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Locoregional Lymphadenectomy in the Surgical Management of Anorectal Melanoma

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ABSTRACT

Background. The effect of lymph node metastasis on local tumor control and distant failure in patients with anorectal melanoma has not been fully studied. Understanding the significance of lymphatic dissemination might assist in stratifying patients for either organ preservation or radical surgery.

Methods. A retrospective review of all patients with anorectal melanoma who underwent surgery at our institution between 1985 and 2010. Abdominoperineal resection (APR) was performed in 25 patients (39 %), and wide local excision (WLE) in 40 (61%). Extent of primary surgery and locoregional lymphadenectomy (mesorectal vs. inguinal vs. none) and pattern of treatment failure were analyzed. Recurrence-free survival (RFS) and disease-specific survival (DSS) were calculated.

Results. In patients undergoing APR, DSS was not associated with presence (29 %) or absence (71 %) of metastatic melanoma in mesorectal lymph nodes. There was a trend toward improved DSS in patients with clinically negative inguinal lymph nodes ($n = 17$) compared with patients with proven inguinal metastasis ($n = 6$; $P = 0.12$). Type of surgery (WLE vs. APR) was not associated with subsequent development of distant disease. Twelve patients (18 %) had synchronous local and distant recurrence. Synchronous recurrence was not associated with surgical strategy used to treat primary tumor ($P = 0.28$). Perineural invasion (PNI) was significantly correlated with RFS ($P = 0.002$).

Conclusions. Outcome following resection of anorectal melanoma is independent of locoregional lymph node metastasis; lymphadenectomy should be reserved for gross symptomatic disease. PNI is a powerful prognostic marker warranting further exploration in clinical trials.

INTRODUCTION

Recent advances in the understanding of melanoma have translated into improved systemic treatment strategies that target the BRAF and cKIT mutations, as well as drugs that target the immune system, such as ipilimumab.[1] There also have been advances in the understanding of the natural history and molecular biology of anorectal melanoma, which accounts for 24 % of mucosal melanomas and less than 1 % of all melanomas.[2,3] For example, activating KIT mutations have been identified recently in 15 % of anorectal melanoma cases, which may predict a benefit from treatment with KIT-directed therapy.[4–6]

Many unanswered questions remain about the natural history, molecular biology, and treatment of anorectal melanoma. The majority of patients with anorectal melanoma experience distant disease recurrence, even after apparent complete resection. The 5-year disease-specific survival (DSS) remains less than 20 %.[3,7] This figure stands in sharp contrast to that for primary cutaneous melanoma: 80 % of patients with primary cutaneous melanoma are cured after definitive surgery.[2] The identification of prognostic factors for anorectal melanoma has been limited by the rarity of the disease and by the limited number of data sets available for analysis.[7,8] It has become apparent that, in cases where the

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primary lesion can be completely removed by local excision, the extent of primary surgery does not affect the success of organ preservation.[8,9]

The importance of locoregional lymph node involvement and the role that lymphadenectomy plays in anorectal melanoma remain unclear, and these are the focus of the present study. We retrospectively assessed the clinical value of locoregional lymphadenectomy (inguinal and mesorectal), the patterns of treatment failure, and the identification of prognostic factors in a cohort of patients treated at Memorial Sloan-Kettering Cancer Center (MSKCC) during a 25-year period.

MATERIALS AND METHODS

With approval of the institutional review board and in accordance with Health Insurance Portability and Accountability Act regulations, we performed a retrospective review of 86 consecutive patients with anorectal melanoma who were treated at MSKCC between 1985 and 2010. Fourteen patients presented with metastatic disease, and four patients were lost to follow-up. One patient was excluded from the analysis due to incomplete resection. Sixty-five patients with primary anorectal melanoma underwent resection with curative intention. Patients treated before 2003 may have been reported in previous studies from our institution.[9,10] These studies reported lymph node status and its effect on outcome in selected patients.[9,10] However, because the specific roles played by locoregional lymphadenopathy and lymphadenectomy were not addressed, these patients were included in the present study.

