Surgical Therapy for Anorectal Melanoma

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BACKGROUND: Anorectal melanoma is a rare but highly lethal malignancy. Historically, radical resection was considered the "gold standard" for treatment of potentially curable anorectal melanoma. The dismal prognosis of this disease has prompted us to recommend wide local excision as the initial therapeutic approach. The purpose of this study was to review our results in patients who underwent wide local excision or radical surgery (abdominoperineal resection [APR]) for localized anorectal melanoma.

STUDY DESIGN: We reviewed the charts of all patients referred for resection of anorectal melanoma between 1988 and 2002. Endpoints included overall survival, disease-free survival, and local, regional, or systemic recurrence.

RESULTS: Fifteen patients underwent curative-intent surgery; four underwent APR and 11 underwent wide local excision. Eight patients (53%) are alive; 7 (47%) are disease-free (followup 6 months to 13 years). Of 12 patients who have been followed for more than 2 years, 4 are alive (33%) and 3 are disease-free (25%). Seven patients have been followed for more than 5 years and two are alive and disease-free (29%). All of the longterm survivors underwent local excision as the initial operation. There were no differences in local recurrence, systemic recurrence, disease-free survival, or overall survival between the APR group and the local excision group. Local recurrence occurred in 50% of the APR group and 18% of the local excision group; regional recurrence occurred in 25% versus 27%. Distant metastases were common (75% versus 36%).

CONCLUSION: In patients who have undergone resection with curative intent for anorectal melanoma, most recurrences occur systemically regardless of the initial surgical procedure. Local resection does not increase the risk of local or regional recurrence. APR offers no survival advantage over local excision. We advocate wide local excision as primary therapy for anorectal melanoma when technically feasible. (J Am Coll Surg 2003;196:206–211. © 2003 by the American College of Surgeons)

Anorectal melanoma is rare, comprising less than 1% of all anorectal malignancies and 1% to 2% of melanomas.[1-4] Despite many advances in the treatment of melanoma, prognosis for patients with anorectal disease remains poor. Overall, five-year survival is reported to be 10% or less and many patients present with systemic metastasis or deeply invasive tumors or both at the time of diagnosis.[5-8] Some patients with anorectal melanoma present with isolated local or locoregional disease. Because patients with early-stage cutaneous melanoma can be cured with surgical resection, it is thought that patients with melanoma limited to the anus might also be cured surgically.

Historically, radical surgery (abdominoperineal resection [APR]) had been our preferred curative treatment for anorectal melanoma. This was consistent with the treatment offered at other major centers.[9] APR is a technically demanding procedure with a considerable postoperative morbidity. APR is associated with hemorrhage (4%), wound infection (11% to 16%), and wound dehiscence (14 to 24%).[10-14] Postoperative sexual dysfunction, voiding dysfunction, and small-bowel obstruction are not uncommon.[10,11,13-15] Finally, the need for a permanent stoma can be problematic for some patients. In addition to the major morbidity associated with APR, our experience was that most patients with anorectal melanoma died despite having undergone a radical APR. For these reasons, our preferred treatment strategy

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Abbreviations and Acronyms
APR = abdominoperineal resection

for localized anorectal melanoma gradually changed. In the past fifteen years, we have stopped recommending APR as the preferred surgical procedure and instead recommend wide local excision when technically feasible. The purpose of the current study was to review our results in light of this change in treatment philosophy.

METHODS

We performed a retrospective chart review of all patients referred to our practice for resection of anorectal melanoma between 1988 and 2002. Patients with known distant metastases who underwent palliative resection were excluded from the analysis. Because regional lymph node metastases can be resected for cure in patients with cutaneous melanoma, the presence of lymph node metastasis alone was not considered reason for exclusion. Patients who underwent wide local excision were compared with those who had undergone APR. Endpoints included overall survival, disease-free survival, and local, regional, or systemic recurrence. Local recurrence was defined as recurrent melanoma in the perineum or anorectum. Regional recurrence was defined as recurrent melanoma in either inguinal or iliac lymph nodes. The presence of distant metastases was considered systemic recurrence. Results were compared by Fisher's exact test where appropriate.

