ONCOLOGY LETTERS 31: 82, 2026

# Systemic treatment for a young patient with stage IV melanoma: A case report

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Received May 20, 2025; Accepted November 11, 2025

DOI: 10.3892/ol.2025.15435

**Abstract.** Melanoma is a highly malignant tumor with a marked propensity for metastasis, and liver metastasis in particular is consistently associated with a poor prognosis. The current study reports the case of a 24-year-old man who presented with multiple systemic metastases 3 years after undergoing radical resection of a cutaneous melanoma. Genetic testing identified a BRAF mutation, which led to the initiation of targeted therapy using dabrafenib in combination with trametinib. After 2 months of treatment, imaging revealed a partial response in the liver metastases. However, by the fourth month, the disease progressed rapidly due to acquired resistance, causing the patient to succumb to liver failure and multiple organ dysfunction. The present case highlights the key need for vigilance, as even young patients with early-stage melanoma remain at risk of rapid disease progression. Therefore, implementing rigorous postoperative patient education and follow-up protocols is key to the early detection of recurrence and timely intervention. Simultaneously, the present case illustrates the challenge of acquired resistance to targeted therapy, underscoring the importance of developing strategies to overcome such resistance to potentially improve patient survival in the future.

## Introduction

Melanoma, a malignancy arising from melanocytes, demonstrates a rising global incidence, although a concurrent decline in mortality has been observed in recent years (1). Histopathologically, melanomas have been classically categorized into three main subtypes based on the presence of a radial growth phase: Nodular melanoma, superficial spreading melanoma and lentigo maligna melanoma (2).

Melanomas were divided into those etiologically related to sun exposure and those that are not, as determined by their mutational signatures, anatomic site and epidemiology. Melanomas on the sun-exposed skin were further divided by the histopathologic degree of cumulative solar damage (CSD) of the surrounding skin, into low and high CSD, on the basis of degree of associated solar elastosis. Low-CSD melanomas include superficial spreading melanomas and high-CSD melanomas incorporate lentigo maligna and desmoplastic melanomas. The 'nonsolar' category includes acral melanomas, some melanomas in congenital nevi, melanomas in blue nevi, Spitz melanomas, mucosal melanomas and uveal melanomas (3).

Furthermore, an increased number of melanocytic nevi and the presence of atypical nevi are established risk factors for melanoma development. Notably, the presence of multiple atypical nevi is associated with a six-fold increase in the risk of melanoma formation, a stronger association compared to the presence of a single atypical nevus (4).

Surgical resection remains the primary treatment for early-stage disease. However, melanoma is highly aggressive and prone to distant metastasis. For patients with stage IV melanoma, where the disease is generally no longer amenable to curative surgical resection, systemic therapy thus becomes particularly crucial. Currently approved first-line regimens for advanced melanoma include programmed cell death protein-1 (PD-1) inhibitors as monotherapy, nivolumab plus relatlimab, and ipilimumab combined with nivolumab, and for patients with BRAF mutation, combination BRAF/mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor therapy (5). Nevertheless, the efficacy of targeted therapy is often compromised by the emergence of drug resistance. For instance, resistance to BRAF inhibitors, such as PLX4720 (an analog of vemurafenib) and dabrafenib, can reduce their efficacy (6). Additionally, in the context of combined BRAF and MEK inhibition, studies using the well-characterized mutant V600E BRAF model have demonstrated that acquired resistance can develop. Specifically, continuous treatment with the combination of PLX4720 and PD0325901 (Mirdametinib) for >77 days

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*Key words:* melanoma, immune checkpoint inhibitors, targeted therapy, combination therapy

led to the development of acquired resistance, evidenced by the regrowth of three combination-resistant tumors (7). Furthermore, several novel treatment modalities under investigation, such as oncolytic viruses (OVs) and neoadjuvant therapy, hold notable promise. The present study describes the case of a young male patient with early-stage cutaneous melanoma who developed widespread systemic metastases and acquired resistance to targeted therapy 3 years after surgery. The present case highlights the key need for rigorous postoperative follow-up and emphasizes the urgency of developing strategies to potentially overcome resistance to targeted agents in the future.

## Case report

In November 2024, a 24-year-old man was admitted to Binzhou People's Hospital (Binzhou, China), due to epigastric pain and discomfort lasting for 10 days. In January 2021, approximately 3 years prior to this, the patient had presented with black papules on the anterior chest that had been present for over a decade, which were initially excised in an outpatient setting at Binzhou People's Hospital (Binzhou, China) under the diagnosis of a dermal melanocytic nevus. Postoperative pathology revealed cutaneous epithelioid malignant melanoma with a Breslow thickness of 0.75 mm and no ulceration (Fig. 1). In January 2021, the patient underwent wide local excision of the anterior thoracic lesion, along with sentinel lymph node biopsy of the left supraclavicular region under general anesthesia. Pathology from this procedure revealed acute and chronic inflammation of the skin and subcutaneous tissues without evidence of tumor cells (according to pathology report; data not shown). The histopathological analysis was performed according to standard procedures. None of the nine lymph nodes examined contained metastatic tumor. Based on these findings and the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Eighth Edition (2017), the patient was classified as having T1aN0M0, stage IA disease (8). No adjuvant therapy was administered postoperatively. Follow-up imaging, including chest (Fig. S1A and B) and abdominal (Fig. S1C and D) CT, and ultrasounds of the submandibular (Fig. S2A and B), cervical supraclavicular (Fig. S2C and D), axillary (Fig. S2E and F) and inguinal (Fig. S2G and H) regions, conducted 6 months and 1 year after surgery, demonstrated no abnormalities. In January 2022, the patient underwent a laparoscopic appendectomy for acute appendicitis; intraoperative exploration at that time revealed no notable visceral abnormalities.

