Postoperative Radiotherapy in Head and Neck Mucosal Melanoma

A GETTEC Study

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Objective: To report patterns of failure according to treatment modality, with an emphasis on the role of postoperative radiotherapy in patients with localized head and neck mucosal melanoma (HNMM) treated during a 28-year period in a multi-institutional setting.

Design: Retrospective review.

Setting: French medical institutions.

Patients: A total of 160 patients with nonmetastatic HNMM treated from 1980 through 2008.

Interventions: Treatment modality consisted of surgery alone (hereinafter, S group) (n=82 patients) or with postoperative radiotherapy (hereinafter, SRT group) (n=78). Patients and tumor characteristics were similar in the 2 groups. There was a nonsignificant trend (P=0.11) for more locally advanced tumor stage (38.9%) in the SRT group compared with the S group (24.5%).

Results: Patients in the S group had an increased probability of locoregional recurrence as a first event (55.6%) compared with those in the SRT group (29.9%; P<.01). After adjusting for tumor stage (T1/T2 vs T3/T4), the subdistribution hazard ratio of locoregional relapse was 0.31, (95% confidence interval [CI], 0.15-0.61; P<.01). The rate of distant metastasis as a first event was significantly higher in the SRT group (40.6%) compared with the S group (19.9%; P=.01). Regardless of their treatment, patients who had a locoregional relapse during follow-up had an increased risk of subsequent distant metastasis (hazard ratio, 3.07; 95% CI, 1.65-5.67) and death (hazard ratio, 3.01; 95% CI, 1.91-4.78).

Conclusions: This large retrospective study suggests that postoperative radiotherapy improves the locoregional control of HNMM. The higher rate of distant metastasis was due to more advanced disease in the SRT group.


HEAD AND NECK MUCOSAL melanoma (HNMM) is a rare tumor, representing 3% of all melanoma cases and 0.4% to 10% of head and neck melanomas.1 The therapeutic strategy includes surgery alone or followed by postoperative radiotherapy. When the surgical approach is not feasible, radiotherapy is often used, sometimes in combination with chemoimmunotherapy in a palliative setting. Because most studies in the literature have focused on the results of the surgical approach, the potential role of radiotherapy has not been defined. Since the first description of HNMM, the largest retrospective studies of the Rare Cancer Network2 and the Gustave Roussy Institute3 have included 59 and 69 cases, respectively. While these 2 studies have shown a benefit in the local control of tumors by postoperative radiotherapy, there remains great skepticism, mostly among head and neck surgeons. No prospective trials have been or will likely be performed, owing to the rarity of the disease.

The aim of this largest study to date was to perform a retrospective analysis of this rare tumor presentation within the framework of the French GETTEC (Groupe d’Etude des Tumeurs de la Tete et du Cou), which includes a number of centers in France. The GETTEC’s aims were to identify the best treatment approaches, with an emphasis on the role of postoperative radiotherapy, and the influence of locoregional relapse on metastasis-free survival (MFS) and overall survival (OS).

