Scholars Journal of Dental Sciences (SJDS) **ISSN 2394-496X (Online)**
Sch. J. Dent. Sci., 2015; 2(6):349-354 **ISSN 2394-4951 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com DOI: 10.36347/sjds.2015.v02i06.002

Research Article

Quantitative evaluation of serum iron, ferritin and Total iron binding capacity (T.I.B.C.) in patients with oral cancer and pre cancers

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Abstract: Iron is an essential nutrient playing a central role in metabolism and also is an essential component in DNA synthesis and respiratory and oxidative metabolism which relate to the properties of unremitting proliferation and a more anaerobic metabolism that may contribute to a selective advantage of neoplastic cells over non neoplastic cells. Clinical correlations have been made linking cellular iron content to the development of cancer in human. We investigated the correlation between the serum levels of iron, ferritin and T.I.B.C. (Total iron binding capacity) in patients with oral cancer and precancers. Study includes a total of 60 patients, which included 20 patients of histo pathologically confirmed oral cancer, 20 patients of histo pathologically confirmed oral precancers and 20 healthy controls. The serum levels of iron, ferritin and T.I.B.C. were evaluated. It was noted that there was decrease in levels of serum iron and serum ferritin in progressive stages of cancer. Also, there was decrease in levels of serum iron and ferritin in patients with O.S.M.F. as compared to patients with leukoplakia. There was a lot of variation in levels of various cases and was statistically not significant. The present study could not establish total iron levels as an early marker of oral cancer and precancer, but serum iron, ferritin, T.I.B.C. levels are good indicators of total iron levels and should be evaluated compulsorily in both oral cancer and precancer.
Keywords: serum iron, ferritin, Total Iron Binding capacity, oral cancer, precancer.

INTRODUCTION

Oral cancer has always been a great challenge to clinical science owing to the anatomic complexity associated to this region. Oral cancer constitutes as much as 4 percent of all malignant tumors in man of which oral squamous cell carcinoma being the 6 thmost common cancer worldwide[1].In India there is an striking incidence of oral cancer and it accounts for as many as 50% of all cancers. While cases of oral cancer are seen in patients who do not use tobacco, these constitute a very small percentage of oral cancer. OSCC may be preceded by clinically evident PMLs, particularly leukoplakias and oral sub mucous fibrosis [2]

Iron is one of the most abundant and necessary transition metals in the body. It is most commonly associated with the oxygen carrying function of heme iron, and the medical profession is more concerned with the effect of low iron which leads to anaemia, decreased oxygen carrying capacity of blood and related diseases. Non-heme iron participates in a range of reactions that are necessary for cell viability and cell proliferation. It is an essential component in DNA synthesis and in respiratory and oxidative metabolism. The role of iron in cancer etiology is supported by several possible mechanisms. As transitional metals, iron can generate the reactive oxygen species including hydroxyl radical. These reactive oxygen species can attack DNA and cause various DNA mutations thereby contributing towards pathogenesis of cancer [3]

Deficiency as well as excess body iron, both may cause carcinogenesis. Some researchers have emphasized that few habitual etiology have synergistic effect on iron to cause carcinogenesis[4].In case of pre malignancies it has been supposed that the transformed cells which are already existing may be affected by iron deficiency and may prove to be an etiological factor in promotion of precancerous and cancerous lesion of the oral cavity[5]

According to Weinberg [6] research and clinical observations during the past six decades have shown that: 1. Iron promotes cancer cell growth; 2. Hosts attempt to withhold or withdraw iron from cancer

cells; and 3.Iron is a factor in prevention and therapy of neoplastic disease. When studying indices of bodily iron stores in an untreated cancer patient, all these aspects have to be borne in mind, i.e. deficient or excess intake of iron could have contributed to the carcinogenesis, habits could have altered iron intake as well as its metabolism and influenced tumor genesis, and presence of the malignancy itself could have altered iron homeostasis [3].

Under these circumstances the present study is undertaken to correlate the levels of serum iron, serum ferritin and T.I.B.C. in patients suffering from oral cancer and precancer. And whether it could be used as an early marker.

MATERIALS AND METHODS

A detailed history of histo pathologically confirmed case of oral cancer(20) precancers (20) and 20 healthy patients including age, sex, and the duration of habits were taken and were subjected to quantitative assessment of serum iron, ferritin and T.I.B.C.

