Distribution Agreement

In presenting this thesis or dissertation as a partial fulfilment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ 11-12-2018

Sylvie Madeyo Mimche Date

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

By

Sylvie Madeyo Mimche

MPH, Emory University, 2018
(Applied Epidemiology)

Timothy L Lash, DSc, MPH
Committee Chair

John Hyngstrom, M.D
Committee Member

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

By

Sylvie Madeyo Mimche, MSc

Emory University School of Medicine

Fall 2018

Thesis Committee Chair: Timothy L Lash, DSc, MPH

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health in Applied Epidemiology

2018

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

By

Sylvie Madeyo Mimche

Emory University School of Medicine
Fall 2018

Thesis Committee Chair: Timothy L Lash, DSc, MPH

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Applied Epidemiology
Fall 2018

AKNOWLEDGEMENT

I would like to acknowledge Pr. Timothy Lash, Dr. John Hyngstrom, and Carolyn Ross for their selfless support for my thesis project. Under their guidance, I have gained not only insights into the world of epidemiology and biostatistics, but also tremendous confidence in my public health career. I will always be encouraged by their dedicated pursuit of true science and their contribution to this field.

TABLE OF CONTENTS

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 substage (IIIA, IIIB, IIIC 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, IIIC and IIID 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, IIIC and IIID), 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 (8^{th} 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 reccurent 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 (Table8).

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 (46-60years) 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 2-4mm (HR1.79 CL 1.3-2.6, p=0.001) and two fold for 4+mm (HR 2.32, CL1.6-3.3, 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 (Table9).

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. Patient 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, IIIIC and IIID were 62, 57, 44 and 26 months. The estimated 5year crude OS rate decreased as the sub-stage III at diagnosis increased from IIIA to IIID ranging from 88% to 29% (Table10). 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 (Fig3-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 (Table12). 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, CL1.4-3.4, 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, CL2.2-4.7, p<0.0001). Similarly, the hazard of death for acral/lentigo and nodal metastasis were (HR:2.69 CL1.7-4.3, 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%) , follow 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 [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 [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 [24,25]. Median age at diagnosis was 55 years, which is about similar to what has been observed in previous international studies [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 [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 [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 *et al* [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 5years MSS rate to be 92%, 83%, 71% and 46% for stage IIIA to IIID respectively, which is in agreement with recent studies [11,14]. Gershenwald et al during the 8th AJCC edition classification showed approximatively 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 7th AJCC edition, however the 5-year MSS rates for patients with stage IIIA, IIIB and IIIC were 78%, 59% and 40% respectively [4,5]. The magnitude of observed improvement in prognosis from the 7th edition to the 8th 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 7th versus 8th 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 [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 7th 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 [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 [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 IIIC 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

1. Eggermont AMM, Spatz A, Robert C. Cutaneous melanoma. Lancet. 2014; 383(9919):816–827.
2. American Cancer Society. Cancer Facts & Figures 2018. Atlanta: American Cancer Society; 2018. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed October,20 2018.
3. Guy GP, Machlin SR, Ekwueme DU and Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. *Am J Prev Med* 2014; 104(4): e69-e74. doi: dx.doi.org/10.1016/j.amepre.2014.08.036.
4. Balch CM, Soong SJ, Gershenwald JE, et al. Melanoma of the skin. In: Edge S, Byrd D, Compton C*, et al,* eds. *AJCC Cancer Staging Manual*. Seventh ed. New York: Springer Verlag; 2009.
5. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009; 27(36):6199-6206.
6. Dickson PV, Gershenwald JE. Staging and prognosis of cutaneous melanoma. *Surg oncol Clin* North Am 2011; 20:1–17.
7. Salama AKS, de Rosa N, Scheri RP, Pruitt SK, *et al.* Hazard-Rate Analysis and Patterns of Recurrence in Early Stage Melanoma: Moving towards a Rationally Designed Surveillance Strategy. *PLoS ONE*, 2013; *8*(3), e57665. http://doi.org/10.1371/journal.pone.0057665
8. Podlipnik S, Carrera C, Sánchez M, *et al*. Performance of diagnostic tests in an intensive follow-up protocol for patients with American Joint Committee on Cancer (AJCC) stage IIB, IIC, and III localized primary melanoma: A prospective cohort study. *J Am Acad Dermatol* 2016; 75:516–24.
9. Tas Faruk. Metastatic behavior in melanoma: Timing, pattern, survival, and influencing factors. J Oncol 2012: 647684.
10. National Comprehensive Cancer Network. Guidelines for patients: Melanoma, 2018. Date accessed: October 20, 2018. https://www.nccn.org/professionals/physician_gclinically apparent lypmhls/pdf/melanoma.pdf.
11. Gershenwald JE, Scolyer RA, Hess KR, *et al.* Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017; 67(6):472-492.

12. Balch CM, Gershenwald JE, Soong S-J, *et al*. Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: Comparison of nodal micrometastases versus macrometastases. J Clin Oncol. 2010;28(14): 2452–2459.
13. Romano E, Scordo M, Dusza SW, *et al.* Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol. 2010; 28:3042e4047.
14. Haydu LE, Scolyer RA, Lo S, Quinn MJ, *et al.* Conditional Survival: An Assessment of the Prognosis of Patients at Time Points After Initial Diagnosis and Treatment of Locoregional Melanoma Metastasis. *Journal of Clinical Oncology* 2017 35:15, 1721-1729 doi: 10.1200/JCO.2016.71.9393.
15. Lim KHJ, Spain L, Barker C, *et al.* Contemporary outcomes from the use of regular imaging to detect relapse in high-risk cutaneous melanoma. ESMO Open 2018;**3**: e000317. doi:10.1136/ esmoopen-2017-000317
16. Meyers MO, Yeh JJ, Frank J. Method of detection of initial recurrence of stage II/III cutaneous melanoma: analysis of the utility of follow-up staging. Ann Surg Oncol. 2009; 16:941e947.
17. Hofmann U, Szedlak M, Rittgen W, *et al.* Primary staging and follow-up in melanoma patients: monocenter evaluation of methods, costs and patient survival. Br J Cancer. 2002; 87:151e157.
18. Eggermont AMM, Chiarion-Sileni V, Grob J-J, *et al.* Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. N Engl J Med. 2016;375(19): 1845–1855.
19. Balch CM, Gershenwald JE, Soong S-J, *et al.* Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27(36):6199–6206.
20. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al., editors. AJCC Cancer Staging Manual. 8. New York: Springer International Publishing; 2017. pp. 563–585.
21. Turner RM, Bell KJ, Morton RL, *et al.* Optimizing the frequency of follow-up visits for patients treated for localized primary cutaneous melanoma. J Clin Oncol. 2011;29(35):4641–6.
22. Jemal A, Siegel R, Ward E, Hao Y, Xu J, and Thun MJ, "Cancer statistics, 2009," CA Cancer Journal for Clinicians, vol. 59, no. 4, pp. 225–249, 2009.

23. Atkins MB, Hauschild A, Wahl RL, and Balch CM. "Diagnosis of Stage IV melanoma," in Cutaneous Melanoma, C. M. Balch, A. N. Houghton, A. J. Sober, S. J. Soong, M. B. Atkins, and J. F. Thompson, Eds., pp. 573–602, Qual

24. Rockberg J, Amelio JM, Taylor A. *et al*. (2016). "Epidemiology of cutaneous melanoma in Sweden-Stage-specific survival and rate of recurrence." *Int J Cancer* 2016 **139**(12): 2722-2729.

25. Fleming, Nathaniel H. *et al*. "Impact of Age on Management of Primary Melanoma Patients." *Oncology* 85.3 (2013): 10.1159/000351499. *PMC*. Web. 21 Oct. 2018.

26. Erdei E, Torres SM. A new understanding in the epidemiology of melanoma. Expert review of anti- cancer therapy. 2010; 10:1811–23. doi:10.1586/ era.10.170.

27. Hayat MJ, Howlader N, Reichman ME, *et al*. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist 2007; 12:20–37.

28. Joosse A, de Vries E, Eckel R, Nijsten T. *et al*. Gender differences in melanoma survival: female patients have a decreased risk of metastasis. *Journal of Investigative Dermatology* 131, 719–726 (2011).

