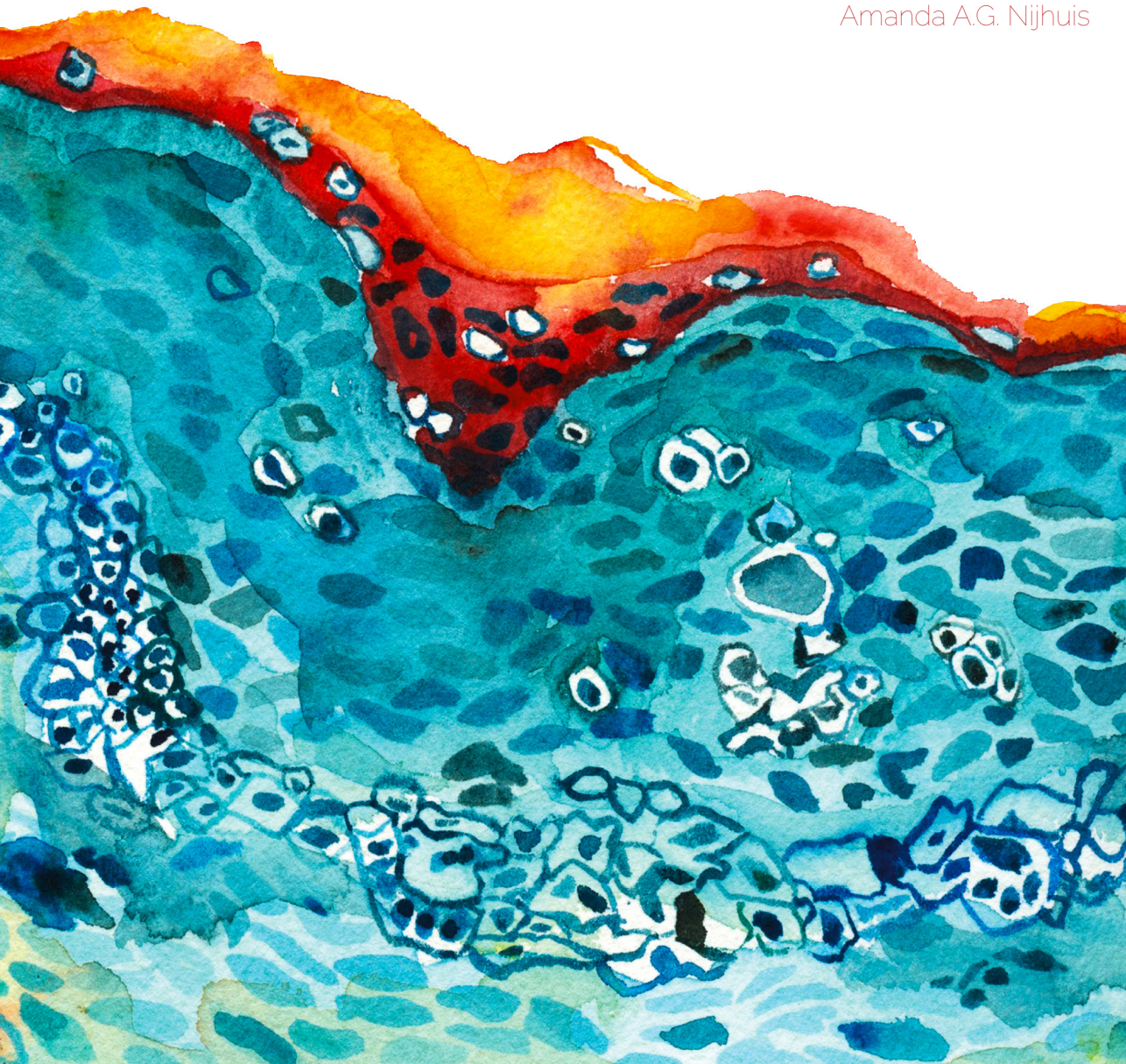
High-risk melanoma patients

identification, surgical management and follow-up

Amanda A.G. Nijhuis



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High-risk melanoma patients identification, surgical management and follow-up

Patiënten met een hoog risico melanoom identificatie, chirurgische behandeling en follow-up

(met een samenvatting in het Nederlands)

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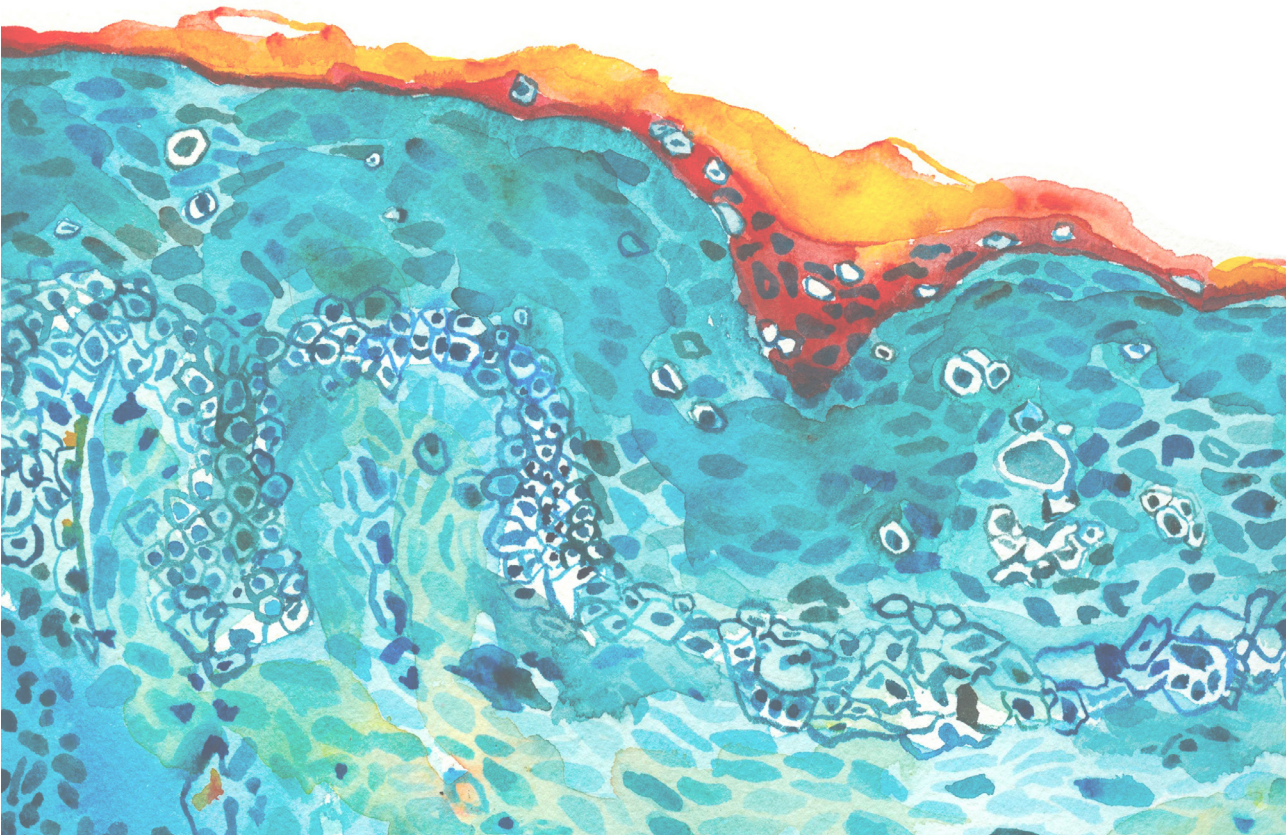
Those who lose dreaming are lost

- Australian aboriginal proverb

Contents

Chapter 1

Introduction



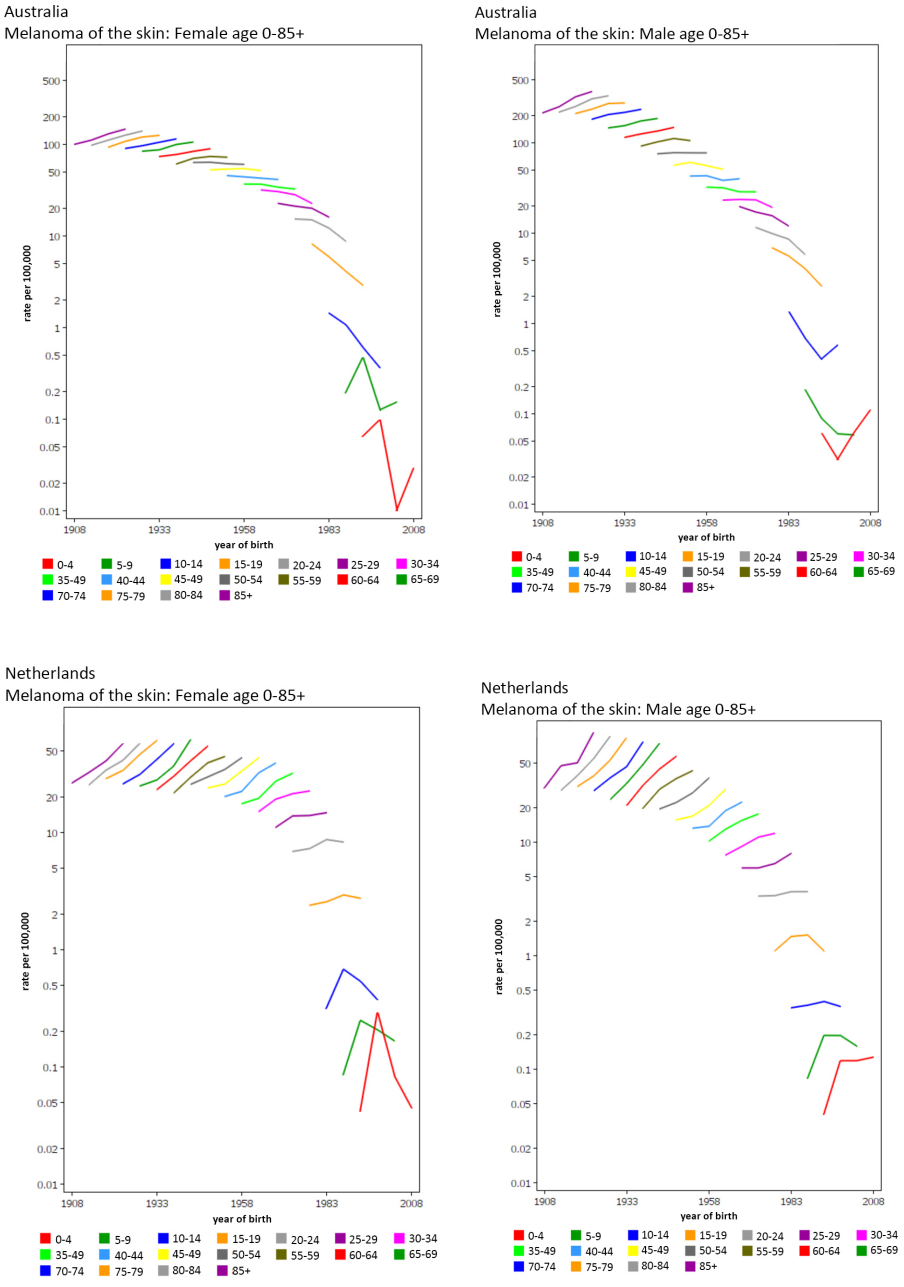
Epidemiology and etiology

The incidence of melanoma is on the rise. In 2015, this aggressive form of skin cancer was diagnosed in more than 350,000 people worldwide and led to the death of almost 60,000 patients.[1] In the Netherlands, the incidence of melanoma has increased yearly by five percent since 1980, with an increase in mortality as well.[2] In 2017, 6700 new melanoma patients were diagnosed and almost 800 people died of the disease.[2,3] Australia and New-Zealand have the highest incidence of melanoma.[4] The risk of having been diagnosed with invasive melanoma by the age of 85 is 1 in 13 for Australian men and 1 in 22 for Australian women.[5,6] This high incidence is attributed to the combination of strong ambient UV radiation, lifestyle and fair skin of the non-original inhabitants, who often have Keltic ancestry.[7] However, unlike the rest of the world, the incidence of melanoma in Australia has been stabilizing over the last few years. In younger birth cohorts, the incidence is even decreasing (figure 1.1).[8] This is thought to result from the proactive role of the Australian government in the prevention of melanoma through public awareness and skin protection campaigns.[9] Examples are the 'Slip! Slop! Slap!' campaign (Slip on a shirt, Slop on the 50+ sunscreen, Slap on a hat), the legal ban of commercial tanning services in all states and territories and the national SunSmart skin cancer prevention program.[10–12]

Diagnosis, staging and treatment

Melanoma patients typically present with a pigmented skin lesion that is changing in appearance.[13] The diagnosis is established by pathology evaluation after a shave, punch or excision biopsy of the lesion. Most patients have a localized melanoma. The standard treatment for these cutaneous lesions is (re-)excision with a 1 to 2 cm margin. Sentinel node (SN) biopsy (SNB) is recommended for staging in patients with a melanoma of intermediate Breslow thickness (1 to 4 mm). The procedure may also be recommended in patients with a thick (>4 mm) lesion, and should be considered in case of a thin (<1 mm) melanoma with unfavorable features.[14] A SN is defined as any lymph node that receives lymphatic drainage directly from the primary tumor.[15,16]

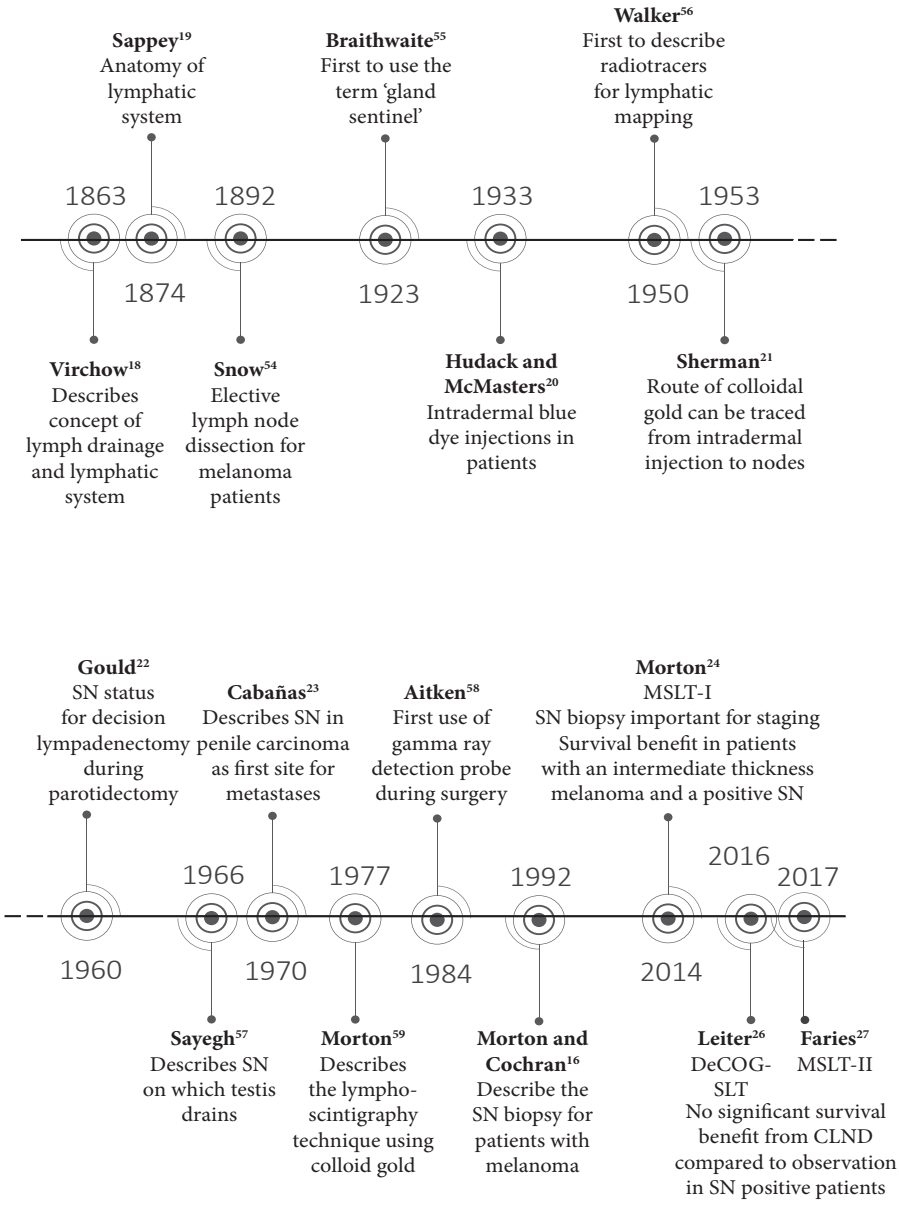
Figure 1.1 Changes in melanoma incidence in males and females in different age cohorts from Australia and the Netherlands. Reproduced with permission from the International Agency for Research on Cancer[53]



SNs are usually located in the major regional lymph node fields in the neck, axilla and groin, but can also be found in smaller nodal regions or as interval nodes along a lymphatic vessel.[17] SNs are visualized by dynamic and static lymphoscintigraphy and single photon emission computed tomography with computed radiographic tomography (SPECT/CT). Combined with the intraoperative use of a gamma ray detection probe and blue dye, SNs can be retrieved in almost all patients. Pathology evaluation involves multiple sections of the node and sensitive immunohistochemistry staining.

A long history of research precedes our current understanding of lymphatic dissemination (figure 1.2). The German pathologist Virchow is at the root of our knowledge of lymph nodes and lymph node metastases. In 1863 he described that lymph fluid from specific body areas flows to a specific lymph node before progressing to the other lymph nodes.[18] He proposed that tumor cells travel via lymph vessels to lymph nodes and suggested that these nodes function as a filter. In 1874, an anatomic atlas of the lymphatic system was published by Sappey, who visualized lymph vessels by injecting them with mercury mixed with tin and lead.[19] Hudack and McMasters were the first to use blue dye to visualize lymphatic vessels in patients in 1933.[20] In 1953, Sherman et al. reported the use of intradermal radiocolloid gold injections for imaging of the lymphatic system.[21] The first procedure that was a rudimentary SNB was performed by Gould in 1951.[22] During a total parotidectomy, a normal appearing node at the junction of the anterior and posterior facial veins was pathologically assessed to identify micrometastases. Radical neck dissection was performed only if tumor was found in this "SN". In the late 1960s, the SN concept was also studied by Cabañas.[23] He made lymphangiograms of patients with penile carcinoma and reported consistent drainage to one SN located near the superficial epigastric vein. In all patients who had metastases, this SN was also tumor positive. Therefore, he suggested a SNB to guide the decision on groin dissection. Both Gould and Cabañas described a static concept of SNs, with lymphatic drainage from a certain body area to a lymph node that was always in the same location. This appeared sensible for cancer of the parotid and penile cancer, as - in contrast to melanoma - the primary tumor is typically in the same location.

Figure 1.2 Timeline with pivotal studies on lymphatic drainage, lymph nodes and sentinel nodes[16,18,19–24,26,27,54–59]



In 1992, Morton and Cochran published their SNB technique as a staging procedure for patients with melanoma.[16] Unlike their predecessors, they developed a dynamic concept based on physiology rather than anatomy. This implies variability in SN numbers and locations between individuals depending on the pattern of lymph flow. Patent blue dye was used intraoperatively to visualize the lymphatic channels leading to SNs. They proposed the definition of a SN being a lymph node receiving lymphatic drainage directly from the primary tumor site.[15,16] Their report describes 259 SNBs in 194 patients. All patients underwent SNB and completion node dissection (CLND), regardless of SN tumor status. Forty-seven SNs (18%) were tumor positive. In only two patients with a negative SN (1%) tumor was found in non-SNs in the lymphadenectomy specimen. Based on these findings, SNB became a commonly used procedure in patients with melanoma.

The value of modern-day SNB was studied in the first international Multicenter Selective Lymphadenectomy Trial (MSLT-I), in which 2001 patients were randomized to SNB followed by CLND if dissemination was found, or to nodal observation with CLND only if a nodal recurrence became evident during follow-up.[24] Although the trial showed no ten-year melanoma-specific survival difference between the two main groups, there was a melanoma-specific survival benefit from SNB and CLND in the primary aim population of lymph node-positive patients with an intermediate thickness primary tumor. The trial also demonstrated the tumor status of the SN to be the most important prognostic factor for survival.[24] As a result of this trial, SNB with CLND in case of a positive SN became standard of care.

Subsequently, the need for CLND was questioned, as it was found that 80-88% of the SN-positive patients did not have additional lymph node metastases and the dissection carried a significant risk of morbidity.[25] Two trials were initiated to address this issue, MSLT-II and the Dermatologic Cooperative Oncology Group Selective Lymphadenectomy Trial (DeCOG-SLT).[26,27] These studies randomized SN-positive patients to immediate CLND or to observation with regular ultrasound examination of the lymph node field(s) at risk and delayed CLND only if nodal recurrence became

evident later on. The melanoma-specific survival rate in MSLT-II and the distant metastasis-free survival rate in DeCOG-SLT were not statistically different between the two arms. The studies did have some limitations. There was a preponderance of patients with a low tumor burden in their SN. DeCOG-SLT was terminated early because of slow patient accrual and it reached a statistical power of only 50%. Furthermore, in 84% of the patients the number of removed lymph nodes was less than 15 or unknown. The follow-up of both studies was only three years, but a statistical difference after a longer period was deemed unlikely. Although CLND has largely been abandoned since the trial results were published, the procedure does have some advantages. CLND improves staging, reduces the risk of nodal recurrence and the operation can at times be less extensive than when done for a nodal recurrence. The need for adjuvant radiotherapy is unlikely at this early stage. Delayed lymphadenectomy for nodal recurrences results in more lymphedema and hospital stay is longer.[28] Despite these advantages of early dissection, the lack of survival benefit and the morbidity of immediate CLND make observation the preferred management in the majority of patients with a positive SN. Still, individual circumstances and personal preferences can justify a CLND.

Patients with clinically palpable nodal metastases have stage IIIB or IIIC disease. Their nodal metastases are managed with a therapeutic lymph node dissection, followed by adjuvant radiotherapy of the nodal field in case of extra-nodal disease extension or other unfavorable factors. The value of adjuvant systemic immunotherapy and targeted therapy has recently been demonstrated in three phase 3 trials.[29–31] Adjuvant immunotherapy with nivolumab or pembrolizumab, or targeted therapy with dabrafenib plus trametinib in BRAF-positive patients improves recurrence-free survival after twelve months of treatment.[29–31] The toxicity of these drugs is considerable and grade 3 to 5 immune related adverse events, including deaths, have been reported in 14% to 46% of the trial participants receiving drug therapy. The toxicity caused discontinuation of therapy in 10% to 43% of the patients. All three trials concerned high-risk stage III patients with metastases >1.0 mm and patients were required to undergo CLND. It is unclear if these results can be extrapolated to all SN-positive

patients, most of whom would not have eligible for these trials.

Patients with distant metastases have stage IV disease, and their prognosis is grim. Until recently, surgery was the only successful management option in selected patients. The introduction of effective systemic therapy caused a paradigm shift. The three-year survival rate improved to 45% for treatment with a combination of dabrafenib and trametinib.[32] Five-year overall survival was 34% in patients treated with pembrolizumab.[33] The new drugs are the mainstay of the treatment of patients with distant metastases. Their management is often complex and warrants a multidisciplinary approach.[34]

Follow-up of high-risk melanoma patients

Melanoma patients have a lifelong risk of developing a recurrence and an increased risk of a new primary melanoma.[35] Therefore, they are usually followed up regularly. For patients with stage III melanoma, the five-year disease-specific survival rates vary from 93% for stage IIIA to 32% for stage IIID.[36] Chest radiography and general blood tests are not of value in the follow-up of these patients.[37–39] It is unclear if imaging with regular (PET/)CTs should be part of the follow-up. The aim of surveillance imaging is to identify disease recurrence at an early stage. This is supposed to increase the chance of therapy being successful, although a survival benefit has not yet been convincingly demonstrated in melanoma or other cancers.[40,41] Follow-up guidelines vary from one country to another and patients adhere to various surveillance schedules with different imaging modalities.[42–46] Despite the lack of evidence, the use of CT and PET/CT has increased substantially over the last twenty years.[47,48] In addition to the perceived benefits, frequent scanning is associated with certain disadvantages. It can increase patient anxiety.[49] It often exposes patients to ionizing radiation, which increases the risk of secondary cancers.[50] Scans are expensive, and it is unclear whether a scan-based follow-up strategy is cost-effective.[51] Furthermore, surveillance imaging may discover other abnormalities of uncertain nature. Often, these abnormalities are unrelated to melanoma or initially thought to be melanoma but ultimately found to be something

different. These incidental findings and false-positive results can prompt unnecessary additional diagnostic tests, invasive procedures and doctor's visits, and further increase patient anxiety and costs. Even the early discovery of other cancers is not always beneficial for the patient and overdiagnosis has been described as a substantial problem in cancer screening.[52] These downsides of routine surveillance imaging in melanoma patients have not been studied.

Outline of this thesis

This thesis describes the management of high-risk melanoma patients, and focuses on their identification, surgical treatment and follow-up. The great majority of SNs is found in the three major lymph node fields in the axilla, groin and neck, but a SN can also be located in a smaller lymph node region, like the popliteal fossa. These SNs are infrequently encountered and have not been very well studied. The importance and surgical management of SNs in the popliteal fossa are described in **chapter two**.

Management of SN-positive patients has changed considerably since mid-2017. After the MSLT-II and DeCOG-SLT interim results were published, observation with ultrasonography of the nodal field(s) largely replaced CLND. In **chapter three**, the literature on CLND is critically reviewed and the advantages and disadvantages of performing CLND are outlined. Multiple trials showed an improved recurrence-free survival with adjuvant systemic therapy for more advanced stage III melanoma patients. **Chapter four** describes the paradigm shift in surgical and adjuvant management of SN-positive patients treated at the Melanoma Institute Australia following these recent developments.

Patients with an isolated local recurrence or in-transit metastasis are typically managed with excision. These patients have a poor prognosis. **Chapter five** describes the value of SNB in these patients to diagnose lymph node involvement at an early stage and to identify those at high risk of distant metastases. When patients present with in-transit metastases, ultrasonography of the tissue surrounding the lesion and leading up to the regional lymph nodes can potentially identify additional lesions that are not yet palpable. This approach has not been described before. **Chapter six** describes the value of ultrasound examination for this purpose, and the changes in management when such additional lesions are found.

High-risk patients are followed up regularly to detect recurrences at an early stage. The majority of studies on imaging focus on true-positive findings and disregard potential disadvantages. **Chapter seven** describes a study of incidental and false-positive

findings in high-risk melanoma patients undergoing annual surveillance imaging and the associated downstream healthcare usage as a direct result of these findings.

This thesis aims to provide a better understanding of the altered landscape of stage III melanoma patients and a notion of the current role of the surgical oncologist in the management of these patients.