Method of measuring serum iron and T.I.B.C:

Iron and T.I.B.C.is quantitated by Ferrozine/T.I.B.C. measurement method using Vitros DT 60 II Automated chemistry analyzer/Bayer RA 50

Method of measuring serum ferritin:

Serum ferritin is measured by chemiluminescence technology which is done on fully automated ADVIA Centaur (Siemens India)

RESULTS

The mean values of Serum Iron in Cancer group is 69.3 ± 20 in Pre-Cancer group is 77.9 ± 25.3 and in Control group is 76.2 ± 11.2 . The P-value when Cancer group was compared with Pre-cancer group is 0.358, and when Cancer group and Pre-cancer group was compared with Control was 0.516 and 0.959 respectively, that is >0.05 and hence is statistically not significant. The mean values of Serum Ferritin in Cancer group is 49.9 ± 32.4 in Pre-Cancer group is 38.1 ± 31.3 and in Control group is 46.3 ± 6.7. The P-value when Cancer group was compared with Pre-cancer group is 0.334, and when Cancer group and Pre-cancer group was compared with Control was 0.900 and 0.585 respectively, that is >0.05 and hence is statistically not significant. The mean values of Serum T.I.B.C. in Cancer group is 362.8 ± 38.1 in Pre-Cancer group is 373.6 ± 34.7 and in Control group is 360.8 ± 17.6. The P-value when Cancer group was compared with Pre-cancer group is 0.523, and when Cancer group and Pre-cancer group was compared with Control was 0.979 and 0.407 respectively, that is >0.05 and hence is statistically not significant(Table 1).

Out of 20 patients in Cancer group ,serum iron in 15 patients(75%) was normal, 5 patients (25%) was lower than the normal range, for serum ferritin 15 patients(75%) was normal, 5 patients (25%) was lower than the normal range and for serum T.I.B.C. 19 patients(95%) were normal and 1 patient(5%) was above the normal level.

Out of 20 patients in Pre-cancer group, serum iron 15 patients(75%) was normal, 5 patients (25%) was lower than the normal range, for serum ferritin 12 patients(60%) was normal, 8 patients (40%) was lower than the normal range and for serum T.I.B.C. 16 patients(80%) were normal and 4 patient(20%) was above the normal level.

In Control group for serum iron 19 patients(95%) was normal, 1 patients (5%) was below the normal range, for serum ferritin 20 patients(100%) was normal and for serum T.I.B.C. 20 patients(100%) were normal. Serum iron levels did not differ significantly between three study groups (P>0.05 for all). Serum ferritin levels did not differ significantly between cancer and pre-cancer groups (P>0.05 for all). Decrease in serum ferritin levels is significantly higher in cancer group compared to control group (P<0.05). Decrease in serum ferritin levels is significantly higher in pre-cancer group compared to control group (P<0.01). Serum TIBC levels did not differ significantly between three study groups (P>0.05 for all)(Table 2).

The mean values of Serum Iron in Habitues are 75.6 ± 21.2 and in Non Habitues is 71.3 ± 14. Habit v/s Non habit P= 0.474, and P>0.05 hence does not differ significantly between Habitues and Non Habitues. The mean values of Serum Ferritin in Habitues are 45.4± 30.0 and in Non Habitues is 43.1 ± 9.2. Habit v/s Non habit P= 0.772, and P>0.05 hence does not differ significantly between Habitues and Non Habitues The mean values of Serum T.I.B.C. in Habitues is 367.9 ± 34.4 and in Non Habitues is 359.1 ± 19.5. Habit v/s Non habit P= 0.348, and P>0.05 hence does not differ significantly between Habitues and Non Habitues (Table 3).

The mean values of Serum Iron in Males are 77.3 ± 20.4 and in Females is 68.0 ± 17.0. Hence, Males v/s Females P= 0.098, and P>0.05 hence does not differ significantly between Males and Females. The mean values of Serum Ferritin in Males are 47.8 ± 29.9 and in Females is 37.7 ± 13.3. Hence, Males v/s Females P= 0.173, and P>0.05 hence does not differ significantly between Males and Females. The mean values of Serum T.I.B.C. in Males are 366.6 ± 32.8 and in Females is 363.6± 28.8. Hence, Males v/s Females P= 0.737, and P>0.05 hence does not differ significantly between Males and Females(Table 4).

Table 1: The distribution of biochemical parameters studied between three study groups.

