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CASE REPORT
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METASTAZA KUTANOG MELANOMA U DEBELOM I TANKOM CREVU: PRIKAZ SLUČAJA I PREGLED LITERATURE

CUTANEOUS MELANOMA METASTASIS TO THE LARGE AND SMALL INTESTINE: A CASE REPORT AND REVIEW OF THE LITERATURE

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Sažetak

Uvod: Metastaze malignog melanoma u gastrointestinalnom traktu (GIT) nisu česta pojava. Maligni melanom u GIT-u obično je metastatskog porekla, s obzirom na to da su primarni melanomi ove lokalizacije izuzetno retki. Veoma je važno napraviti razliku između primarnog melanoma u GIT-u i metastatskog melanoma.

Prikaz slučaja: Kod žene stare oko 65 godina, sa istorijom primarnog kutanog melanoma u predelu glave iz 2019. godine, dve godine kasnije razvio se metastatski melanom u debelom crevu i terminalnom ileumu. Nekoliko meseci nakon postavljanja dijagnoze metastatskog melanoma došlo je do letalnog ishoda.

Zaključak: Postavljanje dijagnoze metastatskog melanoma zahteva multidisciplinarni pristup kako bi se odredila prava i definitivna dijagnoza, kao i pravovremena terapija, a sve u cilju poboljšanja kvantiteta i kvaliteta života pacijenata.

Ključne reči: melanoma, kutani melanom, metastatski melanom gastrointestinalnog trakta

Abstract

Introduction: Metastatic melanoma rarely metastasizes to the gastrointestinal tract (GIT). However, melanoma in the gastrointestinal tract is usually of metastatic origin, given that primary melanomas in this location are extremely uncommon. It is very important to differentiate between primary melanoma in the mucosa of the GIT and metastatic melanoma.

Case Presentation: A 65-year-old woman with a history of primary cutaneous melanoma in the head region dating back to 2019 developed metastatic melanoma of the large intestine and terminal ileum after two years. Several months later, the patient died.

Conclusion: The diagnosis of metastatic melanoma requires a multidisciplinary approach to determine the precise and definitive diagnosis as well as timely therapy, all with the aim of improving the quantity and quality of life of patients.

Key words: melanoma, cutaneous melanoma, metastatic melanoma, gastrointestinal tract

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Uvod

Kutani melanomi su maligni tumori koji infiltrišu okolno tkivo i daju limfogene i hematogene metastaze. Retke su metastaze melanoma u gastrointestinalnom traktu. Naime, melanom u gastrointestinalnom traktu (GIT) obično je metastatskog porekla, budući da su primarni melanomi ove lokalizacije izuzetno retki. Javljaju se u svega oko 1% slučajeva¹. Postavljanje dijagnoze metastatskog melanoma u GIT-u zahteva multidisciplinarni pristup i predstavlja veliki izazov za patologa. Veoma je važno postavljanje rane i precizne patohistološke dijagnoze kako bi se započeli pravovremeno i adekvatno lečenje i terapija, te poboljšali prognoza bolesti, ukupno preživljavanje, kao i preživljavanje bez bolesti. U ovom radu prikazuje se slučaj žene stare oko 65 godina sa metastatskim melanomom u gastrointestinalnom traktu, kod koje je kasnije utvrđen primarni kutani melanom u predelu glave.

