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Patterns of Recurrence and Survival in Stage III Melanoma Patients: Implications for Follow-Up Guidelines

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Patterns of Recurrence and Survival in Stage III Melanoma Patients: Implications for Follow-Up Guidelines

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An abstract of

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Abstract

Patterns of Recurrence and Survival in Stage III Melanoma Patients: Implications for Follow-Up Guidelines

By Sylvie Madeyo Mimche

BACKGROUND:
Standard cancer staging and prognosis estimates are determined at the time of the patient’s initial disease presentation. Melanoma stage III is associated with a high risk of recurrence and mortality. With the introduction of new and innovative therapies for the treatment of patients with melanoma and the recent revision of the seven editions of the AJCC staging systems; The understanding of the pattern of recurrence and the survival outcomes of these high-risk patients is important to improve early detection and management of the disease. We propose to evaluate the patterns of recurrence and the survival prognosis of patients with melanoma stage III at diagnosis.

METHODS: A retrospective study of patients followed and treated at the Huntsman Cancer Institute of Utah between 2000 and 2015 was undertaken. We assessed the site and time of the first recurrence (TTR), the recurrence-free survival (RFS), the melanoma specific survival (MSS) and overall survival (OS) using Kaplan Meier survival probabilities and Cox-proportional hazard analysis.

RESULTS: A total of 554 patients with melanoma stage III at diagnosis were included in the analysis. Of these, 34% were stage IIIA, 22% stage IIIB, 42% stage IIIC and 4% stage IIID. The median age at diagnosis was 55 years and the median follow-up time was 51 months. One third of this cohort relapsed with a median time to recurrence of 14 months. The main site of recurrence was nodal (34%), local or in-transit (20%), lung (20%) and brain (10%). The majority of patients who relapsed within one year after curative surgery were from stage IIIA (31%), IIIB (42%) IIIC (41%), and IIID (67%). The estimated 5-years RFS rates for stage IIIA, IIIB, IIIC and IIID were 83%, 73%, 56%, and 47%; the MSS rate were 91%, 83%, 71% and 45.5% and the OS rate were 88%, 79%, 60% and 29% respectively.

The adjusted multivariable Cox regression models showed that stage IIIC (HR= 2.74, 95%CL 1.3-5.4) and IIID (HR=3.86, 95%CL 1.4-10.5) were associated with an increase in the hazard of relapse compared to stage IIIA. Similarly, stage IIIC (HR= 3.5, 95%CL 1.9-6.7) and IIID (HR= 9.6, 95%CL 4.0-23.1) were associated with an increase in the hazards of death compared to stage IIIA.

CONCLUSIONS: Our data suggest that substage IIIC and IIID at diagnosis are associated with the higher risk of relapse and death. The fact that the majority of patients relapse before 2 years urges us to concentrate follow-up surveillance within this time period.
Patterns of Recurrence and Survival in Stage III Melanoma Patients: Implications for Follow-Up Guidelines

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Fall 2018

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I. LITERATURE REVIEW AND BACKGROUND

BACKGROUND:

Cutaneous melanoma is the most aggressive skin cancer in the United States, and its incidence has risen rapidly over the past 30 years \[1\]. Melanoma accounts for less than five percent of all skin cancer cases, but is responsible for the majority of skin cancer related deaths due to its tendency to metastasize to regional and distant sites. In the past decade (2008 – 2018), the number of new melanoma cases diagnosed has increased by 53 percent, and the annual incidence rate is estimated to be 26 per 100,000 population this year \[2\]. The American Cancer Society estimates that approximately 91,270 Americans (55,150 men and 36,120 women) will develop invasive cutaneous melanoma in 2018 and more than 50 per cent of those diagnosed are less than 65 years old. The estimated mortality rates from melanoma is 9,320 (5,990 male and 3,330 female) deaths in 2018\[2\].

The rapid increase of melanoma over the years has contributed to the growing burden on the health care system. The annual cost of treating skin cancers in the U.S. is estimated at $8.1 billion, with about $4.8 billion for nonmelanoma skin cancers and $3.3 billion for melanoma (cancer facts, 2018). Previous study has suggested that early diagnosis and treatment could reduce deaths from metastatic melanoma in the USA between 21% and 71% \[3\].

According to the 2009 American Joint Committee on Cancer (AJCC) for melanoma staging and classification system, melanoma patients with regional metastasis are at high risk for recurrence and death, with historical five-year survival ranging between 30 and 70% depending on sub-stage classification \[4\]-\[6\]. Recent studies have reported that patients with stage II and III melanoma have a 30-46% risk of disease recurrence, including those with asymptomatic
metastases [7-9]. Despite the high rates of recurrence and effective systemic and surgical therapies to offer, there are no current standard guidelines for surveillance. The National Comprehensive Cancer Network (NCCN) recommends routine clinical examination and consideration of imaging for stage IIB-IIIC patients every 3-12 months with no distinction between substages and no recommendation for preferred imaging type [10]. With the introduction of new and innovative therapies for the treatment of patients with melanoma and the recent revision of the seven editions of the AJCC staging system to its eighth edition, which divides the pathologic stage III into 4 substages (IIIA, IIIB, IICC and IIID) [11]. The understanding of the pattern of recurrence and the survival outcomes of these higher risk patients is important to improve early detection and management of the disease. We propose to identify the patterns of recurrence and to evaluate the 5-year crude and adjusted recurrence free survival, melanoma specific survival and overall survival of patients with melanoma stage III at diagnosis.
INTRODUCTION

The prognosis of melanoma patients with loco-regional metastasis varies widely and there is no consensus regarding surveillance after appropriate initial therapy for patients with stage III melanoma \[5,12\]. The risk of relapse for stage III patients is high and varies by substage at diagnosis. The goal of follow up is to be able to detect first relapse as soon as possible in order to improve survival. A study by Romaro et al first reported the site and timing of relapse in melanoma stage III patients. They estimated a 5-year risk of relapse at any site to be 48% for stage IIIA, 71% for stage IIIB, and 85% for stage IIIC and the overall relapse free survival to be 63%, 32% and 11% respectively \[13\]. Other studies reported between 30-46% risk of disease recurrence in patients with stage II and III melanoma, including those with asymptomatic metastases \[7,8\]. For stage IIIA and IIIB patients, lung and liver were the most common sites of systemic relapse, with a higher rate of relapse within one year for stage IIID \[14,15\]. Also, many studies have demonstrated the use of imaging and clinical examination to detect recurrence. An estimated 60% of stage III recurrences were detected by imaging, and less than 40% were identified by clinical examination including physician detection or patient detection \[15-17\]. Similarly, another study demonstrated that only 40%-45% patients will be disease-free by 4 years after recurrence from stage III melanoma \[18\].

According to AJCC staging system 7th edition, prognostic factors predictive of survival include tumor thickness, ulceration and mitotic index, as well as presence of regional (lymph node) and distal metastases \[19\]. However, in the current AJCC 8th edition tumor, node, metastasis (TNM) staging system, stage III has been subdivided into four groups based on tumor thickness, ulceration status and number of tumor-involved lymph nodes (and whether these were clinically occult versus clinically detected), as well as the presence or absence of non-nodal regional metastases (Table2).
The newly classified subgroups D were based on whether the tumor thickness was greater than 4.0 mm with the presence of ulceration, and four or more tumor involved nodes or any number of in-transit, satellite and/or microsatellites metastases with two or more clinically occult and/or clinically detected or the presence of any number of matted nodes (N3a, b and c). Gershenwald et al reported with the 8th edition, a significant difference in prognosis across the four stage III subgroups, with five-year MSS ranging from 93 percent for stage IIIA to 32 percent for stage IIID disease, but nothing is known about the recurrence prognosis of these subgroups[20].

The optimal timing and the modality of surveillance after initial diagnosis and treatment are crucial to improve survival. Despite the high rates of recurrence reported with the AJCC 7th edition, and the effective systemic and surgical therapies available, there are no current standard guidelines for surveillance of these high-risk sub-groups. The National Comprehensive Cancer Network recommendation for stage III is a routine clinical examination and imaging tests for screening stage every 3-12 months based on patients’ risk of cancer recurrence or metastasis, with no distinction between substages and no recommendation for preferred image type [10].

To accurately estimate the prognosis and gauge the therapeutic outcomes, it is essential to understand the patterns of recurrence and the survival outcomes of patients in relation to their stage at diagnosis.

In this study, we use our institutional melanoma database to evaluate the patterns of relapse and the survival prognosis among patients with stage III (AJCC 8th edition) at diagnosis.
**Purpose of the study**

Our specific aims were to

1. describe the pattern of recurrence in stage III melanoma patients;
2. determine the recurrence free survival, the disease specific survival and the overall survival by substage III at diagnosis using the 8th edition of the AJCC staging manual.

**Public health purpose:**

To suggest follow-up guidelines for surveillance that may improve patient’s survival outcomes and reduce the economic burden of melanoma on health care systems.

**Goals of the study:**

To provide clinical recommendations on follow up based on recurrence patterns and survival prognosis of stage III melanoma patients.
II. METHODOLOGY

Data source and study population

This retrospective study used a cohort of patients diagnosed with stage III melanoma treated at Huntsman Cancer Institute (HCI), University of Utah, from January 2000 to December 2015. The main source of data used for this analysis was extracted from the Huntsman cancer registry and patient medical records.

Inclusion/Exclusion criteria

All patients of at least 18 years of age with stage III cutaneous melanoma per the eight editions of the AJCC melanoma staging system with at least two years of follow up were included in this study. We excluded patients with a primary other than cutaneous (i.e. mucosal or ocular), those with stage I, II and IV melanomas at diagnosis and those with multiple primaries or missing data on stage at diagnosis. Patients were followed-up until December 31, 2017 or death.

Staging at baseline

Staging was done according to the eighth editions of the AJCC melanoma staging system. In short, staging was performed based on (1) characteristics of the primary tumor (T) including thickness, ulceration and mitotic rate, (2) extent of lymph node (N) involvement and (3) presence of distant metastases (M). In case of regional lymph node metastases but no evidence of distal metastases, patients were assigned to stage III (regional metastatic melanoma) and depending on
the T, N and M score, the pathologic sub-stage IIIA, IIIB, IIC and IID were assigned as referred in table 2. Stage III melanoma was identify as metastases nearby lymph vessels, lymph nodes, and/or nearby skin (satellites). The clinical staging includes tumors of any depth with metastases in lymph nodes and/or lymph vessels and pathologic staging divides stage III tumors into 4 sub-groups based on ulceration of the primary tumor, the extent of growth into the lymph vessels, lymph nodes, and nearby skin \[11\].

**Study population and covariates**

We identified 664 patients with stage III melanoma between January 2000 and December 2015. A total of 544 patients who met the inclusion criteria were included in the analysis and the remaining 120 patients were excluded. The clinical features recorded for each patient were age at diagnosis (young: 18-45 years, middle: 46-60 and old: 61-97), gender, sub-stage III at diagnosis (IIIA, IIIB, IIC and IID), Breslow’s tumor thickness, Clark’s level of invasion, ulceration, mitotic rate, histological type (superficial spreading, nodular, acral lentiginous and others), anatomic site of the primary, number of positive lymph nodes and sentinel lymph nodes metastases.

**Detection of the recurrence**

Three parameters were considered to define recurrence after no evidence of disease (a) record of restaging to a higher melanoma stage, (b) new diagnosis of metastasis or (c) confirmation with pathology, imaging or biopsy. Descriptive information relative to first recurrence was captured such as type of recurrence (local/in-transit, regional, distant), location of first recurrence (subcutaneous, nodal, systemic), date of first relapse, date and cause of death if applicable, as well
the treatment received at relapse. The treatment received was surgery and adjuvant therapy that included immunotherapy (interferon, hormone, systemic) and non-immunotherapies (radiotherapy and chemotherapy). The pathological examination of the melanoma was done by experienced pathologist on slides stained with haematoxylin and eosin (H&E) and immunohistochemistry. Sentinel lymph nodes status was assessed on H&E slides after SLN biopsy and was defined as positive or negative. Patients who first relapsed at several sites concomitantly were scored on the basis of the site that was most advanced (eg, systemic sites outranked nodal sites which outranked local/ in-transit sites). Local recurrence was defined as a recurrence up to 2 cm from the primary excision and in-transit metastases as the recurrence between the scar (beyond 2 cm) and the regional lymph nodes. The diagnosis of recurrence and/or metastases was established clinically and by imaging (magnetic resonance imaging or computed tomography) and was confirmed histologically when possible. The study was approved by the Institutional Review Board (IRB) at the University of Utah. All analyses were conducted in compliance with the approved study protocol.

