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A retrospective analysis of thyroid dysfunction following multi-modality treatment of head & neck malignancies

Analiza retrospektywna zaburzeń czynności tarczycy po wielomodalnym leczeniu nowotworów głowy i szyi

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ABSTRACT:

Introduction: The purpose of this study was to determine the incidence of radiation induced hypothyroidism after treatment with radiotherapy alone or in combination with surgery/chemotherapy in head & neck cancer patients.

Methods: This study was a retrospective non-randomized trial performed on 100 patients of head & neck cancer in whom definitive radiotherapy, postoperative radiotherapy or radiotherapy in combination with chemotherapy was given. Values of TSH, T3 & T4 were analyzed at baseline and at 6 monthly follow-up. *Subclinical hypothyroidism* was defined as TSH value of > 4 mU/L and *Clinical hypothyroidism* was taken as TSH > 10 mU/L with decreased T3 & T4.

Results: Out of 100 patients, 73 individuals were euthyroid at the end of 2-year follow-up, 21% had subclinical hypothyroidism and 6% had clinical hypothyroidism. The incidence of subclinical hypothyroidism in the surgery plus radiotherapy group and the radiotherapy group was 22.3% & 50%, respectively. The incidence of clinical hypothyroidism in the surgery plus radio therapy group and the radiotherapy group was 6.5% & nil, respectively.

Conclusion: The incidence of hypothyroidism is high in head & neck cancer patients receiving radiotherapy. The risk is higher in patients who undergo surgery in combination with radiotherapy. Regular thyroid function test is, therefore, recommended.

KEYWORDS: head & neck cancer, hypothyroidism, radiotherapy, subclinical

STRESZCZENIE:

Cel: Niniejsze badanie ma na celu określenie występowania przypadków niedoczynności tarczycy wywołanej promieniowaniem po leczeniu radioterapią wyłączną lub w skojarzeniu z zabiegiem chirurgicznym/chemioterapią u pacjentów z nowotworem regionu głowy i szyi.

Metody: Przeprowadziliśmy nierandomizowane retrospektywne badanie, w którym wzięło udział 100 pacjentów z nowotworem regionu głowy i szyi, u których zastosowano radioterapię wyłączną, radioterapię pooperacyjną lub radioterapię w połączeniu z chemioterapią. W okresie wyjściowym, a także w trakcie dalszej 6-miesięcznej obserwacji, zbadano wartości: TSH, T3 oraz T4. Określono, że *subkliniczna niedoczynność tarczycy* charakteryzuje się wartością TSH > 4 mU/l, zaś wartość klinicznej niedoczynności tarczycy wynosi TSH > 10 mU/l ze zmniejszoną ilością T3 i T4.

Wyniki: Pod koniec 2-letniej obserwacji, spośród 100 pacjentów, 73 osoby znajdowały się w stanie eutyreozy, u 21% rozpoznano subkliniczną niedoczynność tarczycy, zaś u 6% zdiagnozowano kliniczną niedoczynność tarczycy. Częstość występowania subklinicznej postaci niedoczynności tarczycy w grupie, w której wdrożono leczenie oparte na zabiegu chirurgicznym połączonym z radioterapią, oraz w grupie, w której zastosowano wyłączną radioterapię, wynosiła odpowiednio: 22,3% i 50%. Częstość występowania klinicznej postaci niedoczynności tarczycy w grupie, w której wdrożono leczenie oparte na zabiegu chirurgicznym połączone z radioterapią, oraz w grupie, w której zastosowano wyłączną radioterapię, wynosiła odpowiednio: 6,5% i zero.

Wnioski: Częstotliwość występowania niedoczynności tarczycy jest wysoka u pacjentów cierpiących na nowotwory regionu głowy i szyi otrzymujących radioterapię. Ryzyko jest wyższe u osób, u których wykonuje się zabieg chirurgiczny w połączeniu z radioterapią. W świetle powyższych faktów zaleca się regularne badanie czynności tarczycy.

SŁOWA KLUCZOWE: niedoczynność tarczycy, nowotwór głowy i szyi, radioterapia, subkliniczna

INTRODUCTION

Carcinoma of the head and neck region is the sixth most common site of malignancy worldwide. As per the GLOBOCON (IARC-WHO), oral cancer is the most common malignancy in Indian males, whereby the number of new cases in 2018 was 16.1%. Overall, it was the second most common malignancy in both sexes at a percentage share of 10.4%, most likely due to increased consumption of chewing tobacco and smoking [1].