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Chapter 2

Clinical importance and surgical management of sentinel lymph nodes in the popliteal fossa of melanoma patients

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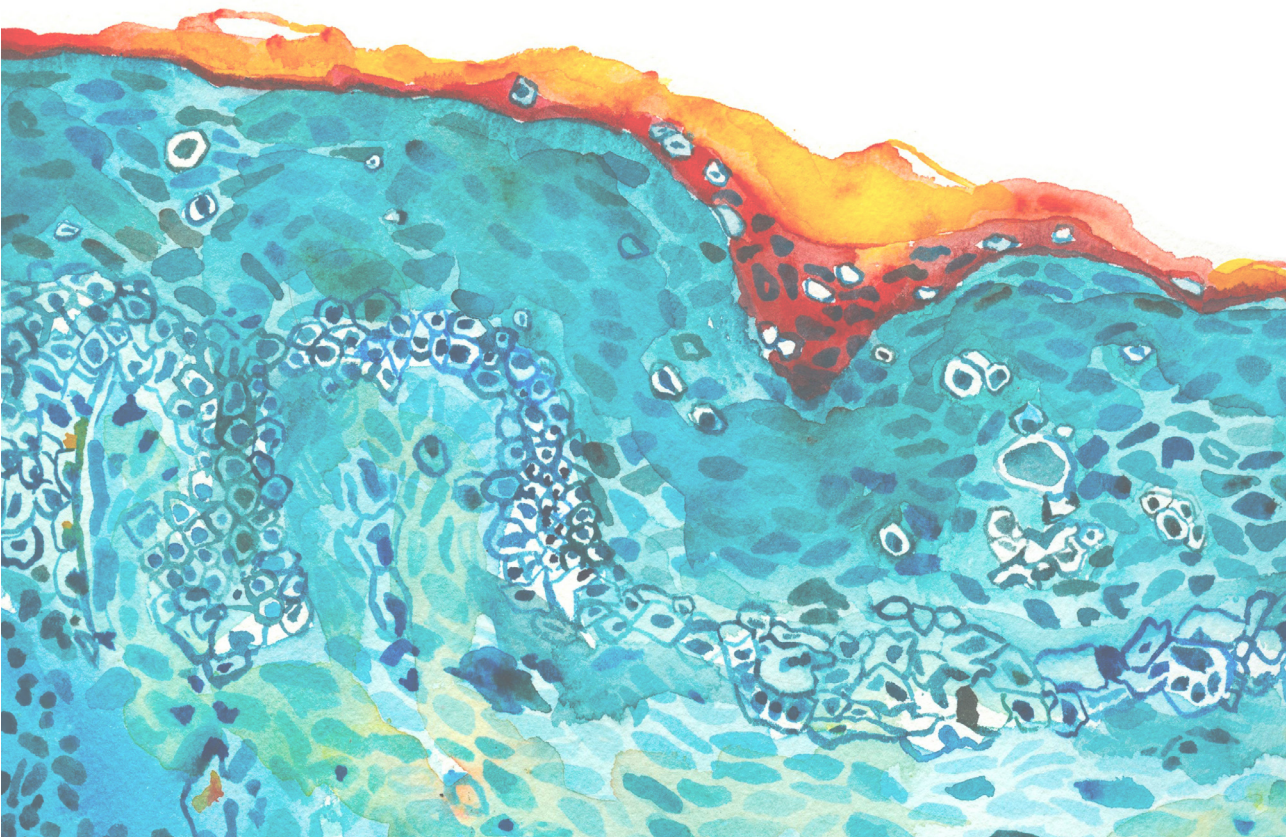


Abstract

Background and purpose - Patients with a primary melanoma below the knee may have lymphatic drainage to a sentinel node (SN) in the popliteal fossa. The purpose of this study was to analyze lymphatic drainage to this site and to describe clinical features and surgical management of SNs in the popliteal fossa.

Methods - Patients with a primary melanoma below the knee presenting to Melanoma Institute Australia between 1992 and 2013 were analyzed. Those found to have a popliteal SN were evaluated. Data on imaging, SN biopsy, completion lymph node dissection, morbidity and follow-up were analyzed.

Results - Lymphoscintigraphy showed drainage to a popliteal SN in 176 of 3902 cases of melanoma below the knee (4.5%). In 96 of these patients (55%) a popliteal SN biopsy was attempted. The procedure failed to identify the node(s) in seventeen of them (18%). Thirteen of the 79 patients (17%) had a positive popliteal SN and in eight (10%) this was the only positive node. The tumor stage of ten patients (13%) changed as a result of the popliteal node biopsy. A positive popliteal node was associated with an increased risk of recurrence and diminished overall survival. Popliteal SN biopsy did not improve regional control or survival.

Conclusion - Melanomas below the knee infrequently drain to lymph nodes in the popliteal fossa. Although popliteal SN biopsy can be challenging, it is worthwhile, providing improved staging and guiding subsequent management.

Introduction

Sentinel node (SN) tumor status is the most important prognostic factor in patients with a clinically localized melanoma.[1,2] Lymphatic drainage from melanomas on the lower limb typically occurs to groin lymph nodes but melanomas below the knee (on the leg or foot) can also drain to nodes in the popliteal fossa. The popliteal fossa is one of the minor nodal regions that contain just a few lymph nodes. Other minor regions are the epitrochlear fossa and the triangular intermuscular space on the back.[3,4] In some patients, a SN in a minor node field is the only positive lymph node, and failure to harvest it can lead to understaging and undertreatment.

Knowledge of the significance of SNs in the popliteal fossa is limited, as popliteal SN biopsy is performed infrequently. Popliteal drainage has traditionally been associated with melanomas on the heel and lateral margin of the foot but we now know that lymphatic drainage to the popliteal fossa can also occur if the lesion is from other sites on the distal lower limb.[5] Lymphatic drainage to popliteal nodes has been described in 1% to 11% of patients with a primary melanoma below the knee.[6–20] These SNs are typically located below the deep fascia, anterior to the tibial and common fibular nerves and sometimes situated anterior to the popliteal vessels.[21] Performing a SN biopsy in this area can be technically challenging and information on the retrieval rate is sparse. Reported popliteal SN positivity rates vary from 11% to 53%, with only 27 cases included in the largest previous study.[6,8,9,13,17–19,22]

Considering the valuable staging and prognostic information provided by SN biopsy and the survival benefit from SN biopsy reported in SN-positive patients with an intermediate Breslow thickness tumor, knowledge of popliteal SN status is likely to have clinical implications.[2,23] The purpose of this study was to describe the incidence, surgical management and clinical relevance of popliteal SNs in a large series of patients with primary melanomas located below the knee.

Methods

Prospectively collected information on patients with a melanoma below the knee treated between 1992 and 2013 was retrieved from the research database of Melanoma Institute Australia. All patients signed an informed consent form for entry of their data into the Institute's database and approval of the institutional research committee was obtained prior to commencing the study.

SN biopsy was recommended in patients with an intermediate thickness melanoma (T2 or T3) and discussed in patients with thin (T1b) or thick (T4) melanomas. Lymphoscintigrams were routinely obtained with technetium-99m antimony trisulfide colloid using dynamic and static imaging. A SN was defined as a lymph node receiving direct lymphatic drainage from the melanoma site.[24] The AJCC-UICC 8th edition staging classification was used.

Patients with palpable popliteal lymph nodes or who had lymphoscintigraphy for recurrent melanoma were excluded. Patients with lymphatic drainage to a popliteal SN on their lymphoscintigram were identified. Patient files were reviewed to collect data on their general characteristics, preoperative imaging, SN biopsy, completion node dissection, morbidity and survival outcome. Patients with a follow-up of less than one month were not included in the follow-up analyses.

Data were analyzed using IBM SPSS Statistics 24 and R version 3.4.0.[25,26] Descriptive statistics were used to evaluate outcomes. Normality of distribution was assessed with the Kolmogorov-Smirnov test and the Shapiro Wilk test. Numbers with percentiles, mean values with standard deviation (SD) or medians with interquartile range (IQR) were reported as appropriate. The chi-squared test and Fisher's exact test were used to evaluate recurrence rates. Overall survival curves were produced using the Kaplan Meier method and the survival distribution was tested using the log rank test (Mantel-Cox).

Results

Lymphoscintigraphy and SN biopsy

Between 1992 and 2013, 3820 patients with 3902 primary melanomas below the knee were treated. Lymphoscintigraphy showed drainage to both popliteal and inguinal lymph nodes in 176 cases (4.5%) (table 2.1). Exclusive drainage to the popliteal fossa was never seen. The primary tumor location was on the posterior leg in 73 patients (42%), foot in 57 (32%), ankle in 25 (14%), and anterior leg in 21 (12%).

The visualized popliteal SN was not surgically pursued in 80 patients (46%). The reasons were documented in 56 cases (70%). In fifteen (27%), the reason was that the lymphoscintigrams showed a complex drainage pattern with numerous sentinel nodes (often >5) in multiple sites, increasing the anticipated difficulty of the procedure and the associated risk of morbidity. Unfavorable patient characteristics such as advanced age and major comorbidities accounted for fourteen cases (25%). Nine patients (16%) declined SN biopsy, primarily because of fear of lymphedema. Seven patients (13%) participated in the first Multicenter Selective Lymphadenectomy Trial and were randomized to observation without SN biopsy.[23] In six cases (11%), no biopsy was performed because of low risk melanoma features such as a relatively thin primary (<1.0 mm Breslow thickness). Other reasons were mentioned in five cases (9%). Eleven of the patients (14%) who did not have a popliteal SN biopsy did undergo a groin SN biopsy, with positive groin nodes in two of them. In three of these eleven patients, there was doubt about the presence of popliteal SNs on review of the lymphoscintigrams; in one other case, the melanoma was thin and the lymphoscintigram showed only faint drainage of radioactive tracer to a popliteal node.

The popliteal fossa was surgically explored in the remaining 96 patients (figure 2.1). No SN was found in twelve of them and the removed specimen did not contain a lymph node in five, resulting in a failure rate of 18%. In two of the latter five patients, the popliteal SNs were described as showing only faint isotope uptake on the lymphoscintigram report.

Table 2.1 Patient and tumor characteristics

Characteristics	Total	No popliteal SN biopsy	Popliteal SN biopsy	Failed biopsy	Missing
Number of patients	176	80	79	17	
Age (SD)	59 (±16)	61 (±18)	58 (±14)	57 (±16)	-
Male	82 (47%)	39 (49%)	36 (46%)	7 (41%)	-
Primary tumor					
Breslow in mm (IQR)	1.8 (1.2-2.8)	1.5 (1.1-2.8)	2.2 (1.5-3.1)	1.4 (1.1-2.3)	1
Ulceration	56 (34%)	21 (27%)	30 (42%)	5 (31%)	12
Mitotic rate per mm^2 (IQR)	3 (1-7)	3 (1-6)	4 (1-8)	5 (1-6)	8
Microsatellite lesions	9 (7.3%)	4 (7.7%)	5 (8.2%)	-	53
In-transit lesions	3 (2.4%)	2 (3.8%)	1 (1.6%)	-	53
Location primary					-
Foot	57 (32%)	27 (34%)	28 (35%)	2 (12%)	
Ankle	25 (14%)	13 (16%)	11 (14%)	1 (6%)	
Posterior leg	73 (42%)	29 (36%)	35 (44%)	9 (53%)	
Anterior leg	21 (12%)	11 (14%)	5 (6%)	5 (29%)	
LN palpable	6 groin 1 ITM*	3 groin	3 groin 1 ITM*	1 groin	
Successful SN biopsies					
Popliteal only		-	4	-	
Groin and popliteal		-	75	-	
Groin only		11	-	12	

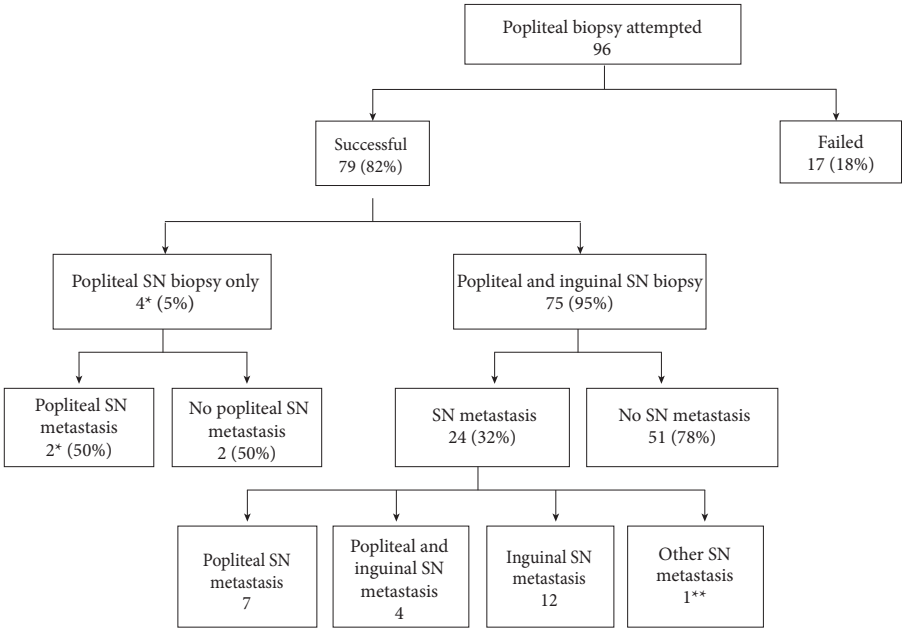
* In-transit metastasis on shin

In four of the 79 patients who had a successful popliteal SN biopsy this was the only nodal region that was explored. In one of these patients the reason was documented: he underwent a concurrent therapeutic ipsilateral inguinal node dissection for palpable disease. The LSG was presumably made to determine whether there was popliteal

drainage as well, but the exact reason was not clearly documented in the patient's records. Both inguinal and popliteal SN biopsies were performed in 75 patients. The popliteal procedure yielded a median of one SN with a maximum of three nodes and the groin procedure a median of two SNs, with a maximum of six. The popliteal lymph nodes were usually just a few millimeters in size and often contained little of the radiopharmaceutical, with low gamma counts when assessed with the gamma detection probe intra-operatively.

In thirteen of the 79 patients (16%), one or more popliteal SNs contained metastatic melanoma. Four of these patients also had inguinal SN involvement and one had palpable groin disease at presentation (figure 2.1). Thus, in eight patients (10%) the popliteal SN was the only tumor-containing node. The finding of a positive popliteal SN altered the AJCC-UICC tumor stage of ten patients (13%).

Figure 2.1 Flowchart of SN biopsy outcomes



* One patient with palpable groin nodes underwent therapeutic inguinal node dissection at the time of the popliteal SN biopsy

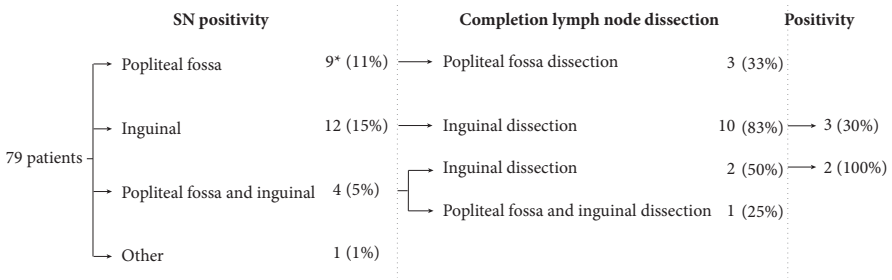
** One patient had a positive in-transit SN on the anterior leg

Postoperative morbidity from the popliteal SN biopsy was reported in one patient (1.3%), who had a wound infection requiring antibiotic treatment. Twenty-one patients (27%) developed lymphedema (generally mild and transient) after SN biopsy of both the groin and popliteal fossa in all but one case.

Completion lymph node dissection

Sixteen of the 26 patients with a positive SN (61%) underwent completion popliteal and/or inguinal lymph node dissection (figure 2.2). In the subgroup of patients with a positive popliteal SN, only four of the thirteen patients (31%) underwent completion dissection of the popliteal fossa. No additional lymph nodes were found in two of these popliteal operative specimens. In the other two patients, one and two additional lymph nodes were retrieved, all without disease. Popliteal dissection alone was not associated with morbidity. One patient developed lymphedema after combined popliteal and inguinal node dissection.

Figure 2.2 Completion lymph node dissections with outcomes



*One patient with palpable groin nodes had a therapeutic inguinal lymph node dissection at the time of the popliteal SN biopsy

Follow-up

Follow-up data were available for 170 patients (median follow-up 54 months; table 2.2). Three patients (3.8%) in whom a SN in the popliteal fossa was not pursued, recurred in this region, and there was recurrence in another three patients (4.0%) in

whom popliteal SN biopsy had been performed. In one of the latter three, a SN had been positive. Neither the recurrence rate nor the overall survival rate was significantly different for the patients who did or did not undergo popliteal SN biopsy (chi-squared test P=0.52 and log rank test P=0.88 respectively). There was no popliteal recurrence in the seventeen patients in whom the biopsy had failed. Formal dissection of the entire fossa was performed in one of the six patients with a popliteal recurrence, two simply underwent excision of the identified mass and three received radiotherapy, of whom one also received systemic therapy.

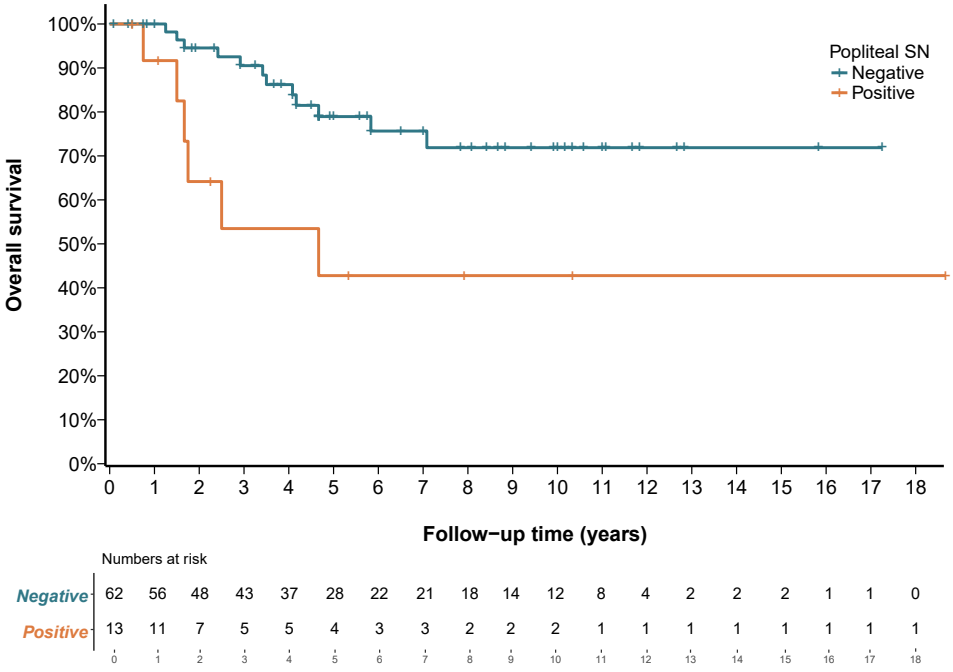
Table 2.2 Follow-up and outcome

	Total	No popliteal SN biopsy	Popliteal SN biopsy	Failed biopsy
Number of patients with follow-up	170	78	75	17
Follow-up in months (IQR)	54 (27-96)	53 (27-80)	54 (22-101)	59 (44-146)
Recurrence	65 (38%)	31 (40%)	26 (35%)	8 (44%)
First recurrence primary site	14	7	4	3
First recurrence in-transit (lower leg)	20	9	6	5
First recurrence regional lymph node (groin)	16	10	6	-
First recurrence systemic	15	5	10	-
Months until recurrence (IQR)	23 (10-39)	20 (9-37)	22 (10-30)	49 (16-90)
Popliteal recurrence	6 (3.5%)	3 (3.8%)	3 (4.0%)	-
Groin recurrence	33 (19%)	19 (24%)	13 (17%)	1 (5.9%)
Systemic metastases	39 (23%)	20 (26%)	17 (23%)	2 (12%)
Alive last follow-up	128 (75%)	58 (74%)	56 (75%)	14 (82%)
Status last follow-up				
Alive without recurrence	107 (63%)	45 (57%)	50 (67%)	12 (71%)
Alive with disease	17 (10%)	11 (14%)	5 (6.7%)	1 (5.9%)
Alive, status unknown	4 (2.4%)	2 (2.6%)	1 (1.3%)	1 (5.9%)
Dead, melanoma	29 (17%)	14 (18%)	13 (17%)	2 (12%)
Dead, other cause	4 (2.4%)	2 (2.6%)	1 (1.3%)	1 (5.9%)
Dead, cause unknown	9 (5.3%)	4 (5.1%)	5 (6.7%)	-

Seventeen of the 66 popliteal SN-negative patients developed a recurrence at any site (27%). Patients with a positive popliteal SN did significantly worse, with nine of the thirteen developing a recurrence (69%, Fisher's exact test P=0.007). Overall survival was also significantly reduced in patients with a positive popliteal SN when compared to those with a negative popliteal SN (median survival 56 months versus median not reached respectively; log rank test P=0.011) (figure 2.3).

In seven patients, the popliteal SN was positive but the groin was SN-negative. Two of these seven patients (29%) later developed an inguinal recurrence.

Figure 2.3 Overall survival, according to popliteal SN tumor status



Discussion

Lymphoscintigraphy and SN biopsy

This study of 3820 patients with 3902 primary melanomas below the knee reports the incidence of popliteal SNs and examines their relevance and the clinical implications of popliteal SN biopsy. Of the cohort of 176 patients with drainage to SNs in the popliteal fossa, only 96 (54%) had a SN biopsy in this region. The procedure had a failure rate of 18%. The popliteal SN was found to be positive in 13 of the 79 patients (16%) in whom the procedure was successful. The occurrence of a positive popliteal SN was associated with an increased risk of melanoma recurrence and was associated with a diminished overall survival compared to patients with a negative popliteal SN.

The quality of the lymphoscintigrams is influenced by the size of the radiotracer particles.[27] In this study, Tc-99m antimony trisulfide colloid was used. This small particle radioactive tracer quickly enters the lymphatic vessels, thereby identifying true SNs with high accuracy on dynamic lymphoscintigrams. Lymphoscintigraphy visualized drainage to nodes in the popliteal fossa in 176 (4.5%) of the patients with a melanoma anywhere below the knee. Previous investigations have been performed but were smaller, including between 57 and 461 patients with melanomas on the distal lower limb. These studies demonstrated popliteal SNs in between 1% and 11% of the patients.[6–20]

Of the total patient cohort, 46% of those who had lymphatic drainage to popliteal lymph nodes did not undergo popliteal SN biopsy. The reasons for this were diverse and included patient refusal, lymphoscintigrams with complex drainage patterns, the surgeon's decision, and clinical trial participation. No previous studies have correlated lymphoscintigraphy findings and the popliteal SN biopsy rate. The afferent lymphatic vessels and the lymph nodes are usually not in the subcutaneous tissue but much deeper.[28] This limits the usefulness of blue dye in SN identification and retrieval. The difficulty of popliteal SN biopsy is evident from the reluctance of surgeons to pursue them and the failure rate of 18% in a specialist melanoma unit. In other nodal regions, SNs are retrieved almost without exception at our institution. Three other investigators

have reported failure rates of 8%, 12% and 62%.[9,13,17] The latter exceptionally high rate was attributed to a low radioactive tracer uptake in the nodes that was sometimes not detectable at the time of surgery. For this reason, the SN procedure should be performed as soon as possible after lymphoscintigraphy.

Retrieved popliteal SNs contained metastases in 16% of the patients, which is in accordance with the experience in other nodal fields.[23] Eleven previous studies reported popliteal SN metastatic rates of 11% to 53%.[6,8,10,12,13,16–19,22] This wide range can be attributed to the small patient numbers in these studies, with seven including less than ten patients and the largest reporting 27 patients.[6]

The popliteal node was the only positive node in 10% of the patients in the present series. In four other studies this ranged from 4% to 36%.[6,8,13,18] Ten of our patients (13%) were assigned to a higher TNM stage on the basis of popliteal SN positivity. This is relevant in view of current developments in systemic therapy as understaging may prevent patients from receiving potentially beneficial adjuvant therapy or participating in clinical trials of adjuvant therapies.[29,30]

Completion lymph node dissection

In the time period of the current study, completion lymph node dissection was the recommended treatment when metastatic disease in a SN was identified.[21] Sixty-one percent of the patients with a positive SN underwent CLND. This is in accordance with earlier research from our institution that showed that 62% of all 599 SN positive patients treated between 2004 and 2014 underwent CLND. The decision to refrain from CLND was most often made by the patient. Patients with interval SNs and multiple SNs were less likely to undergo CLND.[31] It is not clear why only 31% of the patients with a positive SN retrieved from the popliteal fossa underwent CLND of this region, but this might be due to concern about the risk of lymphedema or the complexity of the procedure. Patients with a positive groin SN were more likely to undergo completion lymph node dissection than patients with a positive popliteal SN. Additional lymph nodes were found in only two of the four completion popliteal

lymph node dissection specimens and all were melanoma-free. A combined total of eleven popliteal completion lymph node dissections has been reported in three other studies.[6,8,13] In two of these, no lymph nodes were found, and only one completion lymph node dissection did yield further metastases.[13] So, the collected literature yields only one additional positive lymph node in fifteen completion node dissections. It appears that either there may be no additional lymph nodes in the popliteal fossa or they may be difficult to remove, as very occasionally patients do recur in this region. Given their small size, the pathologist may also fail to find the nodes in a bulky specimen.

There has been controversy about the management of the inguinal nodes in patients with only a positive popliteal SN.[8,9] One of the aims of our study was to clarify this issue. Unfortunately, the study is limited by its retrospective nature, which renders it prone to selection bias. Furthermore, the total of sixteen popliteal SN-positive patients with only four complete popliteal lymph dissections is clearly insufficient to properly address this matter. Even more importantly, however, the recently published interim results of the Second Multicenter Selective Lymphadenectomy Trial and the German DeCOG study largely obviate the need for clarification, as both trials indicate that completion lymph node dissection does not improve survival if the nodal region is followed with regular ultrasound examination.[32,33] The substantial survival benefit in the SN biopsy arm of the First Multicenter Selective Lymphadenectomy Trial, demonstrated by latent subgroup analysis, appears to be mainly attributable to removal of all disease in the SNs, rather than removal of disease in the non-SNs removed at the time of completion lymph node dissection.[23,34]

Follow-up

The overall recurrence rate for the 170 patients with a popliteal SN demonstrated by lymphoscintigraphy and with complete follow-up data available was 40% and for those undergoing popliteal SN biopsy it was 35%. Other studies report recurrence rates after popliteal SN biopsy of 0% to 47%.[6,8,13,17] The 69% overall recurrence rate in the present

study for patients with a positive popliteal SN roughly corresponds to rates in two other studies (75% and 100%).[8,17]

Six patients recurred in the popliteal fossa; three had not undergone a SN procedure, one had a positive popliteal SN biopsy and two a negative biopsy. Five of them developed a recurrence in the groin as well. In this small group, popliteal SN biopsy did not improve locoregional control, as patients undergoing popliteal SN biopsy and those observed had a similar rate of popliteal recurrence. However, in the patients who did undergo popliteal SN biopsy, the finding of a positive popliteal node was of prognostic importance, predicting disease recurrence and a worse overall survival compared to popliteal SN-negative patients. Other studies on popliteal SNs have not provided survival data.

Conclusion

Lymphoscintigraphy revealed a SN in the popliteal fossa in 4.5% of the patients with a primary cutaneous melanoma below the knee. Popliteal SN biopsy was performed in only 55% of these patients and harvesting them was challenging, with an 18% failure rate. Patients should be made aware of this high failure rate. Nevertheless, biopsy of SNs in the popliteal fossa is recommended as it can lead to assignation of a higher TNM stage (in 13% of the patients in our study) and is associated with little morbidity. The tumor status of the popliteal node has predictive value for recurrence and overall survival. Completion popliteal lymph node dissection is not beneficial. In patients with an involved popliteal SN, observation with regular ultrasound examination of the region is recommended, rather than a completion lymph node dissection of the popliteal fossa.