METHODS

PATIENTS

A total of 215 patients were registered with the diagnosis of HNMM at 13 French institutions (academic, tertiary referral centers) over a 28-year period (1980-2008). Medical records were
Table 1. Characteristics of the Overall Patient Population According to Treatment Modality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 160)</th>
<th>S Group (n = 82)</th>
<th>SRT Group (n = 78)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54 (33.8)</td>
<td>27 (32.9)</td>
<td>28 (35.9)</td>
<td>.69</td>
</tr>
<tr>
<td>Female</td>
<td>106 (66.3)</td>
<td>55 (67.1)</td>
<td>50 (64.1)</td>
<td></td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td></td>
<td></td>
<td></td>
<td>.75</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>154 (96.3)</td>
<td>80 (98.8)</td>
<td>73 (93.6)</td>
<td>.27</td>
</tr>
<tr>
<td>2</td>
<td>6 (3.8)</td>
<td>1 (1.2)</td>
<td>5 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinonasal</td>
<td>145 (90.6)</td>
<td>73 (89.0)</td>
<td>72 (92.3)</td>
<td>.25</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>12 (7.5)</td>
<td>8 (9.8)</td>
<td>4 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.9)</td>
<td>1 (1.2)</td>
<td>2 (2.6)</td>
<td></td>
</tr>
<tr>
<td>TMN stage at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/T2</td>
<td>73 (48.2)</td>
<td>40 (75.5)</td>
<td>33 (61.1)</td>
<td>.11</td>
</tr>
<tr>
<td>T3/T4</td>
<td>34 (21.2)</td>
<td>13 (24.5)</td>
<td>21 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>53</td>
<td>29</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Diagnosis period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980-1989</td>
<td>22 (13.8)</td>
<td>10 (12.2)</td>
<td>12 (15.4)</td>
<td>.64</td>
</tr>
<tr>
<td>1990-1999</td>
<td>59 (36.9)</td>
<td>33 (40.2)</td>
<td>26 (33.3)</td>
<td></td>
</tr>
<tr>
<td>2000-2009</td>
<td>79 (49.4)</td>
<td>39 (47.6)</td>
<td>40 (51.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: S, surgery alone; SRT, surgery with postoperative radiotherapy.

STATISTICAL ANALYSIS

Data were summarized by frequency and percentage for categorical variables and by median and range for continuous variables. Differences between groups were assessed using a χ² or Fisher exact test for qualitative variables and the Mann-Whitney test for continuous variables.

All survival times were calculated from the date of the first treatment. Relapse-free survival (RFS), OS, and MFS were estimated using the Kaplan-Meier method and using the following first event definitions: locoregional or distant recurrence for RFS, death for OS, and distant recurrence for MFS (all other events were ignored for this end point). For OS, patients alive at the last follow-up report were censored. For RFS, patients alive or dead without relapse were censored at the last follow-up report or at the date of death. For MFS, patients alive at the last follow-up or dead without relapse were censored at last contact or at the date of death. The log rank test was used to compare treatment groups for OS and RFS survival curves. Multivariate analysis was conducted using a Cox proportional hazard model to study the influence of radiotherapy on RFS and OS after adjusting on prognostic factors.

The competing risks method was used to analyze the pattern of recurrence in the previously defined populations for locoregional and distant metastasis events. The primary advantage of this method was the absence of assumption of independence between tumor events such as locoregional and distant recurrences. Moreover, it permits a simultaneous and unequivocal description of all events intervening in the determination of RFS.\(^5^,^6\) Comparisons of cumulative incidences between groups were performed using Gray’s test.\(^7\)

Multivariate analysis was also conducted using the Fine and Gray model\(^8\) in order to estimate the potential effects of treatment modality on the cumulative incidence in the presence of competing risks (ie, locoregional relapse and distant metastasis). This model does not make a strong assumption of independence between events, and covariate effects can be interpreted directly in terms of the cumulative incidence function. In fact, a subdistribution hazard ratio (sHR) for a covariate greater than 1 implies a constant relative increase of the sHR and hence a higher cumulative incidence. A Cox model using locoregional relapse as a time-dependent covariate was used to estimate the prognostic effect of locoregional relapse as the first event for OS and MFS.\(^9\)

All P values reported are 2-sided. For all statistical tests, differences were considered significant at the 5% level. Stata software (StataCorp LP, College Station, Texas) was used for all statistical analyses, and the cmpsk R package was used for the Gray test.

RESULTS

PATIENT CHARACTERISTICS

The main demographics and clinical characteristics of the 160 patients are reported Table 1 for the overall population and according to treatment groups. The cohort included 54 men and 106 women, ranging in age from 30 to 93 years (median age, 67 years). Most cases were affected by sinonasal mucosal (n = 145 [90.6%]), and the others were primarily diagnosed within the oral cavity (n = 12 [7.5%]). Tumor stage at diagnosis was available for 107 patients: the disease of 73 patients (68.2%) was at an early
stage (T1/T2), and the disease of 34 patients (31.8%) was at a locally advanced stage (T3/T4). The disease of 13 patients in the S group (24.5%) and 21 patients in the SRT group (38.9%) was at a locally advanced stage (P = .11). Neck disease at presentation occurred in 6 patients (3.8%) (S group: n = 1; SRT group: n = 5).

