Association of wait times to surgical, medical and radiation therapies with overall survival in Ontarians with melanoma

Alyson Crawford

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Department of Epidemiology

Faculty of Medicine

University of Ottawa

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Legend

Cancer Care Ontario (CCO): An agency of the Ontario government, accountable to the Ministry of Health and Long-Term Care, which advises on cancer prevention, screening, delivery of care, and patient experience.

Lymph node dissection (LND): A surgical procedure performed to excise lymph nodes that were identified as metastatic, or high-risk for containing metastases, by (1) positive pathology from a sentinel lymph node biopsy (completion LND), (2) clinically or radiologically detected enlarged lymph nodes (therapeutic LND), or (3) patients at high risk for lymph node metastases (elective LND).

Mortality Risk Score (MRS): a scoring system that incorporates age, sex and the Johns Hopkins' Aggregated Diagnosis Groups (ADGs) to predict annual risk of all-cause mortality in adults that has been validated for use in the Institute for Clinical Evaluative Sciences (ICES) administrative databases.

Sentinel lymph node biopsy (SNB): A surgical procedure performed to remove the first draining lymph node from the primary site of melanoma to assess for metastatic spread to the lymph nodes.

Wide local excision (WLE): A surgical procedure performed to excise a margin surrounding the remaining scar or lesion following the melanoma's initial biopsy. This procedure is performed to reduce local recurrence.

Abstract

Purpose:

Assess for an association of wait times to melanoma treatment with overall survival.

Methods:

Retrospective review of Ontario patients with melanoma, with descriptive and survival analyses.

Results:

Median wait times were 43 days (interquartile range (IQR), 24-64) for wide local excision (WLE), 59 days (IQR, 41-81) for sentinel lymph node biopsy (SNB), 63 days (IQR, 43-91) for lymph node dissection (LND), 124 days (IQR, 96-150) for medical therapy, and 130 days (IQR, 89.5-157.5) for radiation therapy. In multivariate analysis, wait times to treatment were not associated with overall survival for WLE (hazard ratio (HR), 0.97; 95% confidence interval (CI), 0.87-1.08; p=0.62), SNB (HR, 0.89; 95% CI, 0.74-1.07; p=0.21), LND (HR, 0.99; 95% CI, 0.89-1.11; p=0.92), medical therapy (HR, 0.94; 95% CI, 0.80-1.10; p=0.41) or radiation therapy (HR, 0.80; 95% CI, 0.61-1.03; p=0.08).

Conclusion:

Overall survival for patients with melanoma was not associated with wait times to surgical, medical or radiation therapy.

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Section A. Introduction

A1. Overview and incidence of melanoma

Cutaneous melanoma is a type of skin cancer consisting of four main subtypes that includes: superficial spreading; nodular; lentigo maligna; and acral lentiginous. Each of these subtypes is associated with a different disease progression and prognosis. The risk factors associated with the development of melanoma include: sun or ultraviolet radiation exposure; personal or family history of skin cancer; fair skin; light blue eyes; history of severe blistering sunburn; and a large number of nevi.

The incidence of melanoma has been increasing in North America, and it is hypothesized that an increase in sun exposure is the most strongly related risk factor. The estimated number of new diagnoses of melanoma in Canada in 2015 will be 6,800, with 1,150 melanoma-related deaths in this same year[1]. In Ontario in 2007, malignant melanoma was ranked as the sixth most commonly diagnosed cancer with 2,273 new cases and 348 deaths[2]. Melanoma incidence in Ontario Caucasians increased by 2.7% per year between 1991 and 2004[2]. The estimated overall incidence rate of melanoma between 2000 and 2004 was 16.6 per 100,000 in Ontario[2]. This incidence rate was similar to that for Caucasians in the United States during the same time period (19.1 per 100,000)[2].

A2. Diagnosis, prognosis and survival of melanoma

Melanoma is diagnosed by one of two biopsy procedures of a suspicious lesion: an excisional biopsy, in which the entire lesion is removed and analyzed; or an incisional biopsy, in which a segment of the lesion is biopsied. The latter method is

used for large lesions or locations that are difficult to biopsy. The preferred method of incisional biopsy is a punch biopsy, so that the entire depth of the lesion can be evaluated and help direct management.

Once a diagnosis of melanoma is confirmed, and high-risk features, such as depth of invasion, ulceration and mitotic rate are reported, cancer staging and initial surgical management can be performed. This is discussed in detail in section A3. The complete treatment protocol is then devised and initiated based on the tumor's location and the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) stage[3] (Appendix A - Table AA.1.).

Prognosis is related to many factors, including: cancer stage; location of melanoma; metastases; gender; age; and treatment received. There are also high-risk pathologic features that worsen prognosis, including: depth greater than 0.75mm; ulceration; and high mitotic rate. Ulceration and lesion depth are directly involved in assigning cancer stage.

Survival for melanoma differs greatly based on stage, and even within each stage. In the final version of the AJCC staging system for cutaneous melanoma published in 2001, the 5-year survival was reported to range from: 89.0-95.3% for stage I; 45.1-77.4% for stage II; 26.7-69.5% for stage III; and 9.5-18.8% for stage IV[4] (Appendix A - Table AA.2.).

A3. Wide local excision for melanoma

The current first step in surgical management of melanoma is wide local excision (WLE) with concurrently performed sentinel lymph node biopsy (SNB), if required. WLE is performed to reduce the chance of local recurrence and involves the removal of a 1 to 2 cm margin around the remaining melanoma lesion (if an incisional biopsy was performed) or biopsy scar (if an excisional biopsy was performed). A 1 cm re-excision margin is indicated for lesions with less than 1 mm thickness, a 1-2 cm re-excision margin is indicated for lesions of 1-2 mm thickness, and a 2cm re-excision margin is indicated for lesions thicker than 2mm. However, it is not always possible to adhere to these excision guidelines for melanomas present in difficult locations, such as on the face, hand or foot.

A4. Sentinel lymph node biopsy for melanoma

Nodal status is the best known prognostic indicator for patients with clinically localized melanoma[5,6]. More specifically, the number of nodal metastases is considered the most important prognostic factor for survival, followed by tumor burden (defined as microscopic or not clinically detectable lymph nodes versus macroscopic or clinically detectable lymph nodes)[7]. SNB for melanoma was first introduced in 1990[8], and has been included in the AJCC staging system for melanoma since 2001[4,9].

The sentinel lymph node is defined as the first lymph node to receive lymphatic drainage from the tumor site. The indications for undergoing a SNB include patients without palpable lymphadenopathy with primary lesions thicker than 1mm, or less than 1 mm but greater than 0.75mm with high-risk features, such as ulceration, high

mitotic rate, or positive deep margin indicating an incomplete biopsy. Male sex, young age, and Clark's level IV or V may also be considered high risk features but are currently being debated by cancer societies for inclusion in guidelines. SNB is most useful for determining prognosis for lesions between 1-4mm, and is associated with a benefit in disease-free survival and possibly overall survival[5] in these patients possibly due to surgical removal of the metastatic disease. For lesions greater than 4mm, SNB is used solely for helping determine prognosis.

SNB is most often performed using the 'triple technique'. This includes (1) pre-operative injection of a radioactive tracer (Technetium-99) at the site of the original lesion and the use of pre-operative lymphoscintigraphy to visualize the uptake of the radioactive tracer in the sentinel lymph node; (2) intra-operative use of patent blue dye to identify the sentinel lymph node using colour; and (3) intra-operative use of a gamma probe to identify the sentinel lymph node with the greatest uptake of radioactive tracer.

In practice, the sentinel node is defined based on the methods used for its identification as the 'hottest' node (when using the gamma probe intra-operatively); as that which is the "bluest" (when using patent blue dye intra-operatively); or as the first node identified with lymphoscintigraphy[10,11]. It has been shown that resection of all blue-stained nodes, and all nodes with greater than 10% of the hottest node's radioactivity (defined as the '10% rule' for SNB) is associated with a low estimated false-negative rate[12,13]. In a large meta-analysis, including 71 studies and 25,240 patients, the false negative rate was found to be 12.5%[14]. It has also been shown that

the sentinel node is correctly identified in 97–100% of patients with melanoma when the 'triple technique' has been used[15,16].

A5. Lymph node dissection for melanoma

A lymph node dissection (LND) is a procedure that involves the removal of all accessible lymph nodes in a lymph node basin. There are three types: a completion LND, which is performed when the results of the SNB are positive for metastases and involves removal of the remaining lymph nodes in the previously sampled basin; a therapeutic LND, which is performed when clinically positive lymph nodes are present; and an elective LND, which was historically performed on all patients with melanoma to stop potential spread. There is a fair amount of post-operative morbidity associated with LNDs including wound complications, nerve dysfunction, chronic pain and lymphedema[17]. Since there is such a negative post-operative course associated with LND, and there is limited evidence for its effect on survival, there is controversy surrounding the guidelines for when a LND should be performed.

Recommendations in the literature regarding LND are inconclusive and vary depending on the extent of nodal metastasis and melanoma stage. For example, one study comparing the depth of sentinel node metastasis below the capsular level (Starz-classification), recommended that patients with greater than 1 mm invasion (S-III) should undergo LND, whereas patients with shallower invasion (S-I/S-II) should be spared further surgery[18]. Another study found that all patients with positive SNB should undergo LND due to a survival benefit[19]. Also in the Multicenter Selective Lymphadenectomy Trial I (MSLT-I), subgroup analysis suggested that completion LND

in sentinel node positive patients had a survival advantage[20]. However, other retrospective studies have shown that a survival advantage does not exist[21], especially in patients where additional positive non-sentinel nodes are identified in the completion dissection, due to a very poor prognosis with a median survival of 36-49 months[22,23]. Only about 10% of patients have additional disease in their completion LND, and thus the surgery is felt by some to have more disadvantages related to morbidity than advantages related to survival. In light of the controversy that exists surrounding guidelines for LND, a large randomized trial (the Multicenter Selective Lymphadenectomy Trial II - MSLT-II) is currently underway to assess outcomes in a direct comparison of LND versus observation in patients with positive SNB. The results of this study will help to delineate recommendations regarding LND. LND remains indicated in patients with palpable disease.

A6. Medical and radiation therapy for melanoma

Medical therapy for melanoma consists of immunotherapy (interleukin-2 [IL-2], interferon alpha [IFNα] and ipilimumab), targeted therapy (vemurafenib, dabrafenib, and trametinib for patients with the BRAF gene mutation) and/or chemotherapy (dacarbazine or temozolomide). IFN is the only therapy approved in the adjuvant setting, where as the other medical therapies and radiation therapy are utilized for metastatic melanoma. In general, patients with stage IIB or greater are recommended for adjuvant medical therapy due to the increased risk of melanoma recurrence.

The effect of current medical therapy on overall survival is minimal to none for patients with melanoma. For example, none of the immunotherapy medications

(including Ipilimunab[24], IL-2[25], or IFNα[26-28]) have shown a benefit in overall survival in patients with resected, high-risk melanoma. However, there is evidence supporting an improvement in recurrence-free survival with the use of INFα in higher stages of melanoma[26,29]. The lack of effect on overall survival has also been demonstrated for chemotherapy medications dacarbazine[30-34] and temozolomide[31] in randomized controlled trials. There are also ongoing trials for the use of other immunotherapies for melanoma. Of note, lambrolizumab (anti-PD1) has shown sustained tumor regression in patients with metastatic melanoma[35], and is expected to greatly improve medical management for melanoma.

Targeted therapy for melanoma refers to the use of either vemurafenib or dabrafenib (which are BRAF gene inhibitors) or trametinib (which is a MEK protein inhibitor) for patients with BRAF mutations. BRAF gene mutations are identified in approximately 50% of patients with melanoma and are especially prevalent in younger patients without a history of chronically sun-damaged skin. The use of vemurafenib[33], dabrafenib[36] and trametinib[37] have been associated with improved progression-free survival and/or overall survival in patients with BRAF gene mutations. Although less common, some melanomas have been found to have c-kit mutations and may respond to imatinib, where as other melanomas have been found to have NRAS mutations for which targeted therapies are currently under development.

Radiation therapy is rarely used for the management of melanoma because melanoma has proven to be relatively resistant to irradiation. However, radiation therapy is sometimes used to manage locoregional disease. In one prospective trial

that compared adjuvant radiotherapy and observation for patients with high risk of regional recurrence after lymphadenectomy (based on number and size of positive nodes, and extracapsular extension), a significant improvement in regional recurrence in the radiation group was found, although there was no difference in overall survival[38,39]. In another study, looking at radiation therapy for brain metastases in melanoma, a combination of local radiation therapy and whole brain irradiation resulted in a significant improvement in survival when compared to either modality alone or no radiotherapy[40].

A7. Association of wait times and outcomes in melanoma

Cancer Care Ontario (CCO) has mandated a target wait time from referral to consultation for systemic treatment of 14 days, and from consultation to initiation of systemic treatment of 28 days for skin cancer patients in Ontario[41]. Taken together, with an additional lead-time, the mandated wait time from diagnosis to initiation of treatment is approximately 50 days. Currently, the majority of hospitals reporting on these data have been able to attain the target time for referral-to-consultation for systemic treatment in approximately 60% to 100% of patients. However, many of the same hospitals have not reported on attainment of target wait time from consult to initiation of systemic treatment[42] (see Appendix A - Figure AA.1).

CCO recommends the same wait time targets for radiation treatment for skin cancers in Ontario. The target wait time from referral to consultation is 14 days, while the target wait time from ready-to-treat (time patient is ready to receive radiation treatment) to initiation of radiation treatment is 28 days[43] (See Appendix A - Figure

AA.2). This again leads to a wait time target from diagnosis to treatment initiation of approximately 50 days.

The mandated wait times for cancer surgery in Ontario are 14 days from consult to decision-to treat, and 28 days from ready-to-treat to time of surgery[44]. For patients requiring urgent surgery for a cancer causing life threatening adverse effects, the target time is immediate. For indolent tumors, CCO mandates the same wait time target of 14 days from consult to decision-to treat. However, CCO suggests an extended mandate of 84 days wait time from ready-to-treat to time of surgery[44] (Appendix A - Figure AA.3). Since the implementation of the target times for surgical wait times in Ontario in December 2005, there have been improvements in wait times across Ontario for cancer surgery[45] (See Appendix A - Figure AA.4). The recommendations for cancer surgery wait time targets in Ontario were supported by a systematic review of the published literature, a review from other jurisdictions, and an expert panel organized by CCO[44] (these documents were inaccessible for review).

There are two publications that have reported on wait times for cancer surgery in Ontario prior to the initiation of the mandated wait times. The first, published in 2001, gave an overview of cancer surgery wait times in Ontario cancer centers[46]. This study concluded that 37.2% of patients had inappropriate wait times from referral to surgery based on surgeon opinion. However, they reported median wait times of 11 days from referral to consult, and 20 days from decision to treat to time of surgery[46]. Based on the current recommended wait times, these data show that the median wait times for cancer surgery in the 1990's fall into the mandated wait time period. The

second paper was published in 2006 and reported on factors affecting increased wait times for cancer surgery in Ontario from 1984 to 2000 as a function of both the type of cancer and patient or health care characteristics[47]. This study stated that the year and age at time of diagnosis, type and location of procedure, and male sex were independent predictors of increased waiting times[47]. In particular, wait times increased as the study year increased, but decreased for older patients.

For all forms of cancer, no impact on survival has been found when the targeted two-week wait time from referral to consult date was met, compared to longer wait times[48]. The authors of this study felt that this could be explained by the relatively small amount of time that two weeks occupies in the 'cancer pathway'[48]. They suggested that the wait time from referral to consultation was insufficient by itself to improve cancer outcomes, and that the only way to improve outcomes was to improve patient education and to reduce delays in all levels of the 'cancer pathway'[48].

Few studies have reported on the effects of diagnostic and treatment delay on outcomes in melanoma. Two studies by Richards *et al*. examined the effects of patient and physician factors on diagnostic delay for melanoma. This was performed by interviews and a standardized questionnaire of consecutive patients with primary melanoma. These studies reported that an "acceptable time interval," based on physician opinion, between noticing a suspicious lesion and seeing a primary care physician was two months, and that 51.9% of patients were seen within this time[49]. It was also reported and that an acceptable time interval between diagnosis and surgical removal of the lesion was less than one month, and 85.8% of patients were treated

within this time[50]. Unfortunately, survival data was not reported in these two publications. Another study, performed in the United Kingdom looked at the effect of introducing a rapid diagnosis and treatment clinic for melanoma on overall survival. This study found that melanomas excised in this clinic were seen for consult and often surgically removed within two weeks compared to previous wait times of 3-34 days from referral to consult, and 4-74 days for treatment[51]. The group treated in the specialized clinic had significantly improved overall survival ($P < 0.001$) compared to those treated previously[51]. Unfortunately, this study was unable to distinguish if the improvement in survival was based on the shorter wait times or the advancement of time in their before and after study design. In a different study by Bennet *et al*, delays in diagnosis of melanoma (mean 14 months) had no effect on outcomes[52].

Only a small subset of publications has reported on outcomes for wait times from diagnosis to surgical treatment in patients with melanoma. McKenna *et al.* found no effect of the wait time between diagnostic excisional biopsy and WLE on overall survival or recurrence[53]. They looked at a cohort of 986 patients registered on a database with records of clinicopathological features, surgical treatment and follow-up information of patients with malignant melanoma in Scotland. Wait times were divided into intervals and the percentage of the cohort for each of the intervals was: 13% with ≤ 14 days; 33% with 15–28 days; 27% with 29–42 days; 25% with 43–91 days; and 2% with ≥ 92 days. The median wait time in that study was 30 days (with a very large range of 1 to 468 days), and the median follow-up period was 5 years (range 27 days to 20.7 years). Another study by Hajdarevic *et al*. based on data retrieved from the Swedish melanoma registry, reported median wait times of 4.0 and 5.0 days from

histopathological diagnosis to referral for WLE, and 50.0 and 57.5 days from referral for WLE to WLE, for public primary health care centers and dermatologist offices, respectively[54]. No survival outcomes were reported. One other study by Murchie *et al.* reported on median wait times from presentation to definitive surgical treatment, however they did not specify exactly what was meant by definitive treatment. They reported median wait times from presentation to definitive surgical treatment as 88.0 days for both patients biopsied by a family physician and in a hospital[55]. Again, no survival outcomes were reported.

A8. Large databases for research on melanoma

There have been many randomized control trials in melanoma research, with 52 relating to the management of malignant melanoma that have been published between 2001 and 2008[56]. Another study design available for assessing outcomes in melanoma is data extraction and analysis of major oncologic databases. Some of the main national melanoma databases include: the American Joint Committee on Cancer (AJCC) Melanoma Database in the United States; the Melanoma Research Database from the Melanoma Institute of Australia; and The Melanoma Database Project in the United Kingdom. There are also the Surveillance, Epidemiology and End Results (SEER) and the National Cancer Data Base (NCDB) in the United States, which capture information on all cancers.

In Canada, specifically in Ontario, there is one large collection of databases housed at the Institute for Clinical Evaluative Sciences [ICES] that can be used to study melanoma outcomes. Of specific interest to this particular study is the Ontario Cancer

Registry (OCR), which contains information on all Ontario residents who have been newly diagnosed with or who have died from cancer. The main data elements of this dataset include patient demographics, details regarding cancer diagnosis, and death information. Thus far, no studies using the ICES databases have been published regarding the association of overall survival in melanoma and time from diagnosis to treatment.

A9. Thesis conceptual framework

The overlying concept of this study was to address the effect of wait times to treatment on survival in patients with melanoma. Although there have not been many papers published on the effect of wait times for treatment of melanoma or other cancers (as reviewed in section A7), the overlying consensus is that increased wait times may lead to worsened cancer burden and prognosis. This question was explored in this thesis by searching for a relationship (or association) between wait times from melanoma diagnosis to treatment and overall survival, while taking into account other factors that might possibly affect the outcome. These factors included: melanoma stage; patient age, sex and residential location; and overall patient comorbidity (described by the Mortality Risk Score (MRS)). The study framework is represented visually in Figure A.1 at the end of this section. It is hypothesized that increased time to treatment, increased melanoma stage, increased age at diagnosis, male sex, and higher MRS will all be independently associated with a worse overall survival.

This overlying concept was adjusted to assess for an effect of the treatment type on overall survival. Again, the same covariates of melanoma stage, age, sex, residential

location and MRS were incorporated into the analysis. This is represented visually in Figure A.2 at the end of this section.

A10. Thesis overview

This study was a retrospective cohort study including all Ontarian patients with melanoma included in the ICES databases, with descriptive and comparative analysis of survival outcomes and time intervals between diagnosis and treatment, stratified by stage. It attempted to fill the knowledge gaps that presently reside in the literature by providing insight into the effects of wait times for melanoma treatment on outcomes. This will hopefully aid with the difficult decisions required in managing this important patient population and alleviate fear and anxiety felt by many patients as they wait for treatment of their melanoma.

