Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 5, pp. 1802–1808, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.09.054

CLINICAL INVESTIGATION **Lymphoma**

THYROID V30 PREDICTS RADIATION-INDUCED HYPOTHYROIDISM IN PATIENTS TREATED WITH SEQUENTIAL CHEMO-RADIOTHERAPY FOR HODGKIN'S LYMPHOMA

Laura Cella, Ph.D.,*† Manuel Conson, M.D.,† Michele Caterino, M.D.,† Nicola De Rosa, M.D.,† Raffaele Liuzzi, Ph.D.,*† Marco Picardi, M.D.,‡ Francesco Grimaldi, M.D.,‡ Raffaele Solla, M.D.,*† Antonio Farella, M.D.,† Marco Salvatore, M.D.,† and Roberto Pacelli, M.D.*†

*Institute of Biostructures and Bioimages, National Council of Research (CNR), Naples, Italy; †Department of Diagnostic Imaging and Radiation Oncology, Federico II University School of Medicine, Naples, Italy; and ‡Department of Biochemistry and Medical Biotechnology, Federico II University School of Medicine, Naples, Italy

Purpose: Hypothyroidism (HT) is a frequent late side effect of Hodgkin's lymphoma (HL) therapy. The purpose of this study is to determine dose–volume constraints that correlate with functional impairment of the thyroid gland in HL patients treated with three-dimensional radiotherapy.

Methods and Materials: A total of 61 consecutive patients undergoing antiblastic chemotherapy and involved field radiation treatment (median dose, 32 Gy; range, 30–36 Gy) for HL were retrospectively considered. Their median age was 28 years (range, 14–70 years). Blood levels of thyroid-stimulating hormone (TSH), free triiodo-thyronine (FT3), free thyroxine (FT4), and thyroglobulin antibody (ATG) were recorded basally and at different times after the end of therapy. For the thyroid gland, normal tissue complication probability (NTCP), dosimetric parameters, and the percentage of thyroid volume exceeding 10, 20, and 30 Gy (V10, V20, and V30) were calculated in all patients. To evaluate clinical and dosimetric factors possibly associated with HT, univariate and multivariate logistic regression analyses were performed.

Results: Eight of 61 (13.1%) patients had HT before treatment and were excluded from further evaluation. At a median follow-up of 32 months (range, 6–99 months), 41.5% (22/53) of patients developed HT after treatment. Univariate analyses showed that all dosimetric factors were associated with HT ($p < 0.05$). On multivariate analysis, the thyroid V30 value was the single independent predictor associated with HT ($p = 0.001$). This parameter divided the patients into low- vs. high-risk groups: if V30 was $\leq$ 62.5%, the risk of developing HT was 11.5%, and if V30 was >62.5%, the risk was 70.8% ($p < 0.0001$). A Cox regression curve stratified by two levels of V30 value was created (odds ratio, 12.6).

Conclusions: The thyroid V30 predicts the risk of developing HT after sequential chemo-radiotherapy and defines a useful constraint to consider for more accurate HL treatment planning. © 2012 Elsevier Inc.

Hodgkin's lymphoma, Radiotherapy, Hypothyroidism, Dosimetric constraints, Thyroid gland.

INTRODUCTION

Hypofunction of the thyroid gland is one of the most common and long-known late side effects described in literature after therapeutic irradiation of the cervical region for neoplasms such as head-and-neck squamous cell carcinoma (1–6) and lymphomas (7–12). Radiation-induced hypothyroidism (HT) may be either subclinical, as manifested by increased serum thyrotropin and normal serum-free thyroxine concentrations, or clinically overt, with laboratory findings showing increased serum thyrotropin and low free serum thyroxine concentrations, eventually coupled with signs such as slow reflexes, bradycardy, hypotension, cold intolerance, fatigue, and unexplained weight gain (13). HT typically occurs within 5 years after completing radiation treatment, with a peak of occurrences at 2 to 3 years (2, 9), but it has been reported even 20 to 25 years after radiotherapy (7, 14).

In Hodgkin's lymphoma (HL) patients, the irradiation of the thyroid region has been documented to induce approximately up to a 50% risk of developing HT and a 20% risk of developing thyroid nodules (11, 12, 15, 16). Among the most important factors associated with the incidence of HT is the total radiation dose, whereas the role of chemotherapy on radiation-induced thyroid dysfunction is not clear and is still debated (2, 14).

