Malignant Melanoma – A Single Institutional Analysis On Real World Data

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Abstract

Background: There are very limited studies on survival analyses of malignant melanoma from the rural and southern part of India and hence we present our retrospective analyses on treatment outcomes of patients diagnosed as Malignant Melanoma from our institution.

Objectives: To calculate the median overall survival [OS] and median Disease Free Survival [DFS] of patients with malignant melanoma diagnosed and treated at our institution.

Patients and methods: Between 2014 and 2022, histologically confirmed patients with malignant melanoma were included and were followed up for the survival analysis.

Results: There were 107 patients analyzed with a median age of 58 years [range 29-85 years], gender wise male patients were 64.5% [n=69] and female patients were 35.5%[n=38]. The most common primary site was extremities 65.4% [n=70]. The median follow up duration of patients was 12 months [range: 1-36 months]. Most commonly patients presented with stage IV disease 52.3% [n=56]. Patients that underwent surgery were 51% [n=55]. Median disease free survival for these patients was 23 months [95% CI-18-28 months]. Median overall survival for the entire group of patients at the end of 3 years was 9 months [95% CI-5.6-13 months].

Conclusion: Malignant melanoma is the most aggressive cutaneous malignancy ever to be discovered by mankind. The battle for cure is far from over and requires an even more aggressive strategy to meagerly improve the outcomes for these patients.

Keywords: Malignant melanoma ; Prognosis ; Chemotherapy ; Survival ; Follow up.

Introduction

The Age-Adjusted Rate [AAR] per 100,000 melanoma of the skin was highest in the North region of India for both males and females with 1.62 and 1.21, respectively. The incidence of non-melanoma of the skin or other skin cancers for males was highest in the East region at 6.2 and for females in the Northeast at 3.49 as per (**Mathews et al., 2018**). Among non-melanoma skin cancers, the northeast region showed the maximum incidence for both male (75.6) and female (43.6) sexes. Globally, the AAR of melanoma of skin for males was highest in the Western Pacific region at 36.9, and for females; AAR was highest in the European region at 31.7. The incidence of non-melanoma of the skin or other skin cancers for males was highest in the Western Pacific region with 225.4 and 68.6 for females as described by (**Damsky et al., 2010**).

It has long been known that melanoma risk has been linked to skin, hair, and eye coloration, people who have light skin that does not tan, blond or red hair, and light eyes have a much higher risk of having melanoma compared to the population as a whole. People harboring less functional variants of MC1R accumulate more mutations due to increased exposure of the nuclei to UV damage. If mutations accumulate in sensitive regions of the genome, then skin cancers can arise. In the 1960s melanomas began to be classified based on histologic patterns. While histology is still important for melanoma diagnosis, one of the most influential shifts in the understanding of cancer progression was the realization that cancer arises due to the accumulation of genetic mutations, leading to the dysregulation of cellular pathways as per (**Behera et al., 2018**).

Among skin cancers, malignant melanoma has been traditionally described to be the most lethal with the poorest prognosis and overall survival. It comprises only 3% of the cutaneous malignancies that are reported in the literature. But among all skin cancers diagnosed each year, it accounts for approximately 75-80% of all skin cancer-related deaths. Whereas both incidence and mortality among the younger generation of individuals in decreasing, the detection rates among the elderly group of the population are on a steady rise consistently throughout the years as explained by (**Crocetti et al., 2015**).

Malignant melanoma has a difference in presentation among genders as given in the paper of (**Leonardi et al., 2020**). The commonest site in males is the trunk followed by the head and neck region, but in female patients, the most common site has been described to be the extremities. Male patients with melanoma present at an older age and a more advanced stage of the disease than female patients. Malignant melanoma incidence in children and adolescents is deemed to be very rare and the incidence has been analyzed in different literature to be approximately around 3% among all childhood neoplasms as elaborated by (**Ugurel et al., 2017**). According to the American Joint Committee on Cancer [AJCC], the 5-year survival for stage I melanoma exceeds 90% but falls exceedingly quickly as the stage progresses with nodal involvement and increasing tumor thickness as given in the paper by (**Lens et al., 2003**).

