INTRODUCTION

Melanoma affects people all over the globe. The incidence of melanoma has steadily increased over the past few decades, with an annual increase in the incidence rate approximately 3–7% per year worldwide for Caucasians Despite the dramatic increase in the incidence of cutaneous melanoma in the recent years, the incidence of mucosal melanoma has been relatively stable ***(Parkin et al., 2001; Patrick et al., 2007).***

Melanoma can be subdivided into cutaneous, ocular and mucosal melanoma. These three entities differ significantly in epidemiological pattern, tumour biology and clinical behaviour ***(Van Dijk et al., 2003).***

Cutaneous melanoma account for 91.2% of cases, whereas mucosal melanoma comprises only 1.3% of all melanoma. Ocular melanoma and unknown primaries are accountable for the remaining 5.2% and 2.2%.

The head and neck region is the commonest site of mucosal melanoma accounting for 55.4% of cases, followed by anorectal tract (23.8%), female genital tract (18.0%) and urinary tract (2.8%) ***(Chang et al., 1998).***

Despite the dramatic increase in the incidence of cutaneous melanoma in the recent years, the incidence of

mucosal melanoma has been relatively stable. Compared to cutaneous melanoma, mucosal melanoma presents late and is often asymptomatic until late stage. Locally advanced tumours in close proximity to critical anatomical structures at presentation are not uncommon rendering surgery difficult and risky, if not impossible ***(Patrick et al., 2007).***

The scarcity of the condition prohibited large-scale prospective randomized controlled studies which are essential to understand the disease nature and to evaluate the safety and efficacy of treatment.

Aim of the Work

The Aim of this work is to provide updated review about head & neck melanomas, with highlight of differences of treatment of other types of head & neck malignancies.

An extensive search of the literature is performed to review current knowledge, summarize global experience and hopefully, have more insight about melanoma of head and neck.

INCIDENCE

According to the Chang's study on the National Cancer Database which included 84 836 cases of cutaneous and non-cutaneous melanoma in the USA, mucosal melanoma comprises only 1.3% of all melanoma, whereas cutaneous melanoma account for 91.2% of cases. Ocular melanoma and unknown primaries are accountable for the remaining 5.2% and 2.2% ***(Chang et al., 1998).***

According to the O'Brien's study on experience with 998 cases treated at the Sydney melanoma unit for cutaneous melanoma of the head and neck over 30 years, most cutaneous melanomas arise in the face (47%). The remainder is found on the neck, which accounts for (29%), the scalp (14%), and the ear (10%). The distribution of anatomical sub sites in cutaneous melanoma of head and neck was summarized in Figure 1 ***(O'Brien et al., 1991; Eicher et al., 2002).***

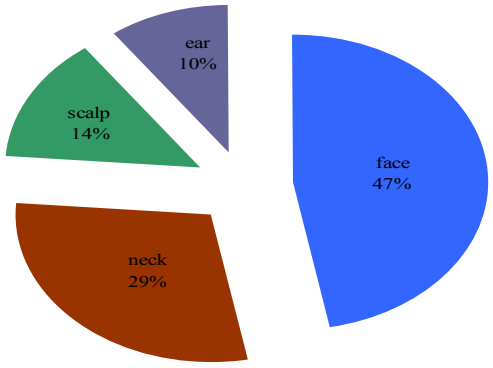

Figure (1): Distribution of anatomical sites of Cutaneous Melanoma of head & neck ***(O'Brien et al., 1991).***

A pooled analysis of more 139 eligible studies that had reported adequate information for analysis for demographic patterns of mucosal melanomas.The analysis showed a total of 3,490 cases of mucosal melanoma of the head and neck have been reported in the literature. Sinonasal mucosal melanomas reported comprising of 66 % of cases, oral melanomas represent 28% of cases, pharyngolaryngoesophageal mucosal melanomas represent 5% of cases and the remaining 1% of tumours originated from the eye (conjunctiva), Eustachian tube, middle ear, parotid gland and the nasolacrimal duct. The distribution of anatomical sub sites in mucosal melanoma was summarized in Figure 2 ***(Chan, 2011).***

