Small bowel involvement by primary and secondary malignant melanoma

Report of three cases and review of the literature

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Abstract. *Malignant melanoma is known by its unpredictability to metastasise to practically any organ. Among gastrointestinal involvement, the small bowel is affected in 30 - 75 % of cases. Primary malignancies of the small intestine in general are unusual, thus malignant melanoma alone represents a significant proportion of all neoplasms in the small bowel. Primary malignant melanoma of the small intestine was described only in few case reports. We describe three cases of small bowel involvement by primary and secondary malignant melanoma.*

Key words: *malignant melanoma, small intestine, enteroscopy*

Douda T, Rejchrt S, Tyčová V, Široký M, Cyrany J, Kopáčová M, Langr F, Burešová E, Zavoral M, Bureš J. Postižení tenkého střeva primárním a sekundárním maligním melanomem. Popis tří případů a přehled literatury. Folia Gastroenterol Hepatol 2004; 2 (4): 184 - 189.

Souhrn. *Maligní melanom může nepredikovatelně metastázovat prakticky do kteréhokoliv orgánu. U gastrointestinálních metastáz je tenké střevo postiženo ve 30 - 75 % případů. Vzhledem k tomu, že primární nádory tenkého střeva jsou vzácné, představuje postižení melanomem poměrně velkou část všech malignit tenkého střeva. Primární maligní melanom tenkého střeva však byl popsán pouze v několika málo kazuistikách. V našem sdělení přinášíme popis tří případů nemocných s primárním a sekundárním melanomem tenkého střeva.*

Klíčová slova: *maligní melanom, tenké střevo, enteroskopie*

Primary malignant tumours of the small bowel are rare, they make up less than 1 % of all gastrointestinal malignancies and less than 3 ‰ of all neoplasms (11,15). Malignant melanoma constitutes 1 - 3 % of all cancers (15,44). Its incidence is increasing among the Caucasian race (40). Malignant melanoma is known by its unpredictability to metastasise to practically any organ. Sixty percent of patients dying from melanoma have gastrointestinal involvement at autopsy, and 1 - 4 % of all melanoma patients have clinical, radiological or endoscopic evidence of gastrointestinal involvement. Among gastrointestinal involvement, the small bowel is affected in 30 - 75 % of cases (9,11,31,44). As primary malignancies of the entire small intestine are rare and the small bowel is susceptible to metastatic spread of melanoma because of its rich blood and lymphatic supply, it is obvious that malignant melanoma alone represents a significant proportion of all neoplasms in the small bowel (9,11). Primary malignant melanoma of the small intestine has been described in only a few

case reports (1,4,5,7,17,18,20,23,27,34). We describe three different patients with small bowel involvement by primary and secondary malignant melanoma.

Case reports

In the first case, a 48-year-old male, presented with dull abdominal pain, anorexia, weight loss and chronic anaemia was referred to enteroscopy for pathological finding in the duodeno-jejunal region found at enteroclysis. There were several ball-shaped tumorous deeply ulcerated lesions (so-called "bull's eye" appearance) in the proximal jejunum, 50 to 60 cm from the ligament

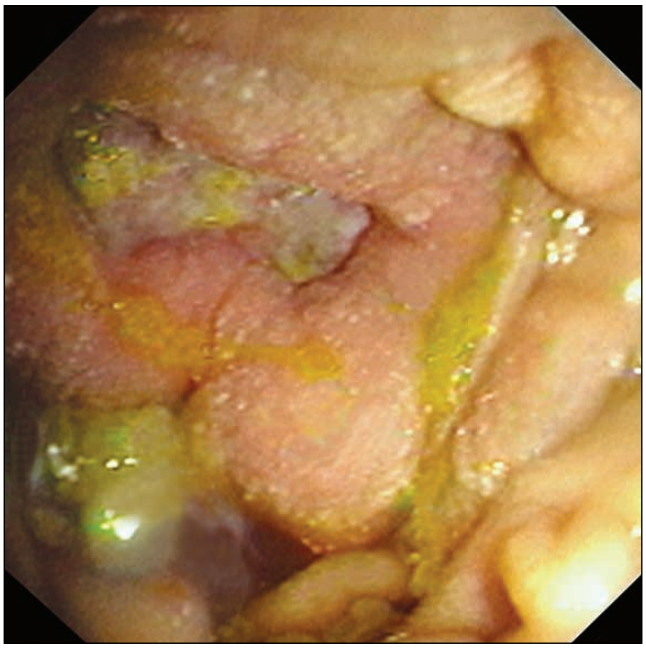

Figure 1
Primary malignant melanoma of the small bowel. Polypoid tumour of the proximal jejunum with a deep central ulcer.