A11. Objectives

1. Describe the characteristics and overall survival of patients diagnosed with melanoma in Ontario for the entire cohort and by melanoma stage.

2. In Ontario melanoma patients, describe the proportion who have undergone and the time from diagnosis to: i) wide local excision (WLE); ii) sentinel lymph node biopsy (SNB); iii) lymph node dissection (LND); iv) medical therapy initiation; and v) radiation therapy initiation for the entire cohort and by melanoma stage.

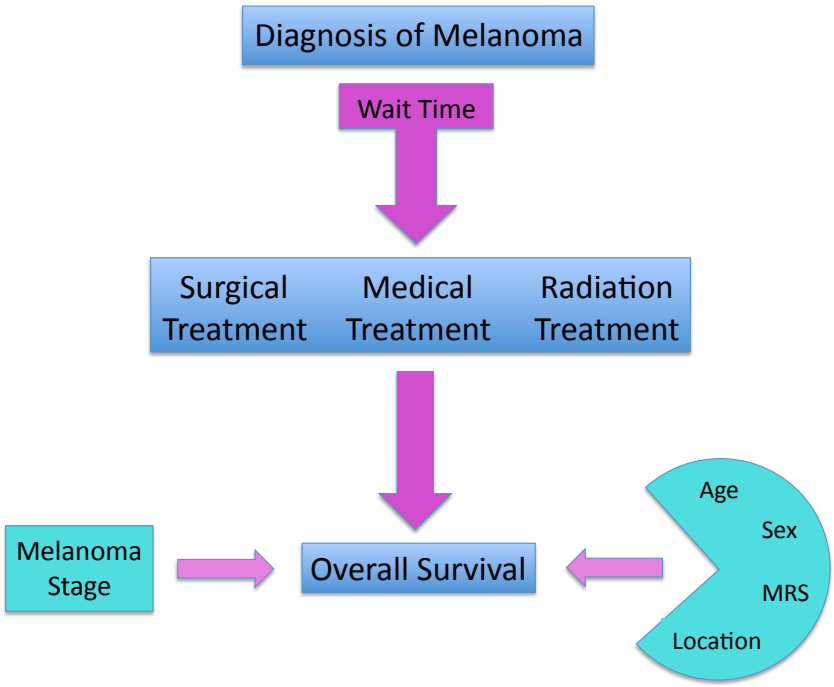
3. Determine the unadjusted and adjusted association of overall survival with type of treatment; and time to treatment accounting for treatment type of patients diagnosed with melanoma in Ontario, as a whole and by melanoma stage.

A12. Ethics statement

Prior to commencing the research for this thesis, ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board (OHSN-REB). Approval and access was also granted by the Institute for Clinical Evaluative Sciences (ICES).

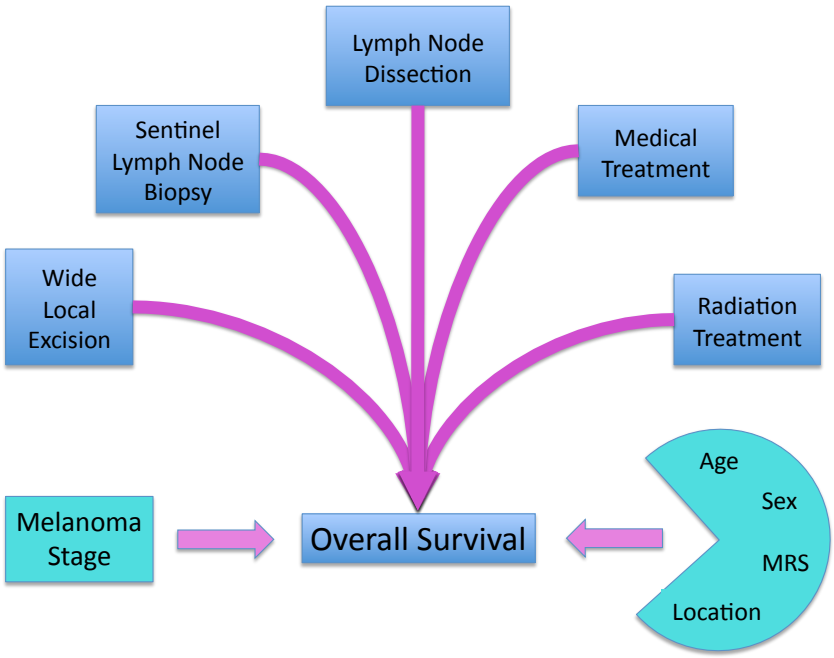
A13. Figures for section A

Figure A.1. Conceptual framework for entire thesis.



Abbreviations: MRS, mortality risk score.

Figure A.2. Conceptual framework for analysis of type of treatment received.



Abbreviations: MRS, mortality risk score.

Section B: Characteristics and overall survival (Objective 1)

B1. Overview

This section discusses the thesis' first objective, to describe the characteristics and overall survival of patients diagnosed with melanoma in Ontario. This was performed for the whole study population and by melanoma stage.

B2. Methods

Databases and variables

The individual databases contained within the ICES databases that were used to gather demographic and oncologic data included: the Ontario Cancer Registry (OCR); the Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD); the National Ambulatory Care Reporting System (NACRS); Registered Person Database (RPBD); the Collaborative Staging Database (CSTAGE); and the Ontario Heath Insurance Plan (OHIP) database. A description of each of these databases, as well as validation for each database, is outlined in Appendix B in Table BB.1. A list of the variables used from each database, along with their descriptions and use, is also included in Appendix B in Table BB.2. Individual ICES key numbers were used to link information from these databases.

Computer programming and Statistical Software

All programming to attain patient data and link databases, as well as perform statistical analysis and output results was performed using SAS statistical software (version 9.3 - SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA).

Patient identification

The OCR was used to identify all patients in Ontario diagnosed with melanoma based on pathology reports between January 1, 2004 and December 31, 2011. Patients less than 18 years old or those who had a documented previous cancer were excluded. Those without staging data, or who had more than one reported primary cancer, or who did not receive any treatment for their melanoma were also excluded. Patients with previous cancers and those with more than one primary were excluded to avoid misinterpretation of treatments received for melanoma and biasing the main outcome measure of overall survival. Patients without staging data were excluded because melanoma stage has a drastic effect on patient survival[4], and thus staging was required to stratify analysis to adjust for known differences in survival. Patients who did not receive treatment for their melanoma were excluded, since the main variable in this study was time to treatment. See Figure B.1 for the patient selection process.

Potential confounding variables

Four potential confounding variables were chosen for the analysis based on their previously reported influence on either wait times or survival. The first possible

confounder was age. Increasing age worsens melanoma survival[57], since older patients are more likely to develop loco-regional recurrences[58]. In contrast younger patients are more likely to have lymph node metastases but better prognosis overall[58]. Sex was the second possible confounder since males are known to have a worse prognosis than females[59,60]. Comorbidity was also controlled for and was measured using the Mortality Risk Score (MRS). The MRS is a scoring system that incorporates age, sex and the Johns Hopkins' Aggregated Diagnosis Groups (ADGs) to predict annual risk of all-cause mortality in adults, and has been validated for use in the ICES administrative databases[61,62]. The Johns Hopkins' Adjusted Clinical Groups (ACGs) software program was used to collapse International Classification of Disease (ICD) codes (9 or 10 version) from CIHI DAD and OHIP to ADG scores, for diagnoses two years prior to the date of diagnosis with melanoma. MRS ranges from -12 to 110, and an increased MRS represents the increased severity of age and comorbidities, and thus an increased probability of death within one year. For example, a MRS of -12 results in a 0.0047% risk of death within one year, where as a 110 MRS results in a 44.78% risk of death within one year. A sample calculation of the MRS can be seen in the appendix of "The Mortality Risk Score and the ADG Score" by P. Austin and C. van Walraven[61]. Finally, location of residence was the final possible confounder since rural and urban residences have been shown to experience differences in wait times for cancer treatment[63]. A rural residence was assigned based on the Statistics Canada definition of "census rural".

Statistical analysis

Patient and melanoma characteristics for all patients in this study were collected from the OCR, CSTAGE and RPDB databases. Total numbers and percentages were determined for categorical variables, and medians and interquartile ranges were determined for continuous variables. The MRS was calculated as described previously[61]. The censoring date was November 30, 2013.

Kaplan-Meier survival analysis was performed for the whole cohort and by melanoma stage to attain median, 1-year and 5-year overall survival, and survival curves. A time trend, dividing patients by year of diagnosis, was performed to assess changes in survival based on year. Kaplan Meier survival methods were used to determine 1-year and 5-year overall survival, and the Tukey-Kramer method for paired comparisons of strata[64] and the log rank test were used to compare survival curves between years and to the first year of diagnosis, 2004, for the study population.

B3. Results

Patient and melanoma characteristics

Between January 1, 2004 and December 31, 2011, 2573 adult patients in Ontario, without a previous or concurrent diagnosis of cancer, who received treatment, were diagnosed with melanoma (Table B.1 and Figure B.1). Patients with stage I melanoma occupied 54.2% of the study population, followed by stage II with 26.5%, stage III with 17.1%, and stage IV with 2.2%. The median age at diagnosis was 58,

ranging from a median of 56 to 64 throughout the different stage groups. Males and females were equally distributed in the study population, however there were some variations in the stage groups. For example, the more advanced stages of III and IV had higher proportions of males, 64.3% and 70.2%, respectively. 17.9% of patients lived in a rural location at the time of their diagnosis with similar proportions for each stage. MRS ranged between -12 and 110 for all patients in the study with a median value of 43 (associated with a median one-year death risk of 0.4%). The median 1-year death risk was highest in the stage II group at 0.6%, and lowest in the stage I group at 0.3%.

The most common type of melanoma histology was superficial spreading in 54.1% of the study population followed by nodular melanoma (22.8%) and "malignant melanoma - not other specified" (15.0%). Patients with stage I melanoma had a greater prevalence of superficial spreading (diagnosed in 70.2% of people) and a lower proportion of nodular type (7.8%). In contrast, patients with stage II disease had a higher prevalence of nodular melanoma (44.0%) with only 33.9% of people diagnosed with superficial spreading melanoma. Both stage III and stage IV groups had similar proportions of superficial spreading (37.7% and 29.8%, respectively) and nodular melanomas (36.8% and 31.6%, respectively). The stage IV group was also noted to have a surprisingly high proportion of spindle cell and epithelioid types of melanoma, with both having a prevalence of 7.0%.

Diagnosis dates ranged from January 7, 2004 to December 28, 2011. The proportion of patients included in the study increased from 2.8% in 2004 to 28.9% in 2011.

Death dates for patients ranged from December 22, 2004 to November 12, 2013. The minimum number of days spent in the study was 14, and the maximum was 3615 with a median observation time of 1222 days (3.34 years). Observation time decreased notably with rising cancer stage: stage I had a median time of 1247 days compared to stage IV with a median of 397 days.

Overall survival

15.4% of the entire cohort died during the study period (Table B.1). This proportion increased with higher stage from 4.7% for stage I to 82.4% for stage IV. Median overall survival was only available for the stage IV group, and was 397 days. 1-year overall survival ranged from 57.9% for stage IV in an increasing fashion to 99.4% for stage I. 5-year overall survival ranged from 16.0% for stage IV to 93.4% for stage I, again increasing with more favourable stage.

Kaplan Meier survival curves for the entire study population and by melanoma stage can be seen in Figure B.2. There was a statistically significant difference in overall survival between melanoma stages (log-rank p-value <0.0001).

Overall survival time trend of study population

Overall survival was compared between each of the years of diagnosis, 2004 to 2011 (Table B.2 and Figure B.3). There were no significant differences in overall survival between years of diagnosis or between the year of diagnosis and the first year of diagnosis, 2004, included in the study. 1-year overall survival was greatest in 2004 at 97.2% and lowest in 2005 at 94.2%. 5-year overall survival showed the same trend with the highest survival of 84.7% in 2004 and the lowest survival of 73.6% in 2005. 5-

year survival was not attainable for diagnosis years 2009 to 2011 because the censoring date of November 30, 2013 did not include five years of follow-up for those patients.

B4. Discussion

Summary

A total of 2573 Ontarian adult patients diagnosed with melanoma between January 1, 2004 and December 31, 2011 were included in this study. The majority of patients included in the study were diagnosed with melanoma in 2010 and 2011. Just over 75% of the patients included had stage I or II melanoma. The median age of the study population was 58 years old, and males and females were equally represented. The study population had a median MRS of 43 and an associated median one-year risk of death of 0.4%. Just over half of patients had superficial spreading histopathology.

The 5-year overall survival for the entire cohort was 81.1%, with worsening survival seen for increasing melanoma stage group. There was no change in overall survival seen for patients included from the beginning of the study in 2004 to the end in 2011.

Notable results and explanations

Patient selection

The majority of patients excluded from the study lacked staging data in the OCR database. Patients without staging data were excluded because of the well known large variation in melanoma prognosis that exists based on stage. Without staging data,

melanoma stage could not be controlled for in survival analyses and a stratified analysis based on melanoma stage could not be performed. If patients without staging data were included in the analysis, the accuracy and applicability of the results would have been limited.

Patient and melanoma characteristics

Male sex accounted for approximately 50% of the entire cohort, as well as for stages I and II. Higher proportions of males were seen in stages III and IV, 64.3% and 70.2%, respectively. This may be explained by the knowledge that men have worse outcomes for melanoma than women[7], however several studies have shown that male sex does not increase the risk of nodal metastases[17,59,65] (patients with stage III or IV melanoma). It is however, hypothesized that men may present with more advanced melanoma because of the higher proportion of men working in professions with a high risk sun exposure, such as farming and construction.

The median age at diagnosis for the study population was 58 years. It would be expected that patients diagnosed with higher stages (stages III and IV) would have been younger than patients with lower stages (stages I and II) as was described in a paper by Kretschmer *et al* where they found that younger patients (less than 40 years) were more likely to have lymph node metastases diagnosed from a sentinel lymph node dissection compared to older patients.[58] This was not the case here as the median age for stage I was 56, compared to 64 for stage II, 58 for stage III, and 59 for stage IV.

The incidence of different melanoma histopathologies is known to be highest for superficial spreading (50%-75%), followed by nodular (15%-35%), lentigo maligna

(5%-15%) and acral lentiginous (5%-10%)[66]. Our results for the study population were similar, however there were some variations when the histopatologies were examined by melanoma stage. For instance, for stage I superficial spreading melanoma was the most common (70.2%) but nodular melanoma was much lower than expected (7.8%). Whereas, for stages II, III and IV, the proportion of superficial spreading and nodular melanomas were very similar (between approximately 30% and 40%). Superficial spreading melanoma is known to be slow progressing and often diagnosed in the early stages, whereas nodular melanoma is associated with later diagnosis and worse prognosis, possibly explaining the distribution of the two histopathologic types of melanoma throughout the different stages.

Almost 60% of patients were diagnosed in 2010 and 2011 alone. The large proportion of patients diagnosed in the last two years of this study compared to the previous years may be explained by the increasing number of cancer centers being established throughout Ontario and that the reporting of melanoma diagnosis, treatment and staging information is becoming more prevalent.

Overall survival

The 1- and 5-year overall survivals for our entire cohort were 96.6% and 81.1%, respectively. When analyzed by cancer stage, the 1- and 5-year overall survivals for this study were comparable with the ranges published by the AJCC[4]. For example, 1- and 5-year overall survival for stage I in our study was 99.4% and 93.4%, respectively, compared to 99.5% to 99.7% and 89.0% to 95.3%, respectively. For stage II, 1- and 5-year overall survival was 97.2% and 75.8%, respectively, compared to 89.9% to 98.2%

and 45.1% to 77.4%, respectively, by the AJCC[4]. See Table AA.2 in Appendix A for further comparisons.

Overall survival time trend for the study population

1- and 5-year overall survival for patients diagnosed from 2004 to 2011 ranged from 94.2% to 97.2%, and 73.6% to 84.7%, respectively. Overall survival did not vary significantly based on the year of diagnosis when each year was compared to the other, or when each year was compared to the first year included in the study, 2004. This suggests that practice changes or the introduction of target wait times to treatment over that time period did not have an influence on overall survival in our cohort.

Strengths and limitations

The main strength of this study is its large study population of 2573 patients, allowing for precision of results[67]. Another overall strength is the division of data and interpretation of results by not only the whole cohort, but also by melanoma stage. This allowed for a more detailed analysis of outcomes.

The main limitation of this study is that it is retrospective in nature, which can lead to selection and information bias. However, selection bias should not be a significant factor in this study due to the large, province-wide database (ICES) that was used, which should provide a representative population. Information bias, or misclassification, is a disadvantage to using large retrospective databases due to the many different healthcare professionals involved in patient care, which can affect the accuracy of information included in the database, and thus the study[68]. Also, reporting

of cancer information is not legally mandated in Ontario, and when reporting does occur it is done passively. There are no employees from ICES that visit the medical facilities to abstract or record case information.

One advantage of using the retrospective cohort design in the form of a large database, is that exposure to risk factors, such as comorbidities, is recorded and available prior to the date of diagnosis[68]. This advantage was utilized in this study to estimate the risk of death based on the mortality risk score for comorbidities recorded two years prior to the diagnosis of melanoma.

A few other limitations were encountered related to data available in ICES. The first was that staging data was not available until 2004, and even then only about 30% of patients diagnosed with melanoma had recorded staging data. Also, when staging data was available it was made up of clinical and pathological staging, and was only entered at the time of diagnosis. If the stage changed during a patient's management, ICES was not updated, which resulted in records that could not be used for analysis and variation in the accuracy of the data. Another missing piece of information from ICES, specific to this section, was histopathology coding for lentigo maligna. As mentioned previously, this is the third most common type of cutaneous melanoma. It was likely recorded as "malignant melanoma - not otherwise specified" (NOS).

Another limitation related to the great degree of variability in survival known to exist between subclassifications of each melanoma stage. For example, stage III consists of both patients with positive lymph nodes and those with in-transit disease but negative nodes, which results in a great discrepancy in clinical presentation and

survival. Although the subclassification of melanoma stage was available in ICES, the statistical analysis required to compare the survival for each subclassification was beyond the scope of this project.

Finally, the last limitation was that patients who did not receive treatment within six months of diagnosis were excluded from the study. If the majority of the patients that were excluded for this reasons were "palliative" or died prior to treatment, the overall survival of the cohort could be slightly increased.

Implications of results

The results in this section were mainly descriptive in nature and could be used for comparison to demographics in future studies.

B5. Conclusions

Demographic information in this cohort is similar to previously published characteristics and risk factors of melanoma. Overall survival was significantly different for each stage, and remained constant from 2004 to 2011.

B6. Tables for section B

Table B.1. Patient and melanoma characteristics of the study population as a whole and by melanoma stage.