Reprint requests to: Roberto Pacelli, M.D., Dipartimento di Diagnostica per Immagini e Radioterapia, Università "Federico II", via S. Pansini 5, edificio 10, 80131, Napoli, Italia. Tel: 39-0817463563; Fax:39-0815457081; E-mail: roberto.pacelli@cnr.it

Conflict of interest: none.

Received June 28, 2010, and in revised form Sept 8, 2010. Accepted for publication Sept 21, 2010.

In HL patients receiving sequential chemo-radiotherapy, the risk of HT, either clinically overt or subclinical, was found to be 51% for patients receiving doses of 35 to 45 Gy (15) and 40% for patients receiving doses of 30 to 36 Gy (14) compared with 12% to 27% for patients receiving doses of 15 to 30 Gy (14, 15, 17, 18). Despite this clear-cut dose–effect relationship, a review of published studies shows that a dose–volume histogram metric for the prediction of the risk of thyroid radiation-induced abnormalities has not yet been determined. The current trend in radiation oncology is to pay more attention in determining acceptable dose–volume constraints for critical organs so as to limit normal tissue risks (19). Recently, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) reviews have given information on dose, volume, and outcome for many different organs but not for the thyroid gland (20). Indeed, to date and to our best knowledge, only a few investigators have performed clinical dose–volume histogram analysis for thyroid disorders after radiotherapy (5, 21, 22). The limitations of these studies are the lack, for most patients, of the baseline hormone values assessed before radiation therapy and the failure to identify a dose–volume threshold value. All of these studies concerned head-and-neck cancer patients treated with doses on the order of 70 Gy, which are much higher than those used in radiotherapy for HL. Noteworthy is the suggestion by Agkun *et al.* (21) and Yoden *et al.* (22) that doses to the neck exceeding 30 Gy have a significant impact on the TSH peak.

In recent years, for HL radiotherapy, several delivery techniques such as intensity-modulated radiation therapy techniques, with or without inverse planning optimization, and even three-dimensional proton radiotherapy have been proposed (23–29). These advanced tools increase treatment accuracy avoiding normal organs (*i.e.,* the heart, lungs, and thyroid) and thus improve long-term effects and quality of life of survivors. Using more sophisticated techniques is of great importance for HL patients in whom low mean age and high rate of cure make them particularly at risk for developing late side effects and secondary neoplasms. In this framework, the definition of dosimetric constraints and predictive factors becomes more clinically relevant so as to plan optimal strategies and to reduce the risk of late radiation effects; thus specific studies on dose–effect relationships for radiation-induced thyroid toxicity are needed.

With the aim to determine thyroid dose–volume constraints that correlate with HT, in the present study we have performed a retrospective analysis of 61 patients treated for HL with chemo- and radiation therapy for whom thyroid hormone levels, clinical data, and thyroid dose distribution were available.

METHODS AND METERIALS

Patient selection

In this study, we reviewed data on 61 consecutive patients with Hodgkin's disease and for whom pretreatment thyroid function tests were available. All patients received postchemotherapy supradiaphragmatic involved-field radiation therapy at the Department of Radiotherapy of the University "Federico II" of Naples between November 2001 and April 2009. The patients' median age was 28 years (range, 14 to 70 years).

Chemotherapy consisted of four to six cycles either of ABVD (doxorubicin 25 mg/m^2, bleomycin 10 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2, all drugs i.v. and administered Days 1 and 15, every 28 days) or VEBEP (vinblastine 6 mg/m^2 i.v., Days 1 and 15; etoposide 80 mg/m^2 i.v., Days 1–3 and Days 15–17; bleomycin 10 mg/m^2 i.v., Days 1 and 15; epidoxorubicin 40 mg/m^2 i.v., Days 1 and 15; and prednisone 40 mg/m^2 p.o., Days 1–5 and 15–19).

Radiotherapy and dosimetric analysis

All patients were treated with full three-dimensional radiation treatment planning and data for dosimetric analysis were retrospectively obtainable for 56 of 61 patients.

