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Original Article

Dosimetric Predictors of Hypothyroidism After Radical Intensity-modulated Radiation Therapy for Non-metastatic Nasopharyngeal Carcinoma☆

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Abstract

Aims: To investigate dosimetric predictors of hypothyroidism after radical intensity-modulated radiation therapy (IMRT) for non-metastatic nasopharyngeal carcinoma (NPC).

Materials and methods: Patients with non-metastatic NPC treated with radical IMRT from 2008 to 2013 were reviewed. Serum thyroid function tests before and after IMRT were regularly monitored. Univariable and multivariable analyses were carried out for predictors of biochemical and clinical hypothyroidism.

Results: In total, 149 patients were recruited. After a median follow-up duration of 3.1 years, 33 (22.1%) and 21 (14.1%) patients developed biochemical and clinical hypothyroidism, respectively. Eight (24.2%) patients who had biochemical hypothyroidism developed clinical hypothyroidism later. Univariable and multivariable analyses revealed that the volume of the thyroid ($P = 0.002$, multivariable), VS60 (the absolute thyroid volume spared from 60 Gy or less) ($P < 0.001$, multivariable) and VS45 ($P < 0.001$, multivariable) of the thyroid were significant predictors of biochemical hypothyroidism. The freedom from biochemical hypothyroidism was longer for those whose VS60 $\geq$ 10 cm^3 (mean 90.9 versus 62.6 months; $P < 0.001$) and VS45 $\geq$ 5 cm^3 (mean 91.9 versus 65.2 months; $P = 0.001$). Similarly multivariable analyses revealed that VS60 ($P = 0.001$) and VS45 ($P = 0.003$) were significant predictors of clinical hypothyroidism. The freedom from clinical hypothyroidism was longer for those whose VS60 $\geq$ 10 cm^3 (91.5 versus 73.3 months; $P = 0.002$) and VS45 $\geq$ 5 cm^3 (91.5 versus 75.9 months; $P = 0.007$).

Conclusions: VS60 and VS45 of the thyroid should be considered important dose constraints against hypothyroidism without compromising target coverage during IMRT optimisation for NPC.

Key words: Dosimetric predictors; hypothyroidism; intensity-modulated radiation therapy; nasopharyngeal carcinoma

Introduction

Intensity-modulated radiation therapy (IMRT) has been extensively investigated and practiced for head and neck cancers for more than 15 years. It has replaced conventional radiation techniques and three-dimensional conformal radiation therapy (3DCRT) as the modality of choice for head and neck cancers, including nasopharyngeal carcinoma (NPC), in virtue of its superior tumour coverage and better sparing of nearby critical organs from unnecessary radiation [1–7]. NPC, a distinctive type of head and neck cancer endemic in southern China and Hong Kong, is a highly curable disease due to its inherent radiosensitivity and chemosensitivity [8]. As a large population of NPC survivors is expected after curative IMRT, long-term IMRT-related complications will gradually emerge. Hypothyroidism is a well-known long-term complication after radiation therapy to the head and neck region for lymphoma and head and neck cancers [9–11]. Previous studies have

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revealed some dosimetric parameters predictive of hypothyroidism in patients treated with 3DCRT and IMRT for their squamous cell head and neck cancers [12–18]. However, they contained a heterogeneous population of patients who suffered from head and neck cancers of different sites and were treated with a mixture of definitive or postoperative radiation therapy. Furthermore, the temporal relationship between biochemical hypothyroidism and clinical hypothyroidism after IMRT remains undefined. In view of the above, we investigated the predictive factors of post-IMRT biochemical and clinical hypothyroidism in patients with non-metastatic NPC treated with radical IMRT.

Materials and Methods

Patient Eligibility and Study Design

Our study was registered at ClinicalTrials.gov (NCT02689609) and approval from the local institutional review board was obtained before the start of the study. Eligible patients included those with previously untreated non-metastatic NPC who received only one course of radical IMRT with or without adjunct chemotherapy as curative treatment between January 2008 and January 2013. Patients who had a history of any thyroid disorders, pituitary disorders, prior thyroid surgery or a drug history of thyroxine (T4) or triiodothyronine (T3) were excluded. Patients who had a history of radiation therapy to other areas were also excluded. Pretreatment investigations included serum haematology, biochemistry, antibodies against Epstein-Barr virus viral capsid antigen and early antigen, fabrication of customised head and neck thermoplastic cast for subsequent contrast-enhanced computed tomography scan from the head to the mid-thoracic region in IMRT treatment position with 3 mm thickness, as well as T1-sequence, T2-sequence and gadolinium-enhanced magnetic resonance imaging of the head and neck region by a 3-Tesla scanner with the images co-registered with the planning computed tomography images for detailed target and organ-at-risk (OAR) delineation and IMRT planning. An additional contrast-enhanced computed tomography scan of the thorax and abdomen was also carried out to rule out distant metastasis.

