Thyroid Cancer

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9.1 Introduction

Thyroid cancer is uncommon and only represents 1% of all diagnosed malignancies and 0.2% of cancer deaths in the USA. The incidence is increasing in part due to a better detection of subclinical disease with imaging studies in the past years. Papillary cancer is the most common thyroid malignancy and represents approximately 80% of all thyroid cancers. Follicular cancer represents approximately 10%, and the remaining 10% of thyroid tumors are medullary, anaplastic, and others. Most commonly, it affects females rather than males with a 3:1 relationship. The majority of thyroid tumors are primarily managed with surgery followed by ± radioactive iodine (RAI) in those with a differentiated thyroid cancer (DTC). Patients with anaplastic carcinoma should be immediately referred and

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have multidisciplinary management in a tertiary cancer center due to the dismal prognosis of the disease [1–3].

The role of external beam radiation therapy (EBRT) in the treatment of DTC is controversial because of a lack of prospective trials and conflicting results in the existing retrospective data [4–6].

The Endocrine Surgery Committee of the American Head and Neck Society recommends EBRT for locoregional control in DTC for patients with gross residual or unresectable locoregional disease, except for patients <45 years old with limited gross disease that is RAI avid. After complete resection, EBRT may be considered in selected patients >45 years old with high likelihood of microscopic residual disease and low likelihood of responding to RAI. EBRT should not be routinely used as adjuvant therapy after complete resection of gross disease or for cervical node involvement [1, 3].

Previously published data have shown the importance of radiation sparing midline structures (i.e., upper larynx, pharyngeal constrictors, esophagus) and other organs at risk (i.e., parotids, submandibular, and minor salivary glands) and the dose correlations of these structures with toxicity [7–10].

Proton beam therapy is a promising modality for the definitive and adjuvant treatment of thyroid cancer. Pencil beam scanning (PBS) using intensity-modulated proton therapy (IMPT) is an emerging technique allowing for conformal dose delivery [11, 12].

The goal of proton therapy is to improve locoregional control by optimizing target coverage while sparing dose to organs at risk (oral cavity, upper larynx, pharyngeal constrictors, uninvolved esophagus, brachial plexus, and lung apices) thereby limiting treatment toxicity.

9.2 Simulation, Target Delineation, and Radiation Dose/Fractionation

The physical exam, diagnostic imaging studies (CT, MRI, PET), and the operative findings should be used for treatment planning.

Fluorodeoxyglucose positron emission tomography (FDG-PET) can be helpful for identification of metabolically active gross disease and for the delineation of target volumes in patients with anaplastic and RAI-refractory differentiated carcinomas.

CT simulation should be performed to help guide the delineation of the primary tumor/surgical bed and lymph node volumes and for the purpose of dose calculation. Typically we recommend 3 mm or less slice thickness.

The use of IV contrast is typically avoided in case that the patient would subsequently need radioactive iodine administration, and it can be only justified in very particular clinical situations such as in undifferentiated or RAI-refractory thyroid cancers.

The different diagnostic imaging studies should be registered to the planning CT for more accurate target delineation. Uncertainties related to image fusion should be considered in the treatment planning process.

Table 9.1 Recommended target volumes and radiation doses

Target volume	Target coverage	Dose
Gross tumor volume (GTV)	Gross primary tumor, involved surrounding structures, regional lymph nodes	70 Gy (RBE)
High-risk clinical tumor volume (CTV_{66})	Areas of positive surgical margin or shave excision or extranodal extension	66 Gy (RBE)
At risk clinical tumor volume ($CTV_{54–60}$)[a]	Areas at risk of microscopic disease primary include tracheoesophageal groove and >5 mm around GTV and CTV_{66} In the postoperative setting, include surgical bed. If tracheostomy is performed, include tracheostomy stoma. Neck: in node-positive disease, include nodal levels II–VII and upper mediastinum to the level of the carina. Level V should be covered in the node-positive neck. Consider coverage of level I and retropharyngeal nodes in the setting of bulky neck disease	54–60 Gy (RBE)

[a]Uninvolved nodal regions may be treated to 54 Gy(RBE) at the discretion of treating physician. In select cases, the lateral necks can be omitted despite having pathologic lymph nodes. Please consult your surgeon

The target volumes and doses are customized for each patient according to the risks of local and regional recurrence [13, 14]. Suggested doses and target volumes are shown in (Table 9.1).

