Original article

Thyroid toxicity after radiotherapy of nasopharyngeal carcinoma

Toxicité thyroïdienne après radiothérapie pour cancer du nasopharynx

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Available online 19 August 2010

Résumé

Objectif. – Analyser rétrospectivement les facteurs de risque de survenue de toxicité thyroïdienne après radiothérapie pour cancer du nasopharynx et montrer l’intérêt d’une surveillance à long terme après irradiation cervicale. Patients et méthodes. – Entre 1993 et 2004, 239 patients atteints d’un carcinome nasopharyngé non métastatique ont été traités par radiothérapie conventionnelle associée ou non à une chimiothérapie. La radiothérapie a été délivrée selon une modalité classique (2 Gy/séance, cinq séances par semaine) pour 157 patients et hyperfractionnée (1,6 Gy/séance, deux séances par jour, cinq jours par semaine) pour 82 patients. Une évaluation de la toxicité thyroïdienne tardive en fonction du stade tumoral, de l’âge, du sexe, du recul, de la modalité d’irradiation et de l’association ou non de chimiothérapie a été réalisée. Résultats. – Après un recul médian de 111 mois, 72 patients (30 %) ont présenté un dysfonctionnement hormonal thyroïdien, primitif et/ou hypophysaire. Il s’agissait essentiellement d’une hypothyroïdie post-radique révélée chez 57 patients (24 %). Elle était d’origine périphérique dans 92 % des cas (biologique 73 %, clinique 19 %) et centrale dans 8 % des cas. Le délai moyen d’apparition de l’hypothyroïdie était de 37 mois. Tous les patients ont reçu un traitement substitutif par l-thyroxine. Le taux actuel de l’hypothyroïdie était de 18,1 % à trois ans ; 24,3 % à cinq ans et 35 % à dix ans. Seul le sexe féminin a été retrouvé comme facteur de risque de survenue d’hypothyroïdie en analyse univariée. Cependant l’âge jeune et le stade tumoral avancé ont été associés à un risque plus élevé d’hypothyroïdie mais la différence était non significative (p = 0,08 pour chacun). La différence était non significative pour les autres facteurs à savoir le stade ganglionnaire, la modalité d’irradiation et l’association ou non de chimiothérapie. L’analyse multivariée n’a retenu aucun facteur de risque particulier. Conclusion. – Le dysfonctionnement thyroïdien après radiothérapie pour carcinomes nasopharyngés est fréquent, ce qui incite à un dépistage précoce pour instaurer une prise en charge plus rapide et adéquate. Seul, le sexe féminin est retrouvé comme facteur de risque en analyse univariée dans cette étude.

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Mots clés : Radiothérapie ; Carcinome du nasopharynx ; Toxicité tardive ; Hypothyroïdie

Abstract

Objectives. – To analyze retrospectively the risk factors for occurrence of thyroid toxicity after radiotherapy for nasopharyngeal cancer and to demonstrate the necessity of a long-term post-therapeutic screening. Patients and methods. – Between 1993 and 2004, 239 patients with non-metastatic nasopharyngeal carcinoma were treated by conventional radiotherapy with or without chemotherapy. Radiotherapy was delivered by a standard fractionation (2 Gy/fraction, 5 fractions/week) for 157 patients and hyperfractionation (1.6 Gy/fraction, 2 fractions/day, 5 days/week) for 82 patients. An evaluation of thyroid late toxicity was performed according to tumor stage, age, gender, time after treatment, irradiation method and association or not with chemotherapy. Results. – After a median follow up of 111 months, 72 patients (30%) had hypothyroidism, peripheral in 92% of cases (biological 73%, clinical 19%) and central in 8% of cases. Hypothyroidism was detected at a mean 37 months follow up. All patients received replacement treatment with l-thyroxin. The actuarial rate of hypothyroidism was 18.1%, 24.3% and 35% at respectively 3, 5 and 10 years. Only female gender was found as a risk factor for occurrence of hypothyroidism in univariate analysis. However, younger age and advanced tumor stage were associated with a higher risk but the difference was

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doi:10.1016/j.ando.2010.06.005
not significant ($P=0.08$ for each). There was no difference for other factors: nodal stage, modality of radiation and chemotherapy treatment. The multivariate analysis did not show any risk factor. Conclusion. – Thyroid dysfunction after radiotherapy for nasopharyngeal carcinoma is frequent and requires systematic screening to begin adequate treatment earlier. Only gender has been identified as risk factor in univariate analysis in this study.

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**Keywords:** Radiotherapy; Nasopharyngeal carcinoma; Late toxicity; Hypothyroid dysfunction

1. **Introduction**

The success of radiotherapy in nasopharyngeal cancer depends mainly on the total dose delivered in the tumor. However, the delivery of this dose is limited by the tolerance of healthy tissues in the irradiated volume. Radiation is responsible for multiple side effects. Endocrine complications, after radiotherapy for nasopharyngeal carcinoma, are mainly thyroid complications, and are more and more documented. This is because the pituitary and the thyroid gland are included wholly or partly within the treatment field. The incidence and severity of these complications depend on several factors. Through a retrospective study of 239 patients, we studied the late toxicity after radiotherapy for nasopharyngeal cancer and we report here the incidence and risk factors of thyroid toxicity occurrence.

