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Optimal management of Melanoma in situ and Stage I melanoma

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Abstract

The incidence of cutaneous melanoma is on the rise. While a significant amount of work has been done to evaluate the importance of various demographic, pathologic and clinical information in patients with melanoma *in situ* and stage I melanoma, no study to our knowledge has comprehensively evaluated this information. In this paper, we performed a retrospective case review of the outpatient management of 208 lesions of melanoma *in situ* and stage I melanoma during the years of 1988-2005. This included 137 melanoma *in situ* lesions and 71 stage I melanoma lesions. We sought to evaluate this continuum of early melanoma because we deemed these to be the vast majority of melanoma lesions presenting to dermatologic surgery centers while realizing that these two categories present two unique entities. 53.85% of the lesions were present in male patients while 46.15% of the lesions were diagnosed in female patients. The mean age of the entire patient population is 65.57 years. The mean age of patients that presented with malignant melanoma, superficial spreading is 63.94 years, while the mean age of the patient population with melanoma *in situ* is 66.67 years. The mean age of males is 68.34 years. The mean age of females is 65.51 years. Of the lesions in males, 37.50% are malignant melanoma while the remaining 62.50% are melanoma *in situ*. Of the lesions on females, 30.21% are malignant melanoma while 69.79% were diagnosed as melanoma *in situ*. Overall, the mean lesion size was 13.90 mm in diameter. The mean size of all of the melanoma *in situ* lesions is 14.50 mm, while the mean size of all lesions diagnosed as malignant melanoma is 11.68 mm. The mean depth of the malignant melanoma lesions is 0.42 mm.

From our data, stage I melanoma, melanoma *in situ*, and all lesions considered in aggregate show a statistically significant predilection to the head and neck areas. Additionally, when comparing stage I melanoma to melanoma *in situ*, the former lesions show a significant propensity for the trunk. Additionally, melanoma *in situ* lesions of the trunk showed a significant propensity for the right side. Our data demonstrates a low local recurrence rate of 4.38% for melanoma *in situ* lesions and a 1.41% local recurrence rate for stage I lesions. Our data indicates that all of the local recurrence occurred on the head and neck. Analysis suggests that lesions of the head and neck are more likely to recur than lesions elsewhere on the body. Further analysis did not suggest a difference of local recurrence rates between those patients treated with currently recommended clinical surgical margins of 5 mm in melanoma in site and 1 cm in stage I melanoma. All recurrences in our study occurred in patients treated with the recommended surgical margins. Finally, lesions of the head and neck were more likely to be melanoma *in situ* lesions than stage I melanoma in a statistically significant fashion.

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Introduction

The incidence of melanoma of the skin has rapidly risen (1). An estimated 59,580 new cases of invasive melanoma of the skin will occur in 2005 resulting in approximately 7,700 deaths. Additionally, another 46,170 new cases of melanoma *in situ* are expected in 2005 (1). At times progressive and deadly, melanoma is a disease of both the young and old. Melanoma is one of the most serious cancers when measured by years of life lost (2). Fortunately today, due to early detection and aggressive treatment, the majority of patients presents with localized disease that is limited to the skin (3) which decreases the mortality rate from melanoma. Increased awareness due to preventive skin cancer education programs has led to the presentation of melanoma at younger ages and earlier stages of disease (4, 5).

In the current staging system for melanoma, the American Joint Committee on Cancer (AJCC) classifies lesions based on tumor thickness (6). This staging system is classified by thresholds that correlate with clinical management and prognosis of melanoma patients. The AJCC designates stage I as tumors less than 1.0 mm thickness, stage II between 1.01-2.0 mm thickness, stage III between 2.01-4.0 mm thickness, and stage IV greater than 4.0 mm thickness. According to an AJCC study, tumor thickness was the most powerful independent prognostic factor for patients with primary cutaneous melanoma (6). Early melanoma includes melanoma *in situ* and invasive lesions less than 1.0 mm in depth (7).

Detection and treatment of melanoma at its earliest stages is usually curative. Detection of melanoma at later stages often leads to significant morbidity and mortality (8). Local surgical treatment of early melanoma remains the standard of care, but the

technique used, especially in relation to the clinical surgical margins remains an area of ongoing debate in current literature. The earliest reports by Samson Handley in 1905 suggested the need for the removal of 2 inches of subcutaneous tissue down to the fascia for melanoma (9). In 1962, Petersen, et al. suggested the need for up to 5 cm margins of normal skin even for thin invasive melanoma (10). These aggressive approaches were based on their belief that these treatments were necessary to prevent local recurrences and metastatic disease. Currently, most physicians follow the National Institutes of Health recommendation of 5 mm of clear clinical margins for melanoma *in situ* and 10 mm of clear clinical margins for stage I melanoma (7). In the case of melanoma *in situ*, local excision results in a 99% disease-free, long-term survival with local recurrence accounting for the other 1%. In the case of thin invasive melanoma, surgical removal results in greater than 90% disease-free, long-term survival (7).

