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Surgical Management of Malignant Melanoma of Gastrointestinal Tract

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1. Introduction

Malignant melanoma of gastrointestinal (GI) tract is a less common condition especially in eastern countries and can be either primary or metastasis. Most of the cases are secondary melanoma. GI metastases are frequently found during autopsy, only small proportion of the patients can be detected while living (2-5% of the patients). Clinically, a primary GI malignant melanoma is suggested if the patient has no obvious primary cutaneous lesion or other extra-intestinal disease especially the ocular system. Malignant melanoma of anorectum is the most common site of the primary tumor of GI tract. For metastasis, small bowel is the most frequently site followed by stomach, large bowel and esophagus. Mucosal melanoma pursued more aggressive nature and poorer prognosis than other subsets of melanomas. Prognosis of malignant melanoma of GI tract is very poor because of difficult to diagnosis.

Malignant melanoma of GI tract can present as abdominal pain, upper or lower GI tract bleeding, obstructive jaundice, obstruction or perforation. Several case reports demonstrated small bowel obstruction from intussusceptions of malignant melanoma. The diagnosis can be made by GI endoscopy or imaging radiographic studies. The definite diagnosis is the pathological examination. Management of GI malignant melanoma depends on the location and number of the lesion. Surgical resection for primary melanoma of GI tract is the mainstay treatment and provides a chance for cure. For metastatic disease, multidisciplinary approach is the best option. Surgery is the alternative way to use in selected patient.

2. Diagnosis and staging

Melanoma originates from melanocyte, a pigmented, dendritic-like cell located in epidermis of skin, eye, epithelium of the nasal cavity, oropharynx, anus and genitourinary system. The diagnosis of melanoma includes assessment of the architectural and cytological features combine with the clinical examination. The only staging system of malignant melanoma is used for cutaneous melanoma because of the high incidence rate compare to non-cutaneous group, accounts about 90% of all melanoma. Of the remaining forms of melanoma, ocular melanoma accounts for 5%, mucosal melanoma for 1% and melanoma of unknown origin

for 2%. Within the mucosal subgroup, half of them are head and neck origin followed by anorectal, female genital, and urinary tract tumors respectively. The pathological staging of primary tumor uses the tumor thickness and ulceration. Ulceration is defined as the absence of the intact epithelium overlying a major portion of the tumor. Ulceration is the result of the thickness of tumor and has a strong correlation to survival.

Recently, American Joint Committee on Cancer (AJCC) presented the 7th edition of the melanoma staging system in 2009. Differences from the 6th edition (2002) included the used of mitotic rate to classify stage 1a and 1b, used of immunochemical detection of nodal metastasis and no lower threshold to define positive nodal status. For stage IV disease, the staging system is not change. The site(s) of metastases and elevated serum levels of lactate dehydrogenase (LDH) are used to divided M stage to three categories; M1a, M1b and M1c. The definition and survival were shown in table 1.

M stage	Site	Serum LDH	One-year survival rates	
			%	*p*
M0	No distant metastases	NA	NA	
M1a	Distant skin, subcutaneous, or nodal metastases	Normal	62	<0.0001
M1b	Lung metastases	Normal	53	
M1c	All other visceral metastases Any distant metastases	Normal Elevated	33	

Table 1. Modification of the 7th AJCC classification of metastatic melanoma.

Most of melanoma in GI tract is metastases. Only 2-15% of all GI melanomas are primary. Whenever a seemingly primary melanoma is detected in GI tract, it is prudent to conduct a through clinical investigation to consider the possibility of metastatic disease including history, physical examination and investigations. Carefully history taking and comprehensive physical examination are the initial crucial step of the approach. Skin and eye examination should be mandatory examination in all patients. Gynecological and abdominal examination include rectal examination should be performed for the next step.

Ozdemir et al. proposed criteria for diagnosis primary bronchial melanoma to be defined as a primary lesion that can apply to GI melanoma as well. The criteria including (1) there is only single lesion in the surgical specimen (2) there must be no previously excised skin tumor (3) no previous ocular tumor (4) morphology must be compatible with primary tumor (5) there must be no other demonstrable melanomas at the time of surgery (6) findings should be confirmed by careful autopsy. The lesions that not fulfill these criteria should be termed secondary. The problem of the criteria is we could know the exact diagnosis after the autopsy when patient passed away. Then, these criteria did not have an impact to the treatment, only for the epidemiology. Blecker et al. suggested the following criteria for a diagnosis of primary intestinal melanoma: 1) no evidence of concurrent melanoma or atypical melanocytic lesion of the skin, 2) absence of extraintestinal metastatic spread of melanoma, and 3) presence of intramucosal lesions in the overlying or adjacent intestinal epithelium.