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Chapter 3

Completion lymph node dissection or observation in patients with melanoma and a positive sentinel node

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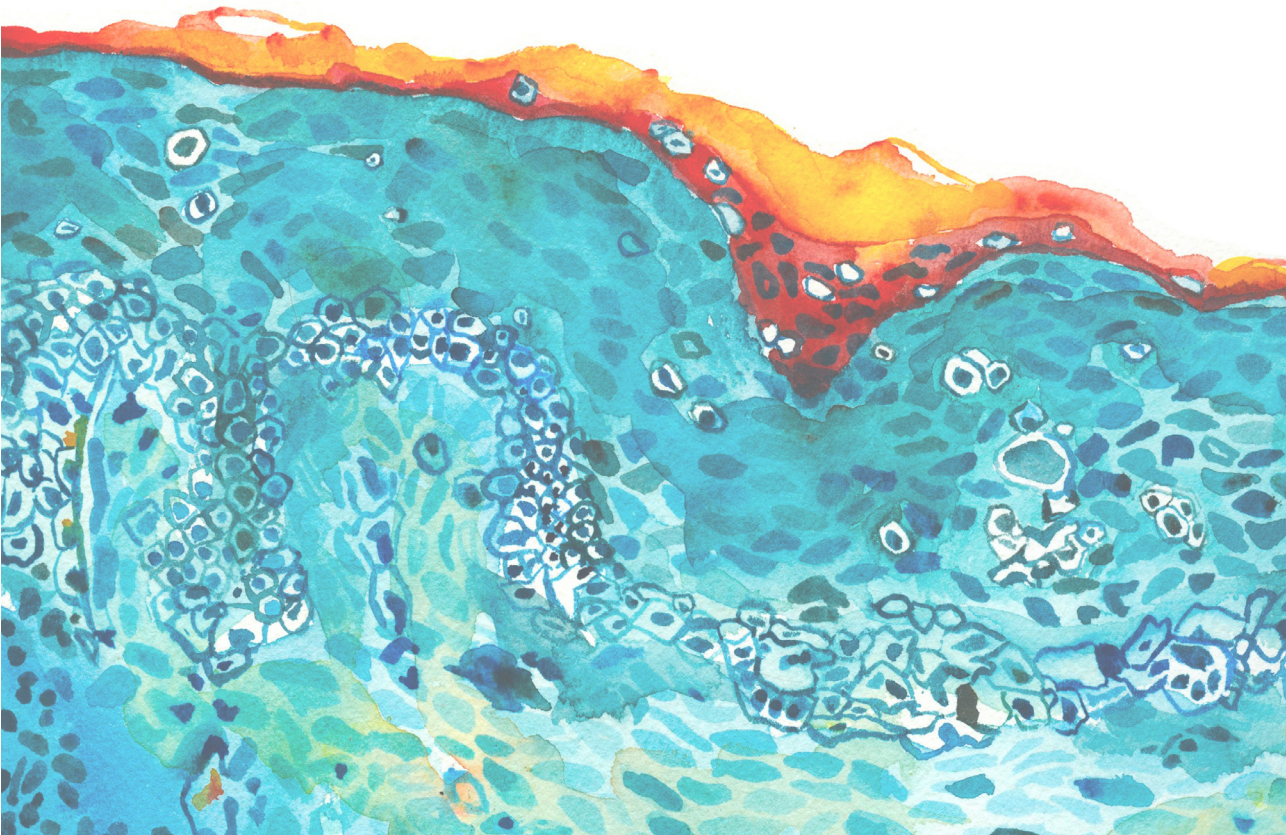
Translation of

Aanvullende lymfeklierdissectie of observatie bij melanoompatiënten met een positieve schildwachtklier. Nederlands Tijdschrift voor Oncologie; 2017;14:221-30



Abstract

Introduction - With the introduction of sentinel node biopsy for melanoma, the question of how to treat node-positive patients arose. The combination of sentinel node biopsy and regional lymph node dissection was found to improve survival in patients with an intermediate thickness melanoma and sentinel node involvement, but it was unclear to what extent completion lymph node dissection contributed to this survival benefit. Multiple retrospective studies and a German prospective randomized controlled trial could not provide a definite answer. The recently published interim results of the Multicenter Selective Lymphadenectomy Trial II clarify the issue, comparing completion lymph node dissection with observation. The present article analyses the literature on lymph node dissection in case of a positive sentinel node and discusses the advantages and disadvantages, with emphasis on the recent publication.

Methods - A literature search was conducted in Pubmed, Embase and Cochrane. The relevant articles were critically appraised. An overview was made of median follow-up, melanoma-specific survival and survival rates at three, five and ten years. The quality of the evidence and the strength of the recommendations were determined using the GRADE system.

Results - Nine studies were included. One prospective study was moderately valid, the other prospective study was highly valid. Neither showed a three-year melanoma-specific survival benefit with completion lymph node dissection. Morbidity, particularly lymphedema, occurred significantly more often after lymph node dissection than after sentinel node biopsy only. The GRADE level of evidence quality was high. Effects on regional tumor control, quality of life and further advantages and disadvantages are discussed.

Conclusion - Completion lymph node dissection can be omitted in sentinel node-positive melanoma patients. Follow-up with regular ultrasound monitoring to detect early nodal recurrence is recommended.

Introduction

A sentinel node (SN) is a lymph node that receives lymphatic drainage directly from a tumor.[1] Sentinel node biopsy (SNB) improves staging in patients with a clinically localized primary cutaneous melanoma. The tumor status of the SN is the most important prognostic factor.[2,3] Patients with a positive SN have a 12 to 20% risk of more tumor-positive lymph nodes in the same nodal region.[4,5] Therefore, SNB is a standard staging procedure.[6,7] Another advantage of SNB in patients with a melanoma of intermediate Breslow thickness (1.2 to 3.5 mm) is the survival benefit of 21% in SN-positive patients who received a completion lymph node dissection (CLND).[2] However, it was unclear whether the survival advantage was due to SNB only, or to a combination of SNB and CLND.

In 2011, a survey including 337 surgeons demonstrated that 92% advised CLND in patients with a positive SN.[8] The strength of the recommendation depended mainly on patient comorbidities and the extent of SN involvement. In 2008, an American study using the National Cancer Database, demonstrated that only 50% of the SN-positive patients underwent CLND.[9] In 2010-2011 this was 60%. In Germany, it was 60% in 2008 as well.[10] CLND was often avoided in older patients and patients with a melanoma on the lower leg.[9–11]

This article provides a review of all studies comparing CLND with observation in patients with a positive SN, with emphasis on the recently published Multicenter Selective Lymphadenectomy Trial II (MSLT-II).[12] In addition, the pros and cons of this procedure are discussed.

Methods

A systematic search was conducted on the 7th of February 2017 in the Pubmed, Embase and Cochrane databases. Synonyms for "melanoma," "lymph node (dissection)," "observation," and "survival" were used. Titles and abstracts were assessed for relevance by two authors (AN, AvO) independently. In case of a difference of opinion, consensus was reached through discussion. Selected articles were read entirely and reassessed. The final selection was made by the aforementioned authors using predetermined inclusion and exclusion criteria (figure 3.1). The interim results of the MSLT-II trial were published on 8 June 2017 and this influential article was added to the literature review.[12]

The validity and applicability of the articles were weighed by the authors using a self-developed scoring method based on Cochrane Risk of bias tool for assessing risk of bias in randomized clinical trials.[13] The exact categories as described by Cochrane were used, with an additional appraisal of study design, baseline characteristics, statistical analysis and conflicts of interest. Furthermore, a scoring system was added in which the articles were assigned points per category, leading to a conclusion regarding validity and applicability.

An overview was made of median follow-up, melanoma-specific survival and overall survival after three, five and ten years. The quality of the evidence and the certainty with which recommendations can be made were assessed via the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system.[14] This system evaluates the level of evidence of the primary outcome. The design of the included studies determines the initial score and this can be increased or decreased by the aforementioned factors. The score represents a conclusion about the quality and certainty of the evidence, ranging from high (very unlikely that further research changes the conclusion) to very low (the conclusion is extremely uncertain).

Results

Search results and selected articles

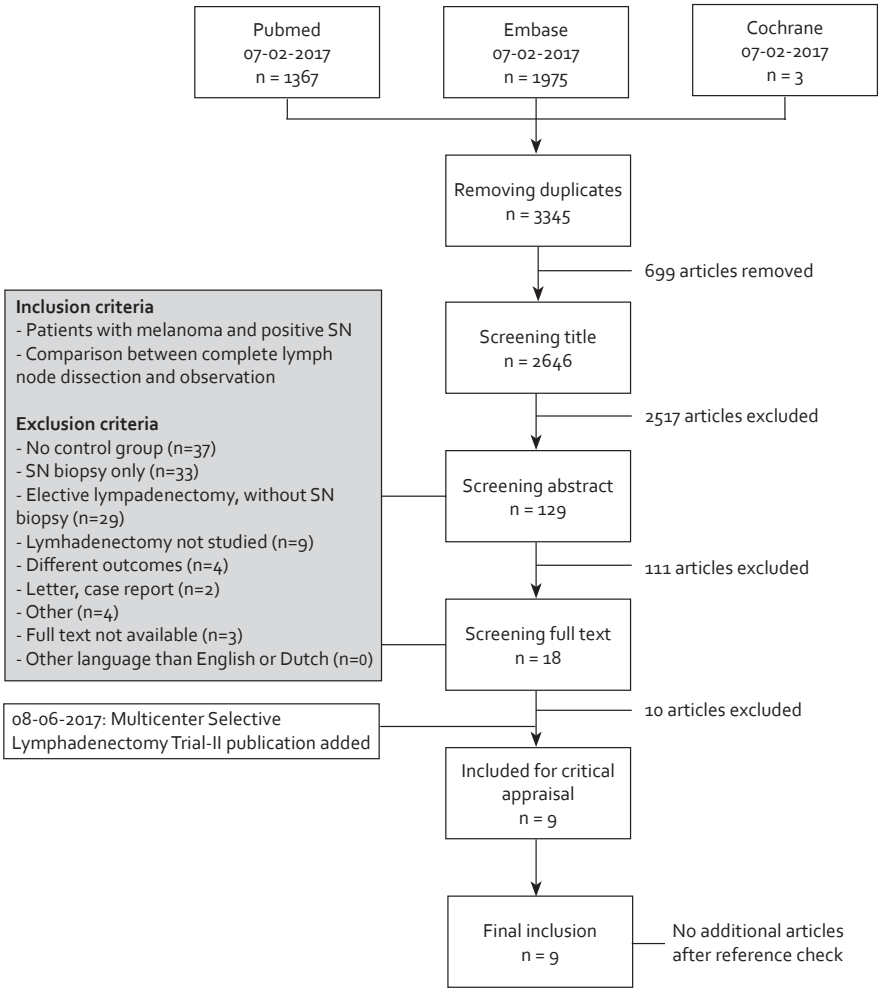
After removing duplicates, the number of articles was 2646 (figure 3.1). Following the screening titles and abstracts, eighteen articles remained for full text assessment. Eight of these were eventually selected.[15–22] Including the MSLT-II publication, this literature overview comprises nine articles.[12]

Table 3.1 shows on which criteria the validity and applicability of the articles were assessed. The prospective study by Leiter et al. had a medium validity and the one by Faries et al. had a high validity.[12,17] The validity of the other seven articles was low. Eight studies had a high applicability and the study by Kingham et al. was found to be moderately applicable due to inclusion of clinically detected nodal metastases.[15] The results of all nine articles are discussed, with emphasis on the prospective studies given their high validity.

In both prospective randomized trials, CLND was compared to observation with ultrasound assessment of the involved lymph node region. The study and patient characteristics of the different studies varied (table 3.2). In the retrospective studies, patient characteristics were often unevenly distributed over the CLND and observation arm, with more favorable tumor characteristics in the observation arm. The characteristics between the two arms were similar in the prospective study by Leiter et al.[17] However, in the discussion of their article the authors mentioned that the research population was a non-random selection. They compared the included group with 786 SN-positive patients who were not included. These excluded patients were significantly older and their nodal metastases were larger. In addition, the researchers failed to recruit the intended number of patients, which reduced the statistical power to demonstrate a survival difference of 10% from 80% to 50%.

Patient numbers were not equally distributed between the study arms in the retrospective studies. The CLND arms were often larger and included up to 95% of the patients studied.

Figure 3.1 Flowchart of literature search



Median follow-up varied from 23 to 81 months and was significantly different between the two patient arms in at least one study. Not all articles stated how long patients were followed up and whether there was a difference in follow-up between the two groups. Follow-up duration, patient groups and reported outcomes differed too much to combine the results of the studies.

Four articles reported that the primary tumor location was significantly different in patients undergoing CLND compared to patients in the observation group.[15,18,20,22] In all four studies, CLND was performed more frequently for melanomas on the trunk, in two articles more often for head and neck melanomas and in one study for melanomas on the upper extremity. The other articles did not describe significant differences in locations of the primary melanomas.

Table 3.1 Critical appraisal of the validity and applicability of the articles, including a description of the scoring method.

	Validity											Applicability				
	Design	Baseline characteristics	Random sequence generation	Allocation concealment	Blinding participants/personnel	Blinding of outcome assesment	Incomplete outcome data	Selective reporting	Statistical analysis	Conflict of interest	**Conclusion**	Population	Intervention	Comparison	Outcome	**Conclusion**
Bamboat, 2014[22]	-	-	-	-	-	+	+	+/-	+	+	-/9	+	+	+	+	+/8
Faries, 2017[12]	+	+	+	+	-	+	+	+	+	+	+/18	+	+	+	+	+/8
Kingham, 2010[15]	-	-	-	-	-	+	+	+/-	+	+/-	-/8	+/-	+	+	+	+/-/7
Lee, 2016[16]	-	-	-	-	-	+	+	+/-	+	+	-/9	+	+	+	+	+/8
Leiter, 2016[17]	+	+/-	+	+	-	+	+/-	+	+	+	+/-/16	+	+	+	+	+/8
Mosquera, 2016[18]	-	-	-	-	-	+	+/-	+/-	+	+	-/8	+	+	+	+	+/8
Satzger, 2014[19]	+/-	+/-	-	-	-	+	+	+/-	+	+	-/11	+	+	+	+	+/8
Van der Ploeg, 2012[20]	+/-	+/-	-	-	-	+	+/-	+/-	+	+	-/10	+	+	+	+	+/8
Wong, 2006[21]	+/-	-	-	-	-	+	+/-	+/-	+	+/-	-/8	+	+	+	+	+/8

Table 3.1 Continues from previous page

Legend

Validity

	+ (2 points)	+/- (1 point)	- (0 points)
Design	Prospective study	Retrospective study, matched pair analysis	Retrospective study
Baseline characteristics	Baseline characteristics well described, not different between groups, judged by the review authors to be of low risk of selection bias	Baseline characteristics not well described, and unclear if there are differences between groups or a matched pair analysis with good pairing or no patient characteristic differences, but selection bias of research population	Baseline characteristics differ between groups, judgded by the review authors to be of high risk of selection bias. A matched pair analysis with insufficient pairing
Randomisation	Random allocation	Insufficient information	No random allocation
Blinding of treatment	Patients and investigators could not foresee assignment to either group or review authors concluded that lack of blinding would not alter outcome	Insufficient information	Patients and investigators could foresee assignment to either group
Blinding participants/ personnel	Blinding of participants and key personnel	Insufficient information	No blinding of participants and key personnel
Blinding of outcome	Blinding on outcome assessment or unlikely a lack of blinding will influence measurement of the outcome	Insufficient information	No blinding of outcome and likely to influence outcome measurement
Incomplete data	No missing data	Missing data not well described, cannot be judged by review authors	Missing data, likely to influence outcome
Selective reporting	Study protocol available and all prespecified outcomes have been reported	Insufficient information	Not all prespecified primary outcomes have been reported or were reported using measurements, analysis methods or subsets of the data that were not pre-specified
Statistical analysis	Intention to treat		Per protocol
Conflict of interest	No conflict of interest or conflict of interest unikely to influence outcome	Conflict of interest not mentioned	Conflict of interest, which might influence outcome
Conclusion	≥17 points	12-16 points	≤11 points

Applicability

	+ (2 points)	+/- (1 point)	- (o points)
Population	Melanoma patients without clinical detectable metastases, without distant metastases, with a positive SN	Melanoma patients with clinical detectable metastases or distant metastases included, but results for subgroups described	Melanoma patients with clinical detectable metastases and distant metastases included
Intervention	Completion lymph node dissection		Anything other than completion lymph node dissection
Comparison	Observation		Anything other than observation
Outcome	Overall survival or disease specific survival	Melanoma-free survival (time to recurrence)	Other outcomes
Conclusion	8 points	6-7 points	≤5 points

Table 3.2 Overview of study characteristics

	Patients			Median follow-up (months)			
	Included	Observation group (%)	Baseline characteristics observation vs CLND	Total	Observation	Dissection	P-Value
Faries, 2017[12] International	1934	968 (50%)	Similar	43			
Leiter, 2016[17] Germany	473	233 (49%)	Similar		36	33	0.26
Satzger, 2014[19] Germany	305	58 (17%)	CLND worse	44			
Van der Ploeg, 2012[20] The Netherlands	1174	61 (5%)	CLND worse		48	34	0.03
Bamboat, 2014[22] United States	495	167 (34%)	Slightly different		23	80	NA
Lee, 2016[16] United States	471	96 (20%)	Slightly different	76	45	81	NA
Kingham, 2010[15] United States	308	37 (12%)	Slightly different		37	43	NA
Mosquera, 2017[18] United States	2172	716 (33%)	Slightly different				
Wong, 2006[21] United States	298	134 (45%)	CLND worse		36	20	NA

Survival analysis

Neither prospective randomized trial showed a significant difference in three-year survival between patients who underwent CLND and those who were observed (table 3.3).[12,17] In MSLT-II, no subgroups could be identified that had a better survival after CLND. The characteristics analyzed for this purpose were gender, age over 60, ulceration, Breslow thickness, location of the primary melanoma, number of positive SNs and size of the largest SN metastasis.

Table 3.3 Results including reported survival

	Melanoma specific survival (months)			Three-year survival			Five-year survival			Ten-year survival		
	Median observation	Median dissection	P-Value	Observation %	Dissection %	P-Value	Observation%	Dissection%	P-Value	Observation%	Dissection%	P-Value
Faries 2017[17]				86% (MS)	86% (MS)	0.42						
Leiter 2016[12]				82% (OS)	81% (OS)	0.87						
Satzger 2014[19]	NA	NA	0.10									
Van der Ploeg 2012[20]							74% (MS)	77% (MS)	0.60	66% (MS)	67% (MS)	0.60
Bamboat 2014[22]	median not reached	110	0.09									
Lee 2016[16]							66% (MS)	74% (MS)	0.02	48% (MS)	67% (MS)	0.02
Kingham 2010[15]	median not reached	73	0.26									
Mosquera 2017[18]							70% (MS)	72% (MS)	0.83			
Wong 2006[21]				NA (OS)	NA (OS)	0.65						

MS = melanoma specific survival, OS = overall survival, NA = not available

The retrospective studies had a low validity and used various survival-related endpoints (table 3.3). In none except one of these retrospective studies a significant survival difference between the two arms was found. Only Lee et al. reported a significantly better ten-year survival for patients undergoing CLND.[16] No survival difference was found in two matched-pair subgroup analyzes in which patients in the CLND arm were matched to patients in the observation arm based on patient and tumor characteristics, nor in an analysis of patients with a SN metastasis of less than 0.1 mm in diameter.[19,20]

Based on the GRADE system, the certainty of evidence for the conclusion on survival difference was judged to be high (table 3.4).

Two articles compared the frequency of nodal recurrences in the observation arm with the cumulative incidence of nodal metastases in patients undergoing CLND.[12,16] The cumulative incidence of nodal metastases is the sum of patients with additional metastases in the dissection specimen and patients with a nodal recurrence during follow-up. In MSLT-II, 26% of patients in the observation group relapsed in the regional lymph nodes.[12] This was 6% more than the cumulative incidence of nodal metastases in the CLND arm (P=0.005). Lee et al. found no difference between the two groups, with nodal disease in 18% and 22% respectively (P=0.185).[16]

Table 3.4 Assessment of the quality of evidence using the GRADE system: High is ≥4 points, moderate is 3 points, low is 2 points and very low ≤1 point

Initial score – type of evidence	Randomized studies	+4
Quality	No blinding	-1
Consistency	Most studies report similar results	0
Indirectness of evidence	Population can be broadly generalized	0
Magnitude of effect	Large magnitude of effect	+2
Conclusion		5 (high)

Discussion

The survival of patients with hematogenic metastases of melanoma has improved in recent years through the development of new systemic therapies. These drugs are also being investigated as neo-adjuvant and adjuvant therapy in patients with regional metastases. The drugs receive a lot of publicity, but recent developments concerning CLND also deserve attention. The important question whether immediate CLND provides a survival benefit in patients with an affected SN has now been answered in the negative, in particular by the recently published interim results of MSLT-II. Both included prospective studies had a relatively short follow-up period of approximately three years.[12,17] This seems too brief for a definitive judgment, since the only (retrospective) study that showed a significant survival benefit of early nodal dissection found this only after ten years of follow-up.[16] However, it is unlikely that a survival benefit will eventually be found given the pattern of the survival curves in both prospective studies.

In MSLT-II, one third of the included patients had a SN metastasis with a diameter of more than 1.00 mm, with median values of 0.61 and 0.67 mm in the CLND and observation arm respectively. In subgroup analyses, CLND was not found to result in survival benefit in the patients with a larger SN tumor metastasis. The study also demonstrated the important prognostic value of the tumor status of the other (non-sentinel) lymph nodes. This information will not be available if CLND is not performed. This might have consequences for the possibility to participate in adjuvant systemic therapy trials. Furthermore, metastases in the remaining nodes are discovered later, which may influence the extent of the operation, regional tumor control and morbidity.[23] More than 30 factors predictive of non-SN involvement have been described. These are patient-related factors like gender and age, factors related to the primary tumor such as Breslow thickness and ulceration, and lymph node associated factors such as the number of affected SNs and the location of metastases.[24] None of these factors appears to predict the presence or absence of further dissemination reliably. Different combinations of factors did not have the desired prognostic value either.[24-26]

Stress and fear of nodal recurrence can be reduced by CLND. Little research has been done on the quality of life of patients with or without CLND. The MSLT-II group will report on this issue. An important part of the MSLT-II observation protocol was the strict follow-up schedule, with four-monthly assessments in the first two years, half-yearly assessments in the following three years and annual follow-up thereafter. All clinic visits were preceded by ultrasound of the lymph node field(s) by experienced radiologists.[12] Metastases were therefore discovered relatively early. One may wonder whether observation is just as safe in patients who are not able to adhere to this regimen. Ultrasound examination of lymph nodes in patients with melanoma requires specific expertise. It is uncertain if nodal metastases are detected just as early by radiologists with less experience.

Like other procedures, CLND is associated with morbidity. In MSLT-II, lymphedema was found in 24% of the patients who underwent CLND, compared to 6% in the patients who were observed.[12] Edema mainly concerns the lower extremity and rarely the arm. This lymphedema is usually chronic and its severity may restrict patients in their daily activities. In MLST-II, edema was mild in 64% of patients, moderate in 33% and severe in 3%.[12]

An article by Burke et al. on the present topic was not included in the current literature overview because it used a hypothetical model based on multiple assumptions and did not include patients.[27] These investigators used a Markov model simulating the prognosis of hypothetical patient cohorts. They selected the parameters from the literature. They reported a better five-year survival, life expectancy and quality-adjusted life expectancy in patients who underwent CLND. However, the model was not validated with actual patient data.

Further staging using imaging in patients with a positive SN is not recommended.[28] It is unclear how patients with lymph node metastases can best be monitored. In MSLT-II, observed patients followed a strict follow-up schedule with ultrasound assessments. They had CT scans of the head, thorax and abdomen once a year. Since the start of that trial, imaging techniques have improved considerably and one may wonder whether a

different approach, for example with PET/CT, would be preferable.

For some, the outcomes of MSLT-II may be a reason to doubt the usefulness of SNB. However, this was not the subject of the trial. Several studies have shown that the tumor status of the SN has a high prognostic value.[2,3] Furthermore, it results in a better survival in patients with a melanoma of intermediate Breslow thickness and a positive SN.[2] The MSLT-II results do not diminish the value of these previously published results and SNB remains a standard staging procedure.

In conclusion, performing CLND does not result in a survival advantage in melanoma patients with a SN metastasis. The morbidity after CLND is higher than after SNB alone. Reasons to perform CLND are the prognostic value of the tumor status of the other lymph nodes, the reduction in nodal recurrence risk, desire to participate in an adjuvant therapy study that requires CLND, or inability to adequately monitor the patient.

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Chapter 4

Current management of patients with melanoma who are found to be sentinel node-positive

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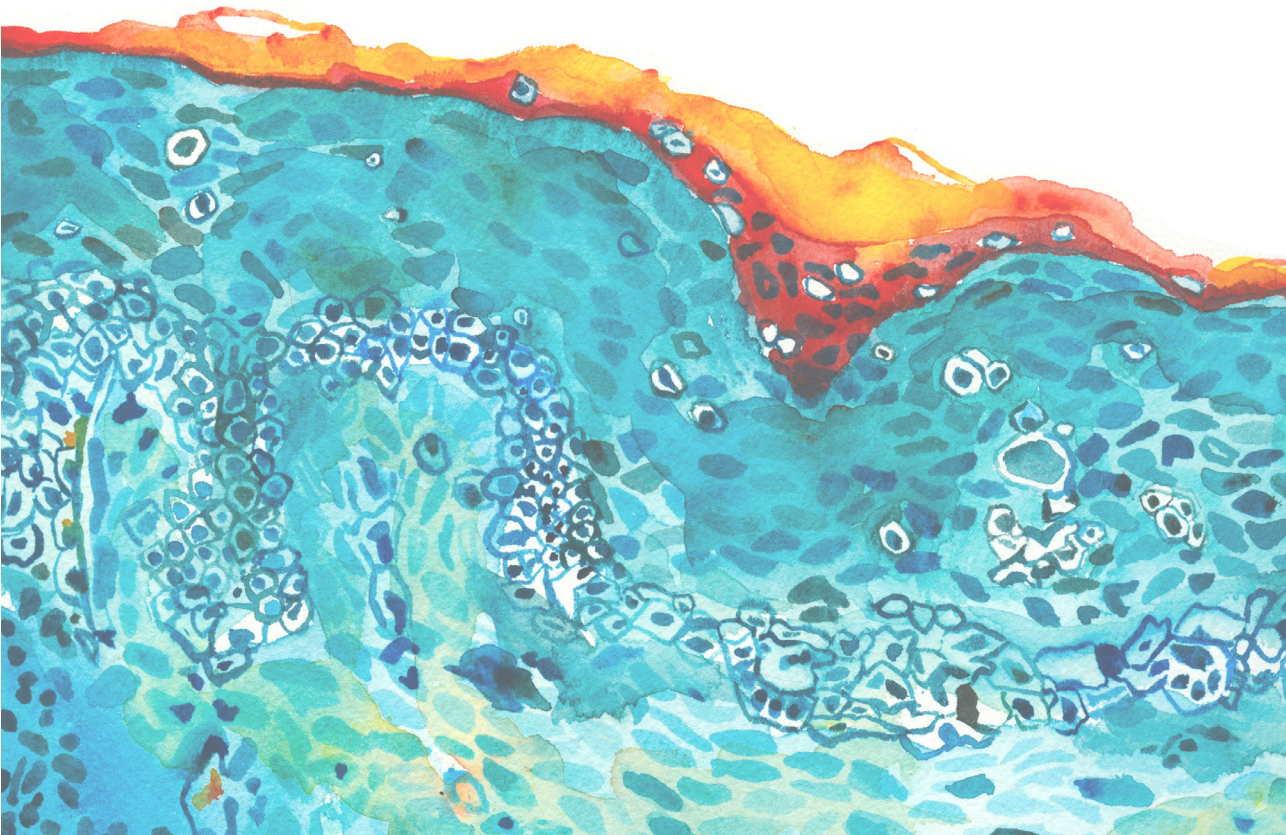

Abstract

Background - The results of the DeCOG-SLT and MSLT-II studies, published in 2016 and mid-2017, indicated no survival benefit from completion lymph node dissection (CLND) in melanoma patients with positive sentinel nodes (SNs). Subsequently, Subsequently, several studies have been published reporting a benefit of adjuvant systemic therapy in patients with stage III melanoma. The current study assessed how these findings influenced management of SN-positive patients in a dedicated melanoma treatment centre.

Methods - SN-positive patients treated at Melanoma Institute Australia (MIA) between July 2017 and December 2018 were prospectively identified. Surgeons completed a questionnaire documenting the management of each patient. Information on patients, primary tumours, SNs, further treatment and follow-up was collected from patient files, the institutional research database and pathology reports.

Results - During the 18-month study period, 483 patients underwent SN biopsy. A positive SN was found in 61 (13%). Two patients (3%) requested CLND because of anxiety about observation in view of unfavourable primary tumour and SN characteristics. The other 59 patients (97%) were followed with four-monthly ultrasound examination of the relevant lymph node field(s). Two of them (3%) developed an isolated nodal recurrence after four and eleven months of follow-up.

