International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Study of 100 Cases of Malignant Melanoma

Dr Jaydeep Bariya[1], Dr Dhaval Jetly[2]

[1]Consultant Pathologist, Sterling Accuris Diagnostics, Bhavnagar, Gujarat, India

[2]Associate Professor, Gujarat Cancer Research Institute, Ahmedabad, Gujarat, India

Abstract: ***Introduction: Malignant Melanoma is a neoplasm arising from melanocytes.The great preponderance of melanomas arises in the skin, other sites of origin include the oral and anogenital mucosal surfaces, esophagus , meninges and the eye. Aims and Objectives: To Study demographics, site of primary tumour and site of metastasis of Malignant Melanoma &To Study the Role of Immunohistochemistry in diagnosis Malignant Melanoma. Review of Literature: The Malignant Melanomas are the Most important group of skin cancers. Although less common than the familiar basal and squamous cell tumours of the skin, they are much more frequently fatal, due to their intrinsic tendency to lymphatic and haematogenic metastasis.[5] Melanoma accounts for less than 2% of skin cancer cases.[6] Melanoma is one of the most important cancers when considered as a cause of loss of life as it is commonly diagnosed in relatively young people and can be fatal if untreated. [9] Intermittent exposure to UVR(Ultraviolet rays) is the major environmental risk factor for melanoma, especially in combination with endogenous factors (skin types I and II, immune deficient status, genetic predisposition). Melanoma arises most commonly on the skin of the back in men and on the lower extremities in women in Western countries, whereas sole of foot is the most common site for melanoma among Indian patients.[13] The most useful criteria for clinical diagnosis of melanoma are asymmetry anduneven pigmentation of the lesion, and have been integrated in the acronym "ABCD" (Asymmetry, irregular Border, uneven Colour, Diameter > 6 mm). The typical example of malignant melanoma is identified microscopically because of its junctional activity; prominent melanin pigmentation; invasion of the surrounding tissue; marked cytologic atypia; nuclear grooves, folds, and pseudoinclusions; large eosinophilic nucleoli; and abundant mitotic figures, some of them atypical. Melanoma is reactive for Melan-A, S-100 protein, HMB-45, Vimentin, Tyrosinase. The treatment of choice of most malignant melanomas is wide excision of the primary lesion. Materials and Methods: This is a prospective+retrospective study conducted in the Department of Pathology of GCRI, Ahmedabad from August 2011 to October 2014. The data of 100 patients of histopathologically confirmed Malignant Melanoma was retrieved from case files. Surgically resected specimen material & biopsies were included in the study. Results: Median age overall: 53.57 years. Male to Female Ratio: 1.7:1. The most common site affected by Malignant Melanoma is Skin of Lower Limb. 22 out of 100 Cases show Metstasis. Our Study shows almost 100% positivity for Vimentin,S-100 and HMB-45. Discussion: In the current study, 100 cases of Malignant Melanoma were studied. Patients in our study belonged to the age group in the range of 22 to 84 years, with mean age being 53.57 years and a sex ratio of 1.7:1. Foot was the most common site for Malignant Melanoma in our study. Study Shows Two cases of Malignant Melanomain Liver which is a very rare site. Summary & Conclusion: To conclude, the current 100 case study of Malignant Melanoma, has illustrated the characteristics of patients of Malignant Melanoma presenting at our institute. Male predominance was seen over the Female. The most common site of Malignant Melanoma was the Skin of Lower Limb. The least common site of Malignant Melanoma was the Liver. In IHC Study, Melan-A, HMB-45, S-100 and Vimentin Positivity & Negativity for AE1, EMA, LCA is helpful for Differentiating Malignant Melanoma from other Poorly Differentiated Tumors and Lymphoma and to arrive at definite diagnosis. This is a Pilot study trying to understand this tumour entity. Further study is advisable on a larger population.***