	Patients, n (%)				
Characteristics	**Total (N = 2573)**	**Stage I (n = 1394)**	**Stage II (n = 682)**	**Stage III (n = 440)**	**Stage IV (n = 57)**
Age at diagnosis, median (IQR)	58 (47-70)	56 (45-67)	64 (53-75)	58 (47-68)	59 (47-69)
Male sex	1341 (52.1)	630 (45.2)	388 (56.9)	283 (64.3)	40 (70.2)
Rural residence	460 (17.9)	256 (18.4)	124 (18.2)	71 (16.1)	9 (15.8)
Mortality risk score, median (IQR)	43 (29-56)	39 (26-53)	48.5 (30-60)	43 (30-60)	42 (33-51)
Estimated risk of death in one year based on mortality risk score, median percentage (IQR)	0.4 (0.1-1.1)	0.3 (0.1-0.8)	0.6 (0.2-1.7)	0.4 (0.2-1.1)	0.4 (0.2-0.7)
Censored	2178 (84.6)	1328 (95.3)	547 (80.2)	293 (66.6)	10 (17.5)
Time in the study, median number of days (IQR)	1222 (908-1731)	1247 (956-1724)	1279 (915-1877)	1098.5 (771.5-1568.5)	397 (136-770)
Melanoma histology					
Superficial spreading	1393 (54.1)	979 (70.2)	231 (33.9)	166 (37.7)	17 (29.8)
Nodular	588 (22.8)	108 (7.8)	300 (44.0)	162 (36.8)	18 (31.6)
Malignant melanoma NOS	387 (15.0)	242 (17.4)	76 (11.1)	60 (13.6)	9 (15.8)
Acral lentiginous	69 (2.7)	24 (1.7)	25 (3.7)	19 (4.3)	1 (1.8)
Spindle cell NOS	42 (1.6)	15 (1.1)	17 (2.5)	6 (1.4)	4 (7.0)
Epithelioid cell	26 (1.0)	6 (0.4)	6 (0.9)	10 (2.3)	4 (7.0)
Desmoplastic	23 (0.9)	6 (0.4)	15 (2.2)	1 (0.2)	1 (1.8)
Mixed epithelioid and spindle cell	19 (0.7)	7 (0.5)	5 (0.7)	6 (1.4)	1 (1.8)
Amelanotic	12 (0.5)	1 (0.1)	4 (0.6)	6 (1.4)	1 (1.8)
Malignant melanoma in giant pigmented naevus	8 (0.3)	3 (0.2)	2 (0.3)	3 (0.7)	0 (0.0)
Malignant, regressing	3 (0.1)	2 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Balloon cell	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (1.8)
Malignant melanoma in junctional naevus	1 (0.04)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Stage classification					
Ia	576 (22.3)	576 (41.3)			
Ib	688 (26.7)	688 (49.4)			
INOS	130 (5.0)	130 (9.3)			
IIa	315 (12.2)		315 (46.2)		
IIb	225 (8.7)		225 (33.0)		
IIc	137 (5.3)		137 (20.1)		
IINOS	5 (0.2)		5 (0.7)		
IIIa	144 (5.6)			144 (32.7)	
IIIb	149 (5.8)			149 (33.9)	
IIIc	84 (3.3)			84 (19.1)	
IIINOS	63 (2.4)			63 (14.3)	
IV	57 (2.2)				57 (100.0)
Year of diagnosis					
2004	72 (2.8)	28 (2.0)	31 (4.6)	11 (2.5)	2 (3.5)
2005	87 (3.4)	41 (2.9)	28 (4.1)	16 (3.6)	2 (3.5)
2006	139 (5.4)	60 (4.3)	47 (6.9)	29 (6.6)	3 (5.3)

2007	181 (7.0)	85 (6.1)	55 (8.1)	33 (7.5)	8 (14.0)
2008	287 (11.2)	136 (9.8)	73 (10.7)	70 (15.9)	8 (14.0)
2009	329 (12.8)	164 (11.8)	103 (15.1)	55 (12.5)	7 (12.3)
2010	734 (28.5)	420 (30.1)	186 (27.3)	111 (25.2)	17 (29.8)
2011	744 (28.9)	460 (33.0)	159 (23.3)	115 (26.1)	10 (17.5)

Abbreviations: IQR, interquartile range; NOS, not otherwise specified.

Table B.2. Proportion of patients who died within the study period and overall survival of the study population, as a whole and by melanoma stage.

	Number of patients, n	**Number of deceased, n (%)**	**Median overall survival (95% CI)**	**1-year overall survival (95% CI)**	**5-year overall survival (95% CI)**
Total	2573	395 (15.4)	-	96.6 (95.8-97.2)	81.1 (79.1-83.0)
Stage I	1394	66 (4.7)	-	99.4 (98.8-99.7)	93.4 (91.2-95.1)
Stage II	682	135 (19.8)	-	97.2 (95.7-98.2)	75.8 (71.5-79.6)
Stage III	440	147 (33.4)	-	91.6 (88.6-93.8)	61.9 (56.3-67.0)
Stage IV	57	47 (82.4)	397 (205-516)	57.9 (44.1-69.4)	16.0 (7.6-27.3)

Abbreviations: CI, confidence interval.

Table B.3. Proportion of patients who died within the study period and overall survival of the whole cohort divided by year of diagnosis (n=2573).

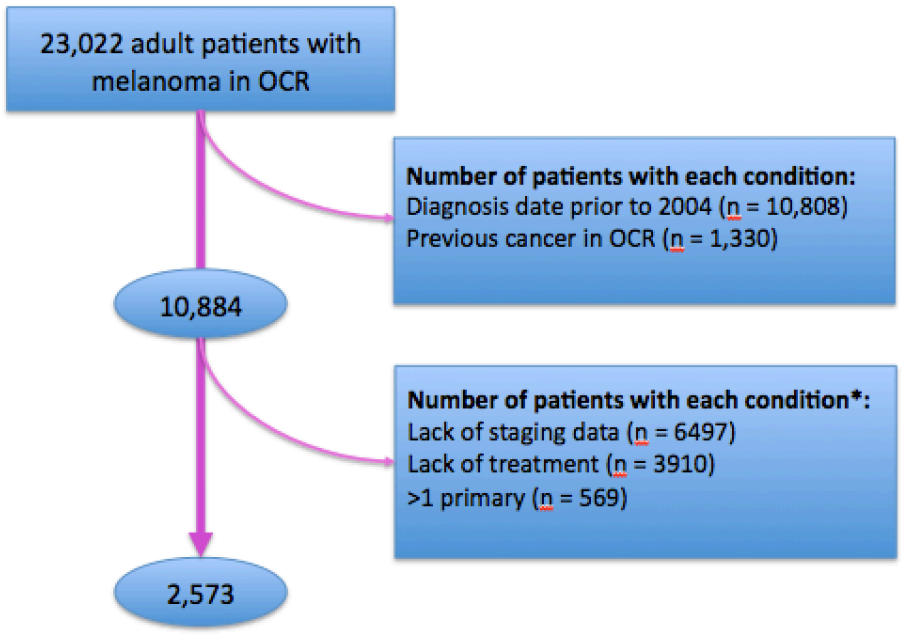
Year of diagnosis	Total, n	Deceased, n (%)	1-year overall survival (95% CI)	5-year overall survival (95% CI)[a]	P-value[b]
2004	72	18 (25.0)	97.2 (89.3-99.3)	84.7 (74.1-91.2)	-
2005	87	28 (32.2)	94.2 (86.7-97.6)	73.6 (63.0-81.6)	0.9293
2006	139	37 (26.6)	96.4 (91.6-98.5)	77.7 (69.8-83.8)	0.9878
2007	181	37 (20.4)	96.7 (92.8-98.5)	81.8 (75.3-86.7)	1.0000
2008	287	67 (23.3)	94.8 (91.5-96.8)	77.0 (71.7-81.4)	0.7691
2009	329	53 (16.1)	97.0 (94.4-98.4)	-	1.0000
2010	734	91 (12.4)	96.9 (95.3-97.9)	-	0.9928
2011	744	64 (8.6)	97.0 (95.5-98.0)	-	0.9248

a - 5-year overall survival was not possible to be calculated for years of diagnosis 2009, 2010 and 2011 because patients were censored prior to 5 years of follow-up.

b - P-values shown here compare each year of diagnosis to 2004 using the Tukey-Kramer method for paired comparisons of strata. Comparisons between each year of diagnosis were also performed and there were no significant differences identified (data not shown).

B7. Figures for section B

Figure B.1. Patient identification flow chart.

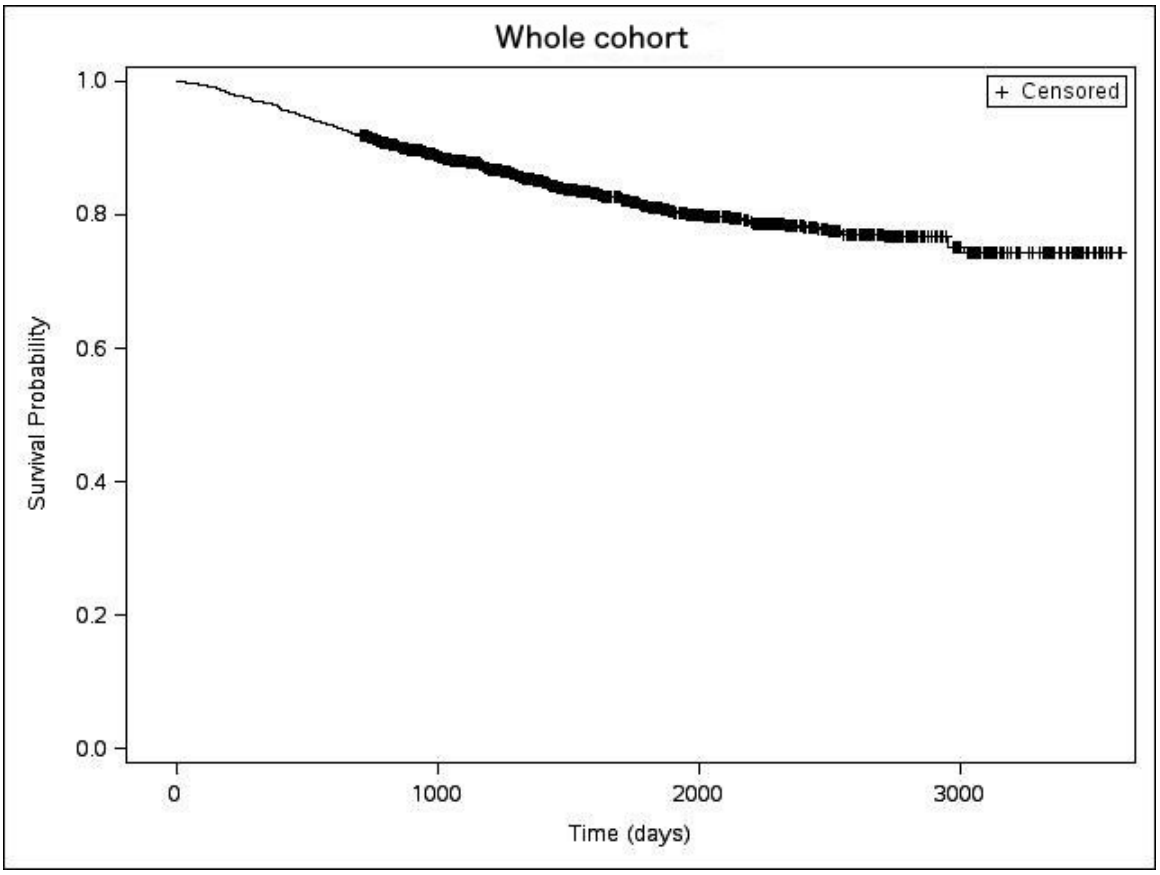


* Patient numbers are not mutually exclusive (ie. a patient may have had more than one condition to warrant their exclusion)

Abbreviations: OCR, Ontario Cancer Registry.

Figure B.2. Kaplan-Meier survival curves of overall survival for (a.) the entire study group and (b.) by melanoma stage.

a.



b.

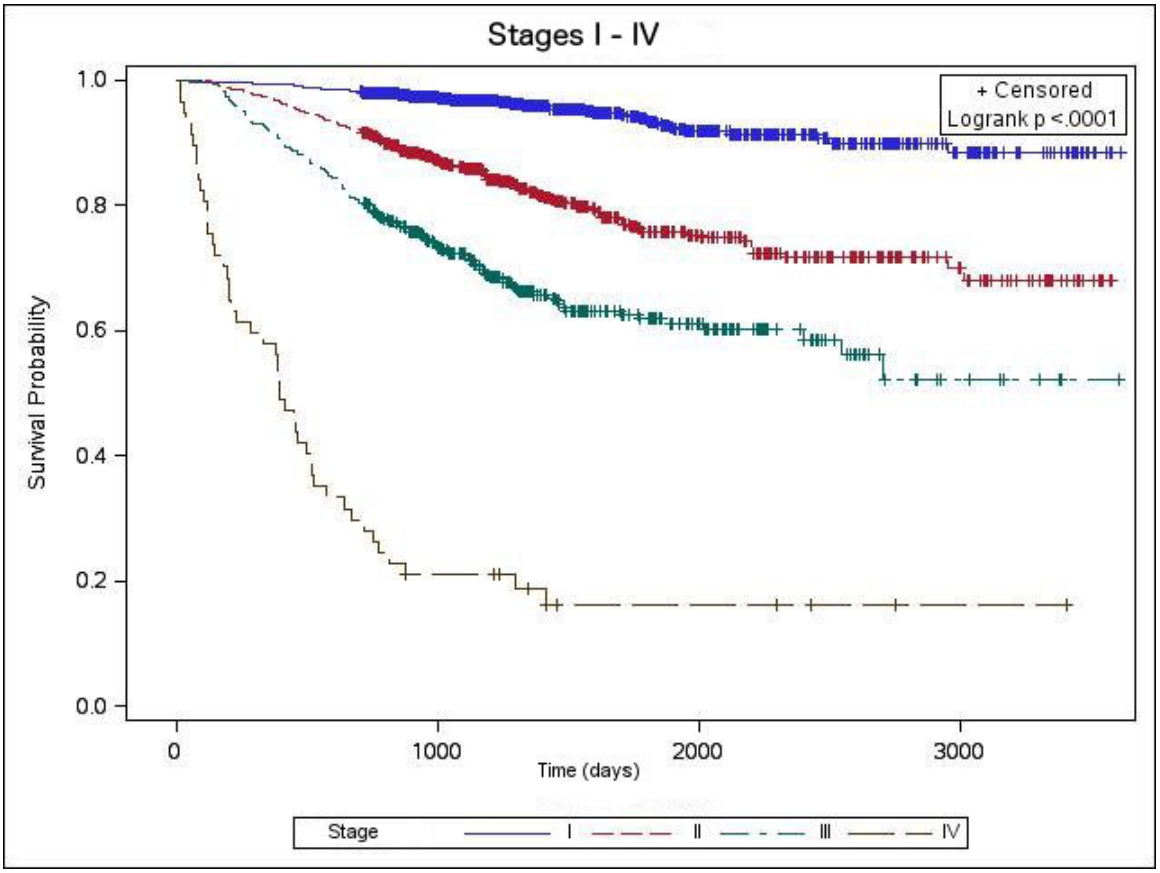
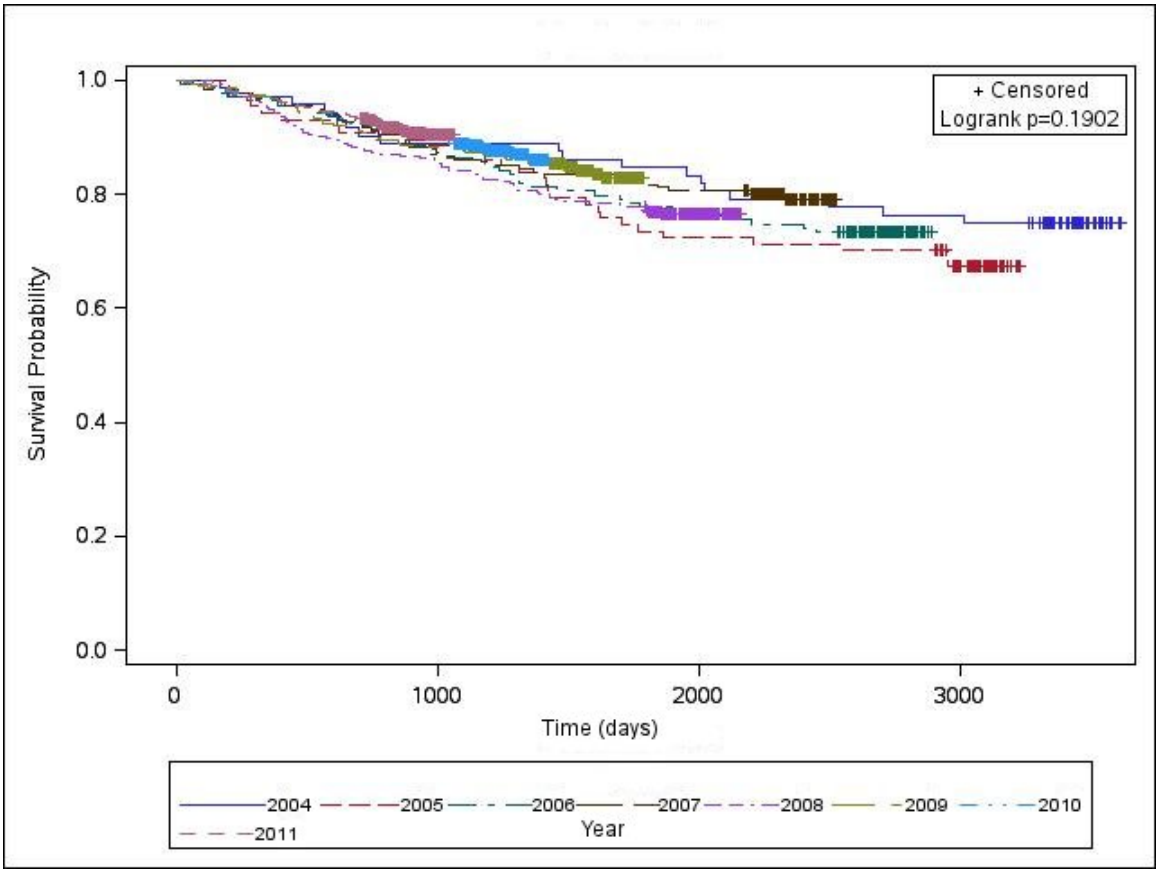

Stages I - IV
+ Censored
Logrank p <.0001
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
Time (days)
Stage
I
II
III
IV

Figure B.3. Kaplan-Meier survival curve of overall survival for the entire study cohort by year of diagnosis (n=2573).



Section C: Type of treatment and time to treatment (Objective 2)

C1. Overview

This section discusses the second objective, namely describing the proportion of patients that underwent each type of treatment and the time from diagnosis to each type of treatment. This was performed for the entire cohort and by each melanoma stage.

C2. Methods

Please refer to section B2 for methods related to databases, statistical software, and patient identification.

Treatment identification

Surgical treatment data was determined by linking to the OHIP database. Surgical procedures of wide local excision (WLE), sentinel lymph node biopsy (SNB), and lymph node dissection (LND) were obtained using fee codes that were provided by the MOHLTC (Figure C.1) and submitted by physicians at the time of the procedure to receive remuneration for the operation. Corresponding date data was obtained for each procedure and used as the time of treatment in analysis. Figure C.1 also provides a breakdown of surgical treatments by melanoma stage.

Medical and radiation treatment data was obtained from the NACRS and CIHI DAD databases. Antineoplastic, immunostimulant and immunomodulating agents given by percutaneous or per orifice routes (including isolated limb perfusion and infusion) were captured using Canadian Classification of Health Interventions (CCI)

codes within both databases (Figure C.1). Radiation therapy was also captured using CCI codes in these databases. Codes were divided into body regions for skin, soft tissue, and lymph node basins. Corresponding date information was obtained for each treatment from the corresponding database and used as the time of treatment in analysis.

Wait time definition

Wait time was defined as the number of days from the diagnosis of melanoma (time equal to zero) to the time of first treatment for each melanoma treatment type including: WLE; SNB; LND; medical therapy; and radiation therapy.

Time to treatment was restricted to patients who received treatment within six months of their diagnosis. This was done to avoid inadvertently including treatment for recurrences or subsequently diagnosed cancers (even though the OCR does not record recurrences). The six month time constraint should have captured the vast majority of primary or index melanoma treatment since the mandated wait time from diagnosis to commencement of treatment is approximately 50 days, as discussed in section A7.

Statistical analysis

The total number and proportion of patients that underwent each form of treatment was determined. Median and interquartile ranges were calculated for time to each type of treatment. This was performed for the entire study cohort, as well as for each stage.

C3. Results

Treatment type descriptions

The most common treatment for melanoma was a WLE, with 82.9% of patients in the study population receiving this treatment (Table C.1). The second most common procedure was a LND at 35.0%, followed by SNB at 28.1% (Table C.1). Only 15.9% of the patients received a WLE and SNB on the same date, while 13.3% of patients received a WLE and a LND on the same date. Medical therapy and radiation therapy were much less common at 11.7% and 2.5%, respectively.

The stage I cohort had a distribution of surgical treatments similar to the entire cohort except 90.4% of patients received a WLE, 22.7% of patients received a SNB and 18.3% of patients received a LND. Patients with stage II disease had similar patterns with 37.7% of patients receiving a LND. 13.8% and 1.0% of patients were noted to have received medical and radiation therapy, respectively. Stage III and IV patients showed appropriate treatment distributions with more patients receiving medical and radiation therapy. Stage III patients received a high proportion of LNDs at 82.3%, whereas only 70.0% received WLEs. The proportion of stage IV patients that received a WLE was lower than the other stage groups at 45.6% with higher proportions of patients receiving medical (36.8%) and radiation (29.8%) therapies.

Wait time descriptions

Median wait times (Table C.1) as well as a graphical representation of the proportion of patients waiting for treatment were presented for all patients (Figure C.2). For the entire cohort, median wait time to surgical treatment was similar for each treatment modality at 43 days for WLE; 59 days for SNB; and 63 days for LND. Median times to medical and radiation therapy were more than double that of surgical treatment at 124 days for medical therapy and 130 days for radiation therapy (medical and radiation treatment are often given following surgery, and would therefore result in longer wait times from date of diagnosis). Figure C.2.a shows that just over 10% of patients received their WLE on day zero, or their date of diagnosis, while 80% received their WLE by 120 days from diagnosis. The proportion of patients undergoing SNB and LND was similar until day 40, after which time more patients underwent a LND. Medical and radiation treatment also overlapped until day 70 when medical therapy was received by more patients.

