Chapter

Adaptive Proton Therapy in Head and Neck Cancer

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Abstract

Anatomic and dosimetric changes occur in head and neck cancer during fractionated proton radiotherapy, and the actual dose received by patient is considerably different from original plan. Adaptive radiotherapy aims to modify treatment according to changes that occur during proton therapy. Intensity modulated proton therapy for head and neck cancer (HNC) patients benefitted by adaptation to correct the dose perturbations caused by weight loss, tumor volume changes, setup and range uncertainties. The following sections have elaborated the rationale of adaptation in HNC, proton physics in HNC, studies comparing non-adaptive and adaptive intensity modulated proton therapy (IMPT) plans, reasons for adaptation and how to mitigate these changes.

Keywords: adaptative radiotherapy, proton, intensity modulated, head and neck cancer, anatomic changes, dosimetric changes, uncertainties

1. Introduction

Intensity Modulated Radiation Therapy (IMRT) with photons has become standard treatment for locally advanced head and neck cancer (HNC) because of its high conformality and better sparing of critical structures [1–3]. However proton therapy using spot scanning (Intensity Modulated Proton Therapy-IMPT) has shown superior dose distribution compared to IMRT in head and neck cancer patients [4–8]. The physical characteristics of proton i.e., its ability of sharp distal fall of inside tissue made substantial advantages over photon therapy. The unnecessary radiation to organ at risks (OARs) and nearby healthy tissues was significantly reduced with proton when compared with photons. The advantages of proton therapy (over photon) in head and neck malignancies have already documented in literature [9, 10]. Protons significantly reduce the risk of xerostomia, dysgeusia, dysphagia, tube feeding dependence and hypothyroidism.

During radiation treatment of Head and neck cancer, changes in anatomy occur like shrinkage of tumor and normal tissues, which is in response to radiation and combined chemotherapy. So plan adaptation is desirable to optimally treat these patients undergoing anatomical modifications and weight loss. These little alterations during proton therapy lead to huge dosimetric changes (like high dose to normal structures and low dose to target volume) because of sharp dose fall off between target volume (TV) and OAR, thus leading to increased complications and marginal failure. The influence of anatomical changes for proton therapy is more pronounced due to range uncertainties. To counteract these limitations, the best

possible strategy is Adaptive Radiotherapy (ART) of proton, i.e., repeat imaging and repeat planning to adapt to actual patient anatomy.

2. Physics: HNC

The anatomy of head and neck is complex and tumor is surrounded by many critical structures or organ at risk (OAR) like parotid, spinal cord, constrictors, thyroid etc.

The physical properties of protons are very useful for the treatment of these cancers. The physical properties of photon Vs proton are depicted in **Table 1**. Protons travel a well-defined distance, losing energy at an increasing rate before stopping, forming the characteristic Bragg peak. The distal penumbra is limited and is well adapted to the treatment of head and neck cancer. Besides this, a therapeutic beam can be produced by (a) Passive Scattering Proton Therapy (PSPT), i.e., where narrow monoenergetic beam pass through a range modulation wheel and scattering it laterally to cover the tumor volume, (b) Pencil Beam Scanning (PBS), i.e., scanning the narrow (pencil) beams magnetically by energy layers. To create homogenous depth dose, the Spread Out Bragg Peak (SOBP) is created by summing of all pristine Bragg peaks.

Passive Scattering PT is not well adapted to the complex anatomies of head and neck cancer compared to pencil beam scanning. In PSPT, the dose distribution is conformed laterally with an aperture, and range uncertainties are minimized through range compensator smearing. In large volume tumors, field junctions are used, known as beam patching. While beam patching is sensitive to set-up uncertainties. However, in Pencil Beam Scanning (PBS), the beam is scanned magnetically which facilitates intensity modulation and allowing to treat tumor surrounded by complex anatomies.

In PBS, there are two different optimization techniques:

i. Single-field optimization (SFO) and

ii. Multi-field optimization (MFO/IMPT).