Primární maligní melanom tenkého střeva. Polypoidní tumor proximálního jejuna s hlubokou centrální ulcerací.

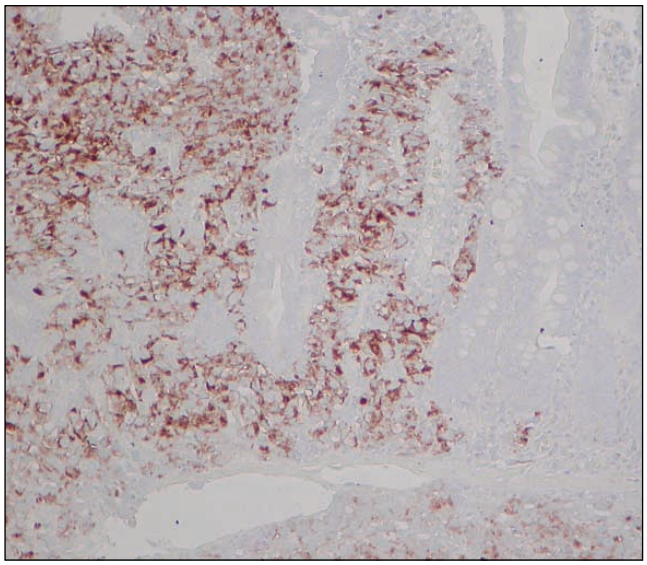

Figure 3
Primary malignant melanoma of the small bowel. Glycoprotein HMB-45 positivity within the tumorous cells. Immunohistochemistry.

Primární maligní melanom tenkého střeva. Průkaz glykoproteinu HMB-45 v nádorových buňkách. Imunohistochemie.

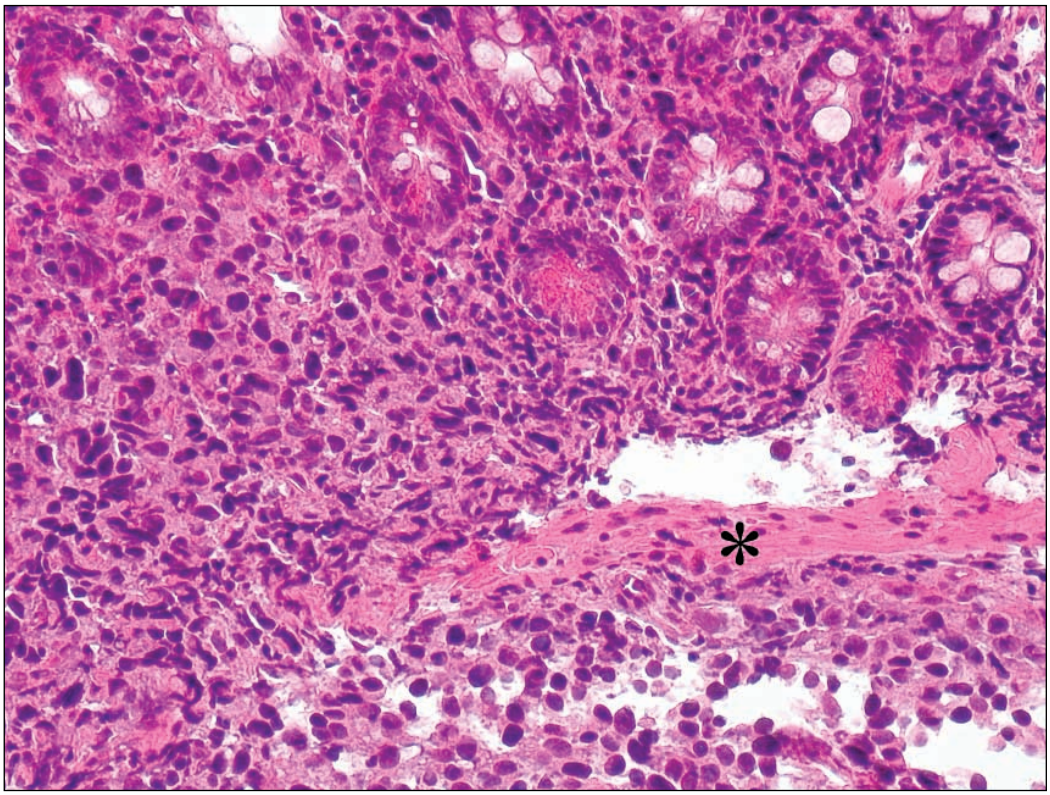

Figure 2
Primary malignant melanoma of the small bowel. Tumorous infiltration penetrates from mucosa through the lamina muscularis mucosae (asterisk) into submucosa. Haematoxylin-eosin.

