CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES

Volume: 04 Issue: 03 | May-Jun 2023 ISSN: 2660-4159

http://cajmns.centralasianstudies.org

# Primary Multiple Skin Melanomas

1. **Rakhimov Nodir Makhammatkulovich**
2. **Shahanova Shakhnoza Shavkatovna**
3. **Murodov Shakhzod Tokhir ugli**
4. **Pulatov Ozod Abdugofurovich**
5. **Allazov Firuz Niyazovich**
6. **Madalimov Axror Alievich**

*Received 2nd Apr 2023,*
*Accepted 19th May 2023,*
*Online 30th May 2023*

[1] Samarkand State Medical University
[2] Samarkand State Medical University
[3] Samarkand State Medical University
[4] Samarkand State Medical University
[5] Samarkand branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology
[6] Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology

**Abstract:** Primary multiple skin melanomas represent a particular interest in modern oncology. Despite numerous studies on this topic in the global literature, most of them present isolated observations. The frequency of primary multiple melanomas in relation to all skin melanomas ranges from 0.54% to 4% according to various authors (American Cancer Society, 2021). In men, the risk of developing primary multiple melanoma is three times higher than in women, especially at a young age (Robert, C., Thomas, L., Bondarenko, I., ODay, S., Weber, J., Garbe, C., Lebbe, C., Baurain, J.F., Testori, A., Grob, J.J., Davidson, N., Richards, J., Maio, M., Hauschild, A., Miller, W.H.Jr., Gascon, P., Lotem, M., Harmankaya, K., Ibrahim, R., Francis, S., Chen, T.T., Humphrey, R., Hoos, A., Volchok, J.D., 2011).

**Key words:** maxillofacial region, inflammatory diseases, phlegmon

INTRODUCTION

El-Safadi S. et al. indicate that multiple malignant melanomas are often classified as superficial intradermal melanoma arising from a pigmented lesion (melanosis or lentigo). However, in some cases, young individuals with multiple chest lentiginosis experience an intense process of multicentric transformation into nodular and infiltrative malignant melanomas. Eells J.T. described 24 cases of

primary skin melanomas. Capatina A.L. states that there are families in which melanoblastomas occur particularly frequently, develop at a relatively early age, and are more commonly multiple.

The etiology of primary multiple skin melanomas remains controversial. Some authors associate it with immune factors, while others believe that genetic defects play a primary role. Some attribute their occurrence to endocrine disorders (Denat, L., Kadekaro, A.L., Marrot, L., & Leachman, S.A., 2014), and finally, the tumor field theory offers an explanation. Studies of the immune status of melanoma patients in recent years have revealed that their sera lack cytotoxic antibodies, which stimulate the growth of autologous tumors . Supporting this, data (Aceves, C., Anguiano, B., & Delgado, G., 2013) observed the development of other malignant tumors in 20% of 154 patients with skin melanoma. Some authors (Russian Society of Clinical Oncologists, 2021.) noted a weak delayed hypersensitivity reaction to the subcutaneous injection of attenuated Calmette-Herpin cultures in all patients with primary multiple melanoma they observed. These facts indicate a weakened defense mechanism against tumor growth. However, the question of whether new foci of melanoma arise due to the suppression of the patient's immune system by the primary tumor or whether primary melanoma and subsequent foci occur against the backdrop of reduced reactivity of the body remains unresolved.

The prognosis for primary multiple melanomas is diverse among researchers. Some authors believe that the prognosis for primary multiple melanomas is no worse than that for primary skin melanoma, while others point to an unfavorable prognosis for this condition.

**Materials and methods:** The study used data from patients treated with a diagnosis of melanoma across the country in the period from 2006 to 2023. At the same time, morphological features of histopreparations were studied. Among the 3634 observed patients with skin melanoma, 40 (1.1%) had primary multiple tumors. The diagnosis was confirmed by histological examination in all patients.