Pikaz slučaja

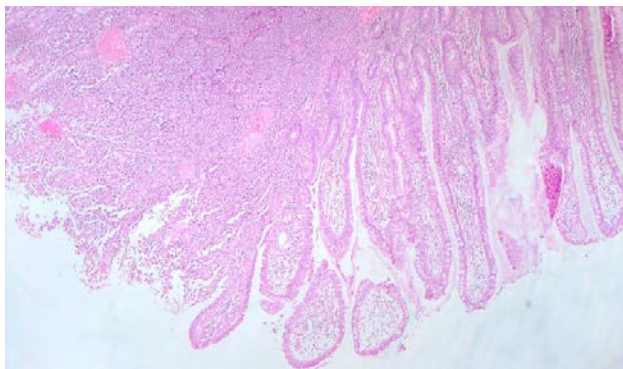
Žena stara oko 65 godina primljena je na Opštu hirurgiju u Univerzitetском kliničkom centru u Nišu zbog opstipacije, opstrukcije debelog creva i perforacije. U martu 2021. godine urađen je klinički pregled prilikom kojeg je otkrivena tumorska masa u debelom crevu u predelu cekuma i u terminalnom ileumu. Tumorska masa u tankom crevu bila je polipoidnog izgleda, sa najvećim promerom od oko 50 mm. U debelom crevu, u predelu Bauhinijeve valvule, bile su prisutne dve polipoidne formacije, najvećeg prečnika od oko 30 mm, a u njihovoj neposrednoj blizini još dve vegetantno-infiltrativne mase najvećeg promera od oko 10 mm i 60 mm. Nakon obrade tkiva i klasičnog bojenja preparata hematoksilin-eosin (HE) metodom, urađena je celokupna analiza parafinskih preseka svih preparata. Na pregledanim presecima bile su prisutne tumorske formacije sastavljene od kohezivnih gnezda epiteloidnih tumorskih ćelija, eozinofilne citoplazme sa oskudnim pigmentom i sa hiperhromnim pleomorfim jedrima i prominentnim jedarcima (Slika 1). U okolnom masnom tkivu izolovano je ukupno 38 regionalnih limfnih nodusa. Nakon pregleda parafinskih preparata, u četiri limfna nodusa detektovane su metastaze već opisanog tumorskog procesa. Urađene su i imunohistohemijske analize na jednom od reprezentativnih uzoraka. Imunoprofil tumorskih ćelija pokazao je jaku i difuznu ekspresiju na MelanA, HMB45 i S100. Ki-67 indeks proliferacije bio je do 38% (Slika 2).

Introduction

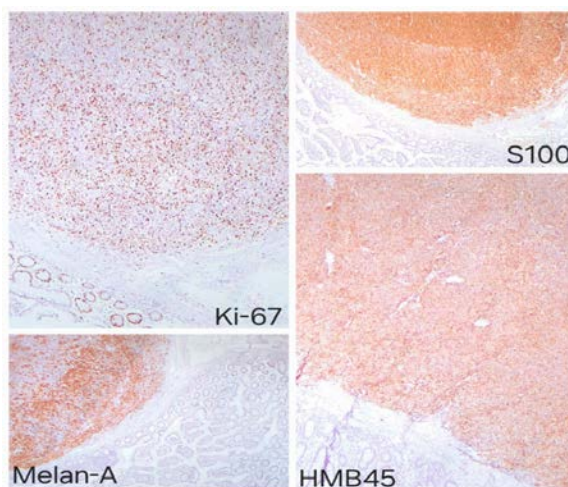
Cutaneous melanomas are malignant tumors that infiltrate the surrounding tissue and produce lymphogenous and hematogenous metastases. Melanoma metastases to the gastrointestinal tract are rare. However, melanoma in the gastrointestinal tract (GIT) is usually of metastatic origin, given that primary melanomas in this location are extremely uncommon. They occur in only about 1% of cases¹. Diagnosing metastatic melanoma in the GIT requires a multidisciplinary approach and represents a major challenge for the pathologist. It is key to establish early and precise pathohistological diagnosis in order to start with timely and adequate treatment and therapy aimed at improving the prognosis of the disease, overall survival, as well as disease-free survival. This paperwork presents the case of a 65-year-old woman with metastatic melanoma in the gastrointestinal tract, who was later diagnosed with primary cutaneous melanoma in the head region.