29. Sondak VK, Swetter SM, and Berwick MA. Gender disparities in patients with melanoma: breaking the glass ceiling. *Journal of Clinical Oncology*, 2012; 30(18), pp. 2177–2178

30. Joosse A, Collette S, Suciu S, *et al.* Superior outcome of women with stage I/II cutaneous melanoma: pooled analysis of four European Organisation for Research and Treatment of Cancer phase III trials. J Clin Oncol 2012;30: 2240–7.

31. Amin MB, Edge SB, Greene FL, *et al.* (eds): AJCC Cancer Staging Manual (ed 8). New York, NY, Springer, 2017 doi:10.1007/978-3-319-40618-3

32. Madu MF, Franke V, Van de Wiel B, *et al*. External validation of the 8th Edition Melanoma Staging System of the American Joint Committee on Cancer (AJCC): Effect of adding EORTC sentinel node (SN) tumor burden criteria on prognostic accuracy in stage III. Journal of Clinical Oncology 2018 36:15_suppl, 9500-9500

TABLES AND FIGURES

Table1: Clinical and Pathologic Characteristics of Patients with Stage III Melanoma

Characteristics	**N (%) N=544**
Gender	
Male (0)	334 (62)
Female (1)	210 (39)
Age category (years)	
1 8- 45	179 (33)
46-60	169 (31)
61-97	196 (36)
Ulceration	
Yes	211 (39)
No	333 (61)
Clark-Level	
I/II	10 (2)
III	47 (9)
IV	379 (70)
V	58 (11)
unknown	50 (9)
Site of the primary melanoma	
Extremities	228 (42)
Head/Neck	131 (24)
Trunk	178 (33)
Other/unknown*[1]	7 (1.3)
Type of primary melanoma	
Acral/Lentinginous	55 (10)

Nodular	128 (24)
Superficial	204 (38)
Other/unknown*[2]	157 (29)
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/mm^2) (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)

IIIC	228 (42)
IIID	22 (4)

***1 mucosal ; *2 desmoplastic, nevoid, spindle, lentigo melanoma.**

Table 2: AJCC Eight Edition Melanoma Stage III Subgroups

(A)

AJCC Eight Edition Melanoma Stage III Subgroups N x T Table

Category N	Category T								
	To	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Gershenwald, Scolyer, et al. Melanoma. In Amin, M.B., et al. (Eds.) AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017

(B)

If T is	and N is	and M is	then Pathological Stage is	Patients (%) N=544
T1a/b, T2a	N1a, N2a	M0	IIIA	184 (34%)
T1a/b, T2a	N1b/c, N2b	M0	IIIB	110 (22%)
T2b/T3a	N1a/b/c, N2a/b	M0	IIIB	
T0	N1b, N1c	M0	IIIB	
T1a/b, T2a/b, T3a	N2c, N3a/b/c	M0	IIIC	228 (42%)
T3b/T4a	any N≥N1	M0	IIIC	
T4b	N1a/b/c, N2a/b/c	M0	IIIC	
T0	N2b/c, N3b/c	M0	IIIC	
T4b	N3a/b/c	M0	IIID	22 (4%)

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)

Disease recurrence	**n (%)**
Yes	181(33)
No	363 (67)
Recurrence type	
Local/In-transit	25 (14)
Regional	66(37)
Distant	90 (49)
Anatomy Site of the first recurrence	
Subcutaneous	36 (20)
Lymph nodes	61 (34)
Lung	37 (20)
Brain	19 (11)
Liver	8 (4)
Bone	4 (2)
Multiple sites	10 (5)
Mucosal/GI	4 (2)
Unknown	3 (2)
Mode of detection of the recurrence	
Imaging	128 (71)
Clinically detected on examination	33 (18)
Patient detected /symptomatic	20 (11)
Recurrence by stage at diagnosis	
IIIA	36 (20)
IIIB	31 (28)
IIIC	102 (45)
IIID	12 (55)
Total dead	159 (29)

Dead after relapse	99 (62)
Median time to recur (95%CL) in months	14.4 (7-26)
Median follow up time (IRQ) months	
IIIA	62 (38-98)
IIIB	56.6 (34-102)
IIIC	44 (26-85)
IIID	26 (9-36)
Total	51 (23-97)

Table 4: Site of first relapse by substage (n%)

Site at first relapse	**IIIA**	**IIIB**	**IIIC**	**IIID**
Subcutaneous	6 (17)	3 (10)	27 (27)	0 (0)
Nodal	13 (36)	15 (48)	30 (29)	3 (25)
Lung	6(17)	6(19)	22(22)	3(25)
Brain	4(11)	3(10)	9(9)	3(25)
Liver	2(6)	0(0)	4(4)	2(17)
Multiples sites	4 (11)	1 (3)	4 (4)	1(8)
Bone	0(0)	2(6)	2(2)	0(0)

Table5: Time to first recurrence by stage at diagnosis (median ± 95%CL)

stage at diagnosis	median TTR (95%CL) months	relapse before 12 months (n, %)	relapse after 12 months (n, %)	total
IIIA	21.5 (17-40)	11 (31%)	25 (69.4)	36 (20%)
IIIB	13.9 (9-23)	13 (42%)	18 (58%)	31 (17 %)
IIIC	14.2 (12-17)	42 (41%)	60 (59%)	102 (56 %)
IIID	5.5 (4-17)	8 (67%)	4 (33%)	12 (7%)
overall	14.4 (7-26)	74 (41%)	107 (59%)	181

Table 6: Mode of detection of the recurrence (n%)

Imaging	128 (71%)
physician detected on examination	36 (20%)
patient detected	17 (9%)

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

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

Table 8: Therapy received for relapse (n%)

Surgery	110 (61)
radiation	50 (28)
Hormone	2 (1.1)
Immuno therapy	55 (30)
neoadjuvant systemic	1 (0.5)
chemotherapy	33 (18)

Table 9: Estimated 1, 3, 5 and 10-years recurrence rates by substage III (n%)

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

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

	Melanoma Specific Survival Rate (95% Confidence intervals)				Overall Survival Rate % (95% Confidence intervals)			
Year	Stage IIIA	Stage IIIB	Stage IIIC	Stage IIID	Stage IIIA	Stage IIIB	Stage IIIC	Stage IIID
1 Year	99.5 (97.8-100)	100 (100-100)	96.1 (93.1-98.2)	77.3 (57.9-91.9)	99.4 (97.8-100)	100 (100-100)	96.6 (87.7-94.8)	68.2 (47.7-85.5)
3 Years	93.7 (89.6-96.8)	89.7 (83.2-94.7)	79.2 (73.6-84.3)	52.07 (30.6-73.1)	91.4 (86.8-95.1)	89.7 (83.2-94.7)	71.7 (65.5-77.4)	36.4 (16.7-58.8)
5 Years	91.5 (86.7-95.3)	83.1 (74.7-90.1)	70.8 (64.3-76.9)	45.5 (24.2-67.8)	88.4 (83-92.9)	79 (69.6-86.9)	59.6 (52.5-66.5)	29.1 (10.6-52.2)
10 Years	80.4 (71.0-88.3)	79.8 (76.4-87.7)	63.8 (56.1-71.3)	45.5 (24.2-67.8)	74.1 (63.8-83.2)	69.8 (16.7-58.8)	48.6 (40.2-57.2)	-----