The median wait times for surgical treatment in the stage I group were almost identical to those for the whole cohort, at 41, 58 and 63 days for WLE, SNB and LND, respectively. In contrast, the median wait times to medical and radiation therapy were slightly smaller. Figure C.2.b shows that approximately 13% of stage I patients received their WLE on the day of diagnosis and that 90% of patients had received their WLE by approximately 140 days following diagnosis.

The stage II group had slightly longer wait times than the entire study population for WLE and SNB, however had a shorter median wait time to LND of 56 days. The median times to medical and radiation treatment were shorter than those for

the whole cohort, however longer than those for stage I melanoma, at 116 days and 97 days, respectively. Figure C.2.c shows that a similarity of proportion of patients and wait times for SNB and LND can be seen. It is also noted that similar trends to stage I and the whole cohort were seen for time to WLE.

The stage III group had a longer median wait time to LND, which was longer than the entire cohort and any of the other stage groups by at least ten days. Wait times to medical and radiation therapy were also noticeably longer than the other stage groups and the study population as a whole. In Figure C.2.d WLE and SNB had similar distributions of wait times and patient proportions to the other stage groups, however LND was noted to have a high proportion of patients being treated between approximately 30 and 120 days. The majority of medical and radiation treatments were performed after 45 days from diagnosis.

The stage IV group was noted to have the shortest median wait times for each type of treatment except medical therapy, which had the second shortest median wait time. In Figure C.2.e it can be seen that, compared to the other stage groups, medical and radiation therapy were initiated much earlier for some patients at approximately 20 to 30 days from diagnosis. Although there were fewer patients in the stage IV cohort, it is interesting to note that WLE, SNB and LNDs were all completed much earlier. For example, no further patients received a WLE after 115 days, where as in the other stage groups, patients received WLEs up to the 180 day cut off point.

Relationship to CCO mandated wait times

The majority of patients were diagnosed following the introduction of mandated target wait times by CCO in September 2005 (Table C.2). 94.5% of patients in the entire study population, with similar proportions for each of the stage groups, were diagnosed after the introduction of target wait times. Close to half (55.1%) of all patients in the study received their first form of treatment in the mandated wait time from diagnosis (approximately 50 days). The lowest proportion of patients treated within 50 days was seen in patients with stage II melanoma at 47.5%, and the highest proportion was 61.4% seen in patients with stage IV melanoma.

Treatment type time trend

The number and percentage of patients who underwent each type of treatment by year of diagnosis for the entire study population and each stage cohort is presented in Table C.3. A slight increase in the proportion of WLEs being performed was noted over years of diagnosis of 2008 to 2011 for the whole cohort and for patients with stage I melanoma. However, there were no similar trends seen over time for stages II to IV. There was a substantial increase in the proportion of SNBs being performed for patients diagnosed in 2010 (an almost 10% increase for the whole cohort) when compared to previous years, and another even more substantial increase in 2011 (almost 40% increase for the whole cohort). A similar trend was observed in SNB for each of the stage cohorts as well. For LND, an opposite trend was seen over the years with the proportion of LNDs being performed decreasing substantially for the whole

study population and for each stage cohort (approximately 50% decrease from 2004 to 2011 for the whole cohort).

Trends over time were less impressive for medical and radiation therapies. Medical therapy demonstrated a slight decrease of about 5-10% for patients diagnosed in 2010 and 2011 compared to previous years for the whole cohort. The stage I cohort showed a drop as well, but from 2007 to 2011, compared to 2004 to 2006. There were no changes seen for the stage II to IV cohorts. There was also no trend determined for radiation treatment over the years in the whole cohort and stages II to IV. Of note, only 3 patients received radiation therapy in the stage I cohort and they were diagnosed in 2010 and 2011.

Wait time to treatment time trend

The median wait times for each type of treatment are demonstrated for the study population by year of diagnosis in Table C.4. A minimal decrease in wait times of approximately five to ten days for WLE for patients diagnosed in 2004 compared to 2011 was demonstrated for the study population. There was no visible trend seen for wait times to SNB. For LND, an increased wait time from 56 days to 81 days was seen for patients diagnosed in 2004 compared to those diagnosed in 2011. There was otherwise no obvious trend for the years in between. Medical therapy demonstrated a slight decrease in wait times from 2007 to 2011. Radiation therapy did not exhibit a trend in wait times over time. There was no obvious change in wait times following the introduction of CCO's mandated wait times in late 2005 and early 2006.

C4. Discussion

Summary

WLE was the most common form of treatment received (82.9%) within the study population, followed by LND (35.0%), SNB (28.1%), medical therapy (11.7%) and radiation therapy (2.5%). The median wait times for surgical treatments ranged from 43 days for WLE, to 59 days for SNB, to 63 days for LND. Wait times for medical and radiation therapy were more than double the times to surgical treatment at 124 and 130 days, respectively. This can be explained by the order of treatment for melanoma, which often starts with surgical treatment, followed by medical or radiation treatment.

The majority of patients in the study were diagnosed following the introduction of CCO mandated target wait times. Also, close to 50% of patients received treatment within the approximate mandated 50 day wait time.

Both WLE and SNB increased in frequency for patients diagnosed closer to 2011. LND and medical therapy both decreased in frequency from 2008 onwards. There was no overlying trend seen for radiation therapy over the study period.

A minimal improvement in wait times for patients diagnosed at the beginning of the study, compared to those diagnosed at the end was demonstrated for WLE and medical therapy. In contrast, the wait time to LND was noted to be somewhat longer in 2011, but this did not show a trend over time. SNB and radiation therapy did not show a change in wait times over the course of the study.

Notable results and explanations

Treatment type descriptions

The stage I cohort had a similar distribution of surgical treatments to the entire cohort (described above in the summary section) except that 90.4% of patients received a WLE, 22.7% of patients received a SNB and 18.3% of patients received a LND. The proportions for the WLE and SNB were consistent with the treatment guidelines for stage I melanoma. However, patients with stage I disease would not routinely undergo a LND, medical therapy, or radiation therapy.

There are a few possible explanations for the discrepancies between treatment type and melanoma stage. The first two explanations are based on the differences in clinical staging and pathologic staging. Clinical staging is defined as microstaging of the primary melanoma and clinical and/or radiologic evaluation for metastases. Where as, pathologic staging is defined as microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy.

The first possibility to explain these discrepancies between treatment type and melanoma stage is that patients were initially diagnosed with, for example clinical stage I melanoma and this information was entered into the database. Subsequently, patients were later "upstaged" based on pathological data without the database records being updated. In these situations, patients would be classified in the database as stage I but would actually be stage II, III or IV.

The second possible explanation for the discrepancy between observed and expected treatment based on registered stage is that clinically staged patients might have been felt to have lymph node metastases (clinical stage III or IV) that were not actually present when a LND was performed (pathologic stage I or II). Such patients could then truly be stage I melanoma and could have been entered into the database as stage I (ie. they were downstaged prior to being entered into the database, but received a LND or medical or radiation therapy). A third possible explanation is described further in the time trend section of this discussion below.

Patients with stage II disease had similar patterns for surgical treatment with 37.7% of patients receiving a LND, even though patients with stage II melanoma would not undergo this treatment. This unexpected finding could be explained by all of the same reasons as for stage I, discussed above. Also, 13.8% and 1.0% of patients with stage II melanoma were noted to have received medical and radiation therapy, respectively. This, however, is as expected since the treatment recommendations include the possibility of medical or radiation therapy for stage IIb or higher, as discussed in section A6.

Stage III and IV patients showed appropriate treatment distributions with more patients receiving medical and radiation therapy. Stage III patients received a high proportion of LNDs at 82.3%, whereas only 70.0% received WLEs. Patients that did not have a primary lesion, but only palpable lymph nodes at presentation could perhaps explain this.

Wait time descriptions

The median wait time to WLE for the entire study population was 43 days. A small subset of papers has published data on wait times from diagnosis to WLE. McKenna *et al.* reported a comparable median wait time to ours of 30 days from diagnostic biopsy to WLE for patients treated in Scotland[53]. Another study by Hajdarevic *et al.* from Sweden reported longer median wait times; they reported median wait times from histopathological diagnosis to referral for WLE of 5.0 days, and from referral for WLE to WLE of 50.0 days in public primary health care centers[54]. They also reported median wait times from referral to WLE of 4.0 days, and from referral for WLE to WLE of 57.5 days in dermatologist offices. To the best of our knowledge, there are no publications assessing comparisons of wait times for the other forms of treatment for melanoma that were assessed in our study.

Some unexpected results were seen when wait times were separated into stage groups. For instance, stage III patients were found to have a longer median wait time to LND than the entire cohort and any of the other stage groups by at least ten days. This seems unusual considering that a LND is often a main part of treatment for stage III melanoma patients, as it remains the best form of treatment for nodal metastasis. Patients diagnosed with stage III melanoma (with either palpable nodes or a positive SNB) require a metastatic work-up, including imaging studies, prior to planning for a LND (because of the high risk of morbidity associated with LND). This requires additional time and may explain the discrepancy in wait times. Another explanation could involve changing surgical opinions surrounding the use of elective and

completion LNDs over time. For instance, elective LNDs were historically included in the mainstay of surgical management for melanoma, but have recently fallen out of favour, and the use of completion LNDs are currently under review and possibly performed less often than previously (as discussed in section A5).

Stage IV patients were noted to have the shortest median wait times for each type of treatment except medical therapy, which had the second shortest median wait time. This is likely explained by the poor prognosis known to be associated with stage IV melanoma, and the urgency of treatment required.

Relationship to CCO mandated wait times

Almost 95% of the study population was diagnosed after the introduction of the CCO's mandated wait time targets for cancer treatment. This would lead us to believe that the majority of patients in our study would have received their first form of treatment within approximately 50 days of diagnosis. Surprisingly, only 55.1% of patients in the entire study population received their first treatment within that time frame. It is speculated that this may have occurred for a few reasons. The first, being that individual physicians and services have been unable to easily track the time lapse between a patient's diagnosis and their first treatment as there are multiple physicians and services involved, and thus were unable to recognize areas requiring improvement. The second, being that there are wait lists for patients to be seen and treated that cannot be managed in that time frame with the current resources. The third is that there have not been any studies to date that support an improved survival outcome

when treated within the mandated target wait times and thus the recommendations may not be considered a priority.

Wait time and treatment type time trend

The changes in treatment patterns and wait times seen over the course of the study likely demonstrate the changes in and adherence to treatment recommendations and guidelines published during that time. For example, the recommendation for performing a WLE on all melanomas has been present for over 100 years. However, there is ongoing debate about the ideal margin size for differing thicknesses of melanoma, and different recommendations have been established in different trials[69-72].

In contrast, SNB for melanoma was first introduced in 1990[8], and was included in the AJCC staging system for melanoma in 2001[4,9]. However, ongoing recommendations continue to change based on new studies, most notably the MSLT-I trial[20] which looked at the outcomes associated with SNB (discussed further in section D4).

LND recommendations are currently hotly debated and the results of the MSLT-II trial will hopefully help clarify the guidelines for LND (this is discussed in section A5). The large difference in patient proportions undergoing LND at the beginning of the study, compared to the end of the study, could be due specifically to decreased number of elective LNDs performed over time.

There are many new advances in medical therapy for melanoma, such as targeted therapies (discussed in section A6), which may have changed the treatment

patterns during the end this study. However, treatment with radiation for melanoma has remained mostly unchanged over time.

Strengths and limitations

The main limitation for this section is the possible inaccuracies in staging data that could have led to the discrepancies in treatment by stage group, as discussed above. The main strength of this study, as mentioned in section B4, is the large size of the study population.

Implications of results

These results show that the majority of patients have been receiving a WLE, which is the best form of treatment recommended to reduce local recurrence of melanoma. This indicates good quality of care in Ontario for patients with melanoma. Also, the median wait time to receive a WLE was 43 days, which is below the approximate 50 days recommended to receive treatment for cancers in Ontario. Therefore, wait time targets set out by CCO seem to be reached for the primary form of melanoma treatment. However, it was surprising to see that only about 50% of patients received their first treatment within approximately 50 days of diagnosis as was mandated by CCO. This implies that significant changes have not been implemented to reach the recommended target wait times for all forms of melanoma treatment in Ontario.

C5. Conclusion

The majority of patients (82.9%) underwent a WLE with a median wait time of 43 days. Only about one third of patients underwent a SNB (28.1%) or a LND (35.0%), with median wait times of 59 and 63 days, respectively. Much smaller proportions of patient underwent medical (11.7%) and radiation therapy (2.5%), with median times of 124 and 130 days, respectively.

Changing trends in proportions of treatment types and wait times to treatment were seen over the course of the study, and likely reflect the ongoing changes in recommendations and guidelines for the treatment of melanoma.

C7. Tables for section C

Table C.1. Treatment and time to treatment for the study population, as a whole and by melanoma stage.

	Whole cohort (N = 2573)	**Stage I (n = 1394)**	**Stage II (n = 682)**	**Stage III (n = 440)**	**Stage IV (n = 57)**
Treatment type, n (%)					
WLE	2132 (82.9)	1261 (90.4)	537 (78.7)	308 (70.0)	26 (45.6)
SNB	723 (28.1)	316 (22.7)	224 (32.8)	170 (38.6)	13 (22.8)
LND	900 (35.0)	255 (18.3)	257 (37.7)	362 (82.3)	26 (45.6)
Medical therapy	302 (11.7)	22 (1.6)	94 (13.8)	165 (37.5)	21 (36.8)
Radiation therapy	64 (2.5)	3 (0.2)	7 (1.0)	37 (8.4)	17 (29.8)
Time from diagnosis to treatment (days), median (IQR)					
Time to WLE	43 (24-64)	41 (21-62)	50 (29-68)	43.50 (27-65)	33.50 (2-57)
Time to SNB	59 (41-81)	58 (41-82.5)	61 (44.5-80.5)	58 (37-81)	27 (18-61)
Time to LND	63 (43-91)	63 (42-83)	56 (41-83)	74 (49-103)	40 (18-61)
Time to medical therapy	124 (96-150)	99 (75-144)	116 (89-139)	131 (113-157)	112 (70-134)
Time to radiation therapy	130 (89.5-157.5)	89 (61-179)	97 (71-153)	137 (120-161)	70 (61-135)

Abbreviations: WLE, wide local excision; SNB, sentinel lymph node biopsy; LND, lymph node dissection; IQR, interquartile range.

Table C.2. Relationship of time of diagnosis and adherence to CCO mandated target wait times.

	Patients, n (%)				
	Total (N = 2573)	**Stage I (n = 1394)**	**Stage II (n = 682)**	**Stage III (n = 440)**	**Stage IV (n = 57)**
Diagnosed post-wait time mandate introduction in September 2005	2432 (94.5)	1336 (95.8)	626 (91.8)	416 (94.6)	54 (94.7)
First treatment received within 50 days of diagnosis	1417 (55.1)	834 (59.8)	324 (47.5)	224 (50.9)	35 (61.4)

Table C.3. Time trend of proportion of treatments received by year of diagnosis, for the study population and by stage cohorts.

	Percentage (%) of patients who received treatment				
Year of diagnosis	**Whole cohort (N = 2573)**	**Stage I (n = 1394)**	**Stage II (n = 682)**	**Stage III (n = 440)**	**Stage IV (n = 57)**
WLE					
2004	76.4	78.6	71.0	90.9	50.0
2005	77.0	75.6	82.1	68.8	100.0
2006	64.8	80.0	55.3	51.7	33.3
2007	66.3	80.0	67.3	36.4	37.5
2008	79.8	89.0	79.4	67.1	37.5
2009	89.4	94.5	86.4	83.6	57.1
2010	89.6	96.7	87.1	73.0	52.9
2011	83.2	89.1	75.5	74.8	30.0
SNB					
2004	12.5	7.1	16.1	18.2	0.0
2005	14.9	14.6	21.4	6.2	0.0
2006	12.2	15.0	6.4	17.2	0.0
2007	13.3	9.4	18.2	15.2	12.5
2008	11.5	6.6	15.1	14.3	37.5
2009	4.6	3.0	2.9	12.7	0.0
2010	25.8	18.6	31.7	43.2	23.5
2011	56.8	43.3	79.9	80.0	50.0
LND					
2004	69.4	46.4	80.6	100.0	50.0
2005	75.9	63.4	82.1	93.8	100.0
2006	70.5	55.0	83.0	82.8	66.7
2007	64.1	44.7	81.8	90.9	37.5
2008	42.2	21.3	42.5	85.7	12.5
2009	34.6	22.6	28.2	81.8	42.8
2010	25.5	10.2	24.2	79.3	64.7
2011	19.9	7.8	12.6	77.4	30.0
Medical therapy					
2004	15.3	3.6	16.1	36.4	50.0
2005	18.4	12.2	10.7	50.0	0.0
2006	22.3	6.7	25.5	44.8	66.7
2007	14.9	1.2	16.4	42.4	37.5
2008	15.3	1.5	17.8	37.1	37.5
2009	11.8	0.0	16.5	38.2	14.3
2010	8.9	0.5	8.1	38.7	29.4
2011	9.3	1.5	12.6	31.3	60.0
Radiation therapy					
2004	0.0	0.0	0.0	0.0	0.0
2005	2.3	0.0	0.0	6.2	50.0
2006	3.9	0.0	2.1	10.3	33.3
2007	3.9	0.0	1.8	9.1	37.5
2008	3.1	0.0	0.0	11.4	12.5
2009	1.5	0.0	1.0	5.4	14.3
2010	3.1	0.2	1.6	10.8	41.2
2011	1.8	0.4	0.6	6.1	30.0

Abbreviations: WLE, wide local excision; SNB, sentinel lymph node biopsy; LND, lymph node dissection.

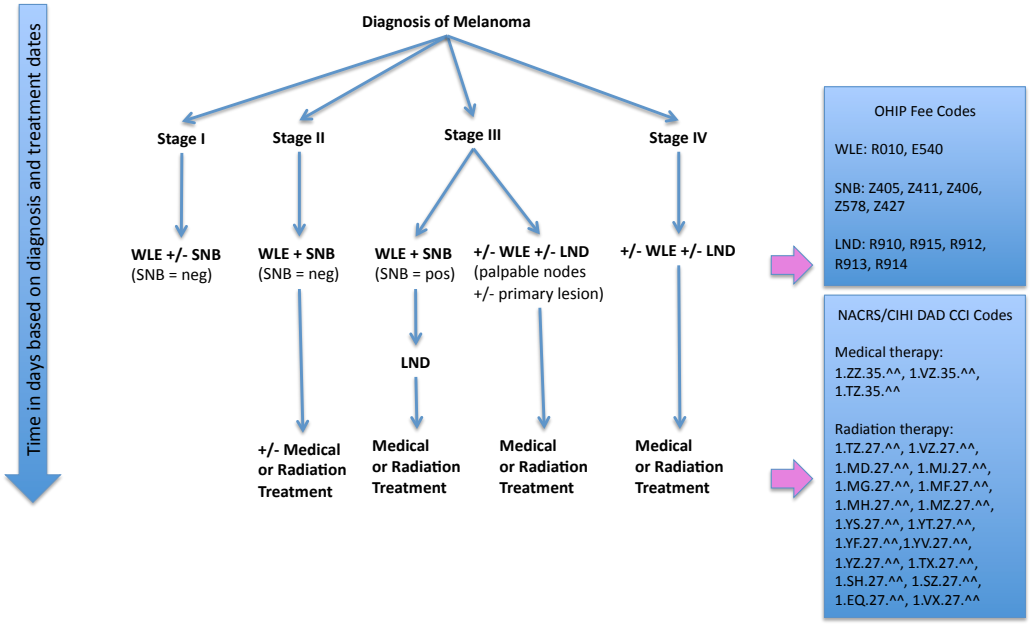
Table C.4. Time trend of median wait times to treatment by year of diagnosis for the entire study population.

	Median number of days (IQR)				
Year of diagnosis	**WLE**	**SNB**	**LND**	**Medical therapy**	**Radiation therapy**
2004	50 (33, 65)	66 (35, 134)	56 (36, 70)	138 (113, 151)	-
2005	54 (23, 78)	78 (63, 88)	56.5 (39, 78)	140 (85, 154.5)	157 (153, 161)
2006	49 (27, 65)	71 (43, 101)	60 (41, 83)	129 (98, 157)	89 (74, 100)
2007	49 (28.5, 71)	56.5 (45, 95.5)	54 (41, 78)	117 (97, 153)	129 (70, 153)
2008	45 (24, 65)	56 (33, 98)	70 (48, 98)	124.5 (90, 152)	132 (92, 172)
2009	45 (25, 66)	77 (58, 125)	59.5 (41, 85)	126 (100, 160)	157 (142, 162)
2010	41 (21, 61)	61 (49, 84)	63 (43, 95)	120 (96, 137)	127 (90, 153)
2011	42 (25, 64)	56 (38, 76)	81 (55, 114)	123 (96, 139)	136 (71, 162)

Abbreviations: WLE, wide local excision; SNB, sentinel lymph node biopsy; LND, lymph node dissection; IQR, interquartile range.