Case Presentation

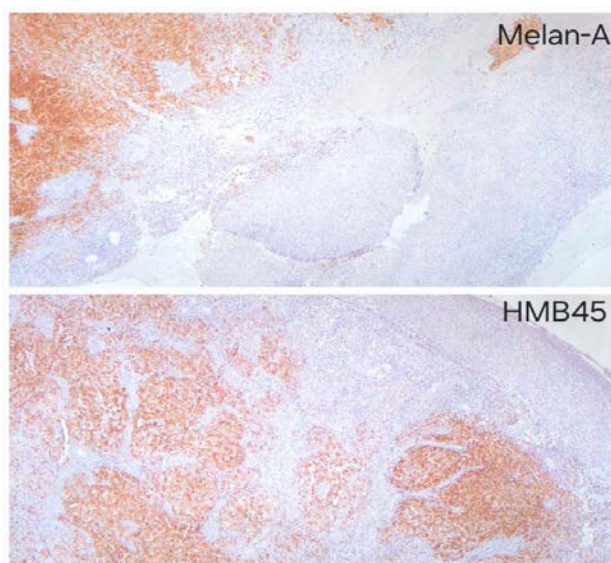
In March 2021, a 65-year-old woman was admitted to General Surgery Department at the University Clinical Center in Niš due to constipation, colon obstruction and perforation. A clinical examination was performed, and a tumor mass was located in the large intestine in the area of the cecum and the terminal ileum. In the small intestine, the tumor mass had a polypoid appearance with a diameter of about 50 mm. Two polypoid formations with the largest diameter of about 30 mm were present in the large intestine in the area of the Bauhinia valve, as well as two more vegetative-infiltrative masses with the largest diameters of about 10 mm and 60 mm in the immediate vicinity. After tissue processing and classical preparation, staining using the hematoxylin-eosin (HE) method, the entire analysis of paraffin sections of all preparations was performed. The examined sections showed tumor formations composed of cohesive nests of epithelioid tumor cells, eosinophilic cytoplasm with scarce pigment and hyperchromatic pleomorphic nuclei and prominent nucleoli (Figure 1). A total of 38 regional lymph nodes were isolated in the surrounding fat tissue. After the examination of paraffin preparations, metastases of the already described tumor process were detected in four lymph nodes. Immunohistochemical analyses were also performed on one of the representative samples. The immunoprofile of the tumor cells showed a strong and diffuse expression of MelanA, HMB45, and S100. The Ki 67 proliferation index was up to 38% (Figure 2).



Slika 1. Mikromorfološki izgled tumorske mase (HE, x40)
Figure 1. Microscopic aspect of the tumor mass (HE, x40)



Slika 2. Imunohistohemijska analiza tumorskih ćelija metastatskog melanoma u gastrointestinalnom traktu (x40)
Figure 2. Immunohistochemical analysis of the metastatic melanoma tumor cells (x40)



Slika 3. Imunohistohemijski profil tumorskih ćelija melanoma kože (x40)
Figure 3. Immunohistochemical profile of the cutaneous melanoma tumor cells (x40)

Mikromorfološki je isključeno postojanje tumorskih ćelija u epitelu, kao i širenje tumorskih ćelija nalik na ono u Pedžetovoj bolesti. Urađene su i detaljne kliničke pretrage, dermatoskopski i očni pregledi. Postavljena je dijagnoza multiple metastaze melanoma u debelom i tankom crevu, sa prisustvom metastaza u četiri regionalna limfna nodusa. Na zahtev patologa Zdravstvenog centra Pirot, urađeni su ponovni pregled i imunohistohemijska analiza biopsijskog materijala melanocitne proliferacije u predelu glave (iz 2019. godine). Tumorski proces bio je izgrađen od kohezivnih gnezda epiteloidnih tumorskih ćelija eozinofilne citoplazme sa uvećanim i vezikularnim jedrima i bez prisustva pigmenta. Imunohistohemijska analiza je pokazala difuznu i intenzivnu ekspresiju na MelanA, HMB45 i S-100 (Slika 3). Postavljena je dijagnoza melanoma kože u predelu glave. Nakon urađenih svih pomenutih analiza, verifikacije prethodne primarne melanocitne proliferacije u predelu glave i pregleda patohistoloških preparata, utvrđena je kompatibilnost obeju tumorskih masa. Nekoliko meseci kasnije, došlo je do letalnog ishoda. Nema podataka o tome da je pacijentkinja primala bilo kakvu terapiju.

Diskusija

Melanomi su maligni tumori porekla melanocita koji su najčešće kutani, mada se mogu javiti primarno i na drugim lokalizacijama². U preostalim slučajevima, najčešći su u oku, leptomeningama, usnoj duplji, nosu, sluzokoži anogenitalne regije, sluzokoži ždrela i jednjaka⁷. Kao primarna lezija GIT-a najčešće se javlja u anusu (31%), rektumu (22%) i nazofarinksu (35%). U jednjaku je zastupljena u oko 6% slučajeva, u želucu u 3% slučajeva, u tankom crevu u 2% slučajeva⁴, a u debelom crevu samo u oko 1% slučajeva⁴.