Fifty-seven patients (93%) were seen following the publication of the first two adjuvant systemic therapy studies in November 2017; forty-six (81%) were referred to a medical oncologist to discuss adjuvant systemic therapy, which 32 (70%) chose to receive.

Conclusion - At MIA most patients with an involved SN are now managed without CLND. The majority are referred to a medical oncologist and receive adjuvant systemic therapy.

Introduction

Sentinel node (SN) biopsy (SNB) is routinely performed in patients with clinically localized intermediate and thick primary cutaneous melanoma. It offers prognostic and staging information and, combined with completion lymph node dissection (CLND), prolongs survival in SN-positive patients with intermediate thickness melanomas.[1] As no additional nodal metastases are found in approximately 80% of SN-positive patients and in view of the associated morbidity, the need for CLND was questioned.[2–4] In 2017, results of MSLT-II and the German Dermatologic Cooperative Oncology Group Selective Lymphadenectomy Trial (DeCOG-SLT) had shown that melanoma-specific survival is not significantly different when SN-positive patients are carefully observed with regular ultrasonography of their node field(s) and undergo a therapeutic dissection upon locoregional recurrence, compared to those having an immediate CLND.[5,6] Although the median follow-up duration of both trials was limited (43 and 35 months respectively) and questions have been raised about the design and limited size of DeCOG-SLT, their conclusion that SN-positive melanoma patients can be safely observed instead of undergoing further surgery (CLND) is considered to be meaningful.[5,6]

There have also been important recent developments in adjuvant drug therapies, which reduce the risk of both locoregional and distant recurrence. In November 2017 the results of two phase three trials were published, followed by a third trial in May 2018, showing a relapse-free survival benefit from adjuvant PD-1 immunotherapy and BRAF/MEK targeted therapy in patients with stage III melanoma.[7–9]

To determine how these recent surgical and medical trial findings have impacted the management of SN-positive patients, we initiated a prospective study immediately following publication of the MSLT-II results.[5] The initial aims of the study were to determine the frequency and the reasons for undertaking of CLND in this setting, as well as to assess the use of adjuvant systemic treatment.

Methods

The study was conducted at Melanoma Institute Australia (MIA). It was approved by The University of Sydney Ethics Committee (identification number 2017/933) and all patients provided informed consent. Participating MIA surgeons signed a separate informed consent form. SNB was generally recommended for patients who had a melanoma with a Breslow thickness of at least 1mm and was discussed in patients with a thinner melanoma if adverse prognostic features such as ulceration and/or an elevated mitotic rate were present. A SN was defined as any lymph node receiving direct lymphatic drainage from the primary tumour.[10] The lymphoscintigraphy method, SNB technique and protocol for pathological evaluation of SNs have been described previously.[11,12]

Between July 2017 and December 2018, melanoma patients with a positive SN were identified from pathology reports. In patients with a positive SN, the advantages and risks of both the option of CLND and of observation with regular ultrasonography of the node field were discussed. Patient preference took precedence in the decision-making process. MIA surgeons filled out a questionnaire for each patient, recording whether CLND was performed and if so, for what reason(s). Referral to a medical oncologist and further treatment were evaluated. All patients were followed up three to four-monthly, with physical examination. Additionally, an experienced radiologist performed ultrasound examination of the relevant draining lymph node fields in patients who had not had a CLND. Patients who received adjuvant systemic therapy often had three-monthly (PET)/CT-scans instead.

Additional information on patient characteristics, primary tumour details, SNB outcomes, further treatment and follow-up was retrieved from the MIA research database, patient files and pathology reports. Follow-up data were obtained until December 30, 2018. Data were analysed using Excel and SPSS. Numbers were reported with percentiles, means with standard deviations, and medians with interquartile ranges (IQR).

Results

Five MIA surgeons participated in the study. A total of 483 patients underwent SNB during the 18 months of data acquisition following the publication of MSLT-II in June 2017. A positive SN was found in 61 of them (13%; table 4.1). The median maximum diameter of the nodal melanoma deposits was 0.6 mm and 40 of the 72 SNs (56%) contained a metastasis <1 mm in diameter (table 4.2).

Two of the 61 patients (3%) requested CLND after a detailed discussion about the risks and benefits of CLND and observation. Both were anxious about observation because of unfavourable prognostic characteristics. The first patient was a 62-year-old male with stage IIIC melanoma. He had a non-ulcerated primary tumour on the back with a Breslow thickness of 8.5 mm and a mitotic rate of 17/mm2. Two SNs were harvested from the axilla, one of which was positive. The tumour deposit was 1.1 mm, it was located subcapsular, extending into the parenchyma, without extranodal extension. The other patient was a 56-year-old male who was stage IIIC as well with an ulcerated primary tumour on his shoulder with a Breslow thickness of 2.8 mm and a mitotic rate of 20/mm2. Two of three axillary SNs were involved. The largest tumour deposit was 1.0 mm. Both patients underwent axillary dissection, yielding 9 and 22 additional nodes, none containing further metastases.

Fifty-seven of the patients were treated following publication of the adjuvant systemic therapy studies in November 2017. Forty-six of them (81%) were referred to a medical oncologist and 32 (70%) received adjuvant systemic therapy. Twelve of the treated patients had stage IIIA melanoma, six stage IIIB and fourteen stage IIIC. Twenty-four patients were treated with a PD1-inhibitor (pembrolizumab or nivolumab) and eight participated in an adjuvant therapy trial, in which they were randomised to receive nivolumab with or without ipilimumab. None received adjuvant targeted therapy with BRAF or MEK inhibitors because at the time it was not funded in Australia and no clinical trials involving BRAF/MEK inhibitors were open.

Table 4.1 Baseline characteristics

Characteristics	Number of patients / Mean / Median
SN-positive patients	61
Female | male	28 (46%) | 33 (54%)
Mean age (SD)	57 (±14)
Stage at presentation	
IIIA	24 (39%)
IIIB	10 (16%)
IIIC	27 (44%)
Primary tumour*	
Breslow thickness	
≤1.0	3 (5%)
>1.0 – 2.0	26 (43%)
>2.0 – 4.0	17 (28%)
>4.0	15 (25%)
Ulceration	22 (36%)
Median mitotic rate per mm^2 (IQR)	4 (3-8)
Microsatellites	3 (7%)
Intravascular or intralymphatic invasion	7 (16%)
Location	
Head/neck	7 (11%)
Trunk	27 (44%)
Upper extremity	12 (20%)
Lower extremity	15 (25%)

* Data missing for microsatellites and intravascular/intralymphatic invasion in 18 patients.

Table 4.2 Sentinel node characteristics

Characteristics	Number of patients / Mean / Median
SN-positive patients	61
Location positive SN	
Groin	17 (28%)
Axilla	36 (59%)
Neck	7 (11%)
Interval node	1 (2%)
Number of SNs harvested	149
Positive SNs*	
Total number of positive SNs	72
Median number of positive SNs	1 (IQR 1-1; range 1-3)
Median largest deposit in mm	0.6 (IQR 0.3 - 1.5, range 0.02 - 4.0)
Median metastasis penetrating depth in mm	0.3 (IQR 0.1 - 1.1; range 0.01 - 6.0)
Extranodal extension	2 (3%)
Location tumour in SN	
Subcapsular	37 (63%)
Subcapsular and parenchymal	20 (34%)
Parenchymal	2 (3%)

* Largest deposit unknown in 4 SNs, maximum metastasis penetrating depth unknown in 29 SNs, extranodal extension unknown in 9 SNs, location tumour unknown in 13 SNs.

Reasons for refraining from adjuvant systemic therapy were the fear for potential side effects, a low expected absolute benefit in some patients, cost of the drugs, ineligibility for trials, patient co-morbidity (combined with age), and inability or unwillingness to travel to the institute on a regular basis.

Neither of the two patients undergoing CLND developed a recurrence. Eight of the patients who were observed did recur, four of them had been treated with adjuvant therapy (table 4.3). Two observed patients developed an isolated recurrence in a lymph node field. Both had consulted a medical oncologist after SNB but decided not to have adjuvant systemic therapy. The first patient was a 61-year-old female with a stage IIIC primary melanoma on her forearm (Breslow thickness 7.1mm, ulcerated). The retrieved SN contained a tumour deposit with a maximum diameter of 3mm. After four months of follow-up, a nodal recurrence was found on physical examination and confirmed by ultrasound with fine-needle biopsy.

Table 4.3 Further management and follow-up

Further treatment and follow-up	Number
Time from primary to last follow-up in months (median, IQR)	7 (3-12)
Time from SNB to last follow-up in months (median, IQR)	5 (2-11)
Patients lost to follow-up (>6 months since last follow-up)*	5
Patients with recurrences	8 (14%)
Type of recurrence	
Local recurrence	1
Nodal metastasis	2
In-transit metastasis	2
Distant metastasis	2
Local and in-transit metastases	1

* Two patients moved overseas and were referred to a local medical oncologist

She was treated with neoadjuvant immunotherapy followed by axillary CLND. The second patient who developed a nodal recurrence was a 50-year-old male who had stage IIIC melanoma on his thigh (Breslow thickness 6.5mm, non-ulcerated) He had one positive SN containing a tumour deposit with a maximum diameter of 2.1mm. After eleven months of follow-up, a nodal recurrence was noted on a surveillance PET/CT scan performed prior to a routine clinical visit, when it was found to be clinically palpable. He underwent CLND of the groin followed by adjuvant immunotherapy.

All patients were alive at last follow-up, with a median time from primary to last follow-up of 7 months (IQR 3 to 12 months, range 1 to 16 months). Five observed patients (8%) did not attend follow-up at MIA for more than six months. Two of them had moved with follow-up by a local specialist, while the three remaining patients (5% of the cohort) were truly lost to follow-up.

Discussion

This study describes how the management of SN-positive patients at a large specialized melanoma treatment centre evolved following publication of the results of two landmark clinical trials in 2016 and 2017.[5,6] We are not aware of other recent studies on the management of SN-positive patients. In the 18 months following the publication of the MSLT-II results, only two of 61 SN-positive patients underwent CLND. Both expressed anxiety about observation because of unfavourable prognostic primary tumour and SN characteristics, although MSLT-II showed no survival benefit from CLND in the subgroups with these features.[5]

Current surgical management at MIA is in accordance with the recently updated Australian Melanoma Management Guidelines that state "CLND is no longer the preferred treatment for patients with a positive SLNB. CLND or active surveillance are equivalent in terms of 3-year melanoma-specific survival but CLND is more morbid."[13] Before the MSLT-II publication, the guidelines recommended that all SN-positive patients should be offered CLND.[14] However, although it was considered

standard management of SN-positive patients, CLND was not practiced as widely as might have been expected. Isaacs et al. reported that 38% of 599 SN-positive patients treated at MIA between 2004 and 2014 were monitored instead.[15] This was usually due to patients' preference rather than to their surgeon's recommendation. Patients with interval SLNs and multiple SLN fields were less likely to undergo CLND. Studies in the United States and Germany have reported similar outcomes, with 43% and 40% respectively of patients being monitored.[16,17]

The most important parameter in this decision-making process is survival. In the absence of a significant survival benefit from CLND, it is understandable that most patients and surgeons opt for observation.[5,6] However, factors other than survival may also play a role in management decisions (table 4.4). CLND provides additional staging information, with an increase in the AJCC-UICC stage in 5-6% of patients.[18,19] It offers prognostic information that is not available in patients who are observed, by providing the number of involved non-SNs, although it probably only detects 50% of the positive non-SNs.[5] Information on non-SN tumour status can help surgeons in subsequent management recommendations. For example, the prognosis of non-SN-positive patients is similar to the prognosis of patients with palpable nodal disease, making adjuvant systemic treatment even more important.[20–22] Return of their disease is a psychologically devastating experience for some patients and the risk of nodal recurrence is diminished after CLND.[5] Follow-up is less burdensome after CLND, as four-monthly ultrasound examination is not necessary. Furthermore, an early CLND causes less lymphedema compared to a delayed CLND and there is no indication for adjuvant radiotherapy at this early stage of nodal involvement.[14] Lastly, patients with head and neck melanoma were not represented in DeCOG-SLT and had a trend towards better survival with CLND in MSLT-II. If these patients have a nodal relapse, CLND is particularly challenging. These advantages of CLND generally do not outweigh the lack of a significant survival benefit and the morbidity associated with the early operation.

Table 4.4 CLND versus observation of SN positive patients. Overview of outcomes, advantages and disadvantages.

	Completion lymph node dissection	**Observation**
Overall survival[5,6]	No significant difference (Even in subgroup analyses of sex, age, ulceration, Breslow thickness, primary site, number of positive SNs and largest SN metastasis) Trend towards better survival with CLND in patients with head and neck melanoma	
Distant-metastasis free survival[5,6]	No significant difference	
Loco-regional recurrences[5,6]	No significant difference	
Nodal recurrence[5,6,27]	Less nodal recurrences	More nodal recurrences, but no loss of regional control with frequent ultrasound examinations
Distant recurrences[5,6]	No significant difference	
Prognostic information[5,6,18,19]	Information on non-SN tumour status, prognostic for systemic recurrence and survival. Non-SNs positive in ±20% of the SN positive patients Change in AJCC-UICC tumour stage in 5-6% of the patients	No prognostic information on non-SN tumour status
Follow-up[5,28]	In Australia, recommended follow-up is four-monthly in the first two years, six-monthly in year three, then annually for five more years. No surveillance ultrasound assessment necessary during follow-up.[13]	In Australia, recommended follow-up is four-monthly in the first two years, six-monthly in year three, then annually for five more years. Ultrasound assessment of the draining lymph nodes at every visit in the first five years

Table 4.4 Continues from previous page

Acute surgical morbidity[14,29]	No significant difference in acute surgical morbidity in patients undergoing direct or delayed completion lymph node dissection	- Acute surgical complications in 14% of the patients having wide local excision - Acute surgical complications at SNB site in 10% of the patients undergoing SNB - Acute surgical complications in nodal region in 37% of the patients undergoing delayed CLND in case of nodal positivity
Lymphedema[5,14,30]	Lymphoedema in about 12% of the patients	- Lymphoedema in 0.3% of the patients after wide local excision - Lymphoedema in 1 to 6% of the patients after wide local excision and SNB - Lymphoedema in 20 to 24% of the patients after delayed CLND for nodal recurrence
Adjuvant systemic therapy	Available for all SN-positive patients, CLND no longer a prerequisite in most centres	

Some have misinterpreted the results of MSLT-II and advocated abandoning SNB.[23] However, the prognostic significance of SN-status, the improved staging and the survival benefit in node-positive patients are maintained. SNB is not obsolete. Indeed, it is more relevant at as it provides the best opportunity for occult node positive patients to avoid CLND. SNB remains standard of care in Australia and internationally.[24,25]

Only two patients developed nodal recurrences after four and eleven months. As the follow-up of our study is relatively short, more (nodal) recurrences may be expected to develop over time.

There is accumulating evidence that adjuvant systemic therapy improves survival in melanoma patients with lymph node metastases. The preliminary results of the COMBI-AD trial showed that one year of adjuvant targeted therapy with a combination of dabrafenib and trametinib prolonged recurrence-free survival in stage

III patients with a melanoma having the BRAF mutation.[7] The EORTC trial in stage III patients also demonstrated an improved recurrence-free survival with adjuvant pembrolizumab compared to placebo.[8] Results of the CheckMate 238 trial showed that recurrence-free survival with adjuvant nivolumab for one year was better than with ipilimumab in patients with stage IIIB, IIIC and stage IV disease, with less toxicity.[9] Local and distant recurrences were reduced on all trials to similar effect. It should be noted, however, that these three trials ran prior to the MSLT-II results were published, and thus all patients underwent CLND. Also, in the first two trials, patients with metastases ≤1 mm were excluded, as were patients with stage IIIA disease in the third trial. The median maximum diameter of SN metastases in our population was just 0.6 mm. Thus, although adjuvant drug therapy improves the short-term survival rate in patients with lymph node metastases, it remains to be determined whether this is true in the long-term for patients who have only a small tumour deposit in their SN. Nevertheless, the current evidence indicates that adjuvant systemic therapy should be considered in these patients. An ongoing trial, comparing nivolumab to nivolumab plus low-dose ipilimumab (CheckMate-915) does not mandate CLND. In MSLT-II and DeCOG, patients were followed with frequent nodal ultrasound assessments. Patients receiving systemic therapy are often monitored with CT or PET/CT instead. Ultrasound examination is more sensitive and specific for detecting lymph node metastases and PET/CT is best to screen for distant metastases.[26]

In conclusion, this study shows that management of melanoma patients with a positive SN at MIA changed remarkably over a recent 18-month period. Between 2004 and 2014, 62% of the SN positive patients at MIA were managed with CLND.[15] After the results of MSLT-II and DeCOG-SLT were published, 97% of SN-positive melanoma patients no longer underwent CLND and had careful clinical follow-up with imaging of the relevant lymph node field(s). The majority of patients were referred to a medical oncologist to discuss the pros and cons of adjuvant systemic therapy, and 70% of them (32/46) chose to receive this. Compliance with the recommended follow-up schedule was high, and only two patients developed a node field recurrence, both of which were resectable.

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Chapter 5

Sentinel node biopsy in melanoma patients with a local recurrence or in-transit metastasis

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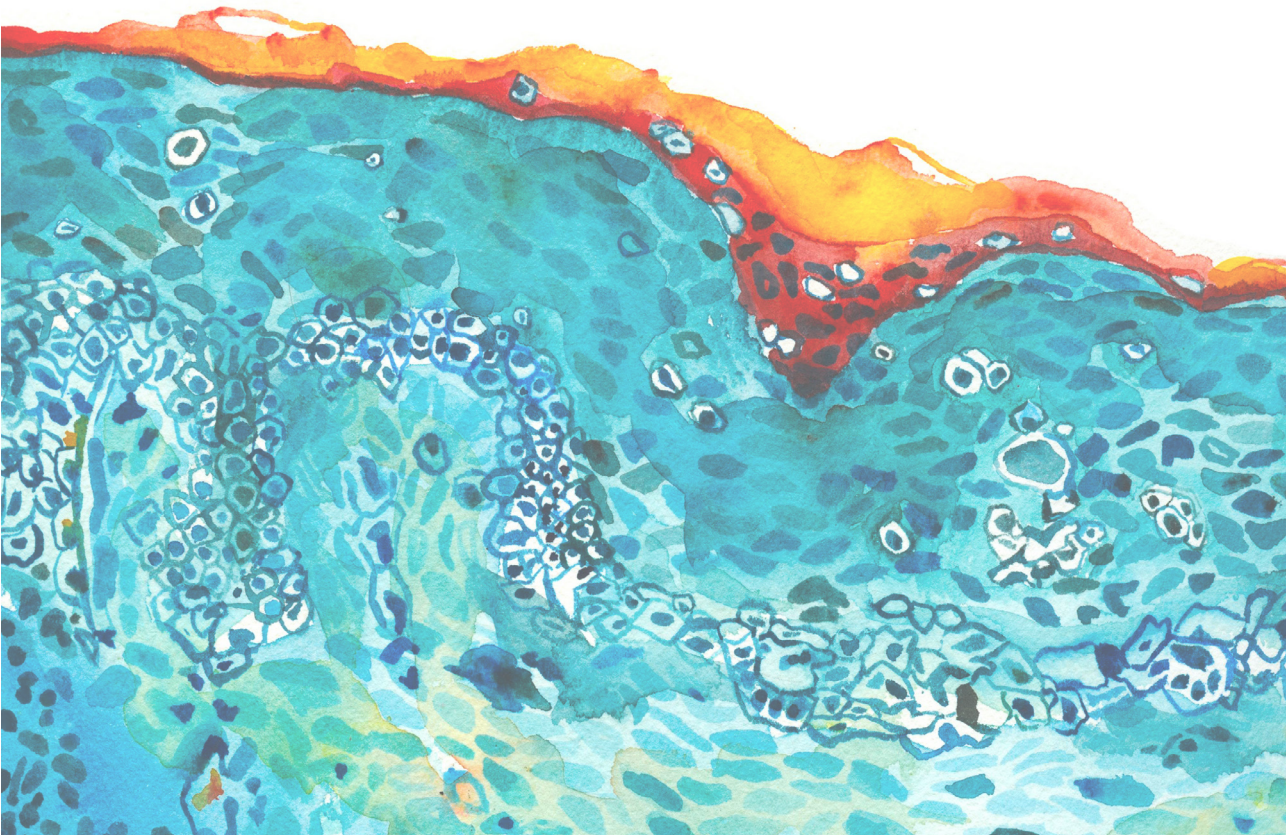

Abstract

Background - Sentinel node (SN) biopsy (SNB) is not routinely performed in melanoma patients with local recurrence (LR) or in-transit metastasis (ITM). The aim of this study was to describe the technique, findings and prognostic value of this procedure, and the outcome in such patients at our institution.

Methods – Prospectively collected data were obtained from the Melanoma Institute Australia database. Patients having SNB for LR or ITM between 1992 and 2015 were included Patient and primary tumor characteristics, lymphoscintigrams, SNB results and follow-up data were analyzed.

Results – Overall, 7999 patients underwent SNB, of whom 128 (1.6%) met the selection criteria. SNB was performed in 85 of 1516 patients who had a LR (6%), 17 of 1671 patients with ITM from a known primary tumor (1%) and 26 of 170 patients who presented with an ITM from an unknown primary (15%). The SN identification rate was 100%. Metastatic melanoma was identified in a SN in 16 of the 128 patients (13%). Follow-up data were available for 114 patients. The false-negative rate was 27%. SN-positive patients had significantly worse overall survival than SN-negative patients, with 5-year survival rates of 54% and 81% respectively (P=0.01).

Conclusion – SNB for LR or ITM was performed infrequently. The SNs were positive in 13% of the patients with a LR or ITM. SN-positivity was associated with worse overall survival. Despite the false-negative rate of 27%, the procedure yielded information that was relevant for staging and prognosis. SNB should be considered in patients with a LR or ITM.

Introduction

Sentinel node (SN) biopsy (SNB) is routinely performed for staging and to improve regional control in patients with a clinically-localized intermediate thickness primary melanoma, with a likely improvement in survival outcome in node-positive patients.[1] The tumor status of the SN is the strongest predictor of recurrence and overall survival.[1]

Information on the results of SNB in patients with a local recurrence (LR) or in-transit metastasis (ITM) is sparse.[2–4] About 5% of melanoma patients develop LR and another 4% ITM.[5] These disease manifestations imply a poor prognosis, with a five-year melanoma-specific survival of 61% for patients with ITM as a first site of recurrence.[5] SNB could be used to select patients most likely to benefit from adjuvant systemic therapy or particularly intensive follow-up, and also to identify lower-risk patients in whom adjuvant systemic therapy might be avoided.[6] The few studies performed previously suggest that SNB may be of value in patients with LR or ITM.[2–4] However, the clinical benefit of the procedure is uncertain, as up to 43% of the patients with ITM as a first site of recurrence will develop distant disease without regional node involvement.[5]

In this study the experience with SNB in patients with LR or ITM at Melanoma Institute Australia was analyzed. The purposes of the study were to assess technical aspects of lymphatic mapping in these patients, the rates of SN identification and involvement, the false-negative rate, the influence of the SNB result on disease staging and the survival outcomes.

Patients and methods

All patients gave informed consent for entry of their data into the Melanoma Institute Australia research database, and approval for the study was given by the Royal Prince Alfred Hospital Research Ethics Committee (MIA 2015-154). Patients undergoing SNB for LR or ITM between 1992 and 2015 were identified from the prospectively collected database.

Three groups were selected: patients with one or more LR from a known primary tumor, patients who recurred with one or more ITM from a known primary tumor, and patients presenting with their first ITM from an unknown primary. Patients with an unknown primary melanoma undergoing SNB for a recurrent ITM were excluded, as were patients in whom the lesion could possibly have been a primary dermal melanoma and patients with distant metastases at the time of SNB. Patients who underwent a simultaneous regional node dissection and patients with less than six months of follow-up were included in the study but excluded from the follow-up analyses.

A LR was defined as a recurrence within 5 cm of the original melanoma site. In patients with a known primary tumor, an ITM was defined as a cutaneous or subcutaneous recurrence located more than 5cm from the primary site, between that site and the draining nodal region. These definitions were used because in the Institute's database, ITMs are defined as lesions located more than 5cm from the primary melanoma scar. In the absence of a known primary tumor, subcutaneous melanoma deposits were considered to be ITMs. For cutaneous lesions, classification as an ITM was based on the opinion of the pathologist, who was made aware that there was no evidence or prior history of a primary melanoma. The technique of lymphoscintigraphy and SNB for primary melanoma at Melanoma Institute Australia have been published previously.[7,8] For the LR and ITMs in our cohort, similar methods for SN retrieval were used. The radiopharmaceutical and blue dye were usually injected at the site of the ITM or local recurrence. In the patients with ITMs, the injections were at the primary tumor site in one patient and at both the primary tumor and the ITM in two patients. In one patient with multiple ITMs, the one closest to the node field was used. The injection was generally intradermal. In one patient, the injection was intradermal and subcutaneous and in another patient it was deep to the ITM.

A SN was defined as any lymph node receiving direct lymphatic drainage from the lesion.[9] A SN procedure was classified as false-negative if nodal recurrence occurred in the region from which a tumor-negative SN was procured. Staging was performed according to the 8th edition AJCC-UICC melanoma staging system.[10]

Data on patient and primary tumor characteristics, lymphoscintigraphy and SNB outcomes, subsequent therapy and follow-up were collected from the database and patient files. Normality of distribution was assessed with the Kolmogorov-Smirnov test. Numbers with percentiles, means with standard deviations or medians with interquartile ranges (IQR) were reported. The false-negative rate was calculated by dividing the number of false-negative procedures by the sum of the false-negative and true-positive procedures. The Fisher's exact test was used to evaluate recurrence rates. The overall survival curves of patients with positive and negative SNs were compared using the Kaplan Meier method and the survival distribution was tested using the log rank test (Mantel-Cox). A multivariate Cox regression was performed to assess overall survival difference between SN biopsy results when taking into account potential confounders. Due to the sample size limitation, only two variables, age and primary site, could be included. Other parameters including Breslow thickness and ulceration were excluded from the multivariate analysis due to the high proportion of missing values. IBM SPSS Statistics 24 and R software were used to analyze data.[11,12]

Results

Of the 7999 patients undergoing SNB between 1992 and 2015, 128 met the study criteria (1.6%). The median follow-up duration from SNB to last visit was four years (table 5.1). A total of 85 out of 1516 patients who had a LR from a known primary (6%), seventeen of 1671 patients with an ITM from a known primary (1%) and 26 of 170 patients with an ITM from an unknown primary (15%) underwent SNB. Thirteen of the 102 patients with a known primary (10%) had a previous SNB for their original melanoma. In two of these thirteen patients (15%) a positive SN had been found at that time, which was followed by a completion lymph node dissection. The current SN was in the same nodal region in all but one of these thirteen patients. In ten patients (8%) there had been another recurrence prior to the recurrence for which the SNB was performed.

Table 5.1 Patient characteristics

Characteristics	Outcome
Number of patients included	128
Local recurrence with known primary tumor	85
ITM with known primary tumor	17
ITM with unknown primary tumor	26
Mean age in years [SD]	61 [11]
Male | Female	64 (50%) | 64 (50%)
Primary tumor*	
Breslow thickness in mm [IQR]	1.2 [0.9-2.0]
Ulceration present	19 (26%)
Mitotic rate per mm^2 [IQR]	2 [1-5]
Location of the primary melanoma	
Head and neck	19 (15%)
Trunk	18 (14%)
Upper extremity	30 (23%)
Lower extremity	35 (27%)
Occult	26 (20%)
AJCC-UICC stage primary tumor (8th edition)	
0 (in situ)	6 (5%)
I	53 (41%)
I/II	9 (7%)
II	25 (20%)
III	30 (23%)
Unknown**	5 (4%)
Prior SNB for primary tumor	13 (10%)
SN tumor positive	2
Completion lymph node dissection	2
Additional non-SNs positive	0

Table 5.1 Continues from previous page

Time from diagnosis of primary to recurrence for which SNB was done in months [IQR]***	40 [17-78]
Overall follow-up in months (primary melanoma to last follow-up) [IQR]	92 [42-155]
Time from SNB to last follow-up	52 [22-95]

* Occult primary with ITM and melanoma in situ at initial presentation excluded from this analysis, characteristics of the remaining 95 patients. Details missing for Breslow thickness in 5 patients, ulceration status in 23 patients and mitotic rate in 15 patients.
** Patients with a Breslow thickness between 1.0 and 2.0 in whom ulceration status was unknown and SNB was not performed.
*** Occult primaries excluded

A SN was successfully retrieved in all 128 patients. It was tumor-positive in sixteen patients (13%, table 5.2). The highest positivity rate (41%) was found in the subgroup of seventeen patients who had an ITM from a known primary tumor. A positive SN was found in three of the eleven patients with a negative SNB for the primary lesion (27%). Twelve of the sixteen patients with a positive SN underwent completion lymph node dissection. In four of them (33%) additional non-SNs were positive. Seven patients received adjuvant radiotherapy and two patients received adjuvant immunotherapy in the CancerVax trial.[13] Adjuvant therapy was usually started in patients with multiple recurrences that developed fast. The SNB outcome never resulted in treatment with isolated limb infusion or perfusion, adjuvant radiotherapy or systemic therapy.

