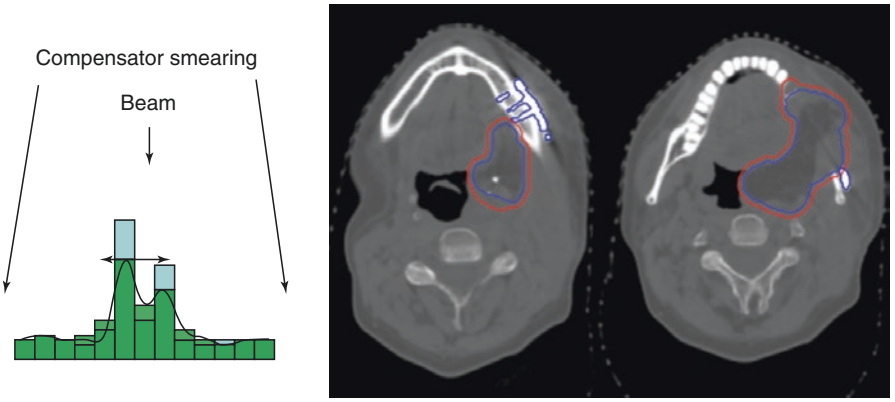

Fig. 5.4 Example of compensator smearing and plan for hardware present within the radiation field

There are times when hardware might be present in the field, such as titanium screws and surgical clips. Avoid traversing through the hardware whenever possible, although this may be unavoidable in certain cases.

Screws and clips should be overridden while creating compensators. An increase in smearing should also be utilized to increase robustness of the plan and reduce pylons in the compensator. Smearing should be at minimum ≥ PTV margin and the Moyer's formula should be considered: Smear = [(3% or range)2 + (3 mm)2 + (motion)2] ½] as a minimum (Fig. 5.4).

The following rules should be followed when performing patch fields:

- Maintain a hot spot between 15% and 20% at the intersection of the patched fields.
- The 95% isodose line should not completely break up when all beams are summed; the 90% isodose line should encompass the target.
- No more than 30% of total dose should be delivered via patched fields (exceptions are made when planning is particularly difficult due to re-treatment limitations; in these cases, a physician and physicist should be consulted).
- End of range effects should be minimized particularly in the brain or near OARs; no more than 30% of beams should end range on an OAR.

5.5 Pencil-Beam Scanning (PBS)

5.5.1 Passive Scattering vs. Pencil Beam-Scanning Comparisons

The same field arrangement used in uniform scanning/passive scanning should be used in PBS, although the number of fields may be decreased.

For oral cavity cases, single field uniform dose optimization (SFUD) should ideally be used as it results in delivery of the most robust treatment plan. Each beam

should be optimized using the target and OAR constraints/objectives set by your institution. Each beam should be evaluated individually to ensure adequate target coverage and then compositely to evaluate OAR constraints and possible hot spots. As robust optimization matures in the clinical environment, intensity-modulated proton therapy (IMPT) may be more extensively used. Even though IMPT may generate a more conformal dose distribution, plan robustness must be carefully evaluated especially when robust optimization is not available on your treatment planning system (Fig. 5.5).

Robust optimization can be achieved when creating optimization constraints and objectives for the targets and OARs. The robustness optimization should be used when clinically needed and available. Each institution will set their robustness optimization parameters based upon the estimated setup tolerances and estimated range uncertainties. Robust optimization will compute, considering the over and under range, isocenter shifts, set up uncertainties, and restrict hot spots if there is over lapping of fields.

Without robust optimization, another option to ensure robustness is to create planning organ at risk volumes (PRVs) and target optimization structures to account for the uncertainties. When possible, planning should be carried out with SFUD as it is currently the most robust option available. As robust optimization is just emerging in the clinical setting, it should be carefully evaluated.

5.5.2 Critical Structures

The ipsilateral parotid gland is a critical avoidance structure, and care should be taken to minimize exposure, reducing the mean dose to <26 Gy (RBE) or, ideally, lower (Fig. 5.6).

The spinal cord should also be taken into account during the planning process. With the unique characteristics of protons, the doses are usually held to a minimum. Due to the beam stopping power of protons, the laryngeal dose can also be significantly lowered to try to maintain a mean dose of ≤15 GyE or lower (Figs. 5.7, 5.8, 5.9, 5.10).

The sharp dose falloff of protons allows for optic nerve sparing.

5.6 Future Developments

As IMPT use becomes more prevalent, additional data on the role of IMPT in oral cavity cancers will become available. The efficacy and toxicity of protons in oropharyngeal cancers is currently being further evaluated in a clinical trial setting, with patients randomized to IMRT or IMPT. The ongoing clinical trial of IMPT vs. IMRT in oropharyngeal cancers will illuminate the differences in efficacy and toxicity.

