Dose constraints for the temporal lobes during the optimization of intensity-modulated radiotherapy treatment plans for nasopharyngeal carcinoma

Background

Nasopharyngeal carcinoma (NPC) is common among Asians, especially in Southern China. Radiotherapy (RT) has been the mainstay of treatment for patients with non-disseminated NPC due to its anatomic location and radiosensitivity. In the management of NPC, incidental irradiation of the temporal lobe with consequent long-term injury is one of the most feared complications after radical radiotherapy, as it is can be devastating for patients and is associated with severe impairment of quality of life. Lee et al. reported a 3% cumulative incidence of temporal lobe injury (TLI) after 2D-RT in a series of 4527 patients [1]. In another study, Lee et al. showed that 64 Gy irradiation (at conventional daily fraction of 2 Gy daily) would lead to a 5% necrotic rate in temporal lobes at 10 years after 2D-RT in NPC patients [2].

Intensity-modulated RT (IMRT) is a major breakthrough in the treatment of NPC, and it was capable of producing highly conformal dose distributions with steep dose gradients and complex isodose surfaces [3]. The design of appropriate dose constraints for the organs at risk (OAR) during the optimization of IMRT treatment plans can enable significantly better OAR sparing and reduce subsequent complications. IMRT technique can reduce the volume of high dose areas in the temporal lobes and thereby reduce risk of toxicities, compared with 2D-CRT [4, 5].

IMRT offers detailed volumetric parameters for temporal lobes based on dose-volume histogram (DVH). Some studies investigated the correlation between the incidence of TLI and IMRT dosimetric parameters. A retrospective study reported by Su et al. demonstrated that the 5-year incidence of TLI for a maximum dose of 64-68Gy or D1cc (the dose delivered to the 1 cubic centimeter volume, Gy) of 52-58 Gy was less than 5.0% after IMRT [6]. Similarly, a recent retrospective analysis of 20 patients with NPC and unilateral TLI showed that a dose of 69 Gy delivered to D0.5cc may be the dose tolerance of the temporal lobes after IMRT [7]. In our previous

study, we reported that the D1cc was the only independent predictor for radiation-induced TLI and estimated that the biologically equivalent tolerance doses at 2 Gy for the 5%,10% and 50% probabilities at 5 years to develop TLI were 62.83 Gy equivalents, 66.67Gy equivalents and 77.58 Gy equivalent, respectively [8]. However, only a few publications have quantified the risk of TLI complications in terms of normal tissue complication probability (NTCP) models.

Recently, we apply on five NTCP models, including (1) Lyman model and (2) logit-formula with dose-volume histogram (DVH) reduced to generalized equivalent uniform dose (EUD), (3) serial reconstruction unit (RU) model, (4) Poisson-EUD model, and (5) mean dose model for TLI to a population of 351 NPC patients treated with IMRT.As assessed qualitatively and quantitatively, the Lyman-EUD model fitted the data very well. The tolerance dose (TD) for the 5% and 10% probabilities of TLI development were 77 Gy and 80.4 Gy for Dm given in 2-Gy fractions (α/β ratio, 3) in the current study (Manuscript has not been published).

According to the ICRU 83 report [9], overlap between the planning target volume (PTV) and the planning organ at risk volume (PRV) leads to a volume that is shared by two contoured volumes. A conflict can occur if the planning aims of the overlapping contoured volumes lack a common desired absorbed-dose range. To ensure that the conflict does not occur in the planning aims, at least two different methods can be applied. One method is based on subdivision of the volumes. Subdivision of the PTV of the gross target volume (PTVnx) into regions with different prescribed absorbed doses (PTVsv1,PTVsv2 ,PTVsv2 is the overlaps between PTVnx and temporal lobe) can be used in cases for which the PTVnx overlaps temporal lobe. When the volume of PTVsv2 is less than 0.2 cubic centimeter (cc), the prescribe dose for PTVsv2 is as the same as that of the PTVsv1, D1cc 63.1Gy, Dmax 72.9Gy for TL (32 fractions). When the volume of PTVsv2 is between 0.2 cc and 0.5cc, the prescribe dose for PTVsv2 is 66Gy, D1cc 63.1Gy, Dmax 72.9Gy for TL (32 fractions). When the volume of PTVsv2 is between 0.5 cc and 1cc, the prescribe dose for PTVsv2 is 66Gy, D1cc 65.8Gy, Dmax 75.2Gy for TL (32 fractions). A study by Ng et al. showed that the 5-year local failure-free rate dropped to 54% if more than 3cc volume within the gross primary tumor was under-dosed to below 65.5 Gy, compared with 90% in patients with smaller under-dosed volumes [10]. So, it is reasonable that prescribe dose for PTVsv2 is 66 Gy. The purpose of this prospective study is to evaluate the feasibility of dose constraints based on D1cc and Dmax for the temporal lobes following IMRT for NPC.