Upon the current admission in November 2024, the patient presented with a cachectic appearance but was otherwise without notable comorbidities. Hematological tests were within normal limits. Gastroscopy, however, revealed extensive melanosis throughout the upper gastrointestinal tract, involving the pharynx (Fig. 2A) and the entire esophagus (Fig. 2B-E). This diffuse black mucosal appearance is consistent with the endoscopic presentation of melanoma metastasis (9,10). A pigmented protruding lesion, ~0.5 cm in diameter, in the gastric body (Fig. 2F) was biopsied and confirmed as metastatic melanoma. These findings not only explained the abdominal pain of the patient but also indicated advanced disease. Immunohistochemistry was key in confirming the diagnosis: Lesional cells from both esophageal (Fig. 3A-D) and gastric (Fig. 3E-H) sites were negative for the epithelial marker pan-cytokeratin (CKpan) (Fig. 3B and F), but positive for the melanocytic markers human melanoma black 45 (HMB45) (Fig. 3C and G) and melanoma antigen A (Melan-A) (Fig. 3D and H), confirming metastatic melanoma. Tissue specimens were fixed in 3.7% neutral buffered formalin at room temperature for 12 h and embedded in paraffin. Sections were cut to a thickness of 4 $\mu$m. The blocking reagent used was 3% $H_2O_2$, applied at room temperature for 10 min. The primary antibodies, all ready-to-use, were obtained from Fuzhou Maixin Biotechnology Development Co., Ltd., and incubated at 37˚C for 30 min (CKpan: Rabbit polyclonal, cat. no. RAB-0050; HMB45: Mouse monoclonal, cat. no. MAB-0360; Melan-A: Mouse monoclonal, cat. no. MAB-0275). The MaxVision™ Detection Kit (HRP-conjugated, ready-to-use; cat. no. KIT-5010) from Fuzhou Maixin was used as the secondary reagent, with incubation at 37˚C for 15 min. A BRAF mutation was also identified, providing a molecular basis for targeted therapy. The BRAF mutation was identified using the Human Braf Gene Mutation Detection Kit (PCR fluorescent probe method) from DoGene Inc., with amplification and detection performed on an ABI 7500 real-time PCR instrument, strictly following the manufacturer's instructions. Abdominal CT (Fig. 4) exhibited numerous metastatic lesions throughout the liver, including a large irregular mass in the porta hepatis compressing the portal vein and inferior vena cava. Chest CT (Fig. 5) and cranial MRI (Fig. 6) further revealed multiple metastases in the lungs and intracranial cavity, respectively. A final diagnosis of stage IV melanoma was established. Due to the extensive metastatic burden, the patient was not a candidate for surgery and the prognosis was considered to be poor. Following a multidisciplinary team discussion in November 2024, combined targeted therapy with dabrafenib (150 mg orally twice daily, administered as two 75-mg tablets per dose) and trametinib (2 mg orally once daily, administered as one 2-mg tablet) was initiated.

Serial abdominal CT scans documented the clinical course, illustrating both initial treatment response and subsequent resistance (Fig. 7). Abdominal CT scans in January 2025 (Fig. 7B and E) revealed marked reduction in liver metastases compared with the first follow-up scan obtained 1 week after treatment initiation (November 2024; Fig. 7A and D), indicating a partial response. However, in early February 2025, the patient suffered a rupture of a liver metastasis, which was managed with emergency transcatheter arterial chemoembolization at Binzhou People's Hospital. Subsequent follow-up imaging in late February 2025 (Fig. 7C and F) revealed notable regrowth of the liver lesions, demonstrating acquired resistance to targeted therapy. Laboratory tests from the same date indicated acute liver failure, with elevated transaminases [alanine transaminase, 523 U/l (reference range, 0-50 U/l); aspartate aminotransferase, 1,541 U/l (reference range, 17-59 U/l)], hyperbilirubinemia [total bilirubin, 115.7 $\mu$mol/l (reference range, 3-22 $\mu$mol/l)] and coagulopathy [prothrombin time, 29.9 sec (reference range 8.8-13.8 sec)].

The patient succumbed to the disease in March 2025, due to liver failure and multiple organ failure. The overall survival from stage IV diagnosis to mortality was 4 months. Fig. 8 provides a visual timeline summarizing this rapid and complex clinical course, from diagnosis and initial treatment response to disease progression and mortality.

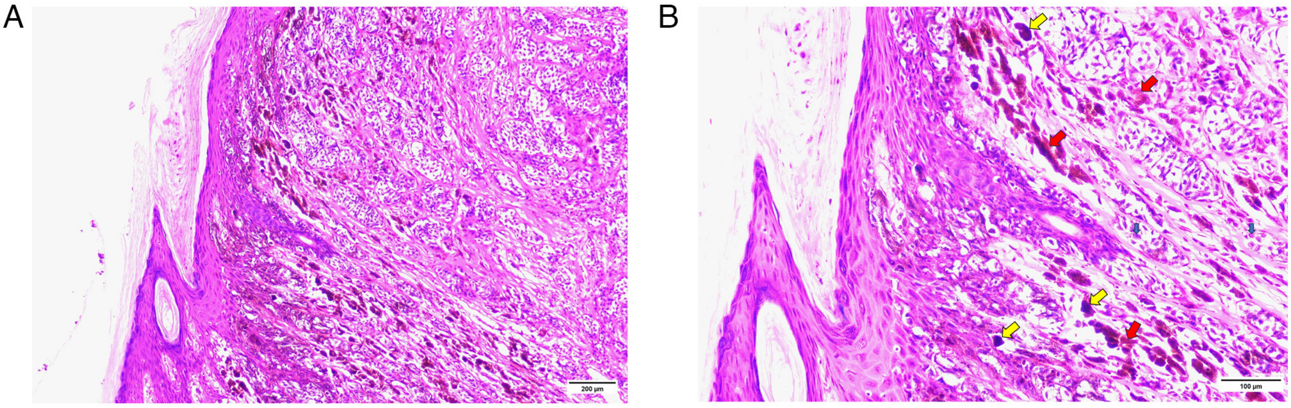


Figure 1. Histopathology of the primary cutaneous melanoma mass. Under light microscopy, tumor cells exhibit diffuse growth, marked variation in size and shape, abundant cytoplasm, nuclear pleomorphism (yellow arrows), prominent nucleoli (blue arrows) and melanin pigment (red arrows) within and between tumor cells. (A) Low-power view (magnification, x100). (B) High-power view (magnification, x200).

