Journal of the Egyptian National Cancer Institute 30 (2018) 33–38

Contents lists available at ScienceDirect

Journal of the Egyptian National Cancer Institute

journal homepage: www.sciencedirect.com

Full length article

Radiotherapeutic factors affecting the incidence of developing hypothyroidism after radiotherapy for head and neck squamous cell cancer

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ARTICLE INFO

Article history:
Received 17 November 2017
Received in revised form 13 January 2018
Accepted 15 January 2018
Available online 7 February 2018

Keywords:
HNSCC
TSH
Dose-volume parameters
Radiation-induced HT

ABSTRACT

Purpose: The purpose of this study is to determine radiotherapy (RT) dose-volumetric threshold of radiation-induced hypothyroidism (HT) in head and neck squamous cell carcinoma (HNSCC) patients.
Patients and methods: The diagnosis of HT in 78 HNSCC patients treated with RT was based on a thyroid stimulating hormone (TSH) level greater than the maximum value of laboratory range. In all patients, dose-volumetric parameters were analyzed according to their relation to development of HT, and thyroid volumes spared from doses ≥10, 20, 30, 40 and 50 Gy (V10, V20, V30, V40 and V50) were analyzed from the dose volume histograms (DVHs).
Results: Median follow-up duration was 31 months. At the end of study, 33 patients (42.3%) developed HT and the cumulative incidence of HT was 24.6%, 36.5% and 42.3% at one, two and three years, respectively. V30 of 42.1% (P = 0.005) was defined as dose-volumetric threshold of radiation-induced HT in HNSCC patients. Our analysis showed that V30 separates patients into low- and high-risk groups; the incidence of radiation-induced HT in the group with V30 < 42.1% and V30 ≥ 42.1% was 29.4% and 71.4%, respectively (P = 0.002).
Conclusions: The V30 may predict risk of developing HT after RT for HNSCC patients. V30 of 42.1%, defined as dose-volumetric threshold of radiation-induced HT, can be useful in treatment planning of HNSCC patients.

Introduction

Head and neck cancers are considered the 6th most common cancer worldwide; more than ninety percent of cancers are SCC that arises from the mucosal cell lining of the oral cavity, larynx and oropharynx [1].

Either surgery or RT as a single treatment modality may be curable for early stage HNSCC in most patients [2]. Combined chemo-radiation (CRT) as first line treatment had improved outcome for patients with locally advanced disease [3], but about 20–30% of patients develop locoregional and/or distant failure [4].

External beam radiotherapy for HNSCC is usually associated with significant late complications such as fibrosis of neck soft tissues and chronic xerostomia [5]. While HT, hyperthyroidism, thyroid cancer, benign adenoma and Graves' disease are radiation-induced thyroid long-term morbidity that reported in the literature [6,7], HT in particular is commonest late adverse effects [5,6,8].

Radiation-induced HT may be either clinically overt, with increased serum thyrotropin (TSH) and low serum-free thyroxine (fT4) concentrations, eventually accompanied with clinical signs such as intolerance to cold, bradycardia, hypotension, fatigability and slow reflexes or subclinical HT manifested by elevated TSH and normal serum-fT4 concentrations [9]. Radiation-induced HT commonly occurs within 5 years [8] and its possibility of occurrence may be prolong from 20 to 25 years post head and neck irradiation [10,11]. The peak incidence of occurrence of radiation-induced HT is at 2 to 3 years after RT [8].

Peer review under responsibility of The National Cancer Institute, Cairo University.
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https://doi.org/10.1016/j.jnci.2018.01.004
1110-0362/

Many risk factors that may affect the incidence of radiation-induced HT such as volume of thyroid gland irradiated, RT dose, follow-up duration and extent of surgery had been reported [12]. The total dose of irradiation is consider as the most important factor that affect the increased incidence of radiation-induced HT while the role of chemotherapy (CT) is still debated [8,11]. There were several limitations of the few studies that analyzed the clinical DVHs for post RT thyroid disorders that includes; lack of data about the pre RT baseline values of thyroid hormone, inability to identify the dose-volume threshold value and lost follow up for majority patients [6,13–15].

However, introduction of novel RT techniques with its advantage of increasing RT dose to target areas and sparing the normal organs (i.e., the heart, lungs, and thyroid) had decreased the late RT adverse effects and improved the quality of life of patients [14,15].

Many of thyroid dosimetric trials investigated radiation-induced HT have concluded that, a thyroid volume absorbing $\geq$30 Gy had associated with increased incidence of HT [5,14,16,17]. However, Kim et al. [13] and Chyan et al. [18] found that, V45 was significant predictor for development of HT. Also, Kim et al. [13] defined V45 of 50% as a threshold value for radiation-induced HT.