The 5-year survival for localized melanoma is approximately 95-99% but drops to 15-20% in the presence of upfront distant metastasis and highlights the importance of the need for early diagnosis and treatment initiation as per (**Tas et al., 2006**). Historically, metastatic melanoma has a dismal prognosis with 5 year OS of approximately 10%. The median survival of malignant melanoma in most published

analyses ranges from 2 to 4 years. Disease-free survival has been described in the ranges of 30% or less among the patients that underwent surgical intervention in various literature studies such as (**Pflugfelder et al., 2011**). The annual cost of melanoma treatment has increased exponentially by 288% in less than ten years, and it is expected to rise even further with the advent of newer and more effective immune checkpoint inhibitors and targeted therapies as explained by (**Young et al., 2001**). Our primary objectives of performing this retrospective analysis are to calculate the median overall survival[OS] and median disease free survival[DFS] of the patients that underwent various treatment modalities at our institution.

Patients and methods

Patients who presented with skin lesions at our institute were histologically confirmed with biopsy as malignant melanoma were included in our analysis. Patients evaluated and diagnosed at our institute from January 2014 to July 2022 were included in our analysis. Staging workup included MRI/contrast-enhanced (CE) CT scan of the affected primary site, whole-body F18 fluoro-deoxyglucose positron emission tomography CECT (FDG PET-CECT), or X-ray and ultrasonography. Patients with melanoma ano-rectum were included along with mucosal melanoma and categorized as Stage IV patients. Baseline demographic features, primary site, stage, histological details, and treatment details were obtained from our hospital-based cancer registry. Mutational analysis was not available at our institute due to resource constraints and hence could not be performed for these patients.

All patients were discussed in the multidisciplinary tumor board (MDT) after the staging and histopathology confirmation of melanoma. Patients with localized melanoma were treated with curative intent with surgery and adjuvant radiation therapy. Patients with metastatic disease at the initial presentation were treated with palliative systemic therapy and response assessment every 3 cycles. Patients who had symptomatic distant metastases were also treated with radiation therapy with palliation as intent. Patients were followed up routinely after every treatment completion at our outpatient department.

Statistical analysis

Disease-free survival (DFS) was defined as the time from the date of diagnosis until any event (including local or distant relapse/failures or progression or death). Overall survival (OS) was defined as the time from the date of diagnosis to death from any cause or last documented follow-up. Patients who were lost to follow-up were censored on the date of their last follow-up. The data were analyzed using IBM SPSS Statistics for Windows, Version 24.0. Descriptive statistics were represented as median or percentage, and group comparisons were made using the c2 test or Mann–Whitney U test, as appropriate. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test.

Results

Analysis of the entire cohort

There were 107 patients included in our analysis, Among the 107 patients, 29.9% of participants were in the age group 61 to 70 years followed by 28% in the age group 41 to 50 years. 23.4% were in the age group 51 to 60 years (**Table.1**). The median age among the participants was 58 years (range 29 to 85 years). The commonest primary site was extremities 65.4% [n-70] followed by mucosal and ano-rectum 19.6%[n-21] and melanoma of unknown primary 9.3% [n-10] (**Table.1 & 2, Fig.1**].

Histologically they were classified into most commonly as acral lentiginous

type 43.9%[n-47] followed by superficial spreading type 29.9%[n-32], nodular type
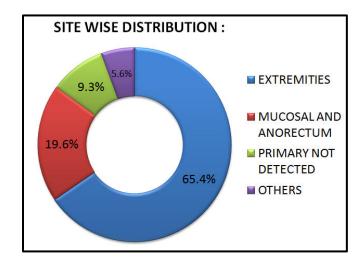
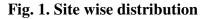20.6%[n-22], and least commonly amelanotic type 5.6%[n-6].

