ejpmr, 2017,4(4), 642-647

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

ASSESSMENT OF HYPOTHYROIDISM IN LOCALLY ADVANCED HEAD AND NECK CANCER TREATED WITH CONCURRENT CHEMO-RADIOTHERAPY

Usha Singh*, Rita Rani, Vinita Trivedi, Richa Chauhan, Abha Kumari and Vasudha Singh

Department of Radiotherapy Mahavir Cancer Institute and research Centre, Patna.

Corresponding Author: Dr. Usha Singh

Department of Radiotherapy Mahavir Cancer Institute and research Centre, Patna

Article Received on 20/02/2017 **Article Revised on 12/03/2017** **Article Accepted on 01/03/2017**

ABSTRACT

Head and neck cancer is 6th most common malignancy world wide.Thyroid gland centrally situated in neck will invariably be included in radiation portal. Tolerance dose of thyroid gland depends upon percentage of thyroid volume receiving radiation.

The present study aimed to evaluate thyroid dysfunction in patients of head and neck cancer treated with concurrent chemoradiotherapy.

This is a prospective non randomized study of 55 patients of locally advanced head and neck cancer patients receiving radiotherapy with median follow up of 2.5 years.

At one month of follow up no hypothyroidism was detected. After six months of treatment hypothyroid were detected in 9% patients .After one year of treatment incidence of hypothyroidism were increased to 36.36% After two years of treatment incidence of hypothyroidism increased to 49.09% out of which 56% patients having clinical hypothyroidism and 44% had sub clinical hypothyroidism.

It was remarkably noted that hypothyroidism were more frequent in female patients in comparison to male. After one year of treatment 54% female developed hypothyroidism while it is observed only in 22.72% male. After two years of treatment 72.72% female had hypothyroidism (P value - 0.0213) while only 43.18% male developed hypothyroidism (P value - < 0.0001, which is highly significant).

Radiation induced hypothyroidism is seen as late complication. Hypothyroidism causes considerable morbidity to patients who undergo chemoradiotherapy. Screening protocol for thyroid dysfunction should be mandatory as routine follow up.

KEYWORDS: *Head and neck cancer*, *hypothyroidism*, *radiotherapy*, *subclinical hypothyroidism*.

1. INTRODUCTION

Head and neck cancer is 6th most common malignancy worldwide. This is one of the commonest malignancies among Indian males. This is probably due to the increased use of tobacco in various forms. The treatment of head and neck cancers include surgery, radiotherapy (RT), chemotherapy, and a combination of these. Radiation with or without chemotherapy is the major treatment modality in locally advanced head and neck cancer.

In Head and-neck cancer patients, radiation doses to the lower neck range from 46 -50 Gy for patients with clinically node-negative disease, to 70 Gy for regions for tumor involvement. Radiation portals, apart from including the primary site of the tumor, will invariably cover the whole neck, thereby including the thyroid gland in the radiation field leading to its dysfunction. Apart from excellent loco-regional control, radiation is often associated with late side effects like xerostomia, dysphagia, hypothyroidism, and subcutaneous fibrosis. Hypothyroidism, being one of them, is a frequently occurring late side effects after curative treatment. The incidence of hypothyroidism after radiation therapy varies between 19% and 53% [Boomsma et al, 2011]. This is much higher than observed in the normal population, in which the prevalence of hypothyroidism is approximately 8% in women and 3% in men [Vanderpump et al, 2002, Hancock et al, 1995]. Hypothyroidism after radiation therapy occurs at a median interval of 1.4-1.8 years [Boomsma et al, 2011]. Radiation-induced hypothyroidism is an irreversible condition, first reported in 1929[Nishiyama K,1996]

Hypothyroidism is classified as clinical or subclinical depending upon laboratory results and presence of symtoms. Clinical hypothyroidism is defiend as an increase in thyroids stimulating harmones (TSH) and decrease in thyroxine (T4) and presence of symptoms eg.weight gain, cold intolerance, fatigue and so on. Subclinical hypothyroidism is defiend as increase in TSH with normal level of circulating T4 and no symptoms. The etiology of radiation induced hypothyroidism is thought to be related to radiation induced fibrosis of gland capsules, vessels damage or autoimmune reaction[Cannon et al, 1994, Feehs et al,

1991, LoGalbo et al, 2007]. In the majority of cases, subclinical hypothyroidism evolves to clinical hypothyroidism.[Tunbridge et al, 1977] .Progression to clinical hypothyroidism occurs at a rate of about 5 to 20% per year. This is a condition requiring lifelong thyroid hormone replacement therapy. Levothyroxin is the drug which helps in reversing the symptoms of hypothyroidism [Larsen, 2003].