Follow-up information was available for 114 patients. Eleven of the sixteen SN-positive patients (69%) and 21 of the 98 SN-negative patients (23%) developed a recurrence (table 5.3; Fisher-exact test P= 0.0003). Eight of the 98 patients with a negative SN (8%) developed a nodal recurrence, six of them in the SNB region (table 5.3). As a result, the false-negative rate was 27%. None of these patients had a prior SNB. One patient who underwent completion lymph node dissection for a positive SN developed a nodal recurrence in the same region. Eighteen patients (16%) developed distant metastases after a median of 76 months (IQR 12-126 months). Six patients with a negative SN (6%) and seven patients with a positive SN (44%) developed their first subsequent metastasis at a distant site (Fisher's exact test p=0.00001).

Table 5.2 Results of SN biopsy and outcome

	Local recurrence with known primary site (85)	ITM with known primary site (17)	ITM with occult primary (26)	Total (128)
Pre-operative lymphoscintigraphy	81 (98%)	13 (76%)	22 (85%)	116 (91%)
Median number of SNs harvested [IQR}	2 [1-4]	2 [2-4]	2 [1-3]	2 [1-4]
Patients with positive SN	7 (8%)	7 (41%)	2 (8%)	16 (13%)
Median number of positive SNs [IQR]	1 [1-1]	1 [1-1]	1 [1-1]	1 [1-1]
Patients available for follow-up analyses	73	17	24	114
Follow-up duration (range in months) [IQR]	58 [28-96]	44 [21-100]	45 [21-100]	56 [29-97]
Status last follow-up				
Alive without disease	44 (60%)	5 (29%)	16 (67%)	65 (57%)
Alive with disease	3 (4%)	4 (24%)	-	7 (6%)
Alive, status unknown	8 (11%)	-	2 (8%)	10 (9%)
Deceased from melanoma	11 (15%)	6 (35%)	4 (17%)	21 (18%)
Deceased from unrelated cause	2 (3%)	1 (6%)	-	3 (3%)
Deceased, cause unknown	5 (7%)	1 (6%)	2 (8%)	8 (7%)

Table 5.3 Recurrences after SNB

		SN positive patients (n=16)				SN negative patients (n=98)			
	Total (n=114)	Local Recurrence (n=7)	ITM with known primary site (n=7)	ITM with occult primary (n=2)	Total for SN positive patients	Local Recurrence (n=66)	ITM with known primary site (n=11)	ITM with occult primary (n=24)	Total for SN negative patients
Recurrences	32 (28%)	3 (43%)	6 (86%)	2 (100%)	11 (69%)	9 (14%)	4 (36%)	8 (33%)	21 (23%)
Local only	1 (1%) *					1 (2%)			1 (1%)*
ITM only	9 (8%)		1 (14%)		1 (6%)	2 (3%)		6 (25%)	8 (8%)
Nodal only	2 (2%) *					1 (2%)	1 (9%)		2 (2%)*
Local + ITM	1 (1%)		1 (14%)		1 (6%)				
ITM + nodal	1 (1%)					1 (2%)			1 (1%)
ITM + distant	1 (1%)	1 (14%)			1 (6%)				
Nodal + distant	1 (1%)					1 (2%)			1 (1%)
ITM + nodal + distant	5 (4%)	1 (14%)			1 (6%)	1 (2%)	2 (18%)	1 (4%)	4 (4%)
Distant only	11 (10%)**	1 (14%)	4 (57%)	2 (100%)	7 (44%)**	2 (3%)	1 (9%)	1 (4%)	4 (4%)**
No recurrence	82 (72%)***	4 (57%)	1 (14%)	0	5 (31%)	57 (86%)	7 (64%)	16 (67%)	77 (77%)

* One patient had a previous local recurrence before the SNB.
** One SN positive patient had previous local, in-transit and nodal recurrences; one SN negative patient had a local recurrence before the SNB
*** Six patients had a previous local recurrence before the SNB; one was SN positive and five SN negative

In the patients with a negative SN, most of the recurrences were ITMs. These occurred primarily in patients with an unknown primary who had ITM (table 5.3).

SN positive patients had a significantly worse overall survival than those with a negative SN (figure 5.1). Median survival was not reached for SN-negative patients and was five years for SN-positive patients. The five-year cumulative overall survival rates were 81% and 54%, respectively (P=0.01). Multivariate analysis result confirmed the survival difference between SN-negative patients and SN-positive patients (table 5.4). Thus, the tumor status of the SN appeared to be an independent predictor for overall survival.

Figure 5.1 Kaplan Meier survival curve, comparing SN positive and SN negative patients

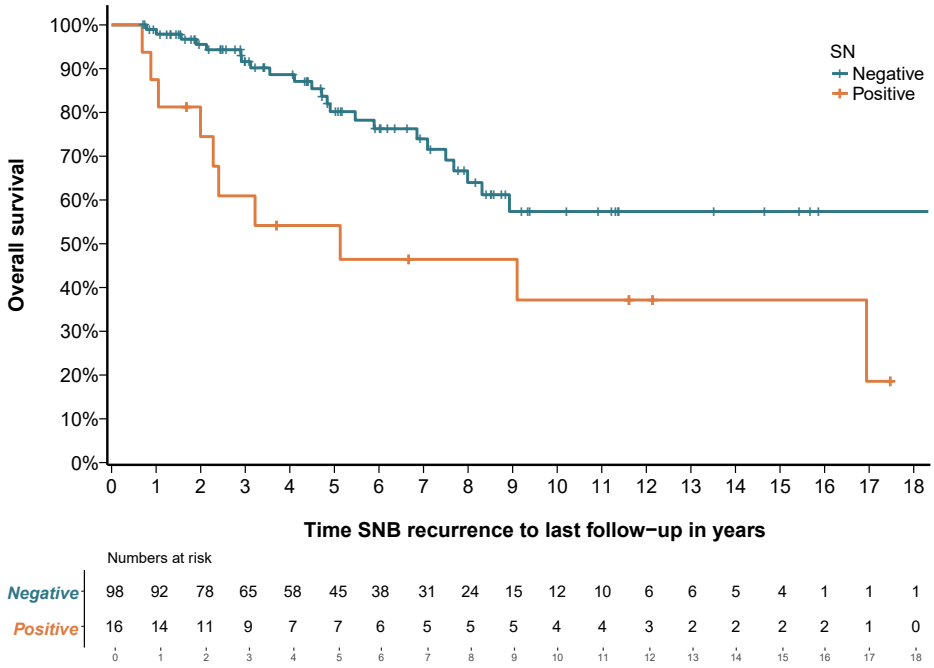

Table 5.4 Univariable and Multivariable Overall Survival Regression

	Univariable		Multivariable	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Positive SNB				
No	1		1	
Yes	2.62 (1.21, 5.64)	0.0141	3.64 (1.43, 9.26)	0.0067
Age (years)	1.04 (1.01, 1.08)	0.0110	1.05 (1.02, 1.09)	0.0046
Breslow thickness (mm)*	1.03 (0.75, 1.40)	0.8666		
Ulceration*				
No	1			
Yes	1.38 (0.52, 3.65)	0.5125		
Primary site				
Head and Neck	1		1	
Trunk	0.95 (0.20, 4.47)	0.9615	0.68 (0.13, 3.46)	0.9613
Upper extremity	1.02 (0.26, 4.02)		0.98 (0.24, 4.02)	
Lower extremity	1.35 (0.37, 4.90)		0.95 (0.25, 3.60)	
Occult	1.08 (0.27, 4.36)		0.69 (0.13, 3.79)	

* Variables are not included in the multivariable model because of the high proportion of missing data.

Discussion

SNB is infrequently performed in melanoma patients with a LR or ITM. At our institution, only 1.6% of all SNBs were performed for these indications. The SN identification rate was 100%. This is similar to the results obtained when the procedure is performed for a primary melanoma, with reported identification rates of 95% to 100%.[14,15] In previous studies of SNB in patients with LR or ITM, the site and depth of injection of the tracer fluids and blue dye with ITM were points of contention. In our population, injections were typically given intradermally around the site of the melanoma recurrence. This seems an appropriate approach from a physiologic point of view and has a high success rate, although there is no evidence that one technique is better than another. In the one patient with multiple ITMs, the lesion closest to the

draining lymph node region was selected. Beasley et al. used the same approach in patients with more than one ITM.[16] Gipponi et al. divided the total dose of radiotracer equally over the lesions.[4] Most studies used intradermal injections, although intra- and peri-tumoral injections have also been described.[2,4,16,17]

The SN-positivity rate of 13% in this study is at the low end of the 12-25% range reported when the procedure is done for a primary melanoma.[1,18,19] Earlier studies reported substantially higher positivity rates in patients with a LR or ITM.[2,3,16,17,20,21] In the most recent (2017) and largest previous publication, Beasley et al. described 59 patients with LR and 48 with ITM.[3] SNB failed in four patients (4%) and SNs were positive in 41 cases (40%). Their patient population may have had more advanced disease than ours, but this cannot be assessed because details of the primary tumors were not provided. Their SN-positivity rates in patients with LR were similar to those with ITM. In our study, 41% of the patients with an ITM from a known primary tumor had an involved SN, which was higher than the 8% in both the patients with a LR and those with an ITM from an occult primary. In five smaller studies of 12 to 38 patients with a LR or ITM, SNs were positive in 27-53% of the cases.[2,4,16,17,20] Two of these studies included patients with more advanced primary tumors and more patients with multiple ITMs.[4,16] In the other three publications these primary lesion characteristics were not reported in detail.[2,17,20] The high false-negative rate in the current cohort must be at least partly responsible for the low SN-positivity rate. If these missed metastases had been found during SNB, the positivity rate would have been 17% (22 of 128 SNs positive). Only two other studies, with sixteen and seven SN-negative patients, looked for false-negative procedures but none were found with 23 and 20 months follow-up, respectively.[2,17]

SN positive patients had a higher chance of developing recurrences than SN negative patients, particularly distant metastases. Although the subgroups were small, analysis of the type of recurrences in the different groups showed that patients with ITM (either from a known primary or with an unknown primary), who had a positive SN, had the highest chance of developing distant metastases. In SN negative patients, recurrences

were most often ITMs. These recurrences were mainly in the group of patients who presented with an ITM from an unknown primary. For unknown reasons, some melanomas predominantly metastasize through lymphatics.[22] Read et al. reported that disease was limited to ITMs, without distant metastases, in 36% of the 190 patients with ITM as first site of recurrence.[5]

A meaningful finding of the current study was the correlation between SN tumor status and prognosis in this population. Five-year overall survival was 81% for patients with tumor-free SNs and 54% if a SN was involved (P=0.01). Several other papers describe a (non-significant) trend towards improved survival for patients with a negative SN.[2–4] The additional information on staging and prognosis is valuable in view of the results of studies of adjuvant targeted therapy and immunotherapy for high risk stage III patients. In three recent studies, adjuvant nivolumab for resected stage IIIB, IIIC and IV disease, adjuvant pembrolizumab in stage III patients and adjuvant targeted therapy with dabrafenib plus trametinib for resected stage III melanoma were found to significantly improve recurrence-free survival.[23–25] In patients with a LR or ITM, SNB could be used to select higher-risk patients who may have a greater chance to benefit from these adjuvant regimens.

The finding of a positive SN changed management in 9% of our patients, as they had a completion lymph node dissection. In patients undergoing SNB for a primary melanoma there is a paradigm shift away from completion node dissection. Both the second Multicenter Selective Lymphadenectomy Trial and the DeCOG trial demonstrated that survival of SN-positive patients is equally good with observation and ultrasound follow-up.[18,26] It is unclear if the implications for management can be extrapolated to patients with a LR or ITM, although this seems plausible.

The false-negative rate after a median follow-up of four years was 27%, since six SN-negative patients developed a nodal recurrence in the biopsied region. False-negative rates for SNB in patients with primary melanoma range between 6% and 38%.[27,28] At our institution, the false-negative rate of SNB for primary melanoma is 13%.[29] One explanation for the high rate found in the present study may be that an occult LR or

ITM disperses melanoma cells to an additional lymph node. Also, nodal involvement can originate from the previously removed primary tumor. As both sources do not necessarily drain to the same lymph node, this may suggest that the tracers should also be injected at the primary lesion site, if SNB was not previously performed.

A limitation of our study is its retrospective design. Subgroups were small because SNB is not performed regularly in patients with LR or ITM, which prohibited detailed analyses. Also, the definition of an ITM was different from the definition in the 8th AJCC-UICC staging manual. In our database, an ITM is defined as a lesion occurring more than 5cm from the primary lesion, instead of the 2cm used in the staging manual.[22]

In conclusion, this study showed that SNB can be performed in patients with a LR or ITM with a high identification rate, although the false-negative rate was considerable (27%). A tumor-positive SN was found in 13% of the patients and was associated with more recurrences and a worse overall survival rate. In patients with a LR or ITM, SNB improves staging and provides prognostic information. The presence or absence of SN involvement may play a useful role in the decision-making process to give or refrain from giving adjuvant systemic therapy and may influence decisions on the appropriate surveillance strategy.

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Chapter 6

Ultrasound examination of the lymphatic drainage area and regional lymph nodes in melanoma patients with in-transit metastases

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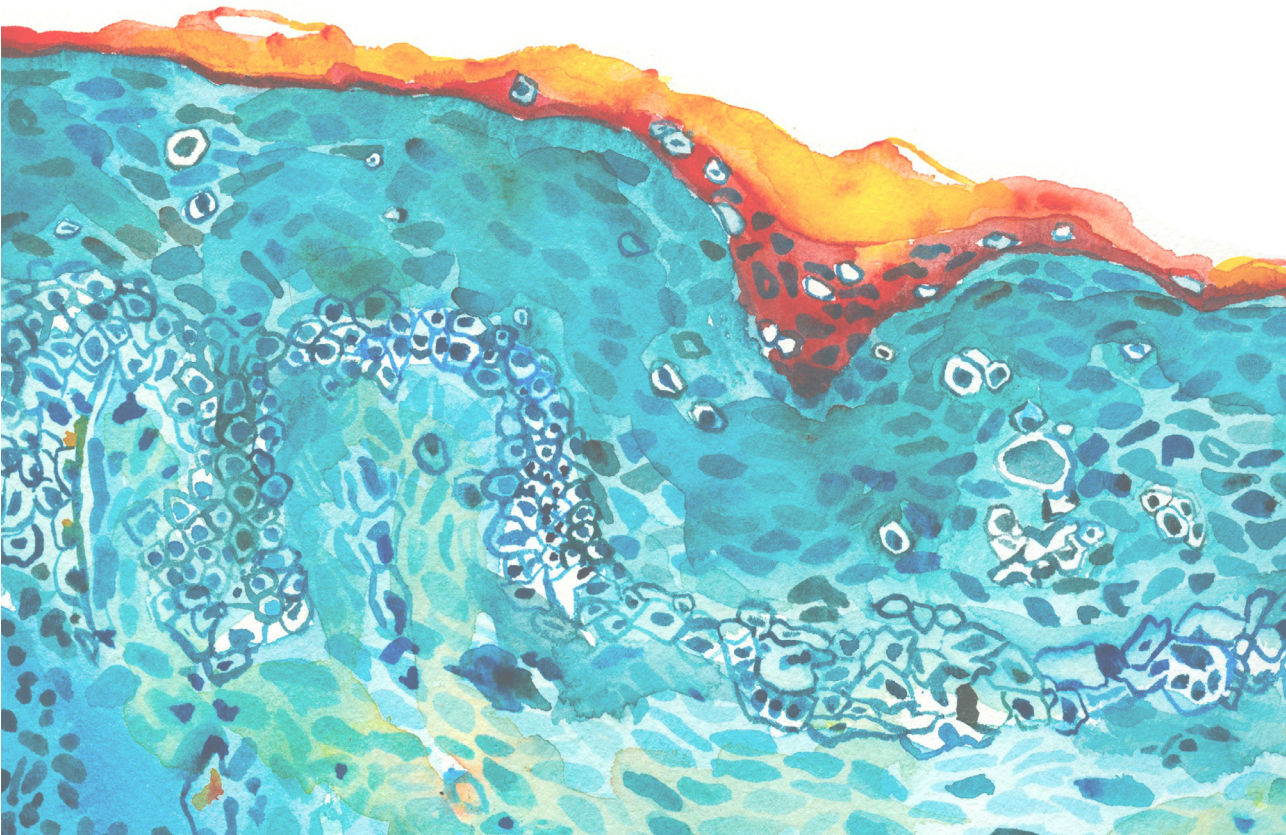


Abstract

Background - In-transit metastases (ITMs) are cutaneous or subcutaneous regional metastases that may occur in patients with melanoma. ITMs are often multiple and new lesions tend to appear over time. Ultrasonography can detect impalpable subcutaneous tumors. The aim of this study was to assess the value of ultrasound examination in detecting additional, non-palpable ITMs and to determine their relevance.

Methods - Melanoma patients with ITMs who underwent regional ultrasound examination of the skin and subcutaneous tissue between the wide excision scar of the primary melanoma and the regional lymph node field were identified. In most, ultrasound assessment also included the regional lymph node field. Relevant data were collected and analyzed.

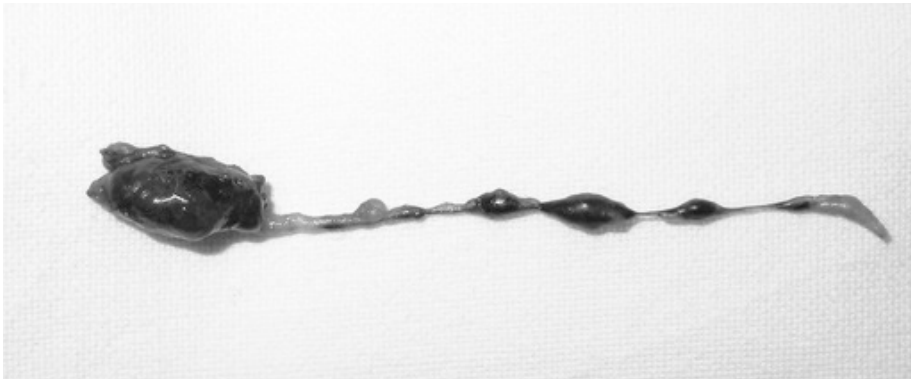
Results - Thirty patients presenting with a total of 42 ITMs were included. Ultrasound examination identified additional ITMs in 16 patients (53%). No impalpable nodal recurrences were detected. Most additional lesions were found closer to the regional lymph nodes than the original ITM. Management was influenced by the ultrasound findings in ten patients (33%). Six of these patients had more extensive surgery, three received systemic drug therapy instead of surgery and in one surgery was delayed and follow-up intensified. In one patient, only subcutaneous fat was found in the excised specimen and the ultrasound was classified as false positive.

Conclusion - In melanoma patients with ITMs, ultrasonography of the lymphatic drainage area provided valuable information, as additional ITMs were identified in more than half of them and management was influenced in a third.

Introduction

In-transit metastases (ITMs) occur in about 4% of patients with cutaneous melanoma.[1,2] ITMs develop in cutaneous or subcutaneous lymphatics between the primary tumor site and the regional lymph node field (figure 6.1). Multiple ITMs often appear simultaneously and additional lesions tend to become apparent over time.[3] The prognostic implications of ITMs are serious, as some 43% of patients will also develop potentially lethal distant metastases.[1] Patients presenting with ITMs are classified by the American Joint Committee on Cancer (AJCC) as having stage N1c disease and have a ten-year survival rate of 77%.[4] Patients who develop more ITMs later on have a worse prognosis, with a ten-year survival rate of 30%.[1]

Figure 6.1 Example of a chain of ITMs in a lymphatic vessel leading to a lymph node



In addition to considering general patient factors, the management of ITMs depends on their number, size, location, and the presence of other regional or distant metastases.[2] First-line treatment for one or a few ITMs is surgical excision.[5] If the disease progresses or if excision is not an option, a range of other loco-regional treatment modalities is available including cryotherapy, electrocoagulation, intralesional or topical drug administration, electrochemotherapy, laser therapy, radiotherapy, isolated limb perfusion and isolated limb infusion.[5,6] Systemic drugs are increasingly being used as first line therapy in advanced cases or as adjuvant treatment after surgical excision.

High-frequency ultrasound is commonly used for the examination of soft-tissues and is particularly suitable for lesions within a few centimeters from the skin surface.[7] Subcutaneous melanoma metastases have specific characteristics on ultrasonography. They project as solid, hypoechoic nodules that are usually well-defined, with irregular or lobular margins.[8] Vascular signals are often seen on color-Doppler ultrasound, but may not be identified in smaller lesions.[9] When multiple, ITMs often appear as a chain of lesions becoming smaller as they approach the regional node field. This chain defines the lymphatic vessel with which these metastases are associated. Abnormalities under 2mm in diameter can be identified.[10] Such small lesions are seldom palpable and are unlikely to be detected with other imaging modalities.

At our institution, a number of patients with one or a few visible or palpable ITMs have been referred for ultrasonography to screen the subcutaneous tissues between the primary melanoma site and the regional lymph nodes for additional ITMs. To our knowledge, this approach is rarely practiced elsewhere. Only one article from 1996 described a similar series, although in that study patients with palpable lymph nodes were also included.[11] The current study assessed the value of high-frequency ultrasound examination in melanoma patients with ITMs. Specific aims were to establish incidence of additional ITMs, the false positive rate and impact on management.

Patients and methods

This retrospective study was of patients treated at Melanoma Institute Australia (MIA), with approval from the local ethics committee (MIA 2019/257). All patients provided informed consent permitting entry of their data into the MIA database.

Ultrasound reports of patients seen between 1 January 2014 and 31 December 2016 were queried to identify those who had an in-transit recurrence and had ultrasound screening of subcutaneous tissues and regional node fields for further metastases. Patients were excluded if it could not be determined whether the findings on ultrasound and physical examination differed.

Two high frequency linear transducers (18-7 MHz and/or 14-5 MHz, Toshiba Aplio 300, Tokyo, Japan) were used for the ultrasound examinations. In patients with severe lymphoedema, a lower frequency curvilinear transducer was used when required to investigate the full thickness of the subcutis (6-1 MHz, Toshiba Aplio 300, Tokyo, Japan). The ultrasound examination encompassed the skin and subcutaneous tissue. The distal extent of the area examined was at least 10 cm distal to the wide excision scar of the primary melanoma or the most distal ITM, whichever was furthest from the melanoma site. The proximal extent of the examination was the regional lymph node field as determined by previous lymphoscintigraphy or, if not available, by clinical judgment. For example, a lower limb examination would cover its full circumference of dermis and subcutis, with screening of the popliteal and inguinal lymph nodes as indicated. The field of view of the ultrasound was adjusted so that the deep margin of the subcutis was at the base of the monitor. When an additional ITM was found, its size was measured, its position was referenced by distance from a fixed anatomical landmark and its precise location was recorded by a surface mark on the skin, with corresponding uncompressed depth. If clinically indicated, confirmation by ultrasound-guided fine needle biopsy was performed.

Patient files and the MIA database were used to gather additional information on patient demographics, primary tumor characteristics, other imaging results, treatment, recurrences and follow-up. The number of ITMs found on ultrasound was compared to the number of lesions detected on physical examination and to the number of lesions identified by further imaging. Data were analyzed using Excel and SPSS.

Results

Thirty patients presenting with a total of 42 ITMs were studied (table 6.1). In 16 of them (53%), this was the first ITM. The lesions were located on the lower extremity in 17 patients (57%). Ultrasound assessment identified additional ITMs in 16 patients (53%; table 6.2).

Table 6.1 Patient, primary tumor and ITM characteristics

Characteristics	Number of patients / median
Male | Female	16 (53%) | 14 (47%)
Age (median, IQR)*	63 (54 - 70)
Primary tumor characteristics**	
Breslow thickness	
≦1.0	6 (20%)
>1.0 - 2.0	10 (33%)
>2.0 - 4.0	8 (27%)
>4.0	6 (20%)
Ulceration	6 (20%)
Mitotic rate ≥1/mm^2	23 (92%)
Location primary	
Head/neck	2 (7%)
Trunk	8 (27%)
Upper extremity	3 (10%)
Lower extremity	17 (56%)
Sentinel node biopsy for primary tumor	15
Positive sentinel node	7
First ITM	16 (53%)
Location of ITM	
Head/neck	2 (7%)
Trunk	8 (27%)
Upper extremity	3 (10%)
Lower extremity	17 (56%)
Method of detection	
General practitioner	4 (13%)
Patient	12 (40%)
Specialist	1 (3%)
Unclear patient or specialist	8 (27%)
Surveillance PET/CT	4 (13%)
Ultrasound	1 (3%)

* At time of melanoma diagnosis

** Missing values for ulceration in 4 patients, for mitotic rate in 5 patients

Table 6.2 Detection of ITMs

Characteristic	Number of patients / number of lesions
Number of lesions on physical examination	
0*	8
1	12
2	5
≥3	5
Number of lesions on ultrasound	
0	3
1	8
2	9
≥3**	10
Number of patients with staging PET/CT	19 (63%)
Number of lesions on PET/CT	
0	-
1	6
2	5
≥3	4
Unclear or 'multiple'	4

* Five patients presented after the general practitioner had excised an ITM. In three patients, the ITMs were detected on PET/CT and these were not identifiable on physical examination.
** In one patient, three ITMs were palpable. On ultrasound examination, a series of additional lesions were seen, but their number was not specified.

Most of these lesions were located closer to the regional lymph node field than the clinically-apparent ITM(s). The smallest ITM that was identified measured 2 x 2 x 3 mm. The ultrasound was false-positive in one patient who presented with three ITMs on the calf. Ultrasound showed a suspicious lesion in the thigh. Excision was performed, but histopathological examination revealed only normal subcutaneous fat. This patient later developed multiple histologically-confirmed ITMs in the thigh. Staging PET/CT was performed in 19 patients (63%) and identified fewer ITMs than ultrasound in six patients and more lesions in one. The PET/CT revealed asymptomatic distant disease in two patients.

In ten patients (33%), subsequent management was influenced. This was because of the ultrasound result in eight patients, including the false positive case, and by a combination of ultrasound and PET/CT in two. Surgery was more extensive than the initially planned simple excision in six of these patients and three received systemic therapy instead of undergoing excision. In the remaining patient with three palpable ITMs, ultrasonography revealed extensive non-palpable disease and the planned excision of the palpable lesions was cancelled in lieu of further staging. Just one lesion was excised for mutation testing and follow-up was intensified. Further lesions were excised when they became palpable. Altogether, immediate excision was performed in 25 of the 30 patients (83%). Two received neoadjuvant systemic therapy followed by excision. One of these two patients was already enrolled in a neoadjuvant therapy trial at the time of the ultrasound and the other received off-trial neoadjuvant therapy. Three patients received systemic therapy only.

In 24 patients (80%), the ultrasound examination included the regional lymph node field. Two of these patients already had palpable lymphadenopathy when they presented with ITMs. In one of them, nodal disease was confirmed with fine needle aspiration biopsy. The second patient was found to have concurrent distant disease on PET/CT and the lymph node was not biopsied. In two other patients with normal nodes on physical examination (8%), ultrasound suggested metastatic disease, but no nodal involvement was found on further examination and follow-up. In one of them, the node subsequently decreased in size. In the other, fine needle aspiration biopsy did not reveal metastatic disease.

