Anal Melanoma

Marc Singer, M.D.¹ and Matthew G. Mutch, M.D.¹

ABSTRACT

Anal melanoma is rare and aggressive malignancy. Patients commonly present with advanced, even metastatic disease. Unlike cutaneous melanoma, anal melanoma has no known risk factors. Surgical excision remains the cornerstone of therapy. There are no long-term survivors of stage II or III disease; therefore, early diagnosis and treatment remain crucial. There are no trials definitively proving abdominoperineal resection (APR) or wide local excision (WLE) to yield superior long-term survival. APR may offer a higher rate of local control, whereas WLE offers a much less morbid operation. Adjuvant chemotherapy, interferon, and radiation may offer some benefit.

KEYWORDS: Melanoma, anal, malignancy, abdominoperineal resection, wide local excision

Objectives: Upon completion of this article, the reader should be able to summarize the management of anal melanoma.

Malignant melanoma of the anorectum is a highly aggressive and fortunately, very rare tumor. Surgery is the mainstay of treatment, and adjuvant therapies are of limited value. Despite this, the most appropriate operation remains questionable. The prognosis of anal melanoma remains grim, and additional research is required to understand better the biology and behavior of this disease.

CLINICAL PRESENTATION

Anal melanoma constitutes only 0.5 to 2% of all anorectal malignancies and less than 2% of all melanomas.¹⁻⁸ Anal melanoma is the third most common melanoma after the cutaneous and ocular varieties. It is the most common site for primary gastrointestinal melanoma.⁴ Cutaneous melanoma metastasizes to the gastrointestinal tract only 2% of the time, and of these metastases only 2% are to the rectum.⁹ Metastatic disease to the anus is exceedingly rare. There may be

a higher proportion of anal melanoma among all patients with melanoma.¹⁰ The exact incidence of primary disease is difficult to determine because of the relative rarity and lack of large published cohorts. A sampling of cancer registries in U.S. cities revealed an incidence of 1.7 cases per 1 million per year.⁷

The median age at presentation is 55 years, although the range is wide, 29 to 91.^{1,2,7,11-20} There may be regional variation of anorectal melanoma as with cutaneous melanoma, which is significantly more common in certain areas of the world, such as Australia and New Zealand. The reported incidence of anal melanoma is 0.04% in Australia,⁶ 0.5% in New York City,¹⁶ 1% in Milan,¹⁷ and 1.19% in China.⁴ Cutaneous melanoma is 20 times more common in whites than blacks, but there is no such evidence for anal melanomas. There is a strong association with Caucasian race, as most series have a preponderance of Caucasian subjects. The Memorial Sloan Kettering series was 95% white.¹⁶ Perhaps this was a result of

¹Section of Colon and Rectal Surgery, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri.

Address for correspondence and reprint requests: Matthew G. Mutch, M.D., Section of Colon and Rectal Surgery, Department of Surgery, Washington University School of Medicine, 660 S. Euclid Ave., Box 8109, St. Louis, MO 63110-1010. E-mail: mutchm@wudosis.wustl.edu.

Uncommon Colorectal Neoplasms; Guest Editor, Matthew G. Mutch, M.D.

Clin Colon Rectal Surg 2006;19:78-87. Copyright © 2006 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.
DOI 10.1055/s-2006-942348. ISSN 1531-0043.

the referral pattern; however, there have not been adequate population-based studies to draw definitive conclusions. There may be a female predominance, as some authors report,^{11,21} but individual series are too small to make definitive conclusions, and most publications do not suggest significant gender differences.^{5,7,15,22}

ETIOLOGY

All melanomas, whether cutaneous or mucosal in origin, originate from melanocytes, which are cells derived from the embryologic neural crest. During fetal development, these cells migrate to many sites throughout the body, primarily to the skin. However, melanocytes also reside in the eyes (retina and uveal tract) and mucosal surfaces (head and neck, anorectum, female genitalia). The melanocytes are subjected to carcinogenic stimuli and subsequently undergo malignant transformation into melanoma. It is well documented that the risk of cutaneous melanoma is increased with exposure to sunlight, particularly ultraviolet B (UVB) radiation.²³ It is also clear that individuals with fair complexions who receive intermittent sunburns are at the highest risk for developing cutaneous melanoma. As the anal mucosa is essentially never exposed to sunlight, it is not obvious what triggers the development of anal melanoma. In addition, other known risk factors for cutaneous melanoma, such as dysplastic nevus syndrome or xeroderma pigmentosum, have no known association with anal melanoma.

Many appear without pigmentation, and 20% are truly amelanotic on histologic examination.^{11,16,24,25} Melanin pigment within the malignant cells is the basis for histologic diagnosis. The appearance of junctional changes, that is, the presence of atypical epidermoid cells or pleomorphic spindle cells adjacent to the focus of malignant tumor, helps to make the diagnosis.²⁶ Junctional changes may be difficult to identify in the ulcerated lesions. Without melanin or junctional changes, traditional histology may not be adequate to make a diagnosis, in which case immunohistochemistry may be helpful. Melanoma antigens S-100, HMB-45, and vimentin are stained positively in 78, 94, and 100% of tumors.²⁵ Polyclonal antiserum to carcinoembryonic antigen (CEA) and monoclonal antibodies to CEA can help to distinguish it from a poorly differentiated epidermoid carcinoma.

DIAGNOSIS

The most common presenting complaints of patients with anal melanoma are bleeding, anal pain, anal mass, pruritus, tenesmus, and change in bowel habits.^{4,13,15,16,20,22,24,25,27} If metastatic disease is present, symptoms may include weight loss, anemia, fatigue,

groin masses, pelvic masses, or even bowel obstruction. The most common symptom is bleeding, which should initiate an evaluation of the entire colon and rectum. The highest risk age group for anal melanoma is similar to the demographic of patients at risk for adenocarcinoma of the colon or rectum. Although anal melanoma is rare, adenocarcinoma is common; therefore, patients presenting with bleeding should undergo a complete examination of the colon and rectum.