2. METHODS AND MATERIALS

This is a prospective non randomized study .Total 55 patients of locally advanced head and neck cancer patients either primary or postoperative cases receiving radiotherapy with or without chemotherapy were included in study during periods of January 2013 to February 2014.This study was done in department of Radiation oncology of the Mahavir Cancer Sansthan Patna which was approved by their ethical committee followed during median follow up of 2.5 years. Data was collected and statistical analysis for ANOVA through graphpad prism software.

Inclusion criteria comprised of patients of age between 18 to 70 years of KPS >70. They were previously untreated patients with normal thyroid function, kidney function, liver function tests and complete blood counts. Assessment for thyroid function included analysis of Free T3 (normal value-0.6 -1.8ng/ml), Free T4 (normal value-1.9 -13.3ng/ml) and TSH (0.35 -5.5 uIU/ml). Thyroid function test was done before External beam radiotherapy, after completion of radiotherapy at intervals of 1 month, 6 months, 1year and 2years. Hypothyroidism was defined as increase of serum TSH value greater than maximum value of lab range regardless of symptoms.

The thyroid gland was included in the radiation field either used to treat primary tumor or regional lymph node areas. All patients were treated on Tele Cobalt machine.

2.1: Radiotherapy detail-

External beam radiotherapy were delivered by telecobalt machine using bilateral parallel opposed beam for treating primary tumor and lymph node with standard fractionation 2 Gy per fraction 5 days per week.

Radiotherapy was delivered a total dose of 70Gy to tumor with margin and involved cervical lymph node and 46-50 Gy to remaining submicroscopic disease, when treated radically with chemoradiotherapy.

Radiotherapy 60-66 Gy to postoperative cases depending upon histopathological report. Suitable patients were treated by weekly concurrent chemo radiotherapy with cisplatin 30 mg/m2 body surface area.

Risk factors evaluated in this study included age, sex, tumor stage, tumor site radiotherapy dose, chemotherapy and time after treatment.

3. RESULTS

In this prospective nonrandomized clinical study out of 55 patients 44(80%) were males and 11 (20%) were females. Most of them belonged to age group of 30 to 70 years. Primary site of tumor was 21(38%) in oral cavity, 18(33%) in oropharynx, 10(18%) in larynx,6(11%) in hypopharynx. Most of the patients were of T2 19(34%) and N2 31(56%).status. Surgery were done in16 patients (29%) prior to chemoradiotherapy, majority cases were of oral cavity. 39 patients (71%)did not undergone surgery, because of unresectable or in view of organ preservation.Total 42 patients (76%) underwent concurrent chemoradiotherapy and 13 patients(24%) radiotherapy alone.

Out of 55 patients 12 patients received 60Gy/30#, 4 patients received 66 Gy/33# for they had positive margin and 39 patients were on treatment with radical intent for a dose of 70Gy/35#. Thus total of 16 patients were post operative,39 patients were treated radically with concurrent chemo radiotherapy.

At one month of follow up no hypothyroidism were detected. After six months of treatment hypothyroidism was observed in 9% patients. out of this one fifth developed clinical hypothyroidism and rest had developed sub clinical hypothyroidism.At the end of one year incidence of hypothyroidism increased to 36.36%, out of which 45% developed clinical hypothyroidism and 55% had sub clinical hypothyroidism.

After two years of treatment incidence hypothyroidism increased to 49.09% out of with 56% patients having clinical hypothyroidism and 44% having sub clinical hypothyroidism. It was remarkably noted that hypothyroidism was more frequent in female patients in comparison to males.

After one year of treatment 54% female developed hypothyroidism while it was observed only in 22.72% male. After two years of treatment 72.72% female had hypothyroidism (P value - 0.0213) while only 43.18% male developed hypothyroidism (P value - < 0.0001, which is highly significant).

Mean age of patients was 53.71 ± 1.374years. Mean age of male patients was 53.75 ± 1.612. Age of female patients was 53.55 ± 2.506. There is no change in age group of patients.

In age group of 51 to 60 years-out 0f 26 patients 17 (65.4%) patients developed hypothyroidism.