**Result:** It can be noted that the patients were approximately equally distributed by gender, with 18 (45%) being male and 22 (55%) being female. The age of the patients ranged from 18 to 83 years, with an average of 44.6 years. In 72.5% of cases, the condition was detected during the 4th to 6th decade of life.

A total of 92 tumors were detected in 40 patients with primary multiple melanomas, including two in 77.5% of patients, three in 15% of patients, and four in 7.5% of patients. Among the 92 tumors, 41 (44.6%) were located on the trunk, 29 (31.5%) on the lower extremities, 14 (15.2%) on the upper extremities, and 8 (8.7%) on the head and neck. It should be noted that the most common locations for tumors in primary multiple melanomas are the trunk and lower extremities. Furthermore, the localization of tumors differed between men and women. Specifically, 72.2% of men had one or more tumors on the trunk, while 54.5% of women had a combination of tumor localization on the trunk and lower extremities.

Symmetrical tumor distribution was observed in the majority of patients (70%), while asymmetrical distribution was less common (30%). Among the 20 patients (50%) who developed melanomas, an equal number occurred on intact skin and on a nevus. Among them, 8 patients had multiple pigmented spots on the skin upon examination.

The synchronous and metachronous occurrence of tumors was equally frequent in cases of primary multiple melanomas. The clinical characteristics of these tumors are presented in Table 18. It should be noted that synchronous development of tumors predominated in men, while metachronous development predominated in women ($p < 0.01$). Synchronous tumors were primarily localized in one anatomical

region, while metachronous tumors were distributed across different anatomical sites ($p < 0.001$). For example, in cases of synchronous melanoma development, tumors were located solely on the trunk in 9 cases, on the lower extremity in 6 cases, on the upper extremity in 2 cases, and on the head in one patient.

Regarding metachronous development of melanomas, tumor localization on a single anatomical site was observed in only 4 patients, including 1 on the trunk and 1 on the lower extremity. Synchronous tumors predominantly arose on intact skin, while metachronous tumors developed on a nevus ($p < 0.001$). Figures 82 and 83 illustrate patients with synchronous and metachronous occurrence of primary multiple tumors.

**Table 1**

**Clinical characteristics of synchronous and metachronous tumors in patients with primary multiple skin melanomas.**

| Clinical features | | Synchronous tumors | | p | Metachronous tumors | |
|---|---|---|---|---|---|---|
| | | No. of cases | Percentage (%) | | Percentage (%) | No. of cases |
| Patients' gender | Males | 13 | 72,2±10,8 | 0,001 | 27,8±10,8 | 5 |
| | Females | 7 | 31,8±10,1 | | 68,2±10,1 | 15 |
| | Upper extremity | 18 | 90,0±6,8 | 0,001 | 21,0±9,1 | 4 |
| | Lower extremity | 2 | 10,0±6,8 | | 80,0±9,1 | 16 |
| Melanoma background | Intact skin | 18 | 90,0±6,8 | 0,001 | 10,0±6,8 | 2 |
| | Nevus | 2 | 30,0±10,5 | | 90,0±6,8 | 18 |

Duration of medical history in cases of primary-multiple melanomas ranged from 1 to 72 months, with an average of 18.8±3.1 months. In the case of metachronous development of melanomas, the time between the appearance of the primary and secondary tumors ranged from 1 to 192 months, with an average of 48.8±2.4 months. Only 4 patients (10%) sought treatment within the first 3 months of onset, while the rest sought treatment 3 months or more after the initial clinical signs of the disease. Upon admission, 32 patients (80%) had a localized disease (Stage I), 5 patients (12.5%) had locally-regional disease (Stage II), and 3 patients (7.5%) had disseminated disease (Stage III). Among the 40 patients with primary-multiple melanomas, 6 patients (15%) had a history of malignancies of various locations in their close relatives, including cancers of the oral cavity, stomach, larynx, uterus, ovaries, liver, and one observation of a malignant spinal cord tumor. No evidence of melanoma was found in the relatives.