Patients with anal melanoma often suffer a delay in diagnosis, which occurs for a variety of reasons. First, patients tend to delay presentation to their doctors. Patients commonly report symptoms for 4 to 6 months prior to presentation.¹¹ It is not possible to know whether this delay would have changed outcomes, but it certainly suggests that patients do not perceive these symptoms as urgent. Second, patients cannot see asymptomatic lesions. Many patients may even be aware of the "ABCD" (asymmetry, borders, color, and diameter) of screening for cutaneous melanoma, but they cannot see anal lesions; therefore, the screening tool simply does not apply. Finally, the symptoms of anal melanoma are commonly misdiagnosed as those of other anorectal pathologies such as hemorrhoids, skin tags, or polyps.²⁸

A timely diagnosis of anal melanoma is made even more difficult by the fact that up to 80% of lesions lack obvious pigmentation and up to 20% of tumors are even histologically amelanotic.^{22,29} Physicians should obtain biopsies of any suspicious lesions that do not respond to simple treatments. Anal melanoma may be discovered at the time of screening endoscopy for unrelated symptoms. Rarely, melanoma can be identified during the routine pathology examination of a hemorrhoidectomy specimen.¹⁸

Because of the delays in diagnosis and the aggressive nature of the disease, patients with anal melanoma frequently present with advanced disease. Melanoma spreads locally but normally is not so aggressive as to invade the prostate or bladder. The lesions are usually polypoid, ranging in size from 1 to 6 cm. The tumors are generally more than 1 cm thick at diagnosis. Ulceration is also quite common.^{24,25,30} Lymphatic spread to the inguinal or inferior mesenteric nodal basins is common. Weyandt et al reported that 32% of patients have metastatic disease at the time of diagnosis.¹⁸ The most common sites for metastases are inguinal lymph nodes, mesenteric lymph nodes, hypogastric lymph nodes, para-aortic lymph nodes, liver, lung, skin, and brain.^{22,24}

Anorectal melanoma arises from the anus, and diagnosis can be made with visual inspection and anoscopy. Very rarely, melanoma can arise within the rectum, without any anal or cutaneous disease. There are a small number of case reports of primary rectal melanoma.³¹⁻³⁴ Rectal melanoma arises like other rectal tumors, with symptoms such as constipation, bleeding,

and change in stool caliber. These symptoms are best evaluated with endoscopy and biopsy, although one recent article described the use of computed tomography (CT) scanning to diagnose primary rectal melanoma in eight patients.³⁵ CT scanning is certainly not the preferred diagnostic modality to evaluate hematochezia or alteration in bowel habit; however, this review documented the ability of the CT scan to identify lymphadenopathy correctly in all eight of these patients. This may prove to be a valuable tool in the assessment of regional disease, especially if additional treatment modalities, such as chemotherapy or radiation therapy, are being considered.

Metastatic disease is likely to occur in the liver, lung, or pelvis, and imaging should be directed at these systems. Ultrasonography has become an important staging tool for rectal adenocarcinoma, but its role in melanoma remains unclear. Limited numbers of patients have been reported, and the influence on treatment or outcome is unknown.² Positron emission tomography (PET) is useful for staging cutaneous melanoma and may be helpful for staging of anorectal melanoma. In published series, the sensitivity was 74 to 100% and specificity 67 to 100%.³⁶

The staging of anal melanoma differs from that of cutaneous melanoma, which is based primarily on thickness in millimeters (Breslow classification). Anal melanoma is staged on a clinical basis, focusing on locoregional and distant spread. Stage I is local disease only, stage II is a local disease with regional lymph nodes, and stage III is distant metastatic disease.

TREATMENT

The treatment of anal melanoma, unfortunately, is only moderately successful. Surgery remains the cornerstone of treatment. Chemotherapy, radiation therapy, and immune therapy have a limited role. The role of lymphadenectomy is not well defined.

Surgery

Surgical excision remains the primary treatment of anal melanoma. In addition, surgery plays an important role in palliative care and management of locally recurrent disease. There is no doubt that with the current state of chemotherapy, radiation therapy, and immune therapy, surgical excision provides the best chance of curing this aggressive disease. The only uncertainty is the extent of excision, that is, a limited excision (wide local excision [WLE]) or radical excision (abdominal perineal resection [APR]). There is a lack of prospective or randomized data to allow meaningful conclusions. There are no randomized, comparative trials, rather, only retrospective reviews and institutional case series, most of which are relatively small in number and contain limited

follow-up. The rarity of this disease and the limited number of patients who present with stage I disease have prevented definitive trials examining the optimal treatment of curable anal melanoma. In addition, much information has been derived or extrapolated from the cutaneous melanoma literature, which is not always a valid comparison. A well-conducted, adequately powered randomized trial may never occur because of the relative infrequency of this entity. The decision remains unclear.

The majority of patients are diagnosed at a relatively late course in their disease, and therefore curative surgery is simply not possible for these patients. Although APR carries the theoretical benefits of a wider excision and mesenteric lymphadenectomy, the clinical superiority of this operation has never been authoritatively proved in a prospective fashion. It is true that a majority of long-term survivors have been treated with APR, but this type of retrospective comparison cannot be considered definitive.^{5,15,16,22,24,30,37-39} WLE offers patients a seemingly equivalent opportunity for cure with significantly less morbidity and avoidance of a permanent colostomy. There are many issues to consider for the individual patient. Anal melanoma recurs early and frequently includes distant metastasis. This fact is independent of the method of excision of the primary tumor. The prognosis is generally poor. Are the known disadvantages of longer hospital stay, increased postoperative morbidity, and need for permanent colostomy justified? Is radical surgery appropriate in this scenario? Local excision carries minimal morbidity or mortality; however, regional disease is not addressed, and this may not provide adequate local control or palliation for large bulky tumors. A review of the evolution of treatment and publications may be helpful in understanding this debate and in decision making for the future. The main focus of this debate revolves around the extent of excision, that is, APR versus WLE, as the preferred treatment for curable disease. There are no reported cases of long-term survivors of stage II/III disease. Surgery for those patients must be centered on local control and palliation of symptoms until adjuvant therapy is improved.