**Outcomes:**

The key outcomes evaluated were time-to-relapse (TTR), characteristics of recurrence (site and type of metastasis), method of first relapse detection, treatment received, recurrence free survival (RFS), melanoma specific survival (MSS) and overall survival (OS). TTR was defined as the period of time between excision of melanoma and the first recurrence for those who recur.
The RFS was defined as the period of time between excision of melanoma and the first recurrence or last follow-up for the whole cohort. Patients who did not recur and were alive at the last follow-up were censored cases, while patients who recurred were considered an “event”. The MSS was determined from the diagnosis date of the primary tumor to the date of death due to melanoma or last follow-up. The OS was determined from the diagnosis of primary tumor to the date of death (regardless of the cause) or last follow-up.

We sought to explore the pattern of recurrence and determine the five-years recurrence-free survival, the melanoma specific survival and overall survival stratified by substage III at diagnosis.

**Statistical Analysis**

Descriptive data were presented as median (interquartile range, IQR), mean ± standard deviation (SD) and proportions were expressed as a percentage. Chi-square analysis was used to compare categorical variables, and Student’s t-test was used to analyze continuous variables. P values were two tailed. Survival curves and median follow-up time were estimated using Kaplan-Meier method. Univariate and multivariate Cox proportional hazard models were built to obtain the Hazard ration (HR), the 95% confidence limit and the P value using two-sided log rank test statistic. Categorical variables were dummy coded to adhere to the linearity assumption of multivariable regression model. Multivariable Cox model were adjusted for age, gender, body site of the primary, histologic type, Breslow thickness and Clark level. The proportional-hazards assumption was checked using log-log survival and Schoenfeld residuals. Confounding was assessed by checking the effect of each remaining non-significant variable, which was not in a model, on factors in the model. If changes to the regression coefficient of a factor in the model of 5% or more occurred, then the respective variable was considered a confounder and the model was
adjusted for it. Two-sided $P$-value of less than 0.05 was considered statistically significant. All the analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

III. RESULTS

Stage at diagnosis and patient characteristics

For this study, a total of 544 patients were diagnosed with initial locoregional metastasis (8th edition AJCC stage III). Of these, 184 (34%) had stage IIIA, 110 (22%) had stage IIIB, 228 (42%) had stage IIIC and 22 (4%) had stage IIID (Table 2). The median age at diagnosis was 55 years (IRQ:39-66 years) and age was further categorized into young 18-45 years (33%), middle age 46-60 years (31%) and old 61-97 years (36%). Overall, there were more male 334 (61%) than female 210 (39%). The body site of the primary melanoma were extremities (42%), truncal (33%), head and neck (24%) and mucosal 1.3%. Table 1 outlines the baseline characteristics of this study cohort.

A total of 159 (29%) patients died during the follow up, of these 118 (74%) were melanoma specific deaths and 99 (55%) died after the recurrence. The overall median follow-up time was 51 months (range 30-92 months).

Patterns of Recurrence:

Overall,181 patients (33%) in this cohort relapsed by the end of follow up period. Of these, 20% were diagnosed with stage IIIA, 28% with stage IIIB, 45% with stage IIIC and 55% with stage IIID (table 3). The overall median time to recurrence was 14.4 months (range: 7-26.4 months) and for Stages IIIA, IIIB, IIIC and IIID were 21months (range: 6-48) ,13.9 months (range:8-30), 14months (range:7-25) and 5.5 months (range:3.6-12.5) respectively (Table3).
Of those who relapsed, 90 (50%) were distant, 66 (37%) were regional and 25 (14%) were local or in-transit (Table 3). Among those diagnosed with initial stage IIIA, 47% had a systemic recurrence, 36% nodal and 17% subcutaneous. Among stage IIIB, 48% recur in the lymph nodal, 42% had a systemic relapse and 10% subcutaneous. Among stage IIIC, 44% had a systemic relapse, 29% nodal and 27% subcutaneous. Similarly, patients with stage IIID relapse in majority at the systemic level (75% and only 25% in the lymph nodes. (Table 3)

The most common sites at first relapse were in lymph nodes 61 (34%), lung 37 (20%), subcutaneous 36 (20%), brain 19 (11%), liver 8 (4.4%) and bone 4 (2.2%) (Table 3). When stratifying by sub-stage, stage IIIA patients relapsed mostly in the lymph nodes (36%), followed by lung (17%) subcutaneous (17%) and brain (11%). Stage IIIB relapsed predominantly in the lymph nodes (48%), lung (19%), subcutaneous and brain (10%). Stage IIIC relapsed mostly in the lymph nodes (29%), then subcutaneous (27%), the lung (22%) and brain (9%). Finally, stage IIID patients relapsed mostly in the brain (25%), lung (25%), lymph nodes (25%), liver (17%) and multiples sites (8%) (Table 4).

**Time of first recurrence**

Overall, 181(33%) patients in this cohort relapsed with a median time to recurrence of 14 months (95%CL 7-26). The median TTR for stages IIIA, IIIB, IIIC, and IIID were 21 months, 14 months, 14.2 months and 5.5 months respectively. A subset analysis looking at those who relapsed showed that overall, 74 (41%) relapsed within one year and 59% relapsed after one year. The majority of patients who relapsed within one year after curative surgery were from stage IIID.
(67%), IIIC (41%), IIIB (42%) and IIIA (31%). We also noticed that 81% relapsed by 3 years and 91% relapsed by 5 years. When stratified by substage, 67% of stage IIID, 42% of stage IIIB, 41% of IIIC and 31% of stage IIIA recurred within a year. (Table 5)

**Mode of detection**

Recurrence was detected by imaging in 71% (n=128/181) of recurrent patients, Physicians detected 20% (n=36/181) of recurrence whereas patient detected recurrence was 9.4% (n=17/181) (Table 6).

**Treatment on relapse**

Following relapse, 61% (n=110/181) of patients received surgery, 30% immunotherapy, 28% received radiation therapy, 18% had chemotherapy and 2% had hormonal and neoadjuvant systemic therapy (Table 8).

**Recurrence Free-Survival by stage at diagnosis**

A total of 159 patients died during the follow-up period and 99 (55%) deaths were observed after melanoma recurrence. The estimated 1, 3, 5- and 10-year crude recurrence rate increased as the sub-stage III at diagnosis increased from IIIA to IIID. The unadjusted 5-year recurrence free-survival rate for stage IIIA, IIIB, IIIC and IIID were 83%, 73%, 56% and 47% respectively; (Table 9). The RFS curve showed that stage IIID had a worst survival prognosis compared to Stage IIIA, B and C, with the plateau at 3 years of follow up for stage IIID and 10 years for stage IIIA, B and C (Fig1). The univariable cox proportional hazard ratio demonstrated a significant increase in the hazard of relapse from Stage IIIA to Stage IIID. The crude HR of stage IIIB, IIIC and IIID
compared to IIIA were HR: 1.56 (95% CL, 0.9-2.5), HR: 2.78 (95% CL 1.9-4) and HR: 4.4 (95% CL, 2.2-8.70) respectively.

The Cox proportional hazards adjusted for age, gender, Breslow thickness, histological type and body site, showed that the HR remained high (IIIB: HR 1.89; IIIC: HR 2.74 and IIID: HR 3.86). There was no difference in the hazard of relapse between male and female in both crude and adjusted analysis. Male gender had a 16% greater hazard of relapse compared to female (HR: 1.16 Cl:0.7-1.7). Similarly, age group was not found to be a predictive factor for relapse, the HR for recurrence of middle age (46-60 years) was 12% and old age (61-97 years) was 9% compared to young age (18-45 years) (HR: 1.12 Cl:0.7-1.7 and HR: 1.09 Cl:0.7-1.8). However, in the univariable analysis old age had a 44% (HR: 1.44, Cl 1-2.1) increase in the hazard of relapse compared to young age. Other covariates such as Breslow thickness, histology type and body site of the primary did not significantly increase the hazard of relapse in the adjusted analysis, but in the crude analysis, Breslow thickness showed an increase in the risk of relapse. Also, the hazard of relapse for Breslow thickness increased by 79% for 2-4 mm (HR 1.79 Cl 1.3-2.6, p=0.001) and two fold for 4+ mm (HR 2.32, Cl 1.6-3.3, p<0.0001) compared to less than 2 mm Breslow thickness. Similarly, the histology type of the metastasis showed a 43% increase in the hazard of relapse for nodal metastasis compared to superficial metastasis. Also, the hazard of recurrence was 74% higher when the disease was diagnosed at the head and neck compared to the trunk (HR 1.74 Cl, 1.2-2.5). The univariable and multivariable analysis of other covariates showed that Clark level, was not significantly associated with the RFS (Table 9).
**Melanoma Specific Survival:**

Of a total of 159 patients who died during the follow-up period, 118 (74%) deaths were tumor specific deaths. The estimated 5 year crude MSS rate decreased as the sub-stage III at diagnosis increased from IIIA to IIID ranging from 92% to 46% respectively (Table 10). The MSS curve showed the worst survival prognosis for stage IIID compared to stage IIIA, B and C with a plateau at 3 years of follow up for stage IIID and 10 years for stage IIIA, B and C (Fig2). The univariable and multivariable cox analysis showed that the hazard of death increased with substage III. The adjusted HR for stage IIIB, IIIC and IIID compared to IIIA were 1.86 (CL 0.9-3.8, p=0.08), 3.65 (CL 1.7-7.7 p<0.0001) and 8.2 (CL 2.9-22.5 p<0.0001) respectively (Table11). Among covariates, the univariable analysis showed a two fold increase in the hazard of death among males compared to females (HR 2.01 CL 1.4-3.1, p<0.001). Also, middle and old age have a higher increased in the hazard of death compared to younger age (HR 1.67, CL1.0-2.7, p=0.04) and (HR 2.28, CL1.4-3.7, p<0.001), with the worst prognosis for old age. Patients with Breslow thickness greater than 4mm had three time increase in the hazard of death compared to tumor thickness less than 2mm (HR 2.86, CL1.8-4.4, p<0.001). The anatomic site of the recurrence was also associated with a higher hazard of death. Patients who recurred at the systemic site had a higher hazard of death compared to those who recurred at the local or in transit site (HR:2.82, CL 1.4-5.5, p=0.002) (table 11). However, in multivariable analysis Breslow thickness, histology type and body site, were not significantly associated with the increase in the hazard of death. (Table11)
**Overall survival:**

We calculated the overall survival for each substage from the time of diagnosis. The median follow-up time for Stage IIIA, IIIB, IIIC and IIID were 62, 57, 44 and 26 months. The estimated 5-year crude OS rate decreased as the sub-stage III at diagnosis increased from IIIA to IIID ranging from 88% to 29% (Table 10). The OS curve showed a worst survival prognosis for stage IIID compared to stage IIIA, B and C with the plateau at 3 years of follow up for stage IIID and 10 years for stage IIIA, B and C (Fig 3-A). The univariable and multivariable cox analysis showed that the overall hazard of death increased significantly with substage III. The adjusted HR for stage IIIB, IIIC and IIID compared to IIIA were 1.68 (CL 0.9-3.1, p=0.1), 3.55 (CL 1.9-6.7 p<0.0001) and 9.59 (CL 4.0-23.1 p<0.0001) respectively (Table 12). Among covariates, both univariable and multivariable analysis showed that gender and age were significantly associated with the overall survival whereas Breslow thickness, and histology type were associated with survival only for the univariable analysis. Male had 84% increase in the adjusted hazard of death compared to female (HR 1.84 CL 1.2-2.7, p<0.001). Also, old age had a higher increase in the hazard of death compared to younger age (HR 2.2, CL 1.4-3.4, p<0.0001).