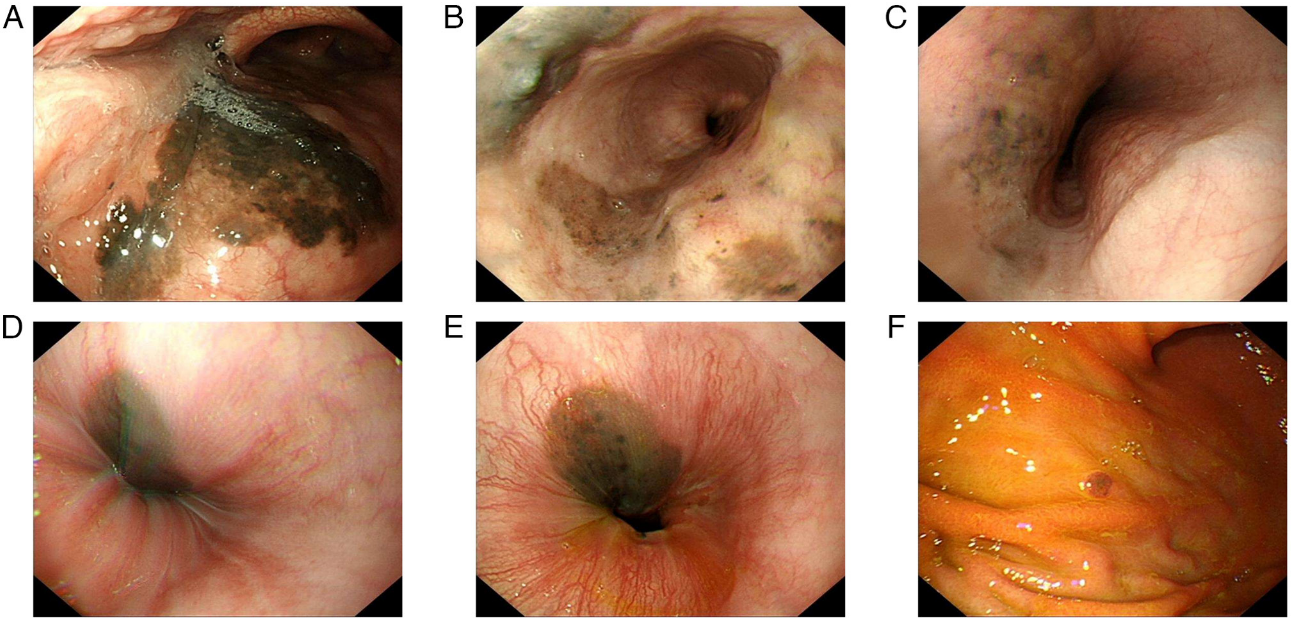


Figure 2. Endoscopic findings of metastatic melanoma. (A) Pharynx. Endoscopy demonstrates diffuse melanosis, evident as black mucosal discoloration. (B-E) Esophagus. Serial endoscopic views reveal extensive, multifocal melanin pigmentation. (B) Esophagus showing extensive melanin pigmentation. (C) Esophagus revealing scattered, multifocal melanin deposits. (D) Esophagus displaying patchy areas of melanin pigmentation. (E) Esophagus demonstrating sheet-like melanosis. (F) Gastric body. A pigmented, broad-based, elevated lesion measuring ~0.5 cm in diameter is seen, consistent with a metastatic deposit.

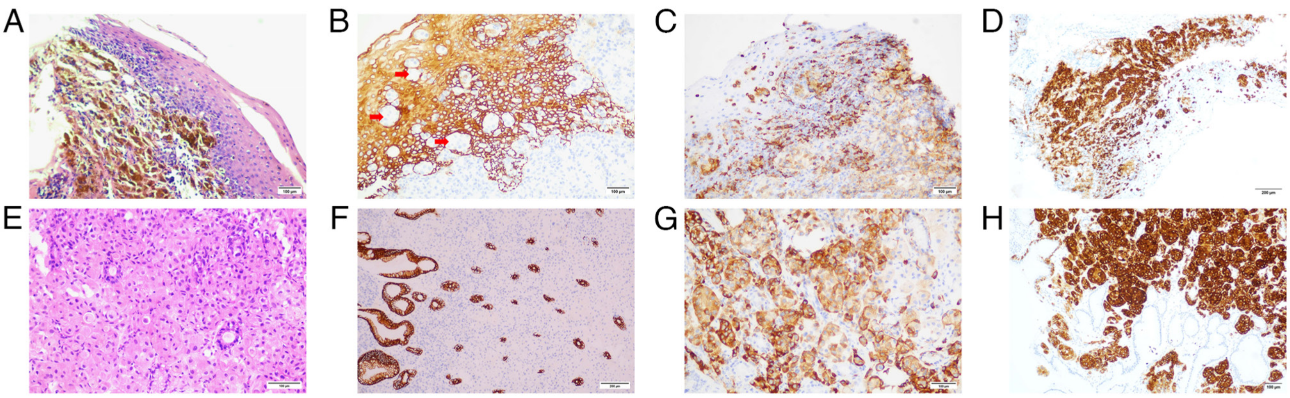


Figure 3. Histopathological and immunohistochemical features of metastatic melanoma. (A-D) Esophageal metastasis. (A) H&E stain shows tumor cell nests. (B) CK-Pan negative (red arrows indicate tumor cells). (C) HMB-45 positive (magnification, x200). (D) Melan-A positive (magnification, x100). (E-H) Gastric metastasis. (E) H&E morphology of the metastatic deposit (magnification, x200). (F) CK-Pan negative (magnification, x100). (G) HMB-45 positive. (H) Melan-A positive (magnification, x200). H&E, Hematoxylin and eosin; HMB, human melanoma black; CK-Pan, Pan-cytokeratin.