For many years, it was believed that only a radical excision could potentially cure anal melanoma. Many authors recommended APR as the only definitive surgical cure.^{13,15,16,38,40} The purported benefits included wide margins and excision of mesenteric lymph node drainage. Some surgeons even advocated pelvic exenteration.⁴¹ More recently, some authors, many from large cancer centers, have suggested that WLE may be as efficacious as APR, with significantly fewer perioperative morbidities.^{1,2,15,16,27,30,37,42,43}

Moore first described anorectal melanoma and its treatment with local excision in 1857.⁴⁴ In 1931, Miles reported the outcome of three patients with anal melanoma. He performed APR on these patients, all of

whom died of their disease. He concluded that anal melanoma should not be treated with the operation that came to bear his name.⁴⁵

Years later, a series of authors advocated aggressive, radical surgery. In 1967 Pack and Oropeza described their experience with 20 patients diagnosed with anorectal melanoma.^{14,29} They suggested that APR in combination with bilateral inguinal lymphadenectomy was the optimal treatment. The basis for their recommendation was twofold. First, anorectal melanoma spreads through inguinal as well as mesenteric lymph nodes; therefore, inguinal lymphadenectomy was an essential component of a curative resection. Second, anal melanoma is an aggressive tumor that metastasizes early and is difficult to cure when lymphatic spread occurs. They believed that observation of normal lymph nodes until they became clinically suspicious would miss the short window of opportunity to cure these patients. Only 1 of 20 patients in their study survived more than 5 years, and this patient underwent APR with bilateral inguinal lymph node dissection.⁵

The issue of inguinal dissection was not settled. Shortly after Pack's endorsement of inguinal lymphadenectomy, Quan and Deddish described a higher incidence of mesenteric lymph node metastasis compared with groin lymph node metastasis. For this reason, they recommended APR alone as the best potentially curative surgery.^{5,12}

In 1980, Chiu and colleagues from the Mayo Clinic reported a series of 33 patients with anorectal melanoma, including 10 who underwent WLE and 19 who underwent APR. Only four patients survived more than 2 years, all of whom were treated with APR.³⁸ These data seemed to confirm that APR offered the best chance of curative excision, and by this time APR had very much become the standard of care for anal melanoma.

After this publication, however, during the 1980s, the value of radical excision of anal melanoma was questioned, as relatively few patients survived in the long term and the majority of patients died of metastatic disease. For these reasons, WLE was being considered by several investigators.

Cooper and colleagues²⁴ at the University of Virginia reviewed 12 of their own patients as well as 255 additional patients identified from the literature in 1982. They evaluated patients treated with APR as well as those treated with WLE and found no difference in 3-year (31 versus 20%) or 5-year survival (21 versus 16%). Sixty percent of patients suffered metastatic disease at the time of presentation. Mesenteric lymph node metastases were identified in 69% of patients who underwent APR. Neither the size of the tumor at diagnosis nor the method of treatment affected survival. These authors concluded that APR was not the preferred operation because most patients presented with meta-

static disease and excision of mesenteric nodes did not improve the overall survival at 3 or 5 years follow-up. The fact that 69% of patients had mesenteric lymph node disease provides some support for performing APR because WLE would fail to address this nodal disease in a large proportion of patients. However, because there was no significant difference in short- or long-term survival, perhaps it is best to consider APR as a palliative operation for patients with stage II/III disease. If so, APR seems too invasive and aggressive as palliation. The goal should be relief of symptoms. A highly invasive operation with high morbidity and permanent colostomy hardly seems like reasonable palliation.

The following year, Siegal et al³⁹ reported similar survival for patients in Israel treated with APR and WLE. Interestingly, this cohort included two long-term survivors treated by WLE. This publication described a strong relationship between survival and clinical stage. Survival for stage I patients was 48 months, stage II was 12 months, and stage III was 10 months. The authors concluded that APR was rarely indicated because it did not improve survival; rather, the stage at presentation was the main determinant of clinical outcome. Also significant was the documentation that WLE can serve as a curative operation in selected patients.

Ward et al published a discussion of the therapy offered to 21 anal melanoma patients in England over a 44-year interval. Patients were treated with APR during the first 24 years, and the subsequent patients were treated with WLE. There were no differences in survival related to the type of surgical treatment. The authors concluded that APR, with its associated morbidities, is not recommended and that WLE with a 2-cm margin provides adequate local control.⁴⁶

In 1990, Ross et al reported a review of the experience at M.D. Anderson Cancer Center with 32 melanoma patients. The authors identified a trend toward improved locoregional control with APR (42% recurrence) compared with WLE (71% recurrence) but no improvement in survival (19.5 months APR versus 18.0 months WLE). Nine of 11 patients with local recurrence also experienced distant metastasis. This cohort again demonstrates that anorectal melanoma recurs early, with a very high incidence of distant metastasis regardless of the choice of local therapy, suggesting that APR provides an unfavorable burden of morbidity compared with its long-term benefits.³⁷

It had become clearer that APR did not offer a significantly better chance of survival despite the increased costs to the patients. However, many centers continue to offer APR as the best chance of curative surgery. For this reason, in 2003, the University of Minnesota group examined their own results. Bullard et al conducted a retrospective review, which identified 15 patients with a mean follow-up of 25 months. Four of

these patients underwent APR, and 11 underwent WLE. In the WLE patients, tumor excision was performed so that a 1- to 2-cm margin of grossly normal skin was removed with the melanoma. One of these patients had obvious lymphadenopathy and therefore also underwent therapeutic inguinal dissections. There were no significant differences between the APR and WLE groups with respect to overall survival (25 versus 64%), local recurrence (50 versus 18%), regional recurrence (25 versus 27%), or distant recurrences (75 versus 36%), although the numbers were small, especially in the APR group. Mean disease-free survival was 10 months in the APR group and 14 months in the local excision group. All of the patients who survived more than 2 years underwent local excision as their first operation. Two patients who underwent WLE experienced isolated regional metastasis and subsequently underwent therapeutic lymph node dissections and adjuvant therapy. These patients are disease free for more than 5 years. This suggests that locoregional recurrences can be resected for cure. The authors concluded that a policy of WLE as the primary treatment minimized the morbidity and mortality without affecting recurrence or survival. Most recurrences occurred systemically, independent of the surgical treatment of the primary disease; therefore, WLE is their treatment of choice unless the primary tumor is found to invade the sphincter or is circumferential.²

In 2003, Weyandt et al¹⁸ expressed significant concern that WLE could lead to a higher rate of local recurrence with significant symptoms of incontinence, chronic bleeding, and so forth. To examine the results of WLE, they reviewed the outcomes of 19 patients. Outcomes were not related to the management of the primary tumor; however, a trend was identified related to tumor depth. It seemed that prognosis was related to tumor thickness at the time of presentation. This may represent selection bias because more patients with thicker lesions underwent APR compared with WLE. The effect on survival remains unclear.