In 61 to 70 years age group of patients out of 12 patients 10(83.3%) patients developed hypothyroidism. In chemo radiotherapy treatment group 47% patients developed hypothyroidism. While in patients receiving radiotherapy at dose of 60Gy only 25% patients developed hypothyroidism while 56% patients developed hypothyroidism in patients who received 66Gy to 70

Gy.. In patients who received only radiotherapy hypothyroidism was observed in 53% patients.

Table 1-Age of the patients

Age(years)	No.of patients	% of patients
21-30	2	3
31-40	4	7
41-50	11	20
51-60	26	47
61-70	12	21

Table 2-Sex of the patients

Sex	No. of patients	% of patients
Male	44	80
Female	11	20

Table3- Tumor site

Site	No of patients	% of patients
Oral cavity	21	38
Oropharynx	18	33
Hypopharynx	6	11
Larynx	10	18
Nasopharynx	0	0

Table 4-Tumor stage

Tumor	No.of patients	% of patients
T1	14	26
T2	19	34
T3	8	14
T4	14	26

Table 5-Node stage

Node	No. of patients	% of patients
N0	4	7
N1	20	36
N2	31	56
N3	0	0

Table 6-Surgery done

	No. of patients	% of patients
Yes	16	29
No	39	71

Table 7-Radiation dose

Gy	No. of patients	% of patients
60	12	22
66-70	43	78

Table-8 Concurrent chemo radiotherapy

	No.of patients	% of patients
Yes	42	76
No	13	24

Table -9 Status of hypothyroidism after radiation

	1month	%	6month	%	1year	%	2 year	%
Normal	55	100	50	91	35	64	28	51
Subclinical	0	0	4	7	11	20	12	22
Clinical	0	0	1	2	9	16	15	27

The euthyroid group and hypothyroid group of patients were analysed with respect to different clinical parameters.

Table-10 Distribution of clinical factors between euthyroidism and hypothyroidism

Variables	Euthyroidism	Hypothyroidism at 2 years	P value
Age(years) 51-60	26	17	0.0004
Age(years)61-70	12	10	0.0705
Gender –Male-44	25	19	0.0018
Female-11	3	8	0.0036
Surgery-yes- 16	11	5	0.0015
No-39	17	22	0.0033
Concurrent chemoradiotherapy-Yes 42	22	20	0.0705 (NS)
No 13	6	7	0.2879 (NS)
Radiation dose 60 Gy-(12patients)	9	3	0.0017
66-70Gy(43 patients)	19	24	0.0034

4. DISCUSSION

Hypothyroidism after radiation for head and neck cancer is a common complication [Koc et al, 2009]. It affects the quality of life of cancer survivors because this complication occurs frequently[Nelson et al,2006]

The National Comprehensive Cancer Network (NCCN) recommends that thyroid function tests should be repeated every 6–12 months. Keeping this in mind this study was conducted in our hospital for patients undergoing radiotherapy for head neck cancer patients. Blood samples were collected for thyroid function test before and after radiotherapy at regular intervals. Impact of radiation on thyroid function was first reported in 1929.[Vanderpump et al, 2002]. A number of studies done as early as in 1960s have reported the development of hypothyroidism after radiation for head and neck malignancies. [Felix et al,1961 and Markson et al, 1965]

Documented incidences of primary hypothyroidism after RT have varied from 3 to 47%. An incidence of 20 to 30% has been reported by most investigators. [Bhandare et al, 2007] However in our study hypothyroidism was 9% at 6 months, 36% at 1 year and 49% at 2 years. This is at par with the various studies done. In general, it seems that external irradiation of the normal thyroid may cause dysfunction of the gland within months to years following treatment.

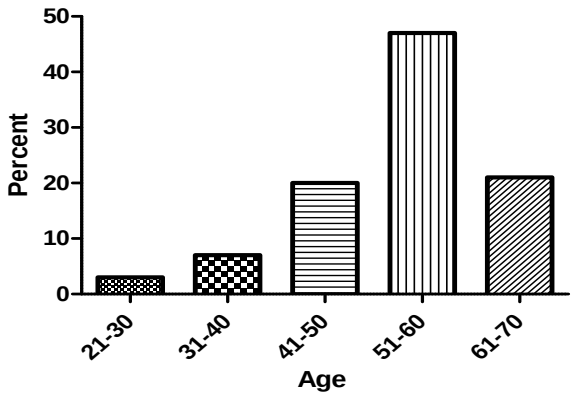
The study with the longest follow-up of patients was that presented by Einhorn and Wikholm. With 10-year follow-up in 41 patients of carcinoma of the larynx and hypopharynx treated with radiation, the incidence of established hypothyroidism was 7.3% [Einhorn et al, 1967]. In our study the duration of follow up is much shorter and incidence of hypothyroidism is quite high. This could be one of the reasons for higher incidence of hypothyroidism in our patients.