In the univariable analysis, Breslow thickness and histology site are both associated with increase hazard of death. Breslow thickness greater than 4mm had three times increase in the hazard of death compared to less than 2mm tumor thickness (HR 3.25, CL 2.2-4.7, p<0.0001). Similarly, the hazard of death for acral/lentigo and nodal metastasis were (HR:2.69 CL 1.7-4.3, p<0.0001) and (HR:1.52, CL 1.0-2.3, p=0.04) respectively compared to superficial metastasis. In the multivariate model, Breslow thickness, histology type and body site of the primary were not significantly associated with the increased risk of death. The anatomic site of the recurrence was also associated with the higher hazard of death. Patients who recurred had four time the risk of
death (HR: 4.13, CL 3.0-5.7, p=0.001) compared to those who did not recur. Also, those who recurred at the nodal and systemic site had a 20% (HR: 1.20, CL 0.6-2.2, p=0.5) and 85% increase in the hazard of death (HR: 1.85, CL 1.0-3.2, p=0.03) compared to those who recurred at the local or in-transit site (Table 12).

**IV. DISCUSSION**

This study provides the recurrence and survival estimates for AJCC 8th edition stage III melanoma subgroups A to D, using data from a single institution (Huntsman cancer registry) cohort who had locoregional metastasis at the time of initial presentation. Our findings demonstrate that in patients with high-risk cutaneous melanoma stage III at diagnosis, the highest percentage of recurrence was among stage IIID (54%), followed by stage IIIC (45%), stage IIIB (28%) and stage IIIA (20%); which are consistent with other studies [7,14,15]. Also, patients with stage IIIA to IIID had a 5 years recurrence free-survival rate ranging from 83% to 47%.

The majority of patients who relapsed within one year were from stage IIID (67%), IIIC (41%), IIIB (42%) and IIIA (31%) after curative surgery. This is consistent with other studies showing that most high-risk metastases developed within the first few years after initial diagnosis [7,13,21].

The median TTR of 14 months was greater than 10 months reported by Lim et al in their studies of 173 patients but they had a greater proportion of stage IIIB and IIIC cases and they used AJCC 7th edition staging system. Although fewer in number (n=12), patients with stage IIID disease who relapsed had a particularly short median TTR of 6 months, compared with overall median TTR of 14 months for Stage IIIC and IIIB (Fig 1).
Others studies showed that few patients with newly diagnosed melanoma have clinical evidence of distant metastases at the initial diagnosis \cite{22,23}. But over time the majority of patients who presented with early stage initially, develop metastatic disease as a consequence of disease recurrence or progression. Our results showed that nearly one-third of all stage III patients experienced disease recurrence, consistent with previous studies \cite{7,9,15}. For most patients, the time to recurrence varies inversely with tumor stage at presentation. For patients with thicker tumors (stage IIID) the risk of recurrence is the greatest in the first year after treatment and declines steadily over time. In addition, patients with stage III nodal metastases, have recurrences earlier than patients whose lymph nodes are negative.

Patients’ age at diagnosis can also influence the timing of recurrence. Patients older than 60 years of age have been shown to relapse sooner than younger patients \cite{24,25}. Median age at diagnosis was 55 years, which is about similar to what has been observed in previous international studies \cite{26,27}. Gender was not a significant prognostic factor for recurrence in our study, however men was found to have a higher risk of death compared to female. This is in agreement with previous studies reporting that male had twice the risk of death compared to female \cite{28,29,30}. This may be explained by the fact that women are more careful about their appearance, which lead to early detection of the metastases and better survival. The main sites of relapse were lymph nodes, lung and subcutaneous tissues, consistent with others \cite{8,15}. Most patients who relapsed (53%) had metastatic disease, with the smaller proportion (36%) having locoregional disease. The detection of recurrence was done by imaging (70%) for the majority of our patients, physician and patient detection occurred in only 30% of cases, which suggested that clinical review and patient education regarding signs of potential relapse remain important. These results are similar to those reported by Lim \textit{et al} \cite{15}, which showed 65% of recurrences detected by imaging. Also, our data showed
that surgery (61%) was the first course of treatment used for relapse in those with locoregional disease, followed by immunotherapy (30%) and radiation (28%). The risk of recurrence at local/in-transit site and nodal site occurred early while the distant metastasis to lung and other sites occurred later.

In accordance with published literature, stage at diagnosis was correlated with melanoma specific survival and overall survival. Our results analysing 554 melanoma stage III patients showed an estimated 5 years MSS rate to be 92%, 83%, 71% and 46% for stage IIIA to IIID respectively, which is in agreement with recent studies \cite{11,14}. Gershenwald et al during the 8\textsuperscript{th} AJCC edition classification showed approximately the same results, 32% MSS rate for stage IIID. We observed a similar trend with the 5-year overall survival for stage IIIA to IIID to be 88%, 79%, 60% and 29% respectively. In the 7\textsuperscript{th} AJCC edition, however the 5-year MSS rates for patients with stage IIIA, IIIB and IIIC were 78%, 59% and 40% respectively \cite{4,5}. The magnitude of observed improvement in prognosis from the 7\textsuperscript{th} edition to the 8\textsuperscript{th} edition is an important survival information for patients and their treating clinician. Perhaps most impressive is the improvement of 5-year MSS for stage IIIA, IIIB and IIIC subgroup by 17%, 41% and 77% increase compared to previous AJCC edition. These differences are likely due to changes in the 7\textsuperscript{th} versus 8\textsuperscript{th} edition staging classifications, in which patients with stage IIID disease are classified as having more than 4-mm tumor thickness, ulcerated melanomas with more than three positives nodes or the presence of microsatellites/in-transit lesions with more than one positive node \cite{31}. Our results showed that stage IIID subgroup had a high recurrence and poor survival prognosis, albeit a small proportion of all patients with stage IIID, with a high hazard of death even 5 years after diagnosis. This group is small (4%) probably because of the high incidence of concurrent distant metastatic melanoma, and the fact that they were separated out and reclassified from stage IIIC in the 7\textsuperscript{th} edition AJCC
staging. This subgroup of patients had a poor survival prognosis which could have clinical implications in decision making for follow up and treatment.

It is important to recognize that, unlike the 7th edition, for which melanoma-specific survival rates were well-differentiated throughout follow-up for patients with stage IIIA, IIIB, and IIIC disease, the 8th edition failed to differentiate melanoma-specific survival for patients with IIIA and IIIB, which overlap for the first 4 years after diagnosis in both univariate and multivariate model. This result is consistent with a study by Madu et al using 640 melanoma cases from a Netherlands Cancer Institute database which showed an overlap in the IIIA and IIIB survival curves over the first four years of follow-up \cite{32}. They suggested that the 8th edition IIIA subgrouping should be stratified further using European Organization for Research and Treatment of Cancer (EORTC) criteria for sentinel node tumor burden, which can be a powerful adjunct to AJCC staging, especially in a post-completion lymph node dissection era where less staging information will be available \cite{32}.

V. LIMITATIONS

This study is limited by its retrospective design, and the lack of routine sentinel lymph node biopsies during the time period which may have influenced timing and pattern of recurrence. Also, information regarding subsequent therapy and other patient related factors was not possible to identify in this retrospectively analyzed dataset. However, the effects of this limitation and confounding factor are likely to have been small because the cohort was largely acquired before the availability of efficacious targeted and immune therapies. Nevertheless, this is a large cohort of stage III melanoma treated at a single institution and it serves to provide an initial framework
for analyzing the pattern and timing of disease recurrence and survival using the 8th AJCC edition for melanoma staging. This report represents an initial step to formulate a data-based follow-up guideline for stage III patients by subgroup, which is a critical step to the development and implementation of high-risk melanoma surveillance and therapy protocol.

VI. CONCLUSIONS

This study demonstrates that patients with stage III melanoma are at highest risk of recurrence and poor survival, especially, male gender, older age at diagnosis, and patients with thicker tumor (stage IIID) during the first 3 years of follow up from melanoma. We notice an increase in 5-year melanoma specific survival and overall survival from the 8th edition compared to the 7th edition of the AJCC staging system. Patients with high-risk Stage III melanoma have a substantial relapse rate within the first 2 years of follow-up, with the majority of relapses detected by imaging surveillance. After 3 years of survivorship from melanoma, with the possible exception of patients with stage IIID disease, a potential toxicity of ongoing adjuvant treatments and cost are less likely to outweigh the benefits with respect to long-term survival from stage III melanoma. The fact that over half of all recurrences occurred within 2 years urges us to concentrate follow-up in the early time periods following diagnosis. A subsequent reduction in the frequency of scheduled follow-up visits and investigations may be justified after 5 years of survivorship for patients with stage IIIA, IIIB and IIC disease. However, stage IIID patients should be followed more closely for the first 3 years due to their higher risk of relapse and death. More research is needed to assess melanoma-specific death rates for this group after 5 years.

Patients with stage IIIC and IIID had a higher hazard of relapse and death compared to patients with stage IIIA and B. Considering the short median TTR in our study, we recommend a more
intensive CT surveillance schedule of every 3 months for the first year, followed by every 6 months until 3 years and every year after for this high-risk group patients.

With the landscape of new and innovative systemic therapeutic options for advanced melanoma, patients may stand to benefit from early treatment when they are asymptomatic, along with a structured surveillance program that maximizes the potential advantages of early detection without placing an undue burden on patients or the healthcare system. In the current era of resource management, a data driven method of surveillance for melanoma patients, as well as the determination of the most common sites of recurrence may allow for a defined surveillance strategy that is both cost effective and patient focused.
VII. REFERENCES


TABLES AND FIGURES

Table 1: Clinical and Pathologic Characteristics of Patients with Stage III Melanoma

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%) N=544</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male (0)</td>
<td>334 (62)</td>
</tr>
<tr>
<td>Female (1)</td>
<td>210 (39)</td>
</tr>
<tr>
<td>Age category (years)</td>
<td></td>
</tr>
<tr>
<td>18-45</td>
<td>179 (33)</td>
</tr>
<tr>
<td>46-60</td>
<td>169 (31)</td>
</tr>
<tr>
<td>61-97</td>
<td>196 (36)</td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>211 (39)</td>
</tr>
<tr>
<td>No</td>
<td>333 (61)</td>
</tr>
<tr>
<td>Clark-Level</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>10 (2)</td>
</tr>
<tr>
<td>III</td>
<td>47 (9)</td>
</tr>
<tr>
<td>IV</td>
<td>379 (70)</td>
</tr>
<tr>
<td>V</td>
<td>58 (11)</td>
</tr>
<tr>
<td>unknown</td>
<td>50 (9)</td>
</tr>
<tr>
<td>Site of the primary melanoma</td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td>228 (42)</td>
</tr>
<tr>
<td>Head/Neck</td>
<td>131 (24)</td>
</tr>
<tr>
<td>Trunk</td>
<td>178 (33)</td>
</tr>
<tr>
<td>Other/unknown*†</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>Type of primary melanoma</td>
<td></td>
</tr>
<tr>
<td>Acral/Lentiginous</td>
<td>55 (10)</td>
</tr>
<tr>
<td></td>
<td>Count</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Nodular</td>
<td>128 (24)</td>
</tr>
<tr>
<td>Superficial</td>
<td>204 (38)</td>
</tr>
<tr>
<td>Other/unknown*2</td>
<td>157 (29)</td>
</tr>
</tbody>
</table>

**Breslow thickness (mm)**

| T1 (0.01-1.00)                | 92 (17) |
| T2 (1.01-2.00)                | 167 (31) |
| T3 (2.01-4.00)                | 157 (29) |
| T4 (>4)                       | 128 (24) |

**Tumor mitotic rate (mitoses/mm²) (median ± range)**

| 2 (0-60) |

**Extranodal spread**

| Yes   | 31 (6) |
| No    | 477 (88) |
| unknown | 36 (7) |

**Positives sentinel Lymph Nodes**

| 0     | 89 (16) |
| 1     | 329 (61) |
| 2     | 99 (18) |
| 3 or more | 27 (5) |

**Number of involved Lymph Nodes**

| 0     | 61 (11) |
| 1     | 323 (59) |
| 2-3   | 130 (24) |
| 4 or more | 30 (6) |

**Stage III (AJCC 8th edition)**

| IIIA | 184 (34) |
| IIIB | 110 (22) |
*1 mucosal ; *2 desmoplastic, nevoid, spindle, lentigo melanoma.