1. Introduction

Malignant Melanoma is a neoplasm arising from melanocytes .Malignant melanoma affects predominantly fair-skinned caucasians, although they also occur in other population. Majority of melanomas arise after puberty, but they can also occur in children.[1] The presence of a large number of melanocytic nevi represents a risk factor for melanoma. The great preponderance of melanomas arises in the skin, other sites of origin include the oral and anogenital mucosal surfaces, esophagus , meninges and the eye . Most Melanoma cells make melanin so melanoma tumors are usually brown or black. But some melanomas do not make melanin and can appear pink, tan, or even white.[2]

The most useful criteria for clinical diagnosis of melanoma are asymmetry and uneven pigmentation of the lesion, andhave been integrated in the acronym "ABCD" (Asymmetry, irregular Border,uneven Colour, Diameter > 6 mm).Most melanomas have two phases of growth, an initial radial (horizontal) and a later vertical growth phase. The radial phase is not associated with spread, but once vertical phase supervenes, it gives rise to cell population that can metastasize.[3]Melanoma can be lethal due to high propensity for regional and systemic spread. Because melanomas evolve over time from localizedskin lesions to aggressive tumors that metastasize and are resistant to therapy, early recognition and complete excision are critical.[4]

2. Aims and Objective

- To Study demographics, site of primary tumour and site of metastasis of Malignant Melanoma
- To Study the Role of Immunohistochemistry in diagnosis Malignant Melanoma

3. Review of Literature

- The Malignant Melanomas are the Most important group of skin cancers.
- Although less common than the familiar basal and squamous cell tumours of the skin, they are much more frequently fatal, due to their intrinsic tendency to lymphatic and haematogenic metastasis.[5]

Epidemiology

- Melanoma accounts for less than 2% of skin cancer cases.[6]
- Approximately 79,000 males and 81,000 females were diagnosed with melanoma world-wide in 2002, of which about 80% occurred in the predominantly white

populations of Northern America, Australia, New Zealand and Europe.

- Cancer registries in India report that the age specific incidence rates for Malignant Melanoma are less than 0.5 per 1,000,000.[7]
- On a global scale, malignant melanoma was the 16thand 15th most commonly diagnosed cancer in males and females respectively.[8]
- Melanoma is one of the most important cancers when considered as a cause of loss of life as it is commonly diagnosed in relatively young people and can be fatal if untreated.[9]

Etiology

- **Exposure to Ultraviolet Radiation :**Intermittent exposure to UVR is the major environmental risk factor for melanoma, especially in combination with endogenous factors (skin types I and II, immune deficient status, genetic predisposition).[10]
- **Ozone layer:** Another explanation for the increases is the depletion of the ozone layer, which protects the earth's surface against UVR by filtering out a large part of the UVR from the sunlight before it reaches the earth's surface.[11]
- **Socioeconomic Status**: Melanoma is more common among people with a higher socio-economic status, probably due to a higher excessive intermittent exposure to UVR (outdoor sports, winter sports, sunbathing, getting a tan).[12]

Sites of involvement

Melanoma arises most commonly on the skin of the back in men and on the lower extremities in women in Western countries, whereas sole of foot is the most common site for melanoma among Indian patients.[13]

Age distribution

Malignant melanoma is a tumour affecting predominantly adults and elderly patients, with a peak of incidence around the sixth decade of life.[14]

4. Diagnosis

Clinically

The major clinical diagnostic criteria have been summarized as the ABCD criteria, which include lesional *Asymmetry* (one half of a lesion does not match the other in shape or incolor distribution), lesional *Border* irregularity (lesions tend to have an indented coastline like the map of a small island), lesional *Color* variegation (the surface is multicolored and mayinclude shades of tan, brown, blue-black, gray-white, and other variations), and lesional *Diameter* generally greater than 6mm (although some melanomas are smaller). The letter E could be addedto the criteria to indicate the "evolving" nature of a changing melanocytic lesion.[15]