Pessaux and colleagues¹¹ at the Institut Gustave Roussy in France reviewed their records of 40 patients treated from 1977 to 2002. They examined the survival and responses to surgical therapy. The average duration of symptoms was 6 months in this group. Nine of 40 (23%) tumors were amelanotic. Twenty-four patients were stage I, 6 were stage II, and 10 were stage III at the time of diagnosis. Patients with stage I or II disease underwent potentially curative APR (9) or WLE (21). Morbidity after APR and WLE was similar, although the length of hospital stay was significantly longer for the APR patients. The overall 5-year survival for the entire cohort was 17%. The 5-year survival for stage I patients was 24%, and there were no survivors with advanced disease. There was no difference in survival between patients who had undergone WLE or APR (16 versus

2%). Local recurrence was more common in the WLE patients (48%) than the APR patients (22%). Significant associations were found between survival and duration of symptoms, inguinal lymphadenopathy, stage of disease at time of diagnosis, and the presence of amelanotic melanoma, probably related to a delay in diagnosis. Pessaux et al recommend WLE as the preferred treatment, reserving APR for lesions not amenable to WLE or for salvage surgery. Lymph node dissection did not improve survival but did incur significant morbidities.^{17,21,40}

In a recently published review, Yap and Neary⁴⁷ reviewed the results of 17 previously published case series. The median survival for all patients was 20 months (10 to 30 months). These 17 studies revealed 5-year survival to be 0 to 22% for WLE compared with 0 to 25% for APR. The recommended procedure varied by study, and there was no definitive conclusion. Kaplan-Meier analysis of the two largest studies^{1,42} suggested that there was no difference in 5-year survival for stage I or II patients treated with APR or WLE. Most studies in the review suggested that APR does not confer survival advantage and should be reserved for lesions not amenable to local excision or as palliation for obstructing lesions.⁴⁷

In 2005, Droesch et al²⁰ performed a systematic review of published studies regarding the treatment of local or locoregional anal melanoma. Twenty-two studies, which included 533 patients, were identified. This represents the largest cumulative review to date. Within these data, median survival data were available such that a comparison was made for 301 patients undergoing resection (129 WLE, 172 APR). The median survival was 21 months for the WLE patients compared with 17 months for the APR patients. This is not a statistically significant difference. One hundred ninety-six patients underwent resection with curative intent (96 WLE, 100 APR). Local recurrence was 47% for WLE versus 23% for APR. The authors elected to use median survival, as opposed to 5-year survival, because most of the patients were dead before 5 years and the authors believed it not to be as useful a statistic. The improved survival of stage I patients may be due to the lower postoperative mortality with WLE or to selection bias of less aggressive disease toward WLE. The tumor- and patient-related characteristics required to define this were not included in the analysis. Although local recurrence was higher in WLE, there was no difference in survival. This review does not examine quality of life measures. Because the survival of the two treatment groups was similar, the quality of life becomes even more important. It seems likely that the APR patients, with associated perineal wound and stoma complications, would have greater morbidity. The authors concluded that WLE should be the initial treatment of choice for early-stage disease. APR should be

reserved for recurrent or more advanced disease. The most significant factor arguing against APR as the preferred surgical approach is that there are very few, if any, long-term survivors who have node-positive disease. As a result, it becomes difficult to argue that radical excision of the rectum and clearance of the mesorectal lymph nodes is beneficial.

These series indicate that there may be higher local recurrence with WLE, but local recurrence does not usually cause severe local symptoms; therefore, close surveillance and aggressive reexcision seem like a plausible option to minimize local disease. It is metastatic disease that ultimately causes the death of most patients, and future research should be directed to that.

Lymphadenectomy/Sentinel Lymph Node Dissection

Lymph node dissection may be indicated in clinical apparent disease or for occult disease identified with sentinel lymph node (SLN) techniques. SLN dissection has largely been accepted as the standard of care for intermediate-thickness cutaneous melanoma.^{48,49} The experience with cutaneous melanoma has revealed a survival benefit if lymph node dissection is performed.^{50–53} SLN dissection has been used with anorectal melanoma.² A few case reports exist regarding the technical feasibility of sentinel node biopsy with anorectal melanoma,⁵⁴ but the efficacy remains unknown. Sentinel node biopsy may detect clinically unapparent groin adenopathy, and the subsequent inguinal dissection may provide a curative resection for a small subset of patients. It is technically feasible, but the numbers are too small to draw any meaningful conclusions at this time.

Adjuvant Therapies

There are no standards regarding systemic therapy for disseminated disease. Reports are scarce, and efficacy and toxicities are largely unknown. There are many strategies aimed at local control of anal melanoma but few palliative techniques.

VACCINES

Vaccines have been examined with some mixed results. This remains an area of significant research effort and may play an important part of the nonoperative treatment of melanoma in the future. There are not sufficient data for anorectal melanoma.^{55–60}

CHEMOTHERAPY

The role of chemotherapy for melanoma remains unclear. Many agents have been employed, including dacarbazine, vincristine, nimustine, bacillus Calmette-Guérin, levamisole, and interferon. None of these

have shown a significant survival benefit in cutaneous melanoma, and certainly no group has proved the utility of any regimen for anorectal melanoma.^{61–67} Dacarbazine is the most commonly studied agent, but response rates are only about 20%. Similarly, combination chemotherapy had poor results.⁶⁸ Immunotherapy may be helpful⁵¹ in the future. Some authors advocate using adjuvant chemotherapy,⁶⁹ whereas some reserve chemotherapy for palliative efforts only.^{14,17,22} There are some case reports of good outcomes with chemotherapy.⁷⁰

