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CLINICALLY OCCULT METASTASES IN PATIENTS WITH CUTANEOUS MELANOMA

Detection with Sentinel Lymph Node Biopsy and Whole Body Positron Emission Tomography

by

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Dedicated to

those who matter the most

ABSTRACT

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Clinically occult metastases in patients with cutaneous melanoma. Detection with sentinel lymph node biopsy and whole body positron emission tomography.

From the Department of Surgery, University of Turku, Turku, Finland.
Annales Universitatis Turkuensis, Medica-Odontologica Series D, Turku, Finland, 2008.

Objective: The aim of this study was to investigate the use of sentinel lymph node biopsy (SLNB) and whole body positron emission tomography (PET), with emphasis on surgical treatment and prognosis, in the detection of clinically occult metastases in patients with clinically localized cutaneous melanoma.
Patients and methods: The study population consisted of 1255 patients with clinical stage I–II cutaneous melanoma, operated at Turku University Hospital between 1983 and 2007. 334 patients underwent SLNB and they were compared to 921 retrospective patients. A subgroup of 30 symptom-free patients with high risk melanoma underwent prospectively whole body PET 6–24 months postoperatively.
Results: Overall, the disease-specific survival rate was 84.4 % at five years. Sex, Breslow thickness, age and nodal status were independent prognostic factors for survival. SLNB revealed occult nodal metastases in 17 % of the patients. There was no significant difference in disease-specific overall survival between SLNB patients and controls, but the nodal disease-free time was significantly longer suggesting better local control after SLNB and subsequent completion lymph node dissection. The follow-up time was different between the study cohorts and initial surgery was performed during different time periods. SLNB detected micrometastases in seven of 155 patients (4.5 %) with thin T1 primary melanoma and in four of 25 patients (16 %) with head and neck melanoma. In six of 30 asymptomatic patients with high risk melanoma (20 %), whole body PET detected occult distant metastases.
Conclusion: Both SLNB and whole body PET were reliable methods to detect clinically occult metastases in patients with cutaneous melanoma. This upstaging altered the treatment in each case.

Key words: Melanoma – Sentinel node – Positron emission tomography – PET

TIIVISTELMÄ

Ilkka Koskivuo

Vartijasolmukebiopsia ja koko kehon positroniemissiotomografia ihomelanooman kliinisesti piilevien etäpesäkkeiden diagnostiikassa

Kirurgia, Turun yliopisto, Turku.
Annales Universitatis Turkuensis, Medica-Odontologica Series D, Turku, 2008.

Tavoite: Tutkimuksen tarkoituksena oli selvittää vartijasolmukebiopsian ja koko kehon positroniemissiotomografian (PET) käyttöä piilevien melanooman etäpesäkkeiden diagnosoinnissa.
Potilaat ja menetelmät: Aineistona oli 1255 TYKS:ssa vuosina 1983–2007 leikattua potilasta, joilla oli diagnosoinnin aikaan kliinisesti paikallinen invasiivinen ihomelanooma. 334 potilaalle tehtiin prospektiivisesti vartijasolmukebiopsia, ja heidän hoitonsa tuloksia verrattiin 921 retrospektiivisen kontrollipotilaan hoidon tuloksiin. Lisäksi 30 oireettomalle korkean uusiutumisriskin melanoomapotilaalle tehtiin prospektiivisesti koko kehon PET-tutkimus 6–24 kuukautta leikkauksen jälkeen.
Tulokset: Tutkimuspotilaiden melanoomaspesifinen viiden vuoden elossaolo-osuus oli 84.4 %. Sukupuoli, Breslow´n aste, ikä ja imusolmukkeiden tila olivat itsenäisiä ennustetekijöitä. Prospektiivisen vartijaimusolmukeryhmän potilaista 17 %:lla todettiin kasvaimen lähialueen imusolmukkeissa piilevä mikrometastaasi. Kontrolliryhmään verrattuna vartijasolmukebiopsia ja täydentävä imusolmukkeiden evakuaatio vähensivät melanooman uusiutumista paikallisiin imusolmukkeisiin, mutta eivät vaikuttaneet kokonaiskuolleisuuteen merkitsevästi. Tutkimusryhmien seuranta-ajat olivat eripituiset, ja melanoomaleikkaukset oli tehty eri ajanjaksoina. Vartijasolmukebiopsian perusteella todettiin piilevä imusolmukkeen mikrometastaasi seitsemällä potilaalla 155:sta (4.5 %), joilla oli pinnallinen T1-luokan melanooma sekä neljällä potilaalla 25:sta (16 %), joiden melanooma sijaitsi pään ja kaulan alueella. Kuudella oireettomalla korkean riskin melanoomapotilaalla 30:sta (20 %) koko kehon PET-tutkimus havaitsi kliinisesti piileviä etäpesäkkeitä.
Päätelmät: Sekä vartijasolmukebiopsia että koko kehon PET-tutkimus olivat luotettavia menetelmiä kliinisesti piilevien melanooman etäpesäkkeiden diagnosoinnissa. Piilevän etäpesäkkeen löytyminen vaikutti potilaan hoitoon kaikissa tapauksissa.