**Table 2: AJCC Eight Edition Melanoma Stage III Subgroups**

(A)

<table>
<thead>
<tr>
<th>Category</th>
<th>N1a</th>
<th>N1b</th>
<th>N1c</th>
<th>N2a</th>
<th>N2b</th>
<th>N2c</th>
<th>N3a</th>
<th>N3b</th>
<th>N3c</th>
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<tr>
<td></td>
<td>N/A</td>
<td>B</td>
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<td>N/A</td>
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<td>N/A</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td></td>
<td>A</td>
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<td>B</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<td>B</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td></td>
<td>C</td>
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<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

(B)

| If T is | and N is | and M is | then Pathological Stage is | Patients (%
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a/b, T2a</td>
<td>N1a, N2a</td>
<td>M0</td>
<td>IIIA</td>
<td>184 (34%)</td>
</tr>
<tr>
<td>T1a/b, T2a</td>
<td>N1b/c, N2b</td>
<td>M0</td>
<td>IIIB</td>
<td>110 (22%)</td>
</tr>
<tr>
<td>T2a/T3a</td>
<td>N1a/b/c, N2a/b</td>
<td>M0</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>N1b, N1c</td>
<td>M0</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T1a/b, T2a/b, T3a</td>
<td>N2c, N3a/b/c</td>
<td>M0</td>
<td>IIIC</td>
<td>228 (42%)</td>
</tr>
<tr>
<td>T3b/T4a</td>
<td>any N≥N1</td>
<td>M0</td>
<td>IIIC</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>N1a/b/c, N2a/b/c</td>
<td>M0</td>
<td>IIIC</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>N2b/c, N3b/c</td>
<td>M0</td>
<td>IIID</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>N3a/b/c</td>
<td>M0</td>
<td>IIID</td>
<td>22 (4%)</td>
</tr>
</tbody>
</table>

*Legend*

- **A**: stage IIIA
- **B**: Stage IIIB
- **C**: Stage IIIC
- **D**: Stage IIID
- **N/A**: not assigned

### Table 3: Patterns of Recurrence (n%)  
**Description of recurrence (n=181)**

<table>
<thead>
<tr>
<th>Disease recurrence</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>181 (33)</td>
</tr>
<tr>
<td>No</td>
<td>363 (67)</td>
</tr>
</tbody>
</table>

**Recurrence type**

<table>
<thead>
<tr>
<th>Type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local/In-transit</td>
<td>25 (14)</td>
</tr>
<tr>
<td>Regional</td>
<td>66 (37)</td>
</tr>
<tr>
<td>Distant</td>
<td>90 (49)</td>
</tr>
</tbody>
</table>

**Anatomy Site of the first recurrence**

<table>
<thead>
<tr>
<th>Site</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous</td>
<td>36 (20)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>61 (34)</td>
</tr>
<tr>
<td>Lung</td>
<td>37 (20)</td>
</tr>
<tr>
<td>Brain</td>
<td>19 (11)</td>
</tr>
<tr>
<td>Liver</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Bone</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Multiple sites</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Mucosal/GI</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

**Mode of detection of the recurrence**

<table>
<thead>
<tr>
<th>Mode</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging</td>
<td>128 (71)</td>
</tr>
<tr>
<td>Clinically detected on examination</td>
<td>33 (18)</td>
</tr>
<tr>
<td>Patient detected /symptomatic</td>
<td>20 (11)</td>
</tr>
</tbody>
</table>

**Recurrence by stage at diagnosis**

<table>
<thead>
<tr>
<th>Stage</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>36 (20)</td>
</tr>
<tr>
<td>IIIB</td>
<td>31 (28)</td>
</tr>
<tr>
<td>IIIC</td>
<td>102 (45)</td>
</tr>
<tr>
<td>IIID</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Total dead</td>
<td>159 (29)</td>
</tr>
<tr>
<td>Site of first relapse</td>
<td>IIIA</td>
</tr>
<tr>
<td>----------------------</td>
<td>------</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Nodal</td>
<td>13 (36)</td>
</tr>
<tr>
<td>Lung</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Brain</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Liver</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Multiples sites</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Bone</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 5: Time to first recurrence by stage at diagnosis (median ± 95%CL)

<table>
<thead>
<tr>
<th>stage at diagnosis</th>
<th>median TTR (95%CL) months</th>
<th>relapse before 12 months (n, %)</th>
<th>relapse after 12 months (n, %)</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>21.5 (17-40)</td>
<td>11 (31%)</td>
<td>25 (69.4)</td>
<td>36 (20%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>13.9 (9-23)</td>
<td>13 (42%)</td>
<td>18 (58%)</td>
<td>31 (17%)</td>
</tr>
<tr>
<td>IIIC</td>
<td>14.2 (12-17)</td>
<td>42 (41%)</td>
<td>60 (59%)</td>
<td>102 (56%)</td>
</tr>
<tr>
<td>IIID</td>
<td>5.5 (4-17)</td>
<td>8 (67%)</td>
<td>4 (33%)</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>overall</td>
<td>14.4 (7-26)</td>
<td>74 (41%)</td>
<td>107 (59%)</td>
<td>181</td>
</tr>
</tbody>
</table>
### Table 6: Mode of detection of the recurrence (n%)

<table>
<thead>
<tr>
<th>Mode of Detection</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging</td>
<td>128 (71%)</td>
</tr>
<tr>
<td>physician detected on examination</td>
<td>36 (20%)</td>
</tr>
<tr>
<td>patient detected</td>
<td>17 (9%)</td>
</tr>
</tbody>
</table>

### Table 7: Type of melanoma at first recurrence by substage (n%)

<table>
<thead>
<tr>
<th>Type of melanoma at first relapse</th>
<th>IIIA</th>
<th>IIIB</th>
<th>IIIC</th>
<th>IIID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant</td>
<td>19 (53)</td>
<td>12 (39)</td>
<td>50 (49)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Local/In-transit</td>
<td>4 (11)</td>
<td>3 (10)</td>
<td>18 (18)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Regional</td>
<td>13 (36)</td>
<td>16 (52)</td>
<td>34 (33)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>31</td>
<td>102</td>
<td>12</td>
</tr>
</tbody>
</table>

### Table 8: Therapy received for relapse (n%)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>110 (61)</td>
</tr>
<tr>
<td>radiation</td>
<td>50 (28)</td>
</tr>
<tr>
<td>Hormone</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Immuno therapy</td>
<td>55 (30)</td>
</tr>
<tr>
<td>Neoadjuvant systemic</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>33 (18)</td>
</tr>
</tbody>
</table>
Table 9: Estimated 1, 3, 5 and 10-years recurrence rates by substage III (n%)

<table>
<thead>
<tr>
<th>Years</th>
<th>Stage IIIA (Recurrence Rate %)</th>
<th>Stage IIIB</th>
<th>Stage IIIC</th>
<th>Stage IIID</th>
<th>Stage IIIA (Recurrence Free- Survival Rate %)</th>
<th>Stage IIIB</th>
<th>Stage IIIC</th>
<th>Stage IIID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% Confidence intervals)</td>
<td></td>
<td></td>
<td></td>
<td>(95% Confidence intervals)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>6 (3.0-9.9)</td>
<td>12 (6.5-18.5)</td>
<td>19 (13.7-23.8)</td>
<td>38 (19-59.3)</td>
<td>94 (90-97)</td>
<td>88 (81.5-93.5)</td>
<td>82 (76.2-86.3)</td>
<td>62 (40.7-81)</td>
</tr>
<tr>
<td>3 years</td>
<td>12 (7.7-17.2)</td>
<td>24 (16.5-33)</td>
<td>39 (32.5-45.3)</td>
<td>53 (31.7-73.4)</td>
<td>88 (82.7-92.2)</td>
<td>76 (67.2-83.40)</td>
<td>61 (54.6-67.4)</td>
<td>47 (26.5-68.3)</td>
</tr>
<tr>
<td>5 years</td>
<td>7 (12.0-23.4)</td>
<td>27 (18.6-35.7)</td>
<td>44 (37.4-50.8)</td>
<td>53 (31.7-73.4)</td>
<td>83 (76.5-88.1)</td>
<td>73 (64.3-81.4)</td>
<td>56 (49.1-62.5)</td>
<td>47 (26.5-68.3)</td>
</tr>
<tr>
<td>10 years</td>
<td>25 (17.4-33.3)</td>
<td>32 (22.5-42.0)</td>
<td>48 (40.9-55.1)</td>
<td>53 (31.7-73.4)</td>
<td>75 (66.6-82.5)</td>
<td>68 (58-77.5)</td>
<td>52 (44.8-59)</td>
<td>47 (26.5-68.3)</td>
</tr>
</tbody>
</table>