**TREATMENT**

Surgical removal of the primary tumor was associated with a neck dissection in 8 cases. Six patients with stage II disease underwent a therapeutic neck dissection and postoperative radiotherapy. Two patients with stage I disease required only elective neck dissection. Among the 78 patients in the SRT group, data on dose to the primary tumor were available in 40 patients, and the median dose was 60 Gy (range, 25-70 Gy).

**OUTCOME IN THE OVERALL POPULATION**

After a median follow-up of 65.2 months (95% confidence interval [CI], 44.5-73.2), relapse occurred in 104 patients (65%). As the first relapse, there were 53 local metastases (33.1%), 11 regional metastases (6.9%), and 40 distant metastases (25.0%). The 5-year cumulative incidence rates of locoregional recurrence and distant metastasis were 43.1% and 28.9%, respectively.

At last follow-up, 83 patients had died. The median and 5-year OS were 37.5 months (95% CI, 27.1-54.9) and 37.8% (95% CI, 28.8%-46.7%), respectively.

**OUTCOMES BY TREATMENT MODALITY (S VS SRT)**

Relapse-free survival and OS by groups are plotted in Figure 1. No significant difference was observed between groups for OS and RFS. The 5-year RFS rates were 26.5% (95% CI, 16.3%-37.9%) and 29.4% (95% CI, 16.9%-41.8%; P = .63) for S and SRT, respectively (Table 2). The 5-year OS rates for the S and SRT groups were 46.2% (95% CI, 33.5%-58.0%) and 27.5% (95% CI, 15.7%-40.6%; P = .31), respectively. After adjusting for tumor stage (T1/T2 vs T3/T4), the hazard ratio (HR) of relapse was estimated to be 0.85 (95% CI, 0.51-1.40; P = .63) for S and 0.83 (95% CI, 0.42-1.64; P = .63) for SRT (Table 3). The HR of death was 1.08 (95% CI, 0.62-1.84; P = .80) for the SRT group compared with the S group.

The 5-year cumulative incidence of locoregional and distant recurrence is summarized in Table 2 according to treatment modality. The patients in the SRT group had a significantly lower rate of locoregional recurrence compared with those in the S group (P < .01). The 5-year cumulative incidence of locoregional recurrence was estimated to be 55.6% and 29.9% for the S and SRT groups, respectively (Figure 1). Conversely, the cumulative incidence of distant metastasis was significantly lower in the S group compared with the SRT group; the 5-year rates were estimated as 17.9% and 40.7%, respectively (P = .01; Figure 2).

Recurrence was reduced by radiotherapy (sHR, 0.31; 95% CI, 0.15-0.61; P < .01). Patients treated by SRT were associated with an increased rate of distant metastasis as the first event (sHR, 4.17; 95% CI, 1.5-11.6; P < .01).

**DISTANT METASTASIS IN PATIENTS WHO DEVELOPED A LOCOREGIONAL RECURRENCE**

Of the 160 patients, 62 had distant metastasis during follow-up, 40 as a first recurrence of the disease and 22 after locoregional failure. The 5-year MFS rate was 51.9% (95% CI, 40.4%-60.4%). A time-dependent Cox regression model showed that patients developing a locoregional recurrence had a risk of relapsing from distant metastasis that was 3.07-fold greater than the risk for patients who did not develop a locoregional recurrence (95% CI, 1.65-5.67; P < .01). The HR for distant metastasis adjusted by treatment modality was 3.45 (95% CI, 1.95-6.13) for patients with locoregional relapse compared with others, which was similar to the unadjusted HR.