Biochemotherapy refers to the administration of both a biologic agent and a traditional cytotoxic chemotherapeutic agent. This strategy has been used successfully to treat metastatic cutaneous melanoma^{71–73} with overall response rates of 40 to 60%. In fact, complete response can be achieved in 5 to 20% of patients. Ten percent of patients receiving interleukin-2 (IL-2) survived more than 5 years.⁷² A prospective trial demonstrated that patients receiving biochemotherapy enjoyed improved survival and disease-free survival compared with patients receiving chemotherapy alone.⁷³ On the basis of these results in the treatment of cutaneous melanoma, Kim and colleagues⁷⁴ from M.D. Anderson Cancer Center reviewed their experience in the treatment of metastatic anal melanoma with biochemotherapy. Thirty-nine patients treated from 1991 to 2001 were identified, and 18 of the patients had undergone biochemotherapy, with at least one chemotherapeutic agent and one biologic agent (either interferon α -2b or IL-2). Chemotherapeutic agents included cisplatin, vinblastine, dacarbazine, and temozolomide. All patients had either distant metastatic disease or bulky primary tumors with lymph node involvement. Thirteen patients received biochemotherapy as first-line treatment, and 14 patients received cisplatin, vinblastine, dacarbazine, interferon, and IL-2, all administered either concurrently or sequentially. Forty-four percent had major responses, including two patients (11%) who had complete responses. No patient with metastatic anorectal melanoma has ever been documented to survive more than 5 years; however, the median survival in this series was 12 months, somewhat longer than the previously reported 4 to 9 months.^{1,7,22,27,30,39,42} This emphasizes the importance of clinical and experimental studies to elucidate further the molecular biology of mucosal melanomas so as to develop effective treatments. Biochemotherapy represents the best available adjuvant therapy after surgery and should be considered in the treatment of advanced or metastatic anorectal melanoma.

INTERFERON

Lens and Dawes⁶⁷ conducted a systematic review of randomized controlled trials comparing regimens with

and without interferon α . Interferon α has antitumor effects related to a combination of direct activities and indirect immune-mediated effects. The side effects of this therapy are significant. The review found that there may be some benefit in the treatment of cutaneous melanoma, but the side effects are significant, and no standard treatment regimen has been established. There is insufficient evidence to draw any conclusions regarding its efficacy in the treatment of anal melanoma.

Ulmer et al⁷⁰ presented an interesting case study that described a method of palliation that employed intratumoral injections of interferon β along with systemic dacarbazine. An 80-year-old woman was treated for a painful, bleeding, 3-cm melanoma situated between the anus and vagina. Anoscopy revealed circumferential involvement of the anal canal. She also had metastatic disease to bilateral inguinal lymph nodes, an iliac lymph node, a pararectal lymph node, and both lungs. Systemic chemotherapy with dacarbazine was initiated, and the tumor was injected with natural interferon β . Other than mild fever, there were no side effects. A second cycle was administered and a third cycle 4 weeks later. The perineal tumor significantly decreased in size and her local symptoms were controlled. CT scan showed complete remission of pulmonary metastases and partial remission of the lymph node metastases. The perianal lesions were biopsied, and no melanoma cells could be identified. This treatment regimen controlled the disease for 2½ years. Other than APR, there are few effective choices for palliation of symptomatic lesions. This case provides encouraging, albeit limited, results. In addition to the local control of the primary tumor in this case, the unexpected benefit of resolution of the pulmonary metastases was found. It is impossible to know whether this was due to the interferon, the dacarbazine, or the combination. Interferon is absorbed through lymphatics; therefore a systemic effect is possible. This may represent an alternative, less invasive, palliative treatment option rather than APR.

RADIATION THERAPY

The use of radiation as part of the management of anorectal melanoma has been reported,^{2,75} but its utility remains unclear. Its use has been demonstrated to improve locoregional control in cutaneous melanoma in the head and neck, axilla, and vagina.^{76–80}

Ballo et al¹⁹ evaluated a treatment strategy that included local excision followed by postoperative radiation therapy at the M.D. Anderson Cancer Center. Twenty-three patients underwent local excision, with or without inguinal lymphadenectomy, and postoperative irradiation with 30 Gy (five fractions over 2½ weeks). In addition, nine patients underwent systemic chemotherapy with one or more agents (cisplatin, vinblastine, dacarbazine, IL-2, interferon). Actuarial 5-year survival

was 31% and disease-free survival was 37%. If nodes were involved, actuarial 5-year survival was 0% and 5-year local control rate was 74%. This compares with the local control rate offered to many series of patients treated with APR.^{1,16,22,30,37,43,81} This strategy does not offer an improvement in survival but certainly can change the quality of life for patients by avoiding a major operation and permanent colostomy. Radiation therapy of the primary lesion as well as the inguinal and pericolic lymph nodes seems important for the locoregional control of this disease. This regimen can be delivered quickly, with minimal toxicity and maintenance of sphincter function, which are all important factors in a cohort with a survival of less than 2 years.

Moozar et al⁸² reviewed the experience at a large Canadian referral center to examine the effects of surgery, radiation, or combination therapy. Fourteen patients (10 treated with WLE, 4 treated with APR) were identified with at least 28 months follow-up. Seven patients received pelvic irradiation, using 20 to 50 Gy, with three patients receiving concomitant chemotherapy with 5-fluorouracil. Overall survival was 12 months. The radiated patients had median survival of 16 months, versus 5 months for surgery alone. In this series, the addition of radiotherapy did not change local recurrence. Three patients were treated with preoperative radiotherapy, but this had little effect on tumor burden. There were no differences in survival in patients undergoing surgery versus those undergoing surgery and radiation therapy. The authors suggested that radiation should be considered for local control.

Another method of local control is electrochemotherapy, which consists of electrical stimulation to the tissues creating a transient permeabilization of the plasma membrane. Theoretically, this allows direct access of the chemotherapeutic agents into the cytosol of tumor cells. This is a treatment known to provide effective local control of cutaneous melanoma by using electroporation for enhancing drug delivery into the tumor.^{83,84} Snoj et al⁸⁵ described extensive treatment of a 52-year-old patient with anorectal melanoma diagnosed after an excisional hemorrhoidectomy. There was residual tumor, and a sphincter-saving excision was not possible because of the location at the anal verge. Staging with a CT scan identified large inguinal nodes in the groin, which were biopsy-proven metastases. The patient was then treated with a deep lymph node dissection and simultaneous electrochemotherapy to the primary lesion was performed. Cisplatin was dissolved in water, and a total of 6 mg was injected directly into the lesion; a total of five applications of electric pulses with a needle electrode were used. After 1 month, the tumor had regressed significantly in size, and the electrochemotherapy was repeated. The lesion subsequently became necrotic and ulcerated, and 3 weeks later a sphincter-saving local excision was performed. This was followed