Tumor specimens from 42 patients were available for review and were examined by a single pathologist (JS). Demographic and clinical characteristics (including age, sex, tumor-related symptoms, tumor location, death, and length of follow-up), extent of resection (wide local excision [WLE] vs. abdominoperineal resection [APR]), and histopathologic features were examined. The histopathologic features assessed include tumor thickness, maximum diameter, perineural invasion (PNI), lymphovascular invasion (LVI), the presence of tumor ulceration, and necrosis. The location of the tumor was categorized as above the dentate line or at/below the dentate line. In the present study, locoregional lymphadenectomy was defined as resection of the mesorectal lymph nodes in patients undergoing APR and/or resection of the inguinal lymph nodes. The effect of mesorectal lymph node status on recurrence and survival was assessed in 25 patients who underwent rectal resection with complete pathologic evaluation of the mesorectum. Similarly, the effect of inguinal metastasis on DSS was compared between patients with histologically proven recurrence in the groin ($n = 9$) and those with clinically negative inguinal lymph nodes on physical examination ($n = 22$).

DSS and recurrence-free survival (RFS) were calculated using the Kaplan-Meier product-limit method, and the significance of clinicopathologic variables was measured by the log-rank test. Pearson's χ^2 test was used to analyze associations between two variables. Continuous variables, including tumor thickness, tumor diameter, and patient age, were examined using Cox proportional hazards regression analysis. Multivariate analysis was performed using the Cox proportional hazards regression method. Continuous variables are reported as median and interquartile range (IQR). Statistical analyses were performed with IBM SPSS software version 19.

RESULTS

The median age of the 65 patients (31 males, 34 females) was 60 years (interquartile range (IQR), 50–74 years). Twenty-five patients (39 %) underwent APR, and 40 (61 %) underwent WLE. Twelve patients (18 %) underwent microscopically incomplete tumor resection (R1) after initial surgery. Of those, nine patients had undergone WLE, and four had undergone APR. All patients in the WLE group underwent reexcision, by means of repeat WLE ($n = 9$), and subsequently were found to have a clear resection margin. The patients in the APR group underwent reexcision, and of those, three patients had no residual disease and one had still viable tumor with positive reexcision margin. This patient was referred for adjuvant radiation and was excluded from the subsequent recurrence and survival analyses. Clinical parameters were comparable between treatment groups (Table 1) except that patients undergoing APR had larger tumors. A total of 18 patients (26 %) underwent adjuvant treatment: 5 in the APR group and 13 in the WLE group. In the WLE group, three patients underwent adjuvant radiation, nine underwent adjuvant chemotherapy, and one underwent a combination of radiation and chemotherapy. Adjuvant chemotherapy consisted of imatinib mesylate-, interferon-, temozolomide-, and dacarbazine-based regimens. Complete clinical follow-up was available for all patients (median, 20 months [IQR, 12–35]).

Lymph Nodes

Of the 25 patients in the APR group, 24 had documented pathologic assessment of the mesorectal lymph nodes available for analysis. Seventeen of 25 patients (71 %) had negative mesorectal lymph nodes, and 7 of 25 (29 %) had metastatic melanoma in the mesorectal lymph nodes. The location of the primary tumor ($P = 0.33$) and tumor thickness ($P = 0.29$) were not associated with lymphatic spread to the mesorectum. RFS and DSS (Fig. 1) were not

TABLE 1 Clinicopathologic characteristics of 65 patients with anorectal melanoma

Parameter	No. of patients with data	APR ($n = 25$)	WLE ($n = 40$)	P[a]
Age (year)	63	57 (47–67)	61 (51–76)	NS
Sex (F:M)	65	9:16	25:15	NS
Thickness (mm)	58	8 (5–19)	6.5 (4–11)	NS
Diameter (mm)	49	30 (17–55)	15 (8–24)	0.01
Symptoms	60			NS
Bleeding		16	27	
Mass		6	2	
Obstruction		0	2	
Location	63			NS
Above dentate line		2	5	
At/below dentate line		22	33	
Recurrence	62			
Distant		16	19	NS
Both		3	2	
Death	62	22	28	NS
Follow-up (months)	65	30 (12–55)	18 (12–26)	0.07

Continuous values are shown as median and interquartile range

APR abdominoperineal resection, *NS* not significant, *WLE* wide local excision

[a] The Mann-Whitney test was used for continuous variables; Pearson's χ^2 test was used for binary parameters