Obtaining standard surgical margins in the treatment of early melanoma is not always practical. Often patients of advanced age or patients with lesions in cosmetically difficult areas require the use of narrower clinical margins or alternative therapies. Imiquimod, cryotherapy, and Q-switched ruby laser have all been suggested as alternatives to surgical treatment especially in patients of advanced age with melanoma *in situ*. Additionally, the use of clinical margins less than those previously suggested as the standard of care, especially in cosmetically sensitive areas such as the face, have been used with varying success (11-13). Although most physicians agree that obtaining 5 mm and 10 mm clinical margins for melanoma *in situ* and thin invasive melanoma respectively is optimal, significant exploration around the use of smaller margins continues. Although a number of researchers have evaluated the use of narrow margins

for intermediate invasive melanoma (13-15), few have examined the use of narrow margins in melanoma *in situ* and early invasive melanoma (12). Further research is needed to evaluate the use of narrow margins because the current evidence is not sufficient to address optimal surgical margins especially in the case of early melanoma.

The importance of cure at the time of initial treatment is due to the fact that local recurrence of melanoma may lead to considerably worse prognosis (16, 17). Some studies have suggested an association between narrow excision margins and recurrence rates (17). Reports of the rate of local recurrence of all melanomas even melanoma *in situ* vary dramatically from 0-50% within 5 years (18-20). One recent article reported a 6.8% 5-year recurrence rate for surgically removed melanoma *in situ* lesions. Further, this study suggested that treatment other than excision as well as site of involvement were significant prognostic variables in relation to recurrence. Patient age at treatment was not found to be a significant variable in this study (20).

In addition to the debate regarding surgical margins in melanoma, the optimal excision technique employed for the removal of early melanoma remains controversial. Some physicians suggest the use of Mohs' micrographic surgery (21, 22), though the use of frozen sections for evaluation of disease-free margins remains controversial. Staged excision procedures using permanent sections are often employed for the treatment of melanoma (23). This technique employs serial sections when necessary to spare tissue while ensuring the removal of the entire lesion.

Because of the lack of definitive guidelines regarding the optimal management of early stage melanoma, we reviewed a range of established clinical parameters to clarify better the useful treatment approaches for early melanoma. Our review that follows

presents one of the most complete and thorough reviews of treatment and pathological criteria of melanoma *in situ* and stage I melanoma.

Specific Aims and Hypotheses

Aims

1) To define practical clinical parameters for the treatment of early melanoma including clinical margins.
2) To evaluate predictors of recurrence of early melanoma.

Hypotheses:

1) Age, sex, body site, and treatment modalities used in the treatment of melanoma affect the recurrence rate.
2) However, "suboptimal" margins do not affect recurrence rates; therefore current recommendations of 5 millimeters for melanoma *in situ* and 10 millimeters for stage I melanoma need not be absolute guidelines under certain circumstances especially in cosmetically sensitive areas and in patients with advance age.

Methods

We performed a retrospective case review of the outpatient management of melanoma *in situ* and stage I melanoma at Yale Dermatologic Surgery and Cutaneous Oncology Section in the Department of Dermatology. The study period was 1988-2005. The study was approved under Human Investigation Committee protocol # 27327. In order to define our patient population, we performed a search of all pathological specimens for any diagnosis including melanoma. All patients with the diagnosis of melanoma *in situ* and stage I melanoma, superficial spreading type with a depth less than 1.0 mm were included in the study. In patients with multiple primary lesions, each lesion was treated as a separate individual case.

Patients who presented with stage I melanoma, superficial spreading type with a depth greater than 1.0 mm were excluded. Likewise, patients with stage I melanoma, acral lentiginous type and nodular type were excluded because they represent unique diagnostic and treatment entities. Also excluded from statistical analysis were all patients treated with non-surgical methods including imiquimod and Q-switched Ruby Laser. These excluded patients are discussed anecdotally in the results and discussion sections. Patients that were definitively treated by other providers who were referred as local recurrences were likewise excluded. Additionally, patients with metastatic disease at presentation were excluded. Patients who were not definitively treated at our clinic including those who presented for consultation only or those patients who were referred to other physicians for definitive treatment and often sentinel node biopsy were likewise excluded. Although rare, patients with incomplete or unavailable charts were excluded.

All data was recorded in a Microsoft Excel 2002 spreadsheet under human investigation committee protocol and all data was analyzed using the chi-square test in SAS program (SAS Institute Inc. SAS Release 8.2. Cary, NC; 2001) unless otherwise indicated. Margin data was recorded from the operative report and added to the margins of the previous stage(s) of excision if multiple stages were taken. In the rare case in which data about the clinical surgical margins or clinical size of lesion was not recorded in the patient chart, these values were calculated using the measurements of the pathological specimen with the assumption that specimens shrink approximately 30 percent from their *in vivo* state. In the case when clinical margins were not recorded, the width of the ellipse or the diameter of the circle of the pathological specimen was multiplied by 1.3 and the larger diameter of the lesion was subtracted to approximate thee clinical margin. Conversely, if the clinical size of the lesion was not recorded, then the width of the ellipse or the diameter of the circle of the pathological specimen was multiplied by 1.3 and then the recorded clinical margin was subtracted from the calculated value to obtain the approximate diameter of the lesion (see figure 1).