C8. Figures for section C

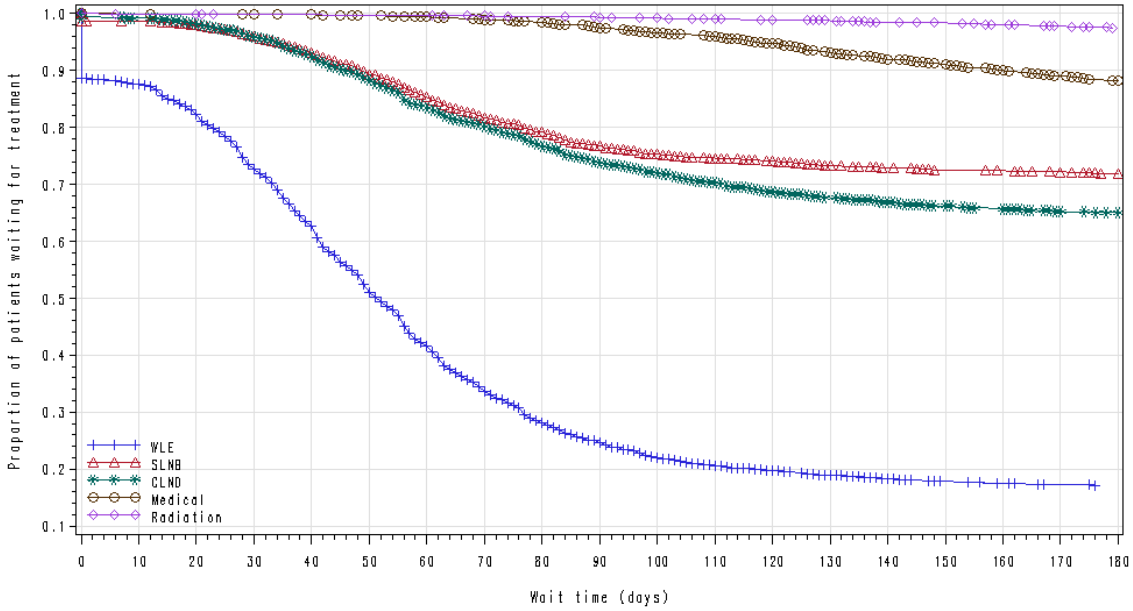
Figure. C.1. Treatment identification flow chart.



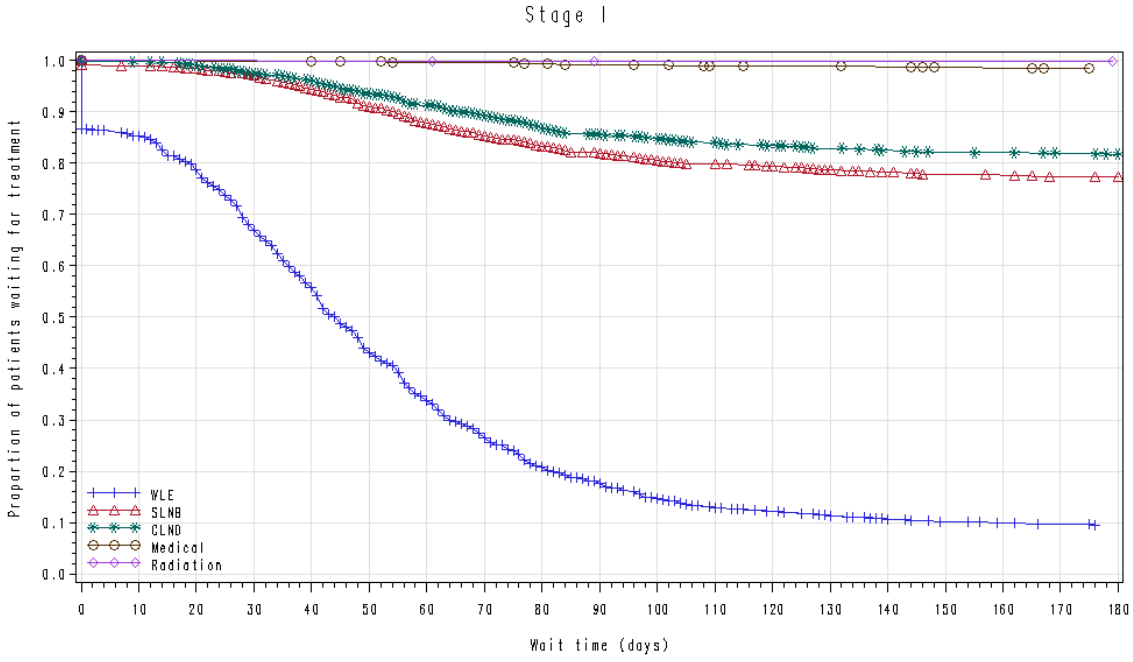
Abbreviations: WLE, wide local excision; SNB, sentinel lymph node biopsy; LND, lymph node dissection; OHIP, Ontario Health Insurance Plan; NACRS, National Ambulatory Care Reporting System; CIHI DAD, Canadian Institute for Health Information Discharge Abstract Database; CCI, Canadian Classification of Health Interventions.

Figure C.2. Time from diagnosis to treatment for the study population as (a.) a whole and (b. - e.) by melanoma stage.

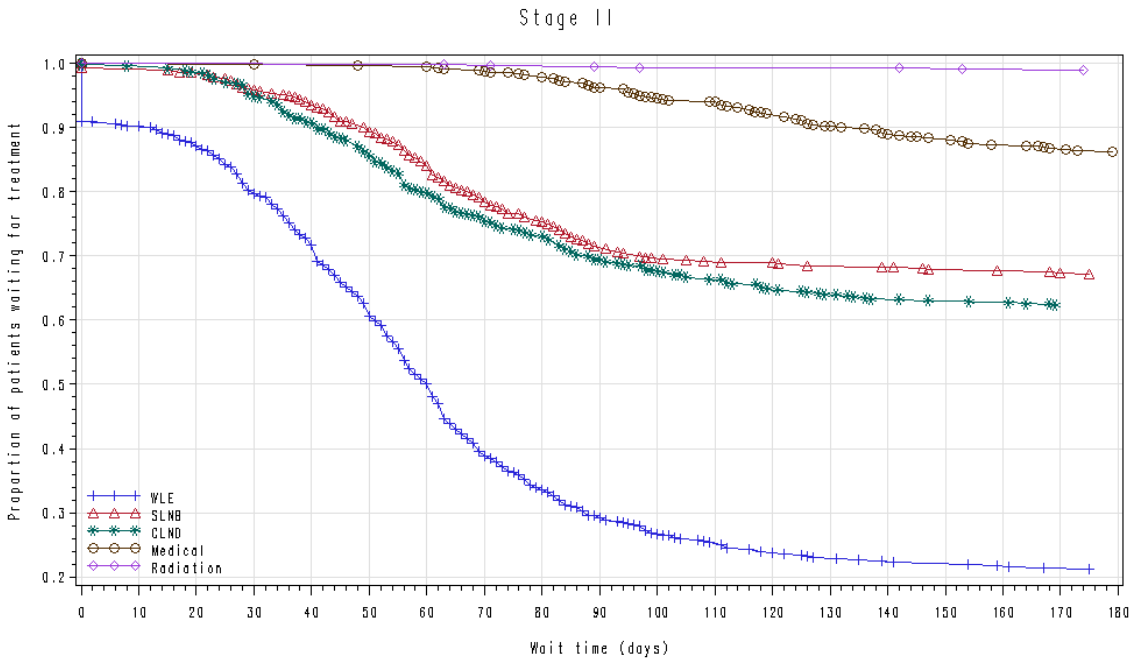
a.



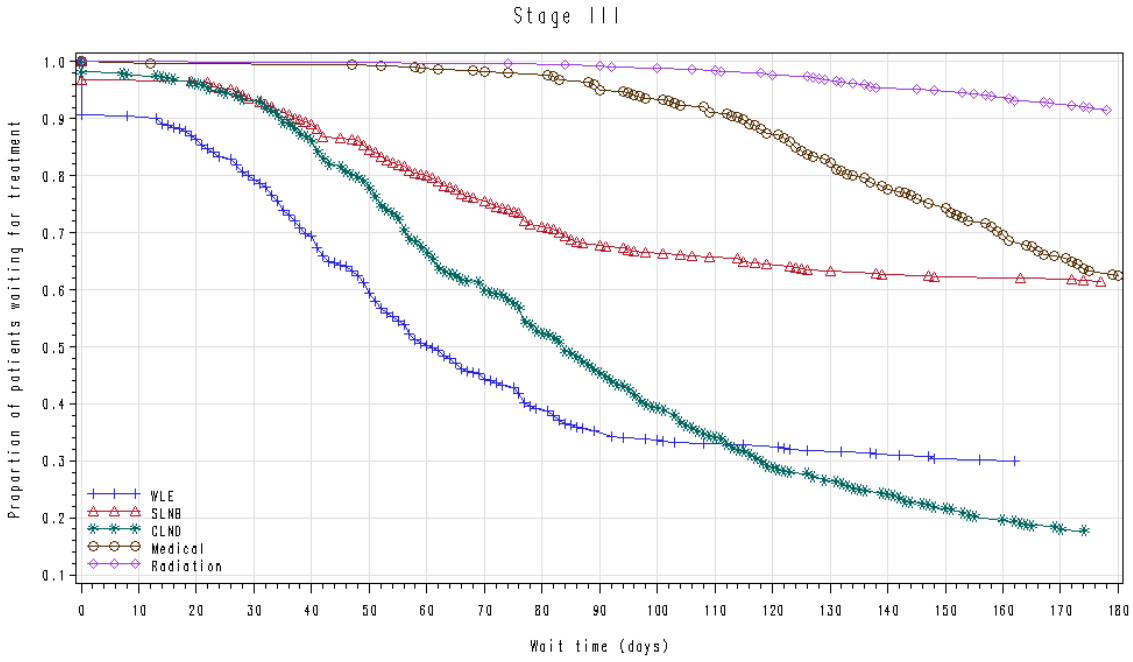
b.



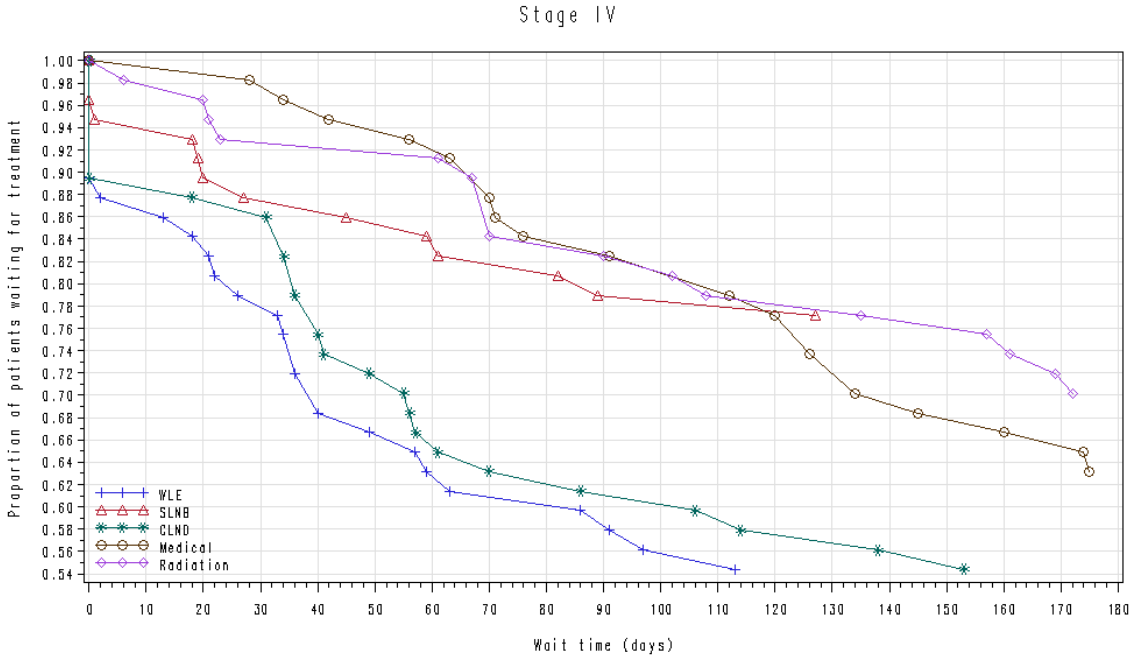
c.


Stage II
Proportion of patients waiting for treatment
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
WLE
SLNB
CLND
Medical
Radiation
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
Wait time (days)

d.


Stage III
Proportion of patients waiting for treatment
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
WLE
SLNB
CLND
Medical
Radiation
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
Wait time (days)

e.



Abbreviations: WLE, wide local excision; SLNB, sentinel lymph node biopsy; CLND, lymph node dissection.

Section D: Association of type of treatment and time to treatment with overall survival (Objective 3)

D1. Overview

This section reports on the unadjusted and adjusted association of overall survival with: type of treatment; and time to (and the actual conduct of) particular types of treatment in Ontario patients diagnosed with melanoma. This analysis was done for the complete cohort and by melanoma stage.

D2. Methods

Please refer to section B2 for methods related to databases, statistical software, confounding variables, patient identification, and refer to section C2 for treatment identification and the wait time definition.

Statistical analysis

Separate Cox proportional hazard models were used to assess for a relationship between overall survival and: (1) type of treatment received (treatment effect); and (2) time to treatment accounting for type of treatment (an example of the SAS code for this model can be seen in Appendix C). Overall survival was chosen as the main outcome measure over recurrence-free or disease-free survival for multiple reasons. First, overall survival is the standard outcome measure used in the majority of studies involving cancer treatment. Second, overall survival is simple to measure and easy to interpret. Third, the OCR does not record recurrence data, and thus the data required to calculate recurrence- or disease-free survival would be difficult or impossible to obtain through ICES databases. And fourth, competing risk events are inherently

present in survival analyses that have outcomes other than all cause mortality. For example, melanoma-specific survival may be biased by a number of uncontrollable or unknown events such as death from other causes. Thus, overall survival was chosen because it is all encompassing for treatment effect.

Univariate and multivariate survival models were used. Multivariate models included the following covariates: patient age and sex; rural residence; and mortality risk score (MRS, described in section B2). Models were constructed for the entire study population and were also stratified by melanoma stage. As mentioned previously, the date of diagnosis was collected between January 1, 2004 and December 31, 2011, and the date of censoring was November 30, 2013. Time of diagnosis was designated as time zero, and time of death or censoring was designated as the end time point in the study. Time to treatment was analyzed in months and patient age was analyzed in decades.

Whether or not patients received a particular type of treatment, and wait time to each type of treatment were both treated as time-dependent covariates. Time-dependent covariates, or time-varying covariates, are used in survival analysis when a variable is not constant throughout the whole study period. For example, time to treatment increased by one day with each day of observation from the date of diagnosis until the date of treatment; after a patient underwent treatment, time to treatment remained the same number of days throughout the remainder of the study. For example, consider a patient who had surgery three days after their date of diagnosis; the time to treatment one day after diagnosis would be one, two days after diagnosis

would be two, three days after diagnosis would be three, and then remain as three until the patient died or was censored. Bias occurs when variables, with unknown baseline values, are treated as fixed variables instead of time-dependent covariates[73]. For example, patients who die within a few weeks of their diagnosis of melanoma, may never have the chance to receive treatment. If time to treatment was analyzed as a fixed covariate, not receiving treatment could be erroneously associated with a worse survival outcome, and thus bias the results. The bias would occur because death resulted in the lack of treatment, not the lack of treatment resulting in death. It was therefore necessary to analyze time to treatment and treatment effect as a time-dependent covariate. Time to treatment was always treated as a continuous variable.

Determining the best fit or 'shape' in our model for continuous covariates was important to maximize the model's ability to identify associations. A SAS macro designed for regression polynomials, named MFP8, was used to determine the best transformation for continuous covariates (age and MRS) in our model. This method was used to preserve the continuous nature of the covariates in a regression model because it was suspected that some of the relationships may not be linear. This 'backfitting' algorithm constructed a transformation for each continuous covariate while fixing the other covariates, and terminated when the functional forms of the covariates no longer changed[74]. Time to treatment, albeit continuous, was modeled as a linear covariate since the methods used to calculate fractional polynomials for time-dependent covariates is methodologically beyond the scope of this study and is computationally intensive[75]. However, a log transformation was assessed for the time to treatment variable within the Cox model used, and was found to be equal to the

linear or untransformed time to treatment model.

D3. Results

Transformation for continuous covariates

Age and MRS were the two continuous covariates analyzed for best possible transformation. Age did not require transformation and its association with survival was found to be linear in nature. However, the best transformation found for MRS was a cubic transformation. MRS was therefore cubed for all multivariate analysis. Because of this transformation, the hazard ratios (HRs) for MRS could not be interpreted directly and had to be presented graphically in the results section.

Univariate and multivariate analyses of treatment effect

The association of each form of treatment with overall survival is presented in Table D.1. Patients who received a WLE had a slightly reduced, although not significant, risk of death compared to patients who did not undergo WLE. This insignificant association was seen in both the univariate and multivariate analyses for the whole study population and within each melanoma stage. The one exception was in multivariate analysis for stage III, where a HR of 1.04 was found, although this too was insignificant. Of note, the stage IV group had HRs of 0.67 and 0.66 for univariate and multivariate analyses, respectively, for WLE treatment (these values were considered lower than those for any other cancer stage). However, there was no statistically significant association between receiving a WLE and overall survival in any of the results.

Receiving a SNB resulted in a slightly reduced risk of death in both the univariate and multivariate analyses for all patients except in those with stage IV disease, who had HRs of 1.05 and 1.22, respectively. Again, these results were not statistically significant, but the P-values for univariate analysis for the whole cohort and stage III melanoma approached significance with values of 0.07, and in the multivariate model for stage III, a p-value of 0.05.

Univariate and multivariate analyses differed for patients receiving a LND for the entire cohort, where the HR for univariate analysis showed decreased risk of death at 0.95, but multivariate analysis showed increased risk of death with a HR of 1.13. However, these results were not statistically significant. For patients who received a LND with stage I melanoma, the risk of death was significantly elevated for both univariate (HR 1.79) and multivariate (HR 2.13) analyses. Stage II showed a slightly improved risk of death for both univariate and multivariate analyses, whereas stage IV showed an obvious improvement. However, the results for these two stages were not significant.

An increased risk of death was seen for the entire cohort and for each stage, except for univariate analysis of the stage III group, for both univariate and multivariate analyses when patients received medical therapy. The worst HRs were seen in the stage I group, where univariate analysis yielded a HR of 2.98 and multivariate analysis yielded a HR of 5.14. Highly significant results of worsened risk of death were demonstrated for patients receiving medical therapy from multivariate analyses for the entire cohort, stage I and stage II.

Radiation therapy was found to have a strong association with worsened risk of death for the whole cohort and for each stage group, omitting stage I as there were less than 5 (total 3 patients) patients in the stage I cohort that underwent radiation therapy, and thus were not appropriate for regression analysis. Also of note, only seven (1.0%) patients in the stage II cohort underwent radiation therapy. Patients in the entire cohort, and stages III and IV were found to have increased risk of death with radiation therapy by about three times.

Age was found to have a mild association with overall survival with HRs just greater than one. This increased risk of death with increasing age was statistically significant for the whole cohort and for stage I for each form of treatment, however not for stages II, III and IV. Males were also found to have a slightly worse risk of death with HRs of 1.45 to 1.47 for the whole cohort. This was strongly significant for the whole cohort, however p values of close to 0.05 were seen for stages I and II, without statistical significance seen for stages III and IV. The HRs for patients living at rural residences at the time of diagnosis ranged from 0.86 to 0.89 for the whole cohort, without statistical significance. Adjusted HRs for MRS can be seen in Figure D.1, and were presented graphically because of the transformation performed to run an accurate Cox regression analysis, as discussed previously (section D2). As was previously reported, the median MRS for the whole cohort was 43. It can be seen that the association between increasing MRS and death risk did not become apparent until the MRS score reached approximately 40. Compared to patients with low MRS scores, the adjusted risk of death did not double until the MRS reached approximately 80 regardless of the treatment that was given. The association of MRS with overall

survival was strongly significant with p values of <0.0001 for the whole cohort and different stage groups.

Univariate and multivariate analyses for wait time to treatment

The association of overall survival with time to treatment accounting for treatment effect is displayed in Table D.2. Patients who received a WLE had slightly reduced risk of death, although not significant, compared to patients who did not for the whole cohort, and stage I and II cohorts, in both univariate and multivariate analyses. However, HRs slightly above one, and again not statistically significant, were seen in univariate and multivariate models for WLE status for stages III and IV cohorts.