3. Investigation

3.1 Endoscopy

Small bowel is the most common site of GI melanoma and bleeding is one of the most frequent presentations of the patients. Therefore, a GI endoscopy with magnification should be the procedure of choice to diagnose malignant melanoma of GI tract. Multiple black, depressed lesions (1+ 5 mm in diameter) with a "bull's eye" appearance are usually viewed in the GI mucosa (Figure 1). At present endoscopic ultrasonography (EUS) guided fine needle aspiration (FNA) may play an important role for cytological diagnosis in the patients with advanced disease (Figure 2).

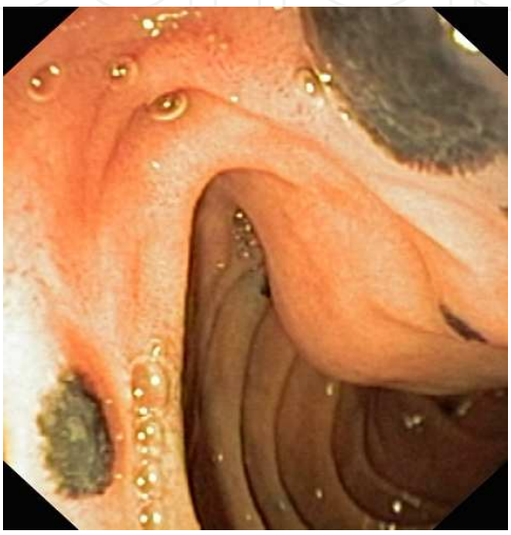

Fig. 1. Endoscopic view showed multiple typical black color lesions in the second part of duodenum.

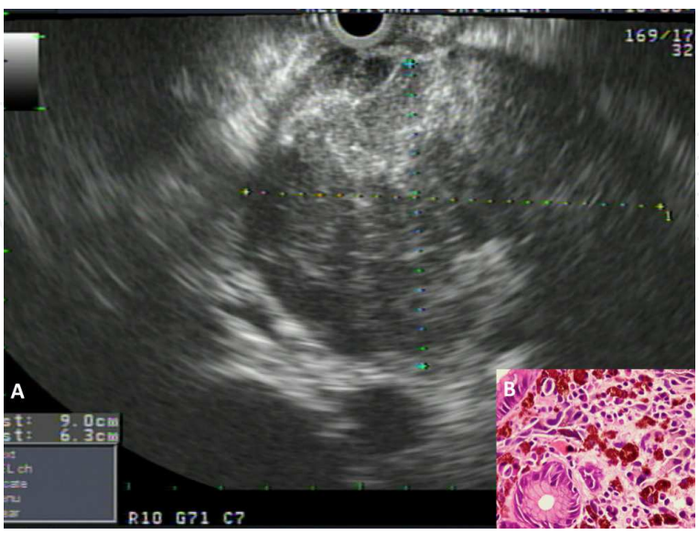

Fig. 2. EUS-guided (A) FNA for cytological confirmation (B) in the patient with advanced malignant melanoma.

3.2 Barium study and capsule endoscopy

Small bowel metastatic may present as varying sized single or multiple nodules that can have polypoid or infiltrating appearance. Central ulceration can occur when lesions outgrow their blood supply, giving a "target" appearance on barium study. The target sign can be found with other hematogenous metastases such as lymphoma or sarcoma. For small bowel metastatic, the lesion can be intraluminal involvement and act as leading point for intussusceptions.

Capsule endoscopy (CE) is the current standard and one of the most sensitive investigations for detection of small bowel lesion. The finding could be a polypoid lesion with central umbilication or an ulcerative lesion with bleeding. Prakosa et al. reported a series of 21 patients diagnosed malignant melanoma and underwent positron emission tomography (PET) scanning and CE. They suggested that CE could identify and provide confirmation of small-bowel involvement in patients with metastatic melanoma after PET scanning. These two investigations are recommended as part of the work-up of all patients with or without GI symptoms.

3.3 Computed tomography (CT) and magnetic resonance imaging (MRI)

Computed tomography (CT) is the most commonly used imaging technique for staging and follow up in the malignant melanoma patients. Two studies have compared staging with Positron emission tomography (PET) and CT scan in all stages. Both studies found PET to be superior in terms of sensitivity and specificity to CT in all stages of Melanoma. In the contrary, Krug et al. demonstrated inferiority of PET to CT for the detection of lung and liver metastases.

Magnetic resonance imaging (MRI) is a good investigation for detection of brain and bone metastases. For anorectal region, MRI and endorectal ultrasonography are the good investigational methods for preoperative evaluation both of primary tumor and local nodal status. In one prospective study of 64 patients, whole-body MRI has been reported to have an overall accuracy for the detection of lesion slightly lower than PET-CT (78.8% vs. 86.7%), but the sensitivity for the detection of bone and liver metastases was better than PET-CT.

3.4 Positron emission tomography (PET)

Positron emission tomography (PET) is an advanced diagnostic imaging technique. This technique exploits the increased metabolism of glucose in malignant viable cells. ^{18}F-fluorodeoxyglucose (FDG) is one of the most commonly used radioisotopes. FDG is transported into tumor cells like glucose molecule. There is a many-fold increase in glucose metabolism in malignant tumors as compared with normal cells, therefore, the different in metabolism of tumor call and normal tissue can be detected by this technique. The potential benefits of FDG-PET for melanoma included the detection of locoregional and distant metastasis for staging.