In the SFO approach, each beam is optimized independently to achieve a uniform dose to the target. SFO is quite robust to changes. With IMPT, the optimization

Variable	Photon	Proton
At beam entrance	i. Maximum dose in beam path	i. No maximum dose, Flat entrance dose
	ii. Skin sparing effect present (build up dose after certain depth)	ii. No skin sparing effect
Around target	No distal fall off	Distal fall off seen (proton stop)
After target	Exit dose seen	No exit dose (no dose behind target)
Laterally	Lateral penumbra is stable relative to depth	Lateral penumbra increase with depth
Everywhere	Electron contamination	Neutron contamination

Table 1.
Physics: photon vs proton.

process simultaneously optimizes the intensities of the spots from all of the beams, thereby irradiating the tumor heterogeneously with each beam but providing a uniform dose to it. IMPT is therefore more relevant for the complex head and neck anatomy and OAR constraints. IMPT is clearly less robust than SFO in the presence of uncertainties.

The advantage in IMPT, we can use multiple field arrangements for better curvilinear dose distributions around critical structures and this is less easily achieved with single field optimization. The critical structures are better spared in MFO/IMPT than SFO. The MFO plan can be made more robust by taking into account setup and range uncertainties during optimization.

3. Dosimetric studies

In photons, adaptive planning is done mainly because of change in size of tumor and relative shift in critical structures. While in protons, the sharp dose fall off and air-borne interface (different stopping power) makes proton very sensitive to variations in treatment depths. Proton therapy is more susceptible to tissue density heterogeneities as proton range is density dependent. In the proton beam path if bone is present the beam is pulled back, while beam is pushed forward if air is in the path.

Multiple studies have shown that proton therapy in head and neck malignancies produce similar or better target coverage and conformity than IMRT. Minor variations in change in anatomy would result in significant change in dose distribution in proton therapy. Very few studies have quantified the degree of dose variations during treatment for patients undergoing IMPT. The three studies are summarized in **Table 2**.

Parameter	**Simone et al., 2011 [11]**		**J Gora et al., 2015 [12]**		**Wu et al., 2017 [13]**	
Number	n = 10		n = 6		n = 10	
Location	oropharynx		oropharynx, hypopharynx		oropharynx	
Prescribed dose (GyE)	70		70, 63, 56		70	
Timing of replanning	After 36 Gy (week 4)		Week 4		Week 4	
IMPT plan	Non-adaptive	Adaptive	Non-adaptive	Adaptive	Non-adaptive	Adaptive
BS (Dmax, Gy)	31.3	29	24.7	21.1	10.15	9.8
SC (Dmax, Gy)	30.5	28.4	25.3	20.8	10.95	10.58
I/L parotid (Dmean, Gy)	32.9	29.8	—	—	7.64 (Rt parotid)	7.26 (Rt parotid)
C/L parotid (Dmean, Gy)	19.5	18.3	20.7	20.8	8.73 (Lt parotid)	8.75(Lt parotid)
Glottic larynx (Dmean, Gy)	35.3	31	39.4	45.9	—	—

IMPT-intensity modulated proton therapy, BS-brain stem, SC-spinal cord, I/L-ipsilateral, C/L-contralateral.

Table 2.
Studies showing dosimetric results and comparison between non-adaptive and adaptive IMPT plans.

4. Reasons for adaptation

i. Target deformation:

In patients of head and neck cancer treated with photons, various studies shown that the reduction in target volume ranges from 5 to 13% during treatment [14–16]. In Gunn et al. [17], out of 50 patients of oropharyngeal cancers treated with IMPT, in view of weight loss and tumor volume changes 19 patients (38%) had adaptive replanning.

ii. Anatomical and OAR deformation

The potential anatomical changes are weight loss, decrease in size of surgical flap, reduction in swelling, parotid gland shrinkage etc. [16, 18, 19]. **Figure 1** depicts the reasons of replanning.