Treatment planning was based on CT performed with the patient in supine position using vacuum-locked mattress with the patient's arms above the head. Scans were acquired using 5-mm slices of a multislices scanner. CT images were electronically transferred to the Focal Ease 4.2 CT Simulation software (Computerized Medical System, St Louis, MO) for target and critical organs contouring. Clinical target volume (CTV) included the nodal sites involved at the time of diagnosis (29); planning target volume (PTV) included CTV plus a 1-cm margin. For all patients, the thyroid gland was deliberately delineated by the same radiation oncologist.

All patients underwent three-dimensional treatment planning using XiO computer software (version 4.4, Computerized Medical System, St. Louis, MO). The dose distribution was calculated using an appropriate algorithm in the presence of heterogeneous tissues.

Radiotherapy was administered using 6- to 20-MV photon beams from a linear accelerator with AP and PA fields shaped to the projection of the PTV in the beam's-eye view. The prescription dose was specified at the centre of PTV. Field weightings were adjusted to achieve the maximum possible uniform distribution in the target volume (95% of prescription dose delivered at least to 95% of the PTV). A total median dose of 32 Gy (range, 30–36 Gy) in 20 daily fractions of 1.5 to 1.6 Gy was planned. The AP-PA fields included the entire thyroid gland, a part of it or did not include the thyroid at all, depending on the target to be irradiated.

For the thyroid gland, the absolute volume, the dose–volume histogram (DVH), the minimum, maximum, and mean doses (TD_{min}, TD_{max}, and TD_{mean}), the percentage of thyroid volume exceeding 10, 20, and 30 Gy (V10, V20, and V30 respectively) were calculated. Furthermore, we assessed the normal tissue complication probabilities (NTCP) for the thyroid. We used a NTCP tool in XiO based on Lyman–Kutcher–Burman (LKB) model (30–32). The parameters for NTCP calculations were volume effect = 0.22, slope = 0.26, and tolerance dose $TD_{5/5}$ = 45 Gy.

Thyroid function follow-up evaluation

Initial and follow-up evaluation consisted of history and physical examination and thyroid hormones serum determination that were recorded before chemotherapy and periodically after the end of the radiation treatment. No patient had comorbid conditions such as diabetes and collagen vascular disease. Thyroid stimulating hormone (TSH), free triiodo-thyronine (FT3), free thyroxine (FT4), and thyroglobulin antibody (TGA) blood levels were evaluated.

The time of onset of HT was defined as the interval between the end of radiotherapy and the first altered thyroid hormone laboratory

value. It must be remarked that we consider an out-of-range value as an alteration when confirmed by a subsequent laboratory test.

A diagnosis of HT was based on TSH value grater than the maximum value of laboratory range and/or FT3 and/or FT4 values lower than the minimum value of laboratory range, regardless of whether any symptom was present.

Statistical analysis

Univariate analysis was used to evaluate correlations between clinical factors (sex, age, disease stage, and thyroid gland volume), dosimetric factors (total prescribed dose and dosimetric parameters from the thyroid DVH), and the incidence of HT after radiotherapy. Dichotomic variables were tested by Pearson Chi-square test. The median and the interquartile range were used to describe all continuous variables and nonparametric techniques were used for analyzing them (Mann–Whitney *U* test). For multivariate analysis on significant dosimetric parameters the Cox regression was adopted. A receiver operating characteristic (ROC) curve analysis was performed to find possible threshold values for dividing patients in high-risk and low-risk groups regarding dosimetric parameters. Cumulative incidence of HT was calculated using Kaplan–Meier survival analyses. All statistical tests were two-sided, and a p value of 0.05 was considered statistically significant. Statistical analysis was performed with SPSS 15.0 statistical software (SPSS Inc., Chicago, IL).

RESULTS

Thyroid hormone levels were basally evaluated on 61 patients. Eight patients (13.1%) had HT before treatment, and were consequently excluded from further evaluation. Demographic, disease, and treatment characteristics of the remaining 53 patients are shown in Table 1.