The presence or absence of regional lymph node metastases is an important prognostic factor for patients with melanoma. FDG-PET has shown a limitation of sensitivity and wide variation of the data from previous studies. The sensitivity of FDG-PET is varied from 8% to 100%. Moreover, in the subgroup of subclinical nodal disease in stage I and II melanoma, the sensitivity of FDG-PET is only 14-17% whereas, sentinel node biopsy reached 86-94%. Crippa *et al*. identified the correlation between size of lymph node and sensitivity; sensitivity is 23%, 83% and 100% for lymph node less than 5mm, 6-10mm and greater than

10 mm in diameter, respectively. Therefore, FDG-PET might not be the investigation of choice for locoregional evaluation especially for clinically nonpalpable group.

For the distant metastatic evaluation especially in curative intent resected patients, the precise identification of the location and number of metastatic lesions could be important for surgical planning. From several studies, FDG-PET has been shown to be more accurate than conventional modalities such as ultrasonography, CT, and MRI. Then, FDG-PET is most commonly used for suspected or known distant metastases. The sensitivity is varied from 79% to 92% and specificity is varied from 86% to 90%. Several reports identified the influence of therapy by FDG-PET, 17- 48% of patients were changed their treatment plan. In the same way, FDG-PET is highly sensitive and specific for detection or restaging of melanoma. Prichard *et al.* reported the sensitivity and specificity of FDG-PET for detection of recurrent melanoma, 74-100% and 67-100%, respectively. Figure 2 is the one example of PET scan of intraabdominal metastatic of melanoma.

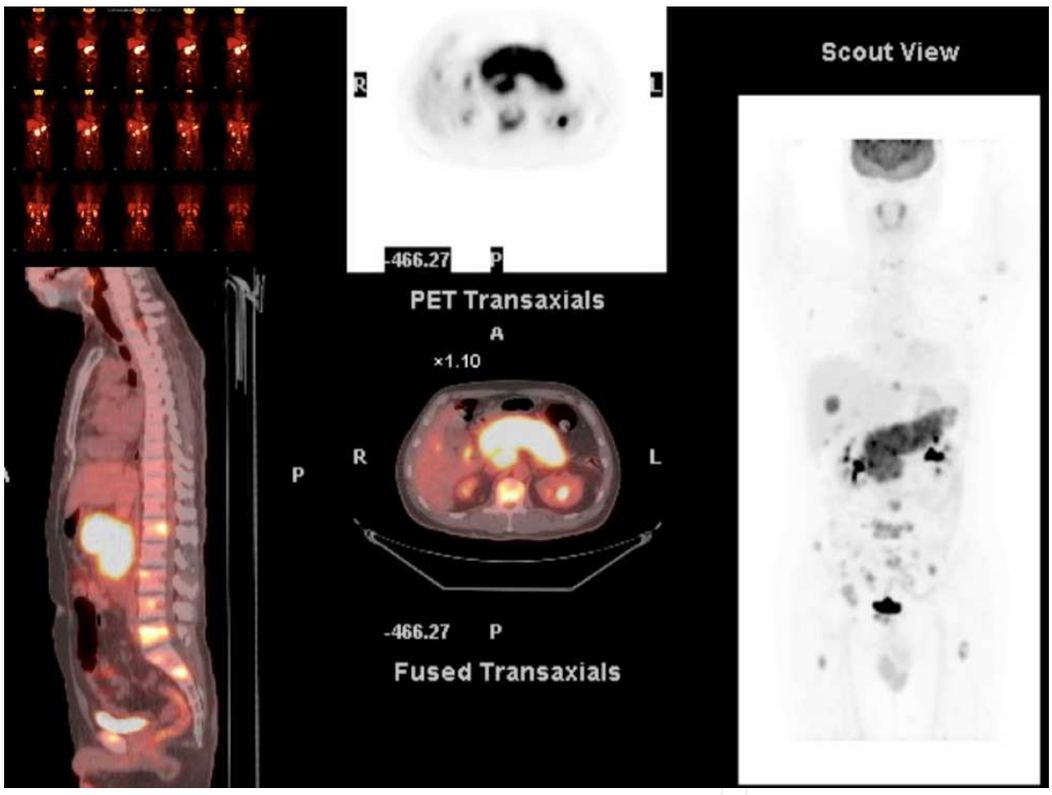

Fig. 3. PET scan revealed multiple metastasis lesions of malignant melanoma of gastrointestinal tract such as pancreas, liver and small bowel.