Results

Inclusion & Exclusion

A total of 275 patients were identified using the study criteria. A total of 77 patients were excluded (see Table 1). The charts of 14 patients were either incomplete or unavailable. 3 patients with malignant melanoma, acral lentiginous type and 2 with nodular type were excluded. A total of 14 patients were treated with non-surgical modalities including 10 treated with imiquimod and 4 treated with Q-switched ruby laser. Of note, 7 of the 10 patients that were treated with imiquimod have been followed clinically without any indication of recurrent melanoma *in situ*. Three patients presented with local recurrences. Two patients treated with the laser therapy required further excision while the other 2 required no further treatment.

Melanoma *in situ* lesions on three patients proved extremely difficult to remove completely; after multiple stages with positive margins, the decision was made to follow these lesions clinically. Other excluded patients include: 21 patients who were referred to other physicians for definitive treatment and sentinel node biopsy; 2 patients that presented for consultation only; 4 patients who presented with local recurrence; and 4 patients who presented with metastatic disease. Finally, 10 patients with stage I melanoma, superficial spreading type were excluded with lesions between 1.0 mm and 2.9 mm in depth. Of note, our charts including outside consultation notes on these patients indicated that none of the 10 patients excluded based on depth of lesion experienced recurrence.

A total of 198 patients with 208 primary lesions were evaluated in the statistical analysis that follows (2 patients were treated for 2 primary lesions and 2 patients were treated for 3 primary lesions).

Patient Demographics

112 (53.85%) of the lesions were present on male patients while 96 (46.15%) of the lesions were present on female patients. The mean age of the entire patient population was 65.57 +/- 14.43 years. The mean age of patients that presented with stage I melanoma, superficial spreading was 63.94 +/- 16.76 years, while the mean age of the patient population with melanoma *in situ* is 66.67 +/- 12.78 years. The mean age of males was 68.34 +/- 13.08 years. The mean age of females was 65.51 +/- 15.00 years. The mean time since treatment was 6.78 +/- 4.17 years in the entire patient population with a median of 6.67 years. The range was 2.5 months to 14 years.

Description of Lesions Based on Diagnosis

In the entire patient population, 71 (34.13%) of the lesions were stage I melanoma while the remaining 137 (65.87%) were melanoma *in situ*. Of the lesions on males, 42 (37.50%) were stage I melanoma while the remaining 70 (62.50%) are melanoma *in situ*. Of the lesions on females, 29 (30.21%) were stage I melanoma while 67 (69.79%) were diagnosed as melanoma *in situ*.

Description of Lesions Based on Size and Depth

In order to evaluate the size of the lesion, the greatest clinical measurement was used. Overall, the mean lesion size was 13.90 +/- 8.62 mm in diameter. The mean size of all of the melanoma *in situ* lesions was 14.50 +/- 8.84 mm, while the mean size of all

lesions diagnosed as stage I melanoma was 11.68 +/- 7.02 mm. The mean depth of the stage I melanoma lesions was 0.42 +/- 0.21 mm.

Description of Lesions Based on Location

Table 2 illustrates the distribution of stage I melanoma and melanoma *in situ* by body site and side. Body site is divided into 4 categories: head and neck (HN), upper extremity (UE), trunk (T), and lower extremity (LE). Laterality is divided into left, middle, and right. In Table 3 the lesions are further divided by diagnosis, body site category, and side. Finally, in Table 4 the lesions of the trunk and head and neck are separately divided into specific sites within the specific body site category. For the trunk lesions, they are divided into front, back, and other (including shoulder and flank). For the head and neck lesions, 10 separate subsets were employed: cheek, chin, ear, eyelid, forehead, lip, neck, nose, scalp, and temple.

Pathologic Descriptors of Stage I Melanoma

Table 5 allocates the stage I melanoma lesions into categories based on pathological criteria. These criteria include: the Clark's level, the presence or absence of ulcerations, and the growth phase.

Recurrences

The overall local recurrence rate observed in our study population was 3.37% with a 4.38% local recurrence rate for melanoma *in situ* lesion and a 1.41% local recurrence rate for stage I melanoma. We are not aware of any metastatic disease occurring in our patient population. In our entire study population including melanoma *in situ* and stage I melanoma, there was an overall 4.17% recurrence rate among female

patients and a 2.68% recurrence rate among male patients. Similarly, 4.27% of the lesions on patients older than the mean age recurred while only 2.68% of the lesions on patients younger than the mean recurred. All local recurrences arose on the head and neck. The overall recurrence rate on the head and neck was 5.88% (6.81% for melanoma *in situ*, 3.22% for stage I melanoma). Finally, 4.65% of lesions larger than the mean size when measured by greatest clinical diameter recurred while only 2.46% of lesions smaller than the mean size recurred locally. All of this data along with corresponding statistical values are reported in Table 6. The corresponding values from statistical analysis of potential predictors of recurrence are included in this table.

