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Project Title: Prognostic factors in determining the outcome of head and neck cutaneous melanoma.

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Summary (250 words max single spaced):

Objective: Head and neck melanoma presents a unique problem in terms of complex anatomy and atypical nodal basin drainage, which makes sentinel lymph node biopsy challenging and obtaining wide surgical margins difficult. 25-35% of invasive melanomas are seen in the head and neck region. The purpose of this study was to evaluate prognostic factors determining the oncological outcome of patients with invasive head and neck melanoma.

Methods: Electronic and paper records of a historical cohort of 773 patients with invasive head and neck cutaneous melanoma seen in the province of Manitoba during 1970-2012. Information on tumor stage, margin status, treatment modality, and pathology was collected. Disease free survival (DFS) and disease specific survival (DSS) were calculated by Kaplan Meir method and analyzed by Cox Proportional hazard model for independent variables using SPSS 22.0.

Results: Mean age of the patients at diagnosis was 67.0 + 17.8 years; 49.3% of the patients had Stage I, 26.1% stage II, 9.2% stage III and 3.5% stage IV invasive melanoma. Forty-two patients had sentinel node biopsy, of these 2 had positive nodes. Age of the patient at diagnosis ($p=0.033$), stage of disease ($p<0.001$), and tumour size ($p<0.001$) had significant independent impact on DSS. Margin of resection did not have any significant influence on DSS ($p=0.132$). Margin status had no statistically significant impact on rates of local recurrence ($p=0.100$).

Conclusions: TNM stage, age of diagnosis, and tumour size were independent prognostic factors determining the oncological outcome of invasive melanoma of head and neck region.

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Introduction and Background

Melanoma, a malignancy of melanocytes, is an aggressive and therapy-resistant form of cancer. Melanoma is the cause of 75% of all skin cancer deaths, despite only accounting for 5% of all skin cancers.[1] More than 95% of melanomas are found on the skin, but melanoma is not exclusively a skin cancer. Other sites of melanoma include eyes, mucosa, genitourinary tract, leptomeninges, gastrointestinal tract, and metastatic melanoma to the lymph node, or distant site from unknown primary.[2] Incidence of melanoma has been on the rise over the past several decades in both men and women, with increases of 2.3% per year in men and 2.9% per year in women, between 2001 and 2010.[3] Between 2003-2007 and 2028-2032, there is expected to be a 72% increase in the incidence of melanoma cases.[3] Established risk factors for melanoma include exposure to ultraviolet radiation, fair skinned individuals (particularly redheads), intermittent sun exposure with severe blistering sunburn, dysplastic nevi, personal or family history of melanoma, and immunosuppression.[4] Regarding clinical presentation, approximately half of melanoma is self-discovered, and the remaining either found by medical providers, family members, or others.[5] Most commonly, patients present with colour change or growth of a pre-existing lesion, though other symptoms may include itching, bleeding, ulceration, pain, or paresthesias. More often these other symptoms are a late occurring and found mainly in thick melanoma.[5] The American Cancer Society recommends the ABCDE rule which provides a guideline to detect early warning signs of melanoma where A refers to asymmetry of the lesions, B to border irregularity, C to variegated colour, D to diameter greater than 6mm, and E to evolving (in size, shape, or colour).[6]

Approximately 25-35% of invasive melanomas are seen in the head and neck region.[7] Generally, melanoma develops in areas of highest sun exposure, and in the head and neck region the areas of highest incidence are the face, scalp, neck, and external ear.[8] The majority of head and neck melanomas are seen in patients aged 40-70 years and are rare before the age of 20.[8] Melanoma of the head and neck has four main histological variants, with the occasional rare subtype also reported. Melanoma progresses through an evolutionary sequence from an early lesion, or in situ melanoma (historically called lentigo maligna) through to invasive malignant melanoma.[9] In situ melanoma present as flat, pigmented macules, most often seen in skin with severe solar damage and are confined to the epidermis. Changes such as severe solar elastosis, ectatic vessels, lymphocytic infiltrate, and epidermal atrophy are commonly seen.[9] The in situ melanoma, or lentigo maligna, is accepted to be the in situ precursor to lentigo maligna melanoma, where the dermis has been infiltrated by atypical melanocytes and an invasive component is recognized. The four main subtypes of invasive melanoma are lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma, and acral lentiginous melanoma. Superficial spreading melanoma tends to occur in younger patients than nodular or lentigo maligna melanoma with a median age in the fifth decade, and is the most common subtype. It often presents as a flat, slowly growing lesion with variegated pigmentation that enlarges radially.[10] Nodular melanoma tends to occur in slightly older patients with a median age in the 7th decade of life.[10] Nodular melanoma is considered the most aggressive subtype of invasive melanoma. Clinically, this melanoma subtype presents as a rapidly enlarging nodule that may show ulceration or haemorrhage. The epidermal component in nodular melanoma does not extend beyond the edge of the dermal component.[10] Lentigo maligna melanoma most often occurs in chronically sun-exposed skin, and is therefore particularly common in the head and neck region. It presents as a large, variegated macule with irregular borders in the elderly patient (median age is in the 8th decade of life).[10] As previously mentioned, the accepted precursor lesion is lentigo maligna, or in situ melanoma. Acral lentiginous melanoma involves the acral sites (palms, soles, and subungual regions) and is therefore not seen in head and neck melanoma. Additionally, as technology has advanced in recent years molecular subtypes

of melanoma have been identified which may be amenable to targeting with systemic therapy. Primarily these subtypes involve aberrant activation of the mitogen-activated protein kinase (MAPK) pathway. Mutations in this pathway are found in over 80% of primary melanoma.[10] The four known mutations at this time with the potential to become therapeutic targets are BRAF, GNAQ, CKIT, and NRAS. BRAF in particular has become a popular target because of its high prevalence in melanoma, a molecular structure particularly amenable to blocking agents, and it's lack of activation in normal cells.[10] These systemic therapies still face a number of challenges, resistance and ultimately high incidence of relapse for example, and are in the early stages of development and testing, but they offer the potential for alternative therapies in advanced melanoma, which historically has been extremely treatment resistant.