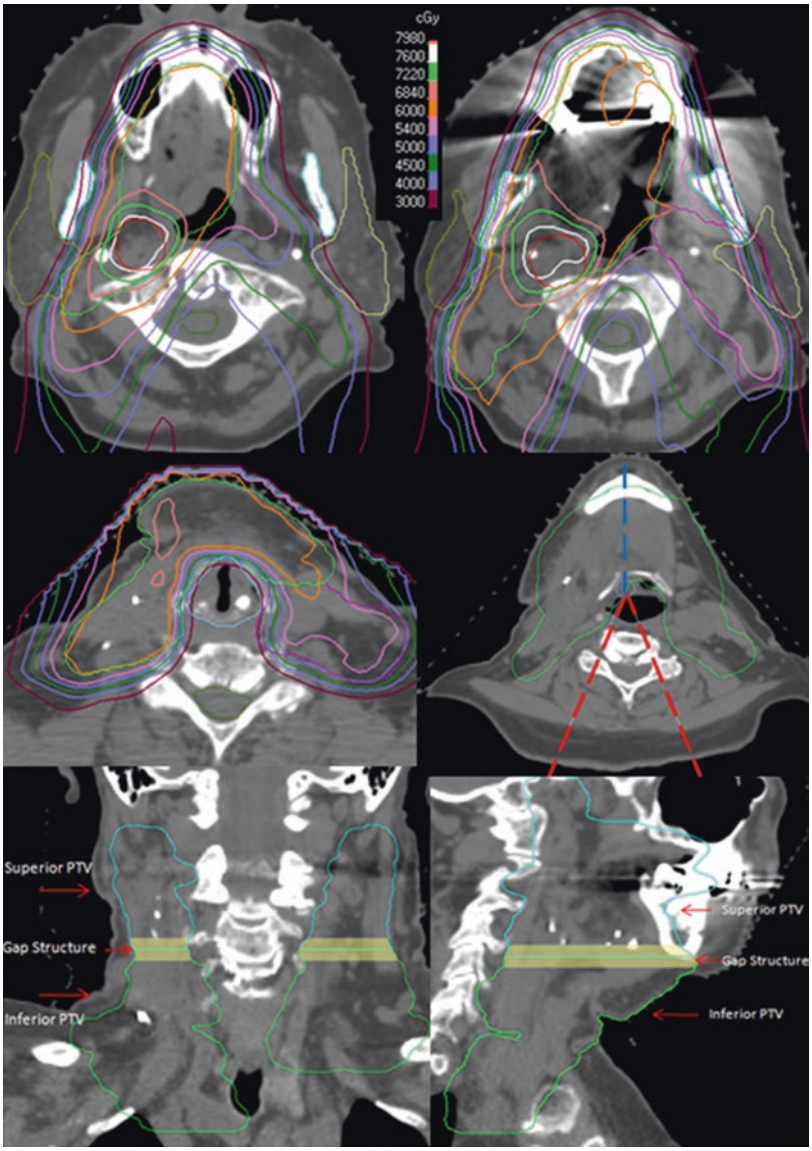

Fig. 5.5 PBS plan of a 72-year-old woman with stage T3N1 SCC of the oral tongue, status post-hemiglossectomy and cervical lymphadenectomy with modified radical neck dissection. Bilateral oral cavity cases are treated using a three-beam approach: AP (*blue dashed line*) and RPO and LPO (*red dashed lines*). The lower anterior neck is treated with the AP and is matched with the posterior oblique beams treating the upper neck and oral cavity. Although counterintuitive, treating the superior PTV with the posterior obliques is more robust than an anterior approach as slight movement in the mandible will adversely affect the beam path. The posterior approach is less susceptible to this variation in setup. This approach also maximizes parotid sparing. The target volume is divided into two parts (superior and inferior PTV), which are treated with independent dose objectives. At the match line, we create a dose gradient using a "gap structure." The structure is 1 cm superior and inferior to the match line defined by PTV volume. The gradient over 2 cm is 5% per mm, so changes in setup in between fields of up to 2 mm would only result in 10% changes in daily delivered dose, thereby reducing excessive hot or cold spots at the match line