Radiotherapy is an important treatment modality in the management of head and neck cancer used either alone or with surgery and chemotherapy. Although the thyroid gland is relatively radio-resistant, thyroid dysfunctions like thyroiditis, autoimmune thyroiditis, hypothyroidism and thyroid tumors have been frequently reported due to therapeutic radiation [2]. The reported incidence of hypothyroidism after radiotherapy in various studies is between 6% and 48% [3–11]. Radiotherapy in combination with surgery further increases the incidence of hypothyroidism but the addition of chemotherapy probably has little or no effect [11]. It increases the manifestations of poor wound healing, cardiovascular diseases, lung diseases and poor quality of life following head and neck surgery.

Thyroid function tests are still not performed routinely during follow-up of head-neck cancer patients treated with radiotherapy with or without surgery and/or chemotherapy. In this study we evaluated the incidence of thyroid dysfunction following treatment in head and neck cancer patients in our institute so that subsequent intervention may help to achieve a better quality of life.

MATERIALS AND METHODS

Inclusion criteria

One hundred patients with histologically proven cancers of the head & neck of the epithelial origin, who had received external beam radiotherapy, were included in this retrospective non-randomized study, over a duration of 5 years, in the department of Otorhinolaryngology and Head-Neck surgery, HIMSR, New Delhi. Patients had stage I to resectable stage IV disease and received radiotherapy alone (60 Gy or more), as an adjuvant to surgery either postoperatively or in combination with chemotherapy (50–55 Gy).

Exclusion criteria

Patients having clinically unresectable disease or with poor general condition at presentation were not included in the study. Also patients having one or more nodules in the thyroid gland as well as those who had undergone laryngectomy before irradiation or after irradiation (thyroid lobectomy is often a part of laryngectomy) were excluded from the study even if they were euthyroid at presentation.

Before initiation of treatment, all patients underwent basic investigations including hemogram, liver & renal function tests, chest X-ray, thyroid function tests, imaging of the primary site and neck and histopathology of biopsy from primary site. Detailed history and physical examination with particular emphasis to that of hypothyroidism, was done in every follow-up visit and thyroid function tests were done at 6 weeks after completion of radiation and thereafter at 3 months interval till 1 year and 6 monthly thereafter. Patients were divided in three groups: radiotherapy group, those who received chemo-radiation and those in whom both surgery and postoperative radiotherapy was given. Values of TSH (Thyroid Stimulating Hormone), T3 (tri-iodothyroxine) and T4 (thyroxine) were analyzed at baseline and at 6 months follow-up. Subclinical hypothyroidism was taken as TSH value of > 4.0 mU/L (milliunits per liter) and clinical hypothyroidism was taken as decreased T3 & T4 with raised TSH > 10 mU/L as per the European Thyroid Association 2013 guidelines.

RESULTS

100 patients of head and neck cancer who were treated in our hospital were included in this retrospective study. Out of these, 84 were male and 16 were female (the male: female ratio was 5.2:1). The majority of patients belong to the age group of 40–50 years with the age range of 22–76 years. The majority of these patients had a primary tumor in the oral cavity (74%) in which the most common subsite was the gingivobuccal complex (39/74) (Fig. 1.). Most of the tumors (96%) were squamous cell carcinoma while 4% were adenoid cystic carcinoma. Most of the patients had an advanced stage at the commencement of treatment, 46% had stage IV and 34% stage III (Fig. 2.). Surgery and postoperative radiotherapy were given to 76% of patients. In all of these 76 patients, neck dissection as a part of surgical procedure was done (Modified Radical Neck Dissection 47%, Selective Neck Dissection 29%). 2% of patients were treated by radiotherapy alone while 22% of patients were treated by chemo-radiation (Tab. I.).

The overall incidence of clinical and subclinical hypothyroidism was 6% and 21%, respectively. 73% of patients were euthyroid. The incidence of clinical hypothyroidism was 4.5% in patients in whom radiotherapy and chemotherapy was given while it was 6.57 % in patients in whom surgery and postoperative radiotherapy were given (Fig. 3.). Out of two patients who received only radiotherapy as a treatment modality, none developed clinical hypothyroidism (Tab. I.). The incidence of subclinical hypothyroidism was also higher (22%) in the surgery and postoperative radiotherapy group as compared to those who received both radiotherapy plus chemotherapy (13%). Out of two patients who received curative radiotherapy, one developed subclinical hypothyroidism. After follow-up of 3 months, the incidence of subclinical hypothyroidism in our patients was 2%, while none of the cases had clinical hypothyroidism. This incidence increased with time and at the end of 2 year follow-up, the incidence of subclinical hypothyroidism was 21%, while that of clinical hypothyroidism was 6%.