2 months later by intracavitary radiotherapy delivering 10 Gy to the resection site using ^{127}Cs . Subsequently, an in-transit metastasis was identified in the perineum, which was excised and externally irradiated with 50 Gy. Four months later, left inguinal adenopathy was identified and treated with deep inguinal dissection and postoperatively irradiated with 46 Gy. A short period later, a metastasis was discovered to the right inguinal region that was treated with four cycles of dacarbazine. Fourteen months after initial diagnosis, the patient was without signs of local recurrence and no incontinence. Because local excision results in a high local and regional recurrence rate, new treatment options were considered. The authors suggested that this treatment with electrochemotherapy allowed conversion of APR to WLE. They further hypothesized that the application of electric pulses to the tumor increases drug delivery into the tumor cells. Although this approach to therapy required multiple additional operations and chemoradiation therapy and its overall success is unclear, it did allow the surgeons to perform a WLE versus an APR. As the operative approach does not seem to change survival, avoidance of a colostomy may be a significant consideration in treatment, and this electrochemotherapy may be one consideration.

PROGNOSIS

Five-year survival for all patients with anal melanoma is only 3 to 22%.^{1,4,7,13,16,17,22,30} Survival in patients with recurrent or metastatic disease is less than 10 months.^{1,7,16,22,30,42} There are no reported cases of long-term survivors if metastatic disease, including inguinal lymph node metastasis, is present. Interestingly, about two thirds of the long-term survivors of anal melanomas are women. This may be a result of selection bias inherent in retrospective reviews.^{7,14-16,22,24,30,37-39} Survival is primarily predicted by the status of regional and distant spread and not method of surgery for local control. It would be desirable to identify other factors preoperatively, or at the time of diagnosis, that would allow better selection of patients to avoid extensive pelvic surgery on patients with little or no chance of cure.

One such factor may be tumor thickness, which is well known to be a prognostic factor for cutaneous melanoma. Wanebo and colleagues¹³ analyzed the results of 33 patients treated at Memorial Sloan Kettering Cancer Center for anorectal melanoma. They again found that APR or WLE did not influence survival. They did identify a trend toward longer survival for patients without nodal disease. In addition, there was a correlation between tumor thickness in millimeters and clinical outcome. All four of their patients who survived more than 5 years were found to have tumors less than 2 mm thick. Also, patients with tumor thickness of 2 to

3 mm had a median survival of 33 months, and patients with tumors larger than 3 mm survived only 8 months. Tumor thickness is a characteristic that can be identified on the preoperative biopsy and therefore may be useful when deciding the most appropriate surgical therapy.

Years later, Brady et al¹⁶ reevaluated the Memorial Sloan Kettering patient cohort and confirmed that lymph node disease did in fact predict poor survival. Considering these two important pieces of information, they recommended APR only for patients without evidence of node metastases and tumors smaller than 2 mm. These patients had the best chance of long-term survival; therefore, more radical surgery would be justified. For tumors with poor prognostic factors, local excision may be the most appropriate therapy, to maintain local control while sparing the morbidity of APR and need for permanent colostomy.

CONCLUSIONS

Anal melanoma is an aggressive malignancy. Patients frequently present with advanced disease. Several small series suggest that APR and WLE afford patients the same long-term outcome. APR may offer a higher rate of local control, whereas WLE offers a much less morbid operation. If diagnosed early (stage I) and treated with postoperative chemotherapy or radiation therapy, patients may have a reasonable prognosis. However, there are no long-term survivors of stage II or III disease undergoing surgery alone. Because anal melanoma recurs so rapidly and there is no proven benefit of performing APR, it should be reserved only for recurrent disease, patients' preference, or inability to perform a WLE successfully. Biochemotherapy or radiation therapy, or both, in addition to surgery is likely to provide the best available treatment options for metastatic disease.

REFERENCES

1. Roumen RMH. Anorectal melanoma in the Netherlands: a report of 63 patients. *Eur J Surg Oncol* 1996;22:598-601
2. Bullard KM, Tuttle TM, Rothenberger DA, et al. Surgical therapy for anorectal melanoma. *J Am Coll Surg* 2003;196:206-211
3. Molino D, Perrotti P, Antropoli C, et al. Primary anorectal melanoma. *Chir Ital* 2000;52:329-334
4. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. *Cancer* 1998;83:1664-1678
5. Pack GT, Lenson N, Gerber DM. Regional distribution of moles and melanomas. *Arch Surg* 1952;65:862-870
6. Miller BJ, Rutherford LF, McLeod GR, Cohen JR. Where the sun never shines: anorectal melanoma. *Aust NZ J Surg* 1997;67:846-848