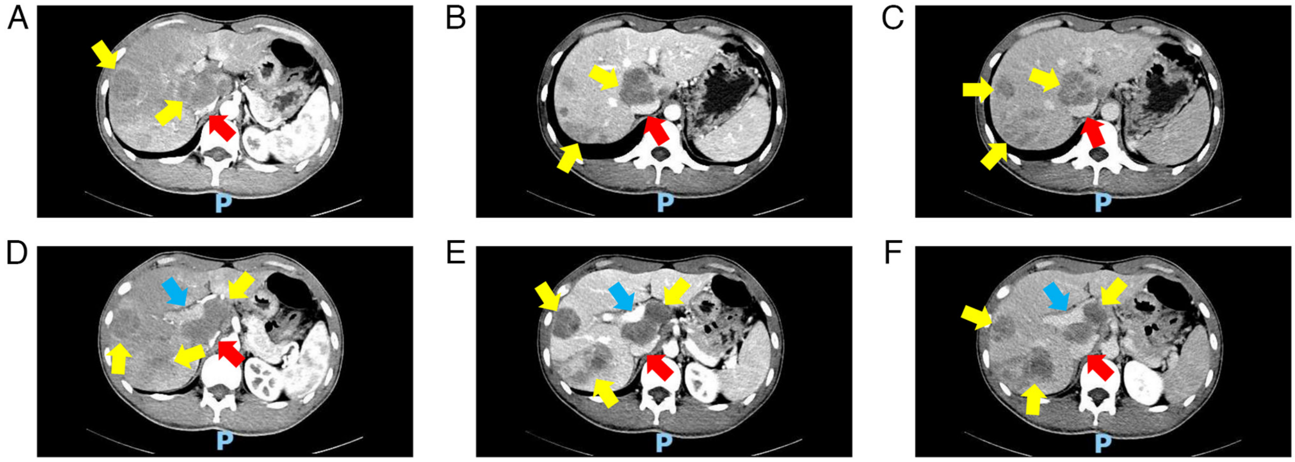


Figure 4. Abdominal CT scan (November 2024). Multiple metastatic lesions (yellow arrows) are present throughout the liver. (A) Arterial phase CT demonstrating the metastatic lesions (yellow arrows) compressing the inferior vena cava (red arrow). (B) Venous phase CT showing the metastatic lesions (yellow arrows) compressing the inferior vena cava (red arrow). (C) Delayed phase CT revealing the metastatic lesions (yellow arrows) compressing the inferior vena cava (red arrow). (D) Arterial phase CT showing the metastatic mass (yellow arrows) compressing both the portal vein (blue arrow) and inferior vena cava (red arrow). (E) Venous phase CT demonstrating the metastatic mass (yellow arrows) compressing both the portal vein (blue arrow) and inferior vena cava (red arrow). (F) Delayed phase CT showing persistent the metastatic mass (yellow arrows) compressing both the portal vein (blue arrow) and inferior vena cava (red arrow). P, posterior.

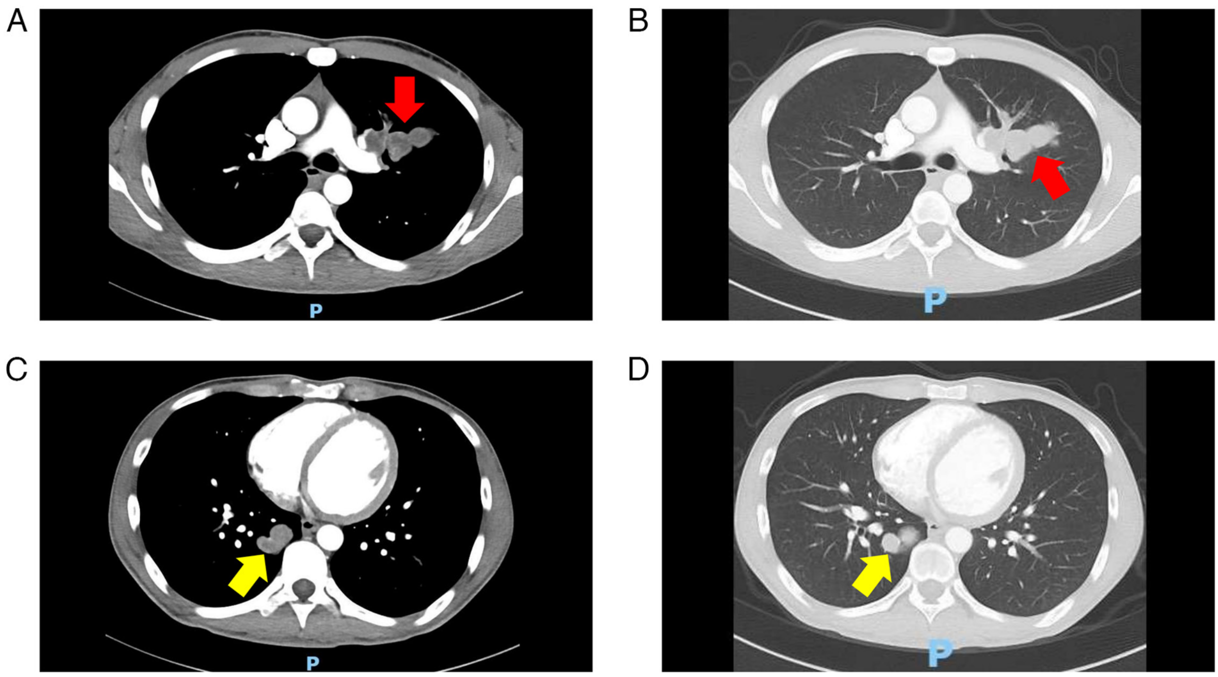


Figure 5. Chest CT scan (November 2024). Multiple metastatic nodules are visible in both lungs, with larger lesions located in (A and B, red arrows) the left upper lobe anterior segment and (C and D, yellow arrows) the right lower lobe basal segment. (A) Mediastinal window CT demonstrating a larger metastatic lesion (red arrow) in the left upper lobe anterior segment. (B) Lung window CT showing the same metastatic nodule (red arrow) with clear visualization of its relationship to the surrounding pulmonary parenchyma. (C) Mediastinal window CT revealing a larger metastatic lesion (yellow arrow) in the right lower lobe basal segment. (D) Lung window CT displaying the same metastatic nodule (yellow arrow) with optimal demonstration of its pulmonary context. P, posterior.

## Discussion

Melanoma ranks among the most serious forms of skin cancer. According to GLOBOCAN 2022 estimates, there were ~331,722 new melanoma cases globally, accounting for ~21% of all skin cancer diagnoses (11). Despite this comparatively lower incidence, melanoma was responsible for ~58,667 annual deaths, resulting in a case-fatality rate of ~17.7%. For context, non-melanoma skin cancers, which comprise ~79% of all skin cancer cases, resulted in an estimated 69,416 deaths in the same period (12). This disparity underscores the disproportionate lethality of melanoma relative to its incidence. In the United States, an estimated 104,960 novel cases of cutaneous melanoma and 8,430 associated mortalities are projected for 2025. Between 2015 and 2021, the 5-year relative survival rate was 94.7% (13). Furthermore, the 5-year relative survival rate

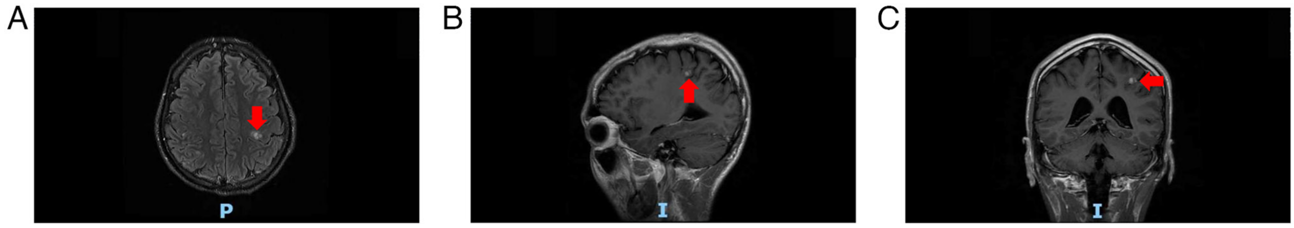


Figure 6. Brain MRI (November 2024). Multiple metastatic foci can be observed, with the largest lesion (red arrows) situated in the left frontal lobe. Images are displayed in (A) axial, (B) sagittal and (C) coronal planes. P, posterior; I, inferior.