Table 11: Hazard ratio for recurrence free survival

Parameter	RFS			
	Univariable		Multivariable (*)	
	HR (95%CL)	P.value	HR (95%CL)	P.value
Substage III				
IIIB vs IIIA	1.56 (0.9-2.5)	0.07	1.89 (0.9-3.6)	**0.05**
IIIC vs IIIA	2.78 (1.9-4.0)	**<.0001****	2.74 (1.3-5.4)	**0.006****
IIID vs IIIA	4.41 (2.2-8.7)	**<.0001****	3.86 (1.4-10.5)	**0.008****
Gender Male vs Female	1.24 (0.9-1.7)	0.16	1.16 (0.7-1.7)	0.51
Age category middle vs young	1.25 (0.9-1.8)	0.24	1.12 (0.7-1.7)	0.65
old vs young	1.44 (0.9-2.1)	**0.05***	1.09 (0.7-1.8)	0.72
Breslow Thickness T3 vs T1/T2	1.79 (1.3-2.6)	**0.001****	0.9 (0.5-1.6)	0.73
T4 vs T1/T2	2.32 (1.6-3.3)	**<.0001****	0.76 (0.4-1.5)	0.46
Histology type Acral/Lentigo vs superficial	1.29 (0.7-2.1)	0.32	1.10 (0.6-1.9)	0.73
Nodal vs Superficial	1..43 (0.9-2.1)	0.06	1.22 (0.7-2.2)	0.5
body site Extremities vs Trunk	1.17 (0.8-1.7)	0.4	1.39(0.8-2.6)	0.15
Head/neck vs Trunk	1.74 (1.2-2.5)	**0.004****	0.99 (0.63-1.5)	0.97
Clark level III vs I/II	0.73 (0.2-2.6)	0.63	0.57 (0.1-2.7)	0.48
IV vs I/II	1.06 (0.3-3.3)	0.91	0.57 (0.13-2.4)	0.44
V vs I/II	2.71 (0.8-8.8)	0.09	1.14 (0.3-5.2)	0.86

***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

Parameter	Melanoma Specific Survival				Overall Survival			
	Univariate		Multivariate (*)		Univariate		Multivariate (*)	
	HR (95%CL)	P. value	HR (95%CL)	P. value	HR (95%CL)	P. value	HR (95%CL)	P. value
Substage III								
IIIB vs IIIA	1.56 (0.8-2.9	0.15	1.86 (0.9-3.8)	0.08	1.41 (0.9-2.1)	0.08	1.68(0.9-3.1)	0.10
IIC vs IIIA	2.85 (1.7-4.6)	**<.0001****	3.65 (1.7-7.7)	**0.0006**	2.42 (1.6-3.6)	**<.0001****	3.55 (1.9-6.7)	**<.0001****
IID vs IIIA	7.4 (3.6-15.4)	**<.0001****	8.2 (2.9-22.5)	**<.0001**	6.46 (3.5-11.8)	**<.0001****	9.59 (4.0-23.1)	**<.0001****
Gender								
Male vs Female	2.01 (1.4-3.1)	**0.0006****	1.89 (1.2-2.9)	**0.006**	2.10 (1.4-2.9)	**<.0001****	1.84 (1.2-2.7)	**0.001***
Age category								
middle vs young	1.67 (1.02-2.7)	**0.04***	1.21 (0.7-2.05)	0.46	1.79 (1.2-2.8)	**0.008***	1.24 (0.8-1.9)	0.36
old vs young	2.28 (1.4-3.7)	**0.0008****	1.87 (1.1-3.2)	**0.01***	3.12 (2.1-4.7)	**<.0001****	2.20(1.4-3.4)	**0.0006****
Breslow								
T3 vs T1/T2	1.44 (0.9-2.3)	0.12	0.64 (0.3-1.2)	0.15	1.65 (1.1-2.5)	**0.01***	0.79 (0.5-1.3)	0.38
T4 vs T1/T2	2.86 (1.8-4.4)	**<.0001****	0.74 (0.4-1.5)	0.40	3.25 (2.2-4.7)	**<.0001****	0.87 (0.5-1.6)	0.64
Histology type								
Acral/lent vs superficial	1.39 (0.7-2.6)	0.29	0.66 (0.3-1.3)	0.25	2.69 (1.7-4.3)	**<.0001****	1.53 (0.9-2.6)	0.11
Nodal vs Superficial	1.52 (0.9-2.4)	0.08	0.73 (0.4-1.3)	0.26	1.52 (1.0-2.3)	**0.04***	0.69 (0.4-1.1)	0.13
body site								
Extremities vs Trunk	0.82 (0.5-1.3)	0.35	0.91 (0.6-1.4)	0.67	0.97 (0.6-1.4)	0.89	0.94 (0.6-1.4)	0.77
Head/neck vs Trunk	1.02 (0.6-1.6)	0.91	0.90 (0.5-1.5)	0.69	1.10 (1.1-2.1)	0.64	0.87 (0.6-1.3)	0.55
Clark level								
III vs I/II	0.37 (0.06-2.02)	0.25	0.48 (0.08-2.9)	0.43	6.78 (0.2-3.7)	0.76	0.93 (0.2-4.7)	0.92
IV vs I/II	1.02 (0.2-4.10	0.98	0.98 (0.2-4.3)	0.98	1.41 (O.34-5.7)	0.62	1.32 (0.3-5.5)	0.70
V vs I/II	2.3 (0.5-9.8)	0.25	1.25 (0.3-5.6)	0.77	3.77 (0.9-15.7)	0.06	1.69 (0.4-7.3)	0.44

Recur site								
nodal vs local/in-transit	1.53 (0.7-3.1)	0.23	------	------	1.2 (0.7-2.2)	0.5	------	------
systemic vs local/in-transit	2.83 (1.4-5.5)	**0.002**	-----	------	1.85 (1.0-3.2)	**0.03**	-----	------
Ulceration Yes vs No	2.1 (1.5-3.0)	**<.0001**	-----	-----	2.06 (1.5-2.8)	**<.001**	-----	------
Recur Yes vs No	7 (5.1-11.9)	**<.0001**	-----	-----	4.13 (3.0-5.7)	**<.001**	-----	------

