

Iatrogenic hypothyroidism: A consequence of external beam radiotherapy to the head & neck malignancies

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ABSTRACT

Background: Hypothyroidism is a known consequence of external beam radiotherapy to the neck encompassing part or whole of the thyroid gland for over 40 years. Still thyroid function tests are not a part of routine follow up of head – neck cancer patients treated with radiotherapy with or without surgery and / or chemotherapy.

Aim: Aim of this study was to find out the incidence of hypothyroidism in head – neck cancer patients treated with radiotherapy with or without chemotherapy where radiation portals included most or whole of the thyroid gland.

Materials and Methods: From September 2001 to November 2003, 187 patients with head-neck malignancies were treated with external beam radiotherapy whose radiation portals included part or whole of the thyroid gland with / without chemotherapy. Thyroid function tests were done at the beginning of treatment, at six weeks after completion of radiotherapy and thereafter at six weeks interval for two years.

Results: Out of 187 patients, five were excluded from the study as they were found to be hypothyroid before the initiation of treatment. Another four were excluded from result analysis because they underwent laryngectomy for uncontrolled disease. Of the patients attending the follow up clinic, 17.8 % and 21.8 % were found to have clinical and sub-clinical hypothyroidism at two year.

Conclusion: As a significant number of patients develop hypothyroidism following radiotherapy to the neck, thyroid function tests should be included in the routine follow up protocol of such patients. But certain questions have emerged from this study which need a large randomized study to find out the answers.

Key words: Iatrogenic hypothyroidism, Thyroid function tests, Head & neck malignancies, Teletherapy

INTRODUCTION

Carcinoma of the head & neck region is the 5th most common malignancy worldwide^[1] and commonest malignancy among Indian males, as per ICMR reports, probably due to increased use of chewing tobacco and smoking. External beam radiation is an integral part of management of such malignancies, used either alone (in early stage tumors) or in combination with surgery and / or chemotherapy (in advanced stages). Target volume of irradiation usually includes part or whole of the thyroid gland. Though adult thyroid cells are relatively radio-resistant due to their low proliferative index^[2], hypo-function of the thyroid gland is a known side effect of radiotherapy to the head and neck malignancies for more than 40 years^[3]. After external beam radiotherapy to the neck, the documented incidence of hypothyroidism varies widely, from 03 %^[4] to 44 %.^[5] When sub-divided, incidence of clinical hypothyroidism (elevated serum Thyroid Stimulating Hormone level and depressed serum Thyroxin level)

varies from 5 to 10%^[6,7] and that of sub-clinical hypothyroidism (elevated serum Thyroid Stimulating Hormone level and normal serum Thyroxin level) is about 6%^[8] in other series. Addition of surgery to the neck region vastly increases the incidence of hypothyroidism but addition of chemotherapy probably has little or no effect.^[9]

Though hypothyroidism has a significant impact on the quality of life, assessment of thyroid function is not yet a part of routine follow up of head and neck cancer patients, even in long term survivors.

In this ongoing non randomized prospective study we have tried to assess

1. Risk of developing hypothyroidism in our patients with head & neck malignancies, where radiation portals included whole or most of the thyroid gland.
2. Whether addition of chemotherapy has any additional effect on developing hypothyroidism in these patients.

MATERIALS AND METHODS

Patients

From September 2001 to November 2003, 187 patients with histologically proved head & neck malignancy of epithelial origin, who were destined to receive external beam radiotherapy to the primary site as well as to the neck, and whose radiation target volume will include whole or most of the thyroid gland, were included in a prospective non-randomized study in the department of Radiotherapy of Nilratan Ratan Sircar Medical College & Hospital, Kolkata. The patients may or may not receive neo-adjuvant or concurrent chemotherapy as part of their management and the decision was left in the hand of the concerned radiation oncologists. Patients having T4 tumors or N3 neck nodes or distal metastasis at presentation were not included in the study because of their expected short survival and possible invasion of the thyroid gland itself (in case of T4 tumors of the larynx). Similarly patients having one or more nodules in the thyroid gland as well as those who underwent laryngectomy before irradiation (thyroid lobectomy is often a part of laryngectomy operation) were also excluded from the study, though they may be euthyroid at presentation. Similarly patients who underwent laryngectomy after irradiation due to uncontrolled tumour were also excluded from the result analysis.