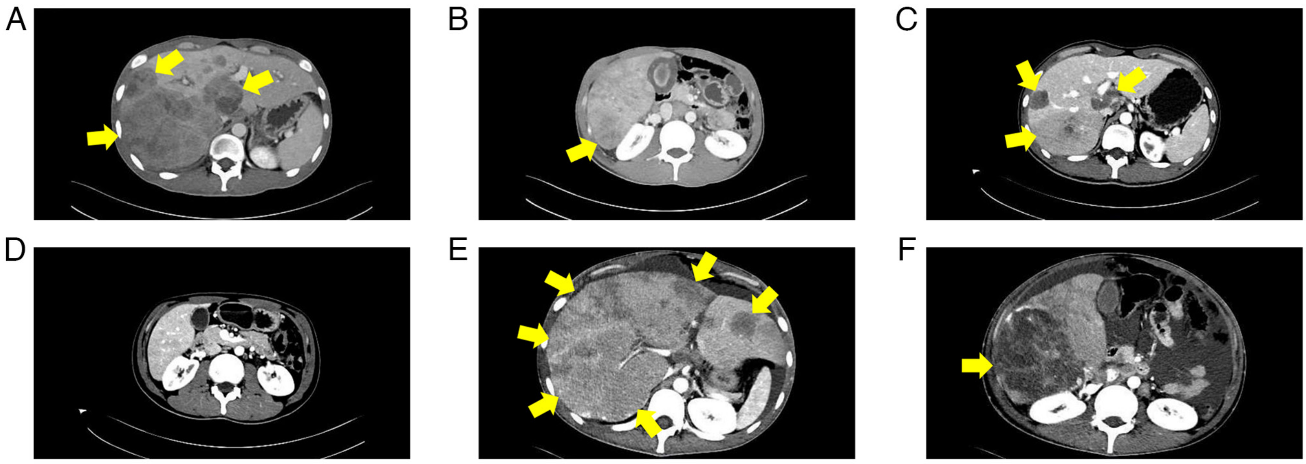


Figure 7. Serial changes in segment 6 liver metastases during targeted therapy. (A and B) In November 2024, the first follow-up scan after treatment initiation revealed tumor burden. (A) Image showing metastatic lesions in segment 6 after treatment initiation. (B) Adjacent slice demonstrating the tumor burden in the same region. (C and D) Follow-up in January 2025 demonstrated a partial response after dabrafenib and trametinib therapy. (C) Follow-up image revealing reduced tumor size following dabrafenib and trametinib therapy. (D) Adjacent slice confirming treatment response. (E and F) Subsequent imaging in February 2025 revealed disease progression (yellow arrows indicate lesions). (E) Subsequent imaging showing recurrent lesion growth (yellow arrows) indicating disease progression. (F) Adjacent slice confirming disease progression with enlarging metastases (yellow arrows).

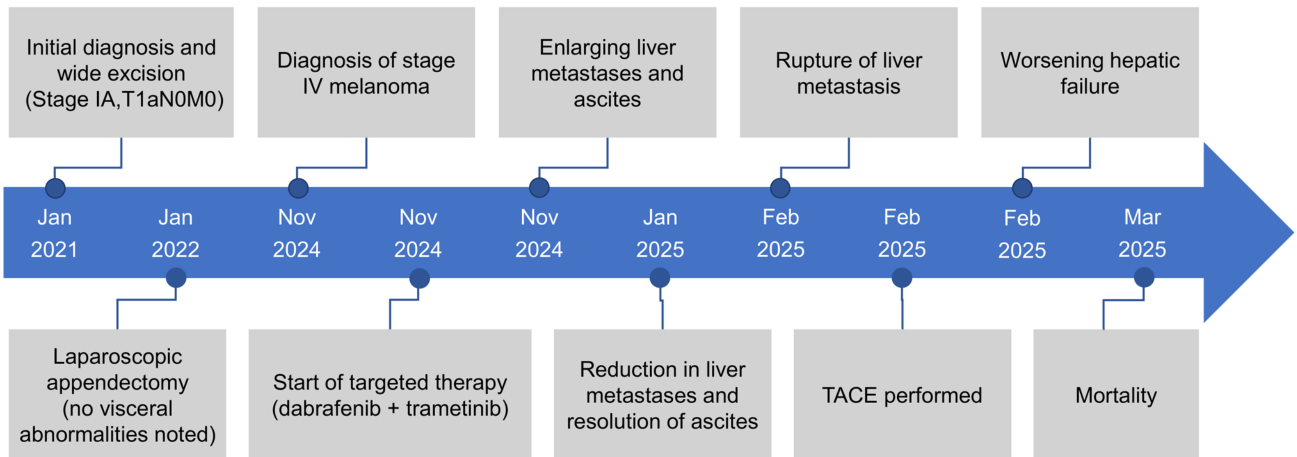


Figure 8. Clinical timeline summarizing the disease course. The schematic illustrates the progression from initial stage IA diagnosis through targeted therapy initiation, transient treatment response and subsequent rapid progression culminating in hepatic failure and mortality. TACE, transcatheter arterial chemoembolization.

for cutaneous melanoma across all ethnic groups in the United States has demonstrated a consistent upward trend from 1975 to 2019 (1). Survival outcomes are strongly influenced by the stage at diagnosis. Specifically, patients with localized melanoma exhibit a 5-year survival rate of ~100%, whereas those with regional lymph node involvement or distant metastases exhibit 5-year relative survival rates of 75.7 and 34.6%, respectively (13).