HRs for time to WLE closely surrounded one in both univariate and multivariate analyses for the whole cohort, and for stage I to III cohorts. These findings were not statistically significant. The exception to this trend was demonstrated in the stage IV cohort, in univariate and multivariate models, where the risk of death was significantly reduced in patients with *longer* wait times for WLE. HRs were reported as 0.60 and 0.57 for univariate and multivariate models, respectively, with p values of 0.04.

Patients who received a SNB demonstrated HRs surrounding one for the whole cohort and stage III, and a slightly higher risk of death for stages I and IV. However, the stage II cohorts showed HRs around 0.60. None of these findings were significant, and they were all consistent in univariate and multivariate analyses.

The time to SNB showed a nonsignificant reduced risk of death with increasing wait times in the HR range of 0.81 to 0.93 for the whole cohort, and stages I, III and IV.

Again, a difference in HRs was seen for the stage II cohort, where HRs were slightly above one. There was consistency between univariate and multivariate analyses, but none of the results were statistically significant.

HRs for the entire cohort for patients who received a LND were 0.97 and 1.14 for univariate and multivariate analyses, respectively. HRs for patients in the stage I and III cohorts were slightly higher, with almost statistically significant heightened risk of death seen in multivariate analysis for stage I with a HR of 2.53 and a p-value of 0.05. For stages II and IV, decreased risk of death was seen with HRs of 0.46 to 0.62. These findings were non-significant except for the HR of 0.50 and p-value of 0.04 demonstrated in univariate analysis for stage II melanoma patients.

The HRs for wait times to LND surrounded one for the whole cohort and each stage in univariate and multivariate analyses, without statistical significance. However, in the stage II cohort, slightly elevated HRs of 1.24 and 1.23, for univariate and multivariate analysis, respectively, approached significance with p-values of 0.06 and 0.07.

For the whole cohort, patients who received medical therapy demonstrated increased risk of death with a HR of 2.01 and p-value of 0.04 in multivariate analysis. The stage cohorts also all demonstrated increased risk of death for patients who received medical therapy in both univariate and multivariate analyses, however the findings were not statistically significant.

Patients with longer wait times to medical therapy were found to have reduced risk of death for the whole cohort, and stage III and IV cohorts. However, for stage I and

II cohorts, HRs were found to be just greater than one. Results were consistent between univariate and multivariate analyses, however were not statistically significant in any cohort.

Patients who received radiation therapy were found to have greatly increased risk of death with high levels of significance in the whole cohort, stage III univariate analysis and stage IV. Patients in the stage I cohort could not be analyzed with Cox regression analysis as there were only 3 patients (ie. <5 per cell) that received radiation therapy. Patients with stage II melanoma also had an increased risk of death for patients who received radiation therapy, however the results were not statistically significant.

Longer wait times for radiation therapy were found to have reduced risk of death for the entire cohort and stages III and IV cohorts with statistical significance demonstrated for univariate analysis for the whole cohort, and univariate and multivariate analyses for the stage IV cohort. Other findings were not statistically significant. Stage I was again unable to be analyzed due to low number of patients that received radiation therapy. Patients in stage II were found to have a non-significant mild increase risk of death with longer wait times.

Increased age at diagnosis was significantly associated with an increased risk of death for the whole cohort and the stage I cohort for each of the treatment types. Stage II and III cohorts also showed a trend towards increased risk of death with increasing age, however the findings were not statistically significant. The stage IV cohort

demonstrated a non-significant reduced risk of death with increasing age for each treatment type.

Male sex was found to have a strong significant association with increased risk of death for the whole cohort for each treatment type. A mild significant association was found for male sex and an increased risk of death in the stage I cohort for SNB and LND treatments. All other cohorts and treatment types found a non-significant association with increased risk of death and male sex.

Rural residence was found to have a non-significant association with reduced risk of death for all cohorts and treatment types, except the stage I cohort, where a non-significant increase in risk of death was seen.

Adjusted HRs for the approximately 50% of patients with MRSs less than 43 surrounded 1, whereas they began to increase with increasing MRS for the other half of patients. The association of MRS with overall survival was strongly significant with p values of <0.0001 for the whole cohort and different stage groups.

Comparison of treatment status alone and when combined with time to treatment

When comparing the results for treatment status between the analysis done for treatment status alone versus treatment status while accounting for time to treatment, HRs and p-values for WLE status for the whole cohort were similar for both univariate and multivariate analyses. SNB status was found to have HRs of 0.80 and 0.82 for univariate and multivariate analyses, respectively, for status alone, and HRs of 1.03 and 1.04 for univariate and multivariate analyses, respectively, for status accounting for

time to treatment. None of the p-values were statistically significant, however in univariate analysis for the treatment status alone, the p-value was approaching significance at 0.07. Results for LND were similar between analyses for both univariate and multivariate analyses. For medical therapy, the combined analyses were found to result in slightly higher HRs, and statistical significance was shown for both analyses using multivariate analysis. There was a large difference seen for radiation treatment between the treatment status alone and combined analyses for both univariate and multivariate analyses with HRs of 3.30 and 2.81, respectively, for status alone, and 10.44 and 7.04, respectively, for the combination of status with time to treatment. All results for radiation treatment were highly significant.

When comparing the results for the covariates between treatment status alone and treatment status accounting for time to treatment, they are all found to be similar with regards to HRs and levels of significance.

D4. Discussion

Summary

There was no significant association of treatment effect for WLE or SNB with overall survival. LND also demonstrated a lack of association with overall survival, except for patients with stage I melanoma for whom a higher risk of death was seen when LND was performed. This finding is unexpected considering patients with stage I melanoma would not undergo a LND, and the possible explanations for this unusual result are discussed further below. Medical therapy was negatively associated with overall survival for multivariate analysis for the whole cohort and for the stage II cohort, and

for both univariate and multivariate analyses for stage I. Similar to LND, stage I melanoma would not usually be treated with medical therapy. These unexpected results are also described in the body of the discussion. Receiving radiation therapy was found to be strongly and negatively associated with overall survival for all cohorts, except stage I where there were only three patients were treated with radiation therapy, and therefore the Cox regression model was not appropriate for analysis.

Wait time to treatment for WLE was not significantly associated with overall survival, except for the stage IV cohort, where longer wait times were mildly associated with *improved* survival. Longer wait times to radiation therapy in univariate analysis for the whole cohort, and both univariate and multivariate analyses for the stage IV cohort, were found to be significantly associated with a reduced risk of death. Radiation wait times in the other cohorts were not associated with survival. Wait time to SNB, LND and medical therapy were also not associated with overall survival.

Increased age, male sex and worse MRS were all associated with an increased risk of death for the whole cohort. Rural residence had no association with overall survival.

Notable results and explanations

Univariate and multivariate analyses of treatment effect

There was no association shown between WLE status and overall survival. Historically, large WLE was performed to decrease the chance of local recurrence[76] and has continued with ongoing controversy on the ideal size of resection margin to balance cosmesis and survival. A recent meta-analysis was performed comparing the use of wide (3-5 cm) and narrow (1-2 cm) excision margins. The results showed no significant difference in overall survival, local or locoregional recurrence between margin sizes[77]. Even though, the size of resection margins continues to be debated, the utility of WLE as a method for reduced risk of melanoma recurrence is well known and supports the ongoing recommendation for the procedure.

A similar lack of association was found for SNB and overall survival for the whole cohort and stages I, II and IV. However, p-values approaching significance where demonstrated in the stage III cohort. Similar findings were recently reported in a large randomized control trial (Multicenter Selective Lymphadenectomy Trial I (MSLT-1)) comparing 2001 patients with primary cutaneous melanomas randomly assigned to undergo WLE and nodal observation, with LND for clinically detected nodal disease (observation cohort), or WLE and SNB, with immediate LND for nodal metastases detected by SNB (SNB cohort). This group found that there was no significant difference in 10-year melanoma-specific survival between the observation and SNB cohorts in the entire study population [20]. However, they did report that mean 10-year

disease-free survival rates were significantly improved in the SNB cohort, compared with the observation group, among patients with intermediate-thickness melanomas (1.20 to 3.50 mm), and thick melanomas (>3.50 mm). Interestingly, they also reported that only 20.8% of the study population had nodal disease, and thus 79.2% of the patients in the study would not have benefited from a SNB.

Univariate and multivariate analyses for treatment effect of a LND showed HRs surrounding unity for the whole cohort, and stages II and III. For patients with stage I melanoma, a LND was associated with a worse survival with significant HRs of 1.79 and 2.18 for the univariate and multivariate models, respectively. This is interesting considering patients with stage I melanoma do not often receive LNDs. As was describe is section C4, there are a few possible explanations for patients in stages I and II for receiving LNDs. To summarize, patients may have been up- or down-staged following the data entry of their melanoma stage into the ICES databases, thus representing patients incorrectly in stage groups for this analysis. Therefore, patients in the stage I cohort, who received a LND, were likely to have had a higher stage of melanoma than was represented in the data, and thus had an inherently worse outcome despite treatment received.

Another possible explanation for patients with stage I and II melanoma, who received LND, could be due to patients undergoing elective LND as this was previously the expected treatment for high-risk melanoma. This may explain why there were larger proportions of patients undergoing LND in the earlier years of the study compared to later years (as discussed in sections C3 and C4 in the time trend results).

In the literature, there is controversy surrounding the utility of LND for node-positive patients. In one study, all patients with positive SNB were recommended to undergo LND due to a demonstrated survival benefit[19]. However, a benefit in survival was not demonstrated in a similar study[21]. In light of the controversy that exists surrounding guidelines for LND, a large randomized trial (Multicenter Selective Lymphadenectomy Trial II - MSLT-II) is currently underway to assess outcomes in a direct comparison of LND versus observation in patients with positive SNBs. The results of this study will help to delineate recommendations regarding LND.

A divide between the results of univariate and multivariate analyses was seen for medical therapy for the entire cohort as well as for melanoma stages I and II. Patients who received medical therapy in stages I and II, which were likely patients that were upstaged from their initial diagnosis without changes being made to the database, had significantly worse survival outcomes with hazard ratios of five times worse for stage I and almost two times more for stage II. These significant outcomes are likely not due to receiving medical therapy itself, but the fact that patients who did receive medical therapy were those that initially had a worse prognosis. Therefore, the negative association with survival can be interpreted as a signal of patient prognosis and not causation from treatment received. This is likely why stage I compared to the other stage groups, had such high HRs, because the patients with the correct stage of I would not have received medical therapy, whereas those who were upstaged or incorrectly entered, and thus had an inherent worse prognosis, would have worse outcomes.

As discussed in section A6, none of the immunotherapy medications (including Ipilimunab[24], IL-2[25], or IFNa[26-28]) have shown a benefit in overall survival in patients with resected, high-risk melanoma. However, there is evidence supporting an improvement in recurrence-free survival with the use of INFα in higher stages of melanoma[26,29]. The lack of effect on overall survival has also been demonstrated for chemotherapy medications dacarbazine[30-34] and temozolomide[31] in randomized controlled trials. Therefore, we would have expected that our results would also show a lack of association with overall survival, however due to the reasons given above, a possibly erroneous significant association was demonstrated.

Similar significant associations of radiation therapy with overall survival were demonstrated in the stage IV cohort, where patients who received radiation therapy were found to have worse survival outcomes. These results suggest that receiving radiation therapy is associated with an increased risk of death, however only the patients with the worst prognoses based on metastatic disease or significant locoregional disease would receive radiation. Thus, these results can likely be better explained by saying that those who receive radiation treatment were worse off initially, and that receiving radiation therapy did not improve their poor prognosis. Stage I patients were not analyzed as only three patients with stage I received radiation. Again, the patients in this cohort that did receive radiation were likely not patients with stage I and were incorrectly included in that cohort. The same can be said for the stage II cohort, where only seven patients with stage II received radiation, which likely explains why higher HRs were seen for this group, and should probably not be interpreted. Another possible explanation for inclusion of patients who received

radiation treatment in stages I and II, is that patients with positive margins following a WLE that could not be re-resected are sometimes offered radiation treatment for local control.

The covariates of age, male sex and MRS demonstrated significant associations with overall survival. Age demonstrated a significantly increased risk of death as the patient aged by the decade. Studies have also shown that older age is associated with worse outcomes in patients with melanoma[57], since older patients are more likely to develop loco-regional recurrences[58]. In contrast younger patients are more likely to have lymph node metastases but better prognosis overall[58]. Male sex was also significantly associated with worsened overall survival. This has been demonstrated in multiple publications[59,60]. Also, as expected, the MRS had a significant association with overall survival as an increased MRS represents the increased severity of age and comorbidities, and thus an increased probability of death within one year[61].

As discussed previously (in section A2 and Figure C.1), treatment choice for melanoma is strongly related to melanoma stage, and melanoma stage is strongly related to survival outcomes. For example, a patient with stage I melanoma has an inherently good prognosis based on the characteristics of their cancer, and although they will undergo a WLE and possibly other treatments, their prognosis will remain favourable. Therefore, the general lack of association demonstrated in this study between treatment for melanoma and overall survival might be due to the strong association inherent between stage and survival.

Univariate and multivariate analyses of wait time to treatment

Wait time to WLE was not associated with overall survival for the whole cohort or stages I to III. However, for the stage IV cohort longer wait times were shown to have a significant association with overall survival. This can likely be explained as a result of patient prognosis at assessment for treatment and not wait times to treatment. Patients with stage IV melanoma are known to have a poor prognosis[4]. There are two possible explanations: (1) patients with shorter wait times were those with worse prognosis on assessment, and thus deemed urgent to receive WLE; or (2) patients with longer wait times for WLE were being treated with medical forms of therapy prior to proceeding to surgery, thus lengthening their wait time to surgical management.

In the literature, to our knowledge, there has only been one publication that has reported on the association of wait time from diagnosis of melanoma to WLE (as reviewed in section A7). In that study, by McKenna *et al*., they were unable to report a significant association with overall survival or recurrence[53]. There were no publications that were identified during our literature search that looked for or reported on an association of wait time to melanoma treatment for SNB, LND, medical, or radiation therapy with overall survival.

Wait times to SNB and LND were not significantly associated with overall survival for the whole cohort, or in individual stage cohorts. This finding is likely related the known lack of association of surgical management with SNB and LND for melanoma and overall survival[20,21]. A similar lack of association with overall survival

was found for wait times to medical management. This may also be due to the lack of association of medical management using chemotherapy and/or immunotherapy with overall survival[24-28,30-34], as discussed previously in this section and in section A6.

Wait times to radiation therapy were found to have a significant association with overall survival for the univariate analysis for the whole cohort and for both univariate and multivariate analyses for the stage IV cohort, where longer wait times were associated with a reduced risk of death. This likely has a similar explanation that applied to WLE, discussed above, where two possibilities could explain these results. First, patients with shorter wait times may have had perceived worse prognosis and proceeded straight to radiation treatment (skipping surgical management), thus having worse outcomes with shorter wait times. Or, second, patients who were being successfully treated with another form of treatment (surgery or medical management) prior to radiation treatment, and thus experienced longer wait times with better outcomes. This coincides with the recommendations for use of radiation treatment is melanoma, which includes adjuvant therapy following surgical management for patients with high risk of recurrence, or palliative therapy for patients with advanced, inoperable disease.

As discussed previously (in section A7), when looking at all cancers, no impact on survival has been demonstrated when the targeted two-week wait times from referral to consult were met, compared to longer wait times[48]. It is felt that the two to three month wait times from diagnosis to treatment seen in this study, likely also lack an association with survival because of the relatively small amount of time that a few

months occupies in the whole 'cancer pathway'. Therefore, the general lack of association demonstrated in this study between wait time to treatment and overall survival may be due to too small of a variation in delay to identify an association with survival.

Strengths and limitations

The main limitation for this section, as was for the preceding section, is the possible inaccuracies in staging data that could have lead to the discrepancies in treatment by stage group, as discussed above.

Another limitation is the lack of inclusion of targeted therapies (discussed in section A6) for melanoma. These therapies, including vemurafenib, dabrafenib, trametinib, received approval for use in treatment of melanoma in only the last few years, and thus would not have been used for the majority of our study population. However, the use of vemurafenib[33], dabrafenib[36] and trametinib[37] have been associated with improved progression-free survival and/or overall survival in patients with BRAF gene mutations. As these treatments were not included in our study, our results on medical therapy may not be generalizable to current medical management, as they are now becoming the mainstay of medical therapies.

The main strength of this study, as mentioned in section B4, is the large size of the study population.

Implications of results and future directions

There is currently a strong focus on attaining recommended target wait times to surgical, medical and radiation treatments for cancer in Ontario. This study demonstrates that there is no association of surgical management with overall survival, and a complex and potentially complicated association of medical and radiation management with overall survival for melanoma. Thus, suggesting that adhering to the currently recommended target wait times may not be as relevant as currently mandated.

However, the implications of these results should be interpreted cautiously for a few reasons. First, the main goal of WLE is to reduce the risk of local recurrence, with most stage I patients being cured by excision alone. A benefit in overall survival from WLE was not demonstrated in this study, however recurrence-free survival in melanoma can have quite a significant effect on the prognosis of melanoma, and is the main goal of treatment.

Second, in patients with stage II and III melanoma, SNB and LND are currently used mainly as staging tools to identify patients who are at high risk of local or distant recurrence, so that adjuvant therapy or selection for clinical trials, in an attempt to improve survival and reduce the risk of local recurrence, can be performed. Local control is again the goal for surgical therapy, hence why an overall survival benefit was likely not seen here. In the future, a study looking for an association of wait times to treatment with recurrence-free survival may be a more appropriate measure specific to

melanoma that's results could have implications in adherence to current wait time guidelines.

Thirdly, regarding stage IV patients, this study was performed in an era where ineffective medical treatments, such as chemotherapy, were being used, which are known to have a very low response rate in melanoma. The landscape for melanoma treatment has since changed with new targeted therapies and immunotherapies that have promising improvements in survival, thus potentially changing the prognosis of this disease and eventually having an effect of overall survival. Wait times to these new forms of treatment may have more of an impact, so a repeat of this study in five to ten years may show differing results.

Finally, given that most of the treatment for melanoma is for local control and reduction of local recurrence that may occur two to five years after diagnosis, it is not surprising that wait times to surgery were not associated with overall survival in this study. The more important wait time, that is not captured here and may have a significant impact on survival, is the time from identification of an abnormal lesion to the time of biopsy. As it is known that thicker melanomas have worse prognoses than thin melanomas, the time from identification to biopsy could potentially be the more important wait time to alter survival. Screening for melanoma may also have implications in reducing melanoma progression and improving survival through reduced wait times to biopsy, and thus further treatment.

D5. Conclusion

There was no association found between the treatment effects of receiving WLE, SNB or LND with overall survival for the whole study population. Medical and radiation therapies did however show worsened risk of death associated with treatment for the whole cohort. There were some variations in results demonstrated by the individual stage cohorts.

Wait time to SNB, LND and medical therapy were not associated with overall survival in each cohort. Wait time to WLE was also not significantly associated with overall survival, except in the stage IV cohort. Wait time to radiation therapy was only found to be associated with overall survival in univariate analysis of the whole cohort and both analyses of the stage IV cohort.

Increased age, male sex and worse MRS were all associated with an increased risk of death. Rural residence had no association with overall survival.

D6. Tables for section D

Table D.1. Univariate and multivariate associations of treatment effect and overall survival for the study population as a whole and by melanoma stage.