7. Weinstock M. Epidemiology and prognosis of anorectal melanoma. *Gastroenterology* 1993;104:174-178
8. Husa A, Hockerstedt K. Anorectal malignant melanoma. A report of fourteen cases. *Acta Chir Scand* 1974;140:68-72
9. Ollila DW, Essner R, Wanek LA, Morton DL. Surgical resection for melanoma metastatic to the gastrointestinal tract. *Arch Surg* 1996;131:975-980
10. Pandey M, Mathew A, Abraham EK, Ahamed IM, Nair KM. Primary malignant melanoma of the mucous membranes. *Eur J Surg Oncol* 1998;24:303-307
11. Pessaux P, Pocard M, Elias D, et al. Surgical management of primary anorectal melanoma. *Br J Surg* 2004;91:1183-1187
12. Quan S, Deddish M. Noncutaneous melanoma: malignant melanoma of the anorectum. *CA Cancer J Clin* 1966;16:111-114
13. Wanebo HJ, Woodruff JM, Farr GH, Quan SH. Anorectal melanoma. *Cancer* 1981;47:1891-1900
14. Pack GT, Oropeza R. A comparative study of melanoma and epidermoid carcinoma of the anal canal: a review of 20 melanomas and 29 epidermoid carcinomas (1930-1965). *Dis Colon Rectum* 1967;10:161-176
15. Abbas JS, Karakousis CP, Holyoke ED. Anorectal melanoma: clinical features, recurrence and patient survival. *Int Surg* 1980;65:423-426
16. Brady MS, Kavolius JP, Quan SHQ. Anorectal melanoma: a 64-year experience at Memorial Sloan Kettering Cancer Center. *Dis Colon Rectum* 1995;38:146-151
17. Rossetti C, Koukouras D, Eboli M, et al. Primary anorectal melanomas: an institutional experience. *J Exp Clin Cancer Res* 1997;16:81-85
18. Weyandt GH, Eggert AO, Houf M, et al. Anorectal melanoma: surgical management guidelines according to tumour thickness. *Br J Cancer* 2003;89:2019-2022
19. Ballo MT, Gershenwald JE, Zagars GK, et al. Sphincter sparing local excision and adjuvant radiation for anorectal melanoma. *J Clin Oncol* 2002;20:4555-4558
20. Droesch JT, Flum DR, Mann GN. Wide local excision or abdominoperineal resection as the initial treatment for anorectal melanoma? *Am J Surg* 2005;189:446-449
21. Cagir B, Whiteford MH, Topham A, Rakinic J, Fry RD. Changing epidemiology of anorectal melanoma. *Dis Colon Rectum* 1999;42:1203-1208
22. Slingluff C, Collmer R, Seigler H. Anorectal melanoma: clinical characteristics and results of surgical management in twenty-four patients. *Surgery* 1990;107:1-9
23. Gilchrist BA, Eller MS, Geller AC, et al. The pathogenesis of melanoma induced by ultraviolet radiation. *N Engl J Med* 1999;340:1341-1347
24. Cooper PH, Mills SE, Allen MS Jr. Malignant melanoma of the anus: report of 12 patients and analysis of 255 additional cases. *Dis Colon Rectum* 1982;25:693-703
25. Ben-Izhak O, Bar-Chana M, Sussman L, Dobiner V, et al. Ki67 antigen and PCNA proliferation markers predict survival in anorectal malignant melanoma. *Histopathology* 2002;41:519-525
26. Mutch MG, Roberts PL. Anal and peri-anal melanoma. *Clin Colon Rectal Surg* 2002;15:271-276
27. Antoniuk PM, Tjandra JJ, Webb BW, et al. Anorectal malignant melanoma has a poor prognosis. *Int J Colorectal Dis* 1993;8:81-86
28. Felz MW, Winburn GB, Kallab AM, et al. Anal melanoma: an aggressive malignancy masquerading as hemorrhoids. *South Med J* 2001;94:880-885
29. Morson BC, Volkstadt H. Malignant melanoma of the anal canal. *J Clin Pathol* 1963;1:126-132
30. Goldman S, Glimelius B, Pahlman L. Anorectal malignant melanoma in Sweden: report of 49 patients. *Dis Colon Rectum* 1990;33:874-877
31. Hazzan D, Reissman P, Halak M, Resnick MB, Lotem M, Shiloni E. Primary rectal malignant melanoma: report of two cases. *Tech Coloproctol* 2001;5:51-54
32. Nicholson AG, Cox PM, Marks CG, Cook MG. Primary malignant melanoma of the rectum. *Histopathology* 1993;22:261-264
33. Nozoe T, Anai H. Amelanotic malignant melanoma of the rectum: report of a case. *Surg Today* 2001;31:527-529
34. Werdin C, Limas C, Knodell RG. Primary malignant melanoma of the rectum: evidence for origination from rectal mucosal melanocytes. *Cancer* 1988;61:1364-1370
35. Kim KW, Ha HK, Kim AY, et al. Primary malignant melanoma of the rectum: CT findings in eight patients. *Radiology* 2004;232:181-186
36. Prichard RS, Hill ADK, Skehan SJ, O'Higgins NJ. Positron emission tomography for staging and management of malignant melanoma. *Br J Surg* 2002;89:389-396
37. Ross M, Pezzi C, Pezzi T, et al. Patterns of failure in anorectal melanoma. A guide to surgical therapy. *Arch Surg* 1990;125:313-316
38. Chiu YS, Unni KK, Beart RW. Malignant melanoma of the anorectum. *Dis Colon Rectum* 1980;23:122-124
39. Siegal B, Cohen D, Jacob ET. Surgical treatment of anorectal melanomas. *Am J Surg* 1983;146:336-338
40. Bolivar JC, Harris JW, Branch W, Sherman RT. Melanoma of the anorectal region. *Surg Gynecol Obstet* 1982;154:337-341
41. Baskies AM, Sugarbaker EV, Chretien PB, Deckers PJ. Anorectal melanoma: the role of posterior pelvic exenteration. *Dis Colon Rectum* 1982;25:772-777
42. Thibault C, Sagar P, Nivatvongs S, et al. Anorectal melanoma—an incurable disease? *Dis Colon Rectum* 1997;40:661-668
43. Luna-Perez P, Rodriguez DF, Macouzet JG, et al. Anorectal malignant melanoma. *Surg Oncol* 1996;5:165-168
44. Moore W. Recurrent melanoma of the rectum after previous removal from the verge of the anus in a man aged sixty-five. *Lancet* 1857;1:290
45. Miles WE. The pathology of the spread of cancer of the rectum, and its bearing upon the surgery of the cancerous rectum. *Surg Gynecol Obstet* 1931;52:350
46. Ward MW, Romano G, Nicholls RJ. The surgical treatment of anorectal malignant melanoma. *Br J Surg* 1986;73:68-69
47. Yap LB, Neary P. A comparison of wide local excision with abdominoperineal resection in anorectal melanoma. *Melanoma Research* 2004;14:147-150
48. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol* 1999;17:976-983
49. Morton DL, Thompson JF, Essner R, et al. Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group. *Ann Surg* 1999;230:453-465
50. Balch CM, Soong S, Bartolucci AA, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann Surg* 1996;224:255-263