Primární maligní melanom tenkého střeva. Nádorová infiltrace přestupuje ze sliznice přes lamina muscularis mucosae (hvězdička) do submukózy. Hematoxilin-eozin.

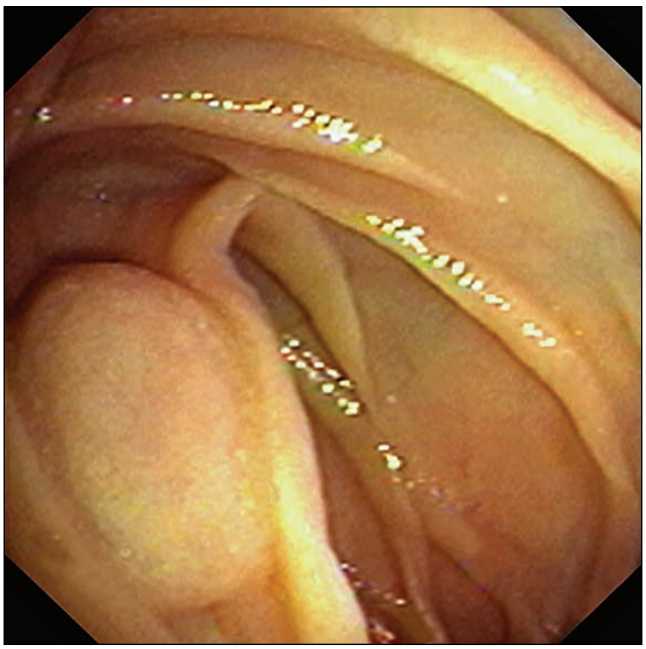

Figure 4
Satellite metastasis of primary jejunal melanoma into the duodenum. Small ball-shaped submucosal tumour (1 cm in diameter) of the pars ascendens duodeni (D4). The same patient as seen in Figs. 1 - 3.

Satelitní metastáza primárního melanomu jejuna do duodena. Malý kulovitý podslizniční tumor (1 cm v průměru) v pars ascendens duodeni (D4). Stejný nemocný jako na obr. 1 - 3.

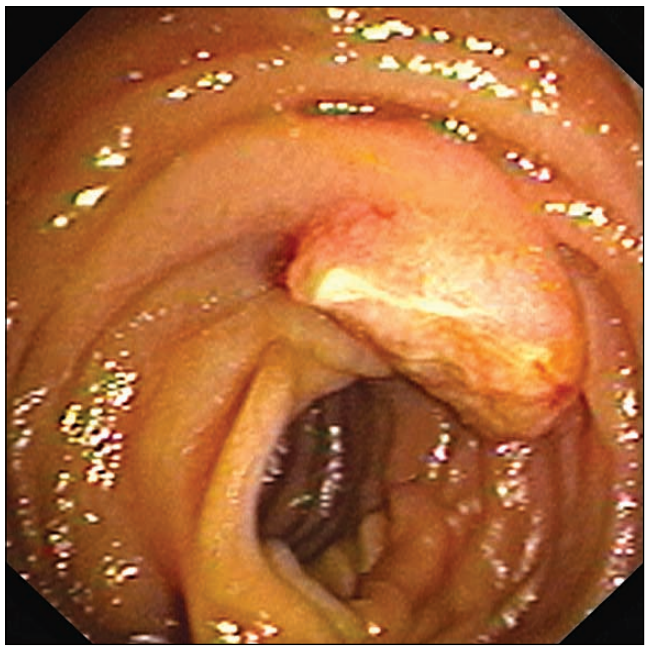

Figure 5
Metastasis of malignant melanoma to the small bowel. Fragile tumour of the proximal jejunum.

Metastáza maligního melanomu do tenkého střeva. Křehký tumor v proximálním jejunu.

