Expansion of Palliative Care in the Gulf Area
Original Articles /Studies

Impact of BMI on Locoregional Control among Saudi Patients with Breast Cancer after Breast Conserving surgery and Modified Radical Mastectomy .......................................................... 07
E.F. Al Saeed, A.J. Al Ghabban, M.A. Tunio

A statistical quantification of radiobiological metrics in Intensity Modulated Radiation Therapy evaluation .......... 15
A. Surega, J. Punitha, S. Sajitha, BS Ramesh, A. Pichandi, P. Sasikala

A method for assessment of radiation treatment chain of cervical cancer with combined external and brachy radiation therapy .......................................................... 24
A. Chaparian, P. Shokrani

Role of Lymphadenectomy and Its Impact On Survival In Endometrial Carcinoma – An Institutional Experience ....30
S. Suchetha, P. Rema, S. Vikram, P.S. George, I. Ahmed

Breast Cancer—Epidemiology, Risk Factors and Tumor Profiles in Bangladeshi underprivileged women .................. 34
M. Rahman, A. Ahsan, F. Begum, K. Rahman

Early hematological effects of chemo-radiation therapy in cancer patients and their pattern of recovery- A prospective single institution study .......................................................... 43

Platinum-based chemotherapy in metastatic triple negative breast cancer: Experience of a tertiary referral centre in India ........................................................................................................ 52

A Single Institution 18-Years Retrospective Analysis of Malignant Melanoma .............................................................. 58
A. Mukherji, A.K. Rathi, P.K. Mohanta, K. Singh

MRI and ultrasonography for assessing multifocal disease and tumor size in breast cancer: Comparison with histopathological results ................................................................................... 65
V. Rudat, A. Nour, N. Almuraikhi, I. Ghoniemy, I. Brune-Erber, N. Almasri, T. El-Maghryb

Patient’s Compliance On the Use of Extended Low Molecular Weight Heparin Post Major Pelvic Surgeries in Cancer Patients at King Hussein Cancer Center .......................................................... 73
M. Baba, M. Al Masri, M. Saltab, M. El Ghanaem

Can we use Sorafenib for advanced Hepatocellular Carcinoma (HCC) Child Pugh B? ............................................... 82
K. Rasul, A. Elessam, S. Elazzazi, R. Ghasob, A. Gulied

Case Reports

The external auditory canal as an unusual site for metastasis of breast carcinoma: A case report ................................. 85

Primary Mixed Cellularity Classical Hodgkin lymphoma of the Lumbar spine – An unusual presentation .............. 88
K.R. Anila, R. A. Nair, S. Prem, K. Ramachandran

Subdural hematoma during therapy of gastro-intestinal stromal tumor (GIST) with Imatinib mesylate .................. 92

Conference Highlights /Scientific Contribution

• Workshop Highlights –The Second Regional Training Of The Trainers’ (TOT) Workshop On Palliative Care, Kuwait, 23-26 November 2014 ............................................................... 96

• News Notes ........................................................................................................................................................................ 102

• Advertisements .................................................................................................................................................................. 107

• Scientific events in the GCC and the Arab World for the 1st Semester of 2015 .............................................................. 108
A Single Institution 18-Years Retrospective Analysis of Malignant Melanoma

A. Mukherji1, A.K. Rathi2, P.K. Mohanta2, K. Singh2

1Dept of Radiotherapy, Regional Cancer Centre, JIPMER, Puducherry, India.  
2Dept of Radiotherapy, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, India

Abstract

Melanoma accounts for about 2% of all cancer-related mortality in western populations. Surgical excision of localized disease is curative in many patients with 80% overall 5-year survival rate. There are many indicators of prognosis of which tumor burden is predicted by primary site with nodal status being the next most important variable. Patients with advanced stage have very high risk of developing distant metastases and should receive systemic therapy. Despite treatment, majority of locally advanced patients develop metastatic disease.

Materials and Methods:

A retrospective analysis of cases of malignant melanoma registered over a period of eighteen years, from October 1990 to September 2007 was done. Patient profile, presentation, disease load, treatment protocols and response on or after treatment were analyzed.