Fig 1. RFS curves stratify by sub-stage at diagnosis

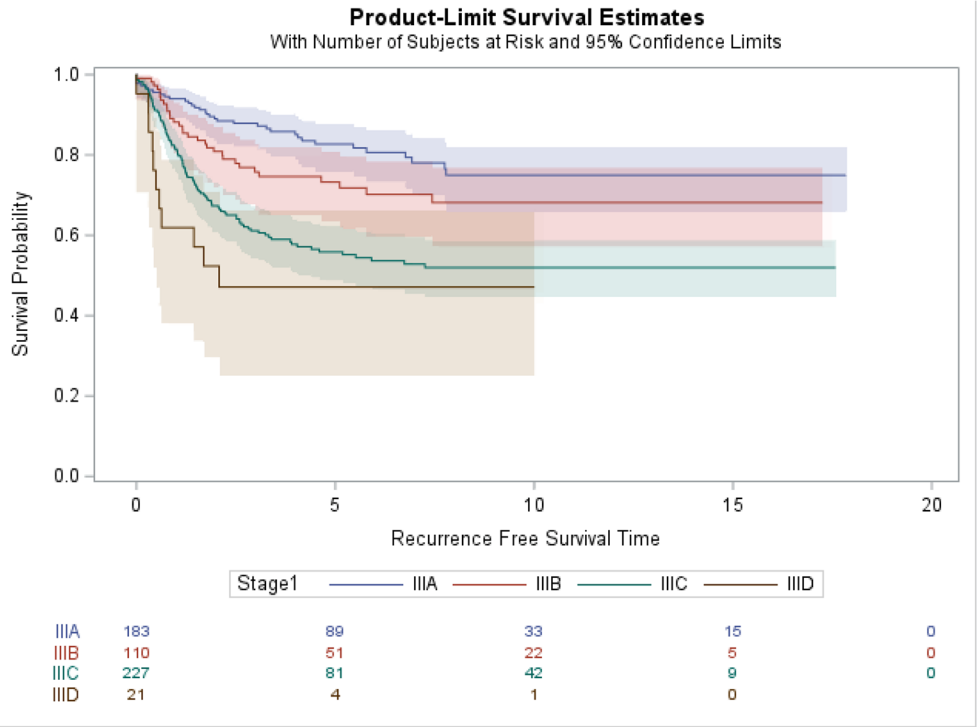


Fig2: RFS curves stratify by age

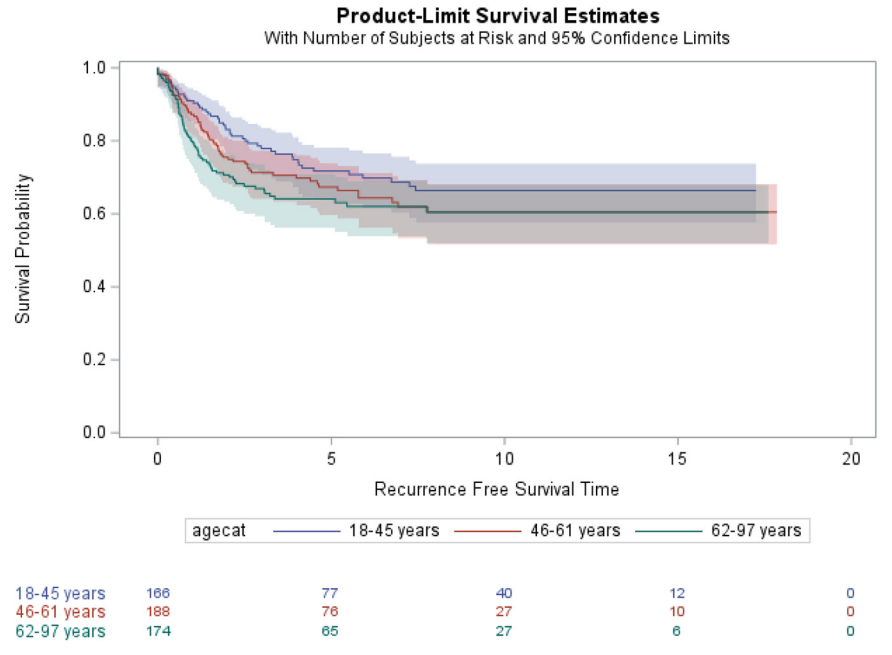


FIG3: RFS curves stratify by gender

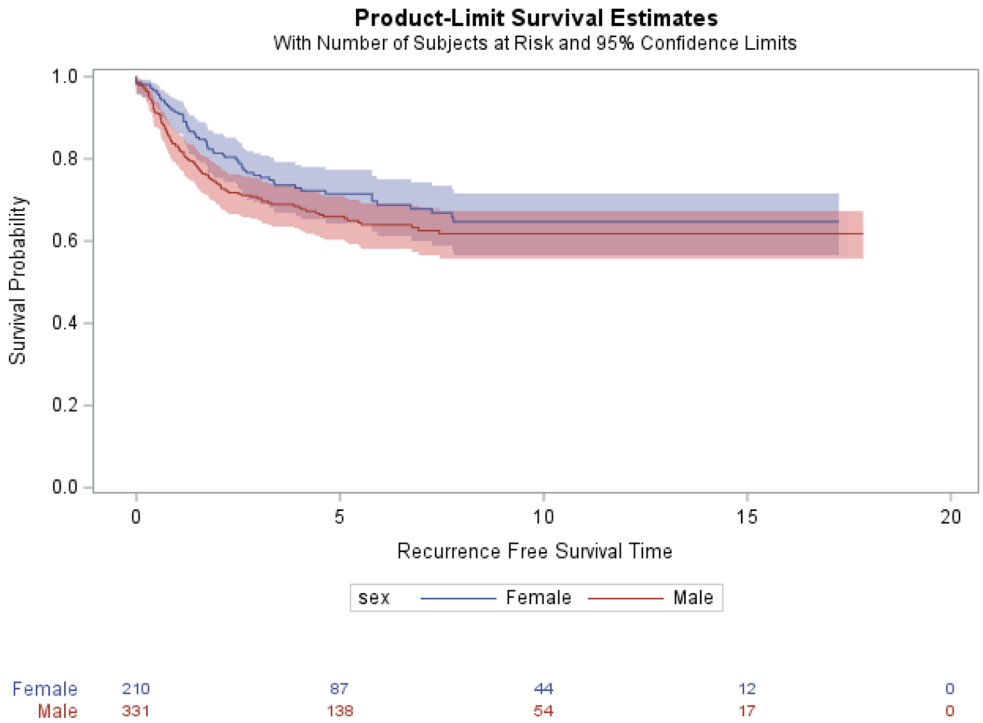


Fig4: RFS curves stratify by ulceration

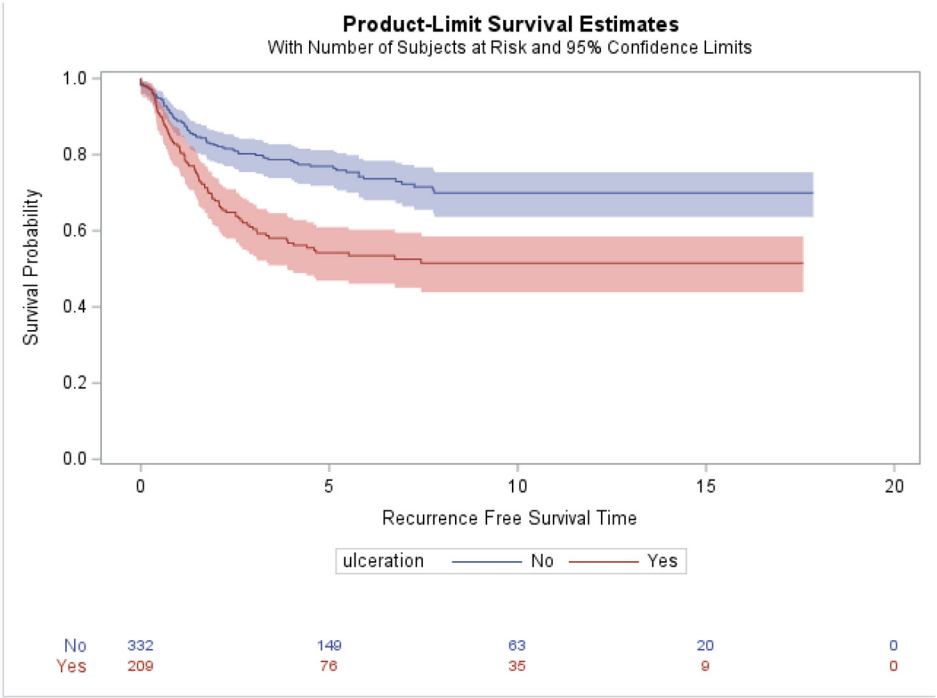


Fig5: RFS curves stratify by Breslow thickness