Nastaju *de novo*, na terenu prethodnih melanocitnih nevusa, displastičnih nevusa ili na terenu celularnog *blue* nevusa – to je najređi put nastanka. Mnogobrojni su faktori rizika za razvoj melanoma: izloženost ultravioletnom zračenju, imunosupresivna terapija, *xeroderma pigmentosum*, sindrom familijarnog displastičnog nevusa, familijarni melanom, prisustvo velikog broja pigmentnih nevusa. Često su prisutni kod osoba sa svetlom kožom i kosom^{5,6}, a predstavljaju najagresivnije neoplazme u koži. Melanomi vrše lokalnu infiltraciju okolnog tkiva, šire se prvo limfogeno u regionalne limfne noduse, a daju i hematogene metastaze u udaljenim organima¹. Najčešće su zahvaćena pluća, jetra, kosti i mozak. Metastaze u gastrointestinalnom traktu nisu uobičajene.

The micromorphological analysis excluded the existence of tumor cells in the epithelium, as well as the pagetoid spread. Detailed clinical examinations, dermoscopic evaluations, and eye examinations were also performed. Multiple melanoma metastases to the large and small intestine were diagnosed, as well as the presence of metastases in four regional lymph nodes. At the request of the pathologist of the Health Center in Pirot, a re-examination and immunohistochemical analysis of the 2019 biopsy material of the melanocytic proliferation in the head region was performed. The tumor process was composed of cohesive nests of epithelioid tumor cells with eosinophilic cytoplasm with enlarged and vesicular nuclei without pigment. Immunohistochemical analysis showed a diffuse and intense expression of MelanA, HMB45 and S-100 (Figure 3). Skin melanoma in the head region was diagnosed. After all these analyses, the verification of previous primary melanocytic proliferation in the head region, the examination of pathohistological preparations and the compatibility of both tumor masses were determined. Several months later, the patient died, and there is no data on whether the woman received any therapy.

Discussion

Melanomas are malignant tumors of melanocytic origin that are most often found in the skin. However, they can occur as primary tumors in other locations as well². They are most common in the eye, leptomeninges, oral cavity, nose, mucous membrane of the anogenital region, mucous membrane of the pharynx and esophagus³. As a primary lesion of the GIT, melanomas most often occur in the anus (31%), rectum (22%) and nasopharynx (35%). They occur in the esophagus in about 6%, in the stomach in 3%, in the small intestine in 2%, and in the large intestine only in about 1% of the cases⁴.

Melanomas arise *de novo*, on the site of previous melanocytic nevi, dysplastic nevi, or on the site of a cellular blue nevus, which is the rarest way of origin. Risk factors for the development of melanoma are numerous and include exposure to ultraviolet radiation, immunosuppressive therapy, *xeroderma pigmentosum*, familial dysplastic nevus syndrome, familial melanoma, and the presence of a large number of pigmented nevi. They are often present in people with fair skin and hair^{5,6}. Melanomas represent the most aggressive skin neoplasms.

Podaci iz literature pokazuju da je oko 60% metastatskih melanoma u GIT-u otkriveno na obdukcijском materijalu, a samo oko 5% na operativnim materijalima. Između pojave metastaza u GIT-u i prethodnog primarnog melanoma u proseku prođe od dva meseca do 180 meseci⁷. Učestalost metastatskih depozita u takom crevu iznosi 35%, u debelom crevu je oko 15,5%, u želucu 7%, a u rektumu 5%; u anusu je najređa i sreće se u oko 1% slučajeva⁸. Iako su metastaze melanoma u GIT-u retke, veoma je važan klinički pregled ove regije budući da kutani melanomi koji se javljaju u predelu glave, vrata, abdomena i ekstremiteta najčešće daju metastaze u GIT-u⁹.

Kao kliničke manifestacije metastatskog melanoma u gastrointestinalnom traktu izdvajaju se pojava krvi u stolici, anemija, opstipacija, opstrukcija creva, perforacija, bol u stomaku, gubitak telesne mase i dr. Većina pacijenata ne pokazuje nikakve simptome. Prognoza je za pacijente sa prethodno navedenim simptomima loša. Studije su pokazale da je kod pacijenata sa perforacijom i opstrukcijom creva preživljavanje kraće, te da u proseku iznosi oko deset meseci^{10,11,12}.