4. Introduction to primary malignant melanoma of GI tract

GI tract is not the normal organ that contain of melanocytes. Then, how be possible primary melanoma can develop in GI tract? One explanation is neural crest cells that demonstrated in the intestines, these cells have a potential to develop to mature melanocyte. Another reason, the aberrant migration of melanocytes that usually migrate from neural crest to the epidermis, hair follicles, oral cavity, nasopharynx, uvea, leptomeninges, and inner ear

during early embryogenesis. These are the reasons that why melanoma can be found in the gastrointestinal tract.

Primary GI melanoma can arise in various GI mucosal sites, including oral cavity, esophagus, stomach, small bowel, colon and anorectum. Distinguish between primary and metastatic from an unknown or regressed cutaneous melanoma may be difficult. Clinically, a primary GI melanoma is suggested if the patient has no obvious primary cutaneous melanoma from history and physical examination. Moreover, the patient has an isolated GI lesion without extraintestinal metastases. For histologically, the presence of atypical melanocytic cells in the basal layer of the epithelium and extending in a pagetoid fashion in to more superficial epithelium, may be reported in 40-100% of primary GI melanoma. The surgical treatment and the outcomes were depended on the organ of tumor involvement. Then, we divided primary melanoma in this section to organ specific. Summarized of the survivals was showed in the table 2.

Organ	Median survival (months)	5-year survival
Oral cavity	27-38.9	30-40%
Esophagus	12-13.4	4.2-14 %
Stomach	5-12	0
Small intestine	16	10%
Colon	27.5	21-56%
Anorectum	15-28.6	17-30.6%
Gallbladder and biliary tract	20.1-41	29 %

Table 2. Summarized of survivals divided by primary organ involvement.

5. Surgery of primary malignant melanoma of GI tract

5.1 Esophagus

Primary malignant melanoma of esophagus is the rare condition, accounts only 0.1-0.2% of primary esophageal tumors. Whereas, cadaveric study from De la Pava *et al*. demonstrated the presence of melanocytes in 4% of all esophageal specimen examined. Then, there are other entities of melanotic condition that can be found in esophagus. One benign condition called esophageal melanocytosis need to differentiate from the esophageal melanoma. This condition described the distribution of melanocytes in the basal layer of the esophageal squamous epithelium. The incidence is about 0.07-2.1% from previous reports. For primary esophageal melanoma is commonest in older males and more found in the middle and lower esophagus.

Patients may present with symptoms of dysphagia, retrosternal discomfort, weight loss, regurgitation or melena. After careful history and physical examination, barium swallow and/or endoscopy is the next investigation same as all esophageal lesions. The characteristic endoscopic appearance of primary malignant melanoma is a polypoid, irregularly pigmented, obstructive esophageal tumor. The tumor most often is polypoid; the nonpolypoid form is extremely rare. The color of the tumor may vary from black to white. An ulcerative lesion of the mucosa can be found in some case, then some tumors may be difficult to differentiate from esophageal carcinoma. Most of the cases are grossly pigmentation, but not almost always. The endoscopic biopsy can diagnose only half of the patients due to submucosal nature of the tumor. Up to 25% of all esophageal melanomas are

amelanotic. Presence of associated benign melanocytes or in situ melanoma from pathological examination favors the diagnosis of primary, rather than metastatic. If primary malignant melanoma is suspected at endoscopy, immunohistochemical staining of biopsy specimens is essential for diagnosis.

Regard to difficulty of the diagnosis, half of the patients are stage IV when diagnosed. The median survival is about one year and 5-year survival varied from 4.2% to 14%. The mainstay of the treatment is still surgical resection with dissection of the regional lymph nodes. Compared with other esophageal tumors, wider margins of resection are required. For early-localized lesion, radical resection had a significantly longer survival compare to local excision. Radiation can increased the mean survival rate from 14.2 months to 16.7 months, while adjuvant chemotherapy have a limited benefit. Only some case reports that demonstrated the long-term survival from surgical resection combine with chemotherapy. There are some alternative techniques such as endoscopic mucosal resection and localized ablative approaches were proposed in case report but the data still limited.

5.2 Stomach

Primary melanoma of stomach is the very rare disease entity and related to poor outcomes. Most of the reports are the case report then, the data is quite limited. The presenting symptoms of gastric melanoma are non-specific including nausea, vomiting, abdominal pain, weight loss and anemia. Perforation and/or upper GI bleeding can be presented as an initial diagnosis in some patients. Barium study, endoscopy and CT scan are the most common investigational methods. In the same way of esophageal melanoma, pigmentation of the lesion is the most clues for diagnosis and found in the majority. The median survival is usually less than 1 year. Cheung *et al.* reported 18 cases of primary gastric melanomas with the median survival is only 5 months without 5-year survival. Regard to limitation of the data, it is difficult to conclude that which operations are the appropriate surgical procedures of primary gastric melanoma.