Biopsy is essential to the diagnosis of melanoma, as well, the results of the biopsy will dictate the definitive management of the malignancy and any further evaluation or metastatic work up that must take place. Ideally, any lesion suspicious for melanoma should be sampled using excisional biopsy, or excision of the lesion in its entirety and down to the subcutaneous fat with 1-2 millimeters of clinically normal tissue around the periphery.[11] This ensures the entire lesion is sampled and an accurate pathological diagnosis can be made with full assessment of the thickness of the lesion, as well as assessment of other prognostic indicators such as ulceration or mitotic index.[11] When excisional biopsy is not possible, either due to the size or location of the lesion, a punch or shave biopsy is acceptable. However, it is important to recognize the potential for diagnostic error, even with careful selection of the biopsy site.[11] Standard treatment for biopsy proven primary cutaneous melanoma is a wide local excision with a safety margin of 1-2cm from the visible primary tumour depending on Breslow tumour thickness within 4-6 weeks of biopsy.[12] Several decades ago it was thought that primary melanoma required a 3-5cm margin of excision. The majority of surgeries required a skin graft to cover the large defect created, and were associated with significant complications such as wound infection or skin graft necrosis.[12] Randomized prospective trails have been conducted in the interim to assess rates of local recurrence, disease-free survival, and overall survival with narrower margins, with no significant difference detected.[12] Currently, the accepted margins of excision are as follows: 0.5cm for a melanoma in situ, 1cm for a melanoma 0.01-2mm thick, 2cm for melanoma 2-4mm thick, and $\geq$2cm for melanoma >4mm thick.[13]

Sentinel lymph node biopsy to assess nodal metastasis is considered in patients with stage IB-II melanoma (0.76-1.00mm thick with ulceration or ≥1 mitosis/mm^2, or >1mm thick with or without ulceration). Sentinel lymph node biopsy can be considered in stage IA melanoma patients with tumour thickness greater than 0.75mm, but for other stage IA melanoma it is controversial if it should be offered, and if it is to be offered which poor prognostic indicators should be an indication.[14] Sentinel node biopsy seems to have no impact on overall survival, but it is an established prognostic indicator. In patients with a negative sentinel node biopsy, no further lymph node surgery is indicated. In patients with a positive node biopsy a radical lymph node dissection is indicated as approximately 5-12% of patients will have involvement in non-sentinel nodes.[15,16] Elective neck dissection, common in earlier decades, is no longer considered as the first line management of invasive cutaneous melanoma as no survival advantage has been described.[16]

Radiotherapy (RT) is rarely indicated in cutaneous melanoma. However, if the primary tumour is not amenable to surgery RT can be used with curative intent. It may also be considered in patients after lymph node dissection to improve local control. RT is also commonly used in palliation, particularly in the case of bone or brain metastasis.[16] Adjuvant immunotherapy with interferon-α has shown a significant improvement in disease-free survival, as well as an impact on overall survival. However, there is significant toxicity associated with interferon and often

patients cannot tolerate it for the full duration of treatment. Studies for targeted adjuvant treatments are currently underway.[16] Regarding treatment of inoperable regional metastasis or distant metastases, systemic therapy is recommended. Few drugs can induce a tumour response, and there is no significant change in overall survival. Studies indicate that new targeted compounds and immunotherapeutic drugs (discussed previously) may prolong survival.[16]

Head and neck melanoma presents a unique problem in terms of complex anatomy and atypical nodal basin drainage, which makes sentinel lymph node biopsy challenging and obtaining wide surgical margins difficult. The purpose of this study is to evaluate surgical margins and other prognostic factors determining the oncological outcome of patients with invasive head and neck melanoma.

Materials and Methods

Study Group

The population-based Manitoba invasive melanoma cohort includes 773 patients diagnosed and registered in the Manitoba cancer registry with invasive head and neck melanoma between January 1, 1970 and December 31, 2012. The Manitoba cancer registry is part of CancerCare Manitoba, which is the sole cancer care centre for the province of Manitoba, serving a population of 1.28 million people. Ethics approval for this study was obtained from the Health Research Ethics Board of the University of Manitoba.

To construct the dataset for the cohort, we reviewed the 505 available electronic and paper charts, as well as 268 pathology reports as stand alone records. Information on patient demographics, disease presentation, tumour stage, margin status, treatment modality, pathological details, recurrence, and final outcome status as of July 1, 2016 was collected. Recurrences were defined as the presence of clinical and/or radiological evidence of disease, with confirmation via biopsy obtained for local or regional relapse. Recurrence within 6 months of treatment was considered as residual disease and a recurrence after 6 months of clinical or radiological absence of disease post-treatment was considered a true recurrence. Patients who migrated out of the province or died during the study period were censored at that point in time. Cause of death was from CancerCare Epidemiology, and was based on autopsy records and death certificates. To confirm the accuracy of this data, individual patient records were reviewed. The AJCC-TNM staging (7^{th} Edition) for melanoma was used to ensure uniformity as the staging has changed over time to incorporate additional prognostic factors such as mitotic index.

Statistical Analysis

To compare group means we used analysis of varianace (ANOVA) and categorical data were compared using the Pearson chi-square test with continuity correction. A p-value <0.05 was the cut-off to indicate statistical significance throughout the analysis and 95% confidence intervals were used to demonstrate the reliability of the estimates. The mean and standard deviation were used to express normally distributed data (such as year or age at diagnosis) after checking for normality assumption. Median with interquartile range was used for nonnormally distributed data (such as histopathologic margin of excision or Breslow thickness).

The data was managed and analysed using SPSS 22.0 (SPSS, IBM Corp., Armonk, NY, USA).