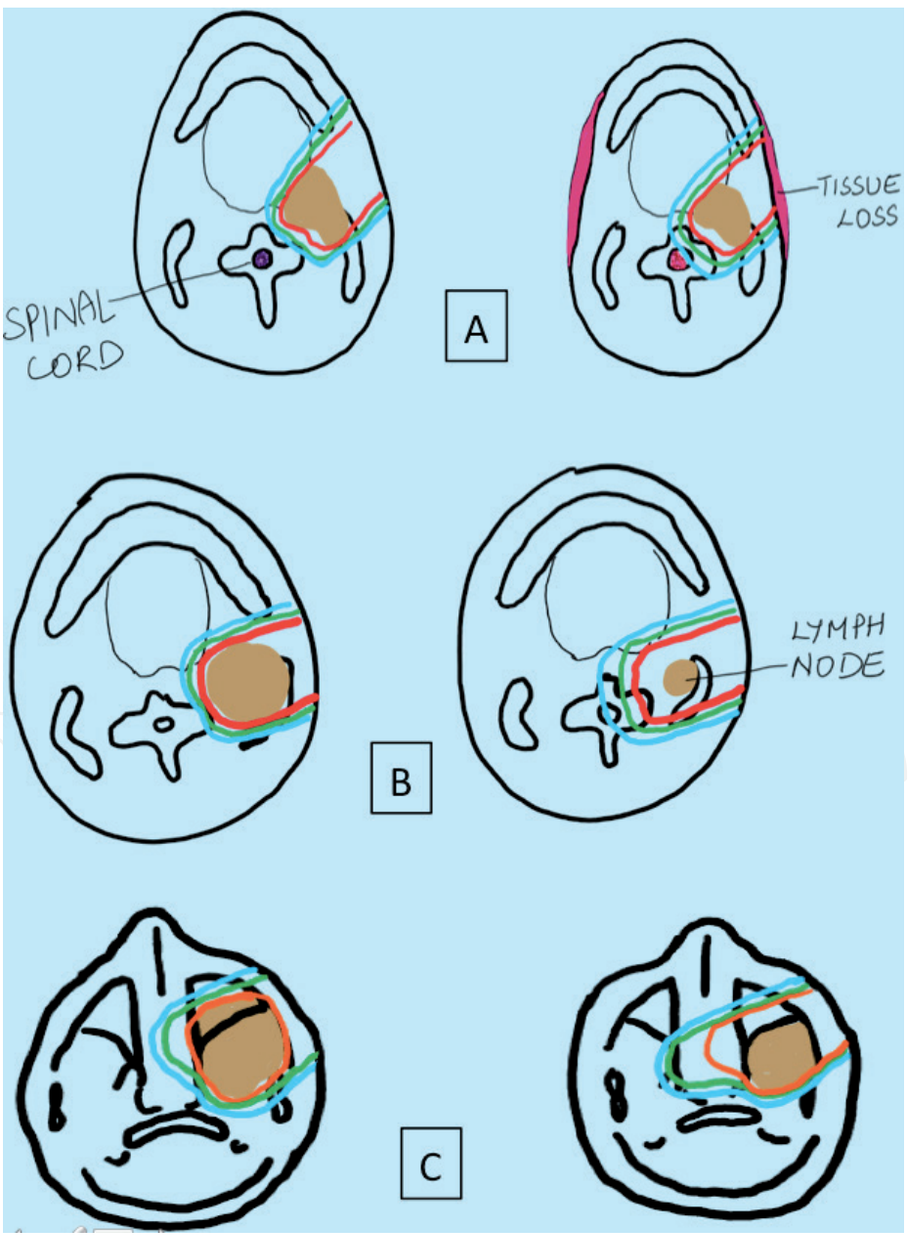

Figure 1.
Reasons for adaptation: (A) anatomical change – weight loss, (B) target deformation – nodal response, and (C) beam path change.