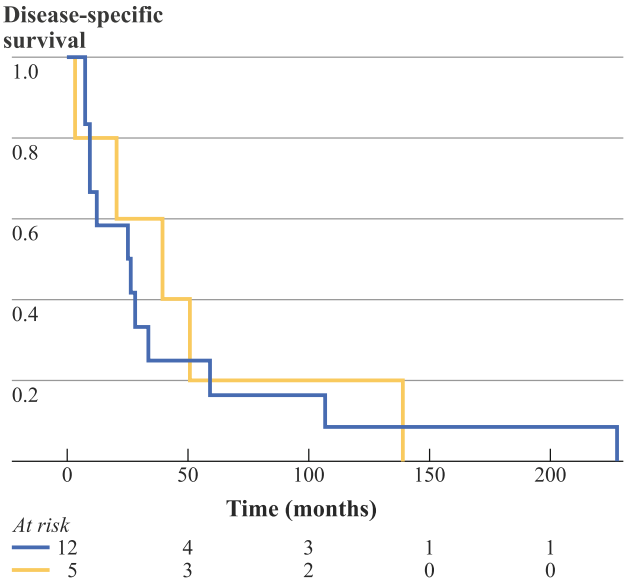

FIG. 1 Disease-specific survival in patients with and without histopathologically confirmed metastatic melanoma in the mesorectal lymph nodes (LNs)

associated with the presence or absence of metastatic melanoma in the mesorectum (Table 2).

A total of 32 patients (32/65, 49 %) in both treatment groups had pathologic and/or clinical information available regarding inguinal lymph node status. A tendency for worse DSS was noted for patients with histologically proven metastatic melanoma in the groin (Table 2). One patient with positive mesorectal lymph nodes also developed inguinal lymphadenopathy. There was no association between the initial tumor site (above or at/below the dentate line) and the pattern of lymphatic spread to either the mesorectal ($P = 0.33$) or the inguinal lymph nodes ($P = 0.78$). Lymphatic spread to either the mesorectum or the inguina was not associated with worse prognosis, compared with that for patients without evidence of nodal disease (Table 2; Fig. 2). Nine patients (13 %) underwent sentinel lymph node biopsy, and seven of them were positive for metastatic melanoma in the groin. Sentinel lymph node biopsy did not predict RFS ($P = 0.34$) or DSS ($P = 0.15$). Of note, sentinel lymph node biopsy was performed only in the WLE group.

Pattern of Treatment Failure

A total of 44 patients (68 %) developed disease recurrence, with an RFS of 10 months (IQR, 5–23) and a DSS of 22 months (IQR, 13–41). At the last follow-up, 43 patients (66 %) had died of disease. RFS and DSS were similar between the APR group and the WLE group. The recurrence patterns observed were (1) distant recurrence only, and (2) synchronous local and distant recurrence. There were no cases of local recurrence only. Thirty-five patients (54 %) developed distant recurrence, including in the lung ($n = 13$), the liver ($n = 15$), the brain ($n = 3$), the retroperitoneum ($n = 2$), and the small bowel ($n = 2$). The type of initial surgical management did not influence the development of distant metastasis: 16 patients (64 %) in the APR group and 19 patients (47 %) in the WLE group experienced recurrence ($P = 0.13$). Twelve patients (18 %) experienced synchronous distant and local recurrence; in this group, local recurrence was asymptomatic in six patients (50 %), but four patients (33 %) had obstructive symptoms, which were treated with pelvic radiation ($n = 2$) or laxatives ($n = 2$). One patient treated with pelvic radiation (8 %) underwent reexcision for symptomatic local recurrence, and one patient was treated with laxatives (8 %) and pelvic radiation for bleeding. There was no statistically significant difference ($P = 0.28$) in the number of synchronous local and distant recurrences between the WLE group ($n = 9$; 22 %) and the APR group ($n = 3$; 12 %).

Prognostic Surgical and Pathologic Factors

Metastatic spread of melanoma to locoregional lymph nodes is not associated with prognosis (Table 2). Factors associated with RFS and DSS are shown in Table 3. As reported in previous studies, the type of surgical resection

TABLE 2 Prognostic role of locoregional lymph node metastasis on recurrence and survival

LN status	No. of patients	RFS (months)	P^a	No. of patients	DSS (months)	P^c
Mesorectum						
Positive	5	31 (5–78)	0.85	5	40 (21–51)	0.78
Negative	15	15 (8–77)		12	26 (10–34)	
Inguinal						
Positive[a]	9	8 (3–NR)	0.94	6	21 (8–34)	0.06
Negative[b]	19	7 (5–77)		17	29 (13–60)	
Any location						
Positive	13	8 (3–78)	0.59	11	21 (13–40)	0.42
Negative	15	15 (8–76)		12	27 (10–34)	