Avainsanat: Melanooma – Vartijasolmuke – Positroniemissiotomografia – PET

TABLE OF CONTENTS

ABSTRACT 5
TIIVISTELMÄ 6
TABLE OF CONTENTS 7
ABBREVIATIONS 9
LIST OF ORIGINAL PUBLICATIONS 10
1 INTRODUCTION 11
2 REVIEW OF THE LITERATURE 13
2.1 Brief history of cutaneous melanoma 13
2.2 Epidemiology and global trends 14
2.3 Pathogenesis and risk factors 15
2.3.1 Environmental factors 15
2.3.2 Host factors 15
2.4 Prevention and screening 16
2.4.1 Primary prevention 16
2.4.2 Secondary prevention 17
2.4.3 Screening 17
2.5 Diagnosis 18
2.5.1 Clinical detection based on morphological subtypes 18
2.5.2 Biopsy 20
2.6 Prognostic factors 20
2.6.1 Demographic factors 20
2.6.2 Pathologic factors 20
2.6.3 Nodal status 23
2.7 Classification and staging 23
2.7.1 AJCC Staging system 23
2.8 Surgical management of the primary melanoma 24
2.8.1 Primary excision 24
2.8.2 Reconstruction 25
2.9 Lymphatic mapping and sentinel lymph node biopsy 26
2.9.1 Preliminary studies on the lymphatic system 26
2.9.2 The sentinel node concept 27
2.9.3 Technical details of sentinel lymph node biopsy 28
2.9.4 Histopathological analysis of the sentinel node 31
2.9.5 Molecular analysis of the sentinel nodes 34
2.9.6 Validation of the sentinel node concept 34
2.9.7 Complications of sentinel lymph node biopsy 35
2.9.8 Patient selection and special indications 35
2.9.9 Contraindications of sentinel lymph node biopsy 37
2.10 Lymph node dissection 38
2.11 Adjuvant treatment 39

2.12 Positron emission tomography 39
2.13 Surgical management of recurrent melanoma 40
3 AIMS OF THE STUDY 41
4 PATIENTS AND METHODS 42
4.1 Patients 42
4.2 Methods 43
4.2.1 Management of the primary lesion 43
4.2.2 Sentinel lymph node biopsy 43
4.2.3 Positron emission tomography 44
4.2.4 Follow-up 45
4.2.5 Statistical analyses 46
5 RESULTS 47
5.1 Study I (Surgical treatment and prognosis) 47
5.2 Study II (Sentinel lymph node biopsy) 52
5.3 Study III (Thin melanoma) 56
5.4 Study IV (Head and neck melanoma) 58
5.5 Study V (Positron emission tomography) 60
6 DISCUSSION 63
6.1 Surgical management and prognosis of cutaneous melanoma 63
6.2 Sentinel lymph node biopsy 64
6.3 Thin melanoma 71
6.4 Head and neck melanoma 73
6.5 Follow-up and positron emission tomography 74
7 CONCLUSIONS 78
8 ACKNOWLEDGEMENTS 79
9 REFERENCES 81
ORIGINAL PUBLICATIONS 93

ABBREVIATIONS

AJCC	American Joint Committee on Cancer
CLND	completion lymph node dissection
CI	confidence interval
CT	computed tomography
DFS	disease-free survival
ELND	elective lymph node dissection
FDG	fluorodeoxyglucose
IFNα	interferon-α
HR	hazard ratio
H&E	hematoxylin and eosin
H&N	head and neck
HPF	high power field
LS	lymphoscintigraphy
MRI	magnetic resonance imaging
MSLT	Multicentre Selective Lymphadenectomy Trial
OS	overall survival
PET	positron emission tomography
RT-PCR	reverse transcriptase polymerase chain reaction
SN	sentinel node
SLNB	sentinel lymph node biopsy
SSM	superficial spreading melanoma
$Tc99^m$	technetium-99^m
TLND	therapeutic lymph node dissection
TNM	tumour-node-metastasis
US	ultrasonography
WHO	World Health Organization
WLE	wide local excision

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numerals (**I–V**).