The target volumes should be expanded typically between 3 and 7 mm depending upon institutional image guidance capabilities and range uncertainty criteria selected by physics. At our institution, proton-based planning target volumes are usually comprised of 5 mm setup margin in all directions, with additional 2 mm of radial margin to account for penumbra laterally and range margins in the direction of the beam determined by the physics team.

The recommended fractionation size of the CTVs is 1.8–2.0 Gy(RBE).

9.3 Patient Positioning, Immobilization, and Treatment Verification

Simulation and treatment should be conducted in the supine position.

To allow for strict immobilization of the head, neck, and shoulder regions, a thermoplastic mask should be used.

At our institution we have selected a base of skull (Qfix® Systems, BoS™) frame assembly with a five-point mask made out of kevlar (Fig. 9.1).

Daily position setup verification should be done with orthogonal X-rays or if available with volumetric imaging.

During the course of the treatment, we recommend a verification CT scan to assess changes in the anatomy of the patient (due to tumor shrinkage, weight loss, etc.). Significant changes may necessitate treatment replanning. These scans are usually ordered during the middle of these treatments around the onset of the fourth week followed by another one in the fifth week.

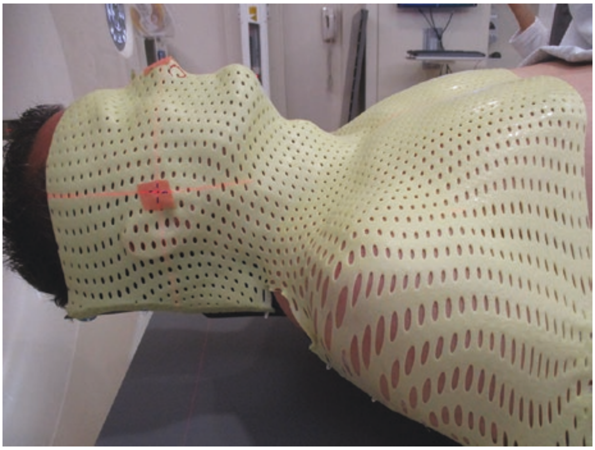

Fig. 9.1 Example of our patient immobilization setup

9.4 Three-Dimensional (3D) Proton Treatment Planning

9.4.1 Passive Scattering (PS)

In cases where scanning beam delivery is not available to treat thyroid cancers, passive scatter treatments can be planned with use of apertures and compensators and beam arrangements consisting of combinations of posterior and anterior oblique requiring craniocaudal tilts. This is to avoid any overlaps or patch within air cavities or in any critical structures such as larynx and esophagus regions. Field size limitations should be kept in mind when creating match fields. Some machines, depending upon the small, medium, or large snout size capabilities, will require either multiple isocentric treatments or larger couch kicks. In either case, match line feathering would be necessary to reduce sharp gradients at the junctions. Additionally, whenever planning with a posterior beam angles, care should be taken with placement of the isocenter in order to avoid potential collisions with the nozzle. One must avoid going through heterogeneities and any high atomic number material present in dental hardware if any. Material-specific relative stopping power value needs to be assigned to the CT value of the material [15]. A routine practice being followed in our clinic is to obtain the sample from surgery and determine the material type and components from the vendors. This is oftentimes then also followed by actual measuring of the relative stopping power in our proton beamline, and thereafter a proper Hounsfield unit gets assigned as depicted in Fig. 9.2. Instances which may/will require CT HU data to be overridden include:

- Tumor margin extending into the lung or deep air pockets that are surrounded by tissue
- Surgical clips (or foreign objects in general)
- Streaking artifacts resulting from high-density artifacts

Design of compensators and apertures is a crucial task for planning these cases as there are significant amounts of midline structures that need to be spared. And due to heterogeneities with the air cavities and bone, there are difficulties maintaining good distal end coverage. This oftentimes requires border smoothing. Care must be taken