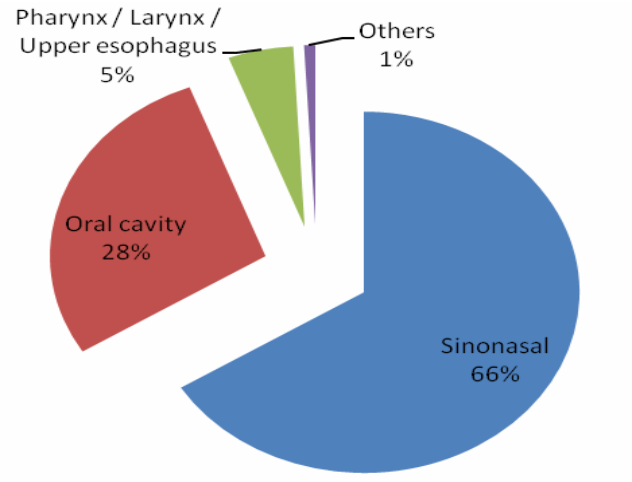

Figure (2): Distribution of anatomical sites of Mucosal Melanoma of head & neck ***(Chan, 2011).***

Sinonasal mucosal melanomas represent <5%of all sinonasal tract neoplasms. Of the nasal cavity common sites in order include the nasal septum, lateral nasal wall, turbinates, and nasal vestibule. Of the sinuses, the maxillary sinus is the most common accounting for 6% of all mucosal melanoma – followed by the ethmoid, frontal, and sphenoid sinus cavites. The distribution of anatomical sub sites in sinonasal mucosal melanoma was summarized in Figure 3 ***(Temam et al., 2005; Chan, 2011).***

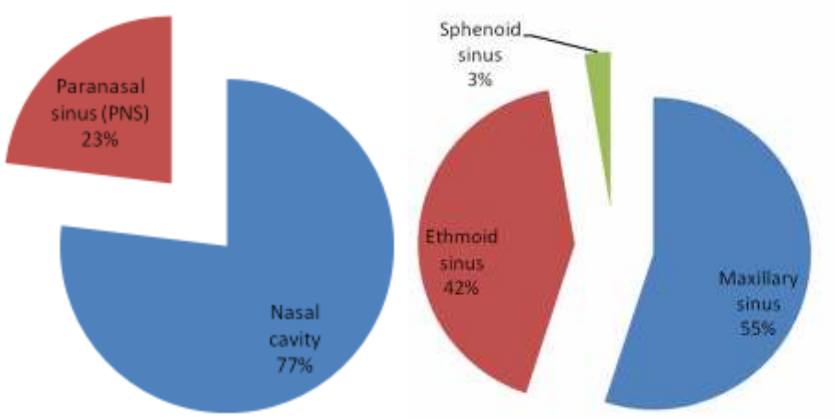

Figure (3): Distribution of anatomical sites of sinonasal mucosal melanoma (left) and subsite distribution of paranasal sinus tumours (right) ***(Chan, 2011).***

Oral melanomas represent 28% of cases (0.5% of oral malignancies) and pharyngolaryngoesophageal mucosal melanomas represent 5% of cases. The distribution of anatomical sub sites in oral mucosal melanoma of head and neck was summarized in Figure 4 ***(Chan, 2011).***

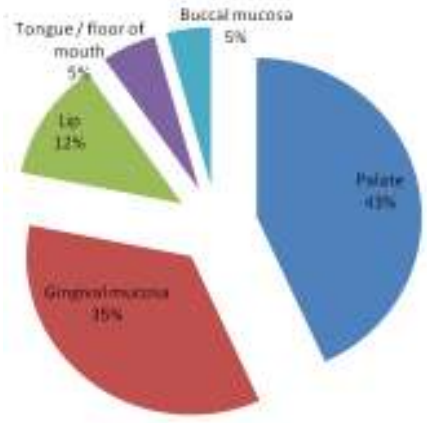

Figure (4): Distribution of anatomical sites of oral mucosal melanoma ***(Chan, 2011).***

EPIDEMIOLOGY

Melanoma is notorious for affecting young and middle-aged people, unlike other solid tumors, which mainly affect older adults. It is commonly found in patients younger than 55 years, and it accounts for the third highest number of lives lost across all cancers. It is particularly common among Caucasians, especially northern Europeans and northwestern Europeans, living in sunny climates. There are higher rates in Oceania, North America, Europe, Southern Africa, and Latin America ***(Parkin et al., 2005).***

Queensland, Australia, has the highest incidence of melanoma in the world, approximately 57 cases per 100,000 people per year. The cutaneous melanoma rates in Australia are twofold higher than in the United States. In Hawaii and the southwestern United States, whites have the highest incidence, approximately 20-30 cases per 100,000 people per year ***(lens and Dawes, 2004).***