Table 1. Patient, disease, and treatment characteristics

Characteristic	*n*	%
Age (y)		
14–25	23	43.4
26–35	13	24.5
36–45	9	17
46–70	8	15.1
Sex		
Male	25	47.2
Female	28	52.8
Histology		
Nodular sclerosis	38	71.7
Mixed cellularity	10	18.9
Lymphocyte-rich-classical	5	9.4
Stage		
I–II	42	79.2
III–IV	11	20.8
Radiotherapy dose delivered		
30 Gy	23	43.4
32 Gy	25	47.2
36 Gy	5	9.4
Chemotherapy regimen		
ABVD	15	28.3
VEBEP	38	71.7

Abbreviations: ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; VEBEP = vinblastine, etoposide, bleomycin, epidoxorubicin, and prednisone.

Of 53 patients, 22 (41.5%) developed laboratory evidence of HT at a median follow-up of 32 months (range, 6–99 months) after the end of radiation treatment. The Kaplan–Meier estimated incidence curve of HT at 5 years is shown in Fig. 1. Estimated incidences of HT at 24 months and at 60 months after treatment were 43.5% and 49.1%, respectively.

The no-HT group and the HT group of patients were analyzed with respect to different clinical parameters. Univariate analysis was performed, and there was no significant difference in the distribution of clinical parameters between the HT and no-HT groups (Table 2).

For 50 of the 53 patients considered so far 3D treatment planning data were available. The following statistical analyses were performed on this subset of patients. Univariate analysis was used on total prescribed dose and on thyroid dosimetric parameters to study their impact on the development of HT. Results are shown in Table 3. All dosimetric parameters resulted significantly associated with HT, but they are not independent of each other, as shown by the multivariate analysis (Table 4). The V30 is the only variable that independently contributes to the prediction of HT (p = 0.001). Figure 2 shows the V30 value distribution between HT and no-HT groups. From ROC analyses (Fig. 3), a V30 of 62.5% resulted as threshold value. Our analysis shows that V30 separates patients into low- and high-risk groups; the incidence of radiation-induced HT in the group with V30 $\leq$ 62.5% and V30 > 62.5 was 11.5% and 70.8% respectively ($p < 0.0001$). A Cox regression curve stratified by two levels of V30 value (odds ratio, 12,6) is shown in Fig. 4a.

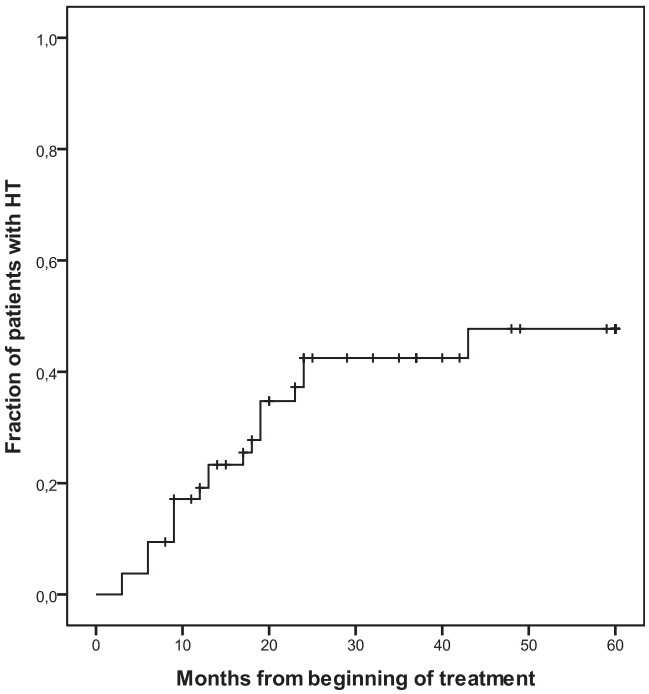

Fig. 1. Kaplan–Meier estimated cumulative incidence curve of hypothyroidism (HT) at 5 years.

Table 2. Clinical factors in patients without hypothyroidism (no-HT) and with hypothydroidism (HT)

	No-HT group	HT group	*p* value
Age (y)	29 (21.0–46.0)	27.5 (21.0–35.3)	0.38*
Thyroid volume (cc)	13.8 (11.6–19.7)	14.5 (9.7–17.3)	0.43*
Follow-up (mo)	30.5 (8–99)	40.0 (6–96)	0.28*
Sex			
Female	46.4%	53.6%	0.059†
Male	72.0%	28%	
Stage			
I–II	51.2%	48.8%	0.16†
III–IV	80.0%	20.0%	

Median value and interquartile range are indicated. For dichotomous variables, percentages are indicated.
* Mann–Whitney *U* test.
† Chi-square test.