Table 1: Basic demographics of the analyzed patients

Variable		Frequency (n=107)	Percentage (%)
Age group (In years)	≤ 40	6	5.6
	41-50	30	28
	51-60	25	23.4
	61-70	32	29.9
	>70	14	13.1
Sex	Male	69	64.5
	Female	38	35.5

Table 2: Site wise distribution of the entire cohort of patients [n-107]

S.NO	Site wise	Percentage
1.	**Extremities**	65.4% [n-70]
2.	**Mucosal and anorectum**	19.6% [n-21]
3.	**Unknown primary**	9.3% [n-10]
4.	**Trunk**	2.8% [n-3]
5.	**Others**	2.8% [n-3]

Fig. 1. Site wise distribution

Among 107 patients with a median follow-up of 12 months [range is 1-36 months], the total number of patients diagnosed with stage IV disease was 52.3%[n-56], stage IIIC was 17.8%[n-19], stage IIIB was 14%[n-17], stage IIC were 3.7%[n-4], stage IIB were 9.3%[n-10] and stage IB was 0.9%[n-1] (**Fig.2 & 3**).
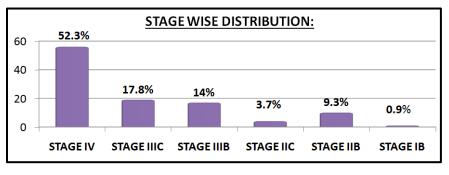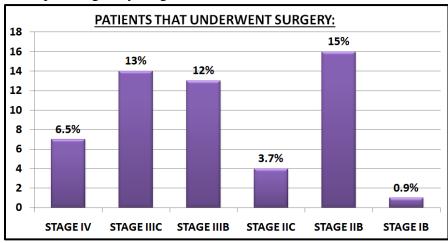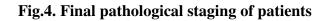
Fig.2. Clinically representative pictures

Fig.3. Stage-wise distribution

Analysis of patients that underwent surgery

The total number of patients that underwent surgery was 51.4%[n-55]. Most commonly the patients that underwent surgery were histo-pathologically staged as stage IIB 15% [n-16] followed by stage IIIC 13% [n-14] and the least commonly staged patients were found to be stage IB 0.9% [n-1] (**Fig.4**).

Fig.4. Final pathological staging of patients

Most of the patients that underwent surgery in our analysis commonly received adjuvant chemotherapy 16.8% [n-18] either with temozolomide or with dacarbazine plus cisplatin and Adjuvant radiation therapy was given to 5.6%[n-6] patients **(Table.3).** Many of the patients defaulted after surgery 20.5% [n-22] due to various logistic difficulties and did not receive any adjuvant treatment at our institution. Adjuvant immunotherapeutic agents were not available at our institute due to resource constraints and hence could not be offered to these patients in our institution.
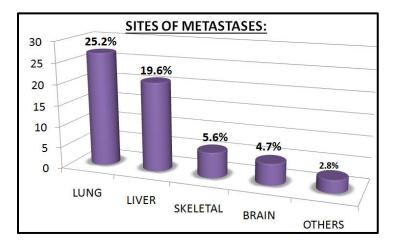
Table 3. Adjuvant treatment received by patients that underwent surgery

S.NO.	Adjuvant treatment	Percentage
1.	Adjuvant chemotherapy	16.8%[n-18]
2.	Adjuvant radiation therapy	5.6% [n-6]
3.	Observation	8.4% [n-9]
4.	Lost follow-up / defaulted	20.5% [n-22]

Metastatic disease analyses

Among Stage IV patients, the most common primary location was noted to be extremities 26.1% [n-28] followed by anorectum 11.2% [n-12], and prim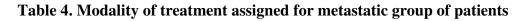ary not detected 5.6% [n-6]. Patients diagnosed with distant metastases were 58%[n-62], the most common site of distant metastases was the lung at 25.2% [n-27], followed by the liver at 19.6% [n-21] and skeletal metastases at 5.6% [n-6] **(Fig.5)**.

Fig.5. Site-wise distribution of metastases

Most commonly patients that presented with metastases were administered palliative chemotherapy 30.8%[n-33]. Patients were most commonly administered temozolomide, and dacarbazine combined with a platin-based regimen **(Table.4)**. Palliative radiotherapy was administered to 6.5% of the patients [n-7] and the best supportive care was decided in our MDT for 15% [n-16] of the patients **(Fig.6)**.