Therefore, efforts are needed to minimize the incidence of hypothyroidism after radiation with or without chemo therapy for head and neck cancer patients [Turner et al, 1995 and Mercado et al, 2001]

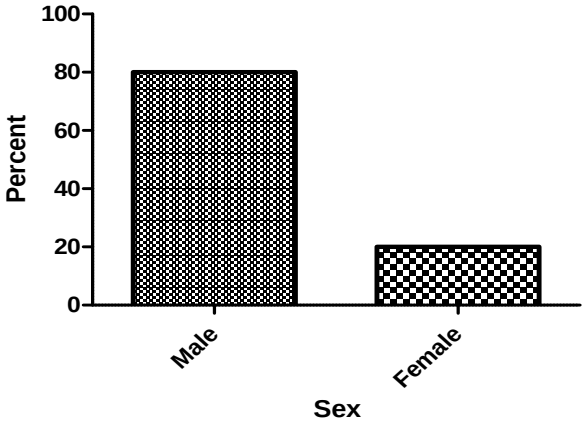
In our study, the age group of patients varied from 30 years to 70 years with a mean age of 53 years. Mean age for hypothyroidism as almost similar for both men and women. Majority of the cancers were seen to arise from the oral cavity(38%). The primary site varied in literature. Aich had a higher percentage of cancers arising from the larynx (49%) [Aich et al,2005].

The primary site of the tumor was not a significant factor as all the patients received whole-neck irradiation and hence uniformity in the volume of thyroid irradiated. Cooper has stated that recognizing and treating subclinical hypothyroidism early has benefits such as prevention of clinical hypothyroidism and reduction in lipid levels, thereby reducing the cardiac complications[Cooper et al, 2001]. Tell *et al*. recommend lifelong TSH testing, as the incidence of clinical hypothyroidism increase with time even after long-term follow-up[Tell et al, 2004].