Pooled data by Mclaughlin et al. (2005) were used to examine the incidence of melanoma for cases diagnosed between 1996 and 2000. For cutaneous melanoma, the rates among whites were 16 times higher than among blacks. White people with dark skin also have a much lower risk of developing melanoma than do those with light skin. The typical patient with melanoma has fair skin and a tendency to sunburn rather than tan. White people with blond or red hair and profuse

freckling appear to be most prone to melanomas ***(McLaughlin et al., 2005)*** Melanoma risk veries according to skin complexion summarized in figure (5) ***(D'Orazio et al., 2013).***

Unlike cutaneous melanoma, mucosal melanoma doesn't show typical patient characters. The reported incidence in the literature demonstrates racial differences with Asians, especially Japanese, having a higher incidence rate of head and neck mucosal melanoma. The oral mucosal melanoma in Japan accounts for 7.5% of all melanomas, significantly higher than the less than 1% rate for the Caucasians. Rates of mucosal melanoma were approximately two times higher among whites compared with blacks ***(Rapini et al., 1985; McLaughlin et al., 2005).***

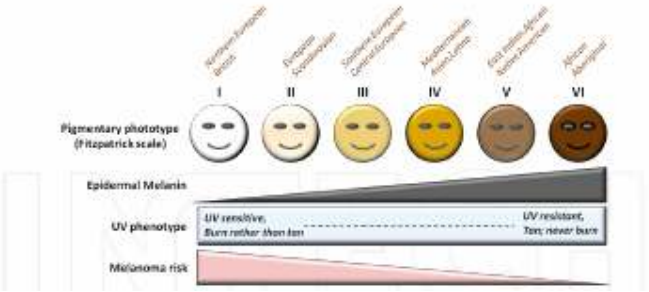

Figure (5): Melanoma risk veries according to skin complexion ***(D'Orazio e tal., 2013)***.

ETIOPATHOGENESIS

Cutaneous melanoma

Primary melanoma is a malignant neoplasm of neural crest–derived melanocytes, specialized pigmented cells predominately found in the basal layer of the epidermis but is also found in the eye, gallbladder, anus, and vagina, and throughout the upper aerodigestive tract. The normal function of melanocytes is to produce and transfer a dark pigment called melanin to mitotically active keratinocytes as a result of stimulation by ultraviolet radiation, which are also found in the epidermis.

The transformation of melanocytes to tumor cells occurs in both genetically normal and predisposed patients. The earliest stage of melanoma starts when the melanocytes begin to grow out of control. This early stage of the disease is called the radial growth phase, and the tumor is less than 1 mm thick ***(Guerry et al., 1993).***

Clark et al. suggested that primary melanomas generally evolve in sequential steps from disease above the basement membrane to invasive disease with ‘‘little or no potential for metastasis’’. The radial growth phase (RGP) was described as ‘‘a lesion composed of melanoma cells within the epidermis and papillary dermis with a lack of biologic potential for metastasis in spite of invasion of the papillary dermis for some

years''. The RGP is often followed by a ''qualitatively different growth pattern the vertical growth phase (VGP) (usually Clark's level II and occasionally Clark's level III), which may give rise to cell populations commonly associated with metastatic disease''. The importance of RGP is best demonstrated by the Taran and Heenan study, which showed development of metastatic melanoma in only 5 of 1716 patients with level 2 melanomas (= 1mm thick) in 7 to 14 years followup, those 5 cases with metastatic melanomas revealed regression ***(Clark et al., 1975; Guerry et al., 1993; Taran and Heenan, 2001).***

Genetic Mechanisms

Many different genes have been associated with increased risk for melanoma. The better characterized mutations involve the highly penetrant gene products of familial melanoma syndromes: p16 (also called cyclin-dependent kinase inhibitor 2A [CDKN2A], or inhibitor of cyclin-dependent kinase 4A, alternate reading frame (ARF), and cyclin-dependent kinase 4 a cyclin-dependent kinase that promotes cell division (CDK4). The low-penetrance melanocortin-1 receptor (MC1R) gene (a transmembrane receptor expressed in melanocytes that mediates melanin production after UV irradiation or stimulation by hormones and they are associated with red hair and fair skin) has also been associated with increased melanoma risk. The p16/ARF locus is the best-characterized high penetrance melanoma gene locus.