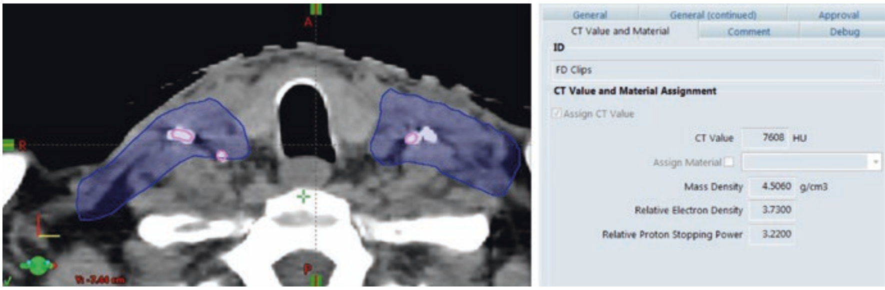

Fig. 9.2 Contouring of high-density structures in proton planning

when applying any border smoothing as it usually reduces dose conformity. To mitigate this, one would then require additional beams which depend on individual cases being planned. Aperture designs should account for air gaps and snout positions in cases of movable snouts. Compensators should be carved out with an appropriate smearing radius (SR) that will allow smooth SOBPs and few perturbations due to conical ridges. Smearing radius can ensure distal coverage; however, it can lead to reduced dose conformity, as discussed, and can be mitigated with additional beam angles.

Ideally one should use less than five beams. In general the workflow of a passive scattered beam line is much more complicated and requires very careful pre-planning preparations as listed below.

9.4.2 Pencil Beam Scanning (PBS)

With modern-day accelerators offering smaller spot sizes and use of range shifters, it has become possible to design highly conformal 3D proton plans without need for multiple beams, compensators, and apertures. The air gap between the patient and the treatment nozzle should be minimized allowing for a smaller spot size. Various methods include the use of a range shifter and/or bolus.

Usually for most of the head and neck cases, we tend to maintain the air gap as small as possible. There are different proton delivery solutions available with some allowing snout movements, while others are some sort of fixed nozzle solutions or patient-related range shifters. However, irrespective of the solution employed, one must try to minimize the air gap between the patient's external and the surface of any energy absorbers in order to keep the spot sizes small.

Scanning beam allows a greater degree of control of the dose distributions in both lateral and proximal distances. With the advent of scanning-based treatment delivery systems, one can perform unique dose painting thereby conforming therapeutic doses to tumor volumes while offering significant sparing of normal tissues. In thyroid cancer, oftentimes, the submandibular glands, oral cavity, parotids, pharyngeal constrictors, and upper larynx can be spared to a greater extent. Since the regions of interest are both distal and lateral to the tumor volumes, it is necessary to choose beam angles and lateral margins judiciously. In most of the cases, a good dose distribution can be achieved with a combination of an anterior-posterior beam angles. This approach requires the physics planning team to design beam-specific optimization target volumes as they apply to each clinical case. At our institution, in addition to the lateral margins and the range

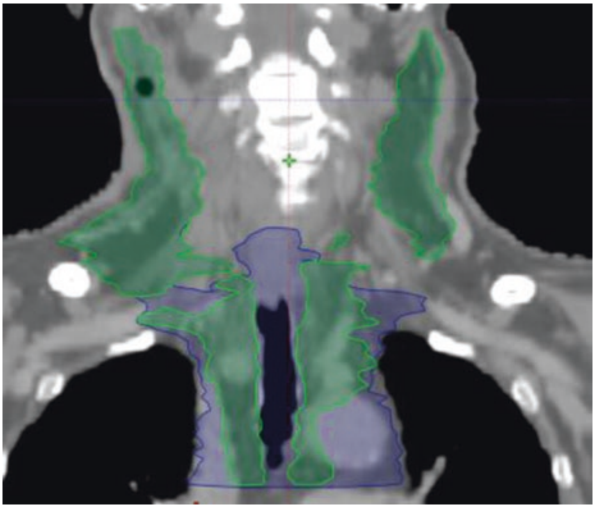

Fig. 9.3 Sub-target volume cropping

margins in the direction of the beam, one spot sigma lateral margin is added to the optimization volume in the beam properties. From our planning studies, we observed a pair of anterior and posterior beam angles suffice achieving highly conformal dose distributions with IMPT. When optimizing to more than one target volume to different dose levels, care must be taken to not have any overlapping margins within the target structures. For an example, if a plan involves two targets, CTV1 and CTV2, where the dose to CTV1 > CTV2, then Boolean operations will have to be used:

CTV1 (high-risk volume) = no Boolean operation needed

CTV1sub = CTV2 − CTV1

where CTV1sub is a new structure as seen in Fig. 9.3 on the right in *blue*. Care must be taken to not alter physician-drawn CTVs as the final dose assessments should be made to the original CTVs.

Generating a robust plan without any computer-assisted robust optimization requires precise preparation of planning structures through which the fluence can be shaped and spot placements can be controlled within and around the target volumes. In our clinic this was achieved by generating optimization target volume (OTV) structures which were beam specific and were carved out around the parotid, submandibular gland (SMG), and the oral cavity. An example shown on Fig. 9.4 is a typical 2 mm cropping of our OTV from the SMG. Typically with these arrangements, one is able to achieve adequate target coverage with robust organ at risk (OAR) sparing. In order to obtain adequate robustness, our OTVs consisted of 3% of the range compounded with 2–3 mm of setup errors which have been established based on our clinical experience and image guidance capabilities. Criteria for evaluating robustness are mostly institutional dependent. For our clinic we evaluate all our head and neck tumors against a setup uncertainty of 3 mm compounded with 3% CT to relative stopping power-based range errors [16]. As an example, based on Eclipse™ (Varian Medical Systems, Palo Alto, CA) Treatment Planning System Ver. 13.6 at our institution, we are able to achieve conformal and robust target coverages. The robustness of our plans is measured as D95 and V95 target doses under worst case scenarios (setup and range).

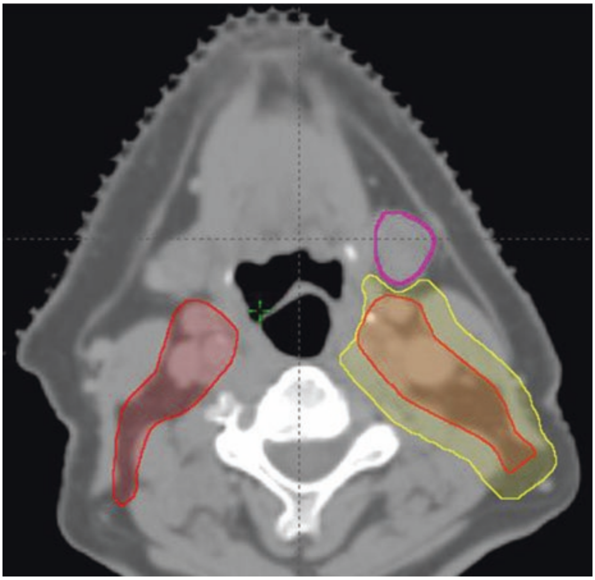

Fig. 9.4 Cropping of OTV from the left submandibular gland (2 mm)