	Whole cohort		Stage I		Stage II		Stage III		Stage IV	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
WLE										
WLE status, univariate	0.90 (0.72-1.13)	0.35	0.88 (0.43-1.78)	0.72	0.93 (0.63-1.39)	0.74	0.97 (0.68-1.37)	0.85	0.67 (0.37-1.22)	0.19
WLE status, multivariate	0.94 (0.75-1.18)	0.59	0.82 (0.40-1.67)	0.58	0.98 (0.66-1.46)	0.91	1.04 (0.73-1.48)	0.81	0.66 (0.36-1.21)	0.18
Age at diagnosis	1.14 (1.02-1.26)	0.01	1.56 (1.20-2.03)	0.0008	1.14 (0.96-1.36)	0.14	1.16 (0.97-1.38)	0.10	0.78 (0.54-1.14)	0.20
Male sex	1.47 (1.18-1.82)	0.0005	1.61 (0.96-2.68)	0.07	1.44 (1.00-2.08)	0.05	1.36 (0.96-1.95)	0.09	1.26 (0.64-2.50)	0.50
Rural residence	0.88 (0.67-1.15)	0.33	1.16 (0.63-2.14)	0.63	0.93 (0.58-1.51)	0.78	0.82 (0.52-1.28)	0.39	0.78 (0.30-1.98)	0.59
SNB										
SNB status, univariate	0.80 (0.62-1.02)	0.07	0.94 (0.48-1.86)	0.86	0.79 (0.52-1.22)	0.29	0.71 (0.49-1.03)	0.07	1.05 (0.52-2.13)	0.89
SNB status, multivariate	0.82 (0.64-1.05)	0.12	0.94 (0.48-1.86)	0.86	0.82 (0.54-1.25)	0.36	0.69 (0.47-1.00)	0.05	1.22 (0.57-2.58)	0.61
Age at diagnosis	1.14 (1.03-1.27)	0.012	1.56 (1.20-2.03)	0.0008	1.14 (0.95-1.35)	0.15	1.18 (0.99-1.41)	0.06	0.78 (0.54-1.12)	0.17
Male sex	1.47 (1.18-1.82)	0.0005	1.63 (0.98-2.71)	0.06	1.46 (1.01-2.09)	0.04	1.33 (0.93-1.90)	0.12	1.26 (0.63-2.54)	0.51
Rural residence	0.86 (0.66-1.13)	0.29	1.16 (0.63-2.13)	0.64	0.93 (0.57-1.50)	0.76	0.81 (0.52-1.26)	0.34	0.77 (0.30-2.03)	0.60
LND										
LND status, univariate	0.95 (0.76-1.20)	0.66	1.79 (1.07-2.99)	0.03	0.81 (0.57-1.16)	0.25	1.03 (0.65-1.61)	0.91	0.58 (0.32-1.08)	0.09
LND status, multivariate	1.13 (0.89-1.42)	0.32	2.18 (1.30-3.65)	0.003	0.98 (0.68-1.41)	0.92	1.18 (0.74-1.87)	0.48	0.54 (0.28-1.03)	0.06
Age at diagnosis	1.14 (1.03-1.26)	0.01	1.60 (1.23-2.09)	0.0005	1.14 (0.96-1.36)	0.15	1.16 (0.98-1.38)	0.09	0.76 (0.52-1.11)	0.16
Male sex	1.46 (1.18-1.82)	0.0006	1.60 (0.96-2.67)	0.07	1.45 (1.01-2.08)	0.05	1.34 (0.94-1.92)	0.11	1.30 (0.66-2.57)	0.44
Rural residence	0.87 (0.67-1.14)	0.33	1.21 (0.66-2.22)	0.54	0.93 (0.58-1.51)	0.78	0.82 (0.52-1.28)	0.39	0.70 (0.27-1.83)	0.47
Medical therapy										
Medical therapy status, univariate	1.07 (0.84-1.37)	0.57	2.98 (1.07-8.33)	0.04	1.19 (0.76-1.87)	0.44	0.88 (0.63-1.24)	0.46	1.38 (0.74-2.57)	0.31
Medical therapy status, multivariate	1.56 (1.20-2.02)	0.001	5.14 (1.80-14.70)	0.002	1.91 (1.18-3.10)	0.008	1.15 (0.79-1.67)	0.46	1.31 (0.68-2.52)	0.42
Age at diagnosis	1.18 (1.06-	0.002	1.59 (1.22-	0.0006	1.19 (0.99-	0.06	1.18 (0.98-	0.07	0.80 (0.55-	0.24

	1.32)		2.07)		1.42)		1.42)		1.17)	
Male sex	1.45 (1.17-1.80)	0.0008	1.65 (0.99-2.76)	0.05	1.39 (0.97-2.00)	0.07	1.36 (0.95-1.94)	0.09	1.22 (0.62-2.41)	0.56
Rural residence	0.89 (0.68-1.17)	0.41	1.21 (0.66-2.23)	0.54	0.96 (0.60-1.56)	0.88	0.83 (0.53-1.29)	0.40	0.79 (0.31-2.03)	0.63
Radiation therapy										
Radiation therapy status, univariate	3.30 (2.33-4.68)	<0.0001	-	-	6.65 (2.71-16.33)	<0.0001	3.23 (2.04-5.10)	<0.0001	2.75 (1.46-5.18)	0.002
Radiation therapy status, multivariate	2.81 (1.99-3.98)	<0.0001	-	-	4.23 (1.70-10.48)	0.002	3.03 (1.89-4.85)	<0.0001	3.01 (1.57-5.76)	0.0009
Age at diagnosis	1.14 (1.03-1.27)	0.01	1.55 (1.19-2.02)	0.001	1.13 (0.94-1.34)	0.19	1.19 (1.00-1.42)	0.06	0.78 (0.55-1.12)	0.18
Male sex	1.46 (1.18-1.82)	0.0006	1.61 (0.96-2.68)	0.07	1.47 (1.02-2.11)	0.04	1.20 (0.83-1.73)	0.32	1.39 (0.68-2.83)	0.36
Rural residence	0.88 (0.67-1.16)	0.36	1.15 (0.62-2.12)	0.65	0.96 (0.59-1.54)	0.85	0.84 (0.54-1.32)	0.45	0.93 (0.37-2.33)	0.87

Abbreviations: HR, hazard ratio; CI, confidence interval, WLE, wide local excision; SNB, sentinel lymph node biopsy; LND, lymph node dissection.

Mortality risk score (MRS) was not presented in this table as it was transformed for analysis and thus could not be interpreted as a hazard ratio. MRS hazard ratios are presented graphically in Figure D.1.

Table D.2. Univariate and multivariate associations of time to treatment accounting for treatment effect and overall survival for the study population as a whole and by melanoma stage.

	Whole cohort		Stage I		Stage II		Stage III		Stage IV	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
WLE										
WLE status, univariate	0.91 (0.69-1.22)	0.53	0.84 (0.38-1.86)	0.66	0.83 (0.50-1.38)	0.47	1.02 (0.65-1.61)	0.92	1.26 (0.58-2.70)	0.56
WLE status, multivariate	0.98 (0.74-1.31)	0.91	0.74 (0.34-1.66)	0.47	0.94 (0.56-1.55)	0.79	1.15 (0.73-1.83)	0.55	1.29 (0.58-2.87)	0.53
Time to WLE, univariate	0.99 (0.89-1.10)	0.85	1.03 (0.82-1.30)	0.80	1.07 (0.90-1.28)	0.45	0.96 (0.80-1.17)	0.71	0.60 (0.37-0.97)	0.04
Time to WLE, multivariate	0.97 (0.87-1.08)	0.62	1.06 (0.85-1.33)	0.60	1.03 (0.86-1.22)	0.77	0.94 (0.77-1.14)	0.52	0.57 (0.34-0.97)	0.04
Age at diagnosis	1.14 (1.03-1.26)	0.01	1.55 (1.19-2.01)	0.001	1.14 (0.96-1.36)	0.14	1.16 (0.98-1.39)	0.09	0.79 (0.55-1.13)	0.19
Male sex	1.47 (1.18-1.82)	0.0005	1.62 (0.97-2.69)	0.07	1.45 (1.01-2.08)	0.05	1.36 (0.95-1.95)	0.09	1.19 (0.60-2.39)	0.62
Rural residence	0.88 (0.67-1.15)	0.35	1.17 (0.64-2.16)	0.61	0.93 (0.58-1.51)	0.77	0.83 (0.53-1.30)	0.42	0.84 (0.33-2.11)	0.71
SNB										
SNB status, univariate	1.03 (0.66-1.59)	0.91	1.36 (0.37-5.02)	0.64	0.64 (0.26-1.55)	0.32	1.09 (0.58-2.07)	0.79	1.35 (0.51-3.56)	0.55
SNB status, multivariate	1.04 (0.68-1.59)	0.86	1.38 (0.41-4.67)	0.60	0.62 (0.28-1.40)	0.25	1.01 (0.53-1.90)	0.98	1.34 (0.48-3.75)	0.58
Time to SNB, univariate	0.88 (0.73-1.06)	0.19	0.84 (0.48-1.47)	0.54	1.10 (0.78-1.55)	0.57	0.81 (0.61-1.07)	0.13	0.83 (0.47-1.46)	0.51
Time to SNB, multivariate	0.89 (0.74-1.07)	0.21	0.83 (0.50-1.39)	0.49	1.14 (0.84-1.54)	0.42	0.82 (0.62-1.09)	0.17	0.93 (0.51-1.68)	0.80
Age at diagnosis	1.15 (1.04-1.28)	0.009	1.56 (1.20-2.02)	0.0008	1.13 (0.94-1.34)	0.19	1.20 (1.00-1.43)	0.05	0.78 (0.54-1.14)	0.20
Male sex	1.46 (1.18-1.82)	0.0006	1.63 (0.98-2.72)	0.06	1.45 (1.01-2.09)	0.04	1.30 (0.91-1.87)	0.15	1.25 (0.62-2.52)	0.53
Rural residence	0.87 (0.66-1.14)	0.30	1.16 (0.63-2.13)	0.64	0.93 (0.58-1.50)	0.77	0.82 (0.52-1.28)	0.38	0.76 (0.29-2.02)	0.58
LND										
LND status, univariate	0.97 (0.70-1.34)	0.85	1.85 (0.74-4.63)	0.18	0.50 (0.26-0.95)	0.04	1.39 (0.79-2.43)	0.25	0.53 (0.22-1.24)	0.14
LND status, multivariate	1.14 (0.82-1.58)	0.44	2.53 (1.02-6.32)	0.05	0.62 (0.32-1.17)	0.14	1.56 (0.88-2.77)	0.13	0.46 (0.18-1.15)	0.10
Time to LND, univariate	0.99 (0.89-1.10)	0.87	0.98 (0.70-1.39)	0.92	1.24 (0.99-1.56)	0.06	0.88 (0.76-1.02)	0.09	1.07 (0.75-1.53)	0.72
Time to LND, multivariate	0.99 (0.89-1.11)	0.92	0.93 (0.66-1.32)	0.70	1.23 (0.98-1.54)	0.07	0.89 (0.77-1.03)	0.12	1.11 (0.74-1.65)	0.62
Age at diagnosis	1.14 (1.03-	0.01	1.61 (1.23-	0.0004	1.11 (0.93-	0.24	1.18 (0.99-	0.07	0.75 (0.51-	0.14

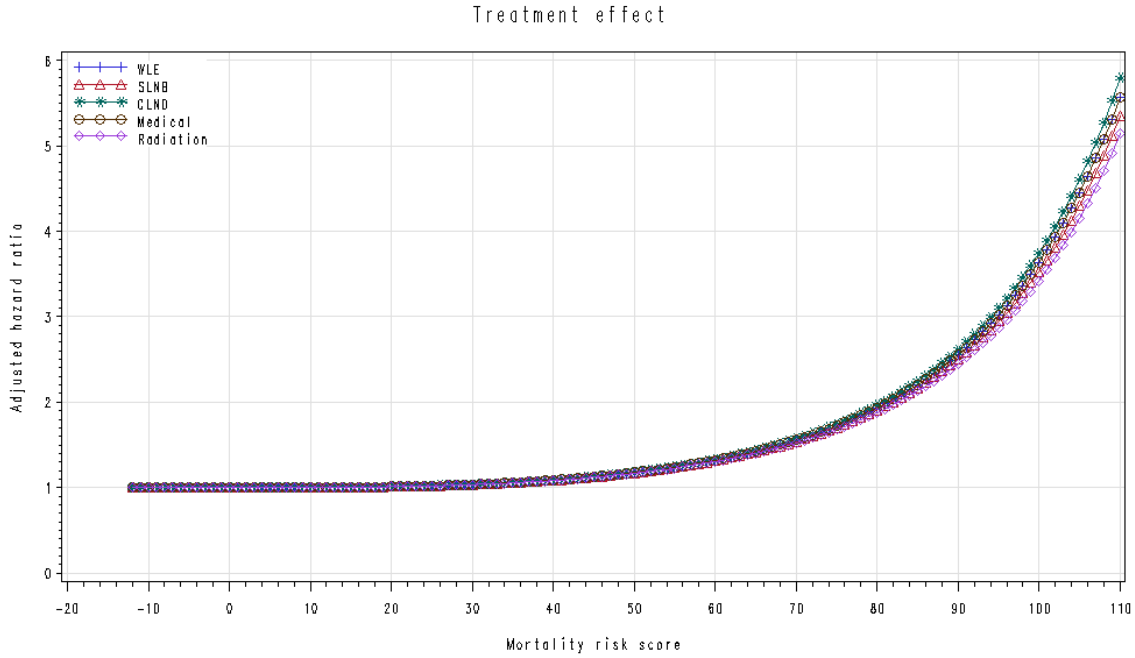
	1.26)		2.10)		1.33)		1.40)		1.10)	
Male sex	1.46 (1.18-1.82)	0.0006	1.61 (0.96-2.67)	0.07	1.47 (1.02-2.12)	0.04	1.34 (0.93-1.92)	0.11	1.27 (0.64-2.52	0.50
Rural residence	0.87 (0.67-1.14)	0.33	1.22 (0.66-2.25)	0.53	0.91 (0.56-1.47)	0.70	0.81 (0.52-1.27)	0.36	0.70 (0.27-1.84)	0.47
Medical therapy										
Medical therapy status, univariate	1.94 (0.98-3.83)	0.06	2.40 (0.16-34.76)	0.52	1.11 (0.24-5.12)	0.89	2.10 (0.67-6.62)	0.20	1.99 (0.65-6.06)	0.22
Medical therapy status, multivariate	2.01 (1.04-3.91)	0.04	3.99 (0.29-54.92)	0.30	1.37 (0.32-5.88)	0.67	1.76 (0.58-5.38)	0.32	2.06 (0.64-6.68)	0.23
Time to medical therapy, univariate	0.86 (0.73-1.02)	0.08	1.06 (0.55-2.04)	0.86	1.02 (0.70-1.49)	0.93	0.82 (0.63-1.06)	0.13	0.89 (0.66-1.20)	0.45
Time to medical therapy, multivariate	0.94 (0.80-1.10)	0.41	1.07 (0.57-2.03)	0.83	1.09 (0.76-1.57)	0.63	0.90 (0.70-1.16)	0.43	0.87 (0.64-1.19)	0.39
Age at diagnosis	1.18 (1.06-1.32)	0.002	1.59 (1.22-2.07)	0.0006	1.19 (1.00-1.43)	0.06	1.18 (0.98-1.42)	0.08	0.80 (0.54-1.17)	0.25
Male sex	1.44 (1.16-1.79)	0.0009	1.65 (0.99-2.76)	0.05	1.40 (0.97-2.01)	0.07	1.35 (0.94-1.92)	0.10	1.25 (0.63-2.47)	0.52
Rural residence	0.89 (0.68-1.17)	0.41	1.21 (0.66-2.24)	0.54	0.97 (0.60-1.56)	0.89	0.83 (0.53-1.30)	0.42	0.72 (0.27-1.92)	0.52
Radiation therapy										
Radiation therapy status, univariate	10.44 (3.90-27.98)	<0.0001	-	-	5.60 (0.33-95.57)	0.23	19.14 (1.90-192.94)	0.01	11.54 (3.34-39.91)	0.0001
Radiation therapy status, multivariate	7.04 (2.42-20.45)	0.0003	-	-	2.36 (0.12-45.72)	0.57	10.69 (0.92-124.84)	0.06	11.35 (3.42-37.69)	<0.0001
Time to radiation therapy, univariate	0.75 (0.59-0.96)	0.02	-	-	1.05 (0.52-2.11)	0.90	0.68 (0.41-1.13)	0.13	0.64 (0.44-0.93)	0.02
Time to radiation therapy, multivariate	0.80 (0.61-1.03)	0.08	-	-	1.17 (0.56-2.43)	0.68	0.76 (0.44-1.30)	0.31	0.66 (0.47-0.95)	0.02
Age at diagnosis	1.14 (1.03-1.27)	0.01	1.55 (1.19-2.02)	0.00	1.12 (0.94-1.34)	0.19	1.19 (1.00-1.42)	0.05	0.79 (0.56-1.13)	0.20
Male sex	1.49 (1.20-1.85)	0.0003	1.61 (0.96-2.68)	0.07	1.45 (1.00-2.09)	0.05	1.21 (0.84-1.75)	0.30	1.43 (0.71-2.89)	0.32
Rural residence	0.88 (0.67-1.15)	0.34	1.15 (0.62-2.12)	0.65	0.96 (0.59-1.55)	0.86	0.85 (0.55-1.33)	0.49	0.92 (0.37-2.32)	0.87

Abbreviations: HR, hazard ratio; CI, confidence interval, WLE, wide local excision; SNB, sentinel lymph node biopsy; LND, lymph node dissection.

Mortality risk score (MRS) was not presented in this table as it was transformed for analysis and thus could not be interpreted as a hazard ratio. MRS hazard ratios are presented graphically in Figure D.3.

D7. Figures for section D

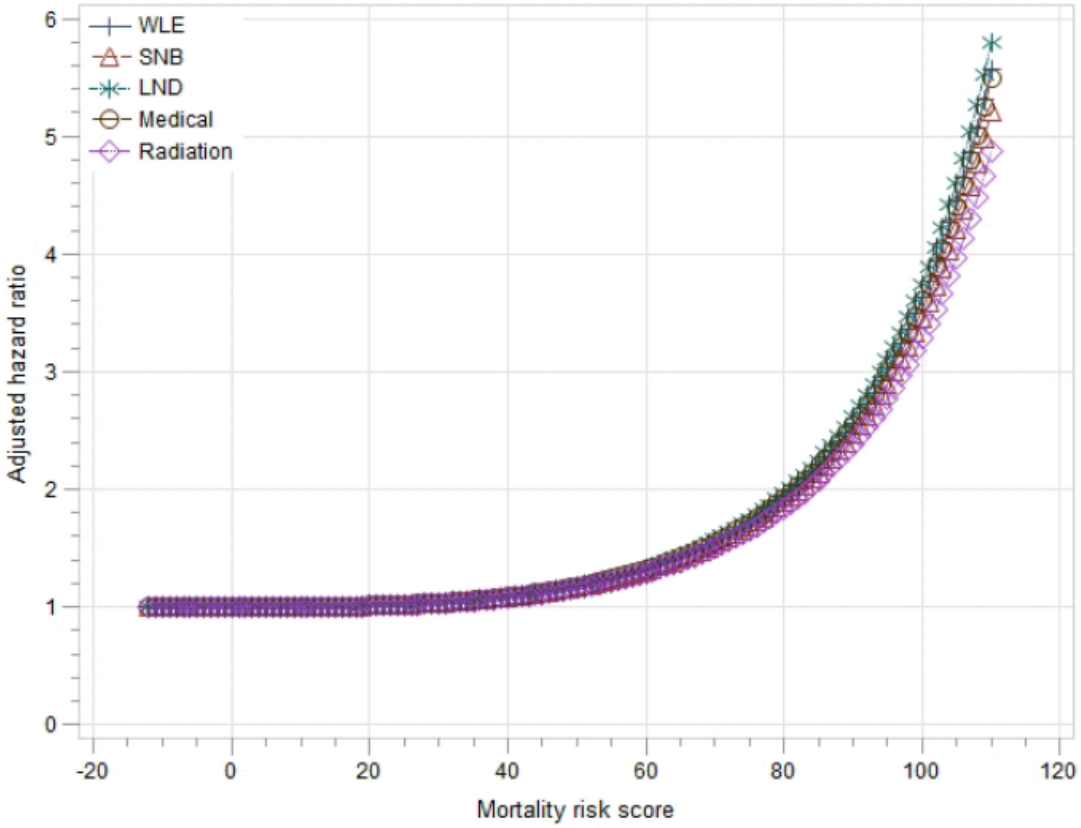
Figure D.1. Adjusted hazard ratios of Mortality Risk Score for its association with survival within each treatment model for the study population.



Abbreviations: HR, hazard ratio; CI, confidence interval, WLE, wide local excision; SLNB, sentinel lymph node biopsy; CLND, lymph node dissection.

Adjusted hazard ratios for Mortality Risk Score for each stage classification were performed and results were almost identical, and are not presented here.

Figure D.2. Adjusted hazard ratios of Mortality Risk Score for its association with survival within the time to treatment model for the study population.



Abbreviations: HR, hazard ratio; CI, confidence interval, WLE, wide local excision; SNB, sentinel lymph node biopsy; LND, lymph node dissection.

Adjusted hazard ratios for Mortality Risk Score for each stage classification were performed and results were almost identical, and are not presented here.

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Appendix A

Table AA.1. Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) staging for melanoma[3].