51. Morton DL, Hsueh EC, Essner R, et al. Prolonged survival of patients receiving active immunotherapy with Canvaxin therapeutic polyvalent vaccine after complete resection of melanoma metastatic to regional lymph nodes. *Ann Surg* 2002;236:438–448
52. Balch CM, Soong S, Ross MI, et al. Long term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0–4.0 mm). Intergroup Melanoma Surgical Trial. *Ann Surg Oncol* 2000;7:87–97
53. Eggermont AMM. Adjuvant therapy of malignant melanoma and the role of sentinel lymph node mapping. *Recent Results Cancer Res* 2000;157:178–189
54. Tien HY, McMasters KM, Edwards MJ, et al. Sentinel lymph node metastasis in anal melanoma: a case report. *Int J Gastrointest Cancer* 2002;32:53–56
55. Rosenberg SA, Zhai Y, Yang JC, et al. Immunizing patients with metastatic melanoma using recombinant adenoviruses encoding MART-1 or gp100 melanoma antigens. *J Natl Cancer Inst* 1998;90:1894–1900
56. Thompson LW, Brinckerhoff L, Slingluff CL. Vaccination for melanoma. *Curr Oncol Rep* 2000;2:292–299
57. Hershey P. Evaluation of vaccine viral lysates as therapeutic vaccines in the treatment of melanoma. *Ann NY Acad Sci* 1993;690:167–177
58. Kim EM, Sivanandham M, Stavropoulos CI, et al. Overview analysis of adjuvant therapies for melanoma—a special reference to results from vaccinia melanoma oncolysate adjuvant therapy trials. *Surg Oncol* 2001;10:53–59
59. Wallack MK, Sivanandham M, Balch CM, et al. Surgical adjuvant active specific immunotherapy for patients with stage III melanoma: the final analysis of data from a phase III, randomized, double blind, multicenter vaccinia melanoma oncolysate trial. *J Am Coll Surg* 1998;187:69–77
60. Haigh PI, Difronzo LA, Gammon G, Morton DL. Vaccine therapy for patients with melanoma. *Oncology* 1999;13:1561–1574
61. Nyui S, Osanai H, Masuoka H, et al. Anorectal malignant melanoma: report of a case. *Surg Today* 1997;27:753–756
62. Terada R, Ito S, Kobayashi M, et al. Anorectal melanoma: successful treatment by surgical excision and combination chemioimmunotherapy. *Hepatogastroenterology* 2002;49:1545–1548
63. Veronesi U, Adamus J, Aubert C, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. *N Engl J Med* 1982;307:913–916
64. Quirt IC, Shelley WE, Pater JL, et al. Improved survival in patients with poor-prognosis malignant melanoma treated with adjuvant levamisole: a phase III study by the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1991;9:729–735
65. Meyskens FL Jr, Kopecky KJ, Taylor CW, et al. Randomized trial of adjuvant human interferon gamma versus observation in high risk cutaneous melanoma: a Southwest Oncology Group study. *J Natl Cancer Inst* 1995;87:1710–1713
66. Eggermont AMM. Strategy of the EORTC-MTG trial programmed for adjuvant treatment of moderate risk and high risk melanoma. *Eur J Cancer* 1998;34:S22–S26
67. Lens MB, Dawes M. Interferon therapy for malignant melanoma: a systematic review of randomized controlled trials. *J Clin Oncol* 2002;20:1818–1825
68. Hill GJ, Kremenz ET, Hill HZ. Dimethyl triazeno imidazole carboxamide and combination therapy for melanoma. IV. Late results after complete response to chemotherapy (Central Oncology Group protocols 7120, 7131 and 7131A). *Cancer* 1984;53:1299–1305
69. Phade VR, Lawrence WR. Anorectal melanoma. *Br J Surg* 1981;68:667–668
70. Ulmer A, Metzger S, Fierlbeck G. Successful palliation of stenosing anorectal melanoma by intratumoral injections with natural interferon- β . *Melanoma Res* 2002;12:395–398
71. Legha SS, Ring S, Bedikian A, et al. Treatment of metastatic melanoma with combined chemotherapy containing cisplatin, vinblastine and dacarbazine (CVD) and biotherapy using interleukin-2 and interferon-alpha. *Ann Oncol* 1996;7:827–835
72. Keilholz U, Conradt C, Legha SS, et al. Results of interleukin-2 based treatment in advanced melanoma: a case record-based analysis of 631 patients. *J Clin Oncol* 1998;16:2921–2929
73. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin-2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 1999;17:2105–2116
74. Kim KB, Sanguino AM, Hodges C, et al. Biochemotherapy in patients with metastatic anorectal mucosal melanoma. *Cancer* 2004;100:1478–1483
75. Bujko K, Nowacki MP, Liszka-Dalecki P. Radiation therapy for anorectal melanoma: a report of three cases. *Acta Oncol* 1998;37:497–499
76. Ballo MT, Strom EA, Zagars GK, et al. Adjuvant irradiation for auxiliary metastases from malignant melanoma. *Int J Radiat Oncol Biol Phys* 2002;52:964–972
77. Morris KT, Marquez CM, Holland JM, Vetto JT. Prevention of local recurrence after surgical debulking of nodal and subcutaneous melanoma deposits by hypofractionated radiation. *Ann Surg Oncol* 2000;7:680–684
78. Stevens G, Thompson JF, Firth I, et al. Locally advanced melanoma: results of postoperative hypofractionated radiation therapy. *Cancer* 2000;88:88–94
79. Bentzen SM, Overgaard J, Thames HD, et al. Clinical radiobiology of malignant melanoma. *Radiother Oncol* 1989;16:169–182
80. Irvin WP Jr, Bliss SA, Rice LW, et al. Malignant melanoma of the vaginal and locoregional control: radical surgery revisited. *Gynecol Oncol* 1998;71:476–480
81. Konstadoulakis MM, Ricaniadis N, Walsh D. Malignant melanoma of the anorectal region. *J Surg Oncol* 1995;58:118–120
82. Moozar KL, Wong CS, Couture J. Anorectal malignant melanoma: treatment with surgery or radiation therapy, or both. *Can J Surg* 2003;46:345–349
83. Sersa G, Stabuc B, Cemazar M, Miklavcic D, Rudolf Z. Electrochemotherapy with cisplatin: clinical experience in malignant melanoma patients. *Clin Cancer Res* 2000;6:863–867
84. Sersa G, Cemazar M, Rudolf Z. Electrochemotherapy: advantages and drawbacks in treatment of cancer patients. *Cancer Ther* 2003;1:133–142
85. Snoj M, Rudolf Z, Cemazar M, Jancar B, Sersa G. Successful sphincter-saving treatment of anorectal melanoma with electrochemotherapy, local excision, and adjuvant brachytherapy. *Anticancer Drugs* 2005;16:345–348