Reference

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Inclusion Criteria:

- Newly-diagnosed and confirmed histopathologic diagnosis of nasopharyngeal squamous cell carcinoma, types WHO II-III, Stage I-IVA (AJCC staging, 2017, 8th edition), treated with intensity-modulated radiotherapy.
- No head and neck surgery of the primary tumor or lymph nodes except for incisional or excisional biopsies.
- Age between 18 years and 70 years
- Karnofsky score ≥80
- WBC≥ 4,000/ul, platelet ≥ 100,000/ul; serum creatinine≤ 1.6 mg/dl or 24hr. calculated creatinine clearance ≥ 60 ml/min.
- Must undergo pre-treatment evaluation of tumor extent and tumor measurement Tumor may be measurable or evaluable.
- Signed study-specific consent form prior to study entry.

Exclusion Criteria:

- Stage IVB
- Evidence of distant metastases
- Previous irradiation for head and neck tumor ≤ 6 months prior to study entry
- Previous chemotherapy ≤ 6 months prior to study entry
- Patient is on other experimental therapeutic cancer treatment
- Other malignancy except non-melanoma skin cancer or a carcinoma not of head and neck origin and controlled at least 5 years

- Active untreated infection
- Major medical or psychiatric illness, which in the investigator's opinions, would interfere with either the completion of therapy and follow-up or with full and complete understanding of the risks and potential complications of the therapy
- Pregnant women

Pretreatment evaluation

Each patient must have completed the following studies within six weeks prior to study entry unless otherwise indicated.

Complete history and physical exam including weight and performance status.

Complete diagrammatic and descriptive documentation of the extent of the primary and regional (if any) following appropriate endoscopic procedures.

Complete dental and nutritional evaluation. Any required dental repairs must be made and prophylaxis instituted prior to radiotherapy.

Completion of the following laboratory studies within 14 days of study entry: CBC and platelet count; serum creatinine, creatinine clearance, BUN, EBV-DNA, serum pregnancy test for women.

Completion of the following laboratory studies within six weeks of study entry: liver function tests including AST, bilirubin, alkaline phosphatase.

Completion of the following radiologic studies within 6 weeks prior to study entry:

Chest CT scan

An MRI of head and neck with T1 contrast with gadolinium and T2 sequences is required.

Abdominal ultrasonography

Bon scan

Radiotherapy

All patients were immobilized in the supine position with a thermoplastic mask. After administration of intravenous contrast material, 3mm CT slices were acquired from the head to the level 2cm below the sternoclavicular joint. Target volumes were delineated according to the International Commission on Radiation Units and Measurements Reports(ICRU)50 and 62. The primary nasopharyngeal gross tumor volume (GTVnx) and the involved cervical lymph nodes were

determined from the imaging, clinical, and endoscopic finding.The enlarged retropharyngeal nodes were outlined, together with primary GTV, as the (GTVnx) on the IMRT plans. The first clinical tumor volume (CTV1) was defined as the GTVnx plus a margin of 5-10mm for potential microscopic spread, including the entire nasopharynx mucosa plus a 5mm submucosal volume. The second CTV (CTV2) was defined by adding a margin of 5-10mm to CTV1 (when CTV2 was adjacent to critical organs such as brain stem and spinal cord, the margin was reduced to 3-5mm) and included the retropharyngeal lymphnodal regions, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus, and posterior edge of the nasal cavity and maxillary sinuses. The upper neck was also included in CTV2. Elective level IB irradiation was decided by the attending physician. The lower neck and the supraclavicular fossae were treated with a single anterior split field by conventional RT. Planning target volumes(PTVs) for all gross tumor volumes and CTVs were generated automatically after delineation of tumor targets according to the immobilization and localization uncertainties. A simultaneous integrated boost method was used. The prescribe dose was 66-70Gy to the PTV of the GTVnx, 60Gy to the PTV of CTV1(i.e., high-risk regions),54-56Gy to the PTV of CTV2 (i.e., low-risk regions),and 60-70Gy to the PTV of the GTVnd for the metastatic cervical lymph nodes in 30-33 fractions. For the GTV and CTV, the target volumes that received more than 95% of the prescribed dose were used to reflect the target coverage. The dose received by each critical organ except temporal lobe was limited to tolerance according to the RTOG 0225 protocol.

Dose constraints for the temporal lobes: D1cc was the only independent predictor for radiation-induced TLI and estimated that the biologically equivalent tolerance doses at 2 Gy for the 5% and 10% probabilities at 5 years to develop TLI were 62.83 Gy equivalents and 66.67Gy equivalents, respectively The tolerance dose (TD) for the 5% and 10% probabilities of TLI development were 77 Gy and 80.4 Gy for Dmax in 2-Gy fractions (α/β ratio, 3). These D1cc and Dmax of temporal lobes are converted to different dose constraints based on different fractions. Subdivision of the PTV of the gross target volume (PTVnx) into regions with different prescribed absorbed doses (PTVnx, PTVsv2, PTVsv2 is the overlaps between PTVnx and temporal lobe) can be used in cases for which the PTVnx overlaps temporal lobe (Figure 1). For example, when the volume of PTVsv2 is less than 0.2 cubic centimeter (cc), the prescribe dose for PTVsv2 is as the same as that of the PTVsv1, D1cc 62.0Gy, Dmax 71.5Gy for TL (30 fractions), D1cc 63.1Gy, Dmax 72.9Gy for TL (32