Results:

The median age at diagnosis in men was 48 years and 50 years in women. At presentation, more than half of studied cases (56.5%) presented with nodal metastases at diagnosis while about three fourths (74%) had distant metastases (stage IV disease). More than half (56%) of the patients had superficial spreading type. The most common presenting complaints were swelling (70% of patients), ulcer (50% of patients) or pain (50%). Primary sites included extremities, central nervous system, abdomen, trunk, and bones. Liver, brain, abdomen and lungs were common metastatic sites. Surgical excision of primary lesion was done in about half of the cases. Four patients subsequently received palliative radiotherapy and two more received adjuvant radiotherapy. Another six patients received adjuvant chemotherapy and radiotherapy. Among treated patients, 26% showed partial response and another 8% have stable disease while 65% patients progressed on or after initial treatment.

Conclusion:

Malignant melanoma carries an overall poor prognosis especially in advanced stages. Multimodality therapy with surgery, radiotherapy and chemotherapy may provide local or nodal remission but cannot improve long term survival in advanced cases.

Keywords:

Malignant Melanoma, Skin cancers, Pigmentary epithelium.

Introduction

Melanoma accounts for about 2% of all cancer-related mortality in the western population. (1,2) Surgical excision of localized primary cutaneous melanoma (stages I and II) can lead to cure in many patients and the overall 5-year survival rate for these patients is about 80%. (3,4) The indicators of prognosis include tumor thickness, age, sex, primary site, Clark stage, mitotic rate, ulceration, and tumor-infiltrating lymphocytes (5-9) Many molecular markers such as HLA, cathepsins and integrins have been evaluated but have not altered the prognosis with median survival averaging a dismal 6 months. (6, 7, 10-12) Patients with thin melanoma (<1.5mm) are deemed as
low risk cases and primary tumor excision is the treatment of choice. Adjuvant therapy is given in patients with thicker lesions if sentinel node biopsy is positive.

Age, site of disease and gender are important factors predicting prognosis. Patients who are older than 60 years as well as male patients have dismal outcomes to therapy for every stage while lesions of the extremities have better prognosis(2, 13-15). In locally advanced disease, the number of positive nodes is an important risk variable. Higher number of positive nodes reflects poorer chance of survival. Presence of ulceration of the primary tumor is associated with a higher metastatic potential from nodes to the distant sites and is an important risk factor for development of distant metastases. Five year survival for non-ulcerated stage III melanoma with favorable disease (young age, occult nodes) is 70% whereas survival in those with ulcerated disease unfavorable characteristics (older age, clinically positive nodes) is 15%. Thus, patients with stage III have a very high risk of developing distant organ metastasis and should be treated with systemic therapy.

Despite treatment, majority of locally advanced patients develop metastatic disease, and the survival is limited in months. The existing treatment protocols do not offer a survival benefit, though they may prolong the time to progression. Systemic therapy may be used in a subset of stage II patients at risk of metastatic disease. In this review we have analyzed the characteristics of patients with malignant melanoma seen in our institution and protocols instituted for their treatment, and have tried to interpret the ultimate outcome of these patients.

**Methods and Materials**

A retrospective analysis of cases of malignant melanoma of all stages registered in the Department of Radiotherapy, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi over a period of eighteen years, from October 1990 to September 2007 was done.

Studied parameters include patient profile, presentation, disease load, treatment given and response as well as survival. All details were noted from case charts present in the departmental records and contact over telephone was made with the family of the patients to inquire about the details not mentioned in the case records wherever possible. This was then compared with existing literature and conclusions have been attempted as to whether there is any difference in the presentation and behavior of Indian patients as seen in our institution when compared to standard literature. The distribution of data on patients’ clinical characteristics and clinical outcomes have been expressed as percentages and proportions.

The total number of malignant melanoma cases registered in the outpatient clinic, MAMC during these eighteen years (1990-2007) was 53. During the same period the total number of cases of malignancy that were registered was 37,793. The crude annual incidence of malignant melanoma among the patients who attended OPD was 0.14%. Out of these, case records of 23 patients were complete; 30 patients were lost to follow up. The authors agree that this large number of cases who could not be followed up or contacted may have influenced the outcomes of this analysis.