Germline mutations in 1 or both of these gene products are associated with familial melanoma, and have been ascertained in 25% to 50% of familial melanoma worldwide and in approximately 10% of patients with multiple primary melanomas ***(Valverde et al., 1995; Pollock et al., 2003).***

In addition, a BRAF (BRAF is a human gene that makes a protein called B-Raf) mutation has been ascertained in up to 60% of cutaneous melanomas. Mutation in BRAF leads to hyperactivity of the mitogen-activated protein kinase (MAPK)–extracellular signal-related kinase signalling pathway stimulating melanoma cell growth ***(Inamdar et al., 2010; Puzanov et al., 2011).***

Second most commonly mutated oncogene in melanoma, NRAS (NRAS is a human gene that makes a protein called N-Ras), is mutated in 15–20% of cases and has been implicated as a prognostic factor in metastatic melanoma **(Jakob et al., 2012).**

A pooled analysis by Lee et al. (2010) of more than 30 studies from 1989-2010 concludes that the incidence of *BRAF* and *NRAS* mutations differ based on histologic subtype and anatomic site. *BRAF* mutations are more commonly detected in superficial spreading melanomas and melanomas that arise on nonchronically sun-damaged skin. *NRAS* mutations are more common in patients with nodular melanomas and melanomas arising on chronically sun-damaged skin. Recent data have

shown that *NRAS* mutations may be associated with thicker tumors (>1 mm) and higher mitotic rate (>1/mm2) compared with mutations in *BRAF*, and that *NRAS* mutation status may be associated with worse clinical outcomes, including shorter melanoma specific survival ***(Lee et al., 2010; Ellerhorst el al., 2011).*** Genetic Mechanisms of melanoma summarized in figure (6) ***(Davies et al., 2002).***

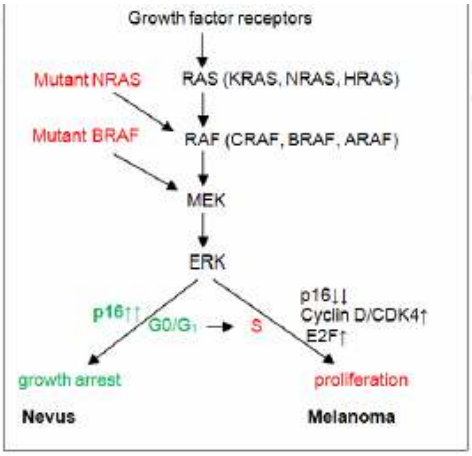

Figure (6): Genetic Mechanisms of melanoma ***(Davies et al., 2002).***

Natural UV radiation exposure

Solar radiation plays a role in the development of melanoma. In June2009, solar radiation has been classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC), an agency of the World Health Organization that classifies carcinogens ***(El Ghissassi et al., 2009).***

A comprehensive meta-analysis of 25 studies showed that an increased risk of melanoma was seen with increasing number of sunburns for all timeperiods (childhood, adolescence, adulthood and lifetime) ***(Dennis et al., 2008)***.

There also appears to be an interaction between chronic UV exposure and the type of melanoma that may subsequently develop. The lentigo maligna variety of melanoma, found most commonly on constantly exposed body sites such as the face, is associated more with possible chronic occupational UV exposure than intermittent burning UV exposure episodes.

Whiteman et al. have taken this observation further and postulated two distinct, partly UV-induced pathways to melanoma that give rise to slightly different clinical outcomes. The first pathway involves intense intermittent exposure on the trunk of individuals who have large numbers of banal naevi and have melanoma diagnosed at a relatively young age. The second pathway probably more related to chronic UV exposure, is found in older individuals who may have a past history of nonmelanoma skin cancer. These melanomas develop on sundamaged, constantly exposed sites ***(Whiteman et al., 2003).***

Artificial UV radiation exposure (indoor tanning)

Sunbeds emit UVA and UVB radiation. In general, sunbeds predominantly emit UVA radiation, which is thought to be the least damaging of the UV radiation spectrum.

However in recent years, sunbeds have been manufactured that produce higher levels of UVB to mimic the solar spectrum and speed the tanning process.

In the 10th report on carcinogens by the National Institutes of Health (NIH), it is stated, ‘‘Exposure to sunbeds and sunlamps is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to sunbeds and sunlamps and cancer’’. The World Health Organization (WHO) recognizes the dangers of sunbed use, as well, and has declared that worldwide, no person under 18 years of age should use a sunbed ***(Levine et al., 2009).***

A study by Lazovich et al. (2010) showed that the number of times an individual is exposed to indoor tanning is more important than exposure to indoor tanning at an early age (strong dose-response relationship between melanoma risk measured by total hours, sessions, or years), these results add considerable weight to the IARC report that indoor tanning is carcinogenic in humans and should be avoided to reduce the risk of melanoma ***(Lazovich et al., 2010).***

Nevi

Most nevi will never cause any problems, but a person who has many nevi is more likely to develop melanoma. Atypical naevi, present in 2–5% of Caucasian adults, are