Major subtypes Clinically

- Lentigo maligna melanoma.
- Superficial spreading melanoma.
- Nodular melanoma
- Acral lentiginous melanoma

Microscopic

The typical example of malignant melanoma is easily identified microscopically because of its junctional activity; prominent melanin pigmentation; invasion of the surrounding tissue; marked cytologic atypia; nuclear grooves, folds, and pseudoinclusions; large eosinophilic nucleoli; and abundant mitotic figures, some of them atypical. Malignant melanoma shows great microscopic variability. The cells can be epithelioid, spindle shaped, or extremely bizarre ('monster cells').[16] Their size can range from small (lymphocyte-like) to that of giant multinucleated forms. The cytoplasm can be eosinophilic, basophilic, foamy, of signet ring type, rhabdoid, oncocytic or completely clear (*balloon cell melanoma*).[] Melanin can be abundant, scanty, or absent (*amelanotic melanoma*). The pattern of growth of melanoma may be *pseudoglandular*, *pseudopapillary*, *peritheliomatous*, *hemangiopericytoma-like*, resembling Spitz nevus (*spitzoid melanoma*), rosette-like, trabecular, verrucous (*nevoid* or *pseudonevoid melanoma*), carcinoid-like, or *follicular*, i.e., centered in the hair follicle and the adjacent dermis. The tumor can be accompanied by marked fibroblastic response, myxoid change, osteoclast-like giant cells, pseudoepitheliomatous hyperplasia of the overlying epidermis,and a variety of divergent differentiations, including osteocartilaginous, rhabdomyoblastic, and neuroendocrine.[17]

Prognosis

Melanoma thickness, body site, histological type of the melanoma, gender of the patient and ulceration are important indicators of patient prognosis.[18]

Prognostic factors[19]

Table 1: Prognostic indicators for melanoma

Prognostic factor	Most favourable when
Breslow thickness	Thin (<1.51 mm)
Histology	Superficial spreading melanoma
Age	Young
Sex	Female
Body site	Not on the trunk, hands, feet
Ulceration	Absent
Mitotic index	Low

Immunohistochemistry[19]

Melanoma is reactive for Melan-A, S-100 protein, HMB-45, Vimentin Tyrosinase, and microphthalmia transcription factor. Vimentin is the most consistent (seen in practically 100% of the cases) but obviously the least useful diagnostically. Positivity for S-100 protein, although alsononspecific, is of greater practical importance because it is negative in many of the tumors that enter in the differential diagnosis. This reactivity is both nuclear and cytoplasmic, and is present in over 90% of the cases. Melanomas (particularly in their metastases) can lose their immunoreactivity for S-100 protein (and most of the markers discussed below) as a consequence of phenotypic dedifferentiation. HMB-45 is a much more specific marker than S-100 protein. It is particularly useful when the differential diagnosis includes a nonmelanocytic tumor that can also be S-100 protein positive, such as breast carcinoma. It may be detected in S-100 protein-negative melanomas, but on the whole it is less sensitive than the latter. Melan-A is

positive in approximately 80% of melanomas and has become a widely used marker for this tumor; however, it also stains steroid-producing cells from adrenal cortex, ovary, and testis, and the tumors originatingfrom them.

Treatment[20]

The treatment of choice of most malignant melanomas is wide excision of the primary lesion. A margin of 3 cm or perhaps even 1 cm is probably sufficient for the average sized tumor. Balch et al, recommended a margin of 2 cm for thin melanomas
(less than 0.76 mm in thickness) and a margin of 3–5 cm for thicker lesions. Thomas et al.found that a 1 cm margin for thick (>2 mm) melanomas was associated with a significantly greater risk of regional recurrence than a 3 cm margin, but that the overall survival rate was the same.

If the regional lymph nodes are clinically considered to be involved, a radical lymph node dissection should be performed. Radiation therapy, chemotherapy, and immunotherapy have so far proved largely ineffective in invasive or metastatic melanoma. Dacarbazine remains the drug of choice in disseminated melanoma; interleukin, biochemotherapy, and interferon have given good results, but only in a small percentage of patients.