DISCUSSION

Hodgkin's lymphoma, characterized by a rate of nearly 90% of long surviving patients and by a low average age at diagnosis, is a highly curable disease thanks to antiblastic chemotherapy and radiation therapy. However, these treatment modalities imply the risk of long-term side effects including HT. It has been previously shown that HT can be caused by radiotherapy on the neck region and that doses even <40 Gy may induce HT in a relevant fraction of patients (14, 18). To treat supradiaphragmatic HL, the planning target volume must frequently include the whole thyroid gland or a large part of it. On the other hand, recent improvements in HL radiotherapy techniques recall attention on dose–volume histogram metrics for the prediction of the risk of HT. Normal tissue late effects of ionizing radiation are an important part of plan evaluation in radiation oncology. The technological advances in radiation therapy techniques make, today more than ever before, a thorough knowledge of the relation of dose, volume, and outcome for the normal tissues in the irradiated field mandatory. Reliable 3D quantitative data on which clinical decisions can be made are already available for many organs (19, 20), but still no data exist for the thyroid.

Table 3. Total prescribed dose and dosimetric parameters from thyroid DVH in no-HT and HT groups

	No-HT group	HT group	*p* value*
D_{Tot} (Gy)	30.0 (30.0–32.0)	32.0 (32.0–32.0)	0.002
D_{min} (Gy)	1.7 (0.8–25.2)	28.8 (17.2–30.3)	0.0004
D_{max} (Gy)	31.2 (30.3–33.0)	32.5 (32.0–33.5)	0.041
D_{mean} (Gy)	18.9 (15.8–29.8)	31.5 (30.4–32.6)	0.0004
NTCP	6.4 (4.1–9.8)	12.4 (10.4–14.7)	0.001
V10 (%)	59.5 (48.4–59.5)	100.0 (100.0–100.0)	0.002
V20 (%)	53.7 (44.8–100.0)	100.0 (100.0–100.0)	0.003
V30 (%)	34.7 (5.0–100.0)	98.1 (80.7–100.0)	0.0002

Abbreviations: D_{max} = maximum thyroid dose; D_{mean} = mean thyroid dose; D_{min} = minimum thyroid dose; D_{Tot} = total prescribed dose; HT = hypothyroidism; NTCP = normal tissue complication probability; VX = percentage of thyroid volume exceeding X Gy.
Median value and interquartile range are indicated.
* Mann–Whitney *U* test.

Table 4. Multivariate analysis of factors related to development of HT after radiotherapy

Factor	*p* value
V30 (%)	0.001
D_{min} (Gy)	0.419
D_{max} (Gy)	0.705
D_{mean} (Gy)	0.759
D_{Tot} (Gy)	0.455
NTCP	0.878
V10 (%)	0.776
V20 (%)	0.808

Abbreviations as in Table 3.

In this study, to derive quantitative information about HT risk for a given treatment plan, we have retrospectively evaluated the outcome of 61 HL patients for whom the thyroid functional status before the treatment was known. We were essentially interested in determining a dose–volume threshold value that could separate patients at HT high risk from those at HT low risk. The final aim was to single out a constraint for plan optimization, for clinical decisions, and for patients risk information.

In our cohort of patients, at a median follow up of 32 months, we found an incidence of HT of 41.5% that is in a good agreement with the incidence of HT reported in the literature by Kuten *et al.* (14) Indeed, the authors reported a 40% incidence of HT after 30 to 36 Gy in HL patients treated with chemotherapy followed by radiotherapy. It must be pointed out that the major limitation of our study could be the lack for some patients (22%) of long-term (>24 months) clinical follow-up. In any case, when correcting for the length of follow-up, no differences in our analysis were found.