Table 10: Estimated 1, 3, 5 and 10 years MSS and OS rates by substage III

<table>
<thead>
<tr>
<th>Year</th>
<th>Stage IIIA (Melanoma Specific Survival Rate)</th>
<th>Stage IIIB</th>
<th>Stage IIIC</th>
<th>Stage IIID</th>
<th>Stage IIIA (Overall Survival Rate %)</th>
<th>Stage IIIB</th>
<th>Stage IIIC</th>
<th>Stage IIID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% Confidence intervals)</td>
<td></td>
<td></td>
<td></td>
<td>(95% Confidence intervals)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Year</td>
<td>99.5 (97.8-100)</td>
<td>100 (100-100)</td>
<td>96.1 (93.1-98.2)</td>
<td>77.3 (57.9-91.9)</td>
<td>99.4 (97.8-100)</td>
<td>100 (100-100)</td>
<td>96.6 (87.7-94.8)</td>
<td>68.2 (47.7-85.5)</td>
</tr>
<tr>
<td>3 Years</td>
<td>93.7 (89.6-96.8)</td>
<td>89.7 (83.2-94.7)</td>
<td>79.2 (73.6-84.3)</td>
<td>52.07 (30.6-73.1)</td>
<td>91.4 (86.8-95.1)</td>
<td>89.7 (83.2-94.7)</td>
<td>71.7 (65.5-77.4)</td>
<td>36.4 (16.7-58.8)</td>
</tr>
<tr>
<td>5 Years</td>
<td>91.5 (86.7-95.3)</td>
<td>83.1 (74.7-90.1)</td>
<td>70.8 (64.3-76.9)</td>
<td>45.5 (24.2-67.8)</td>
<td>88.4 (83.2-92.9)</td>
<td>79 (69.6-86.9)</td>
<td>59.6 (52.5-66.5)</td>
<td>29.1 (10.6-52.2)</td>
</tr>
<tr>
<td>10 Years</td>
<td>80.4 (71.0-88.3)</td>
<td>79.8 (76.4-87.7)</td>
<td>63.8 (56.1-71.3)</td>
<td>45.5 (24.2-67.8)</td>
<td>74.1 (63.8-83.2)</td>
<td>69.8 (61.7-58.8)</td>
<td>48.6 (40.2-57.2)</td>
<td>-----</td>
</tr>
</tbody>
</table>
Table 11: Hazard ratio for recurrence free survival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RFS</th>
<th>Univariable</th>
<th>Multivariable (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CL)</td>
<td>P.value</td>
<td>HR (95%CL)</td>
</tr>
<tr>
<td><strong>Substage III</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III B vs III A</td>
<td>1.56 (0.9-2.5)</td>
<td>0.07</td>
<td>1.89 (0.9-3.6)</td>
</tr>
<tr>
<td>III C vs III A</td>
<td>2.78 (1.9-4.0)</td>
<td>&lt;.0001**</td>
<td>2.74 (1.3-5.4)</td>
</tr>
<tr>
<td>III D vs III A</td>
<td>4.41 (2.2-8.7)</td>
<td>&lt;.0001**</td>
<td>3.86 (1.4-10.5)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs Female</td>
<td>1.24 (0.9-1.7)</td>
<td>0.16</td>
<td>1.16 (0.7-1.7)</td>
</tr>
<tr>
<td><strong>Age category</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>middle vs young</td>
<td>1.25 (0.9-1.8)</td>
<td>0.24</td>
<td>1.12 (0.7-1.7)</td>
</tr>
<tr>
<td>old vs young</td>
<td>1.44 (0.9-2.1)</td>
<td>0.05*</td>
<td>1.09 (0.7-1.8)</td>
</tr>
<tr>
<td><strong>Breslow Thickness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 vs T1/T2</td>
<td>1.79 (1.3-2.6)</td>
<td>0.001**</td>
<td>0.9 (0.5-1.6)</td>
</tr>
<tr>
<td>T4 vs T1/T2</td>
<td>2.32 (1.6-3.3)</td>
<td>&lt;.0001**</td>
<td>0.76 (0.4-1.5)</td>
</tr>
<tr>
<td><strong>Histology type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acral/Lentigo vs Superficial</td>
<td>1.29 (0.7-2.1)</td>
<td>0.32</td>
<td>1.10 (0.6-1.9)</td>
</tr>
<tr>
<td>Nodal vs Superficial</td>
<td>1.43 (0.9-2.1)</td>
<td>0.06</td>
<td>1.22 (0.7-2.2)</td>
</tr>
<tr>
<td><strong>body site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremities vs Trunk</td>
<td>1.17 (0.8-1.7)</td>
<td>0.4</td>
<td>1.39(0.8-2.6)</td>
</tr>
<tr>
<td>Head/neck vs Trunk</td>
<td>1.74 (1.2-2.5)</td>
<td>0.004**</td>
<td>0.99 (0.63-1.5)</td>
</tr>
<tr>
<td><strong>Clark level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III vs I/II</td>
<td>0.73 (0.2-2.6)</td>
<td>0.63</td>
<td>0.57 (0.1-2.7)</td>
</tr>
<tr>
<td>IV vs I/II</td>
<td>1.06 (0.3-3.3)</td>
<td>0.91</td>
<td>0.57 (0.13-2.4)</td>
</tr>
<tr>
<td>V vs I/II</td>
<td>2.71 (0.8-8.8)</td>
<td>0.09</td>
<td>1.14 (0.3-5.2)</td>
</tr>
</tbody>
</table>

*P<0.05   **P<0.001 (*) adjusted for age, gender, body site, Breslow thick, histology type and Clark level
### Table 12: Hazard ratio for melanoma specific survival and overall survival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Melanoma Specific Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate (*)</td>
</tr>
<tr>
<td></td>
<td>HR (95%CL)</td>
<td>P. value</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td>Substage III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB vs IIIA</td>
<td>1.56 (0.8-2.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>IIC vs IIIA</td>
<td>2.85 (1.7-4.6)</td>
<td>&lt;.0001**</td>
</tr>
<tr>
<td>IID vs IIIA</td>
<td>7.4 (3.6-15.4)</td>
<td>&lt;.0001**</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs Female</td>
<td>2.01 (1.4-3.1)</td>
<td><strong>0.0006</strong></td>
</tr>
<tr>
<td>Age category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>middle vs young</td>
<td>1.67 (1.02-2.7)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>old vs young</td>
<td>2.28 (1.4-3.7)</td>
<td><strong>0.0008</strong></td>
</tr>
<tr>
<td>Breslow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 vs T1/T2</td>
<td>1.44 (0.9-2.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>T4 vs T1/T2</td>
<td>2.86 (1.8-4.4)</td>
<td>&lt;.0001**</td>
</tr>
<tr>
<td>Histology type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acral/lent vs superficial</td>
<td>1.39 (0.7-2.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Nodal vs Superficial</td>
<td>1.52 (0.9-2.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>body site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremities vs Trunk</td>
<td>0.82 (0.5-1.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>Head/neck vs Trunk</td>
<td>1.02 (0.6-1.6)</td>
<td>0.91</td>
</tr>
<tr>
<td>Clark level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III vs I/II</td>
<td>0.37 (0.06-2.02)</td>
<td>0.25</td>
</tr>
<tr>
<td>IV vs I/II</td>
<td>1.02 (0.2-4.10)</td>
<td>0.98</td>
</tr>
<tr>
<td>vs I/II</td>
<td>2.3 (0.5-9.8)</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Recur site</td>
<td>Ulceration</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>nodule vs local/in-transit</td>
<td>1.53 (0.7-3.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>systemic vs local/in-transit</td>
<td>2.83 (1.4-5.5)</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Ulceration Yes vs No</td>
<td>2.1 (1.5-3.0)</td>
<td><strong>&lt;.001</strong></td>
</tr>
<tr>
<td>Recur Yes vs No</td>
<td>7 (5.1-11.9)</td>
<td><strong>&lt;.001</strong></td>
</tr>
</tbody>
</table>
Fig 1. RFS curves stratify by sub-stage at diagnosis

![Product-Limit Survival Estimates with Number of Subjects at Risk and 95% Confidence Limits](image1)

### Stage Distribution

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>183</th>
<th>99</th>
<th>33</th>
<th>15</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>183</td>
<td>99</td>
<td>33</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>110</td>
<td>51</td>
<td>22</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>227</td>
<td>81</td>
<td>42</td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IIID</td>
<td>21</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig2: RFS curves stratify by age

![Product-Limit Survival Estimates with Number of Subjects at Risk and 95% Confidence Limits](image2)

### Agecat Distribution

<table>
<thead>
<tr>
<th>Age Range</th>
<th>N</th>
<th>18-45 years</th>
<th>46-61 years</th>
<th>62-97 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-45 years</td>
<td>199</td>
<td>77</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>46-61 years</td>
<td>199</td>
<td>76</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>62-97 years</td>
<td>174</td>
<td>65</td>
<td>27</td>
<td>6</td>
</tr>
</tbody>
</table>
FIG3: RFS curves stratify by gender

FIG4: RFS curves stratify by ulceration
**Fig5: RFS curves stratify by Breslow thickness**

![Graph showing RFS curves stratified by Breslow thickness.](image)

**Fig6: RFS curves stratify by positive sentinel lymph nodes**

![Graph showing RFS curves stratified by positive sentinel lymph nodes.](image)
Fig 7: Melanoma specific survival by substage at diagnosis

![Graph showing melanoma specific survival by substage at diagnosis.]

Logrank p < .0001

Fig 8: Melanoma specific survival by age

![Graph showing melanoma specific survival by age.]

Logrank p = 0.0028
**Fig 9:** Melanoma specific survival by gender

![Graph showing survival probability by gender](image)

**Fig 10:** Melanoma specific survival by Breslow thickness

![Graph showing survival probability by Breslow thickness](image)
Fig 11: Melanoma specific survival by ulceration

Fig 12: Melanoma specific survival by relapse

Fig 13. Overall survival stratify by substage at diagnosis
**Fig 14: Overall survival curves stratify by Age**
FIG15: Overall survival curves stratify by gender

FIG16: Overall survival curves stratify by ulceration
FIG17: Overall survival curves stratify by Breslow thickness

FIG18: Overall survival curves stratify by recurrence
** Melanoma Thesis SAS Code;  
** Sylvie Mimche;  
**09/03/2018;  
* create a libname;  
libname h "H:\thesis";  
run;  
** Import the excel datafile *****;  
proc import datafile="H:\thesis\melanomaV7.xlsx"  
out=h.melanomav7  
dbms=xlsx replace;  
getnames=yes;  
run;  
* 2- check the content of the dataset;  
proc contents data=h.melanomav7 varnum;  
run;  
proc print data=h.melanomav7 (obs=30);  
run;  
** sort the data by ID;  
proc sort data=h.melanomav7;  
by ID;  
run;  
**1- Create Table1**;  
* create demographic table 1 **;  
** 2- check the missing variables;  
proc freq data=h.melanomav7 ;  
tables gender clark_level ulceration histo_type stage1 body_site vital_status extranodal Recur recur_sitel Recur_type tumor_death/missing;  
run;  
proc means data=h.melanomav7 n mean min max median std nmiss;  
var _numeric_;  
run;  
proc freq data=h.melanomav7 ;  
tables stage1;  
run;  
*age by tertiles;  
proc rank data =h.melanomav7 out =new groups= 3;  
var age;  
ranks agegrp;  
run;  
proc means data=new min max;
class agegrp;
var age;
run;
ods rtf;

data melanomav1;
set h.melanomav7;
if gender="M" then sex=0;
else sex=1;
**Age category**;
if 18 <= age <= 45 then agecat=1;
else if 46 <= age <= 62 then agecat=2;
else if 63 <= age <= 97 then agecat=3;
/* Breslow thick*/;
if Breslow <= 2.00 then Breslow_thick=1;
else if 2.01 <= Breslow <= 4.00 then Breslow_thick=2;
else Breslow_thick=3;
/* recur type*/
if Recur_type="Distant" then recur_type1=1;
else if Recur_type="Local/Intransit" then recur_type1=2;
else recur_type1=3;
/* recode mitoses in category, pSLN, and recur site1*/
if mitoses<=1 then mitoses1=1;
else if 2<=mitoses<=3 then mitoses1=2;
else mitoses1=3;
/* recode pLN */
if pLN_all=0 then pLN1=1;
else if pLN_all=1 then pLN1=2;
else pLN1=3;
/* recode sentinel pSLN */
if _pSLN_100d=0 then pSLN1=1;
else if _pSLN_100d=1 then pSLN1=2;
else PSLN1=3;
/* recur site*/
** recode variables sex, agecat, breslow thick and recur type**;
if recur_site1="Subcutaneous" then recur_site=1;
if recur_site1="Lymph Nodes" then recur_site=2;
if recur_site1="Lung" or recur_site1="Liver" or recur_site1="Brain" or recur_site1="Bone" or recur_site1="GI" or recur_site1="Spleen" or recur_site1="mucosa" then recur_site=3;
run;
proc format;
value sexf
0='Male'
1='Female';
run;
proc format;
value agecatf
1='18-45 years'
2='46-61 years'
3='62-97 years';
run;
proc format;
value Breslowf
1='T1/T2 '
2='T3 ' 
3='T4 '
;
run;

proc format;
value recur_sitef 
1='Local/in-transit'
2='Lymph Nodes'
3='systemic';
run;
proc format;
value recur_typef
1='Systemic'
2='Local/in-transit'
3='Nodal';
run;
proc format;
value mitosesf
1='1 mitoses'
2='2 to 3 mitoses'
3='>3 mitoses';
run;
proc format;
value pLNf
1='0 node'
2='1 node'
3='2+ nodes'
;
run;
proc format;
value pSLNf
1='0 SL node'
2='1 SL node'
3='2+ SL nodes'
;
run;

* check if the code work;
proc freq data=melanomav1;
tables  stage1 sex agecat Breslow_thick  recur_type1 recur_site mitoses1 pSLN1 pLN1;
format agecat agecatf. Breslow_thick Breslowf. recur_type1 recur_typef. recur_site recur_sitef.
mitoses1 mitosesf. pLN1 pLNf. pSLN1 pSLNf.;
run;

** check categorical variables;
proc freq data=melanomav1;
tables  sex agecat Breslow_thick clark_level ulceration stage1 body_site vital_status histo_Type recur Recur_type recur_site1 pSLN1 pLN1 tumor_death/missing;
run;