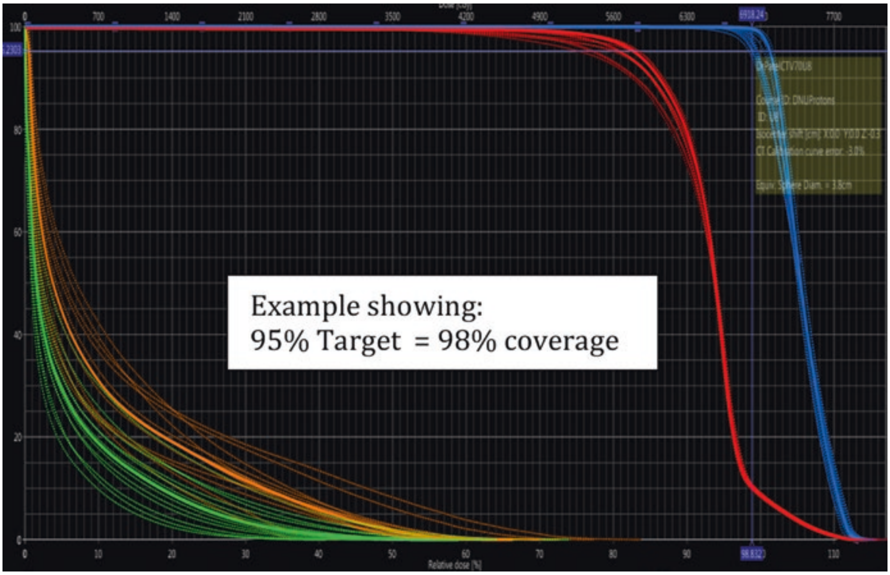

Fig. 9.5 Thyroid plan robustness. DVH band indicates 95% of the target is receiving 98% of the prescription dose

An example of one of the thyroid plan's robustness (Fig. 9.5) is displayed in the DVH band indicating 95% of the target receiving 98% of the prescription dose with 3% and 3 mm setup and range uncertainties. Also, with any opposite beam arrangements, it is important to evaluate inter-field robustness. Essentially, the field tapering and the gradients produced at match lines should be evaluated very carefully for any cold or hot spots shown in Fig. 9.6. We evaluate all our match lines for smooth dose falloffs. It