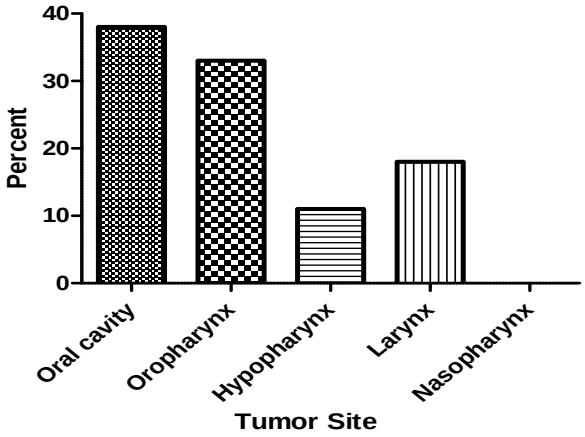
Graph-1: Age of Patients



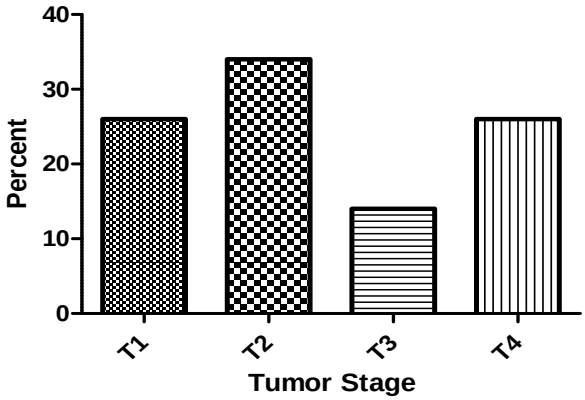
Graph-2: Sex of Patients



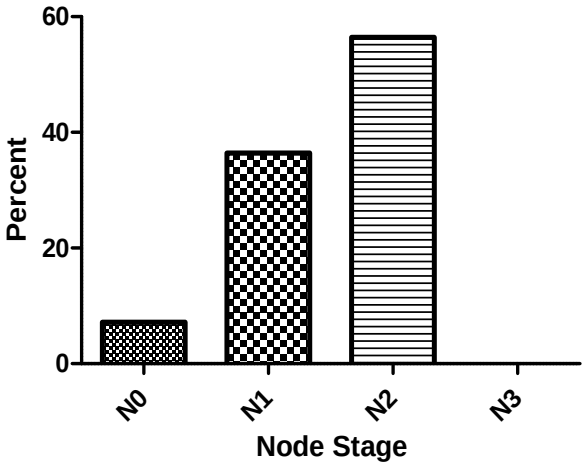
Graph-3: Tumor site of Patients



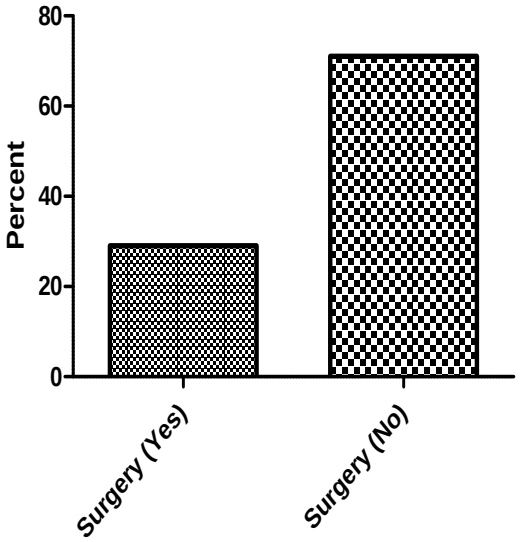
Graph-4: Tumor Stage of Patients



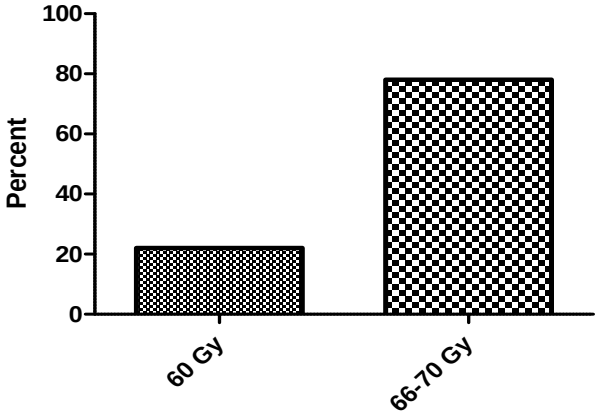
Graph-5: Node Stage of Patients



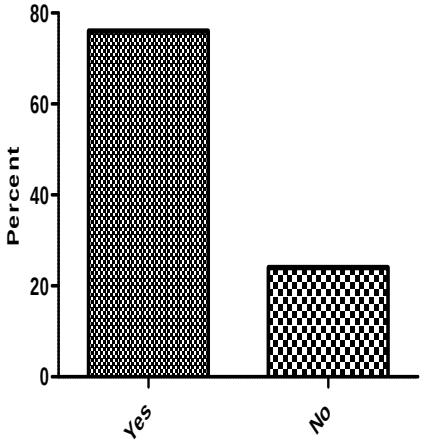
Graph-6: Patients undergone surgery



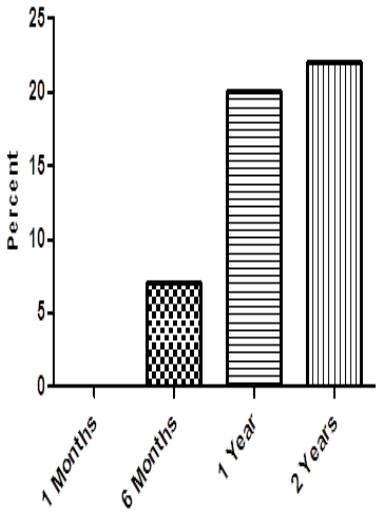
Graph-7: Radiation dose of Patients



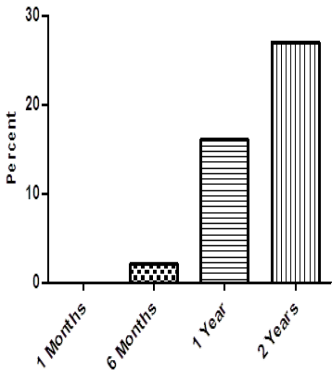
Graph-8: Patients received concurrent Chemo-radio therapy



Graph-9: Development of Subclinical hypothyroidism in patients



Graph-10: Development of Clinical hypothyroidism in patients



5. CONCLUSION

Hypothyroidism (clinical or subclinical) is an under-recognized but a significant complication of external beam irradiation to the neck. The incidence is anywhere between 3 and 40% and it increases with time, with a peak incidence seen at 2 to 3 years. It can occur as early as 3 months following radiation. It is commonly seen following a dose of 40 Gy to the whole neck. However, beyond 40 Gy dose is not a predictive factor. Addition of surgery, particularly thyroid surgery, has shown to increase the incidence, but addition of chemotherapy has shown no difference. Recognizing hypothyroidism (clinical or subclinical) early and treating it can prevent associated complications. Hence, thyroid function tests should be made routine during follow ups from as early as 3 months and carried out lifelong. Use of newer technologies like three-dimensional conformal therapy and Intensity-Modulated Radiotherapy can reduce the dose to the thyroid gland when identified as organ at risk and it can be limited to <40 Gy, which may in future reduce the occurrence of hypothyroid.