Recurrences based on Margins

Margins of 2-10 mm were required to remove the melanoma *in situ* lesions with a mean of 5.15 mm and a standard deviation of 1.60 mm. Margins of 3-20 mm were employed to eradicate the stage I melanoma lesions with a mean of 9.11 mm and a standard deviation of 3.00 mm. A vast majority of both sets of lesions were removed successfully using the recommended 5 mm for melanoma *in situ* and 1 cm for stage I melanoma. Under certain circumstances, narrower margins were employed, while in other cases, larger clinical margins were necessary after repeated stages to remove the entire lesion. The exact margins and number of cases that employ each respective margin are reported in Table 7.

Recurrences based on Stages and Margins

Table 8 shows recurrences based on the number of stages necessary to remove the lesion. For most lesions, only one stage was required to eradicate all disease although up

to five stages were required for one case of melanoma *in situ*. All local recurrences of melanoma *in situ* and stage I melanoma occurred in excisions with a single stage.

Non-Surgical Treatment of Melanoma In Situ

As noted previously, 10 lesions were treated with imiquimod while 4 patients were treated with Q-switched Ruby laser. Seven of the 10 patients treated with imiquimod showed pathological clearance. During our study period, 3 of the 10 or 30% of patients presented with local recurrences. Of the 4 patients treated with Q-switched Ruby laser, 2 cleared clinically while 2 required further excision.

Diagnosis Data

In order to evaluate the impact of sex, age, body site, and lesion size on the diagnosis of melanoma *in situ* or stage I melanoma, the number of stage I melanoma patients in relation to each of these parameters was recorded as seen in Table 9. 30.21% of female patients versus 37.50% of male patients in our patient population were diagnosed with stage I melanoma. 38.10% of patients older than the mean age of our population were diagnosed with stage I melanoma versus 31.45% in patients younger than the mean population. Only 26.05% of the lesions of the head and neck were stage I melanoma versus 44.94% of the lesions diagnosed on the remainder of the body. When lesion size was considered, 37.70% of the lesions larger than the mean size were stage I melanoma while 57.38% of lesions smaller than the mean size were stage I melanoma.

Evaluating Trends

Using data from Table 10, we evaluated potential trends in the depth and size of lesions as well as patient age and sex over three consecutive five year periods. In order to

increase the number of lesions for evaluation and statistical power of the analysis, our entire spectrum of early melanoma including melanoma *in situ* lesions as well as stage I were combined. Corresponding statistical values are included for each analysis performed with the data in Table 10.

Discussion

Based on the recent literature as noted in our introduction, this work presents one of the most complete and comprehensive case reviews of patients with melanoma *in situ* and stage I melanoma. Most previous work focuses on just one of the many clinical parameters that we evaluated in our study. The authors realize that one major shortcoming of some of our analysis is that the cases of melanoma *in situ* were combined with stage I melanoma cases. Previous studies and reviews have evaluated these two entities as early melanoma (24). Although these two entities have very different biologies, especially in regards to the metastatic potential of stage I melanoma (25), local surgical treatment with narrow margins remains the widely accepted standard of care for both processes. Furthermore, these entities represent a majority of melanoma treated by dermatologic surgeons. In order to account for the differences between melanoma *in situ* and stage I melanoma, when possible, analysis was done on the two groups separately and aggregately.

The average time since treatment records only a gross estimate of disease-free survival in these patients. When noted in chart, date of death was taken into account when calculating time since treatment. Patients have not yet been contacted for follow-up, and most likely we are unaware of some patients who are now deceased. We also are aware that some patients may have been treated at other institutions, though none of the patients analyzed in this section submitted a request for transfer of their medical records. Closer follow-up via phone calls and examination will give a better measure of disease-free survival.

Patient Demographics

The larger proportion of male patients (53.85% versus 46.15%) did not indicate a statistically significant differenee in gender distribution (p-value=0.2734). However, our patient population with a mean age of almost 66 years did prove to be a relatively older population compared with recently reported data, including one that reported an average age of 46 years for patients with these lesions (which included melanoma *in situ* and stage I lesions) (4). One interpretation of this data could suggest that there exists a poor awareness among the patient population treated in our study about the signs of melanoma. This data hints at the need for further educational programs about melanoma. The difference in age between patients with melanoma *in situ* and stage I melanoma did not reach statistical significance.