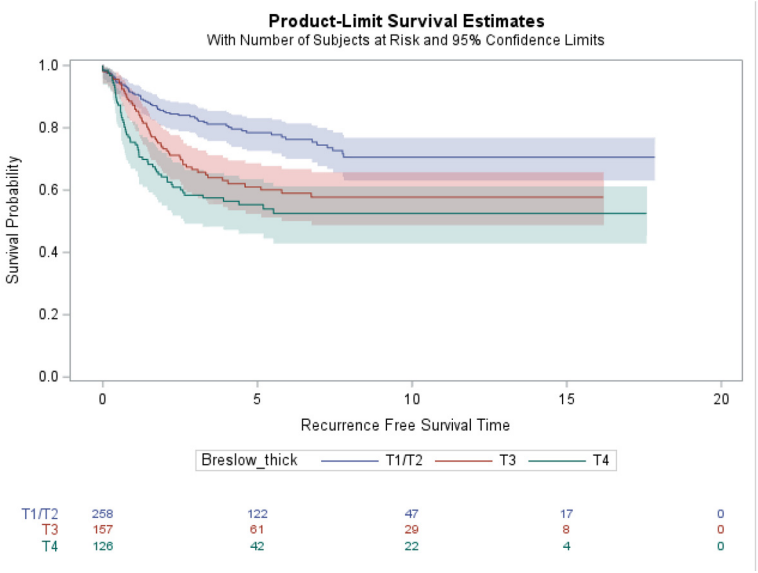


Fig6: RFS curves stratify by positive sentinel lymph nodes

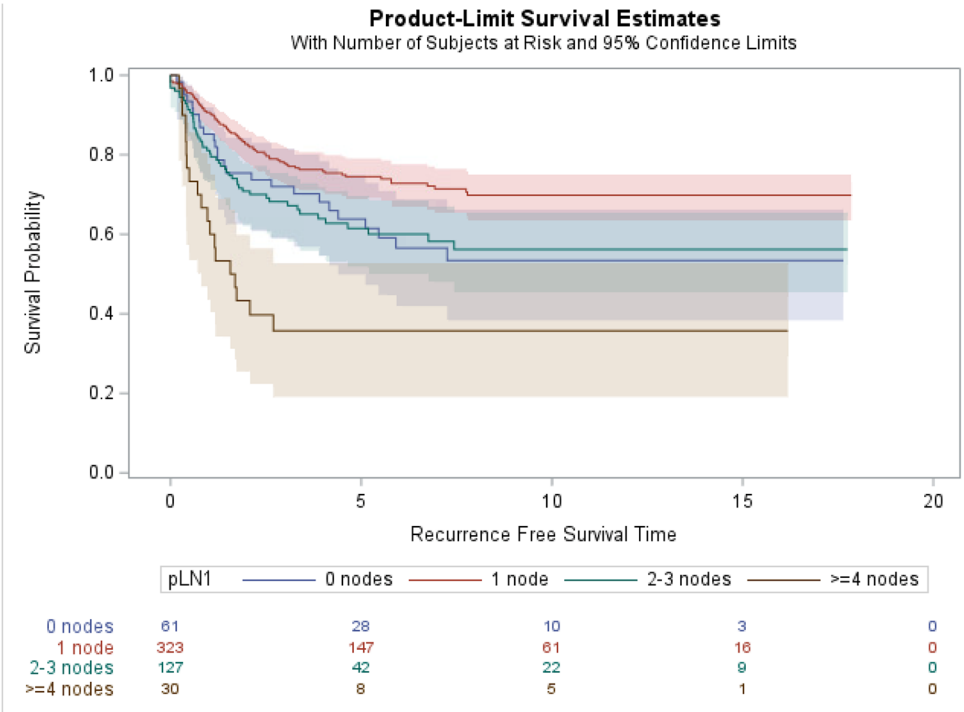


Fig7 :Melanoma specific survival by substage at diagnosis

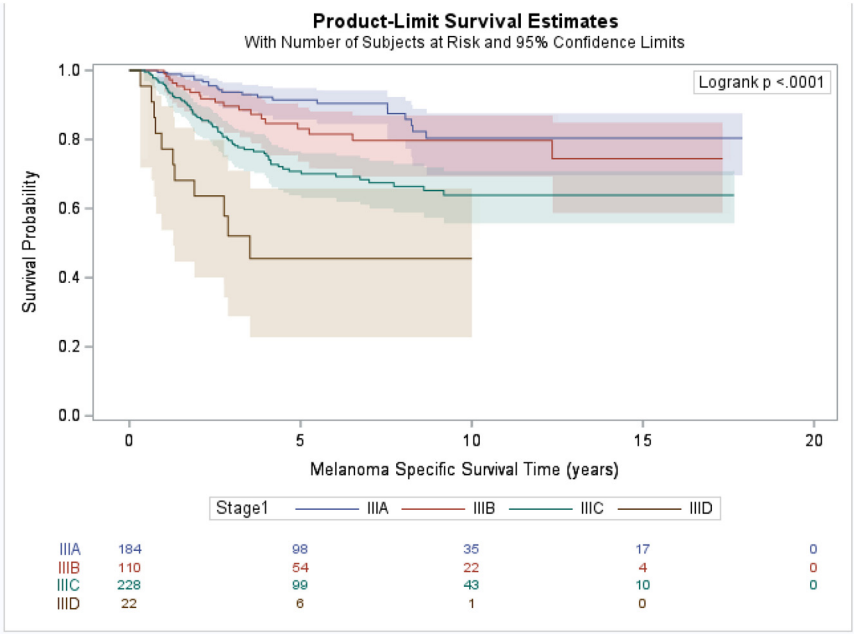


Fig 8: Melanoma specific survival by age

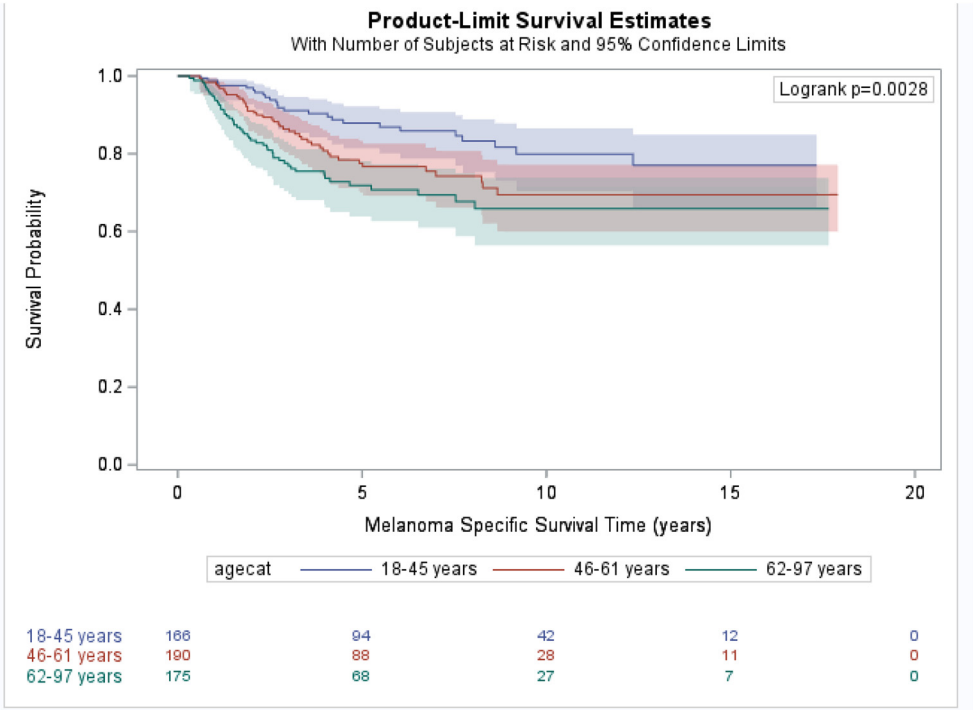


Fig9: Melanoma Specific survival by gender

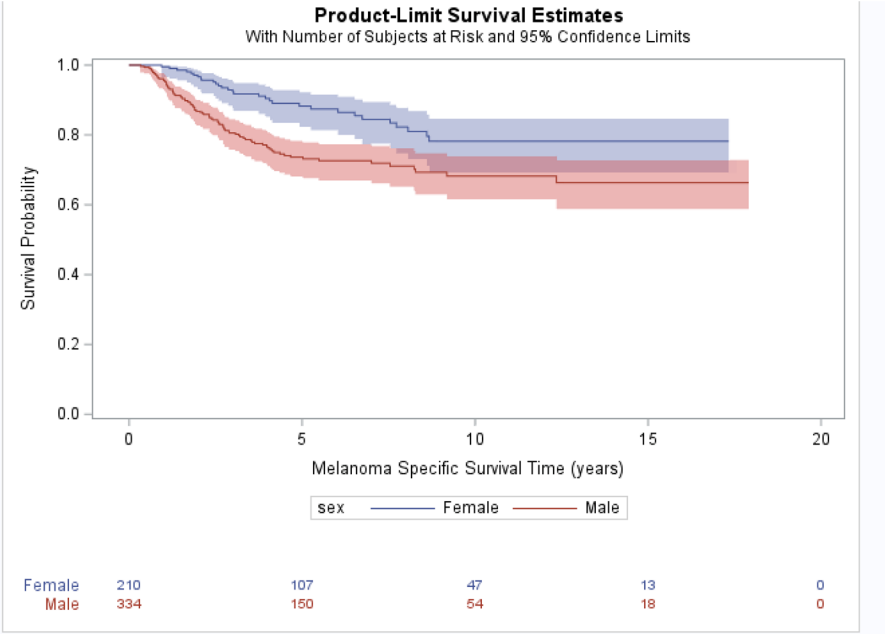