5. Material and Methods

This is a prospective + retrospective study conducted in the Department of Pathology of GCRI, Ahmedabad from August 2011 to October 2014.

Patient selection

- The data of 100 patients of histopathologically confirmed Malignant Melanoma was retrieved from case files.
- Surgically resected specimen material & biopsies were included in the study.
- Cases in which IHC Confirmation has not been done e.g. Poorly Differentiated Malignant Tumor showing Melanin-like or Poorly Differentiated Tumor without Pigment but Morphology suggests Malignant Melanoma and in which Primary Tumor site is Unknown are excluded from the study.

Clinical features

- Data of patient's Age, Sex, Primary Tumour Site, site of metastasis retrieved from case files.

Pathological features

- These 100 cases were thoroughly investigated on Formalin fixed Paraffin embedded specimen and biopsy tissues stained with Hematoxylin and Eosin stain (H & E).
- At our setup, we have the autostainer *VARISTAIN*^{TM} by *Thermoscientific, for H & E staining.*

Immunohistochemical markers

- IHC stains were performed on formalin fixed paraffin embedded sections from each case with antigen epitope enhancement by heat. The diaminobenzidine (DAB) reaction was used as the final detection step. The slides were counterstained with Mayer's Hematoxylin. The method for epitope retrieval was overnight incubation at 60 ^{o}C.
- After antigen epitope enhancement, the staining was performed by fully automated machine VENTANA BENCHMARK XT.

6. Results

6.1 Age Distribution

Range: 22 to 84 years
Male: 28 to 84 years
Female: 22 to 75 years
Median age overall: 53.57 years
Median Age Male: 57.64 years
Median Age Female: 52.66 years

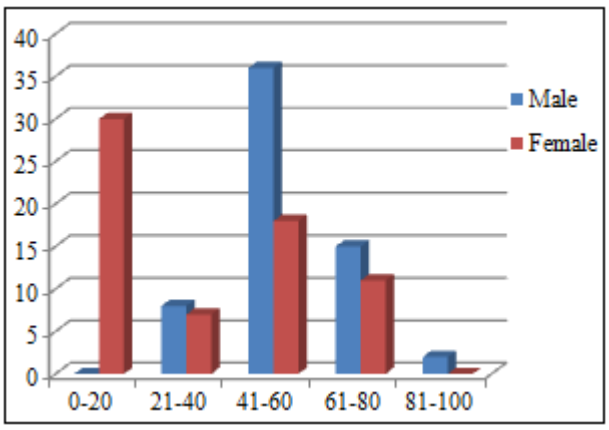
Table 2

Site	Median Age	Median Age Male	Median Age Female
Foot	51.7	52.54	51
Anal Canal	53.85	48	50.92
Rectum	56	60	58
Facial Skin	53	51	52
Vulva	31	-	31
Cervix	70	-	70
Nasal Polyp	70.5	-	70.5
Forearm	53.25	50	56.5
Liver	57	57	-
Skin Chest	55	55	-
Skin Abdomen	62	-	62
Skin Neck	82	82	-
Lower Lip	60	60	-
Eyeball	66.3	62.75	70
Thigh	46	52	40
Gluteal Region	22	-	22

Table 3: Age Distribution of the Patients

Age Group	Male	Female
0-20	0	3
21-40	8	7
41-60	36	18
61-80	15	11
81-100	2	0

Maximum No. of patients are found in the 41-60 years age group.