Table 4. Modality of treatment assigned for metastatic group of patients

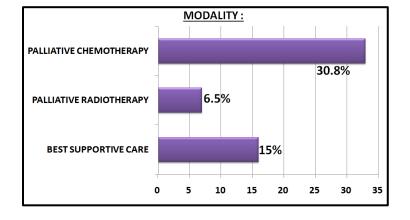| S.NO.	Modality	Percentage
1.	**Palliative chemotherapy**	30.8% [n-33]
2.	**Palliative radiotherapy**	6.5% [n-7]
3.	**Best supportive care**	15%% [n-16]

Fig.6. Palliative modalities of treatments administered

Survival analyses

The median overall survival[OS] of the entire group of patients that were analyzed [n-107] was 9 months [95% CI 5-13 months]. Most participants had a survival time of fewer than 40 months (**Table.5**).

Concerning the period of survival, 48.6% of patients had survived for 1 to 6 months, 18.7% of patients had survived for 7 to 12 months, 13.1% of patients for 13 to 24 months, and 10.3% of patients had survived for more than 36 months.

Table 5. Period of survival distribution

Period of survival (in months)	Frequency (n=107)	Percentage
1-6	52	48.6%
7-12	20	18.7%
13-24	14	13.1%
25-36	10	9.3%
>36	11	10.3%

The median overall survival of patients in stage IV was 5 months [95% CI-3.6-6.4 months]. For Stage III patients, the median overall survival was analyzed to be 16 months [95% CI 7.9-24.1 months] , for Stage II the median overall survival was 46 months [95% CI 43.9-48 months].

The overall median disease-free survival[DFS] of the entire cohort of patients that underwent surgery [n-55] was reported as 23 months [95% CI-18-28 months]. The Median disease free survival[DFS] for Stage IV [anorectum] patients that underwent abdomino-perineal resection[APR] was 24 months [95% CI 17.3-13.7 months], for Stage III patients was 14 months [95% CI 9.9-18.1 months] , for Stage II patients was 26 months [95% CI 18-28.4 months] and for Stage I was 30 months [95%CI 28.2-31.6 months] (**Figs. 7,8 &9**)
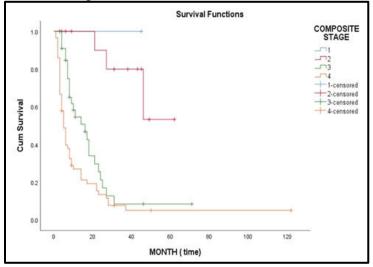

Fig.7. Overall survival of the entire cohort. Survival curves of all the patients according to the stage of the disease.
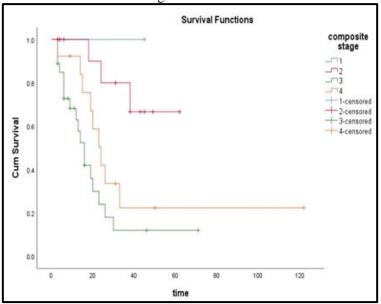

Fig.8. Disease-free survival[DFS]. Survival curves of all the patients that underwent surgery according to the stage of the disease.
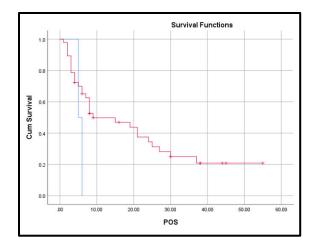
Fig.9.   Overall survival graph of stage iv metastatic patients. Survival curve of the patients with distant metastases.

Discussion

There is a generalized lack of awareness among the population of our country regarding cutaneous malignancies and is deemed to be misdiagnosed due to various attributable factors in our current medical setup. Cutaneous malignancies are more commonly misdiagnosed than any other malignancy in our regional practices. It is believed to be due to the lack of education and proper screening programs as explained by (**Anderson et al., 1995**). The patients usually present to the general practitioner with complaints of non-healing wounds or ulceration or minor skin discoloration and tend to be diagnosed late resulting in early progress and a dismal attitude toward the seriousness of these cutaneous malignancies.