Lesion Characteristics

From our data, stage I melanoma, melanoma *in situ*, and all lesions considered in aggregate show a statistically significant ($p<0.001$) predilection to the head and neck areas, potentially refleeting a referral bias based on expertise. Additionally, when comparing stage I melanoma to melanoma *in situ*, the former lesions show a propensity for the trunk (26.76% versus 14.60%). Additionally, the 19 melanoma *in situ* lesions of the trunk showed a propensity for the right side (55% on the right versus 20% on the left). No other significant relationships were observed within the specific side or site of the body.

The distribution of melanoma *in situ* lesions in regard to head and neck, trunk, upper extremity, and lower extremity were fairly consistent with recently published data (20). Our results suggest a slightly higher preponderance of lesions on the head and neck

areas (64.23% versus 53.4%) with a smaller percentage of trunk (14.60% versus 20.3%) and lower extremity (10.95% versus 16.4%) lesions when compared to the previously mentioned study. These differences did not prove statistically significant.

Unfortunately, due to the significant number of pathological reports that omitted ulceration and growth phase information, little information can be gleaned from this data about the stage I melanoma lesions in our study. None of the pathological data indicated the presence of ulcerations within these lesions. Based on discussions with our dermatopathologists, we can likely assume that none of these lesions were ulcerated. This is not an unexpected result as ulceration is often seen in later stages of melanoma and would warrant further evaluation. Growth phase remains a difficult pathological criterion to evaluate with recent literature suggesting some inter-observer disagreement among non-specialist pathologists (26). Interestingly, only two stage I melanoma lesions in our study were Clark's level I. A vast majority of the lesions were Clark's level II.

Overall Recurrence Data

Based on recent published data, our data suggests an extremely low recurrence rate overall and also when divided between melanoma *in situ* and stage I melanoma. Zalaudek, et al. report a 5-year local recurrence rate of 6.8 +/- 1.3% for melanoma *in situ* lesions (20). Our data shows a local recurrence rate of 4.38% for melanoma *in situ* lesions. Additionally, Ng, et al. reported a 2.58% local recurrence rate for stage I melanoma. Again, our data demonstrate a 1.41% local recurrence rate for similar lesions.

Our data indicate that all of the local recurrence occurred on the head and neck. These data prove to be extremely interesting when compared to previous studies. In one study of stage I melanoma lesions by Ng, et al. (16), the distribution of sites in which

recurrences occurred were much more evenly distributed among the head and neck, trunk, and extremities. In their study, only 26% of the local recurrences occurred on the head and neck. The significance of the difference in their experience as well as the ability to extrapolate those data to our experience with melanoma *in situ* is an area that requires further analysis.

Predictors of Recurrence

Using data from Table 6, we evaluated the significance of sex, age, body site, lesion size, and specific diagnosis on recurrence rates. The only factor that proved to be a statistically significant predictor of recurrence for the lesions in aggregate and also when evaluated separately by melanoma *in situ* and stage I melanoma was the location of the lesion. In aggregate, our analysis suggested that lesions of the head and neck are more likely to recur ($p=0.0186$) than lesions elsewhere on the body. This finding is in agreement with another recent report that also showed that melanoma originating on the head and neck was a statistically significant predictor of recurrence (20). This implies the need for caution when removing lesions of the head and neck and interpreting the pathological specimens. Lesions in patients older than the mean age were 2.5 time more likely to recur than those in patients younger than the mean age, but this did not prove to be statistically significant. In a larger cohort of patients, this may prove to be a more significant predictor of recurrence, although previous reports have shown results similar to ours (20).

The sex of the patient and the size of the lesions likewise did not show statistical significance, though based on the odds ratio our data suggests that lesions on female patients are 1.5 times more likely recur and lesions larger than the mean size are 1.2 times

more likely to recur. The applicability of this information for all patients with melanoma *in situ* or stage I melanoma requires further analysis and future studies in a larger cohort of patients. The pathological diagnosis of melanoma *in situ* did not prove to be a statistically significant predictor of recurrence. This may reflect a more aggressive surgical treatment of stage I melanoma as compared to melanoma *in situ*. In our analysis, we did not evaluate the impact of the depth of invasion of the stage one lesions on recurrence because only one of the 71 lesions recurred and thus proper statistical analysis was not possible for this parameter.

Important Treatment considerations

Treatment for each unique case must be tailored to the patient based on the information the clinician obtains about the lesion. Each instance in which margins less than generally accepted standards of 5 mm for melanoma *in situ* and 1 cm for stage I melanoma was tailored to the specific case. In a number of instances in patients, especially of advanced age with stage I melanoma, an initial diagnosis of melanoma *in situ* was made by biopsy and thus margins less than 1 cm were indicated for the initial excision. If pathologic sections of these lesions revealed disease-free margins, close clinical follow-up was at times deemed the best option for the patient. This was the case in which a 3 mm margin was used on one patient who, after definitive treatment, was diagnosed with stage I melanoma. Patients were made aware of the significance of the diagnosis and importance of close monitoring of the site of involvement. In a number of these patients, after being given the option of another stage of excision or monitoring, the patient chose to monitor closely. Again in these cases, patients were educated about the risks and benefits of monitoring. The ability to closely monitor the aforementioned

patients pivots on a clear and strict understanding of disease-free clinical margins between the surgeon and pathologist.