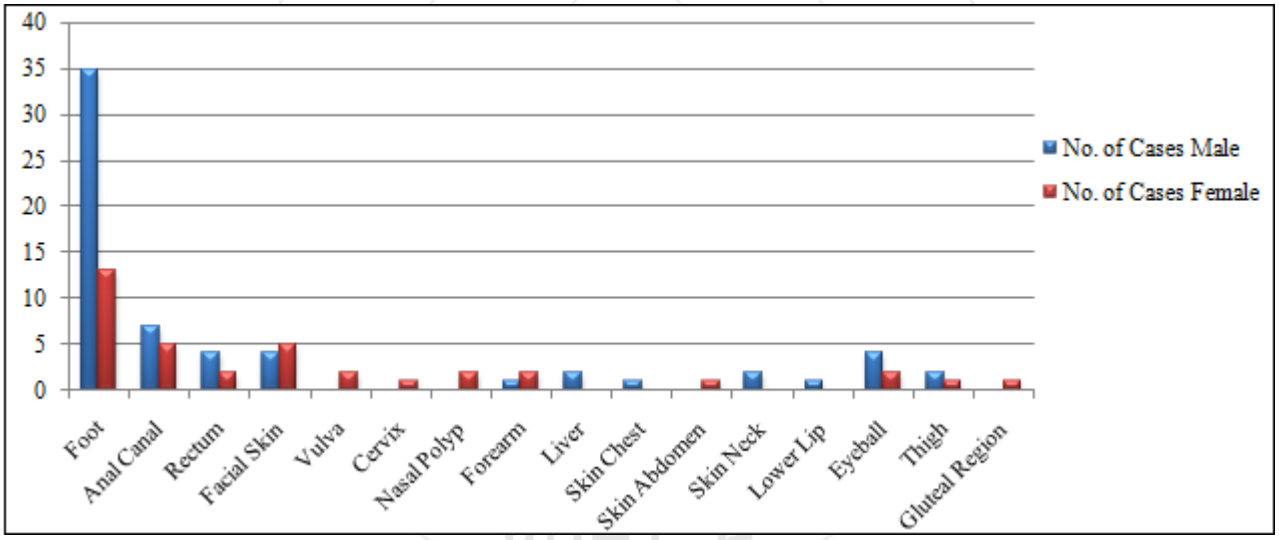
(a) Age Distribution

6.2 Sex Distribution

Total Cases: 100
Male: 63
Female: 37
Male to Female Ratio: 1.7:1

Table 4: Distribution of Cases According to Site and Sex

Site	No. of Cases Male	No. of Cases Female	Total No. of Cases	Male to Female ratio
Foot	35	13	48	2.69:1
Anal Canal	7	5	12	1.4:1
Rectum	4	2	6	2:1
Facial Skin	4	5	9	1:1.25
Vulva	-	2	2	-
Cervix	-	1	1	-
Nasal Polyp	-	2	2	-
Forearm	1	2	3	1:2
Liver	2	-	2	-
Skin Chest	1	-	1	-
Skin Abdomen	-	1	1	-
Skin Neck	2	-	2	-
Lower Lip	1	-	1	-
Eyeball	4	2	6	2:1
Thigh	2	1	3	2:1
Gluteal Region	-	1	1	-



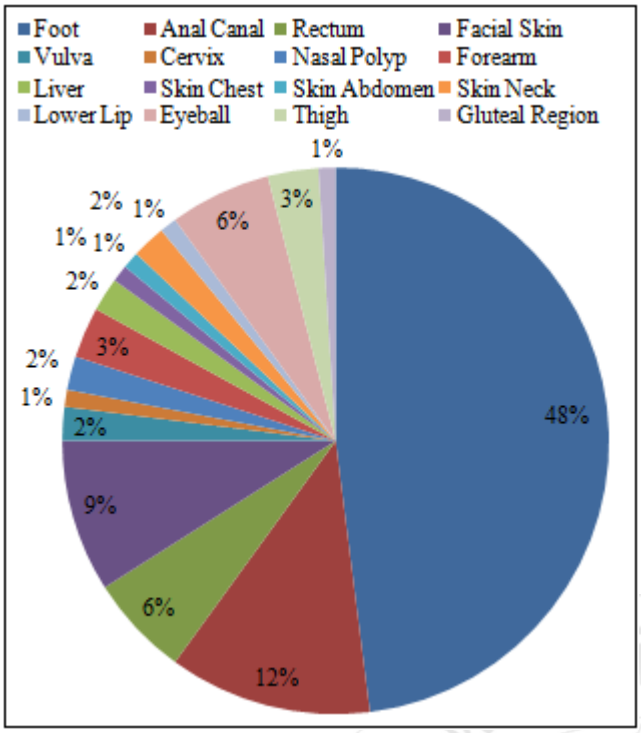
(b) Distribution of Cases according to Primary Site Affected in Male and Female