Data are presented as median (interquartile range)

DSS disease-specific survival, *LN* lymph node, *RFS* recurrence-free survival, *NR* not reached

[a] Histologically proven metastatic disease of the groin

[b] No evidence of metastatic disease at the inguinal lymph nodes, by clinical examination

[c] Kaplan-Meier product-limit method

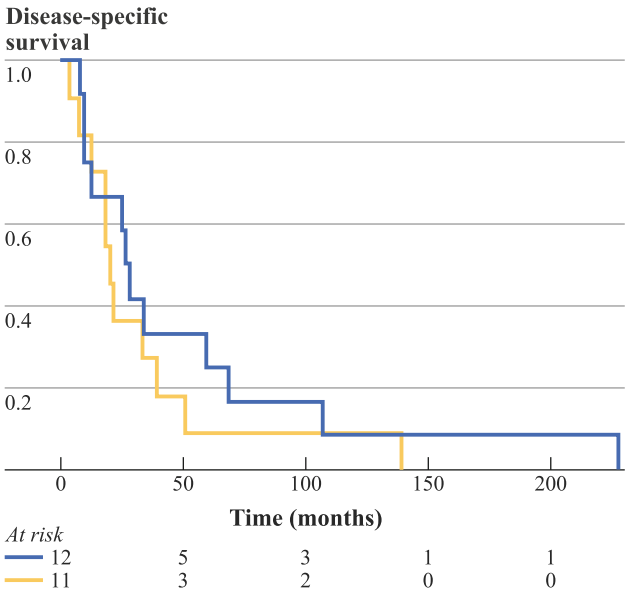

FIG. 2 Disease-specific survival in patients with and without evidence of metastatic disease in the mesorectum and/or groin. The absence of mesorectal disease was confirmed by pathologic examination. The groin was deemed negative if no gross metastatic disease was palpable on clinical examination. *LN* lymph node

did not affect RFS or DSS.[9,11] Patients who underwent APR had a median DSS of 27 months (IQR, 10–51) compared with 19 months (IQR, 13–30) for patients who underwent WLE ($P = 0.2$). The median follow-up was longer ($P = 0.07$) for the APR group (30 months; IQR, 12–55 months) than for the WLE group (18 months; IQR, 12–26 months). Tumor size and thickness did not significantly affect RFS or DSS. Patients with a tumor above the dentate line had a better DSS ($P = 0.03$) compared with patients with a tumor at/below the dentate line (Table 3). Lymphovascular invasion ($P = 0.02$) and tumor necrosis ($P = 0.01$) were associated with significantly shorter DSS (Table 3). The strongest predictor of shorter RFS was the presence of PNI in the primary tumor. PNI was analyzed in 47 patients. Twelve of 47 patients (26 %) had tumor PNI. The median RFS for patients with tumor PNI was 6 months compared with 21 months for patients without tumor PNI ($P = 0.002$). Interestingly, at 2 years after initial surgery, all patients with tumor PNI had experienced recurrence, whereas only 45 % of patients ($n = 22$) without tumor PNI had experienced recurrence ($P = 0.002$). By multivariate analysis that controlled for LVI, necrosis, and tumor site, tumor PNI was an independent prognostic factor for recurrence (Table 4). No independent prognostic factor for DSS was identified.

DISCUSSION

Multiple reports have shown that WLE of the primary tumor achieves similar long-term results compared with more radical surgery with total mesorectal excision.[8,9,12] The benefits of less invasive, organ-preserving procedures are readily apparent and include minimal surgical morbidity, quicker recovery, and improved quality of life, with no need for a permanent colostomy. However, the clinical relevance of locoregional lymph node metastasis on disease recurrence and patient survival has never been systematically analyzed. In cases of primary cutaneous melanoma, the presence of lymph node metastasis is the most significant prognostic factor in early disease.[13] On the basis of previous studies that compared outcomes between patients who underwent APR and those who underwent WLE, we hypothesized that nodal metastasis does not significantly affect RFS or DSS.