An interesting fact was that 8 patients showed delayed hypersensitivity skin reactions to dinitrochlorobenzene (DNCB), while 7 patients had weakly positive reactions (++). The weakly positive reaction indicated a weakened immune response, which likely contributed to the development of primary-multiple tumors in these patients.

Surgical treatment was performed on 35 patients, and cryodestruction of tumors was performed on 4 patients. Among the 32 patients with Stage I disease, wide excision of tumors was performed on 30 patients, including prophylactic lymphadenectomy in 2 of them, and cryodestruction of tumors was

performed on 2 patients. All 5 patients with Stage I disease underwent wide excision of tumors with therapeutic lymphadenectomy. Among the 3 patients with Stage III disease, cryodestruction of tumors was performed for palliative purposes in 2 patients, and one patient received only chemotherapy due to disease dissemination. Among the 32 patients with Stage I disease, 7 underwent surgical treatment only, 16 received combined treatment (surgery + chemotherapy), and 9 received comprehensive treatment (surgery + chemo- and/or immunotherapy).

A study of prognostically significant morphological features was conducted in a large number of patients with primary-multiple skin melanomas, and these data were compared with the results of the study in patients with primary skin melanoma.

**Table 2**

**Comparative data of morphological features in patients with primary and primary-multiple skin melanomas.**

| Morphological Features | | Primary Melanoma | | Primary-Multiple Melanoma | |
|---|---|---|---|---|---|
| | | No. of cases | Percentage (%) | No. of cases | Percentage (%) |
| Clinical-Morphological Tumor Types | Superficial Spreading | 186 | 25,9 | 15 | 41,7 |
| | Malignant Lentigo | 41 | 5,7 | 1 | 2,8 |
| | Nodular | 490 | 68,4 | 20 | 55,5 |
| Lymphoid-Plasma Cell Infiltration | Absent | 22 | 4,3 | 0 | 0 |
| | Weak | 161 | 31,6 | 4 | 25 |
| | Moderate | 194 | 38 | 5 | 31,2 |
| | Severe | 133 | 26,1 | 7 | 43,8 |
| Invasion Levels | I | 4 | 0,5 | 2 | 5,9 |
| | II | 63 | 8,3 | 6 | 17,7 |
| | III | 318 | 41,6 | 10 | 29,4 |
| | IV | 309 | 40,4 | 13 | 38,2 |
| | V | 70 | 9,2 | 3 | 8,8 |
| Tumor Thickness in mm | 0,74 | 34 | 4,6 | 2 | 2,9 |
| | 0,75-1,49 | 137 | 18,5 | 6 | 29,4 |
| | 1,50-2,99 | 226 | 30,5 | 10 | 32,3 |
| | 3,00-4,99 | 187 | 25,3 | 13 | 20,6 |
| | 5,00 и более | 156 | 21,1 | 3 | 14,7 |

It can be noted that in the case of primary-multiple skin melanomas, superficial spreading melanoma was observed in 4.7%, pronounced lymphoid-plasma cell infiltration in 43.8%, I-I invasion level in 23.6%, and tumor thickness up to 1.5 mm in 32.3%. The aforementioned are favorable prognostic morphological features. On the contrary, in primary skin melanomas, unfavorable prognostic morphological features predominated, such as nodular melanoma (68.4%), absence or weak lymphoid-plasma cell infiltration (45.9%), V invasion level (9.2%), and tumor thickness over 1.5 mm (76.9%).

Metastases to regional lymph nodes after treatment of primary-multiple tumors appeared in 14 (47.5%) patients. The time of appearance of regional metastases ranged from 2 to 108 months, with an average of 19.4±7.8 months. Distant metastases also occurred in 14 (35%) patients after treatment, with 3 of them being hematogenous. The time of appearance of distant metastases ranged from 2 to 120 months, with an average of 28.3±48.2 months.

We analyzed the survival of patients with primary-multiple melanoma based on gender, occurrence of melanoma on nevus or intact skin, synchronous or metachronous development of tumors, clinical stage of the disease, and type of treatment.