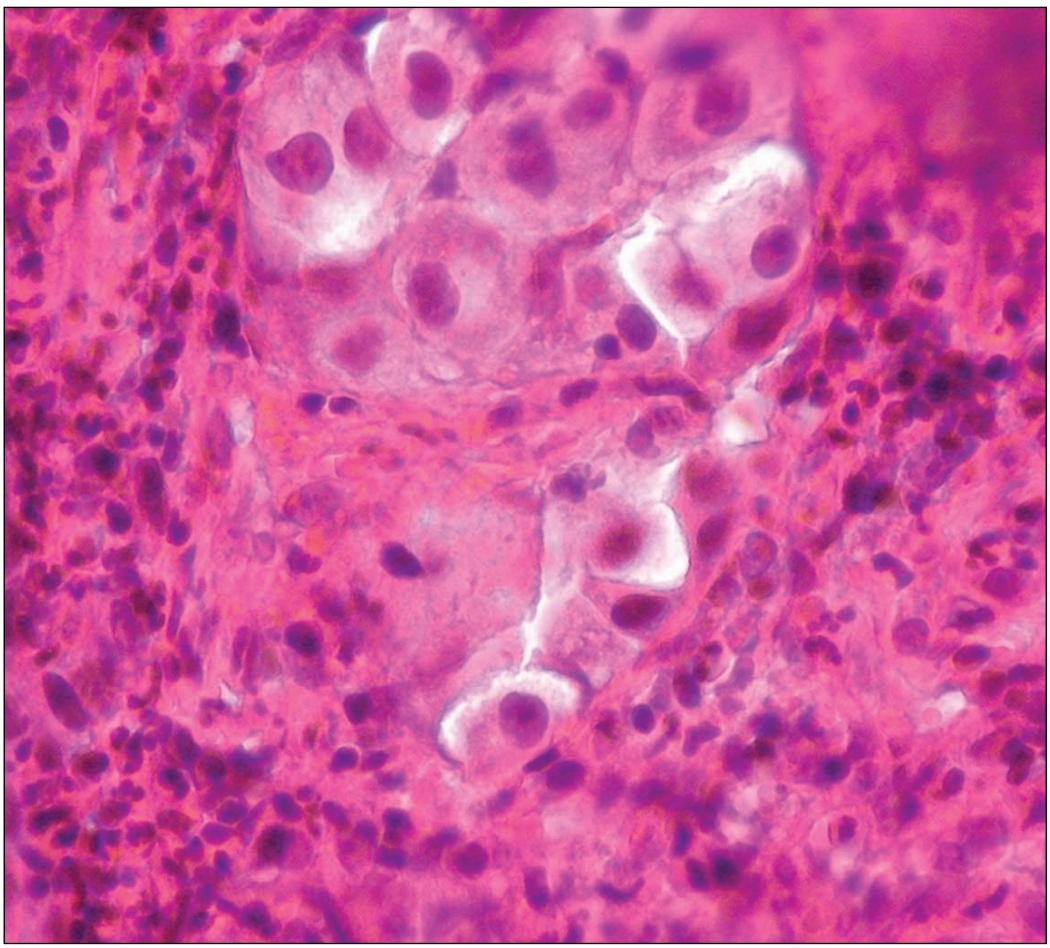

Figure 6
Metastasis of malignant melanoma to the small bowel. Cluster of melanoma cells in the lamina propria with surrounding inflammatory infiltration. The same patient as seen in Fig. 5. Haematoxylin-eosin.

Metastáza maligního melanomu do tenkého střeva. Trs melanomových buněk v lamina propria se zánětlivým infiltrátem v okolí. Stejný nemocný jako na obr. 5. Hematoxilin-eozin.

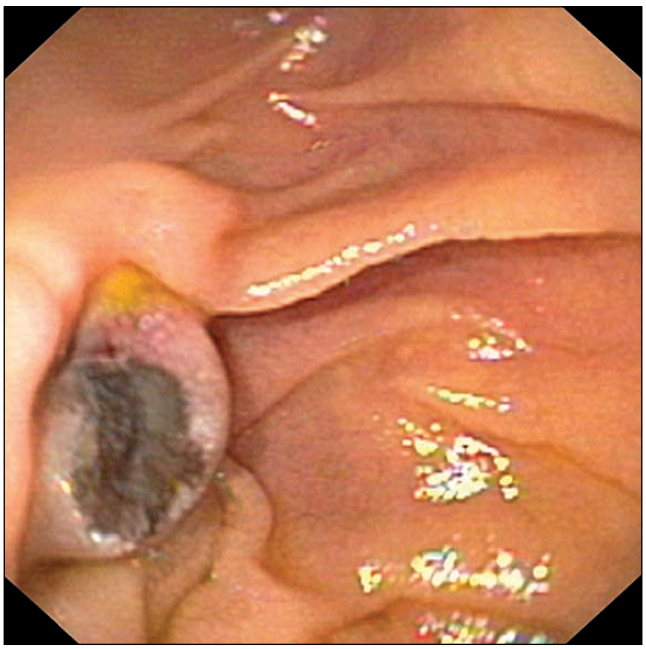

Figure 7
Metastasis of malignant melanoma to the small bowel. Ball-shaped tumour (1 cm in diameter) in the third part of the duodenum (pars horizontalis inferior duodeni) with an ulceration.