Patient characteristics are shown in Table 1.

Treatment

Of the 187 patients, 93 (49.7 %) were planned to receive radiotherapy alone, 71 (38 %) to receive neo-adjuvant chemotherapy with Cisplatin & 5 FU and the rest 23 (12.3%) patients to receive concurrent chemo-radiation. In neo-adjuvant setting, Cisplatin was given in a dose of 50 mg / sq. meter per day on days 1 & 2 and 5-FU 600 mg / sq. meter per day by short infusion on days 1,2 & 3. The cycle was repeated at 21 days interval for 3-4 cycles to be followed by

external beam radiotherapy. In concurrent setting, Cisplatin 20 mg / sq. meter and 5-FU 300 mg / sq. meter were given weekly for five weeks along with radiotherapy, preferably on Fridays to give rest to the patients on weekends for recovery. All patients with or without completion of the proposed neo-adjuvant chemotherapy course, were treated with radiotherapy to the primary site as well as to the neck nodes covering the entire or most of the thyroid gland. Proposed dose of radiotherapy was 6000 – 6600 cGy in 30 to 33 fractions over a period of 40 to 45 days and was delivered by parallel opposing lateral beams with appropriate wedges with Tele-cobalt machine.

Investigations

Before initiation of treatment, all patients underwent

1. Detailed history taking and physical examination, including thyroid gland
2. Complete blood count
3. Kidney function tests
4. Liver function tests
5. X-ray chest
6. CT scan of the primary site and the neck, whenever possible
7. Thyroid function tests.

Treatment started only when the blood examination reports were within normal limits. Thyroid function tests were done by chemiluminescence technique and the accepted normal values were T3: 60.0 – 181.0 ng / dl; T4: 4.5 – 12.6 μ g / dl; and TSH: 0.35 – 5.50 μ IU /ml.

We were not able to organize tests for antibodies against either thyroperoxidase or thyroglobulin where a positive result could indicate thyroiditis.

Detailed history and physical examinations with particular emphasis to those of hypothyroidism, were done in every follow up visit and thyroid function tests were repeated at six weeks after completion of radiation and thereafter at six months interval.

Table 1

| Patient Characteristics (n = 187) | |
|-----------------------------------|----------------|
| Age | |
| Range | 32 to 78 years |
| Median | 53 years |
| Sex | |
| Male | 159 (85%) |
| Female | 28 (15%) |
| Primary Tumor Site | |
| Oral cavity | 24 (13%) |
| Oropharynx | 49 (26%) |
| Larynx | 91 (49%) |
| Hypo-pharynx | 21 (11%) |
| Naso-pharynx | 02 (01%) |
| Neck Node | |
| N 0 | 41 (22%) |
| N 1 | 88 (47%) |
| N 2 | 58 (31%) |

RESULTS

Of the 187 patients, entered in the study, five were excluded after the first thyroid function tests as two of them had clinical and three sub-clinical hypothyroidism and primary goal of our study was to know the effect of radiation on normal thyroid functions and whether effect can be modified by chemotherapy or not. 182 patients were available for the study, of whom 91 patients received radiotherapy only, 68 received neo-adjuvant chemotherapy and the rest 23 patients received concurrent chemo-radiation.

Of the 68 patients selected to receive neo-adjuvant chemotherapy, 41 patients completed the proposed four cycles,

23 completed three cycles and the rest four patients discontinued after two cycles, mostly due to hematological toxicities and to some extent due to their unwillingness to continue further.

Of the 23 patients planned to receive concurrent chemoradiation, 14 completed the five cycles and in the rest chemotherapy was discontinued after three or four cycles mainly due to acute mucosal toxicities.

Whatever be the number cycles of chemotherapy the patients have received, all of them have received external beam radiotherapy. 55 patients received 6600 cGy, 82 received 6000 cGy, 21 discontinued between 5000 – 6000 cGy and the rest discontinued in between 4000 to 5000 cGy.