5.3 Gallbladder and biliary tract

Primary melanoma of gallbladder is extremely rare condition as well as isolated metastasis to gallbladder. Regard to clinical presentation, involvement of the gallbladder rarely produces symptoms. Some case reports presented acalculous cholecystitis as a clinical presentation of these patients. Therefore, it is difficultly to diagnose melanoma of gallbladder preoperatively. Abdominal ultrasonography is a useful, easy, and inexpensive modality for assessing a gallbladder lesion. CT scan and Magnetic resonance cholangiography may add more information. Surgical resection of gallbladder is the treatment of both primary and metastatic lesions. The mean survival times for primary gallbladder melanoma is 20.1 months and for metastatic is 8.4 months, with few patients surviving longer than 2 years.

In 1963, Zaide first described primary malignant melanoma of common bile duct. This is also rarely disease entity same as the others primary GI melanoma. The existence of melanocytes in bile duct tissue is truly possible. Melanocytes derive from cells of the neural crest and can migrate throughout the body. They have been definitely identified in areas of endodermal origin, including gallbladder. The symptoms of this tumor mostly presented with obstructive jaundice. In most of the cases, the diagnosis can be made after the time of surgery. Wagner *et al*. reported the review of 6 cases of primary malignant melanoma of common bile duct from 1963 to 2000.

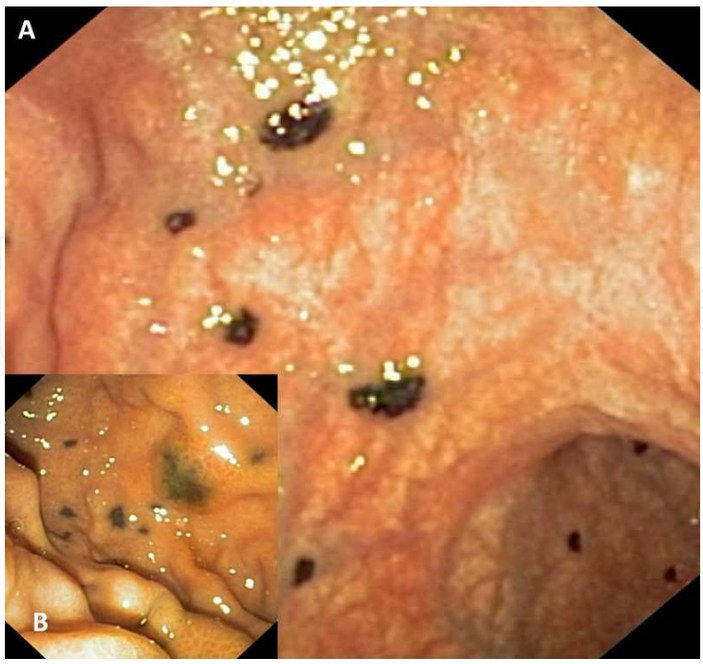

Fig. 4. Gastroscopy revealed multiple lesions of metastasis malignant melanoma in the stomach (A&B).

All of the patients underwent surgery including 4 Whipple operations, 2 partial hepatectomies and one resection of common bile duct. Three of them (2 Whipple and 1 hepatectomy) dead within 6-18 months from distant metastasis whereas three of patients didn't mention about follow up period. Therefore, it is not possible to conclude the optimal surgical option for this disease due to very limited of the data. There are also had a few literatures that reported the extremely rare primary malignant melanoma of intrahepatic duct and liver in a case report format. Because of the limitation of the data, then we not presented the detail of these disease entities in this chapter.

5.4 Small bowel

Cutaneous melanoma is the most common types of the tumor metastasis to GI tract which small intestine is the most common site of metastatic melanoma in the GI tract. However primary melanoma of small intestine is not common. Small bowel lesion can present with bleeding, abdominal pain, obstruction, weight loss and malabsorption. Intussusception can be a presenting symptom of small bowel melanoma. Diagnosis of small intestine lesion is typically made by contrast imaging study (small bowel follow-through), CT scan, endoscopy (push, single or double balloon and capsule endoscopy) and PET. Primary intestinal melanoma tends to be more aggressive and worse prognosis than cutaneous origin. The possible reasons are due to late diagnosis and rapidly growth of the tumor in the rich vascular and lymphatic supply of the intestinal mucosa.

Surgery is the treatment of choice in patients with primary or metastatic intestinal melanoma. Segmental resection with adequate free margins is a recommended procedure. Morbidity and mortality of this type of surgery is very low. Systemic adjuvant therapy has a limited role for this disease. The median survival rate is 16 months and 5-year survival rate is 10%.

5.5 Colon

Primary melanoma of the colon is also a rare clinical entity. Khalid *et al*. (2011) reported their review study of 12 patients with primary melanoma of colon. Right-sided colon is the most common location of the disease; about 65% of the patients. Lower GI bleeding is the most common presentation (50%) followed by abdominal pain (20%), obstruction (20%), and weight loss (16%). Amelanocytic colon melanoma is found in 14% of the cases.