Disease-free survival (DFS) and disease-specific survival (DSS) were calculated by the Kaplan-Meier product-limit method and a log-rank test was used to determine the effect of individual prognostic factors, such as age or stage, on survival. Multivariate analyses with Cox Proportional hazard models were done to determine the impact of individual prognostic factors on DSS in our population based cohort.

Results

Our melanoma cohort included 773 patients with invasive head and neck melanoma with the mean age at diagnosis of 67.0 ± 17.8 years and 454 (58.7%) male patients. There has been an increase in the number of cases of invasive head and neck melanoma diagnosed per year (Figure 1). The incidence of melanoma has steadily increased four-fold from 77 (10.0%) in 1970-1979 to 278 (36.0%) cases in 2000-2009. Between the years 2010-2012 115 (14.9%) cases were diagnosed. This increase in incidence can-not be accounted for just by an increase in the population of Manitoba, which has increased by approximately 22.2% since the 1970's, whereas the provincial incidence of melanoma in Manitoba has increased by approximately 361.0% in the same time period. Three hundred eighty-one (49.3%) patients had Stage I disease, 202 (26.1%) stage II, 68 (9.2%) stage III and 27 (3.5%) stage IV invasive melanoma. Ninety-five (12.3%) patients could not be staged according to current AJCC-TNM staging due to missing components in the pathology report, primarily the Breslow thickness. Histologically, 187 (24.2%) patients had lentigo maligna melanoma, 142 (18.4%) had nodular melanoma, and 204 (26.4%) had superficial spreading melanoma. The remaining 240 (31.0%) cases were either of unspecified type, or one of several uncommon subtypes, such as primary mucosal melanoma. There was one case of Animal Type melanoma, a rare melanoma subtype, within the dataset.

Seven hundred forty-four (96.2%) patients had cutaneous disease while 29 (3.8%) patients had primary mucosal melanoma. High frequency locations for cutaneous melanoma of the head and neck included the cheek with 255 (34.3%) cases, the neck with 131 (17.6%) cases, the ear and external auditory canal with 85 (11.4%) cases, and the scalp with 76 (10.2%) cases. Other locations included the skin of the lip, nose, eyelid, forehead, and jaw, or were of unspecified location. These accounted for 197 (26.5%) cutaneous melanoma cases. The most common site for primary mucosal melanoma was the nasal cavity with 16 (55.2%), followed by the palate and paranasal sinus each with 4 (13.8%) cases. Two hundred thirty-one (29.8%) patients had already had a previous malignancy at the time of diagnosis of their head and neck invasive melanoma. The most common was a non-melanoma skin cancer with 120 (51.9%) cases reported. Twelve patients (1.6%) had had a previous invasive primary melanoma at another site.

Two hundred ninety one patients (37.6%) had a complete or partial metastatic work up done. Full metastatic work up is only indicated in advanced melanoma, which is defined by a deep tumour (>4mm Breslow thickness), node positive, or metastatic at presentation. Within the cohort 118 (15.3%) patients had a tumour thickness >4mm, 66 (8.5%) patients were node positive, and 14 (1.8%) patients had metastatic disease at presentation. Of the 291 patients who had at least a partial metastatic work up 212 had chest x-rays. Of these 4 (1.9%) showed definitive lung metastasis, 3 (1.4%) were indeterminate, and there was 1 (0.5%) case of rib metastasis. The remaining 204 (96.2%) cases showed no evidence of metastasis. One hundred fifty-nine (54.6%) patients underwent a CT scan, of these 4 (2.5%) showed lung metastasis, 11 (6.9%) were indeterminate, 12 (7.5%) had a metastatic node, 5 (3.1%) showed metastasis at multiple sites, there was 1 (0.6%) case of primary lung cancer, and 126 (79.2%) showed no

evidence of metastasis. Fifty-two (17.9%) patients had a bone scan. Five (9.6%) patients showed bone metastasis, 4 (7.7%) were indeterminate, and 43 (82.7%) patients had no evidence of metastasis. Nineteen (6.5%) patients had PET scans, of these 3 (15.8%) showed lung metastasis, 3 (15.8%) were indeterminate, 2 (10.5%) showed a metastatic node, 2 (10.5%) showed metastasis at multiple sites, and 9 (47.4%) showed no evidence of metastasis.

Three hundred seventy-nine (49.0%) patients had a tumour $\leq$1.0 cm in greatest diameter, 214 (27.7%) patients had a tumour 1.01-2.0 cm, 64 (8.3%) patients had a tumour 2.01-3.0 cm, 22 (2.8%) patients had a tumour 3.01-4.0 cm, 11 (1.4%) patients had a tumour 4.01-5.0cm, and 7 (0.9%) patients had a tumour greater than 5cm in greatest diameter. Seventy-five (9.7%) patients had a primary tumour of unstated size, and one (0.1%) patient had no tumour found. Ten (1.3%) patients had a multicentric primary tumour. After primary surgical management, 266 (34.4%) patients had a Breslow thickness less than 1mm, 148 (19.1%) between 1.01 and 2mm, 62 (8.0%) between 2.01 and 3mm, 53 (6.9%) between 3.01 and 4mm, 108 (14.0%) greater than 4mm, and 136 (17.6%) had no stated Breslow thickness. Regarding Clark's level, 194 (25.1%) patients were Clark's level II, 116 (15.0%) Clark's level III, 238 (30.8%) Clark's level IV, 84 (10.9%) Clark' s level V, and 141 (18.2%) were of unspecified Clark's level. One hundred sixty-nine (21.9%) patients had ulcerated tumours, 521 (67.4%) were not ulcerated, and 83 (10.7%) were of unknown ulceration status. Three hundred forty-one (44.1%) patients had a tumour with defined mitotic index; 181 (53.1%) had a mitotic index of <1/mm^2 and 160 (46.9%) had an index of >1/mm^2. Thirty-two (4.1%) patients had microsatellitosis, and 17 (2.2%) had definitive lymphovascular invasion.