2. **Patients and methods**

2.1. **Patients**

Between 1993 and 2004, 239 patients with non-metastatic nasopharyngeal carcinoma were treated by conventional radiotherapy with or without chemotherapy in our hospital. The patients included in this study were those with regular monitoring who had not presented relapse during the year following the end of treatment. The anatomical characteristics and clinical treatment are summarized in Table 1.

Radiotherapy was delivered at a total dose of 70 to 75 Gy to the nasopharynx and involved cervical lymph nodes and 50 to 55 Gy to the remaining N0 cervical areas, according to two protocols: standard fractionation (2 Gy/fraction, 5 fractions/week) for 157 patients and hyperfractionation (1.6 Gy/fraction, 2 fractions/day, 5 days/week) for 82 patients. External beam radiotherapy was delivered by a Cobalt 60 for all patients, using two opposed lateral fields (Fig. 1) for treatment of the primary tumor and the upper neck, associated with an anterior cervical field to treat the lower neck up to 40–44 Gy (Fig. 2). The remaining irradiation dose was delivered via an anterior nasal field, which includes the nasopharynx and all cervical nodes with spinal cord shielding.

One hundred and fifty-nine patients (67%) received neoadjuvant chemotherapy combining cisplatin and epirubicin.

Follow-up was every 3 months for the first 2 years, every 6 months for the next 3 years, and then every year. Monitoring is based on physical examination and routine laboratory tests to evaluate the tumor control and to detect late treatment toxicity. After a median follow up of 111 months (35–176 months), 5- and 10-years overall survivals were 75 and 62%, respectively.

<table>
<thead>
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<th>Patients characteristics ($n=239$).</th>
<th>Caractéristiques des patients ($n=239$).</th>
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</tr>
</tbody>
</table>

Table 1

Fig. 1. Lateral field

Champ latéral.
2.2. Methods

We retrospectively analyzed the late thyroid complications that occurred 6 months or more after radiotherapy. Biological tests of serum free thyroxine (FT4) and thyroid-stimulating hormone (TSH) levels were performed before the beginning of treatment and at each monitoring. A test stimulation of TSH by thyrotropin releasing hormone (TRH) was done when the perturbations of thyroid function tests were not obvious. According to this assessment, the patient could be classified in one of five categories: clinical and biological euthyroidism (normal FT4 and TSH), primary clinical hypothyroidism (elevated TSH and low FT4), primary biological hypothyroidism (normal FT4, elevated TSH and ΔTSH < 25 μIU/ml), central hypothyroidism (low FT4, TSH and ΔTSH < 2 μIU/ml) or mixed hypothyroidism (low FT4, TSH, and 2 < ΔTSH < 25 μIU/ml). Other hormone exploration tests were performed when there were clinical symptoms of dysfunction. Risk factors evaluated in this study included age, sex, tumor stage, radiotherapy modality, chemotherapy and time after treatment.

The Kaplan-Meier method was used to assess the actuarial rate of hypothyroidism. A Chi-square test was used to compare the incidence of hypothyroidism. Univariate analyses as well as multivariate analyses of different factors were analyzed with Cox regression. The statistical significance level was 5%.

3. Results

After a median follow up of 111 months, 72 patients (30%) had primitive and/or pituitary thyroid dysfunction. Fifty-seven patients (24%) experienced hypothyroidism, peripheral in 92% of cases (biological 73%, clinical 19%) and central in 8% of cases (mixed: 3 cases, purely central: one case). Hypothyroidism was detected at a mean period of 37 ± 30 months follow up. The characteristics of these patients are summarized in Table 2. The clinical signs of thyroid deficiency were not specific and in no case revealed the disease. The most frequent signs were cutaneous infiltration, psychomotor slowing, weight gain, cold intolerance and dry skin. All patients received thyroxin replacement therapy. Two cases of infra-centimetric thyroid nodules were diagnosed by a cervical ultrasound performed after a clinical doubt about the existence of lymph node recurrence. The average time of discovery was 38 months. There were no punctures. All patients received replacement treatment with L-thyroxin.

The actuarial rate of hypothyroidism was 2.5, 18.1, 24.3 and 35% at 1, 3, 5 and 10 years, respectively (Fig. 3). Univariate analysis of risk factors for radiation-induced hypothyroidism with TN stage, sex, age, total dose, radiation modality and chemotherapy are summarized in Table 3. The rate of hypothyroidism was 33.3 and 21.8% in younger patients (<20 years) and adults (>20 years), respectively. The differ-
enence was not statistically significant, \( P = 0.08 \). Hypothyroidism was observed in 20% of male patients and 30.7% of females, \( P = 0.04 \). Indeed, this difference was noted after 20 years, 15.2% versus 31.8% \( (P = 0.01) \) for men and women, respectively, while there was no significant difference between the two sexes before the age of 20 years.