For localized disease, surgical resection is the mainstay of the treatment. We cannot conclude that what is the standard of the operation because of the limitation of the data. Most of the patients in the previous studies underwent the oncologic colon resection same as adenocarcinoma. The prognosis of primary malignant melanoma of the colon seems to be better than other types of primary mucosal melanomas. However, colon melanoma is still aggressive than cutaneous origin. One-year and five-year survival rates are 37-60% and 21-33%, respectively and the median survival is 27.5 months.

5.6 Anus and rectum

In 1857, Moore first described anorectal melanoma, a rare and very aggressive tumor with the extremely poor prognosis. The incidence is less than 1% of all melanomas and about 2 - 4% of all anal malignancies. Majority about two-third of all lesions are pigmented. Two-third of anorectal melanoma is located within the anal canal or at the anal verge and the others demonstrated in the rectum. Presentation is often nonspecific symptoms and indistinguishable from other conditions in this area such as rectal bleeding, palpable of anal mass, anal pain or discomfort. Some of the patients underwent an excision due to misinterpreted as a thrombosed hemorrhoid or anal polyp. Anorectal melanoma is diagnosed histologically by melanin pigment. However, immunohistochemical staining of melanoma antigen such as HMB-45 and S-100 protein are adjunctive for diagnosis.

Unlike cutaneous melanoma, noncutaneous origin are more likely to be found metastasized to locoregional lymph node or distal organ when the time of diagnosis. For anorectal melanoma, incidence rate for locoregional lymph node is 61% and distant metastases are 29%. Surgery still is the mainstay of the treatment for primary anorectal melanoma. The extent of resection (wide local excision versus radical resection) and extent of lymphadenectomy remain debated. Early some studies proposed radical resection like abdominoperineal resection was associated with the better outcomes. Unfortunately, other studies have reported similar patterns of recurrence and survival in patients undergoing local excision. Unlike anorectal adenocarcinoma, in the study from Memorial Sloan-Kettering, demonstrated lymph node metastases did not predict outcome of patients undergoing radical resection. Moreover, prophylactic bilateral inguinal lymphadenectomy in the patients with clinically non-palpable lymph node has not shown to improve survival. The details of results from previous studies were summarized in the table 3.

Change of practice patterns over the time depend on the new data that suggested local recurrence and survival are not associated with extent of resection. Moreover, recurrences of primary anorectal melanoma after surgery are more commonly distant and lethal. Then, local excision is the appropriate surgical management for localized primary anorectal melanoma. More radical resection and nodal resection may be needed in selected patients with clinically bulky tumor, involved sphincter complex or nodal positive including locoregional and inguinal area.

Author	Year	N	Abdominoperineal resection vs. Local excision			Entire Series	
			Overall recurrence	DFS	OS	DFS	OS
Slingluff et al. (1990)	1974-1990	24	-	-	-	***6.7***	-
Weinstock (1993)	1973-1987	55	-	-	-	***16***	***22***
Brady et al. (1995)	1929-1993	85	-	***NS p=0.11 (27 vs. 5)***	-	***9.4***	***12***
Pessaux et al. (2004)	1977-2002	40	-	-	***NS (30 vs. 19)***	14	***17***
Yeh et al. (2006)	1984-2003	46	***NS (26 vs. 26)***	-	***NS (32 vs.35)***	-	***35***
Ishizone et al. (2008)	1997-2006	79	-	-	***NS***	-	***28.8***
Nilsson et al. (2009)	1960-1999	251	***NS***	-	***NS (7 vs. 15)***	-	***13.6***

Table 3. Summarized of previous studies of primary anorectal melanoma (DFS: Disease free survival, OS: Overall survival, NS: not significant).

6. Surgery of secondary malignant melanoma of GI tract

Survival rate of stage IV melanoma patient is really worse, typically measured in months rather than years. Recurrence is identified about one-third of the patients, most of them recur at the regional nodes. For distant metastasis, almost major organ and tissue can be a site of metastases. Commonly of metastatic image is a wide spreading disease then role of surgical management is often palliative. In a retrospective review of 4,426 patients with stage IV melanoma treated at the John Wayne Cancer Institute, only 35% of all cases underwent surgical resection. These patients had a 5-year overall survival of 23% compared with 6% in those who were not surgical candidates ($p < 0.001$). Surgery with the intent of providing long-term survival should be considered only when all sites of disease can be completely removed. Therefore, a careful evaluation is an importance step of management and for looking to exclude others organ involvement. Regard to palliative intent, patient's status, comorbidities, symptoms and life expectancy are the clues to decide the operative procedure.

Preoperative evaluations include history taking, physical examination and assessment investigation such as ultrasonography, CT scan and MRI are a useful tool to evaluate status of the patients. CT scan is the most commonly used staging modality and has sensitivity about 60%. PET scan seems to have more sensitivity than CT scan, previously the sensitivity was reported in range from 70-100%. There are some reports proposed that the precise preoperative imaging can change surgical decision making 17-48%.