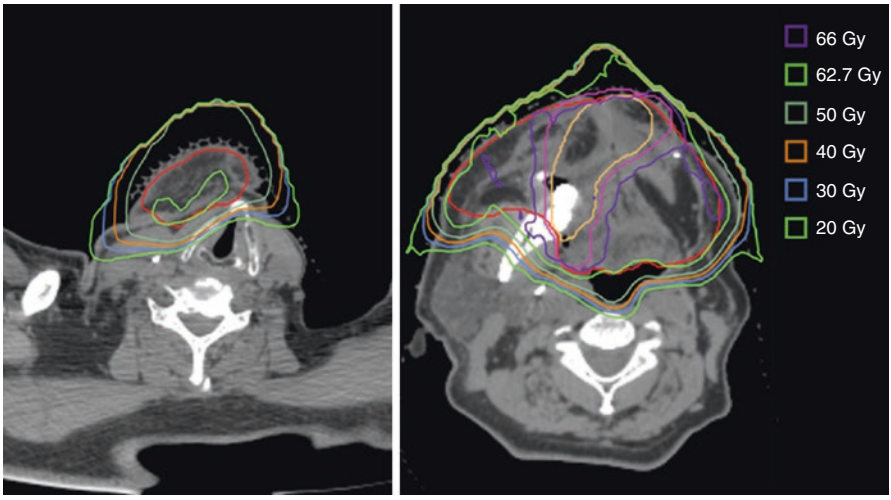

Fig. 5.6 Uniform scanning plan for the treatment of a multiply recurrent squamous cell carcinoma of the oral cavity, status post-multiple resections and postoperative radiation therapy to a total dose of 6300/5400/5000 cGy. Plan illustrates treatment to a recurrence of the gingiva and hard palate post-surgical resection with positive margins, with sparing of the larynx, parotid glands, and spinal cord

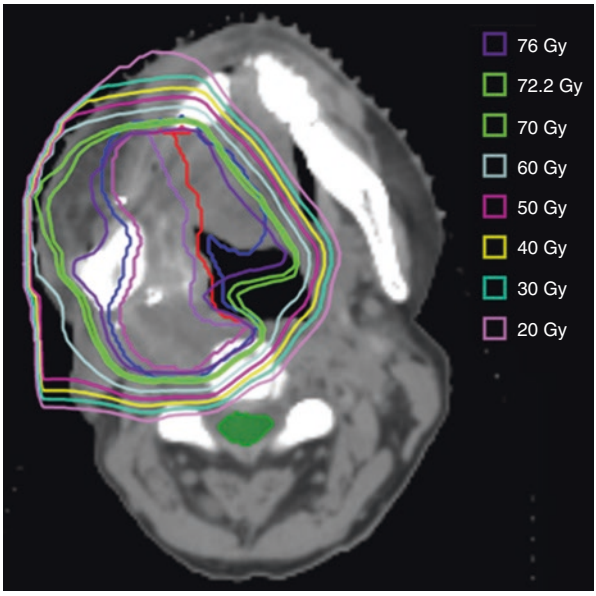

Fig. 5.7 Example of cord sparing in an initial pT1N0 right oral tongue cancer with a large right retromolar trigone recurrence, status post-surgical resection with postoperative RT to 66 Gy and surgery for a pT4aNx recurrence

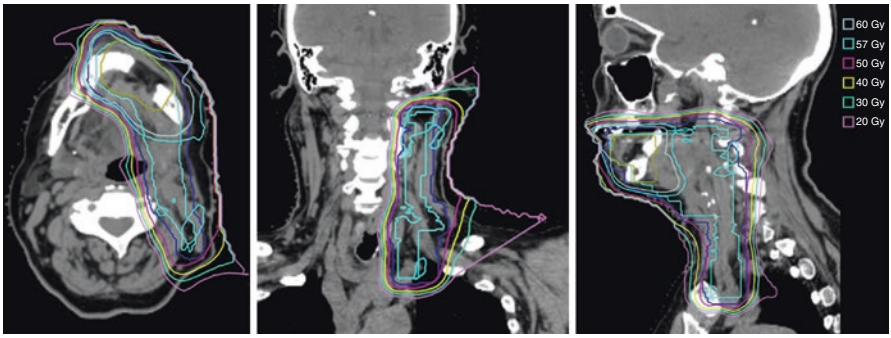

Fig. 5.8 Example of a treatment plan for a pT1N0 spindle cell SCC with 6 mm invasion and perineural invasion, status post-resection with a marginal mandibulectomy and left neck dissection. High-risk primary CTV_{60} is contoured in gold

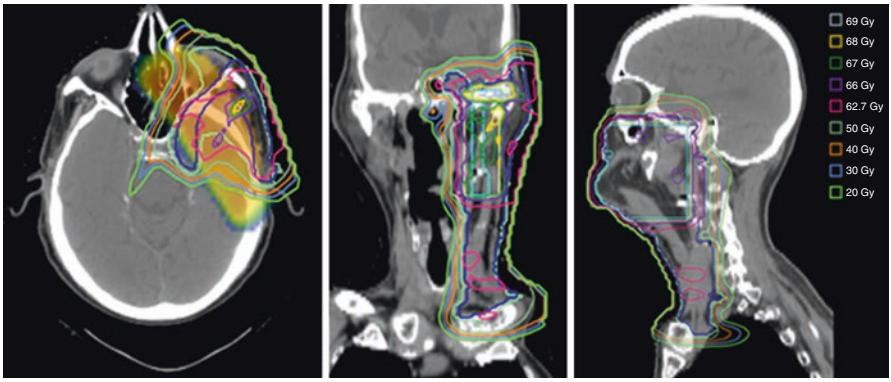

Fig. 5.9 Example of a treatment plan for a rpT4N0M0R0 SCC of the left buccal mucosa, status post-resection with positive margins and recurrent disease resected with extensive PNI, invasive islands, and tumor in the floor of the mouth and palate. Plan demonstrates ophthalmic nerve coverage tracing back to Meckel's cave; the CTV_{50} is contoured in *dark blue*