Fig10: Melanoma specific survival by Breslow thickness

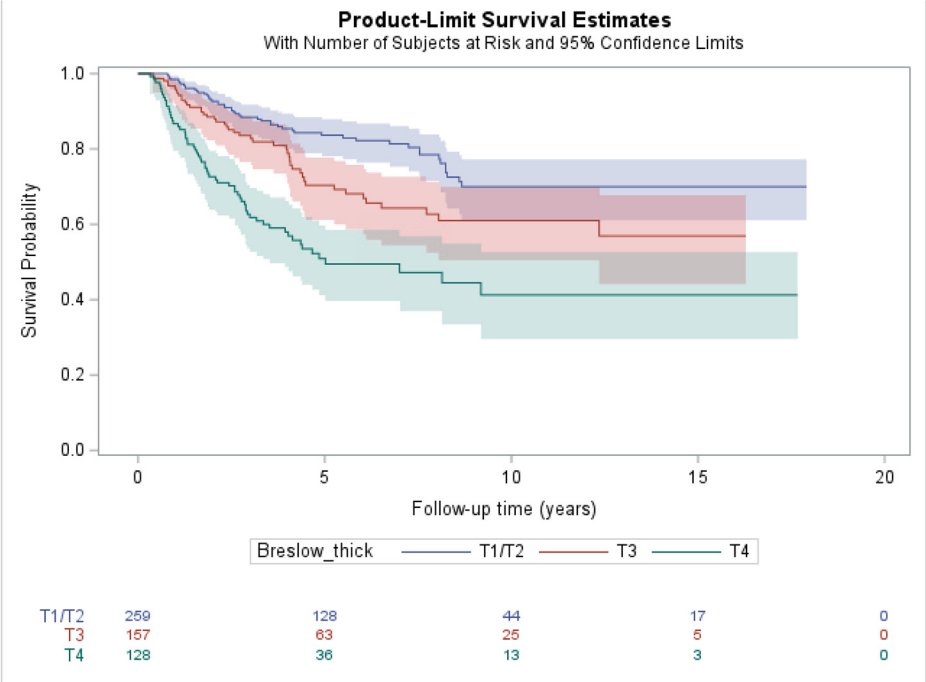


Fig11: Melanoma specific survival by ulceration

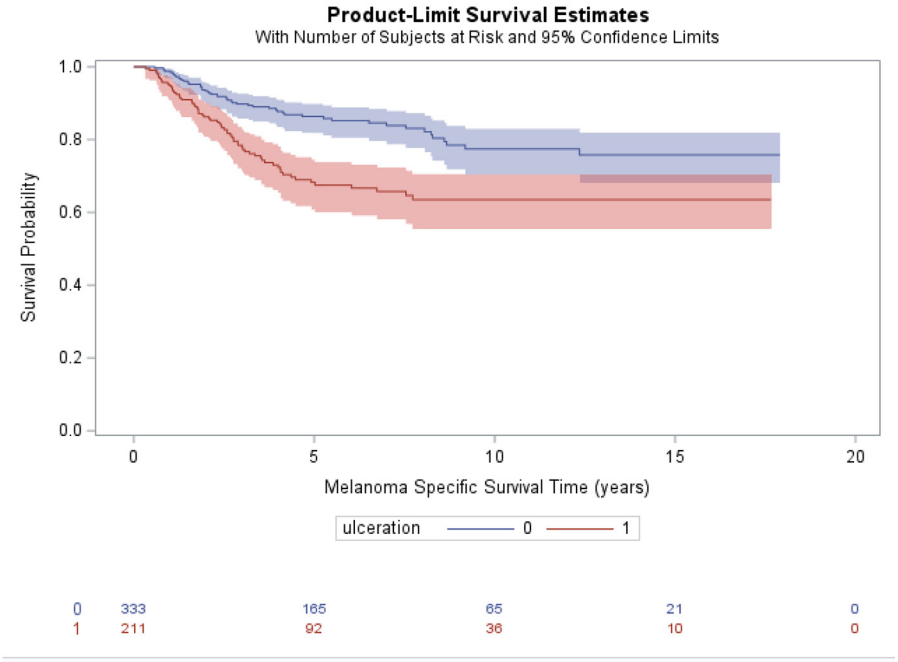


Fig12: Melanoma specific survival by relapse

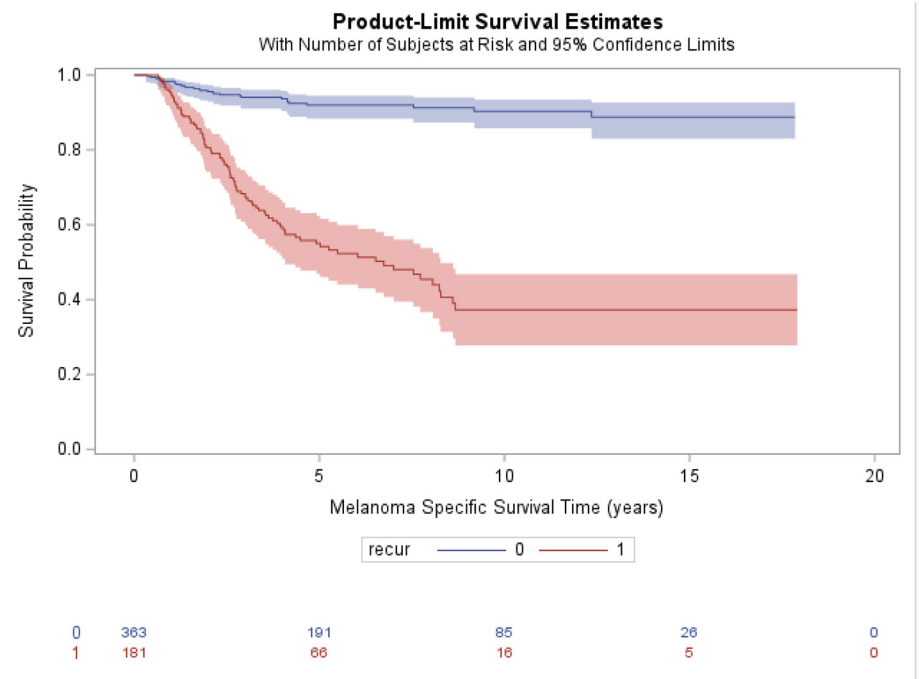


Fig 13. Overall survival stratify by substage at diagnosis

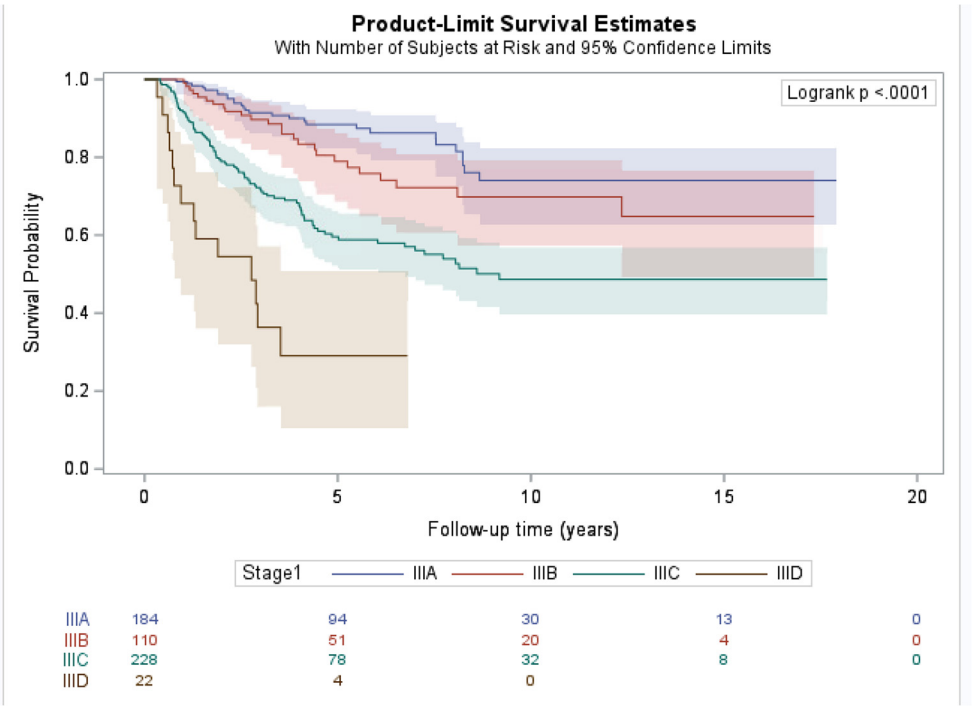


Fig14: Overall survival curves stratify by Age