That being stated, our data suggests that clinical surgical margins narrower than standard recommended margins of 5 mm clinical margins for melanoma *in situ* and 1 cm clinical margins for stage I melanoma may prove to be acceptable on a larger scale. Each case in our panel of patients in which margins narrower than standard recommended margins were employed was carefully evaluated.

"Suboptimally Treated" Patients: The Impact of Surgical Margins Employed

Differing from other studies (14, 16), our analysis did not suggest a significant difference of local recurrence rates between those patients treated with currently recommended clinical surgical margins of 5 mm in melanoma *in situ* and 1 cm in stage I melanoma. As discussed previously, various factors led to many cases in which smaller surgical margins were used. In our patient population, none of the local recurrences occurred in a patient that was treated with narrower margins than recommended. The six melanoma *in situ* lesions that recurred were all treated with 5 mm surgical margins, while the one stage one melanoma lesion that recurred locally was treated with a 1 cm margin. Thus, our experience again suggests that under the right circumstances and in specific situations, narrower surgical margins can be successfully employed for melanoma *in situ* and stage I melanoma without compromising disease eradication. Thus, current recommendations for clinical surgical margins may not need to be strict guidelines. The current guidelines for margins should remain the goal in each case until further controlled studies are carried out to evaluate narrow margins. Again, further study is warranted.

Impact of Number of Stage Employed

As was previously mentioned, all 7 local recurrences occurred in patients who had been treated with a single stage excision. The clinical significance of this finding is yet to be determined. To date, we are unaware of other studies that have evaluated the impact of the number of stages of excision on recurrence. In reviewing the pathology reports from these recurrences, a number of the reports suggest the presence of tumor "close to but not on the specimen margin" or some similar statement. In one report, the tumor was noted to be "greater than 1 mm from the surgical margin." Although outside the scope of the study, further investigation into exactly how the specific pathologists use the term "close" under these circumstances may prove to be useful for future studies.

Predictors of Invasions

From our cohort of patients, we were interested in any clinical or demographic information that may predict the presence of invasion. From our study, women are no more likely to have invasive disease. Men and women are equally likely to suffer from stage I melanoma. Similarly, advanced age as defined by patients older than our mean population age are not more likely to have stage I melanoma than melanoma *in situ*. Therefore, more aggressive lesions such as stage I melanoma in our study are equally likely to present in younger patients (again defined as patients younger than the average patient population) and older patients. Likewise, larger lesions were not more likely to be stage I melanoma than melanoma *in situ*.

On the other hand, lesions of the head and neck were more likely to be melanoma *in situ* lesions than stage I melanoma in a statistically significant fashion ($p=0.0033$).

This statistical significance may reflect the impact of sun exposure on the incidence of early melanoma on the head and neck areas.

Analysis of Trends

To evaluate trends in the diagnosis of these lesions, the number of lesions with a depth greater than or less than the mean depth at diagnosis of stage I melanoma was first evaluated over three separate, approximately five year periods. One may hypothesize that lesions are currently diagnosed at early stages due to better patient and physician awareness and thus the lesions should show a trend of decreasing depth over these time periods. Unfortunately, no statistically significant decrease in the depth of lesions was seen. Conversely, evaluation of these stage I lesions indicated no statistically significant increase in the depth at diagnosis.

Collectively, these lesions were then evaluated based on trends in diagnosis by patient sex, the number of patients older than or younger than the mean patient age, and the number of lesions greater then or less than the mean lesion size. Although combining stage I melanoma lesions with melanoma *in situ* lesions may not prove completely accurate, the idea is to evaluate any potential trends in the diagnosis of the continuum of early melanoma. Neither patient sex nor lesion size showed any statistically significant trends. The number of patients older than the mean patient age, however, indicated a statistically significant ($p=0.0271$) increase over the three time periods. One of the major confounding factors in this evaluation is significant increase in the age of the population, and thus no clear determination about the trend of increasing age in our patient population can be made without further analysis.

Summary

Despite a large body of literature about practical consideration in the treatment of melanoma *in situ* and stage I melanoma, significant gaps in the understanding of practical considerations exists. Our study provides a comprehensive analysis of 208 cases and evaluates the significance of various demographic, pathological and clinical data for these cases. Findings from our study suggests a need for more studies into the significance of narrow surgical margins especially in the treatment of melanoma *in situ* and stage I melanoma.