The GI tract is an uncommon site for malignant metastases, only 2-5% of these patients can be detected clinically. However, melanoma is one of the most common tumors that metastasis to GI tract. Small intestine is the most common size. GI metastases are usually associated with disseminated disease. From previously studies, the median survival time is

only 5-11 months in secondary GI melanoma and estimated 5-year survival is usually less than 10%. Depend on the nature of the disease, the intent of surgical treatment usually for palliation. Surgery can relive the symptoms about 70-90% of the group especially obstruction, bleeding and perforation. The morbidities and mortalities of GI surgery are acceptable usually mortality less than 5% from previous studies.

One paper from Memorial Sloan-Kettering Cancer Center reported 68 patients, who underwent surgical exploration for metastatic GI melanoma from total 7965 melanoma patients. The most common presentations are anemia (60%), abdominal pain (59%) and bleeding (44%). Sixty-two from 68 of patients had small bowel involvement. The median survival was estimated to be 8.2 months (6.9-11.4 months). The 1-, 2- and 5-year survivals were 35%, 23% and 18%, respectively. The significant factors from multivariate analysis were included preoperative serum LDH ($p< 0.01$) and residual disease ($p= 0.03$). Ninety percent of the patients had palliation of symptom after surgery.

Another large series of secondary abdominal melanoma from M.D. Anderson, 251 patients was enrolled from the year 1970-1991. The common metastatic organs are small bowel (62%), mesenteric lymph nodes (45%), liver (37%) and stomach and duodenum (31%). The median of interval time after diagnosis was 38.5 months (1-258 months) and 13% of the cases developed intraabdominal recurrence during the first year of follow-up period. The median survival is 8 months in only intestinal metastatic group, 5 months in only visceral metastatic group and 4 months in both metastatic organs group. For palliative surgical resection, the median survival was increase significantly from 5 months in non-surgical group to 11 months in surgical group ($p< 0.0001$). This benefit of the palliative surgical resection is concordant to our study that previously reported. In the 86 patients' subgroup that had severely symptoms, surgergical approach was associated with longer symptom-free periods compared with non-surgical approach significantly ($p< 0.0001$). The multivariate analysis revealed that complete tumor removal, only intestinal metastasis and interval time of recurrence after diagnosis greater than 48 months were significance associated to better overall survival ($p= 0.0001$, $=0.002$, $=0.005$, respectively). Concomitant to most of the reports that supported complete resection, GI tract as a first site of metastasis, longer of disease free interval or interval from diagnosis, and lower level of LDH were associated to better outcomes. Summarized of favorable factors from multivariate analysis was in table 4.

Favorable factors
- Complete removal of the tumor
- Intestinal metastasis without others abdominal visceral involvement
- Interval time of recurrence after diagnosis greater than 48 months
- GI tract as a first site of metastasis
- Presence of extra-abdominal disease
- Preoperative serum LDH level < 200 u/L

Table 4. Summarized of favorable factors from multivariate analysis.

From these data, we can summarized that for secondary GI melanoma, particularly if the GI tract is the first site of metastasis, the curative surgical resection should be strongly considered not only for palliation of symptoms but also for improvement in survival. Although, improvement of survivals is only in the number of months, but surgery can provide significant improvement in quality of life of the patients with acceptable operative morbidity and mortality.

7. Non-surgical management

Over the past 50 years, more than 100 randomized clinical trials have investigated cytotoxic chemotherapeutic agents and immunostimulants such as Bacille Calmette-Guerin (BCG), *Corynebacterium parvum*, and levamisole. Interestingly, nonspecific immunotherapy declined as more active immunostimulatory cytokines, in particular interferon (IFN), came to clinical practice. In this chapter, we briefly presented the alternative management of surgery including chemotherapy, immunotherapy, vaccination and radiation in the setting of adjuvant and metastatic treatment.

7.1 Chemotherapy

Most of the data are in the setting of treatment of metastatic disease. Apart form IL-2, Dacarbazine (DTIC) is one of the two agents that were approved from U.S. Food and Drug Administration (US-FDA) for the treatment of advanced melanoma. The response rate was 19-28% from previous studies. Unfortunately, no any studies demonstrated the benefit of overall survival of DTIC compare to supportive care in the advanced melanoma patients. Temozolomide (TMZ), an analog of DTIC with similar activity, the potential benefit over DTIC is available in oral form. Several studies suggested TMZ is active against CNS metastases. Therefore, TMZ should be considered in the patient with brain metastases although, no difference of overall survival compare to DTIC.

The combination of chemotherapeutic agents have been developed including BOLD (Bleomycin, Vincristine, Lomustine, and DTIC), CVD (Cisplatin, Vinblastine, and DTIC), The Dartmouth regimen (DTIC, Cisplatin, Carmustine, and Tamoxifen). The response rate was improved, but no difference in survivals compare to DTIC alone. Moreover, the toxicity was increased when used of the combine regimens.