**Results**

**Patient Profile and Treatment given**

In the studied cases, the disease was more prevalent in men (about 75% of cases) compared to women. The median age at diagnosis in men was 48 years (range 8-86 years and mean age of 50 years) and 50 years (range 35-75 years and mean age of 51.5 years) in women. Nearly 70% of cases analyzed belonged to the age group of 30-60 years. More than half of studied cases (56.5%) presented with nodal metastases at diagnosis while about three fourths (74%) had distal metastases (stage IV disease) at presentation. In nearly half of patients (48%) the disease was present for less than 6 months, while the duration of symptoms before presentation was less than 12 months in more than 80% of the cases. Females have presented earlier than males (median 4 months and 8 months respectively). About two-thirds of male patients were smokers (15 out of 17); while only one of the female cases...
was a smoker. More than half (56%) of patients had superficial spreading type of melanoma, more common in males (around 60% of cases). Nodular melanoma was present in around 20% of patients while another about 20% of patients had choroidal melanoma.

The most common presenting complaints were the presence of a progressively increasing swelling (70% of patients) or ulcer (50% of patients) at the primary site. Pain was associated with swelling or ulcer in about 50% of patients. Visual disturbance was the presenting symptom in cases of choroidal melanoma. One third (2 out of 6) of female patients presented with choroidal melanoma while another one third female patients presented with vaginal involvement. On the other hand majority of cases in males involved the extremities with nodal involvement. Primary sites included extremities, CNS, abdomen, trunk and bones (Figure 1). Genito-inguinal area involvement was seen in 13 patients and was seen only in males while limbs were involved in 9 patients. Other presentations have included symptoms involving genito-urinary tract, respiratory, skeletomuscular and CNS systems (Figure 2).

Nodal metastases was seen in about two thirds of the patients (65%) with the most common nodes involved being the inguinal nodes (12 out of 23 cases). Other nodes involved included intra-abdominal nodes like retroperitoneal, periportal as well as femoral and hilar nodes. Distant organ metastasis at presentation was seen in 74% of patients, 60% of these had genito-inguinal melanoma. Liver, brain, abdomen and lungs were the most common sites of distant metastases.

Surgical excision of primary lesion was done in about half (13 out of 23 or 56%) of the cases with others being unresectable. No palliative surgical procedures were done. Chemotherapy and radiotherapy was instituted either as adjuvant / neoadjuvant or palliative modality in a sizable number of patients (Table 1). Of the 13 patients who underwent surgery, four patients subsequently received palliative radiotherapy and two more received adjuvant radiotherapy. Another six patients received both chemotherapy and radiotherapy as adjuvant treatment from which two patients, concurrent chemo-radiation was given. Overall, ten patients (43.5%) were administered first line and another six patients (26%) were given palliative DTIC based chemotherapy which included

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Radical surgery</td>
<td>13 (56.5%)</td>
</tr>
<tr>
<td>Palliative Surgery</td>
<td>0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Neoadj. Chemotherapy</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Adj. Chemotherapy</td>
<td>8 (34.8%)</td>
</tr>
<tr>
<td>Concurrent chemo-RT</td>
<td>2 (8.6%)</td>
</tr>
<tr>
<td>Palliative chemotherapy</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Radical / Adjuvant Radiotherapy</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>Palliative Radiotherapy</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>No treatment</td>
<td>2 (8.6%)</td>
</tr>
</tbody>
</table>

Table 1: Description of various treatment modalities and number of cases treated.
doxorubicin in seven cases (30%), vinblastine/ vincristine in eight cases (35%) and cisplatin in 12 cases (75%). Tamoxifen 20 mg once daily with Levamisole (3 cases) or with chemotherapy (6 cases) was instituted in about 40% of patients (9 cases) while two patients (9%) received best supportive care.

A total of 16 patients (about 70% cases) received hypo-fractionated radiotherapy either as adjuvant or palliative therapy. Of these, 7 cases received adjuvant therapy and 9 cases received palliative therapy. Doses ranged from 7 Gy weekly single fractions to fractionated schedules of up to 60 Gy in 20 fractions. Of the total patients treated, about 40% (9 cases) completed their planned treatments while nearly 60% (14 cases) either progressed while on therapy (13 cases out of 14) or did not complete their therapy (1 case).