Median follow-up of all patients was 31 months (IQR 17-40 months). Twenty patients developed further recurrences after a median of six months (IQR 3–13 months). The first subsequent recurrences were more ITMs in 14 patients, a local recurrence in one, a lymph node recurrence in one and distant disease in four. Five patients died after a median follow-up of ten months (17%, IQR 6-21 months). One died of melanoma, three of other causes and in the remaining patient the cause of death was unknown.

Discussion

Ultrasound examination of the skin and subcutaneous tissue from the primary melanoma site up to and including the regional lymph nodes revealed additional ITMs in 53% of the patients with an ITM. This led to a change in management in ten of the 30 patients. One patient had a false positive ultrasound, although it is possible that the imaging was correct and the surgeon did not remove the actual non-palpable metastasis. This scenario is realistic in view of the ITMs that were subsequently identified in the same area. In one patient, ultrasound found new lesions both proximal and distal from the palpable ITM. The additional ITMs found on ultrasound were closer to the regional node field or adjacent to the palpable ITM in most patients, representing new lesions along the line of the lymphatic that was related to the original ITM(s). Twenty patients (67%) developed more recurrences, after a median of six months of follow-up. In 70% the recurrence was another ITM. At least some of these lesions must have been present at the time of the ultrasound but were not detected. It is unclear whether the ultrasound assessment led to a disease-free survival benefit.

The value of ultrasound in patients with ITMs has been studied before. In 1996, it was reported that ultrasonography led to a change in the treatment plan for 15 of 28 patients (54%) with palpable subcutaneous or lymph node metastases.[11] This is more than the 33% found in the current study but unfortunately no distinction was made between ITMs and lymph node metastases. In most cases, ultrasound examination helped determine whether a lesion was benign or malignant. Another study investigated the value of annual ultrasound examination in the follow-up of 600 asymptomatic patients who had a melanoma with a Breslow thickness ≥1 mm.[12] The scar at the site of excision of the primary tumor and the surrounding tissue within a 10 cm radius were examined. Ultrasound had identified impalpable ITMs or satellite lesions in 63 asymptomatic patients (11%) after a median follow-up of two years.

It is well established that ultrasound examination is more sensitive and specific in detecting nodal metastases than physical examination.[11,13–20] The reported sensitivity of

ultrasound to detect disease in a sentinel node in patients who present with a clinically localized melanoma is low (5-7%).[21,22] On the other hand, ultrasound surveillance of the relevant node field is useful and it has become a routine procedure in the follow-up of sentinel lymph node-positive patients now that it has been shown that observation with regular ultrasound examination of the node field yields a survival rate similar to that of completion lymph node dissection.[23–25] The early discovery of nodal metastases enables timely treatment and virtually eliminates the risk of loss of regional disease control.[25]

Our study has several limitations. Its retrospective design makes it liable to selection bias. As we only included patients in whom the report stated that the surrounding tissue was examined, we may have missed patients in whom ultrasonography was performed but not reported (e.g. because nothing was found). This may have resulted in overestimation of the incidence of further ITMs. The limited number of included patients prevented detailed statistical analyses. Despite these limitations, our study is the first to describe this ultrasonography technique in detail and report the value of ultrasound findings in patients with an ITM. Larger, prospective, randomized studies would be required to determine whether early discovery of additional ITMs improves survival.

There are several other options for the staging of patients with ITMs. PET/CT is the preferred technique to search for asymptomatic distant metastases. In a previous study, we found that the sensitivity of PET/CT for staging patients who had ITMs was 58% and the specificity 83%. The PET/CT led to a change in management in 16% of the patients.[26] Ultrasound is more sensitive than PET/CT in the detection of subcutaneous lesions. The sensitivity of ultrasound to detect ITMs has been reported to be 100%, whereas this was 46% for PET/CT.[27] This sensitivity of 100% may be an overestimation, as no information on the follow-up of these patients was provided in the publication. Sentinel node biopsy can also play a role in the staging of patients with ITMs. A recent study of patients with a local recurrence or ITM undergoing sentinel node biopsy at our institution demonstrated the feasibility and potential relevance of the procedure.[28]

A sentinel node was identified in all 128 included patients and was positive in 13%. Patients with a positive sentinel node had a significantly worse overall survival rate and a higher risk of recurrence, in particular distant metastases. Altogether, patients with ITMs appear to benefit from a comprehensive staging approach with ultrasound examination to detect further ITMs, sentinel node biopsy to detect lymph node micrometastases and whole-body PET/CT to identify asymptomatic distant metastases.

In conclusion, ultrasound examination was a useful staging procedure as it identified additional ITMs that were neither visible nor palpable in more than half of the patients who were assessed. No new lymph node metastases were discovered. The finding of additional ITMs altered subsequent management in a third of the patients.

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Chapter 7

False-positive results and incidental findings with annual CT or PET/CT surveillance in asymptomatic patients with resected stage III melanoma

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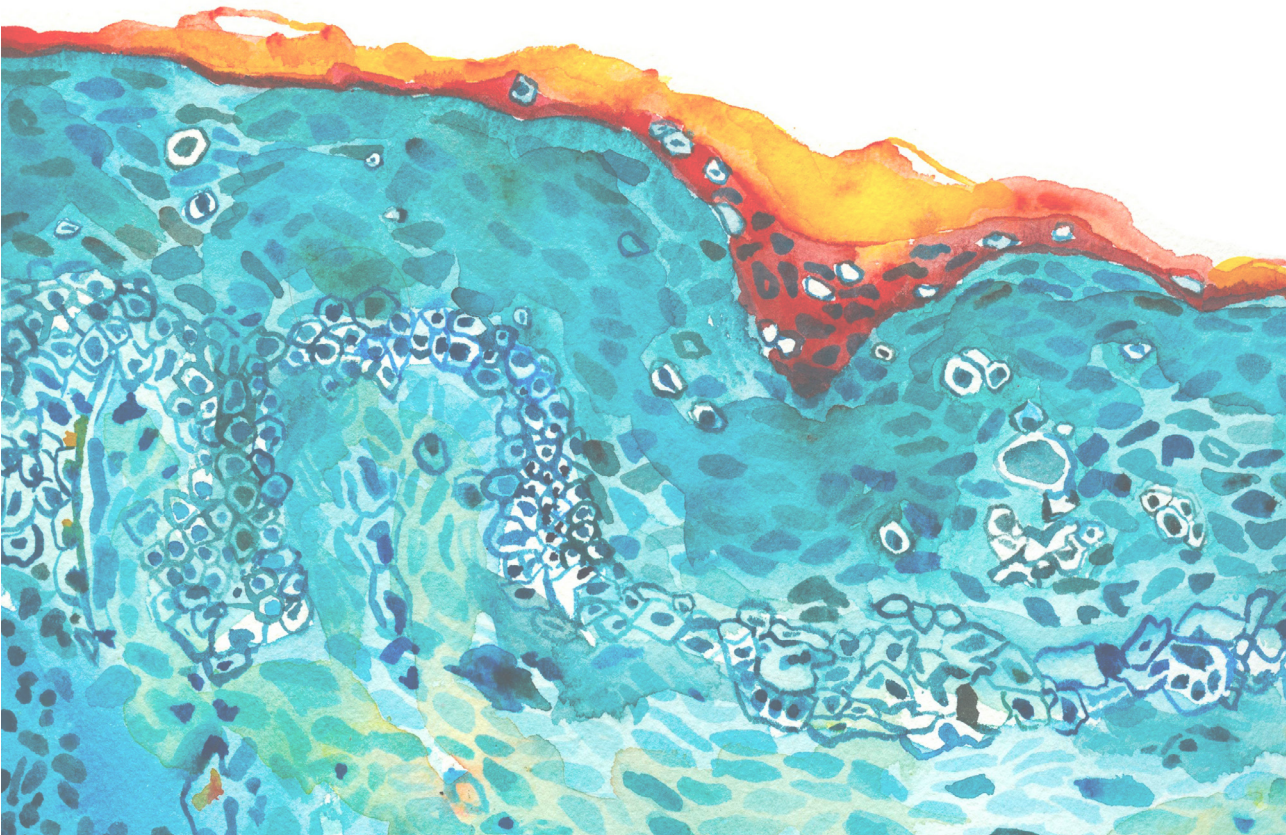


Abstract

Purpose - To quantify false-positive and incidental findings from annual surveillance imaging in asymptomatic, AJCC stage III melanoma patients.

Methods - Cohort study of patients treated at Melanoma Institute Australia (2000-2015) with baseline CT or PET/CT imaging and at least two annual surveillance scans. False-positives were defined as findings suspicious for melanoma recurrence that were not melanoma, confirmed by histopathology, subsequent imaging or clinical follow-up. Incidental findings were defined as non-melanoma-related findings requiring further action. Outcomes of incidental findings were classified as: 'benign' if they resolved spontaneously or were not seriously harmful; 'malignant' if a second malignancy was identified; or 'other' if potentially harmful.

Results - Among 154 patients, 1022 scans were performed (154 baseline staging, 868 surveillance) during a median follow-up of 85 months (interquartile range 64-115); 57 patients (37%) developed a recurrence. For baseline and surveillance imaging, 124 false-positive results and incidental findings were identified in 81 patients (53%). The frequency of these findings was 5-14% per year. An additional 181 tests, procedures and referrals were initiated to investigate them. The diagnosis was benign in 99 of 124 findings (80%). Fifteen patients with a benign finding underwent an unnecessary invasive procedure. Surveillance imaging identified distant metastases in 20 patients (13%).

Conclusion - False-positive results and incidental findings occur in at least half of all patients undergoing annual surveillance imaging, and the additional healthcare use is substantial. These findings persist over time. Clinicians need to be aware of these risks and discuss them with patients alongside the expected benefits of surveillance imaging.

Introduction

Patients treated for stage III melanoma are at high risk of developing distant metastases. The 10-year melanoma-specific survival rates for American Joint Committee on Cancer (AJCC) 8th Edition stage IIIA, B, C and D disease are 88%, 77%, 60% and 24% respectively.[1] In approximately half of the stage III patients, the first relapse is systemic.[2, 3] Early detection enables earlier treatment and increases treatment options. Thus, surveillance imaging has been proposed to improve overall survival, however this has not been demonstrated in randomized trials in other cancers.[4–6]

Clinical trial protocols frequently mandate regular follow-up with computed tomography (CT) or positron emission tomography (PET)/CT.[7–9] For patients who are not in trials, no general consensus exists and various follow-up schedules with different imaging modalities are used.[10] Recommendations for surveillance are based on evidence of moderately high sensitivity for detection of recurrence.[11] However, most studies are retrospective, and report over half of the recurrences in asymptomatic stage III melanoma patients are detected by the patient or physician, rather than through imaging.[2,3,12–16] Therefore, recommendations in international melanoma guidelines vary markedly, from using frequent surveillance imaging in all patients with melanoma staged IIC or higher, to only considering imaging in a specific subset of high-risk patients.[17–22] Clinically, the prevalence of surveillance CT or PET/CT imaging has increased dramatically over the last two decades.[23, 24]

While there may be benefits of surveillance CT or PET/CT imaging, frequent scans also have disadvantages. Surveillance imaging may create anxiety for patients and increases the risk of second cancers due to radiation exposure.[25, 26] Furthermore, annual imaging may reveal other radiologic abnormalities, which is of concern if they are of little or no clinical significance yet result in further diagnostic tests, additional treatments, increased healthcare costs, possible adverse events and further patient anxiety.[27, 28] The aim of this study was to quantify the false-positive results, incidental findings and subsequent healthcare activity related to findings from annual surveillance imaging in

asymptomatic stage III melanoma patients. The true-positive findings are reported, to enable the clinical relevance of the data to be put into context.

Methods

Study design, setting, participants

Consecutive melanoma patients with AJCC-IUCC 8th edition stage III disease, treated at Melanoma Institute Australia (MIA) between 2000 and 2015, who underwent a baseline CT or PET/CT scan and who had at least two annual follow-up scans were identified from the prospectively established MIA database. Our aim was to assess patients undergoing frequent surveillance imaging and this criterion was used to identify a group who underwent a series of scans rather than just one scan. Patients participating in a trial (e.g. MSLT-II, C-VAX, DERMA) who had annual imaging follow-up, were included. Most of these trials included SN positive patients only. CT imaging consisted of CT brain, CT chest and CT abdomen/pelvis. Whole body PET/CT imaging was performed using 18 fluorodeoxyglucose (FDG). Baseline imaging was defined as any scan performed within 3 months after diagnosis. Annual surveillance imaging was defined as a follow-up scan performed 12 months (+/- 3 months) after the prior scan, in a patient without symptoms or clinical suspicion of distant recurrence. Patients were followed until a confirmed diagnosis of stage IV melanoma, death or last follow up (as of September 30, 2017). Approval from the Royal Prince Alfred Hospital Ethics Committee was obtained (MIA2016/182).

Classification of findings

Suspicious findings on CT or PET/CT imaging were categorized as those that did not require action versus those that did require additional action, i.e. further investigations (figure 7.1). Distant metastases identified on surveillance imaging before they were clinically apparent were considered true-positive findings. These were confirmed histologically or radiologically. False-positive results were defined as findings that were

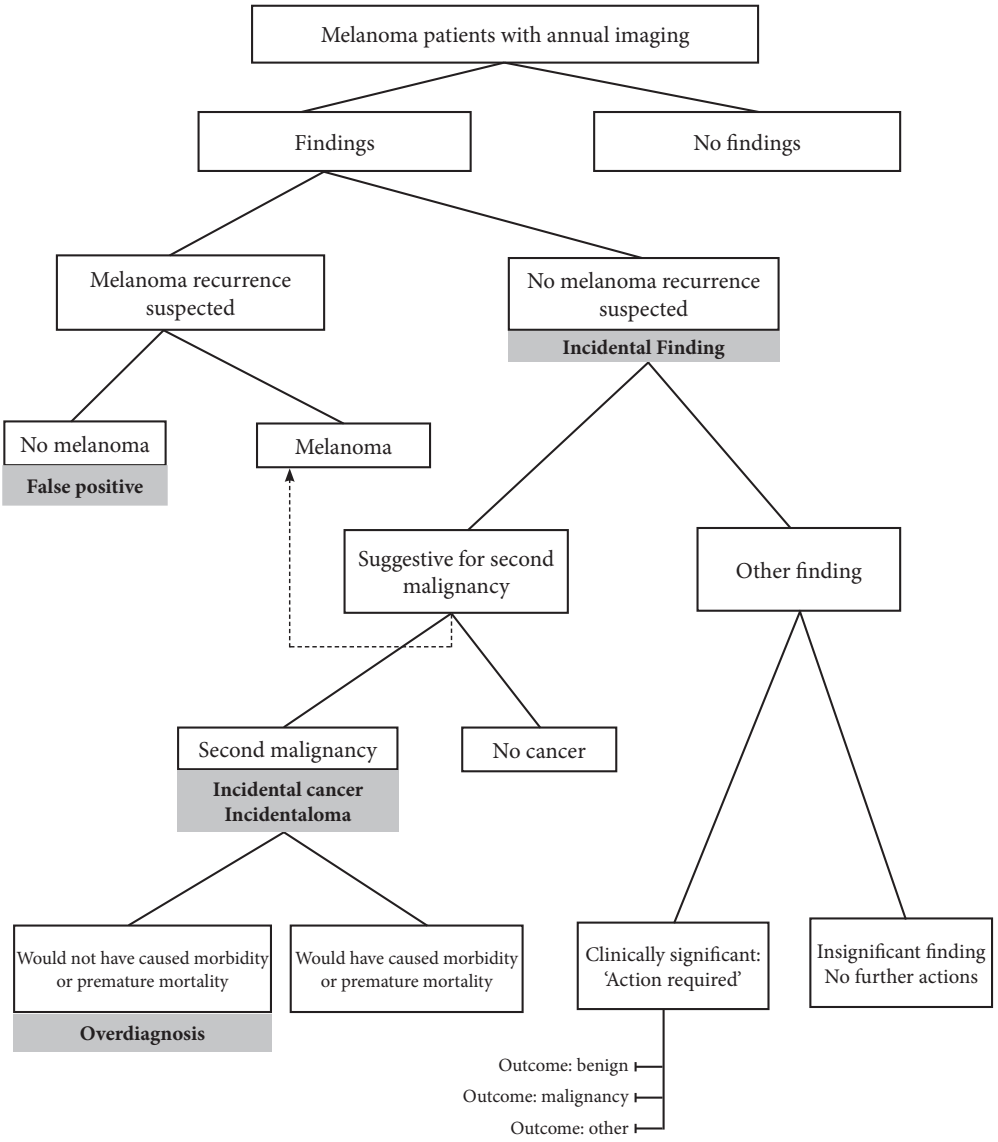
equivocal for metastasis on imaging, required further action to confirm or exclude this, and were ultimately found to be unrelated to melanoma using a reference standard of histopathology, subsequent imaging or clinical follow-up. Incidental findings were defined as abnormalities that were not suspected to be melanoma-related.

The outcomes of incidental findings were classified into 1 of 3 categories: 'benign', if they disappeared spontaneously, did not change or were not seriously harmful (e.g. calcified lung nodule); 'malignant' if a second malignancy was found; or 'other' if they were non-malignant but potentially seriously harmful (e.g. sarcoidosis). Where there was uncertainty in classification, agreement was reached through discussion with authors RM, ON, RS, JT. Findings reported on multiple follow-up scans were counted only once, at the first time of detection.

Data extraction

All CT and PET/CT reports were reviewed by AN. The findings were compared to a blinded examination by MD on a sub-set of randomly selected patients including 30 scan reports, to check inter-rater agreement. The MIA research database, clinical trial files and patient charts were reviewed to extract information on patient and tumor characteristics, scans, clinical decisions, and follow-up. When a finding required further action, information on all additional scans, blood tests, biopsies, surgery, referrals, clinic visits and other activities was sought through clinical notes, referral letters, and subsequent investigation request forms. Adverse events, defined as any untoward events documented as a consequence of further investigations, were recorded. Referrals to other specialists or primary care doctors were followed up by contacting them.

Figure 7.1 Flow chart categorization for false-positive results and incidental findings



Statistical methods

Outcomes were reported as counts and proportions of incidental findings or false-positive findings, per patient over the study period, per single scan and per follow-up year, and additional actions quantified. Results from baseline and follow-up scans were reported and analyzed separately, reflecting differences in clinical practice guidelines and enabling assessment of risk from one-time scanning versus serial scanning. Descriptive statistics were used to summarize the findings. Cumulative incidence was calculated by dividing the total number of patients with findings up to each year, by the number of patients included in the study. Data were analyzed using SPSS v24 software.

Results

Patient characteristics

Three hundred and fifty-one patients with resected stage III melanoma and baseline CT or PET/CT imaging were identified. Of these 154 (44%), mean age 49 years, 68% males, met the inclusion criteria of at least two annual surveillance scans (table 7.1). Median follow up was 85 months [IQR 64-115]. Most patients (147 patients; 96%) had a sentinel node biopsy, which was positive in 143 (97%). Of these, 79 patients (51%) had a completion lymph node dissection, with non-sentinel node metastases found in fourteen patients (18%). The AJCC 8th edition stage for the entire cohort was IIIA in 58 patients (38%), IIIB in 39 (25%), IIIC in 55 (36%) and IIID in 2 patients (1.3%).

In total 1022 scans were performed and evaluated, 154 baseline scans and 868 surveillance scans. The inter-rater reliability between the two assessors was >90%. There were 985 CT-scans and 37 whole body PET/CT-scans. All patients had at least three scans, after which a yearly decline in patient numbers having annual scans was noted (Supplementary figure 1, online only).

Table 7.1 Patient characteristics and outcomes

Characteristics	Number [SD, IQR or %]
Number of patients included	154
Mean age (in years)	49 (SD 14)
Females | Males	49 (32%) | 105 (68%)
Primary tumour*	
Breslow thickness, median (mm)	2.2 (IQR 1.4-3.2)
Ulceration	44 (29%)
Mitotic rate, median (per mm^2)	4 (IQR 2-7)
Microsatellite or in-transit lesions	9 (6%)
Location of the primary melanoma	
Head and neck	19 (12%)
Trunk	63 (41%)
Upper extremity	22 (14%)
Lower extremity	45 (29%)
Occult	5 (3%)
AJCC stage (8th edition)	
IIIA	58 (38%)
IIIB	39 (25%)
IIIC	55 (36%)
IIID	2 (1.3%)
Sentinel node biopsy performed	147 (96%)
Sentinel node positive	143 (97%)
Completion lymph node dissection performed	79 (51%)
Additional non-sentinel nodes positive	14 (18%)
Number of patients that developed recurrence	57 (37%)**
Local	13
In-transit	17
Regional lymph node(s)	32
Distant	36

Table 7.1 Continues from previous page

Median recurrence free survival (months)	30 (IQR 20-40)
Median distant metastasis free survival (months)	38 (IQR 30-60)
Median follow-up time (months)***	85 (IQR 56-112)
Status at last follow-up (until September 2017)	
Alive, no sign of recurrence	119 (77%)
Alive with recurrence	7 (5%)
Alive, status unknown	4 (3%)
Dead, melanoma	24 (16%)

* Data missing for Breslow thickness in 5 patients, mitotic rate in 6 patients and microsatellite or in-transit lesions in 14 patients

** Some patients had more than one recurrence

*** Time until last follow-up or time until distant metastases (stage IV).

SD = Standard deviation; IQR = Interquartile range

Overall, 57 patients (37%) developed a recurrence during the study period; 62 locoregional and 36 distant recurrences (in 36 patients). In 20 patients, distant metastases were identified on surveillance imaging (56% of patients with distant metastases, 13% of cohort). These metastases were identified between scan number three and scan number ten. A median of four scans (IQR 3-5) were performed before a distant metastasis was identified. In 16 of 36 patients, the distant metastases were detected outside surveillance imaging. Two of these recurrences were identified on an additional scan ordered to further assess incidental/true-positive findings.

False-positives and incidental findings

On baseline and surveillance scans, 912 non-melanoma findings were identified in total, of which 124 initiated further evaluation or treatment (table 7.2). Of these 124, 47 were found on baseline imaging and 77 on surveillance scans. In 38 of 154 patients (25%), baseline CT or PET/CT imaging revealed false-positive (n=37) or incidental findings (n=10) requiring action (for the differences between CT and PET/CT see Supplementary table 1, online only). In each subsequent year of follow-up (scan 2 up to 9), 5-14% of the patients had false-positive or incidental findings on surveillance imaging (figure 7.2; table 7.3).

The cumulative incidence of findings on surveillance scans was 14% and 20% for the first and second annual scans respectively (table 7.3). Surveillance imaging identified 49 false-positive results and 28 incidental findings (77 findings in total) in 61 of 154 patients (40%; table 7.2).

Sixty-four (83%) suspicious lesions identified on surveillance imaging were found to be benign (Table 7.4). Eleven findings in eleven patients (14% of the findings on surveillance imaging; 7% of the cohort) were potentially serious. These included two second malignancies (breast cancer and renal cell carcinoma) and nine other findings (four patients with pneumonia, three with severe coronary artery calcification, one with sarcoidosis and one with severe aortic calcification). In two patients, the outcome remained unknown as they were lost to follow-up.

Table 7.2 Non-melanoma findings per patient and per scan for baseline and surveillance imaging

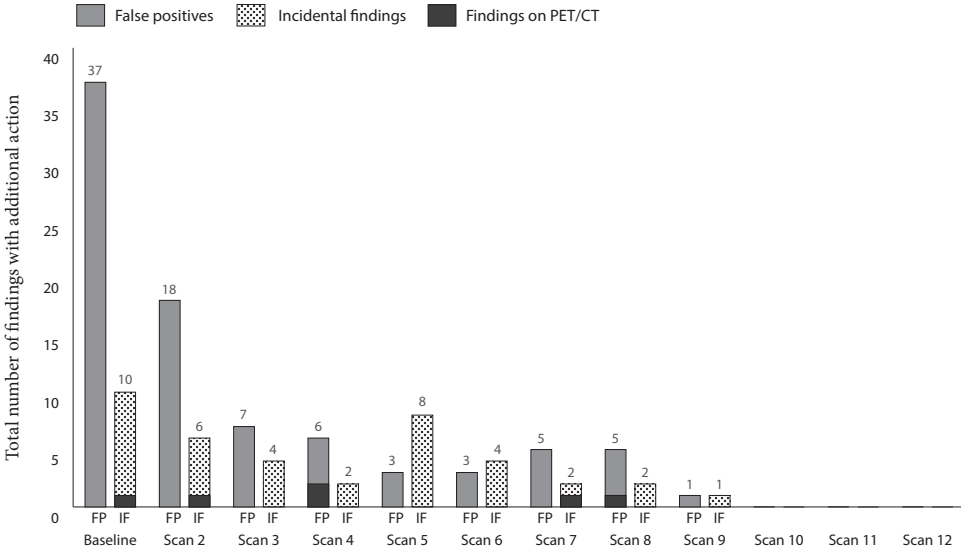
	Findings	Number of scans (n=1022)	Patients (n=154)
Incidental findings not requiring action	788	461	142
Findings requiring action on baseline imaging	47	38*	38* (25%)
False-positives on baseline	37	32	32 (21%)
Incidental findings on baseline	10	10	10 (6%)
Findings requiring action on surveillance imaging	77	69 (7%)	61** (40%)
False-positives	49	45 (4%)	42 (27%)
Incidental findings	28	24 (2%)	21 (14%)
Total number of findings	912	510^^	149^

* Four baseline scans in four patients had a false-positive finding as well as an incidental finding

** Two patients had an incidental finding as well as a false-positive finding on follow-up scans

^ Scans and patients could have more than one finding

Figure 7.2 False-positives and incidental findings requiring additional action, per scan-type, at baseline and per surveillance year



Total findings each year	47	24	11	8	11	7	7	7	2	0	0	0
Total of patients each year	154	154	154	132	116	93	73	58	40	30	15	3
Number of patients with findings	38 (25%)	21 (14%)	11 (7%)	8 (6%)	8 (12%)	6 (6%)	6 (8%)	7 (12%)	2 (5%)	-	-	-

Additional procedures and healthcare utilization

On baseline imaging, 7 of 154 (5%) patients had findings that necessitated invasive procedures. In five of them, (3%), the findings were benign, after undergoing six invasive procedures. Two of these procedures were surgical; an adrenal gland nodule resection (no abnormality was discovered pathologically), and a benign pelvic cyst removal.

For surveillance imaging, a total of 181 additional investigations, procedures, doctor's visits and referrals were undertaken as a result of false-positive or incidental findings (Table 7.4). Subsequent imaging with CT, ultrasound assessment and referral to other physicians were most frequently undertaken.

Table 7.3 Cumulative incidence of false-positives and incidental findings

	Total patients each year	Findings	Patients with findings per year	Unique patients with findings cumulative (including baseline scan)	Unique patients with findings cumulative (surveillance scans only)
Scan baseline	154	47	38 (25%)	38 (25%)	-
Scan 2	154	24	21 (14%)	54 (35%)	21 (14%)
Scan 3	154	11	11 (7%)	60 (39%)	31 (20%)
Scan 4	132	8	8 (6%)	66 (43%)	39 (25%)
Scan 5	116	11	8 (7%)	72 (47%)	46 (30%)
Scan 6	93	7	6 (6%)	75 (49%)	50 (32%)
Scan 7	73	7	6 (8%)	78 (50%)	55 (36%)
Scan 8	58	7	7 (12%)	80 (52%)	60 (39%)
Scan 9	40	2	2 (5%)	81 (53%)	61 (40%)
Scan 10	30	0	0	-	-
Scan 11	15	0	0	-	-
Scan 12	3	0	0	-	-

In 15 of 154 patients (10%) one or more invasive procedures (biopsy, colonoscopy +/- polypectomy, bronchoscopy and/or other surgery) were used to evaluate findings on surveillance imaging (Table 7.4). Ten of these patients (6% of the cohort) were found to have a benign lesion; these patients underwent thirteen invasive procedures including two that were surgical. The surgical procedures consisted of a hemithyroidectomy in one patient (pathologically atypical follicular adenoma), and a hysterectomy with bilateral salpingo-oophorectomy in another patient for a broad ligament fibromyoma (pathologically metaplasia, no malignancy). Additionally, one patient was found to have pneumonia rather than metastases, following a lung wedge resection. Incidental findings are listed in supplementary table 3 (online only). No adverse events were documented as a result of the evaluation of false-positives or incidental findings.