RESULTS

Between 1988 and 2002, 247 patients were referred for resection of an anal canal malignancy. Of these, 16 had melanoma (6.5%). One patient was found to have brain metastases after referral and was excluded from the analysis. Mean age at diagnosis was 65 years (range = 29 to 86 years). Nine were female. Followup ranged from 6 months to 13 years (mean = 25 months; median = 16 months). Of the fifteen patients who underwent surgery with curative intent, four underwent APR and eleven underwent wide local excision. Three of the four APR patients required a radical resection because local tumor characteristics precluded local excision (deep invasion into the sphincter, [1] circumferential tumor, [1] extensive perianal melanosis [1]). The rationale for APR in the fourth patient was unclear. One patient who underwent APR also had a sentinel lymph node dissection; the sentinel node was found in the groin and showed no tumor. In the eleven patients who underwent wide local excision, an attempt was made to obtain a one-to two-centimeter margin of grossly normal skin (frozen sections were not performed); perirectal lymph nodes were not resected. One patient with clinically involved inguinal lymph nodes underwent wide local excision and therapeutic bilateral inguinal lymph node dissections and is included in the wide local excision group for analysis.

Three patients had their tumors evaluated by preoperative endoanal ultrasonographic staging. Ultrasonographic stages were based on depth of invasion and the presence of enlarged perirectal lymph nodes.[16] T1 tumors invaded the submucosa, T2 tumors invaded the sphincter/muscularis propria, T3 tumors invaded the perirectal or perianal fat, and T4 tumors invaded adjacent organs. The presence of any enlarged lymph node was reported as N1. These three patients had preoperative ultrasonographic stages of uT1N0, uT3N0, and uT3N1. All underwent wide local excision. Surgical pathology revealed that the uT1 tumor was 3 mm deep, and the uT3 lesions were 6 mm and >10 mm deep. Two other patients have been followed with endoanal ultrasonography after local resection. Neither has had a detectable recurrence after followup of 15 months and 24 months.

Tumor depths were equally distributed between the APR group and the wide local excision group (Table 1). Over half of the patients who underwent wide local excision had thick melanomas (≥4 mm in depth). After resection, two of the patients who underwent APR were found to have an involved perirectal lymph node.

Eight of the fifteen patients are alive (53% overall survival); seven are disease-free (47% disease-free sur-

Table 1. Depth of Resected Melanoma Specimens

Resection	<0.75 mm	0.75–1.50 mm	1.51–4.0 mm	>4.0 mm	Unknown
Abdominoperineal resection (n = 4)	1	2	0	1	0
Local excision (n = 11)	2	0	2	6	1

p = not significant.

Table 2. Survival and Recurrence Patterns after Resection

	Overall survival	Disease-free survival	Local recurrence	Regional recurrence	Distant recurrence
Abdominoperineal resection	1 (25%)	1 (25%)	2 (50%)	1 (25%)	3 (75%)
Local excision	7 (64%)	6 (55%)	2 (18%)	3 (27%)	4 (36%)

Mean followup, 25 mo; median followup, 16 mo; range, 6 mo to 13 y.
p = not significant.

vival) with followup ranging from 6 months to 13 years (mean 25 months, median 16 months). Twelve patients have been followed for more than two years and four are currently alive (33% 2 year survival), while three are disease-free (25% 2 year disease-free survival). Seven patients have been followed for more than 5 years and two are alive and disease-free (29% five-year disease-free survival). All of the longterm survivors underwent local excision as the initial operation. Mean length of survival among patients who died was 16 months (median 18 months, range 4 months to 30 months).

Tumor depth did not correlate with survival or pattern of recurrence. Of the three patients with thin tumors ($\leq$0.75 mm in depth), one died with distant metastases, one is alive and disease-free after 17 months, and one is alive and disease-free after more than five years despite regional recurrences (see below). Of the two patients with tumors 0.75 mm to 1.5 mm in depth, one died with distant metastases, while the other is alive and disease-free after 11 months. Of the two patients with tumors 1.5 mm to 4.0 mm in depth, one died with distant metastases; the other developed regional recurrence but underwent resection and adjuvant therapy and is alive and disease-free five years later (see below). Finally, of the seven patients with tumors $\geq$4 mm in depth, four died with distant metastases, one is alive but has distant metastases, and two are alive and disease-free after 6 and 24 months.

There were no differences in the rate of local recurrence, systemic recurrence, disease-free survival, or overall survival between the APR group and the wide local excision group (Table 2). Local, regional, and systemic recurrences were common in both groups. Six of the seven patients who died had known systemic recurrence. One patient who underwent local excision died after 11 months, but the pattern of recurrence is unknown. Mean disease-free survival was 10 months in the APR group versus 14 months in the local excision group. Mean overall survival was 14 months in the APR group versus 19 months in the local excision group.