* tumor death **;

proc freq data=melanomav1;
tables tumor_death;
run;
proc freq data=melanomav1;
where vital_status="Dead";
tables tumor_death;
run;
* tumor death after recurrence;
proc freq data=melanomav1;
where recur="Yes";
tables tumor_death;
run;

* death after recurrence;
proc freq data=melanomav1;
where recur="Yes";
tables vital_status;
run;

** positive distant intransit-regional metastasis**;
proc freq data=melanomav1;
where recur="Yes";
tables PDM_image PDM_Patho_45d PDM_clinical PDM_Bone PDM_Brain PDM_Liver PDM_Lung PDM_skin PDM_Pathol_Bone PDM_Pathol_Brain PDM_Pathol_Liver PDM_Pathol_Lung PDM_pathol_Skin Posit_reg_Biopsy Posit_intransit Posit_Satellit Posit_transit_diag Posit_Transit_45d Posit_Reg_Biopsy_45d Posit_satelit_45d nodal_inTransit_diag posit_Nodes_100d vitalSta_NED;
run;

proc freq data=melanomav1;
tables PDM_image PDM_Patho_45d PDM_clinical PDM_Bone PDM_Brain PDM_Liver PDM_Lung PDM_skin PDM_Pathol_Bone PDM_Pathol_Brain PDM_Pathol_Liver PDM_Pathol_Lung PDM_pathol_Skin Posit_reg_Biopsy Posit_intransit Posit_Satellit Posit_transit_diag Posit_Transit_45d Posit_Reg_Biopsy_45d Posit_satelit_45d nodal_inTransit_diag posit_Nodes_100d vitalSta_NED;
run;

proc freq data=melanomav1;
tables PDM_clinical;
run;

** treatment**;

proc freq data=melanomav1;
tables chemo radiation surgery hormone immuno _Neoadj_rad _Neoadj_systemic;
run;
* treatment for recurrence;
** assess continuous variables age breslow mitoses**;

```latex
proc univariate data=melanomav1;
var age Breslow mitoses ;
run;
```

* Sentinal lymph nodes*

```latex
proc means data=h.melanomav7 n min max mean std median q1 q3 nmiss;
var age Breslow mitoses pLN_all _pSLN_100d total_SLN;
run;
```

** patterns of recurrence**;

* recurrence by stage**;

```latex
** stage1 versus recur site;**
proc freq data=melanomav1;
where recur="Yes";
tables stage1*recur_site;
format recur_site recur_sitef.;
run;
```

```latex
** stagel versus recur site;**
proc freq data=melanomav1;
where recur="Yes";
tables stage1*recur_site;
format recur_site recur_sitef.;
run;
```

** site at first relapse by subsatge**;

```latex
proc freq data=melanomav1;
where recur="Yes";
tables recur_site1*stage1;
format recur_site recur_sitef.;
run;
```

```latex
proc freq data=melanomav1;
where recur="Yes";
tables recur_type1;
format recur_type1 recur_typef.;
run;
```

```latex
proc freq data=melanomav1;
where recur="Yes";
tables recur_site;
format recur_site recur_sitef.;
run;
```

```latex
proc freq data=melanomav1;
tables stage1*recur/chisq;
where recur="Yes";
run;
```

* type of recurrence  by stage*;

```latex
proc freq data=melanomav1;
tables recur_type1*stage1;
where recur="Yes";
format recur_type1 recur_typef.;
run;
```

* recurrence by method of detection*;
**Part II- Kaplan Meir and COX for Recurrence free survival overal survival and MSS***

** RFS, use rtime as time to first recurrence**

```sas
data melanomav2;
set melanomav1;
format _excision_date mmddyy10. date_recur mmddyy10. Vitalstatus_date mmddyy10.;
if recur="Yes" then do;
censor=1;
rtime=date_recur - _excision_date;
rtime=rtime/365.25;
end;
else if recur="No" then do;
censor=0;
rtime=mdy(12,31,2017) - _excision_date;
rtime=rtime/365.25;
label rtime='Recurrence Free survival Time (years) ';
end;
run;
proc contents data=melanomav2 varnum;
```
run;
proc print data=melanomav2 (obs=30);
var rtime;
run;

** what is the median recurrence time time**;
ods rtf;

*median time to recur by stagel;

proc means data =melanomav2 min max mean median q1 q3;
    class stagel;
    where censor=1;
    var rtime;
run;

proc means data =melanomav2 min max mean median q1 q3;
    var rtime;
    where censor=1;
run;

proc sort data=melanomav2;
  by stagel;
run;

* KM curve for recurrence Free survival*

* time to recur*
ods graphics on;
proc lifetest data=melanomav2  timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
  time rtime*censor(0);
run;
ods graphics off;

* time to recur by stage*
ods graphics on;
proc lifetest data=melanomav2  timelist=1 2 3 4 5
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
  time rtime*censor(0);
  strata stagel;
run;
ods graphics off;

** RFS follow up time **
ods graphics on;
proc lifetest data=melanomav2  timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
  time rtime*censor(0);
run;
ods graphics off;

** RFS curve for stage **
ods graphics on;
proc lifetest data=melanomav2  timelist=1 2 3 4 5
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
  time rtime*censor(0);
  strata stagel;
run;
ods graphics off;

* RFS with confidence band and homogeneity*;

ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10 plots=survival(cb=hw test nocensor atrisk=0 to 15 by 5);
time rtime*censor(0);
strata stage1/test=logrank adjust=sidak diff=control("IIIA");
run;
ods graphics off;

proc lifetest data=melanomav2 notable plots=none;
time rtime*censor(0);
strata stage1/test=logrank adjust=sidak diff=control("IIIA");
run;

* output survival rate and 95% CL by substage III;

proc lifetest data=melanomav2 notable outsurv= survest conftype=asinsqrt confband=ep bandmintime=1 bandmaxtime=15 timelist=1 2 3 4 5 reduceout noprint stderr;
time rtime*censor(0);
strata stage1;
run;
proc print data=survest;
run;

* output the failure rates and 95% CL;

proc lifetest data=melanomav2 notable outsurv= outsurv conftype=asinsqrt confband=ep bandmintime=1 bandmaxtime=15 timelist=1 2 3 4 5 reduceout noprint stderr;
time rtime*censor(0);
strata stage1;
run;
data outsurv;
set outsurv;
failure=1-survival;
failure_lower=1-sdf_ucl;
failure_upper=1-sdf_lcl;
run;
proc print data=outsurv;
run;

* for others covariates;
proc lifetest data=melanomav2 notable outsurv= outsurv conftype=asinsqrt confband=ep bandmintime=1 bandmaxtime=15 timelist=1 3 5 reduceout noprint stderr;
time rtime*censor(0);
strata sex;
run;
data outsurv;
set outsurv;
failure=1-survival;
failure_lower=1-sdf_ucl;
failure_upper=1-sdf_lcl;
run;

proc print data=outsurv;
run;

*sex agecat Breslow_thick clark_level ulceration body_site vital_status histo_Type recur
Recur_type recur_site1 pSLN1 pLN1 surgery;
ods rtf close;

title 'Kaplan-Meir recurrence curves for Agecat';
ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata agecat /test=logrank adjust=sidak diff=control("IIIA");
format agecat agecatf.;
run;
ods graphics off;

** RFS survival curves by agecat**;

title 'Kaplan-Meir recurrence curves for Agecat';
ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10 plots=survival (cb=hw test
nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata agecat /test=logrank adjust=sidak diff=control("IIIA");
format agecat agecatf.;
run;
ods graphics off;

** RFS survival curves by SEX**;
ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10
plots=survival (strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata sex;
format sex sexf.;
run;
ods graphics off;
ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10 plots=survival (cb=hw test
nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata sex/test=logrank adjust=sidak diff=control("1");
format sex sexf.;
run;
ods graphics off;

* ulceration*;
ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata ulceration;
run;
ods graphics off;

* Breslow thick*;
ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata Breslow_thick;
format Breslow_thick Breslowf.;
run;
ods graphics off;

* positive nodes
ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata pLN1;
format pLN1 pLNf.;
run;
ods graphics off;

* sentinel lymph node;
ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata pSLN1;
format pSLN1 pSLNf.;
run;
ods graphics off;

* surgery;
ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata surgery;
run;
ods graphics off;

ods graphics on;
proc lifetest data=melanomav2 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata recur_site;
format recur_site recur_sitef.;
run;
ods graphics off;

ods graphics on;
** survival curve using macro**;

```sas
%macro pval (data = , var = );
  proc lifetest data = &data plots = survival(strata = overlay) atrisk;
    time rtime*censor(0);
    strata &var;
  run;
%mend;

%pval(data = melanomav2, var = stagel);
```

/*Create dummy variables for age*/
```sas
data melanomav3;
set melanomav2;

if 18 <= age <= 45 then do;
agecat=0; age0=1; age1=0; age2=0;
end;/**/
else if 46 <= age <= 62 then do;
agecat=1; age0=0 ; age1=1; age2=0;
end;/**/
else if 63 <= age <= 97 then do;
agecat=2; age0=0; age1=0; age2=1;
end;
if stagel = "IIIA" then do;
  stage=0; stageA =1;stageB=0; stageC=0; stageD=0;end;
else if stagel = "IIIB" then do;
  stage=1; stageA =0;stageB=1; stageC=0; stageD=0; end;
else if stagel = "IIIC" then do;
  stage=2; stageA =0;stageB=0; stageC=1; stageD=0; end;
else if stagel = "IIID" then do;
  stage=3; stageA =0;stageB=0; stageC=0; stageD=1; end;
/*ulceration*/
if ulceration="Yes" then ulceration=1;
else if ulceration="No" then ulceration=0;
/* histo type*/
if histo_type="Acral/Lentinginous" then histo_type1=1;
if histo_type="Nodular" then histo_type1=2;
if histo_type="Superficial" then histo_type1=3;
/*body_site*/
if body_site="Extremites" then body_site1=1;
if body_site="Head/Neck" then body_site1=2;
if body_site="Trunk" then body_site1=3;
/* recur type*/
if Recur_type="Distant" then recur_type1=1;
if Recur_type="Local/Intransit" then recur_type1=2;
if Recur_type="Nodal" then recur_type1=3 ;
```
/* recode sentinel pSLN */
if _pSLN_100d = 0 then pSLN1=1;
else if _pSLN_100d = 1 then pSLN1=2;
else PSLN1=3;
/* recode pLN */
if pLN_all = 0 then pLN1=1;
else if pLN_all = 1 then pLN1=2;
else pLN1=3;
/* recure site*/
if recur_site1="Subcutaneous" then recur_site=1;
if recur_site1="Lymph Nodes" then recur_site=2;
if recur_site1="Lung" or recur_site1="Liver" or recur_site1="Brain" or
recur_site1="Bone" or recur_site1="GI" or recur_site1="Spleen" or recur_site1="mucosa" then recur_site=3;
run;

proc freq data=melanomav3;
   tables agecat stage histo_type1 body_site1 recur_type1 pSLN1;
run;