Gender: When studying the impact of gender on survival in patients with primary-multiple skin melanoma, we observed higher survival rates in women compared to men throughout the observation period.

Background of melanoma occurrence: Considering this clinical feature that affects the life prognosis, we noted that in patients where the tumor appeared on a nevus, the 3-, 5-, and 10-year survival rates were 87.1%, 71.9%, and 60.9%, with a median of 242.1±49.8 months. On intact skin, the 3- and 5-year survival rates were 57.1%, with a median of 65.2±13.9 months. Differences in the 3-year survival and median were statistically significant ($p < 0.05$ and $p < 0.001$). Therefore, the survival in patients where melanomas appeared on a nevus was higher compared to those where tumors occurred on intact skin.

Synchronous and metachronous occurrence of tumors: As mentioned earlier, synchronous and metachronous tumors in patients with primary-multiple skin melanomas were equally frequent. In patients with metachronous tumor development, the 3-, 5-, and 10-year survival rates were 75.0±9.9%, 50.0±11.4%, and 15.0±8.2%, respectively, which were higher compared to patients with synchronous tumors (40.0±11.2%, 30.0±10.5%, and 10.0±6.9%). However, significant differences were only found in the analysis of the 3-year survival ($p < 0.02$).

Clinical stages of the disease: Among 40 patients with primary-multiple melanomas, 32 (80%) had stage I at the time of treatment, 5 (12.5%) had stage II, and 3 (7.5%) had stage III. For patients with stage I, the 3-, 5-, and 10-year survival rates were 79.0%, 70.7%, and 42.9%, respectively. The survival rate for all observed periods was 66.6% for stage I patients, and only one patient with stage I survived for one year, with a median of 9±5.2 months. Although the 3- and 5-year survival rates for patients with stage I were higher compared to stage II, no significant differences were found ($p > 0.05$). The lack of significant differences in these groups is likely due to the insufficient number of observations in the compared groups.

Treatment. As previously mentioned, surgical treatment was received by 7 patients at stage I of the disease, combined treatment by 16 patients, and comprehensive treatment by 9 patients. The number of patients and survival curves based on the type of treatment are presented in Figure 88 and Table 12 of the appendix.

For patients with primary-multiple melanoma treated with comprehensive therapy, the 3-, 5-, and 10-year survival rates were 88.2%, 74.6%, and 53.3%, respectively, with a median of 240.7±11.2 months. These rates were higher compared to patients who received combined treatment (79.0%, 70.7%, and 29.4%, with a median of 79.2±20.3 months) or surgical treatment alone (77.7%, median not determined). No significant differences in the 3-, 5-, and 10-year survival rates were observed among the groups receiving different treatments ($p > 0.05$). However, a significantly higher median survival

was found for patients who received comprehensive treatment compared to those who received combined treatment ($p < 0.001$). Therefore, the results suggest that comprehensive treatment, including wide excision of tumors with subsequent preventive chemotherapy and immunotherapy, is the most effective treatment method for patients with primary-multiple melanoma at stage I.

The prognosis for patients with primary-multiple melanoma at stage I who received surgical treatment did not significantly differ from the prognosis for patients with primary melanoma. The 3-, 5-, and 10-year survival rates for primary skin melanoma were 77.8%, 69.1%, and 62.0%, respectively, with a median of 189.9±17.4 months. For patients with primary-multiple melanoma, the survival rates were comparable (77.7%, median not determined, $p < 0.05$). Refer to Figure 89 and Table 43 in the appendix for details.

Overall, regardless of the type of treatment, the 3-, 5-, and 10-year survival rates for patients with primary-multiple skin melanoma at stage I were 79.0%, 70.7%, and 42.9%, respectively, with a median of 99.0±26.8 months. These rates were higher compared to primary skin melanoma (65.0%, 48.7%, and 35.8%, median 57.1±3.8 months), but significant differences were only observed in the 5-year survival rate ($p < 0.05$). See Figure 90 and Table 44 in the appendix for more information.