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Figure

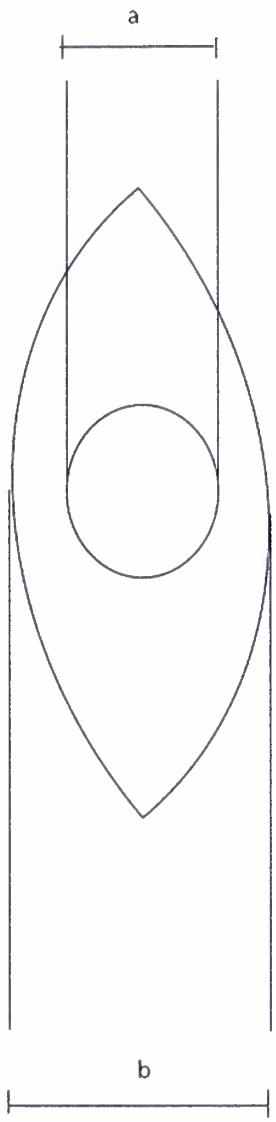

Figure 1: Calculation of Omitted Data: Representation of our method for calculating missing lesion size and clinical surgical margin data. To calculate omitted clinical surgical margins length "b" was subtracted from "a" and divided by 2. To calculated omitted lesion size, the clinical surgical margin was multiplied by 2 and subtracted from value "b."

Tables

Patients Excluded and Exclusion Criteria

Malignant Melanoma, Type	#
Nodular	2
Acral Lentiginous	3
Malignant Melanoma, Superficial Spreading, Depth	
1.0 mm - 2.9 mm	10*
Non-Surgical Treatment	
Imiquimod	10**
Q-switched ruby laser	4
Other	
Patients never cleared of disease pathologically who were followed clinically	3
Patient referred for definitive treatment	21
Consultation only	2
Local recurrence at presentation	4
Metastatic disease at presentation	4
Charts unavailable or incomplete	14

Table 1: Patients Excluded and Exclusion Criteria: The number of patients and reasons for exclusion from our study population. *of the 10 patients with thickness >1.0 mm, no recurrences occurred. **7 of these patients are clinically clear of disease. Abbreviations: mm, millimeters

	MM	% of MM	MIS	% of MIS	total	% of total
HN	31	43.66%	88	64.23%	119	57.21%
UE	8	11.27%	15	10.95%	23	11.06%
T	19	26.76%	20	14.60%	39	18.75%
LE	13	18.31%	14	10.22%	27	12.98%
total	71	100.00%	137	100.00%	208	100.00%

Table 2: Lesion Site by Category: Lesions divided into categories based on diagnosis (melanoma in situ or stage I melanoma) and body site. Abbreviations: MM, malignant melanoma (specifically stage I melanoma in our evaluation); MIS, melanoma in situ; HN, head and neck; UE, upper extremity; T, trunk; LE, lower extremity

Side	MM	% of MM	MIS	% of MIS	total	% of total
Left	28	39.44%	62	45.26%	90	43.27%
Middle	10	14.08%	18	13.14%	28	13.46%
Right	33	46.48%	57	41.61%	90	43.27%
total	71	100.00%	137	100.00%	208	100.00%

Stage I Melanoma

	LEFT	% of site	MIDDLE	%	RIGHT	%	total
HN	13	41.94%	4	12.90%	14	45.16%	31
UE	4	50.00%	0	0.00%	4	50.00%	8
T	5	26.32%	6	31.58%	8	42.11%	19
LE	6	46.15%	0	0.00%	7	53.85%	13
total	28		10		33		71

Melanoma *in situ*

	LEFT	%	MIDDLE	%	RIGHT	%	
HN	43	48.86%	13	14.77%	32	36.36%	88
UE	8	53.33%	0	0.00%	7	46.67%	15
T	4	20.00%	5	25.00%	11	55.00%	20
LE	7	50.00%	0	0.00%	7	50.00%	14
total	62		18		57		137

Table 3: Lesion Site by Side and Category: Lesions divided by diagnosis, body site, and laterality. Abbreviations: MM, malignant melanoma (specifically stage I melanoma in our evaluation); MIS, melanoma in situ; HN, head and neck; UE, upper extremity; T, trunk; LE, lower extremity.

Trunk

	MIS	% of MIS	MM	% of MM
Back	12	60.00%	10	52.63%
Front	5	25.00%	3	15.79%
Other	3	15.00%	6	31.58%
total	20		19	

Head/Neck

	MIS	% of MIS	MM	% of MM
CHEEK	27	30.68%	11	35.48%
CHIN	4	4.55%	1	3.23%
EAR	3	3.41%	5	16.13%
EYELID	2	2.27%	2	6.45%
FOREHEAD	10	11.36%	3	9.68%
LIP	4	4.55%	1	3.23%
NECK	4	4.55%	1	3.23%
NOSE	26	29.55%	4	12.90%
SCALP	4	4.55%	2	6.45%
TEMPLE	4	4.55%	1	3.23%
total	88		31	

Table 4: Site Subsets for Trunk and Head/Neck: Lesions divided by diagnosis and specific sites of the trunk and head and neck areas. Abbreviations: MM, malignant melanoma (specifically stage I melanoma in our evaluation); MIS, melanoma in situ.