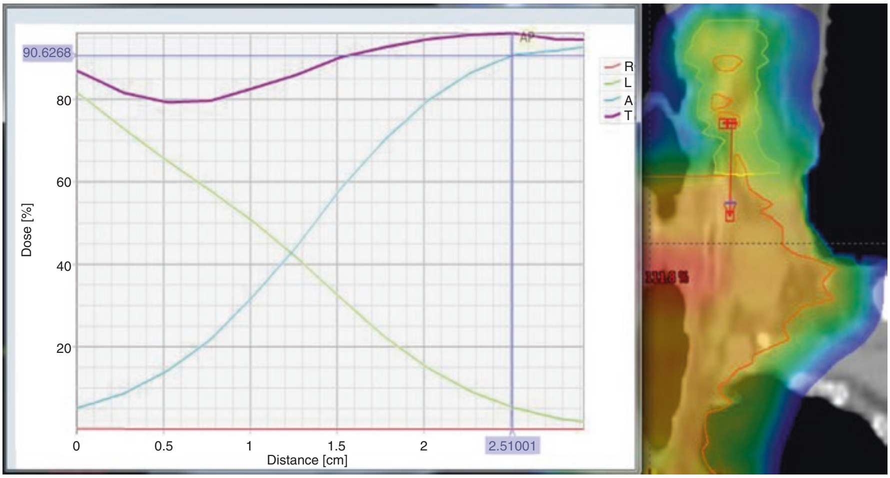

Fig. 9.6 Match lines for smooth dose falloffs

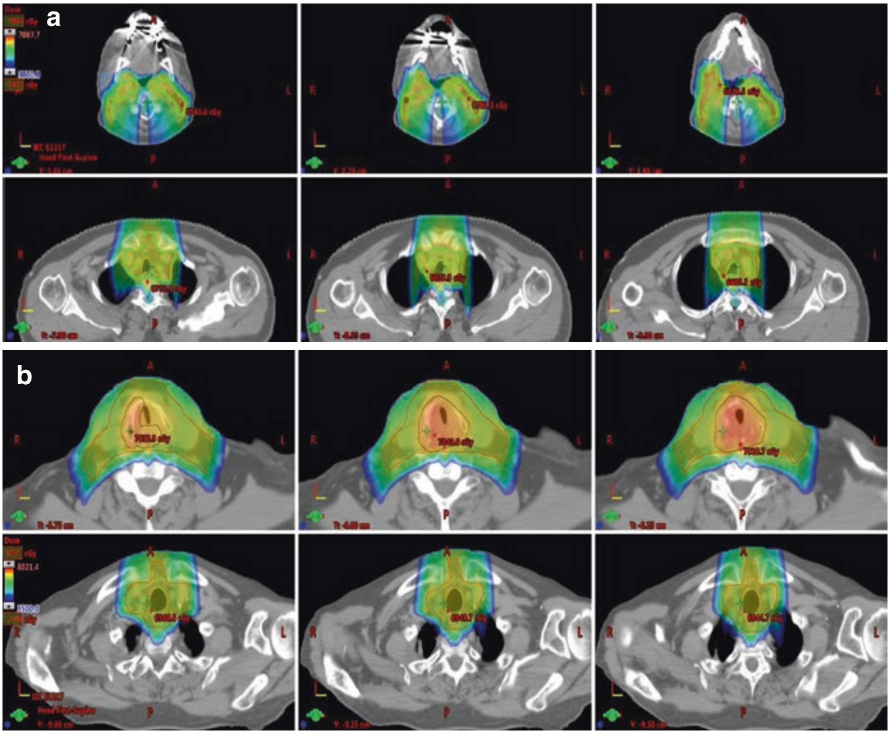

Fig. 9.7 (**a**) A 70-year-old man with anaplastic thyroid cancer involving the right neck, s/p total thyroidectomy, and right modified radical neck dissection. Postoperative chemoradiation therapy was recommended to the thyroid bed, central compartment, cervical neck levels II–VII, and mediastinal lymph nodes to the carina (CTV_{60}). (**b**) A 79-year-old man with recurrent Hurthle cell cancer, s/p total thyroidectomy, and subsequent radioactive iodine documented with local recurrence was recommended definitive radiation therapy to the area of gross disease, central compartment, and bilateral cervical neck levels II–VII (CTV_{70} and CTV_{56})

Table 9.2 Recommended dose constraints to OARs when using proton beam therapy with PBS technique for treatment of thyroid cancer

Organ at risk	Recommended dose constraint
Oral cavity	Mean < 39 Gy (RBE)
Parotid	Mean < 26 Gy (RBE)
Submandibular gland	Mean < 39 Gy (RBE)
Larynx	Mean < 44 Gy (RBE)
Constrictors	Mean < 55 Gy (RBE)
Esophagus	Mean < 34 Gy (RBE)
Spinal cord	Max point dose <45 Gy (RBE)
Brachial plexus	Max point dose <65 Gy (RBE)
Lung	Mean < 20 Gy (RBE), V20 < 37%

These recommendations are adapted from photon/IMRT treatment planning data

should also be noted, since these are mono-isocentric treatments and do not require moving patient support systems between the deliveries of two fields, we can ensure robust intrafractional dose delivery with the immobilization system discussed earlier. Overall, we are able to reach highly conformal target coverage with significant sparing of healthy tissues. Scanning beam offers greater flexibility in calculating a simultaneous integrated boost volume plan with both SFUD and IMPT planning techniques. Shown below in Fig. 9.5a and b, we have dose color wash for cases planned to 60 Gy(RBE) in 30 Fx to a single target (Fig. 9.7a) and dose painting to multiple targets (CTV 70 and CTV 56) in Fig. 9.7b.

9.5 Dosimetric and Toxicity Comparison

The use of proton beam radiation therapy (PBRT), particularly with PBS, for definitive or postoperative cases of thyroid cancer can result in a significant reduction in the dose delivered to different organs at risk (OARs) and potentially translates to a reduction of treatment toxicities compared to photon techniques (Table 9.2) [14].

Efforts should be made by the planner to achieve the lowest dose possible for all normal tissues after maximizing the target coverage.

Dose volumetric comparisons of treatment plans with IMRT or PBRT done at our institution have demonstrated significant dose reduction to the oral cavity, parotids, submandibular glands, upper larynx, pharyngeal constrictors, spinal cord, and lung. With this emerging technique, we hope this will translate in lower rates of acute toxicity including oral mucositis, xerostomia, dysgeusia, and dysphagia and decreased late toxicity such as radiation pneumonitis, brachial plexopathy, and secondary malignancy.

9.6 Future Developments

As proton therapy becomes more available and with better imaging quality verification, the use of PBS with IMPT can be more routinely used for the treatment for thyroid cancers when clinically indicated with the dosimetric advantages of this modality and the benefit of reduced toxicity.

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