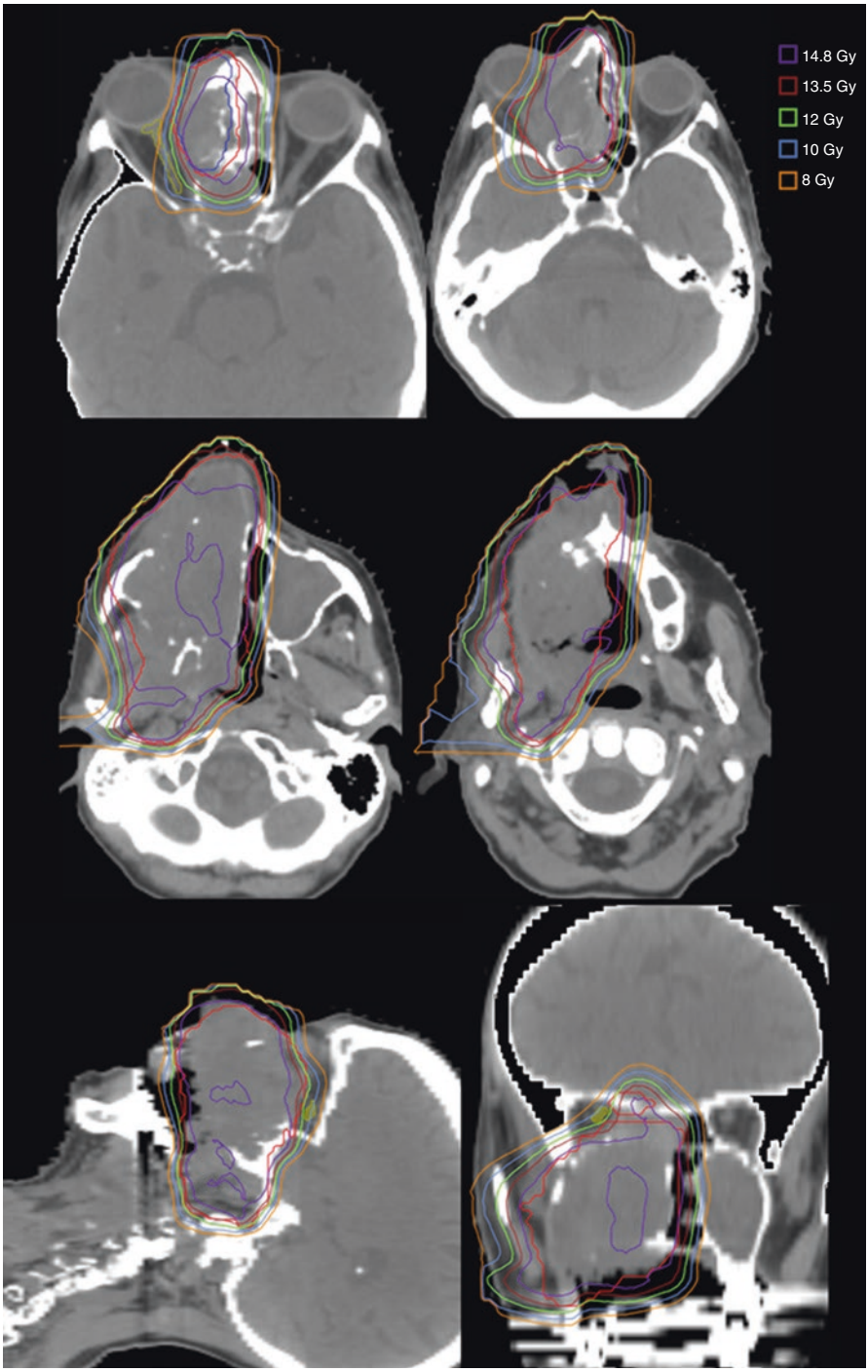

Fig. 5.10 Example of optic nerve sparing in a verrucous carcinoma of the right alveolar ridge extending up to the maxillary sinus, treated with "Quad Shot," status post-maxillectomy with re-resection of recurrence with positive margins that were treated with adjuvant RT to 66 Gy, with bulky local recurrence in the right maxilla

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