Metastáza maligního melanomu do tenkého střeva. Kulovitý tumor (1 cm v průměru) v pars horizontalis inferior duodeni (D3) s ulcerací.

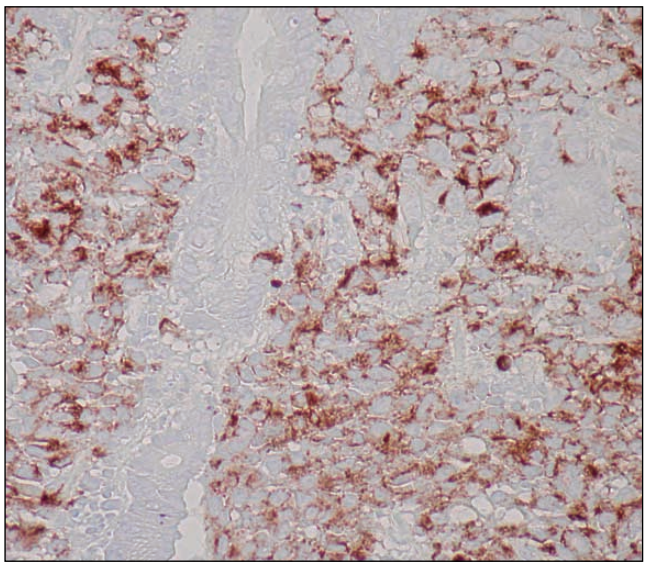

Figure 8
Metastasis of malignant melanoma to the small bowel. Melan A positivity within the tumorous cells. The same patient as seen in Fig. 7. Immunohistochemistry.

Metastáza maligního melanomu do tenkého střeva. Průkaz proteinu melan A v nádorových buňkách. Stejná nemocná jako na obr. 7. Imunohistochemie.

of Treitz (Fig. 1) and a satellite metastasis into the duodenum (Fig. 4). Histology has recognized primary jejunal malignant melanoma (Fig. 2), melan A and HMB-45 (Fig. 3) were positive at immunohistochemistry. The patient had no previous history of skin melanoma, neither halo nevus nor other nevi had been excised.

In the second case, a 47-year-old male was referred for enteroscopy investigation because of obscure overt bleeding presented with melaena. The patient underwent radical extirpation of skin malignant melanoma in the abdominal region and three cerebral metastases were removed several months ago. An elevated discoid tough fragile tumour was found at push-enteroscopy beyond the duodeno-jejunal junction (Fig. 5). Histology revealed this lesion to be a metastatic amelanotic melanoma (Fig. 6). Melan A and S100 protein were positive at immunohistochemistry.

In the third case, a 64-year-old woman suffered for three years for generalized malignant melanoma (with multiple metastases to the liver, muscles and uterus). She was referred for upper GI endoscopy because of severe microcytic anaemia (haemoglobin 50 g/L). Metastasis of melanoma was found in the distal duodenum (Fig. 7). Melan A (Fig. 8) was positive at immunohistochemistry.

Discussion

The small intestine is the most common location of gastrointestinal metastasis from cutaneous malignant melanoma. On the other hand, primary melanoma originating in the small intestine is extremely rare (1, 4, 5, 7, 17, 18, 20, 23, 27, 34). An exceptional case of melanoma in Meckel's diverticulum has also been published (10). Malignant melanoma occurs at various locations, where melanocytes or melanoblasts are present - mostly in the skin, less frequently in the eye (choroids layer), leptomeninges, oral cavity, nasal mucosa, pharynx, oesophagus, bronchus, vaginal or anorectal mucosa (17,44). Primary skin melanoma lesions may precede secondary gastrointestinal involvement by many years, the possibility of undiscovered spontaneously regressing cutaneous lesion has been widely discussed (9,44). Cutaneous lesions, if discovered, precede the onset of gastrointestinal symptoms by an average of 4 years (9,15). Some small bowel melanomas occur without history of antecedent primary lesion and the possibility of primary small bowel melanoma is considered. We report three cases of melanoma involvement of the small intestine. We have concluded the first case as a primary small bowel melanoma while the two remaining patients have had metastases of cutaneous melanoma into the small intestine. All patients presented showed anaemia, either obs-