UICC/ AJCC Stage	TNM Stage			Explanation
0	Tis	N0	M0	In situ melanoma – the melanoma is confined to the epidermis and has not spread to the dermis
IA	T1a	N0	M0	Melanoma is less than 1 mm thick and is not ulcerated. Melanoma has not spread to lymph nodes or distant sites.
IB	T1b or T2a	N0	M0	Melanoma is less than 1 mm thick and is ulcerated, or melanoma is 1.01–2.0 mm thick and is not ulcerated. Melanoma has not spread to lymph nodes or distant sites.
IIA	T2b or T3a	N0	M0	Melanoma is 1.01–2.0 mm thick and is ulcerated, or is 2.01–4.0 mm thick and is not ulcerated. Melanoma has not spread to lymph nodes or distant sites.
IIB	T3b or T4a	N0	M0	Melanoma is 2.01–4.0 mm thick and is ulcerated, or is thicker than 4.0 mm and is not ulcerated. Melanoma has not spread to lymph nodes or distant sites.
IIC	T4b	N0	M0	Melanoma is thicker than 4.0 mm and is ulcerated. Melanoma has not spread to lymph nodes or distant sites.
IIIA	T1a–4a	N1a, N2a	M0	Melanoma is any thickness and is not ulcerated. Melanoma has spread to 1–3 lymph nodes nearby, but spread can only be found by examination under a microscope and the lymph nodes are not enlarged. No distant spread.
IIIB	T1b–4b	N1a, N2a	M0	Melanoma is any thickness and is ulcerated. Melanoma has spread to 1–3 lymph nodes nearby, but spread can only be found by examination under a microscope and the lymph nodes are not enlarged. No distant spread.
	T1a–4a	N1b, N2b	M0	Melanoma is any thickness and is not ulcerated. Melanoma has spread to 1–3 lymph nodes nearby, the lymph nodes are enlarged. No distant spread.
	T1a–4a	N2c	M0	Melanoma is any thickness and is not ulcerated. Melanoma has spread to small areas of nearby skin or lymph vessels in the skin around the tumour. The lymph nodes do not contain melanoma. No distant spread.
IIIC	T1b–4b	N1b	M0	Melanoma is any thickness and is ulcerated. Melanoma has spread to one lymph node nearby and the lymph node is enlarged. No distant spread.
	T1b–4b	N2b	M0	Melanoma is any thickness and is ulcerated. Melanoma has spread to 2–3 lymph nodes nearby and the lymph nodes are enlarged. No distant spread.
	T1b–4b	N2c	M0	Melanoma is any thickness and is ulcerated. Melanoma has spread to small areas of nearby skin or lymph

				vessels in the skin around the tumour. The lymph nodes do not contain melanoma. No distant spread.
	any T	N3	M0	Melanoma is ulcerated. Melanoma has spread to 4 or more lymph nodes nearby or to lymph vessels in the skin around the tumour and any number of lymph nodes, and the lymph nodes are enlarged. No distant spread.
IV	any T	any N	M1	Melanoma has spread beyond the original site to other organs or to distant areas of the skin or distant lymph nodes

Adapted from reference 3.

Table AA.2. Survival rates for cutaneous melanoma TNM and staging categories from the American Joint Committee on Cancer[4].

Pathologic stage	TNM	1-year survival ± SE	5-year survival ± SE	10-year survival ± SE
IA	T1a	99.7 ± 0.1	95.3 ± 0.4	87.9 ± 1.0
IB	T1b	99.8 ± 0.1	90.9 ± 1.0	83.1 ± 1.5
	T2a	99.5 ± 0.1	89.0 ±0.7	79.2 ± 1.1
IIA	T2b	98.2 ± 0.5	77.4 ± 1.7	64.4 ± 2.2
	T3a	98.7 ± 0.3	78.7 ± 1.2	63.8 ± 1.7
IIB	T3b	95.1 ± 0.6	63.0 ± 1.5	50.8 ± 1.7
	T4a	94.8 ± 1.0	67.4 ± 2.4	53.9 ± 3.3
IIC	T4b	89.9 ± 1.0	45.1 ± 1.9	32.3 ± 2.1
IIIA	N1a	95.9 ± 1.3	69.5 ± 3.7	63.0 ± 4.4
	N2a	93.0 ± 2.4	63.3 ± 5.6	56.9 ± 6.8
IIIB	N1a	93.3 ± 1.8	52.8 ± 4.1	37.8 ± 4.8
	N2a	92.0 ± 2.7	49.6 ± 5.7	35.9 ± 7.2
	N1b	88.5 ± 2.9	59.0 ± 4.8	47.7 ± 5.8
	N2b	76.8 ± 4.4	46.3 ± 5.5	39.2 ± 5.8
IIIC	N1b	77.9 ± 4.3	29.0 ± 5.1	24.4 ± 5.3
	N2b	74.3 ± 4.3	24.0 ± 4.4	15.0 ± 3.9
	N3	71.0 ± 2.4	26.7 ±2.5	18.4 ± 2.5
IV	M1a	59.3 ± 3.7	18.8 ± 3.0	15.7 ± 2.9
	M1b	57.0 ± 3.7	6.7 ± 2.0	2.5 ± 1.5
	M1c	40.6 ± 1.8	9.5 ± 1.1	6.0 ± 0.9

Adapted from reference 4.

Figure AA.1. Percent of patients in Ontario with skin cancer seen within provincially set target wait times from referral to systemic treatment consult, and from consult to initiation of systemic treatment[42].

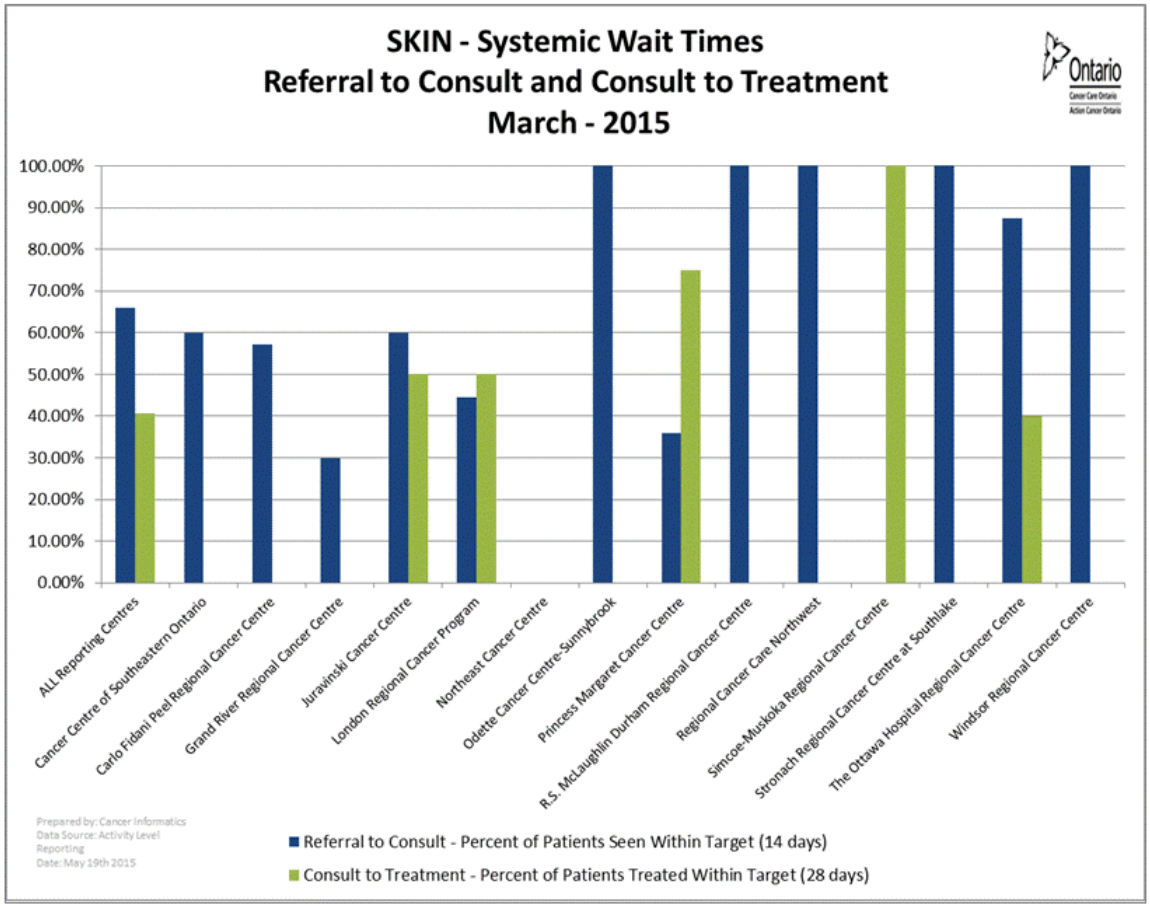


Figure AA.2. Percent of patients in Ontario with skin cancer seen within provincially set target wait times from referral to radiation consult, and from ready to treat to initiation of radiation treatment[43].

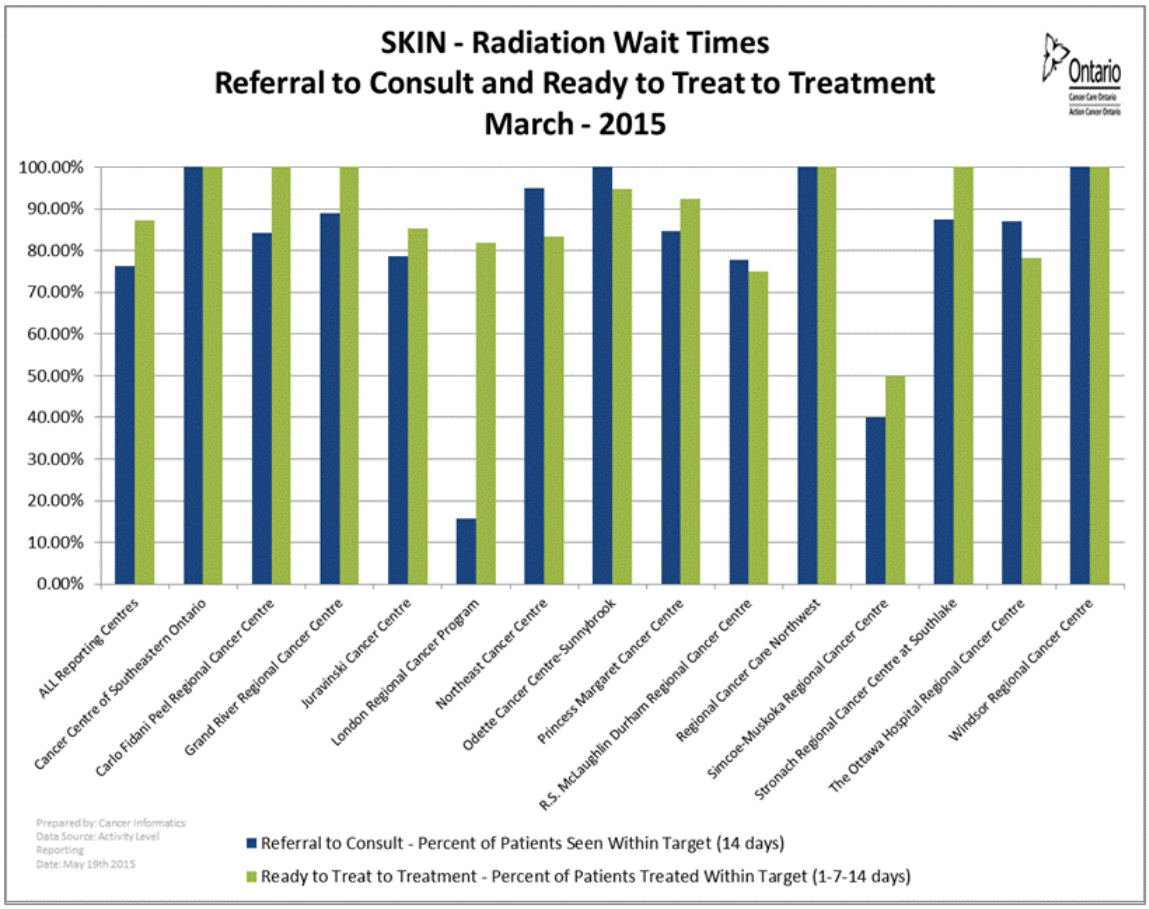
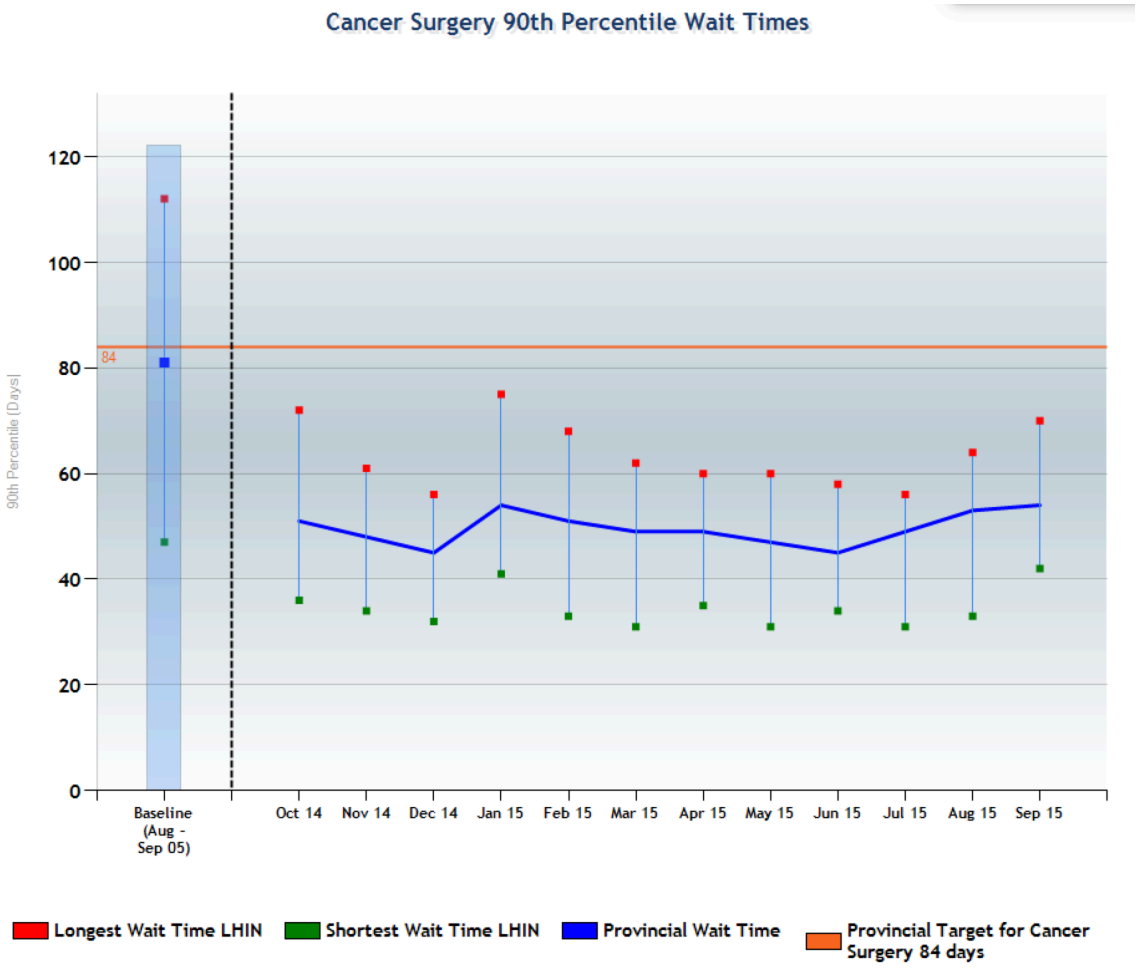


Table AA.3. Cancer Care Ontario (CCO) surgical oncology priority assessment tool and recommended target wait times[44].

		Target wait time (days)	
Priority	**Description**	**Consult to Decision-to-treat**	**Ready-to-treat to Surgery**
1	Patients with known or suspected malignancies requiring emergency surgery for life-threatening conditions	Immediate	Immediate
2	Patients with highly aggressive malignancies	14	14
3	All patients with known or suspected invasive cancer (excluding priorities 1, 2 and 4)	14	28
4	Patients with indolent malignancies	14	84

Adapted from reference 44.

Figure AA.3. Ontario cancer surgery wait time performance trends compared to the baseline cancer surgery wait time prior to the implementation on target wait times[45].



Cancer Surgery	Baseline (Aug – Sep 05)	Oct 14	Nov 14	Dec 14	Jan 15	Feb 15	Mar 15	Apr 15	May 15	Jun 15	Jul 15	Aug 15	Sep 15
Province	81	51	48	45	54	51	49	49	47	45	49	53	54
Longest	112	72	61	56	75	68	62	60	60	58	56	64	70
Shortest	47	36	34	32	41	33	31	35	31	34	31	33	42

Appendix B

Table BB.1. Description and validation of ICES databases used for this thesis.

Name	Description	Validation
Ontario Cancer Registry (OCR)	- information on all Ontario residents who have been newly diagnosed with cancer or who have died of cancer	- validated for use in survival analysis[78] - overall melanoma capture rate of 91% from 1993-2009 when compared to diagnostic laboratory reports[79]
Ontario Heath Insurance Plan (OHIP)	- contains all claims made by physicians for insured services - each record represents a service for a patient, on a specific date	- physician billing claims typically provide accurate records of surgical procedures due to the nature of physician remuneration in Ontario
Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD)	- information abstracted from hospital records - includes patient-level data for acute- and chronic-care hospitals, rehabilitation hospitals, and day surgery clinics - each record corresponds to a single hospitalization	- 95.5% accuracy of interventions is reported as confirmed by chart review[80]
National Ambulatory Care Reporting System (NACRS)	- information on patient visits to hospital and community-based ambulatory care facilities - includes day surgery, outpatient clinic visits, and emergency department visits	- accuracy of CCI codes for interventions is reported at 90.4% for the full code in reabstraction studies[81]
Registered Person Database (RPDB)	- contains demographic information, and captures changes in eligibility for health insurance coverage	- a 2.5% difference in annual death counts was reported when compared to Ontario health planning data (maintained by MOHLTC) in 2003[82]
Collaborative Staging Database (CSTAGE)	- collaborative staging information for records without TNM staging performed at RCCs beginning in 2007 for the four most common cancers (not including melanoma) - for other cancer sites, implementation of collaborative staging began in the 2012 diagnosis year	- timeliness, validity and reliability of collaborative staging data from 2007 and 2008 are considered high quality[83]

Abbreviations: CCI, Canadian Classification of Health Interventions; MOHLTC, Ministry of Health and Long-Term Care; TNM, TNM Classification of Malignant Tumors; RCC, Regional Cancer Centre.

Table BB.2. Descriptions of variables used in this thesis from the ICES databases.

Name	Description	Use
OCR		
Ikn	ICES key number	Link patient data in databases
Valikn	Signifies valid Ikn	Exclude those without valid Ikn
Age	Age at diagnosis	Exclude patients <18 years old Covariate Calculate MRS
Sex	Sex	Covariate Calculate MRS
Bestsource	Type of report	Exclude those without pathology reports
Hist	Histology codes	Select those with melanoma
Dxdate	Date of diagnosis	Time 0 for wait time and time in study determination
Beststage	Cancer stage	Include only those with cancer stage Stratify analysis
N_prim	Number of primaries	Exclude those with more than one primary
CSTAGE		
Derivedajcc7stgrp	Cancer stage	Include only those with cancer stage Stratify analysis
CIHI DAD		
Incode1-20	Intervention codes	Include only those with CCI codes for medical and radiation therapy
Indate1-20	Date of intervention	Determine date of medical and radiation therapy
Dx10code1-25	Diagnosis code	Calculate MRS
NACRS		
Incode1-10	Intervention codes	Include only those with CCI codes for medical and radiation therapy
Regdate	Date of registration	Determine date of medical and radiation therapy
OHIP		
Feecode	Billing code	Include only those with codes for WLE, SNB, LND
Servdate	Date of service	Determine date of surgical treatment
Dxcode	Diagnosis code	Calculate MRS
RPDB		
Dthdate	Date of death	Determine status and time in

		study
Rural	Rural vs urban residence	Covariate

Abbreviations: OCR, Ontario Cancer Registry; CIHI DAD, Canadian Institute for Health Information Discharge Abstract Database; NACRS, National Ambulatory Care Reporting System ; OHIP, Ontario Health Insurance Plan; MRS, Mortality Risk Score; CCI, Canadian Classification of Health Interventions ; WLE, wide local excision; SNB, sentinel lymph node dissection; LND, lymph node dissection; CSTAGE, collaborative staging database.

Appendix C

Example of the SAS code used to run a Cox regression analysis for the univariate model combining treatment effect of a WLE and wait time to WLE treatment (as time dependent covariates) for the whole cohort, controlling for stage.

```
PROC PHREG data = data.analytic;

MODEL time_to_finaldate * status (0) = wle_status wle_time / risk limits ties = efron;

STRATA stage_group;

IF time_to_wle >= time_to_finaldate OR time_to_wle = .

THEN wle_status = 0; ELSE wle_status = 1;

IF time_to_wle >= time_to_finaldate OR time_to_wle = .

THEN wle_time = 0; ELSE wle_time = time_to_wle;

run;
```

Variable descriptions:

time_to_finaldate: time in days from diagnosis to death or censoring

status: dead or censored

wle_status: whether patient received a WLE or not (time-dependent covariate created for this model)

wle_time: the time from diagnosis to treatment (time-dependent covariate created for this model)

stage_group: melanoma stage (I - IV)

time_to_wle: the time from diagnosis to treatment in months (original variable)