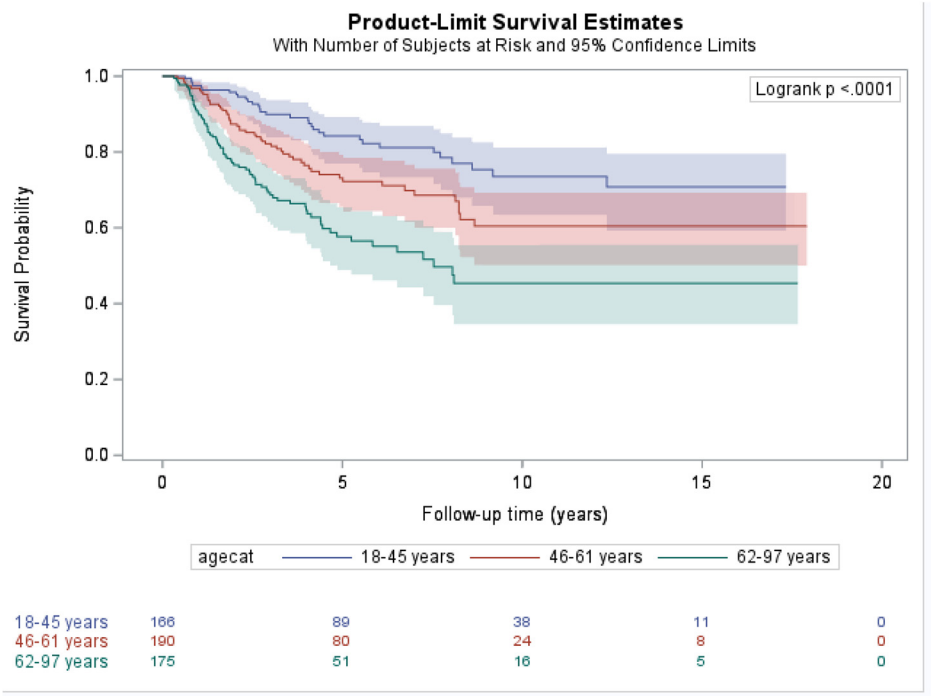


FIG15: Overall survival curves stratify by gender

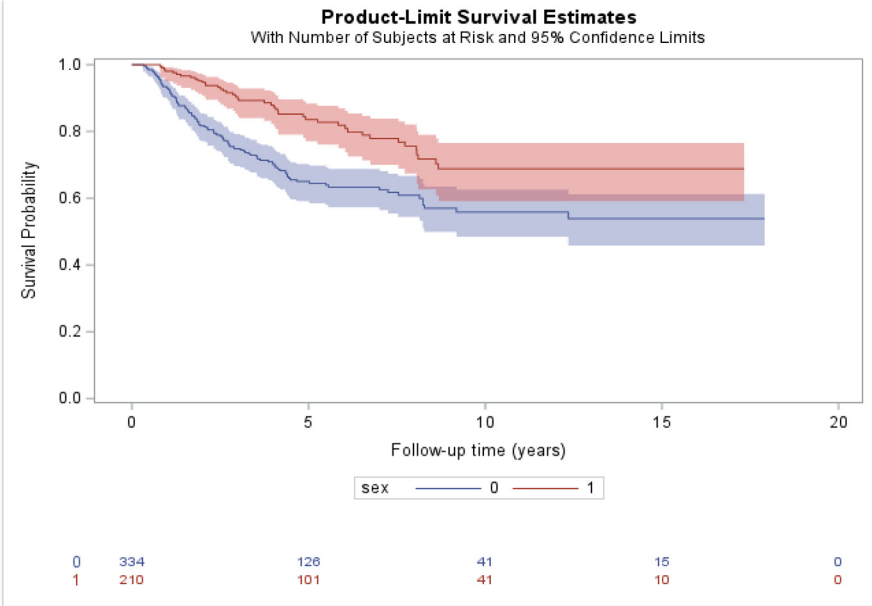


FIG16: Overall survival curves stratify by ulceration

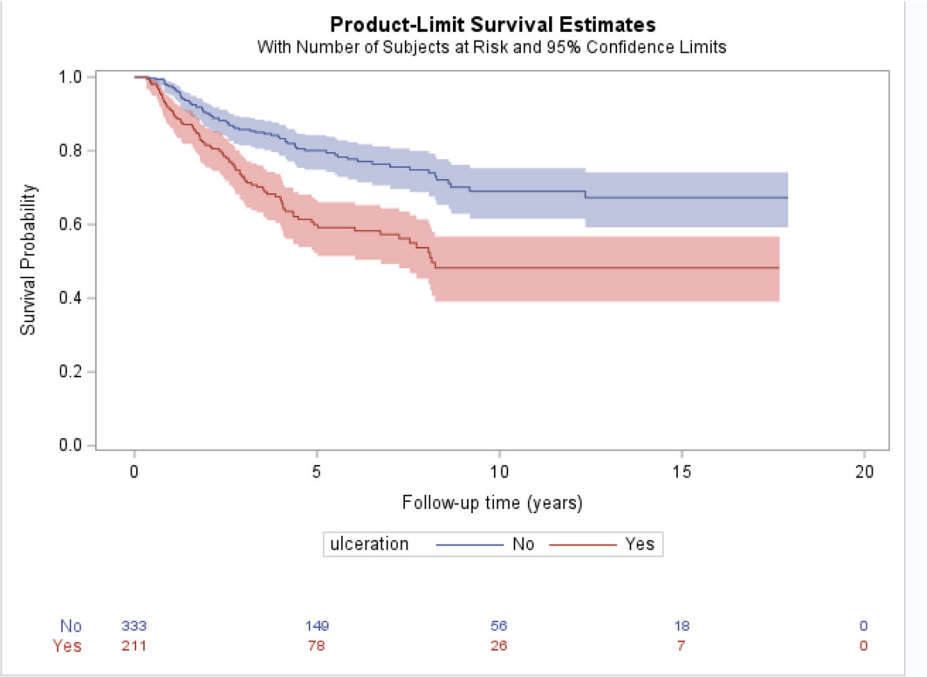


FIG17: Overall survival curves stratify by Breslow thickness

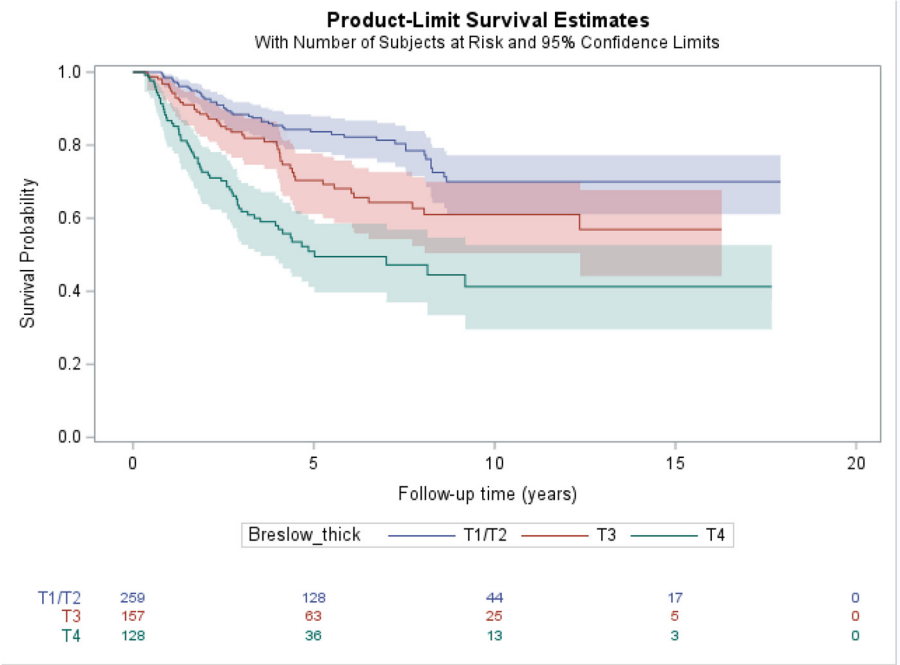
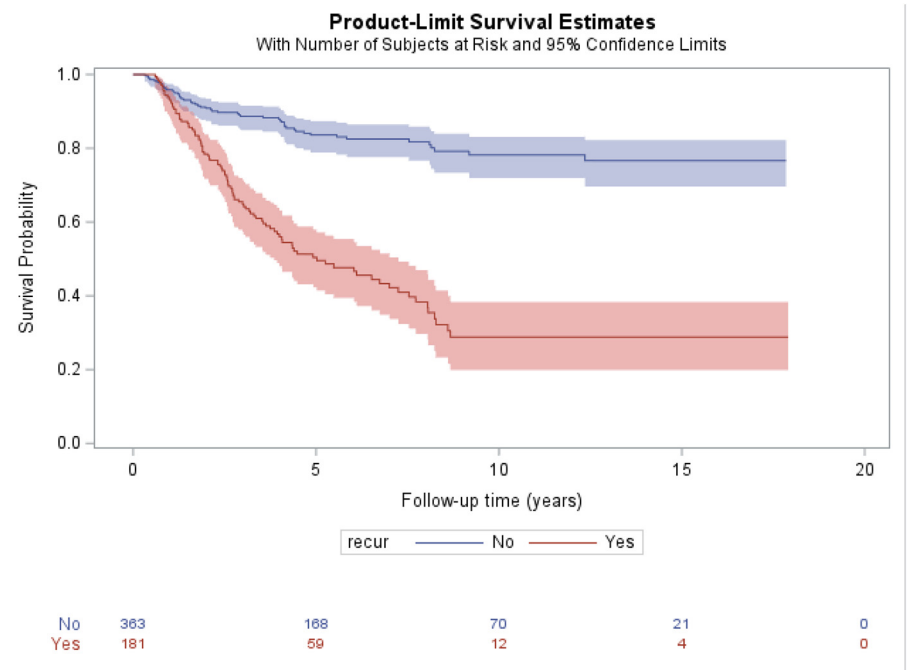