Site:
The most common site affected by Malignant Melanoma is Skin of Lower Limb.

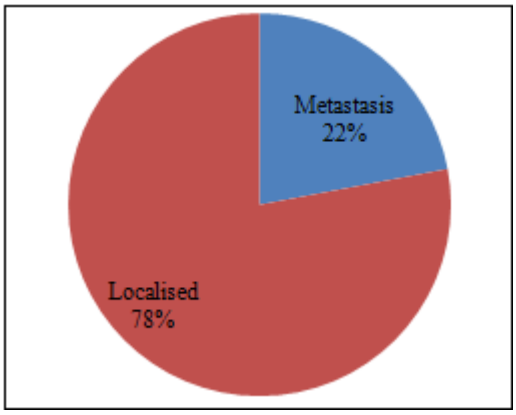
Eyeball	6
Thigh	3
Gluteal Region	1

Table 5: Sites affected by Malignant Melanoma

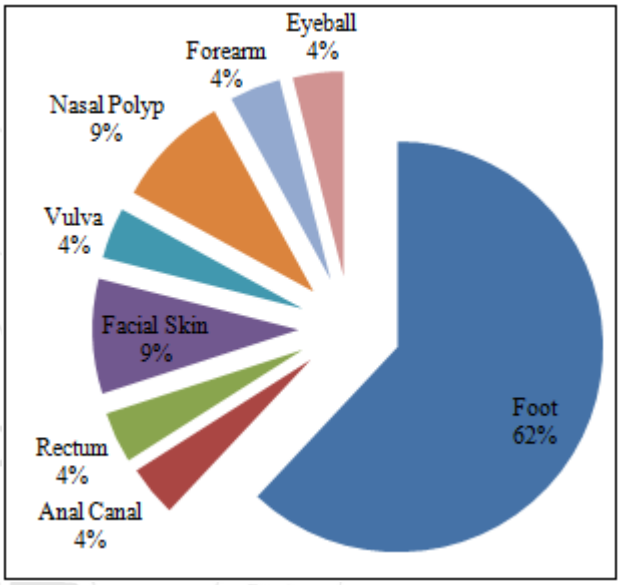
Site	*Total No. of Cases*
Foot	48
Anal Canal	12
Rectum	6
Facial Skin	9
Vulva	2
Cervix	1
Nasal Polyp	2
Forearm	3
Liver	2
Skin Chest	1
Skin Abdomen	1
Skin Neck	2
Lower Lip	1



(c) Distribution of Cases According to Site



(d) Cases Showing Metastasis



(e) Percentage of Primary Tumor Showing Metastasis

Metastasis:
22 out of 100 Cases show Metastasis.