Of the patients who underwent surgical management 655 (84.7%) patients had tumour free margins, of these 49 (7.5%) were free but close within 1mm. There were 61 (7.8%) cases with involved margins, of these 5 (8.2%) were involved only focally. Post–surgical margin status was unknown in the remaining 57 (7.3%). Twenty-three (3.0%) patients received adjuvant radiation treatment and 11 (1.4%) received palliative radiation. Thirty-three (4.3%) patients received adjuvant chemotherapy and 2 (0.3%) patients received palliative chemotherapy. On follow up 213 (27.6%) patients had a recurrence and of those that recurred 57 (26.8%) were local recurrences, 58 (27.2%) regional lymph node recurrence, 75 (35.2%) had distant metastasis, and 23 (10.8%) had a combination of the above mentioned.

Age of the patient at diagnosis ($p=0.033$), as well as overall staging, which encompasses lymph node involvement ($p=<0.001$), particularly stage N2c, satellite or in-transit metastasis without metastatic lymph nodes, ($p<0.001$) or N3, metastasis to four or more lymph nodes, matted lymph nodes, or in-transit metastasis or satellite(s) with metastatic lymph nodes, ($p<0.001$), and distant metastasis ($p<0.001$) had significant independent impact on disease specific survival (DSS). Tumour size was also found to have a significant impact on DSS ($p<0.001$). Histopathologic margin distance had no impact on DSS ($p=0.207$). Primary mucosal melanoma had a significantly lower DSS than cutaneous melanoma ($p<0.001$) (Figure 2, Table 1), consequently they are staged differently (it can only be stage III or IV) and has a significantly different prognosis than cutaneous melanoma. For this reason, we chose to focus solely on cutaneous melanoma for the remainder of the analysis.

Cutaneous Head and Neck Melanoma

In the analysis of 744 patients with invasive cutaneous head and neck melanoma, the mean age at diagnosis was 66.9 $\pm$ 17.9 years and 438 (58.9%) patients were male. These demographics are similar to those mentioned in the above section inclusive of mucosal melanoma. The new

patient characteristics and frequencies for staging, histologic type, and last follow up status exclusive of mucosal melanoma cases can be found in Table 2.

Three hundred seventy-eight (50.8%) patients had a tumour $\leq$1.0 cm in greatest diameter, 211 (28.4%) patients had a tumour 1.01-2.0 cm, 59 (7.9%) patients had a tumour 2.01-3.0 cm, 17 (2.3%) patients had a tumour 3.01-4.0 cm, 8 (1.1%) patients had a tumour 4.01-5.0cm, and 4 (0.5%) patients had a tumour greater than 5cm in greatest diameter. Sixty-six (8.9%) patients had a primary tumour of unstated size, and one (0.1%) patient had no tumour found. Ten (1.3%) patients had a multicentric primary tumour. After primary surgical management, 266 (35.8%) patients had a Breslow thickness less than 1mm, 148 (19.9%) between 1.01 and 2mm, 61 (8.2%) between 2.01 and 3mm, 51 (6.9%) between 3.01 and 4mm, 106 (14.2%) greater than 4mm, and 112 (15.1%) were of unknown Breslow thickness. Regarding Clark's level, 194 (26.1%) patients were Clark's level II, 116 (15.6%) Clark's level III, 237 (31.9%) Clark's level IV, 84 (11.3%) Clark' s level V, and 113 (15.2%) were of unspecified Clark's level. One hundred fifty-six (21.0%) patients had ulcerated tumours, 518 (69.6%) were not ulcerated, and 70 (9.4%) were of unknown ulceration status. Three hundred thirty-five (45.0%) patients had a tumour with defined mitotic index; of these 179 (53.4%) had a mitotic index of <1/mm^2 and 156 (46.6%) had an index of >1/mm^2. Twenty-nine (3.9%) of patients had microsatellitosis, and 16 (2.2%) had definitive lymphovascular invasion.

Of the patients who underwent surgical management 645 (86.7%) patients had tumour free margins, of these 48 (7.4%) were free but close within 1mm. There were 48 (6.4%) cases with involved margins, of these 4 (8.3%) were involved only focally. Fourteen (1.9%) patients received adjuvant radiation treatment and 3 (0.4%) received palliative radiation. Thirty (4.0%) patients received adjuvant chemotherapy and 2 (0.3%) patients received palliative chemotherapy. One hundred ninety (25.5%) patients had a recurrence on follow up and of those that recurred 49 (25.8%) were local recurrences, 53 (27.9%) regional lymph node recurrence, 68 (35.8%) had distant metastasis, and 20 (10.4%) had a combination of the above mentioned.

Age of the patient at diagnosis ($p=0.033$), as well as overall staging, which encompasses lymph node involvement ($p\leq0.001$), primary tumour ($p<0.001$) and distant metastasis ($p\leq0.001$) in particular had significant independent impact on DSS. Tumour size was also found to have a significant impact on DSS ($p\leq0.001$) (Table 2). DSS at five years was 83.6% and at ten years was 79.8%. DSS at 10 years differentiated by stage is as follows: Stage 1 91.8%, Stage 2 62.8%, Stage 3 48.5%, and Stage 4 16.7% (Figure 2 and 3) Recurrence was found to have a significant impact on last follow up status for the patient ($p<0.001$). Last follow up status included no evidence of disease, alive with disease, dead of disease, or dead of other causes, dead of specified second primary tumour, or dead of unknown cause. Whether the melanoma was completely or incompletely resected significantly impacted overall recurrence rates ($p=0.007$). Margin status, either free, free but close within 1mm, involved, or involved with focal extension to the margin, had no significant impact on local disease recurrence in particular ($p=0.1$). Histopathologic margin distance had no impact on DSS ($p=0.132$).