Malignant cutaneous melanoma occurs more frequently in Caucasian populations (14). In Europe, North America and Oceania, the trunk is the most common site of occurrence in men (31-58%), whereas women more commonly develop melanoma on the lower limbs and hips (26-40%). In South-East Asia, both men (41-58%) and women (37-60%) demonstrate a higher incidence of melanoma on the lower limbs and hips (15). Epidemiological studies report that primary melanomas of the head, neck and trunk demonstrate a male predominance (16,17), whereas melanomas of the lower limbs show a female predominance (18). Data from a study of 1,177 patients with stage I-II melanoma identified the head and neck as a high-risk primary site. Head and neck melanomas were overrepresented in metastatic cohorts, accounting for 35 of 108 (32.4%) lymphatic metastases and 37 of 108 (34.3%) hematogenous metastases. Survival analysis further confirmed this elevated risk, demonstrating a 5-year hematogenous metastasis-free survival of 78.9%-the lowest of all sites- and a 5-year lymphatic metastasis-free survival of 84.7%, which was only marginally higher than that for acral melanomas. Consequently, head and neck melanomas feature high aggressiveness, frequent recurrence and a significantly worse overall survival profile (19). Melanoma incidence is generally higher in men, with a rate ~1.6 times higher compared with that in women (20). Nevertheless, melanoma remains one of the most common cancer types in young adults aged 25-29 years, particularly among young women (21,22). In European populations, among adolescents and young adults (aged 15-39 years), the incidence is higher in women (8.99%) compared with that in men (4.86%) (23). According to Surveillance, Epidemiology and End Results data from 2018-2022, the highest proportion of primary cutaneous melanoma cases occurred in individuals aged 65-74 years (27.4%), followed by those aged 55-64 years (21.5%). By contrast, only 4.4% of cases were diagnosed in patients <34 years of age (13). Overall, the risk of developing melanoma increases with age (22).

Melanomas have a pronounced tendency to metastasize to distant sites, with trunk melanomas exhibiting a particularly high risk of distant spread. The most common first site of distant metastasis is the skin (38%), followed by the lungs (36%), liver (20%) and brain (20%) (24). Median survival time varies according to the number of metastatic sites, with 7 months recorded for patients with one distant metastasis site, 4 months for those with two sites and only 2 months for those with three or more sites (24).

However, the clinical features of the present case are markedly divergent from the aforementioned epidemiological statistics, highlighting its distinctive value as a cautionary case. While epidemiological data indicate that primary cutaneous melanoma most frequently occurs in the age group of 65-74 years (13), the present patient was 21 years old at initial diagnosis, representing a considerably younger demographic for this disease. More notably, the primary lesion was located on the chest, with a Breslow thickness of only 0.75 mm, absence of ulceration, no evidence of metastasis and pathological characteristics generally associated with a favorable prognosis. According to the AJCC 8th edition staging system, the patient was classified as stage IA (T1aN0M0) (8). Based on current epidemiological statistics, such patients would be expected to have a 5-year survival rate of 100% (12). However, the patient in the present case developed widespread systemic metastases within 3 years of surgery, with merely 4 years elapsing from the initial stage IA diagnosis to mortality from stage IV disease. This rapid and fatal progression in a patient with initially favorable pathological staging revealed the limitations of relying solely on conventional pathological staging for prognosis prediction. Therefore, for young patients with melanoma, even those with lesions suggesting a favorable prognosis, enhanced post-operative health education and improved follow-up compliance should be implemented in the future. Furthermore, individualized surveillance strategies should be considered, potentially including shortened follow-up intervals or increased imaging frequency, to achieve early detection and timely intervention of tumor recurrence.

Risk factors for cutaneous melanoma are broadly classified as exogenous or endogenous. Exogenous factors include solar and artificial ultraviolet (UV) radiation, specific lifestyle habits and immunosuppression. Endogenous factors comprise skin color, hair color, eye color, the number of melanocytic nevi, the presence of atypical nevi, sex, medical history, hereditary factors and genetic susceptibility (25-27). Among these, UV radiation represents the most notable environmental risk factor for all types of skin cancer (28). The number of common and atypical nevi is also a key independent predictor of melanoma risk. A previous study indicated that patients with a high number of nevi (n=101-120) have a risk ~7 times greater compared with those with few nevi (n=0-15) (4).

Surgical resection remains the primary treatment for early-stage melanoma. However, high-risk patients treated with surgery alone have only a 40-60% probability of remaining disease-free at 5 years and numerous patients may eventually experience locoregional or distant recurrence (29). According to the National Comprehensive Cancer Network (NCCN) guidelines, preferred adjuvant therapy options for patients with stage IIB-IV cutaneous melanoma include anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) agents and anti-PD-1 immune checkpoint inhibitors (ICIs), or for patients with BRAF mutations, targeted therapy. In addition, several emerging immunotherapies and neoadjuvant regimens are becoming viable options for patients with melanoma. Systemic therapies, particularly ICIs (such as ipilimumab, pembrolizumab, atezolizumab and relatlimab) and BRAF-targeted treatments (such as dabrafenib and trametinib), have markedly improved the prognosis of patients with metastatic (stage III and IV) cutaneous melanoma and have also demonstrated notable benefit in early-stage (IIB/C) primary melanoma (30). Although melanoma incidence continues to rise, mortality has been declining by an average of ~4% annually since 2015. This trend reflects major advances in the treatment of advanced and metastatic disease, largely attributable to progress in immunotherapy and targeted agents (31).

ICIs comprise CTLA-4 inhibitors (such as ipilimumab), PD-1 inhibitors (such as pembrolizumab and nivolumab), programmed cell death-ligand 1 (PD-L1) inhibitors (such as atezolizumab) and lymphocyte-activation gene 3 (LAG-3) inhibitors (such as relatlimab). CTLA-4 and PD-1 inhibitors enhance the ability of T cells to eliminate cancer cells by blocking CTLA-4 immune checkpoint molecules and PD-1/PD-L1 interactions, respectively (32). By contrast, LAG-3 inhibitors bind to the LAG-3 receptor and disrupt its interaction with ligands, thereby alleviating LAG-3 pathway-mediated immunosuppression and promoting T-cell proliferation. Checkpoint immunotherapy is indicated for patients with both BRAF mutant-type and wild-type melanoma (33). A previous study reported that 15.5% of patients with unresectable stage IV melanoma achieved a complete response after first-line ICI treatment, with 5-year progression-free survival and overall survival rates of 79 and 83%, respectively, among those achieving a complete response (34).