Parameters	Group 1 Cancer Group (n=20)	Group 2 Pre-Cancer Group (n=20)	Group 3 Control Group (n=20)	P-values (Inter-Group)		
				Group 1 v/s Group 2	Group 1 v/s Group 3	Group 2 v/s Group 3
Serum Iron	69.3± 20.0µg/dl	77.9 ± 25.3 µg/dl	76.2±11.2 µg/dl	0.358 (NS)	0.516 (NS)	0.959(NS)
Serum Ferritin	49.9± 32.4ng/mL	38.1 ± 31.3 ng/mL	46.3±6.7 ng/mL	0.334 (NS)	0.900 (NS)	0.585 (NS)
Serum T.I.B.C	362.8± 38.1 µg/dl	373.6 ± 34.7 µg/dl	360.8±17.6 µg/dl	0.523 (NS)	0.979 (NS)	0.407 (NS)

Values are Mean ± Standard Deviation. P-values are obtained using One-way Analysis of Variance (ANOVA) with Turkey's correction for multiple group comparisons, after confirming the underlying normality assumption. P-value<0.05 is considered to be statistically significant. NS: Non-Significant

Table 2: The distribution of change in biochemical parameters studied between three study groups.

Parameters	Group 1 Cancer Group (n=20)	Group 2 Pre-Cancer Group (n=20)	Group 3 Control Group (n=20)	P-values (Inter-Group)		
				Group 1 v/s Group 2	Group 1 v/s Group 2	Group 1 v/s Group 2
Serum Iron (µg/dl)						
Normal (60-160)	15 (75.0)	15 (75.0)	19 (95.0)	0.999 (NS)	0.182 (NS)	0.182 (NS)
Abnormal (<60)	5 (25.0)	5 (25.0)	1 (5.0)			
Serum Ferritin (ng/mL)						
Normal (22-322)	15 (75.0)	12 (60.0)	20 (100.0)	0.501 (NS)	0.047 (S)	0.003 (S)
Abnormal (<22)	5 (25.0)	8 (40.0)	0			
Serum T.I.B.C. (µg/dl) µg/dl						
Normal (250-400)	19 (95.0)	16 (80.0)	20 (100.0)	0.342 (NS)	0.999 (NS)	0.106 (NS)
Abnormal (>400)	1 (5.0)	4 (20.0)	0			

Values are n (% of cases). P-values are obtained using Chi-Square test. P-value<0.05 is considered to be statistically significant. NS: Non-Significant. S: Significant.

Table 3: The distribution of biochemical parameters studied between the cases with and without habits.

Parameters	Habit (n=45)	Non-Habit (n=15)	P-value (Habit v/s Non-Habit)
Serum Iron(µg/dl)	75.6 ± 21.2	71.3 ± 14.9	0.474 (NS)
Serum Ferritin (ng/mL)	45.4 ± 30.0	43.1 ± 9.2	0.772 (NS)
Serum T.I.B.C. (µg/dl)	367.9 ± 34.4	359.1 ± 19.5	0.348 (NS)

Values are Mean ± Standard Deviation. P-values are obtained using independent sample't' test, after confirming the underlying normality assumption. P-value<0.05 is considered to be statistically significant. NS: non-Significant.

Table 4: The distribution of biochemical parameters studied between male and female cases studied.

Parameters	Male (n=42)	Female (n=18)	P-value (Male v/s Female)
Serum Iron(µg/dl)	77.3 ± 20.4	68.0 ± 17.0	0.098 (NS)
Serum Ferritin(ng/mL)	47.8 ± 29.9	37.7 ± 13.3	0.173 (NS)
Serum T.I.B.C. (µg/dl)	366.6 ± 32.8	363.6 ± 28.8	0.737 (Ns)

Values are Mean ± Standard Deviation. P-values are obtained using independent sample't' test, after confirming the underlying normality assumption. P-value<0.05 is considered to be statistically significant. NS: Non-Significant.

DISCUSSION

In the oral carcinogenesis, several factors have been involved such as age, gender, ethnicity, lifestyle, genetic background, status of health and exposure to carcinogens. Pathological process of cancer could also be initiated because of transitional metals like iron which generates reactive oxygen species including hydroxyl radical which attack DNA and causes mutation.(Huggs and Wells, [3], Graham et al [7], Toykuni [8], Stevens and Kalkwarf[9].