Indeed, patients with and those without lymph node metastasis in the mesorectum had similar prognoses, in terms of local or distant disease recurrence and survival, leading us to conclude that nodal disease at this location does not carry the same biologic significance for anorectal melanoma as it does for primary skin melanoma. In contrast, there was a trend toward worse survival in patients with apparent inguinal lymph node metastasis compared with that in patients with clinically negative inguinal lymph nodes. Although inguinal metastasis is considered locoregional for squamous cell cancer of the anus, in cases of anorectal melanoma it may represent a more advanced stage, with systemic lymphatic and hematogenic melanoma cell spread. Anorectal melanomas are generally large tumors (Table 1), and may be similar to large cutaneous melanomas (>4 mm), which can skip lymphatic spread and metastasize hematogenously to distant sites.[14,15] The systemic dissemination probably takes place at a very early stage in tumorigenesis, and by the time the lesion becomes clinically apparent, micrometastases are fully established. Therefore, to improve outcomes for this lethal disease, future clinical studies should assess the efficacy of targeted systemic treatment options. We were able to identify new risk factors and to confirm previously reported prognostic parameters associated with disease progression and survival, even though the overall outcome for the entire cohort was generally poor.[9] Multiple factors, with varying results, have previously been reported in the literature.[9,10,14–16] In the present study, the primary tumor site, LVI, and tumor necrosis were associated with recurrence. As reported in a previous study from our institution, tumor PNI was a strong predictor of outcome. In the present study, after a median observation period of 5 years, all patients with tumor PNI had experienced recurrence and

TABLE 3 Univariate analysis of surgical and pathologic prognostic factors associated with recurrence and survival

Variable	No. of patients	Recurrence-free survival			Disease-specific survival		
		Median (months)	5-year survival (%)	P^a	Median (months)	5-year survival (%)	P^a
Sex				0.63			0.96
Female	31	14	23		23	13	
Male	29	8	29		21	15	
Dentate line				0.77			0.03
At/below	50	13	26		22	26	
Above	8	10	15		13	0	
Thickness (mm)				0.38			0.08
≤10	36	13	23		27	0	
>10	17	10	31		22	17	
Diameter (mm)				0.59			0.08
≤20	25	14	24		20	19	
>20	20	10	30		13	0	
Surgery				0.36			0.2
APR	21	18	34		27	17	
WLE	39	8	21		19	12	
LVI				0.69			0.02
Yes	32	8	28		13	7	
No	20	14	29		28	16	
PNI				0.002			0.15
Yes	12	6	0		18	0	
No	35	21	40		28	20	
Necrosis				0.11			0.01
Yes	18	14	35		18	0	
No	34	7	0		29	19	
Ulceration				0.48			0.94
Yes	30	10	30		23	15	
No	25	13	23		18	14	

APR abdominoperineal resection, *LVI* lymphovascular invasion, *NR* not reached, *PNI* perineural invasion, *WLE* wide local excision

[a] Survival estimates were calculated by the Kaplan-Meier product-limit method, and differences were analyzed by the log-rank test

TABLE 4 Multivariate analysis of pathologic parameters associated with disease recurrence

Variable	HR (95 % CI)	P^b
PNI	4.4 (1.8–10.9)	0.001
LVI		0.13
Necrosis		0.79
Tumor site[a]		0.54

CI confidence interval, *HR* hazard ratio, *LVI* lymphovascular invasion, *PNI* perineural invasion

[a] Initial tumor site was coded as rectum or anocutaneous area

[b] Multivariate analysis was performed using the Cox proportional hazards regression method

died. Although PNI has been shown to be a poor prognostic factor for intestinal cancers, it appears to indicate a particularly aggressive phenotype of anorectal melanoma.[17]

The present study has several limitations. We compared patients with biopsy-proven inguinal recurrence to those with no evidence of recurrent disease on clinical examination. Therefore, patients with low-volume disease in the groin might have been misclassified as having no metastatic inguinal disease. In addition, a variety of different adjuvant treatment modalities was applied in this cohort and may have contributed to small differences in RFS and DSS.

Our results argue against the use of prophylactic lymphadenectomy to identify and remove occult nodal disease in cases of anorectal melanoma, unless it is done as part of a clinical trial. Locoregional lymphadenectomy does not affect outcome for occult nodal metastasis, as it does for cutaneous melanoma. When treating anorectal melanoma, the emphasis should be on minimizing morbidity and removing all gross disease, while maximizing function and quality of life. Tumor PNI was confirmed to be a strong prognostic factor and should be taken into consideration when patients are stratified according to their risk for disease recurrence and progression. To develop new treatment algorithms that may have an effect on outcomes, future studies that address molecular targets, such as activating KIT mutations in anorectal melanoma, should be pursued.

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