Ipilimumab, the first ICI approved for advanced melanoma, demonstrated a significant survival benefit in stage IV disease by increasing the median overall survival to 10.1 months, compared to 6.4 months with the glycoprotein 100 (gp100) peptide vaccine alone (35). Due to the high immunogenicity of melanoma, anti-PD-1 inhibitors are particularly effective in this malignancy (36). Although randomized clinical trials [CheckMate 238 with nivolumab (37,38); KEYNOTE-054 (39)/716 (40,41) with pembrolizumab] have demonstrated that adjuvant PD-1 inhibitors improve recurrence-free survival in patients with resectable stage IIB-IV melanoma, an overall survival benefit has not been observed to date (42). Ongoing first-line clinical trials are evaluating PD-1 inhibitors in combination with multiple classes of agents, including histone deacetylase inhibitors (HDAC6i Nexturastat A) (43), novel immunotherapies (NT-I7) (44), vaccines (IDO/PD-L1 targeting peptide vaccine) (45) and toll-like receptor 9 agonist (Nelitolimod) (46). For patients with metastatic melanoma harboring BRAF V600E/K mutations, the combination of ipilimumab and nivolumab is considered a preferred first-line treatment regardless of mutation status, establishing ICI as a primary therapeutic option (5). In a previous study by Hodi *et al* (47), 945 patients with unresectable stage III or IV melanoma received either ipilimumab plus nivolumab, nivolumab monotherapy or ipilimumab alone. The 4-year overall survival rate was 53% in the combination group, compared with 46% in the nivolumab group and 30% in the ipilimumab group. Among patients with mutant-type BRAF, the 4-year overall survival rates were 62, 50 and 33% for the combination, nivolumab and ipilimumab groups, respectively; corresponding rates for patients with wild-type BRAF were 49, 45 and 28%. These results suggested that combination therapy may offer enhanced benefit compared with nivolumab monotherapy, particularly in patients with BRAF-mutations.

LAG-3 inhibitors represent the first class of LAG-3 protein inhibitors worldwide. On March 18, 2022, the Food and Drug Administration (FDA) approved the fixed-dose combination of relatlimab and nivolumab for the treatment of adult and pediatric patients aged ≥12 years with unresectable or metastatic melanoma. This combination acts through simultaneous inhibition of LAG-3 and PD-1, and has demonstrated efficacy in previously untreated metastatic or unresectable melanoma (48). For most patients with metastatic melanoma, anti-PD-1-based therapy combined with either ipilimumab or relatlimab offers the potential for long-term survival and possibly a cure (49).

Targeted therapies are designed to specifically address molecular abnormalities or target key pathways essential for melanoma cell proliferation and survival (32). BRAF inhibitors (vemurafenib, dabrafenib and encorafenib) and MEK inhibitors (trametinib and cobimetinib) represent the main classes of agents used in this approach. The BRAF serine/threonine kinase, an isoform of the Raf family, functions within the MAPK pathway, which serves a key role in regulating cell proliferation (50). BRAF mutations occur most frequently in malignant melanoma (51), with the V600E variant accounting for >80% of all BRAF mutations (50). It has been reported that ~50% of patients with metastatic melanoma harbor a BRAF V600 mutation. MEK also serves a key function within the MAPK cascade. In patients with metastatic melanoma (stage IV or unresectable stage III), dabrafenib monotherapy resulted in a median progression-free survival (PFS) time of 5.1 months (52). A previous study by Long *et al* (53) reported that combination therapy with dabrafenib and trametinib in treatment-naive patients with BRAF V600 mutation-positive metastatic melanoma yielded a median overall survival time of >2 years, with ~20% of patients remaining progression-free at 3 years. These findings indicated that the combination was associated with prolonged survival and durable responses in a subset of individuals. In addition, compared with vemurafenib monotherapy, dabrafenib combined with trametinib significantly improved overall survival in previously untreated patients with BRAF V600E or V600K metastatic melanoma, without increasing overall toxicity (54). Due to its generally acceptable safety profile, adjuvant dabrafenib plus trametinib is now considered a reasonable option for patients with advanced resectable BRAF-mutated melanoma (55). Overall, concurrent BRAF and MEK inhibition has been reported to yield notably improved clinical outcomes compared with BRAF inhibitor monotherapy.

In 2022, Corrie *et al* (56) demonstrated that combination therapies outperform monotherapy in BRAF-mutated unresectable or metastatic melanoma. Among these, the atezolizumab/vemurafenib/cobimetinib triple therapy and the encorafenib/binimetinib combination exhibited the most favorable efficacy profiles. Furthermore, encorafenib/binimetinib demonstrated an enhanced safety profile compared with all other combination regimens, including triple therapy. In 2023, results from a phase III trial reported by Haist *et al* (57) indicated that triple combination therapy, comprising an ICI, a BRAF inhibitor and a MEK inhibitor, prolonged response duration and enabled long-term PFS. However, most of these trials did not meet their primary endpoints and therefore do not support the routine first-line use of triple therapy in patients with BRAF V600-mutant melanoma. That said, subgroup analyses and preliminary data in patients with melanoma brain metastases suggested that patients with higher disease burden or rapidly progressing disease may derive greater benefit from such regimens. The addition of atezolizumab to the targeted therapy combination of vemurafenib and cobimetinib was reported to be safe and tolerable, and significantly improved PFS in patients with advanced melanoma harboring BRAF V600 mutations (58). For most patients with BRAF V600-mutant metastatic melanoma, the preferred treatment sequence involves initial therapy with nivolumab plus ipilimumab, followed by BRAF and MEK inhibitors if required (59).

Beyond the established approaches of ICI and targeted therapy, the potential benefits of several emerging immunotherapies and neoadjuvant treatments for patients with melanoma warrant further research in the future.

OVs represent one of the most novel and promising forms of intratumoral immunotherapy. The first OV approved for melanoma treatment was talimogene laherparepvec (T-VEC), a modified herpes simplex virus type 1, indicated for recurrent melanoma after initial surgery (60). Previous studies indicated that T-VEC combined with ipilimumab had a manageable safety profile and appeared to yield notably increased efficacy compared with either agent alone (61). For patients with regional or distant metastatic melanoma, including those with visceral involvement, T-VEC in combination with ICIs may represent a promising novel therapeutic alternative (61).

Neoadjuvant therapy refers to induction treatment administered to reduce tumor burden before primary treatment, typically surgery (62). This approach includes both neoadjuvant immunotherapy and neoadjuvant targeted therapy; it serves a particularly key role in locally advanced, resectable stage III-IV or borderline resectable melanoma. In such settings, neoadjuvant therapy may facilitate early eradication of micrometastases within a more immunologically responsive microenvironment, potentially offering enhanced curative potential compared with adjuvant therapy, while also reducing the need for extensive surgery, achieving microscopic R0 resection, decreasing the risk of distant metastasis and providing key biomarker information to potentially guide subsequent adjuvant treatment in the future (29). Patel *et al* (63) reported that, in patients with high-risk, resectable stage III-IV melanoma, the 2-year event-free survival rate in the neoadjuvant-adjuvant group was ~23% higher compared with that in the adjuvant-only group. Patients receiving pembrolizumab both before and after surgery exhibited significantly longer event-free survival times compared with those receiving adjuvant pembrolizumab alone. Amaria *et al* (64) demonstrated that neoadjuvant treatment with dabrafenib and trametinib in patients with resectable stage IIIB-IV BRAF-mutant cutaneous melanoma significantly improved progression-free survival rate at a median follow-up time of 18.6 months. However, neoadjuvant therapy carries the risk of disease progression during treatment, which may render initially resectable tumors unresectable or lead to distant spread (65).