Response and Survival

There were no cases with complete response after therapy. Of all patients who received initial treatment, 26% showed partial response and another 8% had stable disease; while 65% patients progressed on or after initial treatment. In more than half the patients, the most common site of relapse was distant metastases while nodal relapse accounted for failure in a quarter of patients. Relapse at the local site was seen in nearly 40% of cases.

Eight patients who underwent surgery followed by adjuvant radiotherapy and chemotherapy developed distant metastasis during follow-up after completion of initial treatment but maintained remission at local sites. All these eight cases showed either partial remission or stable disease at the end of their initial therapy. Table 2 describes the distribution of patients who relapsed according to modality of therapy initially given. However those who could not be operated or received only one modality relapsed during therapy and even at local or nodal sites along with distal metastases. All patients who received only chemotherapy (even multidrug regimes) as well as patients who received immune-modulators like tamoxifen or Levamisole developed metastases during the course of their initial therapy. In this respect, patients receiving adjuvant radiotherapy with or without chemotherapy showed better local or nodal control than cases receiving only chemotherapy. Only 3 out of 13 cases who received adjuvant or palliative radiotherapy as initial treatment showed local relapse with no nodal relapse, and all these three cases have received weekly palliative doses.

On follow-up all patients developed nodal or distant metastasis and no long-term survivor was seen. The principal sign of treatment failure in a majority of cases was liver failure or icterus or jaundice representing biliary or liver metastases (in 70% of cases) followed by general debility and asthenia seen in about 20% of cases. Liver eventually was involved leading to hepatic failure and death in 70% of cases. Another significant heralding sign was brain involvement seen in 26% cases. Lung involvement and consequent respiratory distress as a heralding sign of treatment failure was seen in very few patients, but was a significant terminal event, present in 20% of patients. But the major terminal events were liver failure (65% cases), CNS events (65%) or asthenia (78%).

In this study the overall survival was less than 6 months in about 70% cases and less than one year in nearly 87% cases. This reflects the poor

<table>
<thead>
<tr>
<th>Treatment given</th>
<th>Partial response</th>
<th>Complete response</th>
<th>Progressive disease</th>
<th>Stable disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Surgery</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Biotherapy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Modality- and sex-wise distribution of responses to initial therapy seen. (Figures represent number of cases)
response of advanced stage melanoma to all therapy. The longest overall survival (OS) was 16 months and shortest was 0.5 month. The median OS was 4 months overall, in males it was 4 months (mean 4.4 months) and in females it was 8 months (mean 7.5 months). Also an analysis of patterns of survival showed that with surgery or immunotherapy alone, results were dismal with median survival duration of only 2 months and relapses seen locally, nodal and systemically. With radiotherapy alone median survival was 3.5 months with relapses seen systemically and locally (if single fraction palliative radiotherapy given). Similarly cases receiving chemotherapy alone had medial survival of 3 months with both local and distant relapses. When surgery was combined with radiotherapy, survival improved to 4.5 months but relapses were both local and systemic. Combination of surgery with chemotherapy and radiotherapy improved survival to 8 months and relapses were seen systemically only.

**Discussion**

As a disease entity, malignant melanoma, though rare in countries like India carries an overall poor prognosis. This may be due to the advanced stage of presentation and a subsequent lack of an effective therapy. The first multivariate analysis in search of prognostic factors of malignant melanoma was done in 1978 (21,22) and the first multi-institutional experience analysis was published in 1981.(23) Although many well-designed single-institution analyses have been done to understand prognostic factors, few attempts have been made to unify these results into a melanoma staging system to be used in clinical research and clinical practice.(24-26) In our study, superficial spreading type of melanoma was the most common with predilection for extremities and nodes in males and visceral organs (choroid, vagina) in females. The fact that half of the patients have less than six months duration of complaints before presentation and 80% had less than 1 year duration suggests an aggressive behavior of the disease.

In locally advanced disease, the number of positive nodes has been observed to be an important risk variable with poorer survival with increasing number of positive nodes. (3, 16-20) Tumor burden as predicted by the primary site and nodal status is the next most important variable. Presence of ulceration of the primary tumor has been associated with a higher metastatic potential of the disease from nodes to the distant sites compared to the non-ulcerated primary tumor and hence is considered an important risk factor for development of distant metastases.