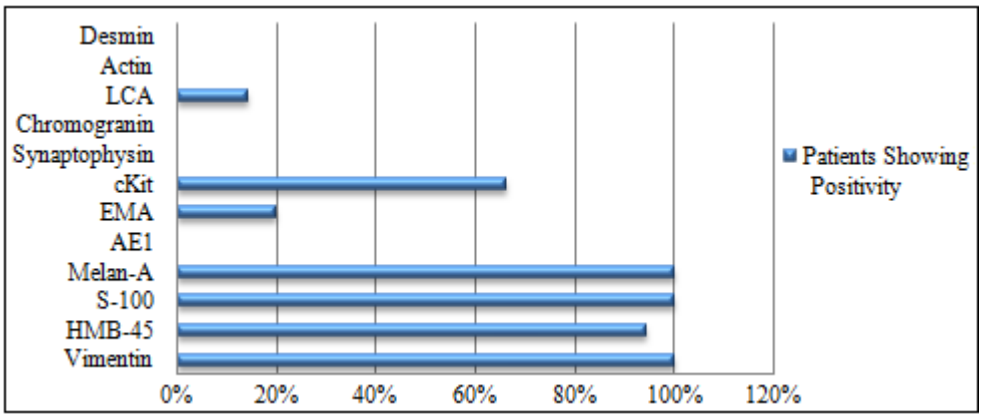
Table 6: Cases Showing Metastasis

Site	Total No. of Cases	No. of Cases Showing Metastasis	Percentage of cases showing Metastasis
Foot	48	13	27%
Anal Canal	12	1	8%
Rectum	6	1	16.6%
Facial Skin	9	2	22.2%
Vulva	2	1	50%
Cervix	1	0	0%
Nasal Polyp	2	2	100%
Forearm	3	1	33.3
Liver	2	0	0%
Skin Chest	1	0	0%
Skin Abdomen	1	0	0%
Skin Neck	2	0	0%
Lower Lip	1	0	0%
Eyeball	6	1	16.6%
Thigh	3	0	0%
Gluteal Region	1	0	0%

Immunohistichemistry
IHC was applied in 40 patients for confirmation and definite diagnosis of malignant melanoma .

Table 7: Positivity for Different Markers

IHC marker	Total No. Of Patients in which IHC done	No. of Patients Showing Positivity
Vimentin	40	40 (100%)
HMB-45	37	35 (94.5%
S-100	39	39 (100%)
Melan-A	5	5 (100%)
AE1	28	0 (0%)
EMA	10	2 (20%)
cKit	3	2 (66%)
Synaptophysin	2	0 (0%)
Chromogranin	1	0 (0%)
LCA	7	1 (14.2%)
Actin	2	0 (0%)
Desmin	2	0 (0%)



(f) Positivity for Different IHC Markers

7. Discussion

- In the current study, 100 cases of Malignant Melanoma were studied.
- Patients in our study belonged to the age group in the range of **22 to 84** years, with mean age being **53.57** years and a sex ratio of **1.7:1**,
- Foot was the most common site for Malignant Melanoma in our study.
- Study Shows Two cases of Malignant Melanoma Iin Liver which is a very rare site.
- There are two cases of amelanotic melanoma which is a rare variant of MalignantMelanoma.
- Our Study shows almost 100% positivity for Vimentin,S-100 and HMB-45 and Negativity for AE1, EMA, LCA, which rules out other tumors like poorly differentiated carcinoma and lymphoma..
- Study shows frequent metastasis in regional lymphnodes, while distant metastasis are seen in sites like liver and brain in very few cases.
- Metastasis to distant sites such as Liver and Brain are seen infrequently, in our study only 3 cases showed distant metastasis.

8. Summary & Conclusion

- To conclude, the current 100 case study of Malignant Melanoma, has illustrated the characteristics of patients of Malignant Melanoma presenting at our institute.
- **Male** predominance was seen over the Female.
- The most common site of Malignant Melanoma was the Skin of **Lower Limb.**
- The least common site of Malignant Melanoma was the **Liver.**
- **In IHC Study , Melan-A, HMB-45, S-100 and Vimentin Positivity & Negativity for AE1, EMA, LCA** is helpful for Differentiating Malignant Melanoma from other Poorly Differentiated Tumors and Lymphomaand to arrive at definite diagnosis.
- This is a Pilot study trying to understand this tumour entity. Further study is advisable on a larger population.

9. Abbreviations

H & E: Hematoxyline and Eosin
IHC : Immunohistochemistry
UVR : Ultraviolet Radiation

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