According to the NCCN guidelines, first-line systemic therapy for advanced BRAF-mutant melanoma includes either combined immunotherapy or combined targeted therapy (66). However, the choice of optimal first-line treatment remains a subject of debate. BRAF/MEK inhibitors typically induce a strong and rapid initial response, yet disease progression remains almost inevitable. By contrast, ICIs may exhibit a lower initial response rate, possibly due to the time required for immune activation, but can provide more durable long-term clinical benefits (67,68). For patients with BRAF-mutant melanoma with active brain metastases, several BRAF/MEK inhibitors have demonstrated notable activity with manageable safety profiles and can lead to marked tumor regression (69-71). By contrast, ipilimumab tends to be more effective when brain metastases are small and asymptomatic (72). Furthermore, a previous study indicated that, although dabrafenib plus trametinib resulted in PFS and overall response rates similar to those of nivolumab plus ipilimumab, dabrafenib plus trametinib was associated with significantly shorter treatment duration and lower healthcare costs (73). In the present case, the poor performance status of the patient and rapid progressive disease necessitated swift disease control to minimize early risks. After multidisciplinary discussion and detailed communication with the patient and family, combined targeted therapy was selected as the first-line regimen, based on its faster onset of action and higher rates of tumor regression. The present case underscores that the optimal first-line strategy for advanced melanoma should be individualized based on a comprehensive evaluation of multiple clinical and patient-specific factors.

Although BRAF/MEK inhibitors demonstrate high efficacy in BRAF-mutant melanoma, their clinical benefits are frequently constrained by intrinsic, adaptive and acquired resistance mechanisms. Intrinsic resistance may result from loss-of-function mutations in PTEN (74,75) and neurofibromatosis type 1 (76,77), leading to activation of the PI3K-AKT-mTOR pathway. Adaptive resistance often involves upregulation of receptor tyrosine kinases (78), which can reactivate ERK signaling and thereby drive treatment resistance. The most prevalent form, acquired resistance, primarily involves MAPK pathway reactivation through various molecular alterations, including MEK mutations (79), BRAF alternative splicing (80) and BRAF amplification (81). These mechanisms collectively contribute to the development of treatment resistance and diminished therapeutic efficacy. To address these challenges, various combination regimens involving inhibitors have been developed. Among these, the combination of BRAF and MEK inhibitors has been reported to yield notably increased overall survival compared with BRAF inhibitor monotherapy (54). Based on this evidence, the dabrafenib plus trametinib combination received FDA approval for patients with unresectable or metastatic melanoma harboring BRAF V600E/K mutations. In the present case, the observed pattern of initial tumor regression followed by rapid progression strongly suggests the emergence of acquired resistance, possibly driven by one or more of the aforementioned molecular events. Thus, the present case highlights the current limitations of combination targeted therapy and supports the need for future research into strategies that can potentially overcome or reverse resistance.

Melanoma exhibits a notable tendency for distant metastasis. Standardized postoperative follow-up is essential for patients with early-stage disease who have undergone surgical resection. According to NCCN guidelines, patients with stage IA melanoma should undergo history and physical examination (H&P) (with emphasis on nodes and skin) every 6-12 months for the first 5 years after surgery, while routine laboratory tests and imaging studies are not recommended (66). However, in the present case, suboptimal adherence to scheduled follow-up visits was noted. Furthermore, clinical experience indicates that disease progression can be markedly rapid in certain young patients following recurrence. Therefore, we propose a dual approach: i) Establishing a structured patient education and follow-up system to ensure consistent implementation of guideline-recommended evaluations through regular reminders; and ii) formulating personalized, risk-adapted surveillance strategies for young patients with high-risk features. This strategy aims to avoid excessive medical intervention while enabling early detection and timely management of recurrent disease.

Dacarbazine served as the key metastatic melanoma treatment for decades; however, its use has declined with the emergence of more effective options such as targeted therapy and immunotherapy (32). Current systemic treatments for advanced melanoma primarily include ICIs and targeted therapies. Anti-PD-1 therapy is now a standard option for resected stage IIB-IV disease, while BRAF-targeted therapy is the standard for resected stage III-IV melanoma. Both modalities have been associated with a 35-50% relative improvement in recurrence-free survival and distant metastasis-free survival rates, although neither has demonstrated a notable overall survival benefit (82). Although combination therapies generally outperform monotherapies, the optimal combination strategy for maximizing patient benefit requires further investigation. In addition, emerging treatments such as OVs and neoadjuvant regimens demonstrate notable promise and may represent future advances in the management of advanced melanoma.

In conclusion, the present report describes the case of a 24-year-old male patient with early-stage cutaneous melanoma who developed multiple systemic metastases 3 years after radical resection and who succumbed 4 months after the diagnosis of metastatic disease. The present case underscores the importance of establishing a strict post-operative education and follow-up system for patients with early-stage melanoma, and developing a personalized risk-monitoring strategy. Treatment selection for advanced melanoma should not be restricted to ICIs or targeted therapy alone; however, a judicious integration of multiple modalities may yield improved outcomes. Novel approaches such as oncolytic virotherapy and neoadjuvant strategies also represent promising treatment options in the future. The field of advanced melanoma treatment continues to present numerous opportunities, innovations and challenges. Novel optimized treatment strategies may become available that potentially prolong patient survival in the future.

**Acknowledgements**

Not applicable.

**Funding**

No funding was received.

**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

DX and PW conceptualized and designed the present case report and provided overall supervision of the research. XH performed a comprehensive literature search, conducted analysis and interpretation of the clinical course, and drafted the initial manuscript. LZ and DX collected and assembled all clinical data, including imaging studies and laboratory results, and confirm the authenticity of all raw data. LZ prepared the figures. DX critically reviewed and revised the manuscript for important intellectual content. All authors read and approved the final manuscript and are accountable for all aspects of the work.

**Ethics approval and consent to participate**

The present case report was approved by the Binzhou People's Hospital Clinical Trial Ethics Committee (Binzhou, China; approval no. YXKYLL-20251101). Written informed consent was obtained from the patient. The present case report complied with the Declaration of Helsinki.

**Patient consent for publication**

Written consent for the publication of data and any related images was obtained from the patient.

**Competing interests**

The authors declare that they have no competing interests.

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