**DEATH IN PATIENTS WHO DEVELOPED A LOCOREGIONAL RECURRENCE AS THE FIRST EVENT**

Among the 64 patients who developed a locoregional recurrence as the first event, 35 were deceased at last follow-
Using time-dependent modeling, the HR of death was estimated to be 3.01 (95% CI, 1.91-4.78; \( P \times 10^{-2} \)) for patients presenting with a locoregional relapse as the first event compared with others. After adjusting by treatment modality, the HR of death was estimated to be 3.30 (95% CI, 2.06-5.27) for patients who had locoregional relapse compared with others, which was essentially the same as the unadjusted HR.

**COMMENT**

Because of its rarity, it is difficult to obtain an accurate incidence of mucosal melanoma; it may account for less than 3% of all melanomas.\(^1\) Head and neck sites comprise approximately half of mucosal melanomas. We report herein the largest series of HNMMs to date.

### STAGING

The nose and paranasal sinuses are the most common sites of origin, followed by the oral cavity.\(^10\) In most of our cases the sites of origin were located in the sinonasal tract. We could not, however, determine the exact origin of sinonasal tumors for many reasons, such as advanced stage at presentation, involvement of multiple subsites, and the lack of fiber optic endoscopy in some patients.

The age range was 30 to 93 years (median, 67 years) in our group of patients. This age range is comparable with those reported by others\(^11,12\) for patients with sinonasal mucosal melanoma. In our experience, most patients have been women (female to male ratio, 106:54).

### Table 2. Five-Year Relapse-Free Survival and Cumulative Incidence of Locoregional (LR) and Distant Metastasis (DM) by Treatment Group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>First Event, No.</th>
<th>5-y Survival, %</th>
<th>( P ) Value(^a)</th>
<th>LR, No.</th>
<th>5-y Cumulative Incidence, %</th>
<th>( P ) Value(^a)</th>
<th>DM, No.</th>
<th>5-y Cumulative Incidence, %</th>
<th>( P ) Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>82</td>
<td>55</td>
<td>26.5</td>
<td>.63</td>
<td>42</td>
<td>55.6</td>
<td>&lt;.01</td>
<td>13</td>
<td>17.9</td>
<td>.01</td>
</tr>
<tr>
<td>SRT</td>
<td>78</td>
<td>49</td>
<td>29.4</td>
<td></td>
<td>22</td>
<td>29.9</td>
<td></td>
<td>27</td>
<td>40.7</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: S, surgery alone; SRT, surgery with postoperative radiotherapy.

\(^a\) Log rank test.

\(^b\) Gray test.

### Table 3. Multivariate Analysis Cox vs Fine and Gray in 107 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Relapse-Free Survival</th>
<th>Fine and Gray (Competing Risks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>( P ) Value(^a)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>1 [Reference]</td>
<td>.51</td>
</tr>
<tr>
<td>SRT</td>
<td>0.85 (0.51-1.40)</td>
<td>.31</td>
</tr>
<tr>
<td>TNM at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/T2</td>
<td>1 [Reference]</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>T3/T4</td>
<td>2.46 (1.47-4.14)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DM, distant metastasis; HR, hazard ratio; LR, locoregional; sHR, subdistribution HR.

\(^a\) See Fine and Gray.\(^8\)

### Table 4. Multivariate Analysis for Overall Survival in 107 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>1 [Reference]</td>
<td>.80</td>
</tr>
<tr>
<td>SRT</td>
<td>1.08 (0.62-1.84)</td>
<td>.90</td>
</tr>
<tr>
<td>TNM stage at diagnosis</td>
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<td></td>
</tr>
<tr>
<td>T1/T2</td>
<td>1 [Reference]</td>
<td>.01</td>
</tr>
<tr>
<td>T3/T4</td>
<td>2.31 (1.29-4.12)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; S, surgery alone; SRT, surgery with postoperative radiotherapy.
microstaging system for patients with stage I primary HNMM. Level I included in situ mucosal melanoma, level II included invasion up to the lamina propria, and level III included deep invasion into the bone, cartilage, or skeletal muscle. In this report, the histologic characteristics of 61 HNMMs was reviewed by 2 pathologists who lacked knowledge of patient outcome. There was a significant and progressive decrease in survival associated with an increasing level of invasion. On multivariate analysis, the level of invasion remained an independent predictor of survival ($P = .03$).