DISCUSSION

The thyroid gland is the largest pure endocrine gland of the body producing two main thyroid hormones (T3 & T4) which are very important in normal growth and development of the human body. Radiation effects on the thyroid gland in head and neck cancer patients were first reported in the 1960 s [12–14]. The exposure of

Tab. I. Table depicting post-treatment thyroid function status at the end of two year follow-up.

THYROID FUNCTION STATUS	RADIOTHERAPY WITH SURGERY		RADIOTHERAPY ALONE		RADIOTHERAPY WITH CHEMOTHERAPY	
CLINICAL	No. of cases	Percentage	No. of cases	Percentage	No. of cases	Percentage
	5	6.5	0	0	1	4.5
SUBCLINICAL	17	22.3	1	50	3	13.1
EUTHYROID	54	71	1	50	18	81.8

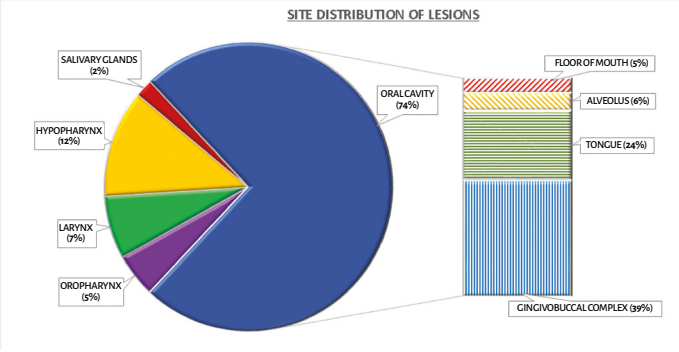

Fig. 1. Site distribution of lesions.

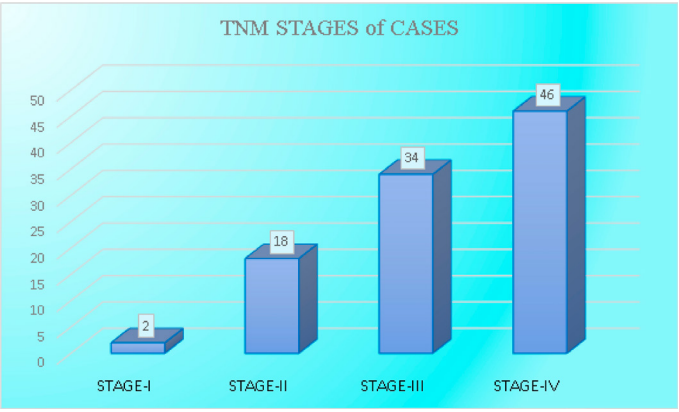

Fig. 2. TNM stages of cases.

radiotherapy to the surrounding tissues in the head and neck area is inevitable due to disseminated irradiation and complex anatomy.

Damage to the thyroid gland by radiotherapy can lead to various thyroid disorders, of which the most common clinical late effect is primary hypothyroidism. This effect may be clinical hypothyroidism characterized by low free T4 and high TSH or subclinical (biochemical or compensated hypothyroidism) with normal free T4 and high TSH [15]. Many theories have been postulated to explain the exact mechanism of thyroid injury due to radiotherapy. Several authors confirm that the damage is due to small vessel destruction and damage to the thyroid capsule [16]. Some also postulate poor dietary habits, prolonged Ryle's tube feeds or immune mediated damage [15, 17, 18].

The reported incidence of hypothyroidism after radiotherapy in various studies is between 6% and 48%, with most analyses reporting it between 20% and 30% [3–11]. The incidence of hypothyroidism can also be as high as 67%, as reported by Mercado et al. on 100 patients of head and neck cancer patients in which hemi-thyroidectomy was not performed [10]. In our study, the incidence of hypothyroidism was 27% at the end of two year follow-up which is in accordance with these studies. Out of these, 21 have developed subclinical hypothyroidism in our study and 6% have developed clinical hypothyroidism. The exact reasons for these varied results in different studies are not entirely clear. One of the factors influencing the incidence of hypothyroidism in head and neck cancer patients is the treatment which they have received. The risk is higher in patients in whom a part or the whole thyroid has been removed as part of the surgical procedure followed by radiotherapy as compared to those who have received radiotherapy alone. It is also reported to be higher in patients in whom cervical surgery (neck dissection) plus radiotherapy has been done as compared to those receiving just radiotherapy or chemo-radiation [19–22]. A similar finding was observed even in our study. The incidence of hypothyroidism was higher (28.9%) in the surgery plus radiotherapy group as compared to individuals who had received just radiotherapy (18.18%). The incidence of subclinical hypothyroidism was higher in patients receiving postoperative radiotherapy (22%) as compared to those who have received chemo-radiation (13%). Similarly, clinical hypothyroidism was also greater in the postoperative radiotherapy group (6.5%) as compared to the chemo-radiation group (4.5%). Some authors postulate that a higher incidence in the surgery and radiotherapy group is due to damage to the arterial supply of thyroid or surgical manipulation of thyroid [23].