Cancer registries in India report that the age-specific incidence rate for cutaneous malignant melanoma is less than 0.5 per 1 lakh population as per (**Lian et al., 2017**). The highest standardized incidence rates per 1 lakh general population were reported in Australia (54.1) and the United States (21.0), while the lowest ones include Asia pacific (0.7) and South Asia (1.1)as given in the paper of (**Tyrell et al., 2018**).

In our study, the most common site affected by malignant melanoma was the extremity[65%] followed by mucosal and anorectum [19%]. In other Indian studies, mucosal melanomas are more common or are of equal incidence to the incidence in the extremities. However, there is a variable pattern that is partly explained by the referral pattern and draining area as elaborated by (**Panda et al., 2018**).

Metastatic malignant melanoma has a dismal prognosis with a higher mortality rate and poorer overall survival than the other cutaneous malignancies that are reported in the literature. The 5-year overall survival of this malignancy has been evaluated and analyzed in various literature is ranged between 5% to 19% depending on the location and number of metastases and associated systemic effects due to those metastases as given in the paper by (**Sahoo SS et al., 2018**). Serum lactate dehydrogenase elevation has been attributed to a poorer prognosis in patients in upfront settings corroborating with (**D'Orazio et al., 2011**).

The median overall survival[OS] for metastatic malignant melanoma patients in our study is 9 months which is relatively similar to various other larger studies in an approximate range of 7-8 months as given in **(Rebecca et al., 2013)**.In our analysis, the most common location for metastases was the lung followed by the liver similar to the incidence reported in various larger retrospective analyses.

Malignant melanoma is the third leading cause of brain metastases next to carcinoma lung and breast. Autopsy records of many metastatic patients showed that these patients had approximately 75% incidence of brain metastases at the time of examination as explained by **(Lee et al., 2013)**. In our analysis, the most common location for metastases was the lung followed by the liver. Brain metastases were found to be at an incidence rate of 4.7%, but this can be attributed to the various resource constraints at our setup for higher imaging and metastatic workup.

Most of the metastatic patients in our analysis received cytotoxic chemotherapy at our institution with either temozolomide as an oral form of therapy or dacarbazine with cisplatin. The tolerance for both these agents in our analysis is questionable due to the lack of proper follow-up and lack of adherence to strict review policies at our institution. Since most of the patients that are analyzed in this study from our institute originate from a poorer socio-economic background there is poorer compliance to various forms of therapy offered and accepted by these patients.

There are many resource constraints at our current setup due to logistic difficulties and hence leading to a lack of standard of care options provided by various international guidelines. Immunotherapy has now shown to be the first line of management even in patients that undergo curative intent surgery in the adjuvant setting. The role of immuno-modulators has been characterized and described by various randomized trials and has been introduced as the standard of care options for melanoma patients as explained by **(Sanki et al., 2009)**.

Most of the patients from this part of India are dependent upon monthly incomes for their well-being and daily living expenditure. The immunotherapeutic agents that are currently available in the medical supply chains would cost an average of 5000 US dollars per patient for a two-weekly schedule as explained by **(Chua TC et al., 2010)**. This is not feasible in real-life practice and becomes an unbearable economic burden to even the patients with sufficient economic support. India's existing data suggests that only 1.6% of the eligible patients could afford immunotherapy, which reflects the gross survival differences in studies from developed countries and developing countries such as India as per **(Sandru et al., 2011)**.

Conclusion

Malignant melanoma in malignancies per se is an evolving topic with various controversies and discussions regarding the standard of care in the management of these patients which causes a huge economic burden. This cutaneous malignancy is rarer in our current setup than in the developed countries in comparison due to various screening protocols and guidelines for referral to a cancer specialist regarding definitive treatment for this disease. Currently, the overall survival rate of malignant melanoma is still poor in our part of the country due to a lack of awareness and late presentations to a tertiary cancer center for definitive management. Improved education and early referral to a tertiary regional cancer institute can be offered as a simple yet underutilized option for not only improving the dismal survival rate of this malignancy but for the overall

lifting of the fallen curves of survival for almost all cancers.

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