One patient underwent preoperative chemotherapy before APR but died 14 months later with distant metastases. One patient underwent postoperative chemotherapy and radiation after an inguinal nodal recurrence but developed distant metastases after 17 months; this patient is currently undergoing interferon-α therapy. One patient underwent postoperative interferon-α therapy followed by biochemotherapy and vaccine therapy after wide local excision; another underwent postoperative chemotherapy and radiation therapy after wide local excision. Both are alive more than five years after diagnosis (see below).

All of the patients who have survived longer than two years underwent wide local excision as the initial surgical procedure. One patient is disease-free after 24 months without adjuvant therapy. One patient has developed distant metastasis after 26 months despite postoperative chemotherapy, radiation, and interferon-α therapy. The two five-year survivors have both required reoperation for regional recurrence. The first of these longterm survivors underwent a wide local excision for a 0.5-mm deep tumor in 1997. This patient developed an inguinal nodal recurrence after 26 months, which was resected, was then treated with chemotherapy and radiation, and is currently disease-free 43 months after the last resection. The second patient underwent wide local excision for a 3-mm deep tumor in 1996 and received interferon-α and biochemotherapy postoperatively. She developed an inguinal recurrence three months later that was resected, followed by an iliac nodal recurrence seven months after her initial operation that was also resected. She then received an allogeneic vaccine and is currently disease-free 60 months after her last resection.

DISCUSSION

Anorectal melanoma remains a highly lethal disease. Patients often present with advanced disease and median survival in most reports ranges from 12 to 18 months.[5,6,9,17-19] Even in patients with local or locoregional disease for whom resection is potentially curative, five-year survival is only 5% to 20%.[9,18,20,21] In this series, we identified 15 patients who underwent surgery with curative intent for anorectal melanoma. Although the

overall survival in this series was good (53%), mean followup is short. Among patients followed for at least two years, disease-free survival was only 25%. We did identify two patients who are alive and disease-free more than five years after diagnosis.

It has been argued that APR is the most appropriate surgical approach for potentially curable anorectal melanoma. Brady and colleagues[9] demonstrated a trend toward improved survival among patients who underwent APR versus those who underwent wide local excision. Systemic recurrence was common (65%) and APR did not protect against either local or regional recurrence, which occurred in 8% and 27% of patients, respectively.[9] Other authors have also recommended radical resection, especially for patients with thin, early-stage tumors,[6,21-24] but a pooled analysis of 428 patients failed to show any survival advantage for radical surgery.[25] More recent reports show similar results, noting that systemic recurrence is common and that APR offers no advantage over wide local excision in overall survival, disease-free survival, or pattern of recurrence.[20]

It has also been suggested that APR can decrease local recurrence. A series of 26 patients from the MD Anderson Cancer Center reported fewer local recurrences after APR (29%) than after wide local excision (58%), but these authors noted that the majority of recurrences occurred in patients who also had regional or systemic metastases and that local recurrence did not affect survival.[18] A series of 71 patients from the Memorial Sloan-Kettering Cancer Center reports isolated local recurrence in 8% of patients after APR, 8% after wide local excision, and 27% after biopsy ± fulguration; regional recurrence occurred in 27% of patients after APR and 8% after wide local excision.[9] In our series, local recurrence occurred in 50% of the patients who underwent APR and regional recurrence occurred in 25%. Both patients with locoregional recurrence ultimately developed systemic metastases. In the group of patients who underwent wide local excision, two developed local recurrences and both have had subsequent systemic recurrences. Four patients developed regional recurrences, and two of these patients have developed systemic disease. Two patients presented with distant metastases as the initial recurrence. Two patients developed isolated regional metastases. Interestingly, both underwent therapeutic lymph node dissection(s) and adjuvant therapy. Both are alive and disease-free more than five years after diagnosis. The survival of these two patients suggests that some locoregional recurrences might be resected for cure and that the addition of adjuvant therapy might benefit selected patients.