The primary end points of this work was analysis of the different predictor variables that affecting the development of HT after RT for HNSCC with determination the possible threshold value of radiation-induced HT and the second end points was analysis of the effect of development of HT on overall survival (OS) and relapse free survival (RFS) rates.

Patients and methods

This is a prospective single arm study included 78 HNSCC patients presented at Clinical Oncology Department, Tanta University hospital and treated with 3-D CRT with or without concurrent CT during the period between January 2013 and December 2014 with 12 months minimal follow up duration.

Eligibility criteria

Patient eligibility criteria included: (a) pathology proven HNSCC; (b) patients with involvement of the thyroid gland in either primary tumor site or locoregional lymphatic RT fields; (c) patients with normal thyroid function (euthyroid) before RT.

Patients who had previous thyroid disease, thyroid surgery, cancer or isotopes treatment and comorbid conditions such as active ischemic heart, cerebrovascular, collagen vascular diseases or congestive heart failure were excluded from this study.

Pretreatment clinical assessment and diagnostic work up included full patients history, local and general examinations, biopsy with pathological examination, dental examination, head and neck computed tomography (CT) and/or magnetic resonance imaging (MRI) and chest X-ray. CT of chest was carried out if indicated. The clinical stage was determined according to the American Joint Committee on Cancer (AJCC) staging system [19].

Thyroid function assessment

Before starting RT, the levels of TSH (normal range; 0.39–3.55 μIU/ml), fT4 (normal range; 0.82–2 ng/dl), and free triiodothyronine (fT3; normal range, 2.1–3.8 ng/dl) were assessed. Hypothyroidism was defined according to the American Thyroid Association recommendations [20] as TSH level more than the normal laboratory range, regardless of symptoms. Patients with normal TSH were defined as euthyroid. The time onset for developing HT was defined as the time of the first reported increased TSH value after the end of RT.

Follow-Up

All patients were followed up by measuring the serum TSH and fT4 levels 1 month after the end of RT, then at 6, 12 months for the first year and then annually or when clinically indicated, when symptoms of HT development.

Radiotherapy

All patients were treated with 3D-CRT aiming at either primary or adjuvant purpose. The patients were treated supine with a head and neck thermoplastic mask for immobilization.

Treatment-planning CT cuts were obtained at 5-mm slice intervals with contouring the target volumes and critical organs at risk. Dose volume histograms were created for all treatment plans and all dosimetric data were transferred to 3-D radiotherapy planning system. Treatment was performed with photons using 6-MV linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). All patients received RT with 2 Gy daily fractions, and all patients received at least 60 Gy RT dose in 30 fractions. Sixty-nine patients received 66 Gy in 33 fractions, 9 patients received RT doses <66 Gy. Forty-one patients received elective node irradiation with either whole-neck irradiation or wide local fields to 40–50 Gy total doses then received booster dose for the gross tumor.

Dosimetric analysis

The different dose-volume parameters including the mean, maximum and minimum doses to the thyroid gland, mean thyroid volume and the thyroid volumes spared from doses $\geq$10, 20, 30, 40 and 50 Gy (V10, V20, V30, V40 and V50) were analyzed from the DVHs.

Concurrent chemotherapy

Out of 78 patients, 60 (76.9%) patients received CT concurrent with RT either as primary or adjuvant therapy as follow: 42 patients with disease stages III and IV, 11 patients with disease stages II nasopharyngeal cancer and 7 patients with high risk disease stages II (4 patients with positive/close resection margins and 3 patients with extra-capsular extension of lymph node metastases). Concurrent CT was administered mostly in form of weekly cisplatin 40 mg/m^2 for 6 or 6.5 weeks starting on day 1 of RT. For all patients, intravenous hydration was given before (1.5 L 0.9% saline over 4 h) and after (1 L 0.9% saline over 3 h) cisplatin perfusion with prophylactic antiemetic and dexamethasone. Creatinine clearance $\geq$60 ml/min was required for cisplatin administration. The CT regimen was administered on an outpatient basis with weekly evaluation of patients during the treatment period.

Symptomatic patients and/or patients who developed high TSH with low fT4 were treated with L-thyroxin therapy.

Statistical analysis of the data

Patients with subclinical hypothyroid functions (normal fT4 concentrations with elevated serum TSH) were considered hypothyroid patients.

Data were fed to the computer and analyzed using IBMSPSS software package version 20.0. Comparisons between groups for categorical variables were assessed using Pearson Chi-square test. Student *t*-test was used for normally distributed quantitative variables, to compare between two studied groups. Receiver operating