The present study is an attempt to evaluate/ establish the levels of serum iron, serum ferritin and total iron binding capacity in patients suffering from oral precancerous and cancerous lesions. Our study consisted of 20 patients in cancer group, 20 patients in precancer group and 20 subjects as control group.

The biochemical parameters Serum iron, ferritin and T.I.B.C. were compared between males and

females (Table 4) and it was found that there was decrease in mean levels of serum iron in females (68.0 ± 17.0) as compared to males (77.3 ± 20.4) also there was decrease in mean levels of serum ferritin females(37.7 ± 13.3) as compared to in males(47.8 ± 29.9), but was not statistically significant.. There was no change in mean levels of serum T.I.B.C. between the genders. Similar findings were noted by Gupta PC *et al.;* [11]. The presence of lower values in females could reflect nutritional deficiency or previous blood loss by menstruation. Heinz *et al.;* [12] reported that alcoholism is also associated with increase in serum ferritin and serum iron levels, so it was evident in our results that males who had habit of tobacco with alcohol showed increase in serum ferritin as well as serum iron levels.

Tobacco, smoking and smokeless form and alcohol are known factors for causing cancer. But it was found that 15 to 20 % of the head and neck cancer had no known history of tobacco or alcohol exposureOut of 20 patients in Cancer group, 18 patients (90%) were habitues and 2 patients (10%) were non habitues. Similar findings were observed by Mehta *et al.;* [13] and Mathew *et al.;*[14]who reported higher prevalence of oral cancer among males consuming tobacco. In the precancer group all the 20 patients (100%) were habitues. In control group 7 volunteers (35%) were habitues and 13 volunteers (65%) were non habitues. The distribution of habitues differs significantly between Cancer and Control groups and Pre- cancer and Control groups (P<0.001). Similar findings were observed by Bhonsle *et al.;* [14], Jayant K *et al.;* [15], Jaber *et al.;* [16], Riebel *et al.;* [17] and Napier *et al.;*[18]who stated that tobacco is a major independent risk factor for the development of cancers as well as oral pre cancers.Distribution of Serum iron, ferritin and T.I.B.C. levels among habitués and non habitués were not significant.

Biochemical parameters were compared in overall subjects in comparison with habits, and it was found that 11 of the subjects had decreased serum iron levels, 13 had decreased serum ferritin levels and 5 had increased levels of serum T.I.B.C. All these subjects had the habit of chewing pan masala and ghutka along with consumption of alcohol for a longer duration of more than 15-20 years. Similar findings were seen with Moreno *et al.;* [19] Turobbaev *et al.;* Gavalov *et al.;* [*20*], Damber and Larsson [21] Rajasinghe *et al.;* [22], who suggested that cigarette smoke induced release of iron could alter iron metabolism of chronic smokers and ethanol metabolism results in the generation of superoxide and related free radicals and mobilization of catalytic iron, and cleavage of double stranded DNA is produced by both free radicals as well as by catalytic iron. This contributes to the increased risk of cancer observed in alcoholics who also had habits of smokeless and smoking tobacco. Lapenna *et al.;* [23] suggested, that cigarette-smoke mediated iron mobilization from ferritin which may represent a specific pro oxidant mechanism related to cigarette smoking in vivo.

In contradiction Heinz *et al.;* [24], Friedman *et al.;* [25], Moirand *et al.;[*26], Kurokawa *et al.;* [27] reported significant elevation of serum iron and increased T.I.B.C. in adolescent male alcohol users and transferring saturation as well, transfer in synthesis increases in alcoholic fatty liver which causes increased uptake of desialylated transfer in by the liver and lead to hepatic siderosis and increased serum ferritin levels.

The average Serum iron, serum ferritin and serum T.I.B.C. did not differ significantly between the three study groups P>0.05 for all ,In the cancer group out of 20 patients 5 showed decreased levels of serum iron and serum ferritin it was noted that they were in progressive stage of cancer with most of them in Stage 3 or Stage 4 and most of them histo pathologically classified as moderately differentiated squamous cell carcinoma Huggs and Wells, [3]stated that iron deficiency has long been known to have profound effects on the oral mucosa and also to have association with both oral and pharyngeal cancer (Paterson–Kelly syndrome), and with chronic candidiasis .Maguire[28], stated that other forms of iron found physiologically might cause considerable oxidative damage. Naturally occurring protein-bound iron, such as ferritin and transfer in, which constitute major forms of transport and storage of iron in vivo, produce considerable mitigation of such toxicity in vivo. Iron deficiency reduces this protection. Rennie and Mac-Donald [29] have shown that in human iron deficiency anemia and in experimental iron deficiency in hamsters, qualitative histological changes in the oral epithelium are demonstrable. Weinberg [6] stated cytokine activated macrophages increases intracellular ferritin retention of metal and scavenge iron in areas of tumor growth and secrete reactive nitrogen intermediates to effect efflux of non heme iron from tumor cells, so this could affect the measured values.