To identify a clinically relevant and accessible factor upon which to classify HL patients at risk for HT, we first analyzed different patient-related factors. Our results showed that age, thyroid volume, and stage were not associated with HT. In particular, it is worth noting that the overall thyroid volume was not correlated with radiation-induced HT. In accordance with the literature (5), a trend was found ($p = 0.059$), suggesting that female gender was associated with a higher risk of thyroid toxicity. In any case, it must be considered

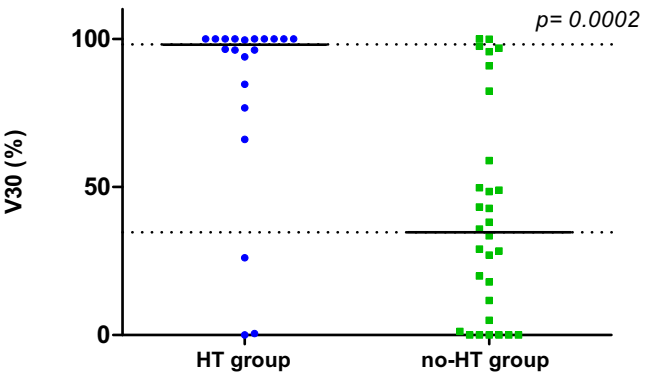

Fig. 2. Thyroid V30 values in the hypothyroidism (HT) group and no-HT group. Lines represent median values for the two groups.

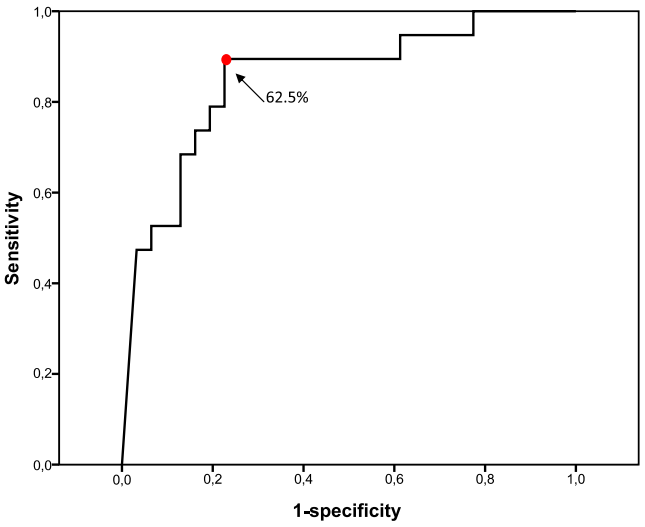

Fig. 3. Receiver operating characteristic (ROC) curve for thyroid V30 threshold definition.

that the estimated rate of HT in the general population is higher in women than in men (33, 34).

The homogeneity of clinical data and therapy, CT-based planning with 1 physician contouring thyroid gland for all patients in the study allowed us to focus on radiation dosimetric factors. Considering dose–volume parameters, the V30 emerged as the only independent predictor of HT. In our results, V30 was shown to be an effective stratification criterion dividing patients into high-risk and low-risk groups with an odds ratio of 12.6 (Fig. 4a). By ROC analysis we identified a threshold value for thyroid V30 of 62.5% that can be used as constraint in HL treatment planning. It is interesting to note that a dose of 30 Gy was previously indicated to significantly affect the thyroid function (21, 22). Considering this finding together with the data on development of HT after hemithyroidectomy, and our results on V30, it is possible to speculate that the dose of 30 Gy represents a critical dose for thyrocyte activity. Indeed, if this dose is given to a volume equal or less than half of thyroid gland, we found a risk of HT of 11.5% comparable with that of hemithyroidectomy reported to be 10.9% (35).

Furthermore, the data coming from univariate analysis suggest that even if V20 and V10 resulted not significant on the multivariate analysis, they may play a role as a constraint in the treatment plans in which the prescription dose is lower than 30 Gy. Repeating the same procedure performed for V30, we found a threshold value for V20 equal to 82.4%. In this case, the incidence of radiation-induced HT in the group with V20 $\leq$ 82.4% and V20 > 82.4% was 13.6% and 60.7% respectively ($p = 0.001$). A Cox regression curve stratified by two levels of V20 value (odds ratio, 9.4) is shown in Fig. 4b. This last result must be considered in view of the data coming from the German Hodgkin Study Group HD10 that, for patients with early stage and favorable histology, defines a new standard of care with two cycles of ABVD and 20 Gy involved-field radiotherapy (36). It should be noted that a threshold value of 82.4% for V20 is quite