Table 7.4 Outcome of CT and PET/CT findings, subsequent tests and healthcare use for baseline and surveillance imaging

	Final diagnoses				
	Benign	Second malignancy	Other	Unknown	Total
Baseline-imaging					
Scan modality on which findings identified					
CT-brain	3**	-	-	-	3
CT-chest	14	1	-	-	15
CT-abdomen	28	-	1	-	29
PET/CT	-	-	-	-	0
Total of findings	45	1	1	-	47
Total of patients with these findings	36	1	1	-	
Subsequent tests and healthcare use*					
CT-scan	16	-	-	-	16
Ultrasound	20	2	-	-	22
PET/CT	8	1	-	-	9
Referral to another doctor	2	1	1	-	4
Extra visits with treating doctor	3	1	-	-	4
Other***	3	-	-	-	3
Biopsy	2	1	-	-	3
Operation	2	2	1	-	5
MRI	3	-	-	-	3
PET-scan	1	-	-	-	1
Blood test	2	-	-	-	2
X-ray	1	-	-	-	1

Table 7.4 Continues from previous page

	Final diagnoses				
	Benign	Second malignancy	Other	Unknown	Total
Surveillance imaging					
Scan modality on which findings identified					
CT-brain	3	-	-	-	3
CT-chest	31	1	8	1^	41
CT-abdomen	25	1	1	1^	28
PET/CT	5	-	-	-	5
Total of findings	64	2	9	2	77
Total of patients with these findings	51	2	9	2	
Subsequent tests and healthcare use*					
CT-scan	39	-	1	-	40
Ultrasound	25	3	-	-	28
PET/CT	16	1	1	-	18
Referral to another doctor	9	1	9	2	21
Extra visits with treating doctor	12	5	1	-	18
Other***	4	4	8	-	16
Biopsy	11	2	1	-	14
Operation	2	4	1	-	7
MRI	4	1	-	-	5
PET-scan	5	-	1	-	6
Blood test	4	-	-	-	4
X-ray	1	-	3	-	4

* Findings could lead to the use of more than one test, procedure or referral

** One CT-brain was part of a PET/CT baseline

*** Other : mammography, radiotherapy, chemotherapy, tamoxifen, sputum sample, antibiotic treatment, bronchoscopy, heart echo, treadmill stress test, thyroid scan, bone scan, pulmonary function test, vein duplex, coloscopy, polyp removal

^ Outcome remained unknown after patients were lost to follow-up

Discussion

In this cohort study, non-melanoma findings requiring further action were identified in 53% of asymptomatic stage III patients as a direct result of CT or PET/CT imaging. The frequency of these false-positive and incidental findings persisted over time. Invasive procedures were undertaken in 14% of patients, with 10% undergoing invasive procedures for benign findings. Potentially serious incidental findings were discovered in 8% of imaged patients.

Surveillance imaging studies have focused on true-positive findings and identification of distant melanoma metastases. Our finding of 13% of asymptomatic stage III melanoma patients having distant metastases detected on annual follow-up imaging (after a median of 85 months follow-up) is in the range of the 5-29% reported in other studies.[12, 29–34] However, in these studies, various surveillance schedules were used, including 3-monthly scans, annual scans and a single scan 3 years post-operatively; and follow-up was substantially shorter, between 2 and 5 years.

False-positives and incidental findings are rarely primary or secondary endpoints in melanoma research and are frequently not documented. In our well-documented cohort, 42% of patients had false-positive findings which is higher than the 7 to 14% described in other studies.[32–34] Our study reported incidental findings in 21% of patients, similar to the upper range reported in previous studies (15 and 23%).[32, 35] Given the limited methods of previous studies, false-positives and incidental findings rates were likely to be underestimated.

Annual surveillance imaging is expensive from the perspective of both the healthcare system and patients. A previous study reports a single surveillance scan after three years of clinical follow-up in stage IIB-III melanoma patients costs US$312,990 per recurrence diagnosed. This was not cost-effective compared with clinical follow-up without imaging.[2]

In the present study, about 8% of the cohort may have benefited from early detection and management of clinically significant non-melanoma findings. Others have included

such findings as true-positives, because the discovery was considered beneficial for the patient.[36] However, the identification of these findings was not the purpose of the imaging and we suggest that they should therefore be counted as incidental findings. Importantly, it is not certain if the early discovery conferred a survival benefit or whether these findings would lead to patient morbidity. This phenomenon is referred to as overdiagnosis and described as an important problem in cancer screening.[37]

The strengths of this study include the use of a very well documented longitudinal cohort of patients who had annual CT or PET/CT surveillance imaging over a median follow-up period of 85 months. The reason for imaging was known, and management details were easily retrieved due to detailed descriptions in high-quality clinical trial files and MIA records.

One limitation of our study is that only patients with at least two annual follow-up scans were included, thereby creating a selected study cohort and possibly decreasing the applicability of the findings to all stage III melanoma patients. This was necessary to ensure the test performance of a series of surveillance scans rather than just one follow-up scan. Our study cohort represents a relatively low-risk stage III population with 37% chance of recurrence and 23% chance of distant metastases after a median follow-up of 85 months.[3, 38] A second limitation is that this study was not intended to quantify the true-positive rate and might therefore have underestimated the true-positive findings of distant metastases on annual imaging. Another further limitation is that most follow-up scans were CTs; only 37 were PET/CTs, reflecting historical practice. At MIA, PET/CT is replacing CT imaging for melanoma surveillance, however, in many other countries CT surveillance is still predominantly used and recommended in clinical practice guidelines.[17, 21] Furthermore, there is no evidence to suggest that imaging with PET/CT-scans would yield less false-positive and incidental findings than imaging with CT.

The advent of more effective systemic therapies for stage III/IV melanoma has led to a more pronounced role for surveillance imaging. In many countries, stage III patients are offered adjuvant immunotherapy and/or targeted therapy. To prevent overtreatment

of these patients, follow-up by medical-oncologists is likely to be frequent and largely based on imaging. The frequency of scans is therefore likely to increase, perhaps even to 3-monthly, consistent with adjuvant therapy trial protocols.[7–9] Prospective cohort studies that record the benefits and harms of imaging are needed, as are cost-effectiveness analyses of long-term imaging schedules, because frequent imaging is likely to impose a huge financial burden on health systems and patients who pay out of pocket expenses. Several studies have been conducted investigating patient and clinicians' views of follow-up in early stage melanoma, however further research is needed to assess the patients' perspective of surveillance imaging in long-term cancer survivorship programs following treatment for stage III or IV disease.[39–45]

In conclusion, false-positive results and incidental findings are reported in at least half of all asymptomatic stage III melanoma patients undergoing long-term annual surveillance imaging, incurring considerable additional healthcare costs, and unnecessary invasive procedures. The risk of false-positives and incidental findings persist over time, and clinicians need to be aware of these risks and discuss them with their patients, at the same time as the expected benefits of surveillance imaging are outlined.

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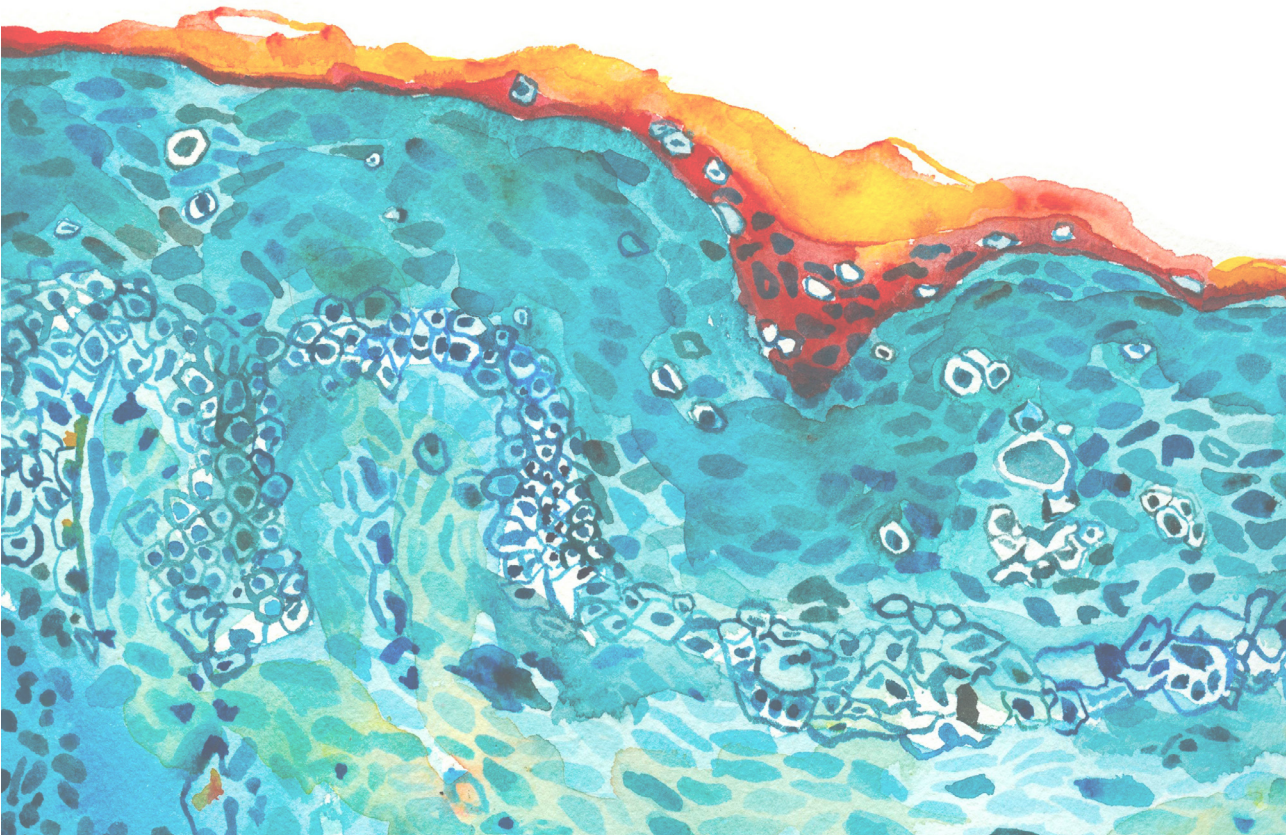
Chapter 8

General discussion and future perspectives



In the past two years there has been a paradigm shift in the management of patients with stage III melanoma, both in surgical approach and in systemic drug treatment. This thesis describes the evolving landscape of management strategies for high-risk melanoma patients, with emphasis on surgical aspects.

Sentinel node biopsy

A sentinel node (SN) is defined as any lymph node on a direct lymphatic drainage pathway from the primary tumor.[1] SN biopsy is a minimally invasive staging procedure with little morbidity. It is based on two principles.[2] The first is that every lesion has a specific draining pathway that leads to one or several nearby lymph nodes. The second is that a lymph node on a direct lymphatic drainage pathway filters out and retains tumor cells. Multiple techniques are used to determine the location of a SN. Preoperative dynamic and static lymphoscintigraphy following injection of a radioactive colloid at the tumor site visualize the SN and its afferent lymph vessel. A gamma ray detection probe is used to find the radiopharmaceutical and guide intraoperative localization of the node(s). Patent blue dye injection at the primary tumor site visualizes the lymph vessel that guides the surgeon to the SN.

The first Multicenter Selective Lymphadenectomy Trial (MSLT-I) was initiated to examine the value of SN biopsy for staging and to determine whether the procedure would improve survival. SN biopsy with completion lymph node dissection (CLND) in case of a tumor-positive SN was compared to observation with lymph node dissection in case of nodal recurrence. Although ten-year disease-free survival rates improved significantly, ten-year melanoma-specific survival was similar in both groups. Among patients with an intermediate thickness melanoma, the estimated ten-year cumulative incidence of nodal metastases was 22% for patients undergoing SN biopsy and 20% for patients in the observation group. The most important finding was a significantly better melanoma-specific survival in the primary aim group of node-positive patients with an intermediate thickness melanoma who underwent SN biopsy with CLND compared to patients who were initially observed and underwent node dissection after

they developed a nodal recurrence (62% vs. 42%). This survival difference remained significant after inclusion of the false negative procedures. In a multivariate analysis, the tumor status of the SN was demonstrated to be the strongest predictor of disease recurrence or death from melanoma. Based on these findings, SN biopsy became standard of care in patients with a melanoma ≥1 mm Breslow thickness, eliminating the practice of elective lymph node dissection.

The importance of SN biopsy is illustrated when patients staged according to the 7th and 8th editions AJCC-UICC staging system are compared.[3,4] In contrast to the 7th edition, the 8th edition is only based on patients diagnosed after 1998 and all patients with a melanoma stage T2 or higher had undergone SN biopsy. In the 8th edition, patients with stage I or II disease have a better survival rate than patients with the same stage in the 7th edition.[4] This difference is mainly attributed to the use of SN biopsy. Patients with occult nodal metastases who did not undergo SN biopsy were included as stage I or II in the 7th edition. Similar patients were classified as stage III in the 8th edition because they did undergo SN biopsy. Tumor in the SN predicts a higher risk of dissemination to distant sites, which is responsible for the mortality. With the introduction of successful adjuvant therapies in patients with stage III melanoma, accurate staging has become even more important. Patients who are erroneously classified as stage I or II will miss out on potentially lifesaving drug therapy.

SNs are typically located in the axilla, groin or neck, although they can be situated in small node fields elsewhere or as interval SNs outside node fields.[5,6] Examples of smaller lymph node regions are the epitrochlear fossa, the triangular intermuscular space on the back, the popliteal fossa and the occipital area.[6] At Melanoma Institute Australia, popliteal SNs were present in 176 of 3902 patients with a melanoma below the knee (4.5%; chapter 2).[7] Metastatic disease was found in 13 of the 79 patients undergoing a successful popliteal SN biopsy (17%), which is similar to the 16% SN-positivity rate in MSLT-I.[8] In 13% of the patients, the AJCC-UICC stage changed due to the popliteal SN biopsy result. As in more common lymph node regions, SN positivity in the popliteal fossa predicted an increased risk of recurrence and a diminished overall survival rate.

Previous studies were smaller and concerned between 57 and 461 patients with melanomas on the distal lower limb.[6,9,18–22,10–17] These studies demonstrated popliteal SNs in 1% to 11% of the patients. Popliteal SN positivity rates varied from 11% to 53%, with only 27 patients undergoing popliteal SN biopsy in the largest previous study.[9,11,14–17,19,21–23] It is worthwhile to pursue SNs in the popliteal fossa to stage patients with drainage to this area, even though the operation is often more complex than in other regions.

Completion lymph node dissection

Since the introduction of SN biopsy, CLND has been the standard treatment for SN-positive patients. The need for CLND was questioned as no additional nodal metastases were found in approximately 80% of these patients, while all were exposed to the risk of the associated morbidity. In 2017, the results of MSLT-II and the German Dermatologic Cooperative Oncology Group Selective Lymphadenectomy Trial (DeCOG-SLT) lead to a major change. Neither prospective trial showed a survival advantage from CLND compared to observation with regular ultrasonography of the nodal region. This new evidence, together with evidence from earlier retrospective studies, obviated the need for routine CLND (chapter 3).[24]

The main reason to refrain from CLND is the lack of a survival benefit. Other reasons are the associated morbidity, in particular the lymphedema that developed in 24% of the patients in MSLT-II, and the fact that additional disease in non-SNs was found in only 12-20% of the patients.[25] Although MSLT-II subgroup analyses including Breslow thickness, ulceration status, number of positive SNs and size of the metastasis did not identify any subgroups with a survival benefit from CLND, the procedure may still be performed in selected patients for a number of reasons. For instance, disease-free survival was better in patients who underwent immediate CLND.[25] This difference was attributed to a reduced risk of nodal recurrence after immediate CLND, with 8% nodal recurrences in the CLND group and 25% in the observation group. Fear of lymph node recurrence can be a psychological burden for patients, fueled by the regular clinic visits

and ultrasound examinations. Follow-up in MSLT-II and DeCOG-SLT was three-to four-monthly in the first two years, six-monthly in years three to five and annually thereafter. Trial results might be less applicable to patients who are not willing or able to comply with these frequent assessments. Delayed lymphadenectomy for a nodal recurrence, especially if palpable, may be a more extensive operation and causes more lymphedema than when the procedure is performed for a SN micrometastasis.[26] Lastly, there is no indication for adjuvant radiotherapy at an early stage of nodal involvement. These advantages of early dissection are almost always outweighed by the lack of a survival benefit and the risk of morbidity of CLND to which all patients are exposed. At Melanoma Institute Australia, 59 of the 61 SN positive patients (97%) seen after the publication of MSLT-II were managed with observation and only two (3%) chose to undergo CLND (chapter 4). These two patients had unfavorable primary tumor and SN characteristics and expressed anxiety about observation. Our study is the first to assess current management of SN-positive patients following the recent trials.

Systemic therapy

Patients with distant metastases from melanoma always had a grim prognosis with a median survival of six to eight months.[27,28] Management was mostly palliative, as effective systemic treatment was lacking. Therapies to increase the efficacy of the immune system were developed, based on multiple observations indicating an important role of the immune system in the body's response to melanoma.[29] Lymphocytes, dendritic cells and antibodies are often present in melanoma tissue and 'spontaneous' regression of melanoma has been observed.[30] Interferon-alpha was one of the first immunology-based treatments for melanoma. Multiple phase III trials of this drug showed only marginally improved response rates and a questionable overall survival benefit in patients with disseminated melanoma, at the cost of substantial toxicity.[31–33] A preliminary report of a randomized clinical trial of adjuvant interferon-alpha in patients with lymph node metastases indicated improved recurrence-free survival with the drug.[34] It also showed and improved overall survival in females

younger than 51 and males older than 50. Unfortunately, the overall survival benefits disappeared with long-term follow-up.[35–37] Subsequently, treatment with the T-cell growth factor interleukin-2 was shown to result in occasional durable tumor responses, albeit with substantial toxicity as well.[38]

Systemic treatment evolved further when immunotherapy based on CTLA-4 or PD-1 inhibition and targeted therapy with B-Raf or MEK inhibition were developed. Targeted therapy drugs (e.g. dabrafenib, trametinib, vemurafenib) were used in patients with a mitogen-activated protein kinase pathway mutation. About 50% the patients with melanoma have an activating mutation in their BRAF gene. Targeted therapy with B-Raf or MEK inhibitors resulted in significant better progression-free survival when compared to chemotherapy, with a median progression-free survival of 5 to 7 months for patients treated with vemurafenib or dabrafenib compared to 2 to 3 months for patients treated with dacarbazine.[39–41] The best results were achieved with combination of B-Raf and MEK inhibition.[42–45] Progression-free survival was 10 to 11 months in patients treated with a combination of vemurafenib and dabrafenib, compared to 6 to 7 months in patients treated with vemurafenib alone and 9 months for patients treated with dabrafenib alone. Unfortunately, almost all patients developed resistance to targeted therapy and had disease progression within a year of therapy.[29]

Immunotherapy inhibits CTLA-4 or PD-1. CTLA-4 is a receptor on cytotoxic T-lymphocytes that downregulates the immune response through binding with CD80 or CD86 on antigen-presenting cells. Blockage of CTLA-4 (e.g. with ipilimumab) thus increases the T-cell antitumor response. Multiple trials showed an improved median survival, although a pooled analysis demonstrated that the median overall survival was only ten months.[46] Inhibition of checkpoint inhibitor PD-1 with nivolumab or pembrolizumab also increases the T-cell antitumor response. These drugs had better outcomes than CTLA-4 inhibitor ipilimumab, with a median progression-free survival of three months for ipilimumab, six months for pembrolizumab and seven months for nivolumab.[47,48] In patients with advanced or metastatic melanoma, median overall survival with pembrolizumab was 23 months.[49] PD-1 inhibitors also cause less adverse

events, with toxicity reported in 14 to 17% of the patients treated with pembrolizumab and 22% with nivolumab versus 20 to 28% of the patients treated with ipilimumab.[48,49] Combining CTLA-4 inhibitors and anti-PD1 therapy had the best outcomes, with a progression-free survival of 12 months, although toxicity was high and grade 3 or higher adverse events were seen in 59% of the patients.[47] Adverse events were typically sequelae of excessive immune system activation. Rash, colitis, hepatitis, pneumonitis and endocrinopathies were frequently observed.

The success in the metastatic melanoma setting spurred exploration of the new drugs in earlier stages of the disease. In 2016, Eggermont et al. reported an improved overall five-year survival for stage III melanoma patients treated with high dose adjuvant ipilimumab after CLND, compared with placebo. Unfortunately, toxicity was very high and 41% of the patients treated with ipilimumab had grade 3 or 4 immune related adverse events, while five patients died due to toxicity (1.1%).[50] Three recent trials showed a recurrence-free survival benefit with adjuvant targeted therapy and immunotherapy in stage III patients.[51–53] Long et al. demonstrated that the combination of adjuvant trametinib and dabrafenib in stage III melanoma patients with a BRAF V600E or V600K mutation improved the three-year relapse-free survival rate from 39% in the placebo group to 58% in the treated group.[52] Only 19% of the patients were stage IIIA, but the benefits were present in all included subcategories of patients. Eggermont et al. showed that pembrolizumab improved the one-year recurrence-free survival from 61% in patients treated with placebo to 75% in patients treated with pembrolizumab.[53] Patients were eligible for the study if they had stage IIIA disease with at least one micrometastases >1 mm, or if they had stage IIIB or C disease. Adverse events grade 3 or higher were reported in 15% of the patients receiving pembrolizumab and one patient died due to toxicity from the adjuvant treatment. Lastly, Weber et al. demonstrated that treatment with nivolumab resulted in a better one-year recurrence-free survival compared to ipilimumab, 76% and 61% respectively.[51] Grade 3 or 4 adverse events were reported in 14% of the patients treated with nivolumab versus 46% of the patients treated with ipilimumab and two patients died because of ipilimumab-related adverse events. Only patients with stage IIIB, IIIC or IV were included. Nineteen

percent had stage IV melanoma. All patients with lymph node metastases in the three trials underwent CLND and patients with metastases smaller than 1 mm were not eligible.

SN-positive patients seldom meet the eligibility criteria of these adjuvant systemic therapy trials, as CLND is no longer routinely performed and the majority of SN-positive patients have small metastases (<1 mm). It remains to be determined whether a long-term overall survival benefit is attained in the average SN-positive patient, although this seems likely as data from stage IV melanoma patients showed better response rates in patients with low volume disease.[45,49,54–56] In Australia, adjuvant systemic therapy has been approved for stage IIIB and IIIC melanoma patients and is being investigated for stage IIIA. In the 14 months following publication of the first two adjuvant systemic therapy trials, 57 SN-positive patients were seen at MIA (chapter 3). Systemic therapy was discussed with a medical oncologist in 81% of them, and 70% of those patients chose to receive adjuvant immunotherapy.

Current trials focus on systemic therapy in the neo-adjuvant setting, and results of phase I and II studies look promising. In a small phase II study, neoadjuvant therapy with dabrafenib and trametinib in bulky but resectable stage III patients resulted in a pathologically complete response in six of fourteen patients (43%), although twelve of the fourteen patients (86%) interrupted drug treatment because of adverse events.[57,58] A phase IB study of 20 patients demonstrated a good tumor response to neoadjuvant immunotherapy, and possible superiority of neoadjuvant use of nivolumab and ipilimumab compared to the adjuvant use.[59] However, toxicity was unexpectedly high with grade 3 and 4 adverse events in nine out of ten patients in both groups. The OpACIN-neo trial aims to find a dosing schedule for neoadjuvant treatment that is just as effective but less toxic. Early results showed a pathological response in 77% of the patients and grade 3 to 4 toxicity in only 20% with two cycles of neoadjuvant ipilimumab 1 mg/kg plus nivolumab 3 mg/kg.[60] The PRADO study aims to further reduce the need for lymph node dissection.[61] A measurable lymph node metastasis is excised and histologically examined six weeks after two cycles of neoadjuvant

ipilimumab and one cycle of nivolumab. The trial will determine whether it is safe to omit CLND in patients with a (near) complete pathologic response in this index node.

Disease recurrence

According to the AJCC-UICC 7th edition, the risk of recurrence within five years is 48% for stage IIIA, 71% for IIIB and 85% for IIIC.[62] Most recurrences happen in the first three years after the diagnosis, although a lifelong risk remains and first recurrences decades after the treatment of the primary tumor have been described.[63,64]

The distinction between high- and low-risk patients is important. A study of 128 patients with a local recurrence or in-transit metastasis (ITM) demonstrated that this distinction can be enhanced by SN biopsy (chapter 5).[65] In this study, the SN(s) could be identified in all patients. A tumor-positive SN was found in 13% of the patients and was associated with a greater risk of recurrence. Distant metastases were seen in 56% of the SN-positive patients, compared to only 9% of the patients with a negative SN. SN-positive patients also had a significantly worse five-year overall (54% vs. 81%). In the most recent (2017) and largest previous publication on this topic, Beasley et al. described 59 patients with a local recurrence and 48 with ITM.[66] SN biopsy failed in four patients (4%) and SNs were positive in 41 (40%). It is not clear why their positivity rate is so much higher than ours. Their patient population may have had more advanced disease, but this cannot be assessed because details of the primary tumors were not provided. Establishing the presence of tumor in the SN could be meaningful in the decision to give adjuvant systemic therapy. It may also be useful to follow these high-risk patients more closely.

Excision remains the first line of treatment for low volume locoregional recurrence.[67] In patients with numerous or frequently recurring ITMs, other treatment options include cryotherapy, electro-coagulation, topical agents, electrochemotherapy, laser therapy, intra-lesional drug injection and regional infusion or perfusion. Ultrasound may steer the management decision. Our study of 30 patients with ITM demonstrated that ultrasound assessment of the subcutaneous tissue around the primary melanoma

site up to the regional lymph nodes identified additional ITMs in 53% and these findings changed management in 33% of all patients (chapter 6). This study is the first to describe this ultrasonography technique in detail and report the value of additional findings in patients with an ITM.

Lymph node recurrences are typically treated with a regional node dissection. In case of extranodal extension or other high-risk features, patients can receive adjuvant radiotherapy.[68] This improves nodal recurrence-free survival rate, although no effect on overall survival has been found.[69] Most patients with a nodal recurrence will be offered adjuvant systemic therapy. Neo-adjuvant therapy looks promising.[59] Depending on the number and location of tumor deposits, patients with distant metastases are treated with an operation, targeted or immunotherapy, and/or radiotherapy.

Follow-up of stage III melanoma patients

The main goal of follow-up is early detection of recurrent disease. Secondary aims are educating patients about self-examination and sun-safe behavior, and identifying new primary skin tumors. Clinic visits with history and physical examination are the mainstay of surveillance regimens. General laboratory tests are not useful in the follow-up of stage III melanoma patients. The tumor marker S100-B, produced by melanoma cells, can be used in the follow-up of high-risk patients, as elevated serum levels of S100B suggest the presence of recurrence with a positive predictive value of 50%.[70,71] A large variety of other biomarkers is being investigated, but so far these seem to lack the sensitivity and specificity to be useful for surveillance.[72]

In SN-positive patients who have not undergone CLND, ultrasound of the regional lymph nodes is performed at every visit during the first five years. The use of other imaging modalities remains a point of contention and national guidelines of different countries vary.[73–78] Systemic therapy for distant metastases appears to be more effective in patients with oligometastases and in patients with a smaller tumor load, making the early discovery of asymptomatic recurrences more relevant.[45,49,54–56] Therefore, surveillance scans are frequently used for follow-up, although a direct survival benefit

from regular imaging has never been proven. The use of imaging modalities is expected to rise even further with the increasing number of patients receiving systemic therapy, as the effect of treatment on the tumor is closely monitored. Surveillance imaging also has disadvantages, but these are infrequently reported. Surveillance imaging for other cancer patients has been shown to increase patient anxiety, as it is a reminder of the disease and the risk of recurrence.[79,80] Ionizing radiation increases the risk of secondary cancers.[81] Regular scans are expensive. Lastly, frequent imaging may reveal unexpected and irrelevant findings. In a cohort study, we found false positive and incidental findings in 53% of 154 asymptomatic stage III melanoma patients undergoing annual surveillance scans (chapter 7).[82] In 88% of the 124 false positive and incidental findings, the lesions were found to be benign. These findings did not progress, were not harmful and many disappeared spontaneously. Fifteen patients underwent an unnecessary invasive procedure before the benign nature of their lesion was established. The additional healthcare usage as a direct result of these false positive and incidental findings was substantial. Imaging studies in cancer patients tend to focus on sensitivity, and false-positives and incidental findings are rarely mentioned. In our well-documented cohort, 42% of patients had false-positive findings, which is higher than the 7–14% described in other studies.[83–85] Our study reported incidental findings in 21% of patients, similar to the upper range reported in previous studies (15% and 23%).[85,86] Awareness of both the benefits and downsides of surveillance imaging enables a balanced follow-up strategy, which is important given the increasing use of imaging in asymptomatic patients.