All the selected patients were euthyroid at beginning of therapy but the incidence of hypothyroidism increased with the passage of time. The results have been shown in [Table 2]. The time period was calculated from the date of completion of radiotherapy. Of the patients with uncontrolled disease post irradiation, four underwent laryngectomy and therefore they were excluded from the analysis, leaving behind 178 patients.

DISCUSSION

Besides surgical intervention, radiotherapy is the only known curative management for the patients with head and neck malignancies. It may be used either alone or in combination with surgery and/or radiotherapy. In 1961, Felix et al^[3] first reported a case of hypothyroidism six years after treatment with external radiotherapy, in a patient of laryngeal carcinoma. Since then, several other investigators have reported the occurrence of hypothyroidism in patients who have received radiotherapy in the neck region. Despite these reports, tests for thyroid functions are not yet included in the follow up protocols of patients with head and neck malignancies.^[10]

Estimation of the magnitude of the problem is very difficult and confusing because of the fact that some series have included patients treated with radiotherapy alone,^[11,12] while

others have included patients that had hemi-thyroidectomy as a part of laryngectomy, in addition to pre- or post-operative radiotherapy.^[13,5,14]

In their study, with a median follow up of 4.4 years, Mercado et al^[15] reported 48 % and 67 % Kaplan – Meier projected incidence of hypothyroidism at 5 and 8 years respectively, when patients with head and neck malignancies were treated with external beam radiotherapy with or without concurrent chemotherapy. The median time to the development of hypothyroidism was 1.4 years. Turner et al^[12] reported 14.3% incidence of clinical and 23.8% sub-clinical hypothyroidism following radiotherapy to the whole of the thyroid gland. They estimated that by 5 years up to 40% of the patients may become hypothyroid. Their estimated incidence of hypothyroidism at 5 years is almost similar to that of Mercado et al but Tell et al^[16] reported a much lower incidence. They treated 264 patients with head and neck malignancies by external beam radiotherapy and at a median follow up of 19 months, 6 % patients developed clinical and 22 % sub-clinical hypothyroidism. Median time to develop hypothyroidism was 15 months. In their series, incidence of sub-clinical hypothyroidism was significantly higher when whole of the thyroid gland was included in the target volume compared to patients where only part of the thyroid gland was irradiated.

There is a general agreement that hypothyroidism is a much more common complication following combined surgical and radio-therapeutic management of head and neck cancers with a frequency ranging in literature from 43 to 66 % often depending upon the duration of follow up^[5,9,14]. On the other hand, some researchers have claimed that hypothyroidism is a rare or nonexistent complication of radiotherapy alone to the neck.^[17,14]

At 2 years, overall incidence of clinical hypothyroidism of our reported patients was 17.8% and of sub-clinical hypothyroidism was 21.8%. Due to diversity of reported incidences, type of managements and duration of follow up in published series, it is almost impossible to compare our results with others. Again as it is a late effect, it is expected that with the passage of time the incidence will increase and some of

Table 2: Incidence of hypothyroidism with passage of time

| Post RT timePeriod | Clinical Hypothyroidism | | | | | Sub-clinical Hypothyroidism | | | | | Number of patents attended in follow up visit | | | | |
|----------------------------------|-------------------------|-------|--------|-------|-------|-----------------------------|----|--------|--------|-------|--|--------|-------|----|----|
| | RT only | | NCT-RT | | CT-RT | RT only | | NCT-RT | | CT-RT | RT | NCT-RT | CT-RT | | |
| 6 Weeks | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 01 | 4.3% | 86 | 66 | 23 |
| 6 Months | 0 | 0% | 0 | 0% | 01 | 4.5% | 02 | 2.5% | 02 | 3.2% | 01 | 4.5% | 81 | 62 | 22 |
| 12 Months | 03 | 4.2% | 02 | 3.7% | 02 | 9.5% | 04 | 5.5% | 04 | 7.4% | 02 | 9.5% | 72 | 54 | 21 |
| 18 Months | 06 | 9.7% | 06 | 12.5% | 02 | 11% | 07 | 11.3% | 08 | 16.6% | 03 | 16.6% | 62 | 48 | 18 |
| 24 Months | 08 | 16.6% | 07 | 17.9% | 03 | 21% | 10 | 20.8% | 09 | 23% | 03 | 21.4% | 48 | 39 | 14 |
| Mean hypothyroidism at 24 Months | | | 17.8 % | | | | | | 21.8 % | | | | | | |