cure overt or obscure occult bleeding. According to literary data, patients with primary melanoma showed diffuse colicky abdominal pain, anorexia, weight loss, and anaemia or gastrointestinal bleeding (1, 4, 5, 7, 17, 18, 20, 23, 27, 34). Persons suffering from metastases of melanoma to the small intestine showed abdominal pain, nausea, vomiting, weight loss, obstructive jaundice, and microcytic anaemia or overt gastrointestinal bleeding (12, 19, 21, 25, 26, 28, 29, 31, 33, 35, 43, 45, 46). It can also mimic acute appendicitis, cause bowel obstruction or intussusception (13, 42), intestinal perforation (16), protein-losing enteropathy (30,37), malabsorption (6) or create encapsulating peritonitis (7). Bender et al. (8) reviewed a series of 32 melanoma patients with metastasis to the small intestine, the most common symptoms were abdominal pain (60 % patients), bowel obstruction (47 %), nausea and vomiting (41 %), gastrointestinal bleeding (30 %) and palpable abdominal mass (10 %). About 50 % with gastrointestinal metastases have three or fewer lesions (8). In another series of 68 subjects with gastrointestinal metastases from melanoma (out of 7,965 melanoma patients treated within a 20-year period) mostly showed anaemia (60 %) and abdominal pain (59 %) (2). The most frequently involved portion of the gastrointestinal tract was the small intestine (91 %) (2).

An analysis of 103 patients with small bowel malignant melanoma obtained from the Armed Forces Institute of Pathology files was carried out by means of regression analysis of age at melanoma small bowel involvement, and the authors concluded that involvement is most probably metastatic even in cases without a known primary tumour (15). Other authors (4, 10, 20, 23) consider primary sources in small bowel melanoblastic cells of the neural crest, which migrate to the ileum through the omphalomesenteric canal or neuroendocrine APUD system (amine precursor uptake and decarboxylation cells). These attractive hypotheses have been deconstructed by finding that such cells are derived from the endoderm and not the neural crest (15,17,44).

Histological recognition of malignant melanoma is realized by means of haematoxylin and eosin staining and confirmed histochemically by Masson Fontana stains, or by immunohistochemistry revealing positivity of the S-100 protein, glycoprotein HMB-45, Melan A, NK1/C3 or tyrosinase-related protein-2 (TRP-2) (22,36). The electron microscope demonstrates melanosomes and premelanosomes in the tumour cells (9,15). Histological criteria for primary melanoma highlight the proliferation of atypical junctional melanocytes. Atypical melanocytic cells in the basal layer extend in a "Pagetoid" fashion in the more superficial epithelium. Other indication of primary lesion is the presence of lymphocytes infiltration surrounding tumorous mass in immunocompetent patients (15,17). However, we have found this sign in the second case reported in this paper (see Fig. 6) that was definitely metastasis of cutaneous malignant melanoma to the small intestine.

Despite the fact that this issue still remains controversial, criteria for diagnosis of primary melanoma of the small intestine according Sachs et al. (32) are solitary tumour, no metastatic lesions other then those of regional lymph node and a disease free survival period of at least 12 months after diagnosis.

The prognosis of untreated metastatic melanoma is poor, 99 % of patients die within a year. Resection of gastrointestinal melanoma should be undertaken for potential prolongation of both overall and symptom-free survival (5-year survival rate up to 20 %) (2,14,21,24,31,41,46). Surgery, despite previously or simultaneously documented visceral metastases, may be beneficial, with palliation of symptoms in some 70 - 90 % of patients who undergo resection or bypass (2), although long-term survival remains poor. Complete resection of the entire visible tumour has resulted in prolonged survival compared to that of palliative resection or non-surgical medical management (2,3,9,21,24,44).

There is no effective immunotherapy and/or chemotherapy available and response rate is only about 10 - 20 %. Adjuvant therapy comprises interferon alfa, interleukin-2, vaccination with modified melanoma cells and high-dose chemotherapy with autologous bone marrow transplants (38,40). Laser photocoagulation or argon plasma-coagulation may be useful for patients with bleeding metastases (15,39,44).

Long-term survival may be accomplished with close follow-up and prompt surgical treatment. Patients with known melanoma who develop gastrointestinal symptoms or chronic blood loss should have full evaluation of their gastrointestinal tract.

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