Intermediate Cutaneous Head and Neck Melanoma

In the subset analysis of 240 patients with invasive cutaneous head and neck melanoma of intermediate thickness (Breslow thickness 0.76-4mm) or aggressive stage T1b (thickness less than 1mm but with ulceration or mitoses greater than or equal to 1/mm^2), the mean age at diagnosis was 70.0 $\pm$ 17.0 years and 144 (60.0%) of patients were male. One hundred twenty-six (52.5%) patients had stage IB disease, 69 (28.7%) stage IIA, 42 (17.5%) stage IIB and 3

(1.3%) stage IV invasive melanoma. Histologically, 54 (22.5%) patients had lentigo maligna melanoma, 67 (27.9%) had nodular melanoma, and 59 (24.6%) had superficial spreading melanoma. The remaining 60 (25.0%) cases were either of unspecified type, or one of several uncommon subtypes. At last follow up, current as of July 1, 2016, 90 (37.5%) patients had no evidence of disease, 4 (1.7%) were alive with disease, 44 (18.3%) were dead of disease, 15 (6.3%) were dead of other causes, 27 (11.3%) were dead of a second primary tumour, and 60 (25.0%) of patients were dead of unknown causes.

High frequency locations for the intermediate cutaneous melanoma of the head and neck included the cheek with 94 (39.2%) cases, the neck with 44 (18.3%) cases, the ear and external auditory canal with 26 (10.8%) cases, and the scalp with 22 (9.2%) cases. Other locations included the skin of the lip, nose, eyelid, forehead, and jaw, or were of unspecified location. These accounted for 54 (22.5%) cases. Seventy patients had already had a previous malignancy at the time of diagnosis of their intermediate head and neck invasive melanoma. The most common was a non-melanoma skin cancer with 41 (54.7%) cases reported.

One hundred thirty-eight (57.5%) patients had a tumour $\leq$1.0 cm in greatest diameter, 75 (31.3%) patients had a tumour 1.01-2.0 cm, 13 (5.4%) patients had a tumour 2.01-3.0 cm, 2 (0.8%) patients had a tumour 3.01-4.0 cm, and 2 (0.8%) patients had a tumour 4.01-5.0cm. Ten (4.2%) patients had a primary tumour of unstated size. Three (1.3%) patients had a multicentric primary tumour. After primary surgical management, 17 (7.1%) patients had a Breslow thickness less than 1mm, 133 (55.7%) between 1.01 and 2mm, 49 (20.5%) between 2.01 and 3mm, 40 (16.7%) between 3.01 and 4mm, and 1 (0.4%) of unknown Breslow thickness. Regarding Clark's level, 13 (5.4%) patients were Clark's level II, 45 (18.8%) Clark's level III, 144 (60.0%) Clark's level IV, 19 (7.9%) Clark' s level V, and 19 (7.9%) were of unspecified Clark's level. Seventy-six (31.7%) patients had ulcerated tumours, 160 (66.7%) were not ulcerated, and 4 (1.7%) were of unknown ulceration status. One hundred thirty-four (55.8%) patients had a tumour with defined mitotic index; of these 55 (41.0%) had a mitotic index of <1/mm^2 and 79 (59.0%) had an index of >1/mm^2. Two (0.8%) patients had microsatellitosis, and 4 (1.7%) had definitive lymphovascular invasion.

Of the patients who underwent surgical management 224 (93.3%) patients had tumour free margins, of these 12 (5.3%) were free but close within 1mm. There were 12 (5.0%) cases with involved margins, of these 2 (16.7%) were involved only focally. The remaining 4 (1.7%) were of unknown margin status post surgical management. In 187 (77.9%) patients the neck was not addressed, 40 (16.7%) patients had only a sentinel node biopsy, 11 (4.6%) patients had a full lateral neck dissection and parotidectomy, either electively or following a positive sentinel node biopsy, and 2 (0.8%) patients had a modified neck dissection. One (0.4%) patient received adjuvant radiation treatment at first presentation. Nine (3.8%) patients received adjuvant chemotherapy. Sixty-nine (28.7%) patients had a recurrence on follow up and of those that recurred 19 (27.5%) were local recurrences, 21 (30.4%) had regional lymph node recurrence, 21 (30.4%) had distant metastasis, and 8 (11.6%) had a combination of the above mentioned.

Disease specific survival at 10 years with no neck management was 76.1%, and 86.5% with sentinel node biopsy. Sentinel lymph node biopsy had no significant impact on DSS when compared to no neck management (p=0.173) (Figure 4). Of the 42 (17.5%) patients who had a sentinel lymph node biopsy only 2 (4.8%) patients had involved sentinel nodes. Sentinel node involvement had no significant impact on recurrence of disease (p=0.495), whether local, regional, or distant.

Discussion

The definitive treatment for invasive melanoma is wide local excision, with the intention of encompassing local invasion and micrometastatic disease that may be in the near vicinity of the primary tumour.[17] As previously stated, 1cm margins are recommended for a melanoma 0.01-2mm thick, 2cm for melanoma 2-4mm thick, and ≥2cm for melanoma >4mm thick. In head and neck melanoma this can present a unique problem as the surgeon must strike a balance between complete excision of the tumour along with its microscopic extension so as to reduce the local recurrence rates, while also ensuring the optimal cosmetic result for the patient. The risk of metastatic spread in melanoma is predicted by several prognostic indicators, such as Breslow thickness, mitotic index, and tumour ulceration.[17] There has been no definitive study to demonstrate how or if the margin distance around the primary tumour affects metastatic spread of the disease. It should be noted that these studies primarily assessed the historically larger margins of 5cm or 3cm versus the currently accepted margins of either 1cm or 2cm as per Breslow thickness.[17–19] Local recurrences do not appear to have a substantial effect on survival, although there is still some uncertainty around this with reports suggesting a significant impact.[19–21] In a study by McKinnon et al., it was shown that histopathologic margins affected the rate of local recurrence, however with an in vivo margin ≥1cm, margin distance no longer predicted local recurrence.[21] This suggests that close margins increase local recurrence, whereas margins greater than 1cm contribute a non-significant risk to local recurrence. In our study, overall disease recurrence had a statistically significant negative impact on patient DSS. Local recurrence was predicted by margins status, whether free or involved after definitive surgical management, however when stratified into more the specific margin status categories of free, free but close within 1mm, focally involved, or involved after surgical management, the impact on local disease recurrence was no longer statistically significant. In our study, age and Breslow thickness, or T stage, were found to be prognostic indicators with a negative independent impact on DSS. This is consistent with the literature consensus on prognostic indicators for invasive melanoma, and contributes to validation of the dataset.[22] According to our findings, histopathologic margin distance had no impact on DSS at any T stage, which is consistent with the recent similar retrospective study done on cutaneous head and neck melanoma by Teng et al.[22]