The role of chemotherapy and immunotherapy in the treatment of melanoma remains controversial. Several regimens have been recommended, including dacarbazine,[26] bacillus Calmette-Guerin,[26] levamisole,[27] and interferon-α,[28-30] but none has shown a survival benefit for cutaneous melanoma.[31-33] There has been increasing interest in the role of interferon-α therapy because of reports of improved disease-free survival among patients treated with this agent.[34-36] A recent metaanalysis by Lens and colleagues[37] demonstrated no clear benefit from interferon-α. Biochemotherapy using cytotoxic chemotherapeutic agents (cisplatin, vinblastine, and dacarbazine) combined with an immunomodulator (interleukin-2 or interferon-α or both) has also been shown to improve survival in some patients.[38] Several vaccines have also been tested for efficacy against melanoma with variable results.[39-44] In our series, one patient is currently receiving interferon-α for systemic recurrence after wide local excision. In addition, both longterm survivors have received adjuvant therapy (biochemotherapy, interferon-α, and vaccine therapy in one and cytotoxic chemotherapy in the other) in addition to resection of regional recurrences. Despite these two successes, the efficacy of chemotherapy for anorectal melanoma requires further study.

The addition of radiation therapy for treatment of melanoma is also controversial. The addition of radiotherapy to surgery can improve local and regional control for high-risk melanoma in the axilla,[45] head and neck,[46] and other cutaneous sites.[47,48] Irwin and colleagues[49] showed that wide local excision followed by radiation provided excellent locoregional control in seven cases of vaginal melanoma. In anorectal melanoma, radiation therapy improved local control in three patients.[50] Only two of our patients received postoperative radiotherapy after wide local excision. One patient has good local control but has recurred systemically. The other patient is alive and disease-free five years after diagnosis. As with adjuvant chemotherapy for melanoma, definitive assessment of the efficacy of adjuvant radiation therapy requires further prospective study.

Endorectal ultrasonography is increasingly employed in the preoperative staging of rectal cancers. Accuracy in evaluating tumor depth ranges from 81% to 94%, and accuracy in detecting lymph node metastases ranges from 58% to 80%.[51] Use of endoanal ultrasonography

for preoperative staging and postoperative followup of patients with anorectal melanoma has not been reported. Three of our patients underwent preoperative ultrasonographic evaluation. Endoanal ultrasonography accurately diagnosed one thin melanoma and detected invasion into perianal tissues in two tumors. Two patients are being followed postoperatively in an attempt to detect early recurrence. While this technology has been invaluable in the preoperative staging of rectal cancer, its accuracy in pre- and postoperative evaluation of anorectal melanoma remains unproved. We are currently evaluating the accuracy of endoanal ultrasonography in the preoperative assessment of melanoma as well as other anal canal malignancies.

In patients with cutaneous melanoma, survival is improved by elective lymph node dissection[52,53] and the role of sentinel lymph node biopsy for detection of occult nodal metastasis is well established.[31] Current recommendations for surgical management of cutaneous melanoma include sentinel lymph node dissection in patients with tumors deeper than 1 mm, followed by therapeutic lymph node dissection if the sentinel node contains tumor cells. Sentinel lymph node dissection has not been widely used in anorectal melanoma, and the benefit of therapeutic lymph-node dissection remains unproved. In our series, one patient underwent sentinel lymph node biopsy after APR; the sentinel node was found in the groin and showed no evidence of melanoma. This patient is currently disease-free after 11 months. Regional recurrence developed frequently after either APR (25%) or wide local excision (27%). In light of this, we believe that sentinel lymph node mapping will prove useful in patients with anorectal melanoma and that this technique can allow us to identify patients who will benefit from early therapeutic lymph node dissection and adjuvant therapy.

Our policy of offering wide local excision for treatment of localized anorectal melanoma seems to have met our goals of minimizing treatment morbidity without increasing the risk of local or regional recurrence. Most recurrences occur systemically, regardless of initial surgical therapy. For this reason, we advocate wide local excision (with 1- to 2-cm margins) for curative treatment of anorectal melanoma when technically feasible. In some patients, wide local excision might not be technically feasible and APR might be required if the tumor involves a notable portion of the anal sphincter or is circumferential. The addition of adjuvant chemotherapy, biochemotherapy, vaccines, or radiotherapy might be of benefit in some patients, but remains unproved. It is our hope that these new techniques and advances in adjuvant therapy will help us to improve survival in these patients.

Author contributions

Study conception and design: Bullard, Rothenberger, Madoff, Finne, Spencer
Acquisition of data: Bullard, Finne
Analysis and interpretation of data: Bullard, Tuttle, Spencer
Drafting of manuscript: Bullard
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Statistical expertise: Baxter
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