The overall effect of these disease characteristics on the survival statistics is reflected in the large variations in the natural history of stage III malignant melanoma. Five year survival for non-ulcerated stage III melanoma with favorable disease characteristics (young age, occult nodes) has been around 70% whereas those with ulcerated disease unfavorable characteristics (older age, clinically positive nodes) show very poor survival of around 15%. (17,19,20) So it has been generally accepted that patients with stage III have a very high risk of developing distant organ metastasis and hence should be treated with systemic therapy irrespective of the primary melanoma thickness. Also in our study, a quarter of patients who presented with stage III disease subsequently went on to develop distant metastases irrespective of the initial therapy and response.

About seventy percent of patients were given some form of systemic treatment with either chemotherapy or Tamoxifen. Dacarbazine (DTIC) was always a part of therapy if chemotherapy was administered. The other most commonly employed drug was Cisplatinum. These two have been the most effective contemporary drugs used for this disease entity. However, the overall response rate of chemotherapy was only 34% (partial response 26%, stable disease 8%). Tamoxifen was associated with much inferior response with rate of disease progression twice that for chemotherapy.

Hypofractionated radiation treatment has been repeatedly reported to be effective in melanoma treatment. Radiation was employed only in about two thirds of the patients of which half had received chemotherapy, presumably because the remaining patients showed either progressive
disease or had poor response to prior therapy that reasonably precluded any further treatment. The overall survival after initiation of therapy was only 4 months. Adjuvant therapy as post-operative therapy with chemo- or radiation did not provide lasting benefit in our patients as many had presented with stage III disease and regional nodes. However any form of combination post-operative treatment did appear to offer a survival advantage; patients survived for a mean of eight months if they received combination of surgery with chemotherapy and radiotherapy but less than 5 months if they received radiotherapy or chemotherapy alone with surgery. With surgery alone or immunotherapy alone, results were even worse with median survival duration of only 2 months. Relapses seen locally, nodal and systemically when surgery or chemotherapy were used alone; but inclusion of radiotherapy led to local and nodal remissions especially with sequential or concurrent chemotherapy regimens.

Even after adequate treatment, a majority of patients with stage III disease develop metastases after which the survival is measured in months rather than years and only a small number of patients survive beyond 12 months. There appear no significant indicators in stage IV disease to separate groups with different prognoses, such as in stage III disease. Subset analysis of study data (15, 27, 28) shows a substantial difference in survival when the metastases occur in non-visceral sites such as lymph nodes and skin compared to visceral organ involvement. Also while involvement of visceral sites portends poor survival outcomes in general, patients with lung involvement had slightly better survival than other visceral sites. (15, 27, 28) Malignant melanoma is known to involve multiple organ systems in its natural course. This pattern was also observed in our study wherein eventually, all of the patients developed distant metastasis and no long term survivor was seen. The major terminal events were liver failure (65% cases), CNS events (65%) or asthenia (78%). Advanced melanoma has been known to lead to very poor survival rates and our patients too had overall survival of months. The existing treatment protocols for metastatic melanoma do not offer a survival benefit, though they may prolong the time to progression of disease. Systemic therapy may be used in a subset of stage II patients who are at the risk of developing metastatic disease. The introduction of interferon alpha-2a in stage II disease offers some advantage but the therapy remains toxic and has not gained acceptance outside setting of clinical trials and metastatic disease. (29, 30) Incorporation of therapeutic options such as immunotherapy may improve outcome.

Conclusion

Malignant melanoma, though rare in countries like India, carries an overall poor prognosis especially in advanced stages. In our study, one fourth of the patients who presented with stage III disease subsequently went on to develop distant metastases irrespective of the initial therapy and response. Thus patients with stage III have a very high risk of developing distant organ metastasis and hence should be treated with systemic therapy irrespective of the thickness of primary melanoma. Multimodality therapy with surgery, radiotherapy, immunotherapy and chemotherapy may lead to local or nodal remission but is unlikely to improve survival in advanced cases.

References