Sentinel lymph node dissection (SLND) was introduced in 1992 by Morton et al as an alternative to elective lymph node dissection (ELND) in patients with intermediate thickness (1-4mm) or aggressive stage I invasive melanoma.[23,24] There was significant morbidity associated with ELND, including injury to the facial and spinal accessory nerves, chylous fistula, skin flap necrosis, and cosmetic or functional defects.[24] There was no survival benefit demonstrated for patients who underwent ELND versus clinical observation, though these studies were done on melanoma at all sites and not head and neck melanoma specifically.[25–27] Sentinel lymph node dissection or biopsy is used to assess nodal involvement, and if positive the patient may continue on to a complete lymph node dissection either unilaterally or bilaterally, depending on the location of the sentinel node(s), which in head and neck melanoma can be unilateral, contralateral, or bilateral. In head and neck melanoma, sentinel lymph node biopsy has several unique challenges not associated with other parts of the body. Lymphoscintigraphy to locate the sentinel node can be limited due to the close proximity of nodal basins to the primary lesion, making it difficult to distinguish the lymph nodes from the lesion because of the background signal from the site of radioactive injection, and also because the distance between the lesion and nodal basin is often small. Additionally, it is not uncommon for the tracer to diffuse quickly from sentinel node to non-sentinel node. Finally, lymph nodes less amenable to biopsy are more common in the head and neck region, for example parotid lymph nodes.[28,29] In our study, we found that sentinel node involvement had no impact on recurrence of disease. In a systematic

review of sentinel node biopsy for head and neck melanoma the opposite was found to be true, with a positive sentinel node status highly predictive of recurrence.[29] Sentinel lymph node dissection is an important prognostic indicator for patients but has no impact on DSS.[30] This is consistent with our data, which showed that SLND did not impact DSS. As well, in our study sentinel lymph node status (either positive or negative) did not appear to significantly impact DSS. However, in a study by Mays et al., sentinel lymph node status was a significant predictor of disease free survival (DFS) as well as overall survival.[31] This discrepancy could be due to the relatively few patients (5%) that had a positive SLND in our study.

Few invasive melanoma studies in the literature have examined the effect of margin distance on DSS survival, particularly across the full range of T stage or Breslow thickness. Many studies look at either melanoma with a thickness of less than or greater than 2mm, but not the entire range. This also applies to studies looking at the effect of margin distance on local recurrence, and the further effect local recurrence has on survival. Our study it is unique in terms of its duration. The study ranges from January 1, 1970 and December 31, 2012, which spans many decades with significant changes in invasive melanoma incidence and treatment modalities. The overall patient follow up was good unless they moved out of the province.

Our study is limited by its retrospective nature; the information available is from the chart, electronic record, or pathology report. In cases where the only record was a single pathology report, patient information and disease course preceding and following surgical management might be missing, which may have some impact on the thoroughness of that particular record as compared to a record with a full chart, inclusive of physician notes, lab reports, surgical notes, and so forth. Additionally, in some cases, only a report of biopsy was available, and definitive management was carried out either with the family physician or plastic surgery and the pathology was unavailable in the CancerCare Manitoba records, giving an incomplete picture of surgical management, and possibly recurrence records as well if the patient was never referred back to CancerCare, even though Manitoba Cancer Registry is linked to the Manitoba Health data base for surgical procedures. Additionally, over time patients are lost to follow up for various reasons such as moving province, and therefore may have incomplete record of surgical management, recurrence, or cause of death. The study is also limited by its forty-year span. Pathological reporting and analysis, staging, and management have all changed significantly over the last 40 years. In the 1970's, tumour thickness as a guide to surgical management and treatment was not yet accepted practice and there was greater reliance on Clark's level. Over time, Breslow thickness was shown to be the more consistent prognostic indicator of the two, though Clark's level is still and important indicator, particularly Clark level V, or invasion of the subcutaneous fat.[32] As a result of this shift, many of the reports for the 1970's have a reported Clark level, but not a quantitatively measured Breslow thickness, and therefore can-not be staged according to current AJCC-TNM staging which relies heavily on Breslow thickness. Other proven prognostic indicators that were less well known, and therefore underreported, in the 1970's and 1980's included lymphovascular invasion, microstallitosis, and mitotic index per millimeter squared. Additionally, less emphasis was placed on histopathological margin distance of excision in millimeters and many pathology reports stated that tumour was "widely clear" of the margin without a quantitative measurement. This limited our analysis in that there was insufficient data to stratify margin beyond free, close within one millimeter, focally involved, or involved.

In our retrospective analysis of 773 patients were diagnosed with invasive head and neck melanoma from January 1, 1970 and December 31, 2012, we found that incidence of disease was increasing over time consistent with statistics released by the Canadian Cancer Society in 2015. We found that patient age at diagnosis, tumour thickness or T stage, lymph node

involvement, distant metastasis, and tumour size were significant prognostic factors for DSS. Margin of excision and sentinel lymph node biopsy had no impact on DSS. We found that margin status had no statistically significant impact on rates of local recurrence. Positive sentinel node status was shown to not be a predictor of recurrence or impact survival, although the consensus in the literature disputes this. This discrepancy may be accounted for by small sample size. In the future, a study inclusive of in situ melanoma in the province, which is currently underway, may display progression trends from in situ to invasive melanoma.