In general, out of the 40 patients with primary-multiple melanomas, 23 (57.5%) remained alive after treatment, including 14 (63.6%) women, one with signs of disease, and 9 (50%) men without signs of disease. Seventeen (42.5%) patients died, including 8 (36.4%) women and 9 (50%) men. Sixteen patients died due to disease progression, and one woman died from another cause. The overall 3-, 5-, and 10-year survival rates for patients with primary-multiple skin melanoma were 7.7%, 64.95%, and 42.6%, respectively, with a median of 96.5±30.4 months. These rates were higher compared to primary skin melanoma (54.2%, 40.2%, and 29.4%, median 41.5±1.8%). The differences in the 3- and 5-year survival rates were statistically significant ($p < 0.05$) and ($p < 0.001$). Refer to Figure 91 and Table 45 in the appendix for further details.

Therefore, the conducted statistical analysis has shown that the prognosis and survival of patients with primary-multiple melanomas are not only not worse but even better than those of patients with primary skin melanoma. The high survival rate in patients with primary-multiple melanomas can be explained by the more frequent occurrence of superficial spreading tumor forms (41.7%), pronounced lymphoid-plasmacytic infiltration (43.8%), stage I-II invasion (23.6%), and tumor thickness less than 1.5 mm (32.3%) compared to primary melanomas.

Thus, out of 3,634 patients with skin melanoma, 40 (1.1%) were identified as having primary-multiple tumors. The disease occurs equally often in men and women, predominantly in the age range of 40-60 years, which accounts for a total of 72.5%. The presence of two tumors is most common (77.5%). The preferred locations for tumors are the trunk (44.6%) and lower extremities (31.5%). In primary-multiple skin melanomas, synchronous and metachronous tumors occur with equal frequency.

Synchronous tumors are more common in men (72.2%), while metachronous tumors are more common in women (68.2%) ($p < 0.01$). Synchronous tumors are more often localized (90%) in the same area, while metachronous tumors are found (80%) in different anatomical areas of the body ($p < 0.001$). Synchronous tumors predominantly arise (90%) on intact skin, while metachronous tumors develop (90%) on a background of a nevus ($p < 0.001$). A significantly high survival rate was observed in women with primary-multiple skin melanomas, as well as in patients where melanoma developed on a background of a nevus and in cases of metachronous tumor development. The most appropriate

treatment method for patients with primary-multiple skin melanoma at stage I of the disease is comprehensive treatment, including wide excision of tumors with subsequent preventive chemotherapy and immunotherapy, with a median survival of 241 months. The prognosis for primary-multiple melanomas is relatively favorable.

The relatively high survival rate in patients with primary-multiple melanomas can be explained by the more frequent occurrence of superficial spreading tumor forms, pronounced lymphoid-plasmacytic infiltration, stage I-II invasion, and tumor thickness less than 1.5 mm compared to primary melanoma.