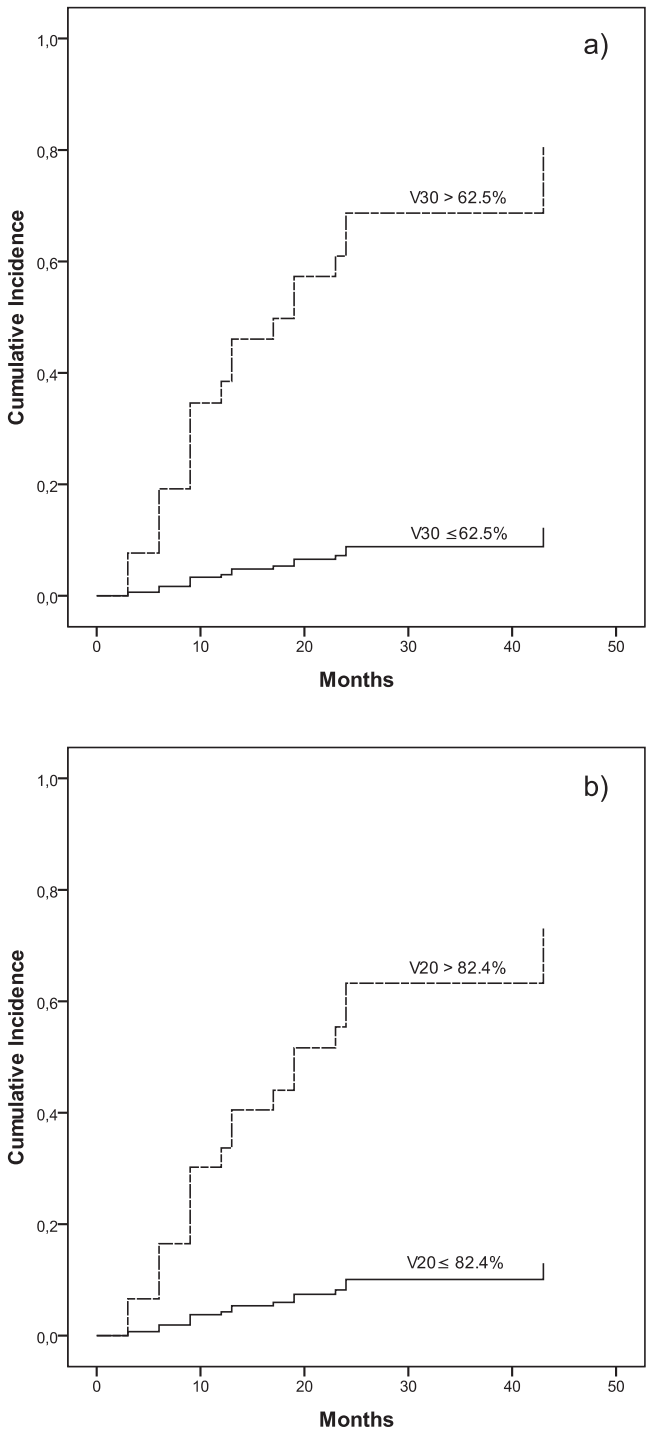

Fig. 4. Cumulative incidence of hypothyroidism stratified by two levels of V30 (a) and by two levels of V20 (b).

a high percentage of thyroid volume and as a consequence not difficult to achieve during the treatment planning phases.

We have recently shown (29) that, using a forward planned IMRT instead of the conventional technique for treating Hodgkin's lymphoma, the thyroid V30 value can be easily reduced, on average, from 80% to 20%, which is much below the threshold value proposed here. Accordingly, in our clinical practice, we adopted forward planned IMRT as a standard technique, and we included thyroid V30 as

a treatment constraint; in particular, we defined a threshold value for V30 of 62.5%. We expect in this way to greatly reduce the incidence of radiation-induced HT in our patients in the future.

CONCLUSION

In conclusion, we identified the thyroid V30 value as a predictor of the risk of developing HT in HL patients treated with sequential chemo-radiotherapy. We have also showed that a V30 of 62.5% is a dose–volume threshold value that can be easily included in the optimization process of treatment planning for supradiaphragmatic HL so as to considerably reduce the risk of developing radiation-induced HT. Additional threshold values have been identified, such as V20, that could be used if a new standard of care with lower doses is adopted for HL in the future.

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