Metastatski melanomi u GIT-u češće se javljaju kod muškaraca nego kod žena, i to u odnosu 1,5 : 1, i pokazuju procentualno veću stopu mortaliteta¹². Dominantna lokalizacija metastatskog melanoma debelog creva je u ascendentnom i descendentnom delu kolona u odnosu na primarni melanom, koji je najčešće lokalizovan u desnostranom kolonu i u cekumu. Metastatski melanomi u GIT-u mogu biti makroskopski u vidu pojedinačnih ili multiplih polipoidnih lezija, ulcerativnih lezija i vegetantnih masa¹³.

Dijagnoza metastatskog melanoma uobičajeno se postavlja kolonoskopijom, ultrazvukom i kompjuterizovanom tomografijom. Oko 60% – 70% metastatskih melanoma u GIT-u vizuelizovano je pomoću kompjuterizovane tomografije¹⁴. Studija Akcalija i saradnika pokazala je da osetljivost i specifičnost ove metode iznosi oko 92%¹⁵. Međutim, kolonoskopija praćena patohistološkom verifikacijom metastatske infiltracije predstavlja zlatni standard sa visokom specifičnošću i senzitivnošću.

Histopatološki pregled primarnog melanoma GIT-a pokazuje prisustvo epiteloidnih i/ili vretenastih atipičnih melanocitnih tumorskih ćelija u bazalnom sloju epitela, kao i širenje tumorskih ćelija u superficijalne delove epitela nalik Padentovoj bolesti.

They perform local infiltration of the surrounding tissue, have primarily lymphatic dissemination to regional lymph nodes, but also give hematogenous metastases to distant organs¹. The lungs, liver, bones, and brain are most often affected. Metastases to the gastrointestinal tract are rare. Literary data show that about 60% of GIT metastatic melanomas were detected on autopsy material, and only about 5% on operative material. The period between the appearance of metastases in the GIT and the primary melanoma ranges between 2 and 180 months⁷. The frequency of metastatic deposits in the small intestine is 35%, followed by around 15.5% in the colon, 7% in the stomach, 5% in the rectum, and around 1% of cases in the anus⁸. Even though melanoma metastases in the gastrointestinal tract are rare, it is essential to perform a clinical examination of this region given that cutaneous melanomas that occur in the head and neck region, abdomen, and extremities most often metastasize to the gastrointestinal tract⁹.

Clinical manifestations of metastatic melanoma in the gastrointestinal tract include blood in the stool, anemia, constipation, intestinal obstruction, perforation, abdominal pain, weight loss, etc. Most patients show no symptoms. Patients with the aforementioned symptoms have a poor prognosis. Studies have shown that patients with intestinal perforation and obstruction have a shorter overall survival of about 10 months¹⁰⁻¹².

Metastatic melanomas in the gastrointestinal tract occur more often in men compared to women, in a ratio of 1.5:1, and have a higher mortality rate¹². The dominant localization of metastatic melanoma of the large intestine is in the ascending and descending part of the colon, compared to primary melanoma which is most often localized in the right-sided colon and cecum. Metastatic melanomas in the gastrointestinal tract may be macroscopic in the form of single or multiple polypoid lesions, ulcerative lesions, and vegetative masses¹³.

Metastatic melanoma is usually diagnosed by colonoscopy, ultrasound, or computed tomography. About 60% to 70% of metastatic melanomas in the gastrointestinal tract are visualized using computed tomography¹⁴. A study by Akcali et al. showed that the sensitivity and specificity of this method is about 92%¹⁵. However, colonoscopy represents the gold standard with high specificity and sensitivity followed by pathohistological verification of the metastatic infiltration.

Histopathological examination of the primary melanoma of the GIT reveals the

Tumorske ćelije mogu sadržati zrnast braon pigment melanin, a mogu biti i amelanotične. Dodatne imunohistohemijske analize, naročito kod amelanotičnih melanoma i melanoma sa atipičnom patohistološkom slikom, mogu biti od koristi prilikom postavljanja dijagnoze. Upotreba antitela S-100, MelanA i HMB45 pokazala je veliku specifičnost i senzitivnost¹⁶. Nakon postavljanja dijagnoze melanoma u GIT-u, neophodno je odrediti da li je posredi primarna lezija ili metastaza.