The timing of onset of clinical or biochemical hypothyroidism is also different in various studies. It generally occurs within 1.5 to 3 years after giving RT to the head and neck area. In our study, the mean duration of the onset of hypothyroidism was 13.5 months. It can be as early as 4 weeks and as late as 20 years [4, 8, 10, 24]. Nishiyama et al. postulated that early onset in some patients could result from the fact that they might have had occult hypothyroidism which could have been aggravated by damage induced by radiotherapy [24]. Late onset of hypothyroidism could probably be due to late thyroid injury through vessel damage, fibrosis or thyroid cell atrophy [25, 26]. Apart from the treatment methods (radiotherapy or surgery) used in head and neck cancer patients, there are many factors that have been postulated to influence the development of hypothyroidism like age, sex, stage, site of tumor, nodal status, radiotherapy techniques etc. [4–8, 10, 11, 21, 24, 27, 28].

Many studies have reported a higher incidence of hypothyroidism in younger patients who have received radiotherapy as compared to older patients, while some have found no correlation between them at all [8, 29]. Hypothyroidism has also been found to be higher in females in some studies [11, 15]. Various authors also report a higher incidence of hypothyroidism in patients who had an advanced stage at the time of presentation, than in those with an early

Fig. 3. Myxedema.

stage of tumor. Similarly, a higher incidence has also been reported in some studies with advanced nodal status. This could be due to the fact that the involvement of neck nodes increases the bulk of tumor area to be irradiated, and consequently the risk of the thyroid's exposure [29]. This was probably because an advanced tumor receives a higher radiotherapy dose to the low neck area and patients were more likely to undergo neck dissection [6]. Even in our study, most patients were at an advanced stage at the beginning of treatment. The limitation of our study was that no correlation between the above risk factors and the incidence of clinical/biochemical hypothyroidism could be found.

It was a common belief that newer radiotherapy techniques would have a lesser incidence of hypothyroidism as they allow better dose distribution with a lower dose to known target organs. However, many studies have found no correlation between the technique of radiotherapy used and the incidence of hypothyroidism. It could be because all radiotherapy techniques involve the use of midline neck shielding [29]. With regards to the dose of radiotherapy given, Posner et al. did not find any correlation between the radiation dose and hypothyroidism incidence [11]. A similar finding was reported by Mercado et al. in their study on 155 patients. They analyzed that the incidence of hypothyroidism was not related to the radiotherapy dose to the primary site or to the neck but found race as the only significant factor [10]. On the contrary, other studies report a direct correlation between radiation doses with hypothyroidism [25, 26]. In their study on 45 patients, Nirmala et al. reported that the radiation dose above 40 Gy is not a significant factor contributing to hypothyroidism [30]. In our study, the radiotherapy dose and radiotherapy treatment schedule were similar for all patient and the correlation between these parameters and hypothyroidism incidence could not be assessed. Subclinical hypothyroidism is defined as normal free T4 and raised TSH with the absence of clinical signs of hypothyroidism. The significance of this disorder and whether to treat these patients is still not clear. The literature suggests that even subclinical hypothyroidism may predispose patients to atherosclerotic cardiovascular disease. Since head and neck cancer patients are already at a higher risk of cardiovascular disease, this further increase in risk is a matter of concern [27]. Treatment of subclinical hypothyroidism following radiotherapy consists either in observation or starting thyroid hormone replacement at the first sign of TSH elevation even if there are no symptoms. It is generally reported that subclinical hypothyroidism following radiotherapy gradually progresses to clinical hypothyroidism [6]. Even in our study, we had started thyroid hormone replacement in patients of both subclinical and clinical hypothyroidism. Garcia Serra et al. [6] recommended that TSH be monitored every 6 months for the first year and every year thereafter. It is also postulated that subclinical hypothyroidism progresses to clinical hypothyroidism in a due course of time [4, 19]. It is also said that a high serum level of TSH persisting for a significant duration increases the risk of thyroid carcinoma [31]. In our study, we did not find any incidence of benign or malignant thyroid tumor in our patients treated with radiotherapy. However, our study was limited in that the follow-up duration of 2 years in these patients was not long enough to support these facts.

CONCLUSION

The incidence of hypothyroidism is high in head & neck cancer patients receiving radiotherapy. The risk is higher in patients who undergo surgery as multi-modality treatment in combination with radiotherapy. Regular thyroid function test is, therefore, recommended to prevent thyroid dysfunction by timely intervention.

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