FIG18: Overall survival curves stratify by recurrence



Appendices:

SAS CODE:

```
** 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_site1 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;

/* recure 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 PMD_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 PMD_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;
```

```
proc freq data=melanomav1;
where recur="Yes";
tables chemo radiation surgery hormone immuno _Neoadj_rad _Neoadj_systemic;
run;

** assess continuous variables age breslow mitoses**;
proc univariate data=melanomav1;
var age Breslow mitoses ;
run;
* Sentinal lymph nodes*;

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**;
*age  statify by recurrence;

** site at first relapse by subsatge**;
proc freq data=melanomav1;
where recur="Yes";
tables recur_site1*stage1;
format recur_site recur_sitef.;
run;
** stage1 versus recur site;
proc freq data=melanomav1;
where recur="Yes";
tables stage1*recur_site1;
format recur_site recur_sitef.;
run;

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

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

proc freq data=melanomav1;
tables stage1*recur/chisq;
where recur="Yes";
run;
* type of recurrence  by stage*;
proc freq data=melanomav1;
tables recur_type1*stage1;
where recur="Yes";
format recur_type1 recur_typef.;
run;

* recurence by method of detection*;
```

```
data melanomaD;
set h.melanomav7;
if PDM_image="Yes"  then detection=1;
if PDM_clinical="Yes"  then detection=2;
if PDM_Patho_45d="yes" then detection=3;
run;

proc freq data=melanomaD;
tables detection;
where recur="Yes";
run;

proc freq data=melanomav1;
tables PDM_Patho_45d*PDM_image;
where recur="Yes";
run;

proc freq data=melanomav1;
tables recur_site*PDM_image;
where recur="Yes";
format recur_site recur_sitef.;
run;
proc freq data=melanomav1;
tables recur_site*PDM_Patho_45d;
where recur="Yes";
format recur_site recur_sitef.;
run;
proc freq data=melanomav1;
tables recur_site*PDM_clinical;
where recur="Yes";
format recur_site recur_sitef.;
run;

**Part II- Kaplan Meir and COX  for Recurrence free survival overal survival
and MSS***;

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


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 stage1;

proc means data =melanomav2 min max mean median q1 q3 ;
      class stage1;
      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 stage1;
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 stage1;
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 stage1;
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;

* positve 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;
```

```
proc lifetest  data=melanomav2  timelist=1  3  5 10
plots=survival(strata=overlay  nocensor atrisk(maxlen=13 outside(0.15)));
time rtime*censor(0);
strata recur_type1;
by stage1;
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 rtime*censor(0);
      strata &var;
run;
%mend;

%pval(data = melanomav2, var = stage1);

/*Create dummy variables for age*/
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 stage1 = "IIIA" then do;
 stage=0; stageA =1;stageB=0; stageC=0; stageD=0;end;
else if stage1 = "IIIB" then do;
 stage=1; stageA =0;stageB=1; stageC=0; stageD=0; end;
else if stage1 = "IIIC" then do;
stage=2; stageA =0;stageB=0; stageC=1; stageD=0; end;
else if stage1 = "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="Extremities" 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 ulcerartion 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 pLN1 pSLN1 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 stage1;
      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 stage1;
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=asinsqrt
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 stage1 = "IIIA" then do;
 stage=0; stageA =1;stageB=0; stageC=0 ;end;
else if stage1 = "IIIB" then do;
 stage=1; stageA =0;stageB=1; stageC=0 ; end;
else if stage1 = "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/Lentinginous'
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**;
```

```
proc phreg data=melanomav5;* using IIIA as ref grp*;
class  stage1(param=ref ref="IIIA");
model stime*failure(0)=stage1 /rl ties=efron;
run;
** Cox model for age, use age=18-45 years as reference group**;
proc phreg data=melanomav5;
class  agecat(param=ref ref="0");
model stime*failure(0)=agecat /rl ties=efron;
run;

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

proc phreg data=melanomav4;
class  ulceration (param=ref ref="No");
model stime*failure(0)=ulceration /rl ties=efron;
run;
proc phreg data=melanomav4;
class  agecat(param=ref ref="1");
model stime*failure(0)=agecat /rl ties=efron;
run;

proc phreg data=melanomav5;
class  body_site (param=ref ref="3");
model stime*failure(0)=body_site /rl ties=efron;
run;
proc phreg data=melanomav4;
class  Breslow_thick (param=ref ref="1");
model stime*failure(0)=Breslow_thick /rl ties=efron;
run;

PROC freq data=melanomav4;
tables Clark_level;
run;
proc phreg data=melanomav4;
class  Clark level (param=ref ref="I/II");
model stime*failure(0)=Clark_level /rl ties=efron;
run;
proc phreg data=melanomav4;
class  extranodal (param=ref ref="No");
model stime*failure(0)=extranodal /rl ties=efron;
run;
proc phreg data=melanomav4;
class    histo_type (param=ref ref="Superficial");;
model stime*failure(0)=histo_type /rl ties=efron;
run;

proc phreg data=melanomav4;
class  recur (param=ref ref="No");
model stime*failure(0)=recur /rl ties=efron;
run;


proc phreg data=melanomav4;
```

```
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;


**-assesss  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(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(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="Survical 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**;

title'Kaplan-Meir Survival curves for 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;
```

```
proc lifetest  data=melanomav6  timelist=1 3 5 10
plots=survival(strata=overlay cl nocensor atrisk(outside (0.15)));
time time*failure(0);
strata histo_type;
run;
ods graphics off;
** MSS survival for PSLN**;
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 pSLN1;
format pSLN1 pSLNf.;
run;
ods graphics off;

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 pLN1;
format pLN1 pLNf.;
run;
ods graphics off;

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_type1;
format recur_type1 recur_typef.;
run;
ods graphics off;

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_site;
format recur_site recur_sitef.;
run;
ods graphics off;



ods rtf close;

** Univariate COX model***********************************;


ods rtf;

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

proc lifetest data=melanomav6  notable  outsurv= Svest conftype=asinsqrt
confband=ep
```

```
bandmintime= 1  bandmaxtime =15 timelist =1 3 5 10  reduceout noprint stderr
;
time time*failure(0);
strata stage1 ;
run;
proc print data=Svest;
run;

proc phreg data=melanomav6;* using IIIA as ref grp*;
class  stage1(param=ref ref="IIIA");
model time*failure(0)=stage1 /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)=pSLN1 /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;
```