Figures and Tables

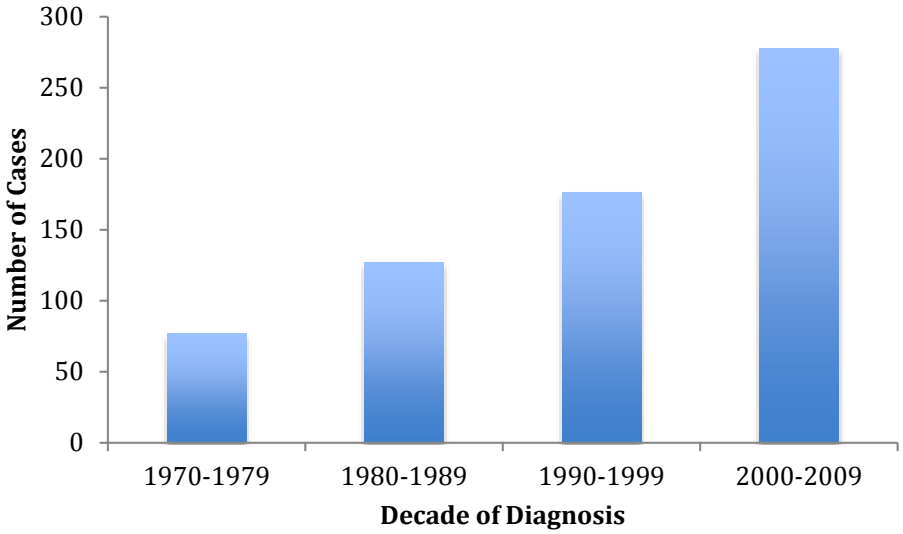

Figure 1. Cases of invasive head and neck melanoma diagnosed per year between the years 1970-2009.

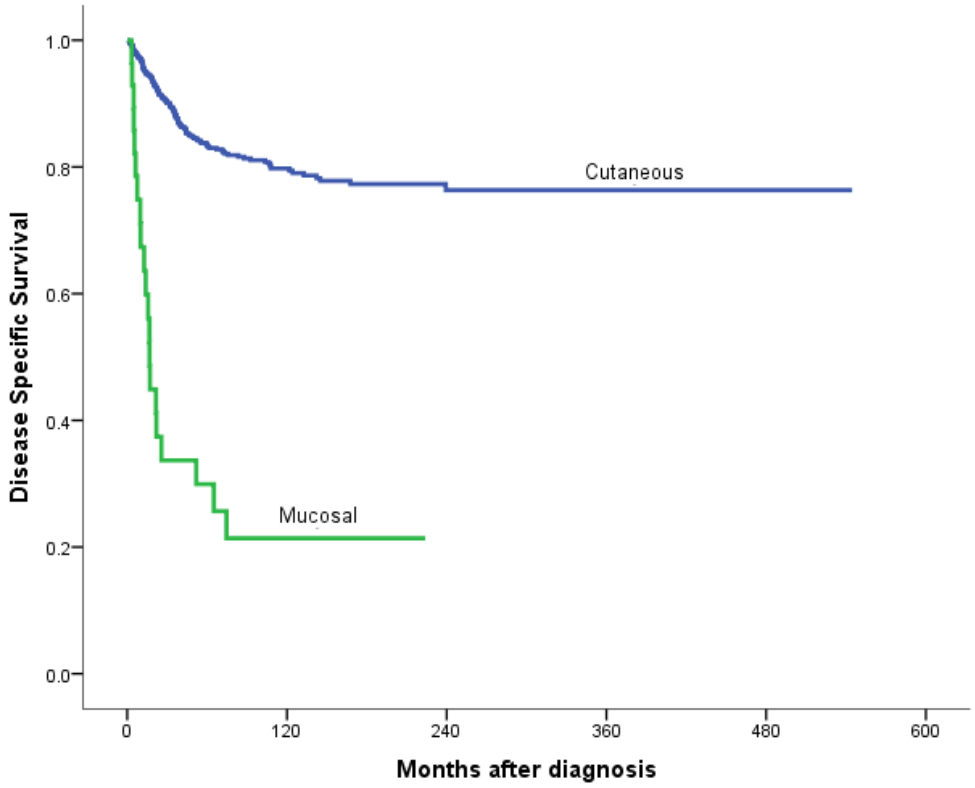

Figure 2: Disease-specific survival of cutaneous versus mucosal invasive head and neck melanoma in the Manitoba melanoma cancer cohort.

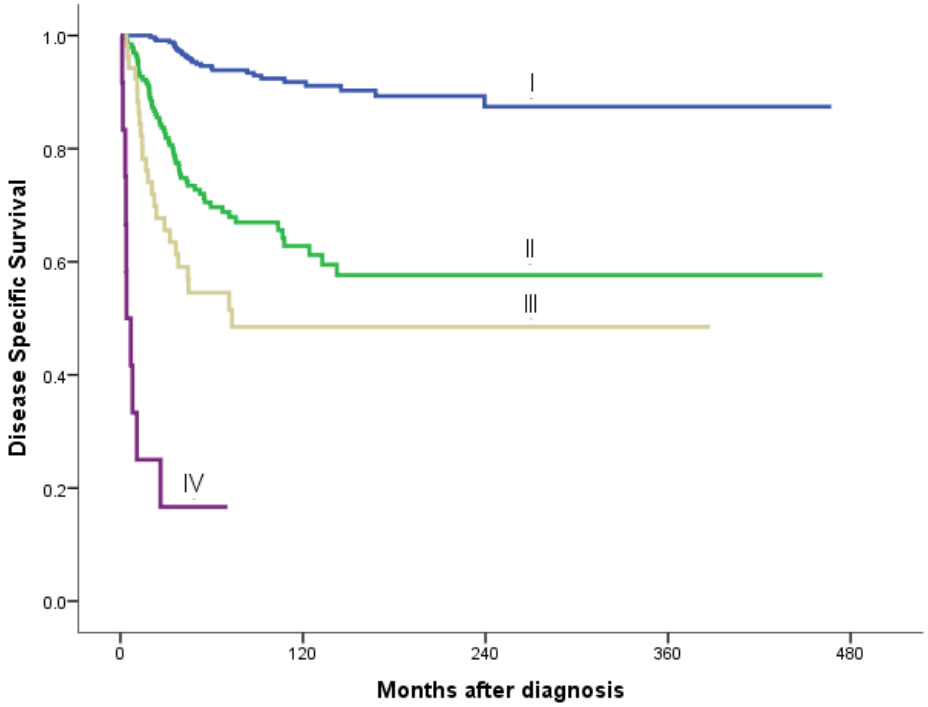

Figure 3: Disease-specific survival of cutaneous invasive head and neck melanoma in the Manitoba melanoma cancer cohort stratified by TNM stage.