fractions) and D1cc 63.7Gy, Dmax 73.6Gy for TL (33 fractions), respectively. When the volume of PTVsv2 is between 0.2 cc and 0.5cc, the prescribe dose for PTVsv2 is 66Gy, D1cc 63.1Gy, Dmax 72.9Gy for TL (32 fractions), D1cc 63.7Gy, Dmax 73.6Gy for TL (33 fractions), respectively. When the volume of PTVsv2 is between 0.5 cc and 1cc, the prescribe dose for PTVsv2 is 66Gy, D1cc 65.8Gy, Dmax 75.2Gy for TL (32 fractions), D1cc 66.4Gy, Dmax 75.9Gy for TL (33 fractions) , respectively (Table 1). If the volume of PTVsv2 is more than 1cc, dose constraints for temporal lobes is not protocolized, and is based on the discretion of the attending physician in individual cases.

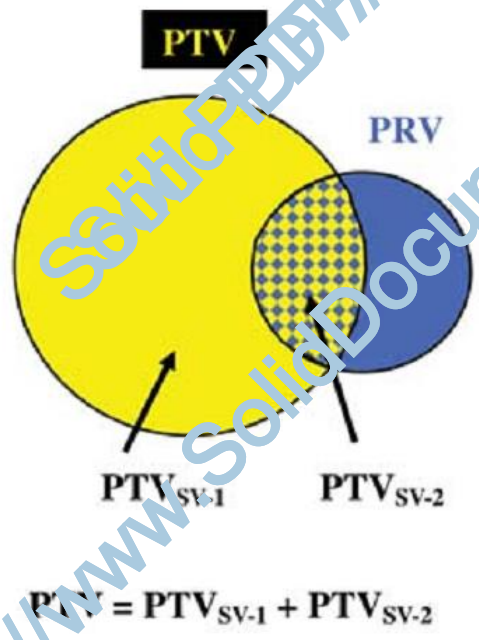

Figure 1. Subdivision of the PTV of the gross target volume (PTVnx) into regions with different prescribed absorbed doses (PTVsv1,PTVsv2, PTVsv2 is the overlaps between PTVnx and temporal lobe) can be used in cases for which the PTVnx overlaps temporal lobe.

Table 1. The relationship between dose constraints for the temporal lobes and the incidence of temporal lobe injury (TLI).

Total dose70Gy/fractions	Incidence of TLI	Volume of TL D1cc	TL Dmax
30	5%	62.0	71.5
	10%	64.6	73.7
32	5%	63.1	72.9
	10%	65.8	75.2
33	5%	63.7	73.6
	10%	66.4	75.9

Chemotherapy

Chemotherapy included concurrent chemotherapy, concurrent chemotherapy combined with induction chemotherapy and/or adjuvant chemotherapy. The regimens of induction chemotherapy and adjuvant chemotherapy included docetaxel and cisplatin (DP), gemcitabine and cisplatin (GP) and 5-Fu and cisplatin(PF). The DP protocol consisted of docetaxel 75mg/m2 IV on day 1, cisplatin 75 mg/m2 on day1. The GP protocol consisted of gemcitabine 1.0g/m2 IV on day 1, 8, cisplatin 75 mg/m2 on day1. The PF protocol consisted of cisplatin 80mg/m2 IV on day 1 and 5-Fu 800mg/m2d continuously IV on day 1-5. For patients who receive induction chemotherapy, both DP, GP and PF are repeated every 3 weeks for 2-3 cycles. This is followed by cisplatin 30mg/m2 IV weekly or

cisplatin 80mg/m2 IV on day1,22 during radiation. For patients who received adjuvant chemotherapy, regimens are repeated every 3 week for 3cycles. Chemotherapy is not protocolized and is used at the discretion of the attending physician in individual cases.

Follow up

After the completion of radiotherapy, all patients will be followed up every 1-3months during the first 2 years, every 6 months in years 2 to 5 and annually thereafter. During the follow-up sessions, disease status and treatment toxicity will be assessed by performing MRI to the head and neck region, chest radiograph, abdominal ultrasonograph, and physical examination. When indicated, as well as whole-body bone scan if required.

Statistical analysis

The sample size will be adjusted by 20% to account for patients that die within the 5 years and are not evaluable for the toxicity endpoint, and for ineligible or inevaluable (no data) cases. The total target accrual is 350 patients. The survival time is measured from Day 1 of RT completion to the date of the event or last follow-up visit. All analyses will be performed with SPSS software, version 19.0.The Kaplan-Meier method is used to calculate the overall survival (OS), local recurrence-free survival (LRFS) rates. Multivariate analysis will be done by using the Cox proportional hazard model to define independent predictors among various side effects.