The analysis of other risk factors (T stage, nodal status, total dose and chemotherapy) showed no significant difference. Multivariate analysis did not select any factor.

4. Discussion

Endocrine toxicities after radiotherapy for nasopharyngeal carcinoma are becoming better known. They are dominated by hypothyroidism, due to irradiation of the hypothalamic-pituitary and thyroid gland. Indeed, the anterior cervical radiation field includes the two thyroid lobes excluding the isthmus receiving a dose greater than or equal to 50 Gy. In theory, the isthmus receives a dose under the shield estimated at 6% of the prescribed dose. However, the pituitary is completely irradiated by the lateral fields and the anterior nasal field of the prescribed dose. However, the pituitary is completely irradiated by the lateral fields and the anterior nasal field of the prescribed dose.

The incidence of radiation-induced thyroid complications for nasopharyngeal carcinoma varies in the literature from 2 to 54%. It was 24% in the present study. Hypothyroidism has been reported by many authors [2–10]. It may be peripheral caused by a direct effect on the thyroid gland or central by acting on the hypothalamic-pituitary axis, or mixed. However, pituitary dysfunction after irradiation has been rarely reported [11].

Age at the start of treatment is considered as an important factor of thyroid complications occurrence [1]. The authors suggest that younger patients are more vulnerable than adults to the radiation effects on the neuroendocrine system, particularly the thyroid gland [7,12]. In this study, the incidence of thyroid toxicity was higher among young patients aged 20 years or younger: 31.7% versus 22.2%. However, the difference was not significant \( (P = 0.08) \).

Gender was found in our study as a significant factor for occurrence of post-radiation hypothyroidism \( (30.7\% \text{ in women versus } 20\% \text{ in men, } P = 0.04) \). Our results are comparable with those of Vrabec and Posner [9,13]. However, the role of female sex remains controversial and is attributed to a greater sensitivity of the thyroid gland to radiotherapy, and a faster depletion of thyroid reserves [9,14].

The thyroid parenchyma is radiosensitive and side effects can be seen after exposure to low doses of radiotherapy [10]. Indeed, the risk of developing radiation-induced thyroid cancer increases up to doses between 20 and 29 Gy. At higher doses, the risk is rather a thyroid deficiency [15]. In our study, we found no significant difference in terms of hypothyroidism among patients treated with a dose below 50 Gy and those treated with a dose greater than or equal to 50 Gy. Our results are comparable to those of Mercado et al. [16] and Posner et al. [9].

The pituitary gland is known for its radiosensitivity. A radiation-induced endocrine dysfunction is generally observed after high doses of radiotherapy [1]. In the study of Bensaadoun, a single case of hypopituitarism including the thyroid axis (1%) was noted after re-irradiation of recurrent nasopharyngeal cancer [11].

The impact of the fractionation schedule in the occurrence of thyroid dysfunction is not well studied and remains controversial. Colevas et al. [17] showed no significant difference in terms of hypothyroidism after irradiation for head and neck cancer \( (n = 118) \) in a bifractionated (1.6 Gy, two times daily) or conventional modality. Similarly, Teo et al. found no difference in thyroid complications after hyperfractionated radiotherapy for nasopharyngeal cancer [18]. These results are similar to those of our study.

Few studies have investigated the effect of chemotherapy on the endocrine system [2]. Its effect remains controversial [1].

In our study, no significant difference was found between patients treated with radiotherapy alone and those treated with both chemotherapy and radiotherapy. In a recent study, Lee et al. examined late toxicity after radiotherapy for nasopharyngeal carcinoma in 422 patients. Age and chemotherapy (concomitant or sequential) were retained as independent factors of late toxicity. The dose escalation and hyperfractionation had not increased the risk of occurrence of severe late complications including hormonal dysfunctions [6].

Reducing the volume of normal tissue included in the radiation field and improving the ballistics of radiotherapy are ways to limit the late effects on the thyroid and the hypothalamic-pituitary axis. Reducing dose in children could also contribute to a decrease in the incidence of thyroid dysfunction in young people. However, hypothyroidism remains a common radiation-induced complication requiring regular and life-long monitoring after the end of radiation to begin adequate treatment earlier [1].
5. Conclusion

Thyroid dysfunction after radiotherapy for nasopharyngeal carcinoma is frequent. The incidence varies in the literature. The risk factors of radiosensitivity include treatment factors and patient factors. Only gender was retained as a risk factor in this study.

Certainly the reduction in the irradiated volume of normal tissue and the use of new radiotherapy techniques will reduce the risk of late toxicity. Indeed, conformal radiotherapy with or without modulated intensity promises highly conformal dose distributions around tumor targets while sparing critical organs. Given the continuously increasing incidence of late-term radiation-induced hypothyroidism, we recommend life-long screening after treatment for nasopharyngeal cancer. Such monitoring allows early detection of hormonal dysfunction and early thyroid replacement therapy for hypothyroid patients to maintain optimal quality of life in cancer survivors.

Conflict of interest statement

No conflict of interest.

References