Clark's Level		
1	2	2.47%
2	52	64.20%
3	27	33.33%
total	81	

Ulceration		
Y	0	0.00%
N	40	50.00%
NR	40	50.00%
total	80	

Growth Phase		
Radial	31	38.75%
Vertical	19	23.75%
NR	30	37.50%
total	80	

Table 5: Pathological Descriptors of Stage I Melanoma: Stage I melanoma lesions divided by Clark's level, presence or absence of ulceration, and growth phase. Abbreviations: Y, presence of ulceration; N, absence of ulceration; NR, no pathological criteria record.

	Recurrence	Out of	%	Chi-Squared	Odds Ratio	Fisher's Exact Test
Melanoma *In situ*	6	137	4.38%			
Stage I Melanoma	1	71	1.41%			
Overall Recurrence	7	208	3.37%			
Sex by Recurrence						
Female	4	96	4.17%			
Male	3	112	2.68%			
total	7	208	3.37%		1.5808	0.2505
Age by Recurrence						
age > mean age	5	117	4.27%			
age < mean age	2	91	2.20%			
Total	7	208		0.2441	2.5962	
Body Site by Recurrence						
Head/Neck	7	119	5.88%			
Other	0	89	0.00%			
Total		208		**0.0186**	N/A	
Lesion Size by Recurrence						
Lesion > mean size	4	86	4.65%			
Lesion < mean size	3	122	2.46%			
total		208			1.2477	0.7751
Diagnosis by Recurrence						
Melanoma *in situ*	6	137	4.38%			
Stage I melanoma	1	71	1.41%			
total		208		0.1982	0.2695	

Table 6: Recurrence Data: Recurrence data based on diagnosis, sex, age, body site, and lesion size.

Melanoma in situ

Clinical margins (mm)	# of lesions	Recurrences
2	3	0
3	12	0
4	3	0
5	107	6
7	1	0
10	11	0
total	137	6

Stage I Melanoma

Clinical margins (mm)	# of lesions	Recurrences
3	1	0
5	16	0
7	1	0
8	1	0
10	47	1
12	2	0
15	1	0
20	2	0
total	71	1

Table 7: Clinical Margins: Clinical surgical margins, number of patients in which each margin was employed, and the number of recurrences based on margins. Abbreviations: mm, millimeters.

# Stages of Excision	Melanoma *in situ* lesions	# of recurrences	Stage I melanoma lesions	# of recurrences	Total recurrences
1 Stage Excision	112	6	54	1	7
2 Stage Excision	19	0	14	0	0
3 Stage Excision	3	0	3	0	0
4 or greater Stage Excision	3	0	0	0	0
total	137	6	71	1	7

Table 8: Stages of Excisions: Number of stages employed for excision based on diagnosis with corresponding recurrences.

	Stage I melanoma	Out of	%	Chi-squared	Odds Ratio	Fisher's test
Sex by Diagnosis						
Female	29	96	30.21%			
Male	42	112	37.50%			
total		208		0.285	0.74	
Age by Diagnosis						
Age > mean age	32	84	38.10%			
Age < mean age	39	124	31.45%			
total		208		0.0571	0.5856	
Body Site by Diagnosis						
HN	31	119	26.05%			
Other	40	89	44.94%			
total		208		**0.0033**	0.4358	
Lesion Size by Diagnosis						
Lesion > mean size	46	122	37.70%			
Lesion < mean size	35	61	57.38%			
total	81	183			0.9253	0.1073

Table 9: Diagnosis Data: Diagnosis of stage I melanoma based on sex, age, body site and lesion size with corresponding statistical data. The "Out of" column represents the totally number of melanoma *in situ* and stage I melanoma patients within each corresponding category.

		1/90-12/94	1/95-12/00	1/01-2/05	total	Chi-squared
Lesion Depth of Stage I Melanoma	**Depth > mean**	11	11	5	27	
	Depth < mean	17	27	11	55	
	Total	28	38	16	82	0.3647
Patient Sex	**Female**	27	37	32	96	
	Male	29	46	37	112	
	Total	56	83	69	208	0.9188
Age	**Age > mean**	24	50	43	117	
	Age < mean	32	33	26	91	
	total	56	83	69	208	**0.0271**
Size	**Size > mean**	24	36	26	86	
	Size < mean	32	47	43	122	
	total	56	83	69	208	0.9442

Table 10: Trends during three 5 year periods: Data used to evaluate trends in patient and lesion characteristics over 15 year time period with corresponding statistical data from the Chi-squared test. Evaluation of patient sex, age, and lesion size included melanoma in situ and stage I melanoma in aggregate in an attempt to increase statistical significance. Mean depth of stage I melanoma was 0.42 millimeters, mean size was 13.90 millimeters, and mean age 65.56 years.

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