** Univariate Cox model for stage, use IIIA as reference group**;
proc phreg data=melanomav3;
   class stage1(param=ref ref="IIIA");
   model rtime*censor(0)=stage1 /rl ties=efron;
run;
** Cox model for age, use age=0 as reference group**;
proc phreg data=melanomav3;
   class agecat(param=ref ref="0");
   model rtime*censor(0)=agecat /rl ties=efron;
run;
proc phreg data=melanomav3; ** sex=0 is Male and Sex=1 is Female**;
   class sex (param=ref ref="1");
   model rtime*censor(0)=sex /rl ties=efron;
run;
proc phreg data=melanomav3;
   class ulceration (param=ref ref="0");
   model rtime*censor(0)=ulceration /rl ties=efron;
run;
proc phreg data=melanomav3;
   class Breslow_thick(param=ref ref="1");
   model rtime*censor(0)=Breslow_thick /rl ties=efron;
run;
proc phreg data=melanomav3;
   class Clark_level (param=ref ref="I/II");
   model rtime*censor(0)=Clark_level /rl ties=efron;
run;
proc phreg data=melanomav3;
   class histo_type1 (param=ref ref="3");
   model rtime*censor(0)=histo_type1 /rl ties=efron;
run;
proc phreg data=melanomav3;
class body_site1 (param=ref ref="3");
model rtime*censor(0)= body_site1 /rl ties=efron;
run;

proc phreg data=melanomav3;
class pSLN1(param=ref ref="1");
model rtime*censor(0)=pSLN1 /rl ties=efron;
run;
proc phreg data=melanomav3;
class pLN1(param=ref ref="1");
model rtime*censor(0)=pLN1 /rl ties=efron;
run;
proc phreg data=melanomav3;
class recur_site1(param=ref ref="Subcutaneous");
model rtime*censor(0)=recur_site1 /rl ties=efron;
run;
proc phreg data=melanomav3;
class recur_site(param=ref ref="1");
model rtime*censor(0)=recur_site /rl ties=efron;
run;

** Multivariate cox model;
* adjusted cox model adjusted by sex agecat body site and histo and Breslow and Clark;
proc phreg data=melanomav3;
class stage1 (param=ref ref="IIIA") sex(param=ref ref="1") agecat(param=ref ref="0") Clark_level(param=ref ref="I/II") sex body_site1(param=ref ref="1") Breslow_thick(param=ref ref="1") histo_type1(param=ref ref="1") ulceration(param=ref ref="0") pLN1(param=ref ref="1");
model rtime*censor(0)=stage1 agecat sex Clark_level body_site1 Breslow_thick histo_type1 ulceration pLN1 /rl ties=efron;
run;

**-assesss these variables satisfy PH assumption using log survival and schroenfeld, ;
*8;
%macro loglog (data = , var = );
proc lifetest data = &data plots = (s lls);
   time rtime*censor(0);
   strata &var;
run;
%mend;

%loglog(data =melanomav3, var = stage1);******Stage1 satisfy PH assumption****;
%loglog(data =melanomav3, var = agecat);***Agecat satisfy PH assumption *****;
%loglog(data =melanomav3, var = sex );***Sex satisfy PH assumption********;  
%loglog(data =melanomav3, var = ulceration);***Ulceration satisfy PH assumption ***;
%loglog(data = melanomav3, var = Breslow_thick); **Breslow thickness satisfy PH assumption**;
%loglog(data = melanomav4, var = body_site); **********Body site don't satisfy PH assumption because it is not parallel between extremeties, head/neck and trunk***;
%loglog(data = melanomav3, var = histo_type); ****Histologic_type satisfy PH assumption*;
%loglog(data = melanomav3, var = recur);
%loglog(data = melanomav3, var = Clark_level); *clark doesn't satisfy PH assumption using log log *;
%loglog(data = melanomav3, var = pLN1);

*** Check assumption using schoenfeld residual;
%macro schoen(predictor =);
%let np = 0;
%do %until(%scan(&predictor, &np+1, " ")=);
%let np = %eval(&np+1);
%end;
proc phreg data = melanomav3 noprint;
class stage1 sex agecat Breslow_thick histo_type body_site Clark_level ulceration pLN1 recur_site;
model rtime*censor(0) = &predictor;
output out = result1 ressch = rsch1-rsch&np;
run;
data events;
 set result1;
 if censor = 1;
run;
proc rank data = events out = ranked ties = mean;
 var rtime;
 ranks timerank;
run;
proc corr data = ranked nosimple;
 var rsch1-rsch&np;
 with timerank;
run;
%mend;

%schoen(predictor = stage1 sex agecat histo_type Breslow_thick body_site Clark_level ulceration pLN1 recur_site);

*best subset selection;
proc phreg data = melanomav3;
 class stage1 sex agecat ulceration body_site Clark_level Breslow_thick histo_type pLN1 pSLN1 recur_site;
model rtime*censor(0) = stage1 agecat sex ulceration body_site Clark_level Breslow_thick histo_type pLN1 pSLN1 recur_site / selection = stepwise include = 1 rl ties = efron;
run;

proc phreg data = melanomav3;
 class stage1 sex agecat ulceration body_site Clark_level Breslow_thick histo_type pSLN1 pLN1 recur_site;
model rtime*censor(0) = stage1 agecat sex ulceration body_site Clark_level Breslow_thick histo_type pSLN1 pLN1 recur_site
/ selection = backward include = 1 rl ties = efron;
run;

** Part II**
**Overall survival - create survival time and censoring variable;

* format the date;

** use stime as date of death;

** data melanomav4;
set melanomav1;
format diagnos_date mmddyy10. Vitalstatus_date mmddyy10.;
if Vital_status="Dead" then do;
failure=1;
stime= Vitalstatus_date-Diagnos_date;
stime=stime/365.25;
end;
else if Vital_status="Alive" then do;
failure=0;
stime=mdy(12,31,2017)-Diagnos_date;
stime=stime/365.25;
label stime='Follow-up time (years)';
title "Overall survival";
end;
run;

proc contents data=melanomav4 varnum;
run;
proc print data=melanomav4 (obs=30);
var stime;
run;

** what is the median survival time time**;

*median follow up time and interval;
proc means data =melanomav4 median q1 q3;
var stime;
run;

** by stage**;

*median follow up time and standard deviation;
proc means data =melanomav4 n median q1 q3 mean std;
class stagel;
var stime;
run;

**KM survival curve for substage ;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10
plots=survival(strata=overlay cl test nocensor atrisk (maxlen=13
outside(0.15)));
time stime*failure(0);
strata stagel;
run;
ods graphics off;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10 plots=survival(cb=hw test atrisk(outside (0.15)));
time stime*failure(0);
strata stage1;
run;
ods graphics off;
* with no band *;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10 plots=survival(test nocensor atrisk=0 to 10 by 5);
time stime*failure(0);
strata stage1;
run;
ods graphics off;

** output the overall survival rate and 95% CL by substageIII;

proc lifetest data=melanomav4 notable outsurv= Ovest conftype=asin sqrt confband=ep bandmintime= 1 bandmaxtime =15 timelist =1 3 5 10 reduceout noprint stderr ;
time stime*failure(0);
strata stage1 ;
run;
proc print data=Ovest;
run;

** output the overall survival rate and 95% CL for others covariates;

proc lifetest data=melanomav4 notable outsurv= Ovest conftype=asinsqrt confband=ep bandmintime= 1 bandmaxtime =15 timelist =1 3 5 10 reduceout noprint stderr ;
time stime*failure(0);
strata Recur_site ;
run;
proc print data=Ovest;
run;

** survival curves by agecat**;
title'Kaplan-Meir Survival curves for Agecat';
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10 plots=survival(strata=overlay atrisk(outside (0.15)) cl test nocensor);
time stime*failure(0);
strata agecat ;
format agecat agecatf.;
run;
ods graphics off;

** survival curves by SEX**;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10 plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time stime*failure(0);
strata sex;
format sex sexf.;
run;
ods graphics off;

** survival curves by ulceration**;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time stime*failure(0);
strata ulceration;
run;
ods graphics off;

** survival curves by breslow **;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time stime*failure(0);
strata Breslow_thick;
format Breslow_thick Breslowf.;
run;
ods graphics off;

** survival curves for recur**;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time stime*failure(0);
strata recur;
run;
ods graphics off;

** survival curves for body_site**;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time stime*failure(0);
strata body_site;
run;
ods graphics off;

** survival for clark-level**;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time stime*failure(0);
strata Clark_level;
run;
ods graphics off;

** survival for histo_type**;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time stime*failure(0);
strata histo_type;
run;
ods graphics off;

** survival for recur site**;

ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time stime*failure(0);
strata recur_site;
format recur_site recur_sitef.;
run;
ods graphics off;

ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time stime*failure(0);
strata Recur_type1;
format recur_type1 recur_typef.;
run;
ods graphics off;

** survival curve using macro**;

%macro pval(data = , var = );
proc lifetest data = &data plots = survival(strata = overlay) atrisk;
time stime*failure(0);
strata &var;
run;
%mend;

%pval(data = melanomav4, var = stage1);
%pval(data = melanomav4, var = sex);
%pval(data = melanomav4, var = agecat);
%pval(data = melanomav4, var = ulceration);
%pval(data = melanomav4, var = body_site);
%pval(data = melanomav4, var = Breslow_thick);
%pval(data = melanomav4, var = histo_type);
%pval(data = melanomav4, var = Clark_level);

/*Create dummy variables for age*/
data melanomav5;
set melanomav4;
if age <18 then agecat=.;
   else if 18 <= age <= 45 then agecat=0;
   else if 46 <= age <= 62 then agecat=1;
   else if 63 <= age <= 97 then agecat=2;
/*stage*/
if stagel = "IIIA" then do;
   stage=0; stageA =1;stageB=0; stageC=0 ;end;
else if stagel = "IIIB" then do;
   stage=1; stageA =0;stageB=1; stageC=0 ; end;
else if stagel = "IIIC" then do;
stage=2; stageA =0; stageB=0; stageC=1 ; end;
else stage=3;

/*ulceration*/
If ulceration="Yes" then ulceration=1;
else If ulceration="No" then ulceration=0;
/*recur*/
If recur="Yes" then recur=1;
else If recur="No" then recur=0;
/*histo_type*/
If histo_type="Acral/Lentinginous" then histo_type=1;
else If histo_type="Nodular" then histo_type=2;
else If histo_type="Superficial" then histo_type=3;
else histo_type=4;
/*body_site*/
If body_site="Extremities" then body_site=1;
else If body_site="Head/Neck" then body_site=2;
else If body_site="Trunk" then body_site=3;
else body_site=4;
/*extranodal*/
If extranodal="Yes" then extranodal=1;
else If extranodal="No" then extranodal=2;
else extranodal=3;
/*clark-level*/
if Clark_level="I/II"  then Clark=1;
else if Clark_level="III" then Clark=2;
else if Clark_level="IV" then Clark=3;
else Clark=4;
/* Breslow thick*/;
if Breslow <=2.00 then Breslow_thick=1;
else if 2.01<=Breslow<4.00 then Breslow_thick=2;
else  Breslow_thick=3;
/* recur type*/
if Recur_type="Distant" then recur_type1=1;
else if Recur_type="Local/IntransIt" then recur_type1=2;
else recur_type1=3;
/*recode pLN */
if pLN_all = 0 then pLN1=1;
else if pLN_all = 1 then pLN1=2;
else pLN1=3;
/*recode sentinel pSLN */
if _pSLN_100d = 0 then pSLN1=1;
else if _pSLN_100d = 1 then pSLN1=2;
else PSLN1=3;
proc format;
value sexf
0= 'Male'
1= 'Female';
run;
proc format;
value ulcerationf
0= 'No'
1= 'Yes';
run;
proc format;
value agecatf
0= '18-45 years'
1= '46-61 years'
2='62-97 years';
run;
proc format;
value Breslowf
1='T1/T2 '
2='T3'  
3='T4' ;
run;

proc format;
value body_sitef
1='Extremities'
2='Head/Neck'
3='Trunk';
run;
proc format;
value clarkf
1='I/II'
2='III'
3='IV'
4='V';
run;
proc format;
value histof
1='Acral/Lentiginous'
2='Nodular'
3='Superficial';
run;

proc format;
value pLNf
1='0 node'
2='1 node'
3='2+ nodes';
run;

proc format;
value pSLNf
1='0 node'
2='1 node'
3='2+ nodes';
run;

* check if the code work;
proc freq data=melanomav5;
tables sex stage agecat ulceration Breslow_thick Clark histo_type body_site extranodal recur pSLN1;
run;

proc freq data=melanomav5;
tables sex stage agecat;
run;
  ** proc phreg unadjusted**;
** Cox model for age, use age=18-45 years as reference group**;
```sas
proc phreg data=melanomav5;
  class agecat(param=ref ref="0");
  model stime*failure(0)=agecat /rl ties=efron;
run;
```