**SURVIVAL AND LOCAL CONTROL**

Our follow-up was longer than that of most other series, with very few patients lost to follow-up. In our series, the OS rates were 63.5% at 3 years and 37.8% at 5 years. Interestingly, these rates are better than those reported by Manolidis and Donald11 in a comprehensive review of the literature (39.2% at 3 years and 17.1% at 5 years, including approximately 962 patients). Nevertheless, the results of Manolidis and Donald11 were derived from compiled data of several different studies.

The propensity of the local treatment of malignant mucosal melanoma to fail at the primary site is a considerable problem for most treated patients. Manolidis and Donald11 pooled the data from 14 series in which specific information about local control was provided; of 484 patients, 258 failed treatment locally (53.3%). Salvage surgery could be successfully performed in some patients in the absence of concurrent distant metastases.14-16

**SURGERY**

Surgery currently offers the best probability of cure and local control of malignant mucosal melanoma and represents the mainstay of treatment. Andersen et al14 showed that all survivors had been treated with a surgical approach, whereas patients treated with radiotherapy or chemotherapy without surgery had either no response or a short-lived response.

The therapeutic approach should be directed toward complete excision with curative intent. Unfortunately, the lesion is usually at an advanced stage at diagnosis. As a consequence, en bloc surgery is rarely feasible for sinonasal melanomas, and it is difficult to ascertain clear margins on a fragmented operative specimen. In contrast, in a series of mostly oral cavity melanomas, Penel et al17 suggested a prognostic value of clear margins.

Many studies have examined patients over several decades, during which surgical treatment may have changed. Lee et al15 attributed a better survival to advancements in surgical techniques and to intraoperative and postoperative patient care that allowed more radical procedures.

However, the issue of such radical procedures, sometimes including orbital removal or anterior craniofacial resection, needs to be put in proper perspective in relation to the overall prognosis of this malignant tumor.

In our series, the incidence of neck disease at presentation was low (3.8%). For this reason, we do not recommend elective neck dissection. The incidence of lymph node metastasis at the time of initial presentation may be higher in melanomas of the oral cavity, up to 25%.18 At this site, the use of sentinel node biopsy should be considered.

**RADIOTHERAPY**

Malignant melanoma is usually believed to be a radiotherapy-resistant tumor. Nevertheless, the role of radiotherapy in the management of this malignant tumor remains controversial.

To our knowledge, this is the largest series of HNMMs ever published. Our results demonstrate the significant benefit of postoperative radiotherapy on local control but not on survival.

In a cohort of 58 sinonasal melanomas, Lund et al19 found that OS did not improve by the addition of radiotherapy. Conversely, other authors3,20 have suggested that combination therapy of surgery with radiotherapy may be useful in the treatment of mucosal melanomas, especially when wide surgery with clear margins is not performed owing to the anatomy of the region.

Temam et al3 also found that the 5-year local control rates were 26% with surgery alone and 62% with postoperative radiotherapy, even though there were many more locally advanced tumors in the radiotherapy group. However, there were more distant metastases and a shorter OS, which was related to the locally advanced stage, in the radiation therapy group.
In all of these retrospective studies, there is a notable selection bias because patients with more advanced tumors are more likely to have received combined radiotherapy. Based on this assumption, we can estimate that if radiotherapy improves local control in the most advanced tumors, it should also benefit patients with smaller tumors. We can speculate that our S group (local failure, 45%) might have had better local control results with the addition of radiotherapy. We indeed found that the locoregional recurrence was the main modality of recurrence for patients who were not irradiated postoperatively.

Other interesting results emerged from our study. The relative risk for metastatic spreading and death was 3 times higher in patients who experienced local or regional failure compared with those who were free of disease. This finding underlines the importance of locoregional management in the treatment of HNMM.