RT: External beam radiotherapy

NCT-RT: Neo-adjuvant chemotherapy and radiotherapy

CT-RT: Concomitant chemotherapy and radiotherapy

the patients with sub-clinical hypothyroidism will progress to clinical one. In this report, our maximum follow up is two years only.

Dose of radiation required to produce hypothyroidism is also confusing. DeGroot^[18] and Hancock et al^[19] suggested that radiation doses in the range of 3000 to 8000 rads are required to produce hypothyroidism. At the same time Hancock et al^[20] reviewed 1787 patients of Hodgkin's disease treated with Mantle field irradiation in the dose of 3500 – 4500 cGy and estimated a 43% actuarial risk of developing hypothyroidism at 20 years.

Still very few studies have described the effect of chemotherapy on thyroid gland. Bajorunas^[21] mentioned L-asparaginase as an agent that may depress thyroid function. It is expected that chemotherapy, particularly concurrent chemotherapy will sensitize the thyroid gland to radiation and will increase the incidence of hypothyroidism. But Posner et al,^[9] Weissler et al^[22] and Sinrad et al^[23] found no effect of combination chemotherapy on thyroid gland in patients with head and neck malignancies. In our patients also we have not found any significant effect of chemotherapy, whether neo-adjuvant or concurrent, on thyroid gland, though both clinical and sub-clinical hypothyroidisms were a bit more common in the concurrent group. But as the number of patients was very small in that group, the incidence has failed to reach a clinically significant level.

How radiotherapy produces hypothyroidism is also incompletely understood. This may be due to direct follicular destruction or prevention of cell division or vascular damage to the thyroid gland or immunologically mediated damage to the thyroid gland or a various combination of the factors. Histological examination of the thyroid gland after external irradiation has documented follicular cell damage and vascular damage following doses as low as 225 cGy.^[12] An immunologic influence has been suggested by Einhorn & Wikholm.^[24] Because adult thyroid cells in vivo are not expected to have a high turnover rate and are well differentiated, it has been postulated that they may undergo radiation induced apoptosis, varying between different patients.

Most of the common signs & symptoms of hypothyroidism e.g. depression, lethargy, skin changes, constipation, weight gain (> 10% of original body weight) etc are ill defined and can be easily overlooked in cancer patients. Because there is a high rate of co-morbidity in them and the disease and its' treatment may have nutritional, physical and psychological consequences in these patients, that may easily mask the clinical features of hypothyroidism. For these reasons, clinical examination of the cancer patients for features of hypothyroidism is not a reliable one.

We have found no effect of age, sex, primary site, neck node status or radiation dose on the incidence of hypothyroidism. Similar were the findings of Mercado^[15] and Tell.^[16]

CONCLUSION

We undertook the study to find out the incidence of hypothyroidism in our patients treated with external beam radiotherapy to the neck and whether addition of chemotherapy has any additional effect or not. Because supplementation of thyroxin will vastly change the quality of life of the hypothyroid patients. But after two years of study we have come out with more questions than answers. Only one thing can be said with certainty that thyroid function tests should be included in the follow up protocol of patients receiving radiation to the neck that has included part or whole of the thyroid gland. The questions remained to be answered

1. When to start the thyroid function tests?
2. How long it will be carried out in euthyroid patients?
3. At what interval the tests are to be done?
4. Does concurrent chemo-radiation increases the incidence of hypothyroidism significantly?
5. Should thyroxin be given to the sub-clinical hypothyroid patients and has it any significant effect on their quality of life?

A large randomized study is needed, preferably multi centered to find out the answers of these questions.

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