** sex=female as ref group (sex=0 is Male and Sex=1 is Female)**;
```sas
proc phreg data=melanomav4;
  class sex (param=ref ref="1");
  model stime*failure(0)=sex /rl ties=efron;
run;
```

** ulceration as reference group**;
```sas
proc phreg data=melanomav4;
  class ulceration (param=ref ref="No");
  model stime*failure(0)=ulceration /rl ties=efron;
run;
```

** body site as reference group**;
```sas
proc phreg data=melanomav4;
  class body_site (param=ref ref="3");
  model stime*failure(0)=body_site /rl ties=efron;
run;
```

** Clark level as reference group**;
```sas
PROC freq data=melanomav4;
tables Clark_level;
run;
```

** extranodal as reference group**;
```sas
proc phreg data=melanomav4;
  class extranodal (param=ref ref="No");
  model stime*failure(0)=extranodal /rl ties=efron;
run;
```

** histo type as reference group**;
```sas
proc phreg data=melanomav4;
  class histo_type (param=ref ref="Superficial");
  model stime*failure(0)=histo_type /rl ties=efron;
run;
```

** recur as reference group**;
```sas
proc phreg data=melanomav4;
  class recur (param=ref ref="No");
  model stime*failure(0)=recur /rl ties=efron;
run;
```
class pLN1(param=ref ref="1");
model stime*failure(0)=pLN1 /rl ties=efron;

run;

proc phreg data=melanomav4;
class recur_site(param=ref ref="1");
model stime*failure(0)=recur_site /rl ties=efron;
run;

** adjusted cox model;

*adjusted for all variables that fit the PH assumption;
proc phreg data=melanomav5;
class stage1(param=ref ref="IIIA") agecat(param=ref ref="0")Clark(param=ref ref="1")
sex body_site(param=ref ref="3") Breslow_thick(param=ref ref="1")
histo_type(param=ref ref="3") ulceration (param=ref ref="1");
model stime*failure(0)=stage1 agecat sex Clark body_site Breslow_thick
histo_type /rl ties=efron;;
run;

* macro for Cox model;

%macro cox (data = , var = );
proc phreg data = &data;
   class &var;
   model stime*failure(0) = &var / rl ties = efron;
run;
%mend;
ods rtf;
%cox(data =melanomav4, var =sex);
%cox(data =melanomav4, var = agecat);
%cox(data =melanomav4, var = stage);
%cox(data =melanomav4, var = ulceration);
%cox(data =melanomav4, var = Clark);
%cox(data =melanomav4, var = body_site);
%cox(data =melanomav4, var = Breslow_thick);
%cox(data =melanomav4, var = histo_type);
%cox(data =melanomav4, var =extranodal);
%cox(data =melanomav4, var =recur);
ods rtf close;
title;

**-assess these variables satisfy PH assumption using log survival and
schroenfeld, ;

*8;
%macro loglog (data = , var = );
proc lifetest data = &data plots = (s lls);
   time stime*failure(0);
   strata &var;
run;
%mend;
%loglog(data = melanomav4, var = stage1);
%loglog(data = melanomav4, var = agecat);
%loglog(data = melanomav4, var = sex);
%loglog(data = melanomav4, var = ulceration);
%loglog(data = melanomav4, var = Breslow_thick)
%loglog(data = melanomav4, var = body_site)
%loglog(data = melanomav4, var = histo_type)
%loglog(data = melanomav4, var = recur);
%loglog(data = melanomav4, var = Clark_level)
%loglog(data = melanomav4, var = pSLN1);

*** Check assumption using schoenfeld residual;
%macro schoen(p predictor = );
%let np = 0;
%do %until(%scan(&predictor, &np+1, " ")=);
%let np = %eval(&np+1);
%end;
proc phreg data = melanomav4 noprint;
class stage1 sex agecat Breslow_thick histo_type body_site Clark_level ulceration pLN1 extranodal;
model stime*failure(0) = &predictor;
output out = result1 ressch = rsch1-rsch&np;
run;

data events;
set result1;
if failure = 1;
run;
proc rank data = events out = ranked ties = mean;
var stime;
ranks timerank;
run;
proc corr data = ranked nosimple;
var rsch1-rsch&np;
with timerank;
run;
%mend;

%schoen(p predictor = stage1 sex agecat histo_type Breslow_thick body_site Clark_level ulceration pLN1);
** the PH assumption using log-log survival**;

ods graphics on;
proc lifetest data=melanomav4 method=km plots=(s lls);
time stime*failure(0);
strata stage1;
run;
ods graphics off;

** Does Sex satisfy the PH assumption using log-log survival**;

proc phreg data=melanomav4;
class sex;
model stime*failure(0)=sex;
strata sex;
baseline out=result1 survival=s1
loglogs=lls1;
run;
proc print data=result1;
run;
title1 "Log-log survival curves for Sex ";
title2 "Using PH model for SEX";
proc sgplot data=result1;
xaxis label="Survival time";
step y=lls1 x=stime/group=sex;
run;  ** answer=Yes**;

** Does age satisfy the PH assumption, log-log-curve for age**;
ods graphics on;
proc lifetest data=melanomav4 method=km plots=(s lls);
time stime*failure(0);
strata agecat;
run; **answer=yes**;
ods graphics off;

* stepwise elimination and best subset selection;

*best subset selection;
proc phreg data = melanomav4;
class stage1 sex agecat ulceration body_site Clark_level Breslow_thick histo_type ;
   model stime*failure(0) = stage1 agecat sex ulceration body_site Clark_level Breslow_thick histo_type pSLN1
   / selection = stepwise include = 1 rl ties = efron;
run;

proc phreg data = melanomav4;
class stage1 sex agecat ulceration body_site Clark_level Breslow_thick histo_type ;
   model stime*failure(0) = stage1 agecat sex ulceration body_site Clark_level Breslow_thick histo_type pSLN1
   / selection = backward include = 1 rl ties = efron;
run;

******************************************************************************
** Melanoma specific survival**;
******************************************************************************;
data melanomav6;
set melanomav5;
format diagnos_date mmddyy10. Vitalstatus_date mmddyy10.;
if Tumor_death="Yes" then do;
   failure=1;
time= Vitalstatus_date-Diagnos_date;
time=time/365.25;
end;
else if Tumor_death="No" or Tumor_death="N/A" then do;
   failure=0;
time=mdy(12, 31, 2017)-Diagnos_date;
time=time/365.25;
label time='Melanoma Specific Survival Time (years)';
title "Melanoma specific survival";
end;
run;

proc contents data=melanomav6 varnum;
run;
proc print data=melanomav6 (obs=30);
var time;
run;

** follow up time by stage**;
proc means data =melanomav6 n min max mean median q1 q3;
class stage1;
var time;
run;
ods rtf;

**KM survival curve for substage ;**
ods graphics on;
proc lifetest data=melanomav6 timelist=1 3 5 10
plots=survival(strata=overlay cl test nocensor atrisk (maxlen=13 outside(0.15)));
time time*failure(0);
strata stage1;
run;
ods graphics off;

ods graphics on;
proc lifetest data=melanomav6 timelist=1 3 5 10 plots=survival(cb=hw test atrisk(outside (0.15)));
time time*failure(0);
strata stage1;
run;
ods graphics off;

* with no band *
ods graphics on;
proc lifetest data=melanomav6 timelist=1 3 5 10 plots=survival(test nocensor atrisk=0 to 10 by 5);
time time*failure(0);
strata stage1;
run;
ods graphics off;

** survival curves by agecat**;

ods graphics on;
proc lifetest data=melanomav6 timelist=1 3 5 10 plots=survival(strata=overlay atrisk(outside (0.15) cl test nocensor);
time time*failure(0);
strata agecat;  
format agecat agecatf.;
run;
ods graphics off;

** MSS survival curves by SEX**;
ods graphics on;
proc lifetest data=melanomav6 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time time*failure(0);
strata sex;
format sex sexf.;
run;
ods graphics off;

** MSS survival curves by ulceration**;
ods graphics on;
proc lifetest data=melanomav6 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time time*failure(0);
strata ulceration;
run;
ods graphics off;

** MSS survival curves by breslow **;
ods graphics on;
proc lifetest data=melanomav4 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time stime*failure(0);
strata Breslow_thick;
format Breslow_thick Breslowf.;
run;
ods graphics off;

** MSS survival curves for recur**;
ods graphics on;
proc lifetest data=melanomav6 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time time*failure(0);
strata recur;
run;
ods graphics off;

** MSS survival curves for body_site**;
ods graphics on;
proc lifetest data=melanomav6 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time time*failure(0);
strata body_site;
run;
ods graphics off;

** MSS survival for clark-level**;
ods graphics on;
proc lifetest data=melanomav6 timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time time*failure(0);
strata Clark_level;
run;
ods graphics off;

** MSS survival for histo_type**;
ods graphics on;
%macro test cautious=0;
%macro t test caution=0;
%macro ttest caution=0;
%macro t-test caution=0;
%macro t-test caution=0;
%macro t-test caution=0;
%macro t-test caution=0;
%macro t-test caution=0;
%macro t-test caution=0;
%macro t-test caution=0;
%macro t-test caution=0;
bandmintime= 1  bandmaxtime =15 timelist =1 3 5 10  reduceout noprnt stderr ;
time time*failure(0);
strata stagel ;
run;
proc print data=Svest;
run;

proc phreg data=melanomav6;* using IIIA as ref grp*;
class stagel(param=ref ref="IIIA");
model time*failure(0)=stagel /rl ties=efron;
run;
** Cox model for age, use age=18-45 years as reference group**;
proc phreg data=melanomav6;
class agecat(param=ref ref="0");
model time*failure(0)=agecat /rl ties=efron;
run;
proc phreg data=melanomav6; ** sex=female as ref group (sex=0 is Male and Sex=1 is Female)**;
class sex (param=ref ref="1");;
model time*failure(0)=sex /rl ties=efron;
run;
proc phreg data=melanomav6; 
class ulceration (param=ref ref="0");
model time*failure(0)=ulceration /rl ties=efron;
run;
proc phreg data=melanomav6;
class body_site (param=ref ref="3");
model time*failure(0)=body_site /rl ties=efron;
run;
proc phreg data=melanomav6;
class Breslow_thick (param=ref ref="1");
model time*failure(0)=Breslow_thick /rl ties=efron;
run;
proc phreg data=melanomav6;
class Clark_level (param=ref ref="I/II");
model time*failure(0)=Clark_level /rl ties=efron;
run;
proc phreg data=melanomav6;
class extranodal(param=ref ref="0") ;
model time*failure(0)=extranodal /rl ties=efron;
run;
proc phreg data=melanomav6;
class histo_type (param=ref ref="Superficial");
model time*failure(0)=histo_type /rl ties=efron;
run;
proc phreg data=melanomav6;
class recur (param=ref ref="0");
model time*failure(0)=recur /rl ties=efron;
run;
proc phreg data=melanomav6;
class pSLN1 (param=ref ref="1");
model time*failure(0)=pLN1 /rl ties=efron;
run;

proc phreg data=melanomav6;
class pLN1 (param=ref ref="1");
model time*failure(0)=pLN1 /rl ties=efron;
run;

proc phreg data=melanomav6;
class recur_site (param=ref ref="1");
model time*failure(0)=recur_site /rl ties=efron;
run;

proc phreg data=melanomav6;
class recur_type1 (param=ref ref="1");
model time*failure(0)=recur_type1 /rl ties=efron;
run;

* Multivariate Cox model, adjusted using variables that fit the PH assumption;

*adjusted for all variables that fit the PH assumption;
proc phreg data=melanomav6;
class stage1 (param=ref ref="IIIA") agecat (param=ref ref="0") Clark (param=ref ref="1")
sex body_site (param=ref ref="3") Breslow_thick (param=ref ref="1")
histo_type (param=ref ref="3");
model time*failure(0)=stage1 agecat sex Clark body_site Breslow_thick histo_type /rl ties=efron;
run;
ods rtf close;