**LITERATURE:**


1. Aceves, C., Anguiano, B., & Delgado, G. (2013). The extrathyronine actions of iodine as an antioxidant, apoptotic, and differentiation factor in various tissues. Thyroid, 23(8), 938-946. doi: 10.1089/thy.2012.0579.
2. Addor, F.A.S. (2018). Beyond photoaging: additional factors involved in the process of skin aging. Clinical Cosmet Investig Dermatol, 11, 437-443. doi: 10.2147/CCID.S177448.
3. Amaravadi, R., & Debnath, J. (2014). Mouse models address key concerns regarding autophagy inhibition in cancer therapy. Cancer Discovery, 4(8), 873-875.
4. American Cancer Society. (2021). Cancer Facts & Figures 2021. Retrieved from https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2021.html.
5. Banchereau, J., Palucka, A.K., Dhodapkar, M., Burkeholder, S., Taquet, N., Rolland, A., Taquet, S., Coquery, S., Wittkowski, K.M., & Bhardwaj, N. (2001). Immune and clinical responses in patients with metastatic melanoma to CD34+ progenitor-derived dendritic cell vaccine. Cancer Research, 61(17), 6451-6458.
6. Bandovkina, V.A., Kit, O.I., Frantsiyants, E.M., Sustretov, V.A., et al. (2018). Effect of estrogens on growth factors in melanoma and nevi. ASCO Annual Meeting J. Clin. Oncol., 36(Suppl.), abstract e21628.
7. Capatina, A.L., Lagos, D., & Brackenbury, W.J. (2020). Targeting Ion Channels for Cancer Treatment: Current Progress and Future Challenges. Reviews of Physiology, Biochemistry and Pharmacology, 1-43.
8. Denat, L., Kadekaro, A.L., Marrot, L., & Leachman, S.A. (2014). Melanocytes as instigators and victims of oxidative stress. Journal of Investigative Dermatology, 134(6), 1512-1518. doi: 10.1038/jid.2014.65.
9. Eells, J.T., Wong-Riley, M.T., & VerHoeve, J. (2004). Mitochondrial signal transduction in accelerated wound and retinal healing by near-infrared light therapy. Mitochondrion, 4(5-6), 559-567.
10. El-Safadi, S., Estel, R., Mayser, P., & Muenstedt, K. (2014). Primary malignant melanoma of the urethra: a systematic analysis of the current literature. Archives of Gynecology and Obstetrics, 289(5), 935-943. doi: 10.1007/s00404-013-3130-3.
11. Pesapane, F., et al. (2020). Imaging diagnosis of metastatic breast cancer. Insights into Imaging, 11(1), 1-14.

12. Robert, C., Thomas, L., Bondarenko, I., ODay, S., Weber, J., Garbe, C., Lebbe, C., Baurain, J.F., Testori, A., Grob, J.J., Davidson, N., Richards, J., Maio, M., Hauschild, A., Miller, W.H.Jr., Gascon, P., Lotem, M., Harmankaya, K., Ibrahim, R., Francis, S., Chen, T.T., Humphrey, R., Hoos, A., Volchok, J.D. (2011). Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. New England Journal of Medicine, 364(26), 2517-2526. doi: 10.1056/NEJMoa1104621.
13. Shavkatovna, S.S., & Rakhimov, N.M. (2021). Morphological Verification Of Malignant Neoplasm Of The Urinary System With Multiple Bone Metastases. The American Journal of Medical Sciences and Pharmaceutical Research, 3(06), 145-149.
14. Shaxanova, Sh.S., Raximov, N.M. (2022). Improving the combined treatment tactics of many osteogen metastases of malignant tumors of the urinary-body system. Web of Scientist: International Scientific Research Journal, 4/30, 1145-1149.
15. Gridneva Ya.V. Urethral melanoma. Cancer urology 2005;1(3):66-70. [Gridneva Ya.V. Urethral melanoma. Cancer Urology 2005;1(3):66-70. (In Russ.)].
16. Malignant neoplasms in Russia in 2019 (incidence and mortality).
17. Clinical guidelines. Skin melanoma and mucous membrane melanoma. / Russian Society of Clinical Oncologists // 2021.
18. Rakhimov N.M., Shahanova Sh.Sh., Khakimov A.A., Kalyuta T.Yu., Velikanova M.G., Korolev A.Yu. Effectiveness of radiation therapy in patients with bone metastases of prostate cancer and renal cell carcinoma. 2022/9/7. Journal of Biomedicine and Practice. Volume 7, Issue 4.
19. Shahanova Sh.Sh., Rakhimov N.M. Multimodal approach to the treatment of multiple osteogenic metastases of kidney and prostate cancer. Clinical and Experimental Oncology 2020, No. 4, Pp. 50-56.
20. Shahanova Sh.Sh., Rakhimov N.M., Koraboev F.T. Increasing the effectiveness of targeted therapy in the treatment of kidney and prostate cancer with osteogenic metastases. Journal of Reproductive Health and Uro-Nephrological Research 2022/6/27, Volume 3, Issue 2.