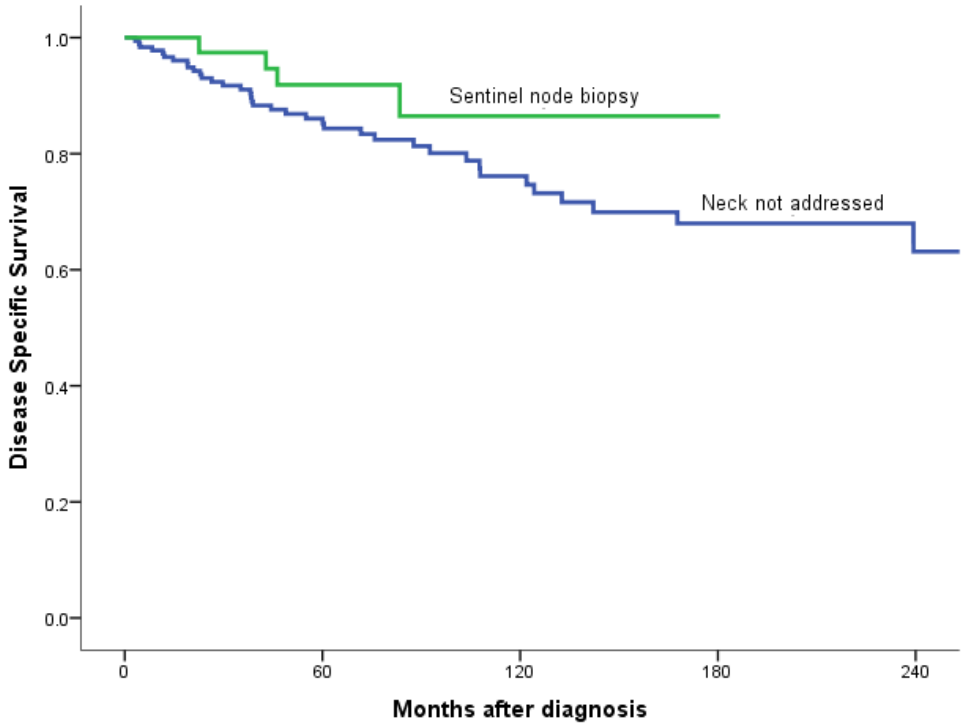

Figure 4: Disease-specific survival of intermediate cutaneous invasive head and neck melanoma in the Manitoba melanoma cancer cohort stratified by neck management.

Table 1. Multivariable analysis by Cox proportional hazard model for independent influence of prognostic factors on disease-specific survival of invasive head and neck melanoma.

Prognostic Factor	**Hazard Ratio (95% CI)**
Age at Diagnosis	1.02 (1.001-1.029), p=0.033
Tumour Size	1.04 (1.019-1.058), p<0.001
Mucosal vs Cutaneous disease	16.80 (14.536-19.060), p<0.001
LN involvement (N stage)	
N1a vs N0	0.00 (0.000-2.515E+237), p=0.969
N1b vs N0	0.90 (0.188-14.511), p=0.896
N2a vs N0	3.50 (0.846-18.992), p=0.084
N2c vs N0	4.95 (2.201-11.115), p<0.001
N3 vs N0	8.72 (3.840-19.793), p<0.001
Distant Metastasis (M + vs M0)	12.55 (5.43-31.213), p<0.001
Gender	p=0.293 (NS)
Margin of Excision	p=0.207 (NS)

Table 2. Patient characteristics of invasive cutaneous head and neck melanoma patients (N=744)

Patient Characteristic	**Number of Cases (%)**
Stage	
I	381 (51.2%
II	202 (27.2%)
III	56 (7.5%)
IV	12 (1.6%)
Cannot stage	93 (12.5)
Histologic Type	
Lentigo maligna melanoma	187 (25.1%)
Nodular	142 (19.1%)
Superficial spreading	203 (27.3%)
Other or unspecified	212 (28.5%)

Last Follow Up Status	
No evidence of disease	318 (42.7%)
Alive with disease	16 (2.2%)
Dead of disease	127 (17.1%)
Dead of other causes	51 (6.9%)
Dead of 2nd primary	93 (12.5%)
Dead of unknown cause	139 (18.7%)

Table 3. Multivariable analysis by Cox proportional hazard model for independent influence of prognostic factors on disease-specific survival of cutaneous invasive head and neck melanoma.

Prognostic Factor	**Hazard Ratio (95% CI)**
Age at Diagnosis	1.02 (1.001-1.029), p=0.033
Tumour Size	1.039 (1.019-1.058), p<0.001
Primary Tumour (T stage)	
T2 vs T1	4.866 (2.149-11.449), p<0.001
T3 vs T1	5.882 (2.554-13.775), p<0.001
T4 vs T1	17.76 (8.044-39.856), p<0.001
LN involvement (N stage)	
N1 vs N0	0.61 (0.138-2.737), p=0.522
N2 vs N0	4.49 (2.177-9.260), p<0.001
N3 vs N0	8.32 (3.640-18.992), p<0.001
Distant Metastasis (M + vs M0)	13.47 (5.567-32.601), p<0.001
Gender	p=0.238 (NS)
Margin of Excision	p=0.132 (NS)

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