6. REFERENCES

1. Boomsma MJ, Bijl HP, Langendijk JA. Radiation-induced hypothyroidism in head and neck cancer patients: a systematic review. Radiat Oncol 2011; 99(1): 1-5.
2. Vanderpump MPJ, Tunbridge WMG. Epidemiology and prevention of clinical and subclinical hypothyroidism. Thyroid 2002; 12(10): 839-847.
3. Hancock SL, McDougall IR, Constine LS. Thyroid abnormalities after therapeutic external radiation. Int J Radiat Oncol Biol Phys. 1995; 31: 1165–70]
4. Nishiyama K, Tanaka E, Tarui Y, Miyauchi K, Okagawa K. A Prospective analysis of subacute thyroid dusfunction after neck irradiation. Int J Radiat Oncol Biol Phys. 1996; 34: 439–44.
5. Cannon CR. Hypothyroidism in head and neck cancer patients:experimental and clinical observations. Laryngoscope 1994; 104: 1–21.
6. Feehs RS, McGuirt WF, Bond MG, Strickland HL, Craven TE, Hiltbrand JB. Irradiation. A significant risk factor for carotid atherosclerosis. Arch Otolaryngol Head Neck Surg 1991; 117: 1135–7.
7. Lo Galbo AM, de Bree R, Kuik DJ, et al. The prevalence of hypothyroidism after treatment for laryngeal and hypopharyngeal carcinoma:are autoantibodies of influence ?Acta Otolaryngol 2007:127; 312-317
8. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: The Wickham survey. Clin Endocrinol (Oxf) 1977; 7: 481–93.
9. Larsen. Williams Textbook of Endocrinology. 10th ed. W B Saunders, Philadelphia, an imprint of Elseivers; 2003.
10. Koc M, Capoglu I. Thyroid dysfunction in patients treated with radiotherapy for neck. Am J Clin Oncol. 2009; 32: 150–3. [PubMed]
11. Nelson M, Hercbergs A, Rybicki L, Strome M. Association between development of hypothyroidism and improved survival in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg2006;132:1041–6.Jpn J Clin Oncol 2014; 44(4): 337.
12. Felix H, Dupre N, Drape M, Court L. Long term influence of radiotherapy for cancer of larynx on the appearance of myxedema. Lyon Med. 1961; 93: 1043–50.[Pu]
13. Markson JL, Flatman GE. Myxoedema after deep X-Ray therapy to the neck. Br Med J. 1965; 1: 1228–30.]]
14. Bhandare N, Kennedy L, Malyapa RS, Morris CG, Mendenhall WM. Primary and central hypothyroidism after radiotherapy for head and neck tumours. Int J Radiat Oncol Biol Phys. 2007; 68: 1131–9.
15. Einhorn J, Wikholm G. Hypothyroidism after external irradiation to the thyroid region. Radiology. 1967; 88: 326–8.]
16. Turner SL, Tiver KW, Boyages SC. Thyroid dysfunction following radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 1995; 31: 279–83.
17. Mercado G, Adelstein DJ, Saxton JP, Secic M, Larto MA, Lavertu P. Hypothyroidism: A frequent event after radiotherapy and after radiotherapy with chemotherapy for patients with head and neck carcinoma. Cancer. 2001; 92: 2892–7.
18. Aich RK, Deb AR, Pal S, Naha BL, Ray A. Latrogenic hypothyroidism: A consequence of external beam radiotherapy to the head neck malignancies. J Cancer Res Ther. 2005; 1: 142–6.
19. Cooper DS. Subclinical Hypothyroidism. N Engl J Med. 2001; 345: 260–5.
20. Tell R, Lundell G, Nilsson B, Sjödin H, Lewin F, Lewensohn R. Long term incidence of hypothyroidism after radiotherapy in patients with head and neck cancer. Int J Radiat Oncol Biol Phys. 2004; 60: 395–400.