Prognoza primarnog melanoma GIT-a bolja je od one koju imaju melanomi sluzokoža drugih lokalizacija. Međutim, prognoza primarnog melanoma sluzokože gora je nego kod kutanih melanoma, i to zbog bogate vaskularizacije i limfne drenaže. Ukupan mortalitet metastatskih melanoma GIT-a iznosi oko 45%, dok je jednogodišnje i petogodišnje preživljavanje od 33% do 66%. Veoma je važno napraviti razliku između primarnog melanoma u sluzokoži GIT-a i metastatskog melanoma; to zahteva detaljna klinička ispitivanja koja uključuju iscrpnu istoriju bolesti i fizički pregled. Postoje strogo definisani kriterijumi primarnog melanoma GIT-a; oni obuhvataju nepostojanje primarne kutane lezije, ranije uklonjene pigmentne promene na koži, nepostojanje tumora oka, tumor koji je u vidu solitarne lezije unutar hiruškog uzorka, morfološku kompatibilnost sa primarnom lezijom, isključivanje postojanja melanoma, naročito u predelu glave, vrata i ekstremiteta, kao i zahvaćenosti drugih lokalizacija i organa^{15,17}.

Zaključak

Otkrivanje melanoma u debelom i tankom crevu retka je pojava i predstavlja veliki izazov za patologa. Stoga, neophodno je da se sprovedu detaljni klinički i anamnestički pregledi kako bi se napravila razlika između primarnog i metastatskog melanoma u GIT-u. Od posebnog su značaja detaljni dermatoskopski i očni pregledi. Kako bi se otkrile eventualne metastaze u GIT-u, koje su uglavnom klinički asimptomatske, veoma je važno da se kod pacijenata sa melanomima i nakon lečenja obave rutinska snimanja i pretrage. Kompletna hiruška resekcija, imunoterapija i ciljana terapija pokazale su bolju prognozu i ukupno preživljavanje, pa trenutno predstavljaju zlatni standard.

presence of epithelioid and/or spindle-shaped atypical melanocytic tumor cells in the basal layer of the epithelium, as well as the pagetoid spread in the superficial parts of the epithelium. Tumor cells may or may not contain the granular brown pigment melanin. Additional immunohistochemical analysis, particularly in amelanotic melanomas and melanomas with an atypical pathohistological picture, may prove useful in diagnostics. The use of antibodies S-100, MelanA, and HMB45 showed high specificity and sensitivity¹⁶. After diagnosing melanoma in the GIT, it is necessary to decide whether it is a primary lesion or a metastasis.

The prognosis of primary melanoma of the gastrointestinal tract is better compared to mucosal melanomas in other locations. However, the prognosis of primary mucosal melanoma is worse compared to cutaneous melanomas due to rich vascularization and lymphatic drainage. The overall mortality for metastatic melanomas of the GIT is about 45%, whereas the one-year and five-year survival range from 33% to 66%. It is very important to differentiate between primary melanoma in the mucosa of the GIT and metastatic melanoma. This requires thorough clinical studies that include a detailed medical history and physical examination. There are strictly defined criteria for primary melanoma of the GIT, and they include the following: the absence of a primary skin lesion, previously removed pigmentary changes on the skin, the absence of an eye tumor, the fact that the tumor must be in the form of a solitary lesion within the surgical specimen, morphological compatibility with the primary lesion, the exclusion of melanoma, especially in the area of the head, neck and extremities, as well as the involvement of other localizations and organs^{15,17}.

Conclusion

The discovery of melanoma in the large and small intestine is a rare entity and represents a great challenge for the pathologist. In this regard, it is necessary to perform detailed clinical and anamnestic examinations in order to differentiate between primary and metastatic melanoma in the GIT. Detailed dermatoscopic and eye examinations are of particular importance. It is considered crucial that patients with melanoma undergo routine imaging and tests even after treatment to detect possible metastases in the GIT, given that they are mostly clinically asymptomatic. Complete surgical resection, immunotherapy, and targeted therapy have shown a better prognosis

Međutim, dijagnoza i terapija metastatskog melanoma zahtevaju multi-disciplinarni pristup da bi se odredila prava i definitivna dijagnoza, kao i pravovremena terapija, kojima bi se kvantitet i kvalitet života pacijenata poboljšali.

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and overall survival and are currently regarded as the gold standard.

However, the diagnosis and treatment of metastatic melanoma require a multi-disciplinary approach to determine the precise and definitive diagnosis as well as timely therapy, all with the aim of improving the quantity and quality of life of patients.

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