Implications of this thesis

This thesis describes the current management of high risk, stage III melanoma patients. The identification of stage III patients is important, especially since it has been established that adjuvant immunotherapy and targeted therapy improve recurrence-free survival. SN biopsy remains standard of care for patients with a clinically localized melanoma. SNs in less common locations like the popliteal fossa should be pursued

as well, as their tumor status provides prognostic and staging information and early treatment of involved lymph nodes improves survival. SN biopsy is also useful in patients with a local recurrence or ITM, as it identifies patients who are at risk of developing distant disease. If a tumor-positive SN is procured, most patients are now followed with regular ultrasound of the lymph node field instead of undergoing CLND. CLND can still be performed in selected patients, for example those who express substantial fear of recurrence or who are unwilling or unable to attend regular follow-up. In patients with an ITM, ultrasonography should be considered as it can establish the presence of additional lesions that elude detection by physical examination and other imaging techniques. Lastly, the number of scans made for follow-up purposes is increasing, especially with the introduction of (neo)adjuvant systemic therapy. These surveillance scans frequently yield false-positive and incidental findings.

Future perspectives

In the past decade, the management of patients with melanoma has undergone a substantial transition and treatment options have increased remarkably fast. Although we have come a long way, plenty of research remains to be done in order to achieve the goal of Melanoma Institute Australia "zero deaths from melanoma" and to improve the quality of life of those affected by the disease. Basic scientists are searching for factors that cause melanoma and factors that determine its biologic behavior. Different biomarkers are being investigated, including immunohistochemical staining, RNA and genomic markers.[87] Liquid biopsy is an area of investigation.[88] With this technique, the presence or absence of circulating tumor cells or cell-free DNA in the blood is used for the diagnosis and follow-up. It may also be useful in predicting response to systemic therapies.

These systemic therapies are evolving rapidly and new drugs tackling different biologic pathways of the disease are being investigated. The prevention and management of drug resistance are subjects of research. Combinations of drugs and the administration of different drugs at different timepoints are being explored. The optimal duration of drug treatment should be determined. The long-term survival rates and risks of drug therapy will be reported in the next few years. Furthermore, the question whether patients with a BRAF mutation should receive adjuvant targeted therapy or immunotherapy remains to be answered, as no study has compared these two treatment options directly. Systemic drugs are also being further investigated in selected patients with earlier stages of the disease, particularly in the adjuvant setting. Neoadjuvant systemic therapy is a subject of great interest. The roles of surgery and radiotherapy in stage III melanoma are likely to diminish in favor of systemic therapy. Surgeons and radiotherapists are collaborating with medical oncologists to find the right indications and timing for systemic therapy in combination with local-regional treatments.

Surgeons continue to explore how to improve outcome while reducing the extent of operations. One of the largest and most important new surgical studies is the

international Melanoma Margins Trial (MelMarT).[89,90] This study compares 1 cm and 2 cm resection margins in patients with a primary melanoma with a Breslow thickness of at least 1 mm. This study may have great implications for patients and health care resources. The PRADO neoadjuvant therapy study aims to reduce the need for full lymph node dissection even further.[61]

Observation has largely replaced CLND for SN-positive patients. The observation schedule in the trials was based on consensus, and evidence-based surveillance schedules should be developed. MSLT-II was a tightly controlled study, with trial nurses tracing patients who were lost to follow-up. It will be interesting to find out how well patients outside these trials follow the surveillance schedule, how often nodal recurrences develop and whether there is true loss of regional disease control. Long-term follow-up results from the MSLT-II and DeCOG-SLT trials as well as from everyday clinical practice are awaited.

Progress should be made in the development of imaging strategies. PET/CT, CT, MRI and ultrasonography are wonderful staging techniques. Prospective studies are necessary to further define their specific indications for staging and their value for surveillance. However, this will be challenging. Survival is often a principal endpoint in cancer research, but it is difficult to determine the influence of imaging on survival, as the subsequent treatment has a larger and more direct influence on patient outcomes.

Prevention remains important as the incidence of melanoma is still rising in many countries. Initiatives to educate the general public about risk factors and early signs of melanoma should be continuing and should be improved. Avoidance of sunburn, especially at a young age, is a major factor in the prevention of skin cancer.[91] The Australian efforts to prevent melanoma are successful, as the incidence curves of melanoma in younger birth cohorts are leveling off.[92] Other countries should follow suit.

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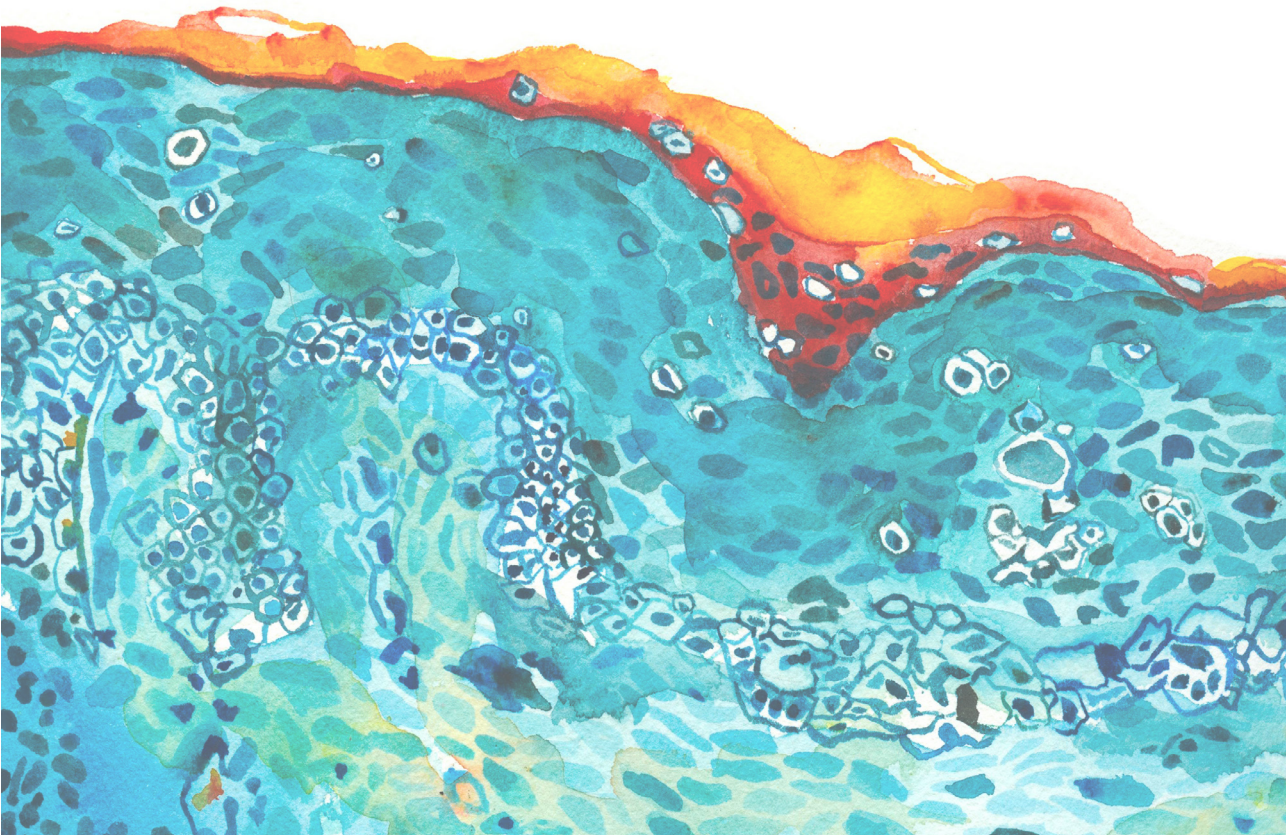
Chapter 9

Summary

Nederlandse samenvatting

List of publications and presentations



Summary

The treatment of stage III melanoma patients has changed remarkably in the recent past. The studies in this thesis concern the identification of these patients with high-risk melanoma, their current management, and follow-up.

Patients with stage III melanoma are frequently identified through sentinel node (SN) biopsy (SNB). Lymph from most of the skin drains to lymph nodes in the axilla, groin and neck. Lymph can also drain to smaller lymphatic regions like the epitrochlear fossa, the popliteal fossa and the triangular intermuscular space on the back. Our study established lymphatic drainage to the popliteal fossa in 176 of 3902 patients with a melanoma below the knee (4.5%, **chapter 2**). SNB was attempted in only 96 of these patients (55%). A SN was retrieved in 79 of them, while the procedure failed in 17 (18%). The SN was positive in 13 of the 79 patients with a successful popliteal SNB (17%) and in eight (10%) this was the only positive SN. The popliteal SN changed the AJCC-UICC tumor stage in 13% of the patients with a successful SNB. A positive SN was associated with a significantly higher risk of recurrence and a diminished survival. Although SNs in the popliteal fossa are uncommon, they have a similar positivity rate and prognostic value as SNs in more common node fields. It is worthwhile to pursue these SNs, although the procedure can be challenging.

Until recently, SN-positive patients routinely underwent completion lymph node dissection (CLND). In June 2017, two large prospective trials of SN-positive patients had shown that survival of those who underwent CLND and those who were observed was similar. The observation regimen involved regular follow-up, including ultrasound assessments of lymph node regions concerned, and a delayed CLND in case of nodal recurrence. The pros and cons of dissection are discussed in the literature review of **chapter 3**. Advantages of immediate CLND are the reduced risk of nodal recurrence, improved staging with additional prognostic information from the tumor status of non-SNs, smaller risk of morbidity compared to delayed CLND for a recurrence and a less demanding follow-up schedule. These advantages of early CLND rarely

outweigh the potential morbidity to which all these patients are exposed and the lack of a significant survival benefit. This was illustrated by our study on the management of SN-positive patients after publication of the aforementioned trials (**chapter 4**). At Melanoma Institute Australia, 59 of the 61 SN-positive patients (97%) were observed with regular ultrasound examinations. Two patients requested CLND because of anxiety about observation in view of unfavorable characteristics of the primary tumor and SNs. In November 2017, it became clear that adjuvant immunotherapy and targeted therapy improve recurrence-free survival of stage III melanoma patients. Our study found that 46 of the 57 SN-positive patients (81%) presenting after November 2017 were seen by a medical oncologist to discuss adjuvant systemic treatment, and that 32 chose to receive such treatment.

Of all melanoma patients, 2 to 5% will develop a local recurrence and some 4% an in-transit metastasis (ITM). The value of SNB in 128 such patients is discussed in **chapter 5**. A SN could be identified in all patients. Metastases were found in 16 of them (13%). The false-negative rate was 27%. Twelve of the sixteen patients with a positive SN underwent completion lymph node dissection. In four of them (33%) additional non-SNs were positive. Patients with a positive SN had a 5-year survival rate of 54% and in patients with a negative SN this was 81% (P=0.01). Four patients with a negative SN (4%) and seven patients with a positive SN (44%) developed their first subsequent metastasis at a distant site. This prognostic information can be useful in the discussion on adjuvant systemic therapy and follow-up management.

Chapter 6 describes 30 melanoma patients with ITMs who underwent regional ultrasound examination of the lymph drainage region up to and including the regional lymph node field. In 16 patients (53%), ultrasound assessment identified more ITMs than physical examination, which changed the intended treatment of ten patients. In six of them the excision was more extensive than initially planned, three patients received systemic therapy, and in one patient excision was delayed and follow-up intensified. Therefore, ultrasound assessment of the lymphatic drainage area was found to be useful in patients with an ITM.

There is no consensus on imaging in the follow-up of patients with high-risk melanoma. Systemic therapy has better outcomes in patients with small lesions and few metastatic sites, so early detection of distant metastases is likely to improve survival. Research on surveillance imaging is usually focused on the detection of metastases (true-positive findings). **Chapter 7** describes a study in which non-melanoma related findings on annual surveillance (PET/)CT scans were investigated. A group of 154 asymptomatic patients underwent a total of 1022 scans, with a median follow-up duration of seven years. False-positive and/or incidental findings led to additional healthcare activities in 81 patients (53%). The lesions proved to be benign in 109 of the 124 false positive and incidental findings (88%). The additional healthcare usage resulting from of these findings was substantial with 254 additional tests, follow-up appointments, referrals and treatments. Awareness of both the benefits and downsides of surveillance imaging enables a balanced follow-up strategy, which is important with the increasing use of imaging in asymptomatic patients.

Nederlandse samenvatting

De behandeling van patiënten met stadium III-melanoom is aanzienlijk veranderd in de laatste paar jaar. Dit proefschrift betreft de identificatie van hoogrisicopatiënten, de huidige behandeling van dergelijke patiënten en hun follow-up.

Patiënten met stadium III-melanoom worden veelal geïdentificeerd door middel van sentinel-nodebiopsie (SNB). Lymfe van het grootste deel van de huid draineert op lymfeklieren in de oksel, de lies en de hals. Soms draineert lymfe naar kleinere klierregio's, zoals de epitrochleaire fossa, de popliteale fossa en de driehoekige intermusculaire ruimte op de rug. In ons onderzoek had 4,5% van de 3902 patiënten met een melanoom distaal van de knie lymfedrainage naar een sentinel node (SN) in de popliteale fossa (**hoofdstuk 2**). Slechts bij 96 van de 176 patiënten met lymfedrainage naar dit gebied werd getracht deze klier(en) te verwijderen (55%). Bij 17 van hen werd geen SN gevonden (18%). De SN was tumorpositief bij 13 van de 79 patiënten met een geslaagde SNB (17%) en bij acht van hen was dit de enige tumorpositieve klier (10%). Bij 13% van de patiënten leidde de vondst van een aangedane popliteale SN tot een verandering in de AJCC-UICC-tumorstadiëring. Patiënten met een positieve popliteale SN hadden een verhoogde kans op recidievering van de tumor en een significant slechtere overlevingskans. De popliteale fossa bevat niet vaak SNs, maar popliteale SNs zijn net zo vaak positief en hun tumorstatus heeft dezelfde prognostische waarde als SNs in meer gangbare klierregio's. Hoewel de procedure lastig kan zijn, is SNB in de popliteale fossa de moeite waard.

SN-positieve patiënten werden tot voor kort behandeld met een completerende lymfeklierdissectie (CLD). In juni 2017 toonden twee grote prospectieve onderzoeken bij SN-positieve patiënten geen betere ziektevrije overleving bij degenen die een directe CLD ondergingen in vergelijking met degenen die alleen vervolgd werden. Bij deze laatste groep patiënten werden de betrokken lymfeklierregio's met echografie vervolgd om een eventueel recidief vroegtijdig op te sporen en te behandelen met een uitgestelde CLD. De voor- en nadelen van directe CLD zijn uiteengezet in de

literatuurbespreking van **hoofdstuk 3**. Voordelen van directe CLD zijn vermindering van het risico op klierrecidivering, nauwkeuriger stadiëring, prognostische informatie van de tumorstatus van de overige lymfeklieren, geringere morbiditeit van vroege CLD in vergelijking met uitgestelde CLD voor een recidief, en de minder intensieve follow-up. Deze voordelen wegen echter zelden op tegen het ontbreken van overlevingswinst van de directe CLD en de bijbehorende kans op morbiditeit waaraan al deze patiënten worden blootgesteld. Dit bleek ook uit ons onderzoek naar de behandeling van SN-positieve patiënten na publicatie van de bovengenoemde trials **(hoofdstuk 4**). In het Melanoma Institute Australia werden 59 van de 61 patiënten met een positieve SN (97%) geobserveerd met regelmatige echografische controle van de betrokken klierregio(s). Slechts twee patiënten opteerden voor CLD uit angst voor recidieven tijdens observatie gezien de ongunstige prognostische kenmerken van de primaire tumor en de SNs. In november 2017 werd bekend dat adjuvante immunotherapie en targeted therapie de ziektevrije overlevingskans van stadium III melanoompatiënten verbetert. In het eerdergenoemde onderzoek van **hoofdstuk 4** vonden we dat 46 van de 57 patiënten (81%) die zich presenteerden na november 2017 werden doorgestuurd naar de internist-oncoloog om adjuvante behandeling te bespreken, en dat 32 er voor kozen behandeld te worden met adjuvante systeemtherapie.

Twee tot 5% van de melanoompatiënten ontwikkelt een lokaal recidief en ongeveer 4% krijgt in-transitmetastasen (ITMs). In **hoofdstuk 5** wordt de waarde van SNB beschreven bij 128 patiënten met een dergelijk recidief. Bij allen kon de SN geïdentificeerd worden. Bij 16 van hen was deze tumorpositief (13%). De SNB was foutnegatief bij 27%. Twaalf van de zestien patiënten met een positieve SN ondergingen CLD. Bij vier patiënten (33%) waren additionele niet-SNs tumorpositief. De algemene vijfjaarsoverlevingskans van patiënten met een positieve SN (54%) was significant slechter dan van patiënten met een negatieve SN (81%, P=0,01). Vier patiënten met een negatieve SN (4%) en zeven patiënten met een positieve SN (44%) ontwikkelden een metastase op afstand als eerstvolgende recidief. De prognostische informatie die de SN-tumorstatus oplevert kan van toegevoegde waarde zijn bij de discussie over adjuvante systeemtherapie en follow-up.

Hoofdstuk 6 beschrijft 30 patiënten met een ITM bij wie echografisch onderzoek van het lymfedrainagegebied tot en met de regionale lymfeklieren werd uitgevoerd. In vergelijking met lichamelijk onderzoek werden bij 16 patiënten (53%) additionele ITMs gevonden. Van tien patiënten werd de beoogde behandeling hierdoor anders. Bij zes was de excisie uitgebreider, drie patiënten kregen systeemtherapie in plaats van excisie en bij een patiënt werd de excisie uitgesteld en werd de follow-up intensiever. Echografie van het drainerende lymfestroomgebied kan van toegevoegde waarde zijn bij patiënten met een ITM.

Er is geen consensus over beeldvorming bij de follow-up van hoogrisicopatiënten. Systeemtherapie lijkt beter te werken bij patiënten met oligometastasen en kleinere laesies, waardoor het aannemelijk is dat vroege detectie van afstandsmetastasen de overlevingskans verbetert. Onderzoek naar de waarde van beeldvorming voor routinecontrole focust meestal op het identificeren van metastasen (correctpositieve bevindingen). In **hoofdstuk 7** wordt een onderzoek beschreven waarbij niet-melanoom gerelateerde bijkomstige bevindingen van jaarlijkse routinematig uitgevoerde scans onderzocht werden. De 154 asymptomatische melanoompatiënten ondergingen in totaal 1022 scans en de mediane follow-up-duur bedroeg zeven jaar. Bij 81 patiënten (53%) werden fout-positieve en/of incidentele bevindingen gerapporteerd die leidden tot meer medische handelingen, terwijl het bij 109 van de 124 gevallen (88%) bleek te gaan om een benigne afwijking. Deze bevindingen leidden tot substantieel extra gebruik van gezondheidszorg en initieerden 254 additionele testen, vervolgafspraken, verwijzingen en behandelingen. Bewustwording van zowel de voor- als nadelen van routinebeeldvorming bevordert een evenwichtige follow-up-strategie. Dit is met name van belang gezien de toename van het gebruik van scans bij asymptomatische patiënten.

Publications

Nijhuis AAG, Chung D, London K, Uren RF, Thompson JF, Nieweg OE, Ultrasound examination of the lymphatic drainage area and regional lymph nodes in melanoma patients with in-transit metastases, submitted

Nijhuis AAG, Spillane A.J., Stretch, JR, Saw RPM, Menzies AM, Uren RF, Thompson JF, Nieweg OE, Current management of patients with melanoma who are found to be sentinel node-positive, ANZ Journal of Surgery 2019; Epub ahead of print

Nijhuis AAG, Dieng D, Khanna N, Lord SJ, Dalton J, Menzies AM, et al. False positive results and incidental findings with annual CT or PET/CT surveillance in asymptomatic patients with resected stage III melanoma. Ann Surg Oncol 2019;26:1860–8.

Nijhuis AAG, de A.O. Santos Filho ID, Uren RF, Thompson JF, Nieweg OE. Clinical importance and surgical management of sentinel lymph nodes in the popliteal fossa of melanoma patients. Eur J Surg Oncol 2019;45:1706–11.

Nijhuis AAG, De AO Santos ID, Holtkamp LHJ, Uren RF, Thompson J, Nieweg OE. Sentinel node biopsy in melanoma patients with a local recurrence or in-transit metastasis. Ann Surg Oncol 2019; Epub ahead of print

Nijhuis AAG, Van Ophem A, Nieweg OE. Completion lymph node dissection or observation in melanoma patients with a positive sentinel node, Ned Tijdschr Oncol, 2017;14:221-30

Publications outside this thesis

Nijhuis AAG, Kluijfhout WP, Twigt BA, Muller A, Borel Rinkes IHM, Van Dalen T, Vriens MR. Recidief hypercalciemie langere tijd na minimaal invasieve parathyreoïdectomie, Ned Tijdschr Heelkunde, Jan 2018

Presentations

2019

Current management of patients with melanoma who are found to be sentinel node-positive

Oral presentation at the European Cancer Organisation (ESSO) congress, Rotterdam

Sentinel node biopsy in melanoma patients with a local recurrence or in-transit metastasis

Oral presentation at the Society of Surgical Oncology (SSO) conference, San Diego

Oral presentation at the Dutch Surgery Days, 'Chirurgendagen', Veldhoven

False-positive results and incidental findings with annual CT or PET/CT surveillance in asymptomatic patients with resected stage III melanoma

Oral presentation at the SSO conference, San Diego

Oral presentation at the Dutch Surgery Days, 'Chirurgendagen', Veldhoven

2018

Clinical importance and surgical management of sentinel lymph nodes in the popliteal fossa of melanoma patients

Oral presentation at the SSO conference, Chicago

Safety of Nearly Invisible Lumpectomy (NIL) procedure in non-palpable early breast cancer

Poster presentation at the SSO conference, Chicago

2017

The harms of annual imaging in the follow-up of high risk melanoma patients: false positives and incidental findings

Oral presentation at the research retreat, Melanoma Institute Australia, Sydney

'Decisions on completion lymph node dissection in sentinel lymph node positive melanoma patients after the recent publication of MSLT-II results

Oral presentation at the research retreat, Melanoma Institute Australia, Sydney

2016

The 'invisible' NIL operation in early stage breast cancer is as safe as a conventional breast operation

Poster presentation at the Bossche Dagen, Den Bosch

Nearly invisible lumpectomy (NIL), 'invisible' and safe

Poster presentation at the SSO congress, Boston

2015

Lange termijn- recidief hypercalciemie na geslaagde minimaal invasieve parathyreoidectomie

Poster presentation at the SSO congres, Houston

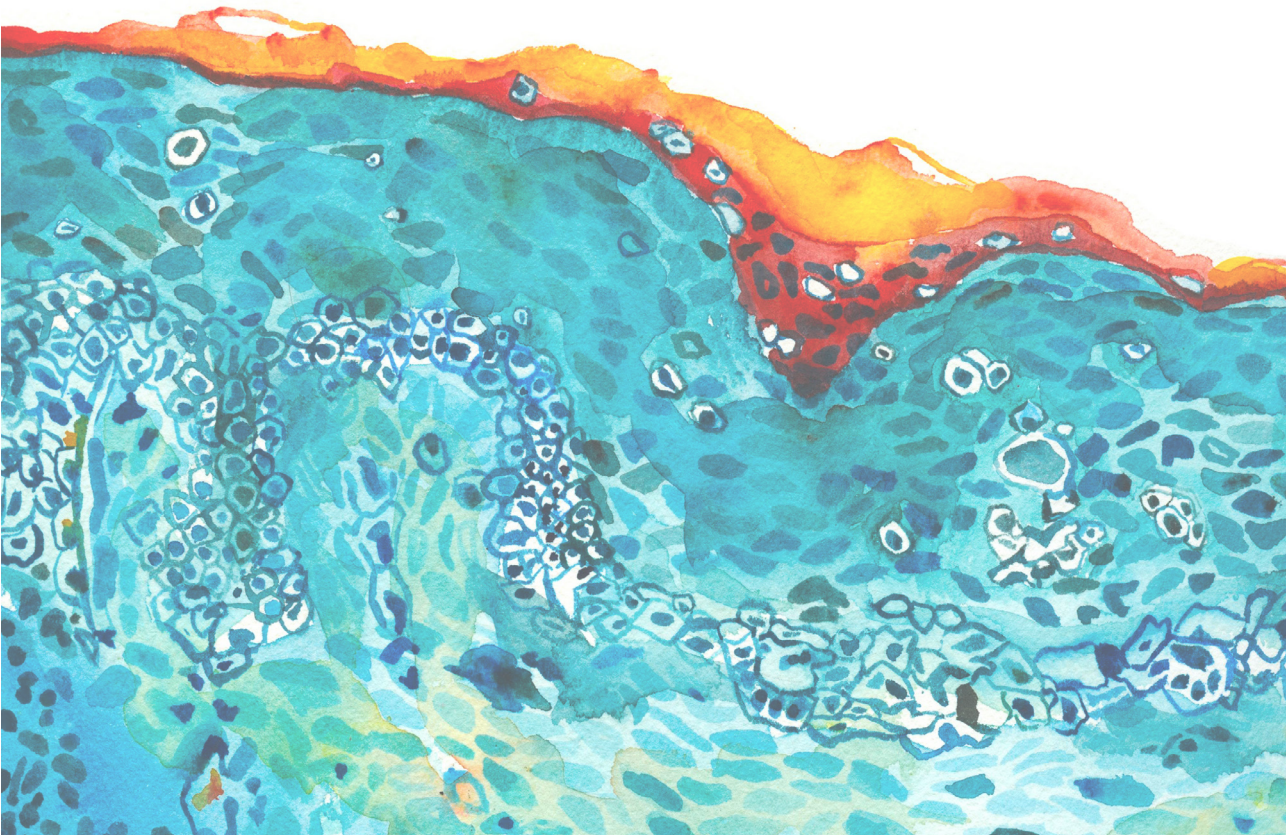
Nearly invisible lumpectomy (NIL), 'invisible' and safe

Poster presentation at the Dutch surgery days, 'Chirurgendagen', Veldhoven

Chapter 10

Acknowledgements

Curriculum Vitae



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Curriculum Vitae

Amanda Nijhuis was born in Eindhoven on the 22nd of August, 1993. During her childhood, she lived in Maastricht, Zuidhorn and Venlo. She obtained her high-school diploma summa cum laude at Valuascollege Venlo in 2011. After graduating, she moved to Utrecht to study Medicine. In the second year of her studies, Amanda started doing research with dr. Van Dalen at Diakonessenhuis Utrecht. This research brought her to the SSO-conference in Houston in 2015, where she met prof. Nieweg and prof. Thompson. In 2017, Amanda moved to Sydney to do research with them at Melanoma Institute Australia. This was the start of her PhD trajectory with prof. Borel Rinkes, prof. Nieweg, and dr. Witkamp. She lived in Sydney for twelve months before returning to the Netherlands to finish her master's degree. During this last year of Medicine, she combined her internships with her PhD research. In October 2018, Amanda graduated Medicine. After six more months of full-time research, she currently works as a non-training surgical resident at the Jeroen Bosch hospital in 's-Hertogenbosch.