One might therefore think that radiotherapy, by reducing local recurrences, could consequently reduce disseminated disease and thus improve survival. This study suffers from the intrinsic weaknesses of retrospective studies; however, to our knowledge, it is the largest study to date and has a confirmatory value for 2 other large retrospective studies regarding the benefit of postoperative radiotherapy on local control in the tumor bed. Obviously, radiotherapy resulted in a substantial improvement in locoregional control but also in an increased frequency of distant metastases as the first site of recurrence. The latter was, however, probably not a true indication of a higher distant recurrence rate in the SRT group but simply a consequence of the lower rate of locoregional recurrences as a first event. The patients who did not receive radiotherapy, however, had a high incidence of locoregional recurrences as a first event that concealed the true frequency of distant metastases. In fact, we observed that locoregional recurrence as a first event increased the risk of secondary dissemination. While radiotherapy was associated with more metastases, it must be noted that the disease of patients treated with radiotherapy is at more advanced stages, that is, these patients have a greater risk of metastases. In our series, there was a strong trend toward more locally advanced stages in the SRT group; however, this was not significant (P = .11). The only way to study the influence of radiotherapy on survival is to conduct a prospective randomized study comparing an arm of patients treated with surgery alone and another arm of patients treated with surgery and postoperative radiotherapy. The rarity of this disease, however, makes such studies difficult to conduct.

Based on radiobiological and retrospective clinical studies on cutaneous melanoma, some authors have stressed the use of hypofractionation. A prospective randomized trial conducted by the Radiation Therapy and Oncology Group compared standard vs a hypofractionated dose regimen for cutaneous melanomas. They were unable to find any difference in survival for the 2 groups. Owing to the risk of damage to normal tissues and the risk of late toxic effects with high doses per fraction, hypofractionation should be used with caution to treat tumors near neuro-optical structures, such as tumors of the sinuses. If hypofractionation is considered, highly conformal techniques (intensity-modulated radiation therapy, stereotactic radiotherapy) or proton therapy must be used. In such cases, standard fractionation might be preferred despite the theoretical yet poorly sustained radiobiological advantage of hypofractionation (with doses >2.5 Gy/fraction) in the clinical use of mucosal melanomas. Another drawback of hypofractionation schemes is that they often include relatively large treatment breaks (“split-course irradiation”) for soft tissues to heal, which are at risk for tumor repopulation.

CONCLUSIONS

This large retrospective study summarizes a multicentric 28-year experience with HNMM. As reported by many authors, this highly malignant tumor continues to represent a challenging problem in head and neck cancer. Surgery, when feasible, represents the mainstay of treatment. Even in the absence of a demonstrated survival benefit, postoperative radiotherapy is strongly recommended and has a clinically significant improvement of local control. The survival benefit of radiotherapy cannot be proven without a randomized prospective study in which the initial local stage should be detailed by a suitable classification. Patients presenting with mucosal malignant melanoma should be registered and entered into national or even international randomized controlled trials.
tegrity of the data and the accuracy of the data analysis.

Study concept and design: Benlyazid and Filleron. Acquisition of data: Benlyazid, Thariat, Temam, Malard, Florescu, Choussy, Makeieff, Poissonnet, Penel, Righini, Toussaint, Lacau St Guily, and Vergez. Analysis and interpretation of data: Benlyazid, Thariat, and Filleron. Drafting of the manuscript: Benlyazid, Thariat, and Filleron. Critical revision of the manuscript for important intellectual content: Benlyazid, Thariat, Temam, Malard, Florescu, Poissonnet, Penel, Righini, Toussaint, Lacau St Guily, Vergez, and Filleron. Statistical analysis: Benlyazid, Thariat, and Filleron. Administrative, technical, and material support: Benlyazid, Malard, Florescu, Penel, Toussaint, and Vergez. Study supervision: Benlyazid, Malard, and Lacau St Guily.

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REFERENCES