7.2 Immunotherapy

High dose of the Interferon α-2b (IFN α-2b) is the only adjuvant therapy for stages II and III cutaneous melanoma that got the approval form US-FDA. Relapse-free survival was significantly prolonged (p= 0.006, HR= 1.30) compared to observational group. Unfortunately, the data did not show a survival benefit. The toxicities considerably affect quality of life over the course of the treatment. The most common toxicity is neutropenia. Interleukin-2 (IL-2) was approved by US-FDA for the treatment of adults with advanced metastatic melanoma. IL-2 toxicity can involve multiple organ system, most significantly cardiovascular, respiratory, and excretory system. Most of the toxicity is related to the capillary leak syndrome. To improve the activity of immunotherapy, combining different chemotherapy agents (Biochemotherapy, BCT) and vaccines has been reported. All of studies concluded that BCT is associated with increased toxicity and the highest response rate is about 50%. A metaanalysis of BCT by the Cochrane Collaboration included 2,625 patients. The response rate is increased in the group of BCT, but no difference in overall survival. (p= 0.31, HR 0.89)

7.3 Vaccines

Melanoma has a unique relationship to the immune system with the development of spontaneous tumor-specific immune responses in patients. For this reason, melanoma has been a frequently targeted disease in the development of cancer vaccines. The various vaccines were used in the treatment of melanoma including DNA vaccine, dendritic cell vaccines, peptide-based vaccines, and viral vaccines. Although vaccines have been

demonstrated to produce immunologic responses, unfortunately, no clinical benefit has been demonstrated in the previous large randomized vaccine trials performed in melanoma in the adjuvant setting.

7.4 Emerging therapeutic agents

Despite of increasing understanding the biology of melanoma, the novel therapeutic agents that developed based on the new knowledge with some demonstrated promising antitumor effect in several clinical trials. Ipilimumab (MDX-010) is an IgG1 antibody. The several of phrase II trials of ipilimumab demonstrated a promising 1-year OS of over 47% and a 2-year OS of over 30% (compare to 25% of 1-year survival from meta-analysis). A double–blinded phrase III randomized study is ongoing. The in depth other agents such as Bevacizumab, Thalidomide is beyond the scope of this review.

The discovery of *BRAF*, *NRAS*, *PTEN* and *KIT* alterations in melanoma has supported the development of various rational therapeutic approaches. Sorafenib, PLX4032, and GSK2118436 are the effective *BRAF* inhibitors. Most of the studies still ongoing, hopefully these new agents may be a novel effective treatment options for the patients with advanced melanoma in the near future.

7.5 Radiotherapy

Although, melanoma is a relatively radio-resistance tumor, undoubtedly, radiation is an effective palliative treatment for the 40 -50% of patients who develop unresectable, locally recurrent, and/or metastatic disease resulting in bone pain, spinal core compression, tumor hemorrhage, and central nervous system dysfunction secondary to cerebral metastases.

8. Conclusion

Malignant melanoma of GI tract is uncommon especially primary GI melanoma. History taking and careful physical examination is the first step of approach to rule out the primary other sources. Skin, eye and rectal examination should be mandatory performed. Investigation including endoscopy, ultrasonography, contrast GI studies, CT scan, MRI, and PET scan can be used for different purposed. Prognosis is quite poor, particularly in secondary GI melanoma. Anorectal melanoma and small bowel is the most common site in the primary and metastatic GI melanoma respectively. Surgery is still the mainstay of the treatment for localized primary disease. Extensive surgical resection is reserved for selected patients. Melanoma is one of the most common tumors that metastasis to GI tract. The median survival is usually less than year and estimated 5-year survival is less than 10%. Palliative surgical resections are recommended for symptoms relieved. Moreover, it can be prolonged survival in the subgroup that completely tumor removal was achieved. Unfortunately, most of the cases after resection will experience recurrence of the diseases. Then, the current adjuvant treatment such as immunotherapy, chemotherapy, targeted therapy, and vaccination may play the important role in this setting.

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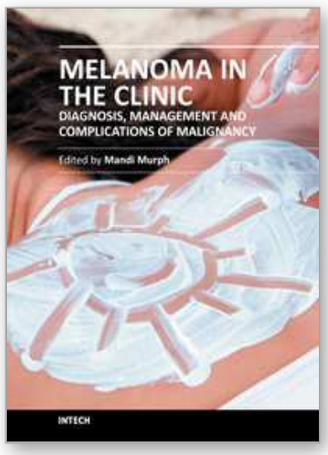

Melanoma in the Clinic - Diagnosis, Management and Complications of Malignancy

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This book provides an excellent overview of how melanoma is treated in the clinic. Since oncologists and clinicians across the globe contributed to this book, each area also explores the unique burdens that geographical areas experience from melanoma subtypes and how these are treated in different settings. It also includes several chapters that illustrate novel methods for diagnosing melanoma in the clinic using new technologies, which are likely to significantly improve outcomes. Several chapters cover surgical techniques and other present very rare or challenging clinical cases of melanoma and how these were treated. The book is geared towards informing clinicians and even patients how melanoma arises, what tools are available and which decisions need to be made by patients and their families in order to treat this devastating disease.

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