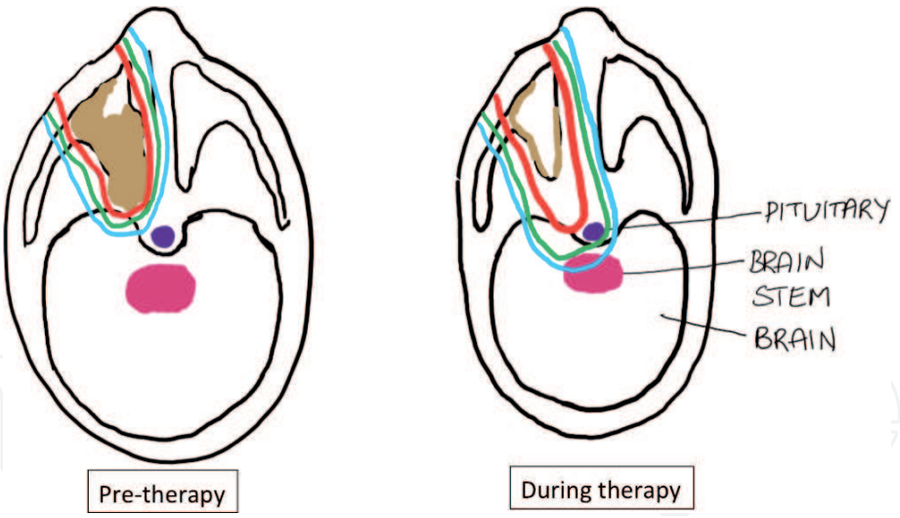

Figure 2.
The variation in filling of maxillary sinus affecting dose distribution during treatment.

iii. Beam path change

As proton range is density dependent, it is more susceptible than photons. The nasal cavity and paranasal sinuses region contains variable amount of complicated structures such as bone, mucosa, tumor tissue, collected fluid, and air, which can alter the different proton beam ranges. Variations in air and fluid content in the nasal cavity and paranasal sinuses during the course of radiotherapy could affect the proton dose distribution. Clearing or opacification of sinuses may result in shift of the high dose deposition, potentially lead to change in dose to the targets and critical structures (**Figure 2**). Late toxicities such as brain injury, cerebrospinal fluid leakage, and vision loss have been reported for patients with head and neck cancer patients treated with proton or carbon therapy [20–22].

In a study by Fukumitsu et al., twenty patients of nasal and paranasal sinuses received proton therapy and in 18 out of 20 cases, the air content in the cavities increased. This resulted an increase in dose to brainstem above 60Gy in 3 patients and increase in dose above 50Gy in 10 patients [23]. Susharina et al. also demonstrated that change in aeration in vicinity of target lead to decreased dose to target (5%) and increased dose to optic structures and brain stem [24].

iv. Uncertainties

The main factors leading to range uncertainty are

a. Range calculation in TPS

   i. Inaccuracies arising from CT (HU to stopping power conversion, CT reconstruction, HU uncertainty like metal artifacts, partial volume effect)

   ii. Inaccuracies arising from dose algorithm

b. Discrepancies between planned and delivered dose – like geometric changes (setup and motion) and density heterogeneities.

5. Practical considerations

The process of adaptive radiotherapy identified by weight loss, mask fitting, changes in patient setup, regularly planned intervals, treatment response assessed by CBCT scans, diagnostic CT or MRI scans (tumor shrinkage), recalculating the dose delivered to targets and OARs.

The other approaches are planning QACT (quality assurance CT) at regular intervals (after every 10 fractions) as reduction in parotid and target volumes occur in early third week resulting in huge dosimetric differences. In the modern proton therapy, image guidance with daily CBCT helps in identifying the anatomical changes and early treatment response.

The IMPT treatment uncertainties can be mitigated by robust optimization. The robust optimization technique is a robust plan generated using CTV as primary target and not requiring geometrically expanded PTV. The robust optimization method takes into account setup and range uncertainty directly during spot weighting. Therefore it does not need extra volume to be irradiated.

There is no consensus on most appropriate timing regimen for adaptation/replanning during proton therapy.

6. Conclusion

Proton therapy in head and neck cancer is associated with tissue and target volume changes leading to higher doses to normal tissues (salivary glands/DARS). Adaptation once or twice in middle of treatment will reduce unnecessary doses to parotid, swallowing structures etc., thus improving patient's quality of life by reducing the risk of xerostomia and tube feeding dependence.

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Conflict of interest

Nil.

Nomenclature

ART	adaptive radiotherapy
BS	brain stem
CBCT	cone beam computed tomography
CT	computed tomography
C/L	parotid-contralateral parotid
DARS	dysphagia/aspiration at risk structures
HU	Hounsfield Unit
HNC	head and neck cancer
I/L	parotid-ipsilateral parotid
IMRT	intensity modulated radiation therapy

IMPT	intensity modulated proton therapy
MFO	multi field optimization
MRI	magnetic resonance imaging
OARs	organ at risk
PBS	pencil beam scanning
PSPT	passive scanning proton therapy
SFO	single field optimization
SC	spinal cord
TV	target volume

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