The average Serum iron, serum ferritin and serum T.I.B.C. did not differ significantly between the three study groups P>0.05 for all, but change in abnormality in serum ferritin levels were statistically significant in precancer group when compared to the control group(Table 2)

Graham *et al.;* [30] Rajendran *et al.;* [31] Vijaya Kumar T *et al.;* [32] anuradha *et al.;* Bhatta-thiri, [5] found reduced levels of iron in oral leukoplakia, OSMF and OSCC. Rajendran *et al.;*[33] noted that sub mucous fibrosis appears as an altered oral mucosa following prolonged period of chronic deficiency of iron which leads to a defective inflammatory-reparative response, culminating in fibrotic healing. Anuradha *et al.;* [32] observed that patients with sub mucous fibrosis (all of whom were heavy tobacco and areca nut users too) that serum iron decreased where as the total tissue collagen

content increased significantly in patients with advanced disease. Cytochrome oxidase is an iron dependent enzyme which is required for the normal maturation of the epithelium; in iron deficiency levels of cytochrome oxidase are low which consequently lead to epithelial atrophy. Utilisation of iron for hydroxylation of proline and lysine leads to decreased serum iron levels.

Conversely Bhattathiri[5] stated that iron deficiency and excess body iron, both may cause carcinogenesis. Simonart T *et al.;* [34] stated that iron chelators have been shown to inhibit the growth and/or induce the apoptosis of malignant cell lines from leukemia, neuroblastoma, melanoma, hepatoma, Kaposi's sarcoma and cervical cancer.

CONCLUSION:

The present study cannot give any proper conclusion, about the role of iron as early marker in oral cancer. Serum iron, serum ferritin and serum T.I.B.C levels are good indicators of total iron levels and should be evaluated compulsorily in both oral cancer and precancer.

Iron deficiency is common in Indian population especially in women, out of place supplementation (in the wrong time) with iron may be deleterious, and where as timely supplementation is a necessity. When giving iron supplements, it has to be ensured as far as possible that no underlying chronic disease and malignancy exists.

REFERENCE:

1. Kumar SKS, Zain RB; Aetiology and Risk factors for Oral Cancer – A Brief Overview. Annal Dent Univ Malaya 2004;
2. Bouquot JE, Whitaker SB; Oral Leukoplakia rationale for diagnosis and prognosis of its clinical subtypes or phases. Quintessence Int 1994;
3. Huggs JM, Wells RS; Chronic mucocutaneous candidiasis associated abnormalities of iron metabolism. B J Dermatol. 1972;
4. Novacek G; Plummer–Vinson syndrome. Orphanet J Rare Dis**,** 2006.
5. Bhattathiri VN; Paradoxes in iron indices in oral cancer patients vis-a-vis tobacco-alcohol habits. Health Administrator 2006
6. Weinberg ED; Roles of iron in neoplasia. Promotion, prevention, and therapy, Biol Trace Elem Res, 34 (1992) 123.
7. Graham S, Dayal H, Rohrer T, Swanson M, Sultz H, Shedd D, *et al.;* Dentition, diet, tobacco and alcohol in the epidemiology of oral cancer. J Natl Cancer Inst. 1977
8. Toyokuni S; Iron-induced carcinogenesis: the role of Redox regulution. Free RadiBiol Med. 1996
9. Stevens RG, Kalkwarf DR; Iron, radiation and cancer. Environ Health Perspect. 1990
10. Sankaranarayan R, Masuyer E, Swaminathan R, Ferley J, Whelan S; Head and neck cancer: a global perspective on epidemiology and prognosis. Anticancer Res 18:4779-86, 1998.
11. Gupta PC, Hebert JR, Bhonsle RB, Murti PR, Mehta H, Mehta FS; Influence of dietary factors on oral precancerous lesions in a population based case-control study in Kerala, India, Cancer, 85(1999) 1885.
12. Heinz R, Lorant P, Stacher A; Alcohol and changes in the hematopoietic system; an epidemiological contribution to the problem of alcoholic anemia, Wien Klin Wochenschr 95 (1983) 624.
13. Mathew Iype E, Pandey M, Mathew A; Squamous cell carcinoma of the tongue among young Indian adults. Neoplasia, 2001; 3, 273-7.
14. Bhonsle RB, Murti PR, Daftary DK, Mehta FS; An oral lesion in tobacco-lime users in Maharashtra, India. J Oral Pathol 1979; 8(1): 47-52.
15. Jayant K; Cancer survival in developing countries. International Agency for Research of Cancer 1988
16. Jaber MA, Porter SR, Gilthorpe MS et al.; Risk factors for oral epithelial dysplasia--the role of smoking and alcohol. Oral Oncol 1999; 35(2): 151-156.
17. Reibel J; Prognosis of oral pre malignant lesions. Significance of clinical, histopathological and molecular biological characteristics. Crit. Rev. Oral Biol. Med. 2003; 14(1): 47-62.
18. Napier SS, Speight PM; history of potentially malignant oral lesions and conditions: an overview of the literature. J Oral Pathol Med 2008; 37:1-10.
19. Moreno JJ, Foroozesh M, Church DF, Pryor WA; Release of iron from ferritin by aqueous extracts of cigarette smoke, Chem Res Toxicol, 1992; 5: 116.
20. Gavalov SM, Soboleva MK, Deriagina LP, Demchenko AE; Effect of active and passive smoking on the course of pregnancy in women and on the establishment of the erythrocytic system in their children. TerArkh, 1991; 63.
21. Damber L, Larsson LG; Combined effects of mining and smoking in the causation of lung carcinoma. A case-control study in northern Sweden, Acta Radiol Oncol 1982; 21.
22. Rajasinghe H, Jayatilleke E, Shaw S; DNA cleavage during ethanol metabolism: role of superoxide radicals and catalytic iron, Life Sci.1990, 47: 807.
23. Lapenna D, de Gioia S, Mezzetti A, Ciofani G, Consoli A, Marzio L *et al.;* Cigarette smoke, ferritin, and lipid per oxidation, Am J Respir Crit Care Med, 1995; 151: 431.
24. Heinz R, Lorant P, Stacher A; Alcohol and changes in the hematopoietic system; an epidemiological contribution to the problem of alcoholic anemia, Wien Klin Wochenschr 1983; 95: 624.
25. Friedman IM, Kraemer HC, Mendoza FS, Hammer LD. Elevated serum iron concentration in adolescent alcohol users, Am J Dis Child, 1988; 142: 156.

26. Moirand R, Lescoat G, Brissot P; Interactions of alcohol and iron proteins, Ann Gastroenterol Hepatol (Paris) 1989; 25: 51-4.
27. Kurokawa H, Tsuru S, Okada M, Nakamura T, Kajiyama M; Evaluation of tumor markers in patients with squamous cell carcinoma in the oral cavity, Int J Oral Maxillofac Surg, 1993; 22.
28. Maguire JJ, Kellogg EW 3d, Packer L; Protection against free radical formation by protein bound iron Toxicol Lett, 1982; 14.
29. Rennie, Mac Donald; Iron and Oral epithelium :A review .Journal of the Royal Society of Medicine 1984
30. Graham S; Dentition, diet, tobacco and alcohol in the epidemiology of oral cancer. J Natl Cancer Inst 1977.
31. Rajendran R, Vasudevan DM, Vijayakumar T; Serum levels of iron and proteins in oral sub mucous fibrosis (OSMF), Ann Dent, 1990; 49.
32. David P Goldstein; MD, FRCSC, Consulting Staff, Department of Otolaryngology, Division of Head and Neck Oncology 2010.
33. Mazarin JJ, Grandic C, Gerbaulet A; Oral cavity. In Souhami AL, Tannock I, Hohenberger P, Horiot JC(eds). Oxford textbook of oncology (2nd edition)2002; Oxford- Newyork : Oxford University Press:1391-408
34. Simonart T, De Dobbeleer G, Stallenberg B; Classic Kaposi's sarcoma of the palm in a metallurgist: Role of iron filings in its development? Br J Dermatol. 2003; 148: 1061–3.