The gross tumour volumes of both the primary tumour (GTV-P) and the radiologically involved cervical nodes (GTV-N) were outlined on the planning computed tomography images with the aid of co-registered magnetic resonance images, as described previously [19]. Subsequently, a clinical target volume (CTV-70) and a planning target volume containing CTV-70 with a 3 mm margin (PTV-70) were generated to take into account the microscopic disease spread, physiological body motions and set-up errors, respectively. Another CTV-66 encompassing the high-risk areas including the posterior half of the maxillary sinuses, nasal cavities, parapharyngeal spaces, styloid processes, basiocciput, basisphenoid, clivus, foramina rotunda and ovale, pterygopalatine fossae, pterygomaxillary fissures, infra-orbital fissures, cavernous sinuses and level Ib and level V nodal stations was also contoured. A corresponding PTV-66 with a 3 mm margin encompassing CTV-66 was created by Boolean operations of the treatment planning system (Eclipse Treatment Planning System, version 8.9; Varian Medical Systems, Palo Alto, CA, USA), which was also used for IMRT optimisation and planning. All OARs including the brainstem, spinal cord, globes, optic nerves, optic chiasm, lenses, temporomandibular joints, temporal lobes, auditory nerves, cochleae, mandible, oral cavity, larynx, parotid glands, vestibules, pituitary and thyroid were then contoured manually before IMRT optimisation [19]. The maximum dose of the brainstem, optic nerves and chiasm must be $\leq$54 Gy (allowing 0.1 cm^3 brainstem $<$ 60 Gy) and spinal cord $\leq$ 45 Gy (allowing 0.1 cm^3 spinal cord $<$ 48 Gy) during the process of dose calculation. Efforts were also made to limit the mean dose of parotid glands to 26 Gy whenever possible and dose to the lenses and temporal lobes as low as reasonably achieved without compromising dose coverage to the PTVs. No dose constraint was given to the thyroid and the pituitary during optimisation of all IMRT plans. All IMRT plans fulfilled these acceptance criteria before treatment delivery.

A seven- to nine-field IMRT plan delivered by step-and-shoot technique with a 6MV linear accelerator (Varian Medical Systems) was generated by Eclipse Treatment Planning System version 8.9 using an anisotropic analytical algorithm (Fig. 1). A total dose of 70 Gy and 66 Gy was prescribed to PTV-70 and PTV-66, respectively, all in 33–35 fractions over 6.5–7 weeks by simultaneous accelerated radiation therapy technique. The whole neck was irradiated with IMRT and no matching anterior field to the lower neck was allowed. This has been the standard prescription and practice in our institution for the past 10 years. Positional verification with on-board imaging was carried out before IMRT commencement. It was repeated again daily immediately before the first three fractions of IMRT and then weekly afterwards during the whole course of IMRT, to track any anteroposterior and lateral body displacements.

All patients had routine six-site nasopharyngeal biopsies at 8 weeks after IMRT to confirm local clinical remission. Repeated nasopharyngeal biopsies were carried out at 10 weeks and 12 weeks after IMRT if residual tumour cells were still observed in previous post-IMRT nasopharyngeal biopsies [20]. Additional radiation therapy in the form of intracavitary brachytherapy, stereotactic radiation therapy or IMRT was given if patients developed local persistence at 12 weeks after IMRT. Patients confirmed to be in local clinical remission received regular clinical follow-up and imaging surveillance every 3–4 months for the first year after IMRT, then every 4–6 months for the second and third years and yearly afterwards to monitor for any treatment-related chronic complications and relapse. Blood tests for thyroid function tests, including free T4 and thyroid stimulating hormone (TSH), were arranged at least once yearly to monitor post-IMRT hypothyroidism. Biochemical hypothyroidism was defined as either elevation of TSH above the upper normal limit or reduced free T4 below the lower normal limit or both, without the presence of clinical symptoms of hypothyroidism. Clinical hypothyroidism was

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