I Koskivuo I, Suominen E (2008)
Ihomelanooman muuttuva kirurginen hoito
Leikkaushoidon tulokset Varsinais-Suomessa 1983–2007
Duodecim 124: 1995-2004

II Koskivuo I, Talve L, Vihinen P, Mäki M, Vahlberg T, Suominen E (2007)
Sentinel Lymph Node Biopsy in Cutaneous Melanoma: a Case-control Study
Annals of Surgical Oncology 14: 3566-74

III Koskivuo I, Suominen E, Niinikoski J, Talve L (2005)
Sentinel Node Metastasectomy in Thin ≤ 1-mm Melanoma
Langenbeck´s Archives of Surgery 390: 403-7

IV Koskivuo I, Kinnunen I, Suominen E, Talve L, Vihinen P, Grénman R (2008)
Head and Neck Cutaneous Melanoma: a Retrospective Observational Study on 146 Patients
Acta Oncologica, in press

V Koskivuo IO, Seppänen MP, Suominen EA, Minn HR (2007)
Whole Body Positron Emission Tomography in Follow-up of High Risk Melanoma
Acta Oncologica 46: 685-90

1 INTRODUCTION

Melanoma, “black cancer”, is a serious form of skin cancer that originates in the pigment-producing melanocytes. In Finland, cutaneous melanoma is the ninth most common cancer in men and eleventh most common cancer in women (Finnish Cancer Registry). It is alarming that incidence rates are increasing rapidly. In contrast to other types of skin cancers that usually develop mostly on sun-exposed areas of the body, melanomas can develop anywhere on the skin surface, as well as on the mucous membranes lining the mouth, nose, gastrointestinal tract and genital areas, or in the eye. Melanoma can metastasize to distant parts of the body much more frequently than is typical for other common types of skin cancers. Melanoma is overwhelmingly responsible of most skin cancer deaths (Lens and Dawes, 2004).

Fortunately, when melanoma is detected at an early stage, excision of the primary tumour is frequently effective in limiting the spread of the disease. However, a proportion of patients with clinically localized cutaneous melanoma carry a risk for developing recurrence and distant metastases after a latent symptom-free period. Whenever occult disease has initially not been detected, the metastases at some stage will grow and become clinically manifest. Nodal metastases are not lethal, but they can be a source of secondary tumours that can affect vital functions and cause death. The discussion, which has been pursued since the last century, concerns the necessity and timing of lymphadenectomy. The utility of elective lymph node dissection (ELND), indeed, has been one of the most debated controversies in surgical oncology; prospective randomised trials have not been able to demonstrate the overall survival benefit of ELND (Veronesi et al., 1982; Sim et al., 1986; Cascinelli et al., 1998; Balch et al., 1996).

The sentinel node concept provides a potential solution to this long-standing debate over ELND. Sentinel lymph node biopsy (SLNB) is a minimally invasive technique to detect occult lymph node metastases at a very early stage of development (Morton et al., 1992). A sentinel node is defined as any lymph node that receives lymph drainage directly from a tumour site. Thus, the sentinel node is the first potential lymph node to contain cancer cells. This concept is based on the historic theory of tumour cell dissemination within the lymphatic system and on the theoretical barrier function of the lymph nodes in the metastatic cascade. Overall, SLNB is able to detect clinically occult micrometastases in approximately 20 % of patients with clinically localized melanoma, and the sentinel node is the only lymph node invaded by tumour cells in most cases (Thompson and Uren, 2005). Whereas SLNB has rapidly become a widely accepted routine procedure in patients with breast cancer, in patients with clinically early-stage melanoma, however, the routine use of SLNB has been criticized, because, currently, no definitive or high-level evidence exists that SLNB, with subsequent completion lymph node dissection (CLND), could improve overall survival in patients with melanoma (González, 2007; Rosenberg, 2008).

The precise indications of SLNB are not fully validated. Particularly thin melanomas and melanomas in the head and neck are challenging the sentinel node concept in terms of sensitivity, cost-benefit or risk for technical failures (Thompson and Shaw, 2006; Tanis et al., 2008).

After the initial surgery, although the patient is clinically disease-free, there still remains a risk for recurrent disease due to clinically occult metastases. The aim of the follow-up examinations is to detect such treatment failure at an early stage, because there may be a potential chance for curative surgery. However, there is only low-grade evidence guiding the follow-up protocols (Francken et al., 2005). To date, almost all recommendations are based more on common-sense or historical practice than on evidence-based guidance. Among imaging modalities, whole body positron emission tomography (PET) is a potential tool to detect clinically occult metastases in melanoma (Tyler et al., 2000). PET is a metabolic imaging method based on abnormal glucose uptake in cancer cells. However, there is no universally accepted consensus of the optimal indications and timing of the use of PET in the follow-up of high risk melanoma (Wagner,2006).

2 REVIEW OF THE LITERATURE

2.1 Brief history of cutaneous melanoma

The first description of a patient with a melanoma was reported by an English surgeon John Hunter (1728-1793) in 1787. He described a case of a 35-year-old gentleman with recurrent nodal metastasis behind the angle of the lower jaw. The original resections specimen is preserved in the Hunterian Museum of the Royal College of Surgeons of England. René Laënnec (1781-1826), a French physician, was the first author who introduced *cancer noire*, the black cancer, as a disease entity. He was the first who used the term *la mélanose* (*melanosis*), which is derived from the Greek word meaning black.

The first case of melanoma in the English literature was reported in 1820 by William Norris (1792-1877), a general practioner in Stourbridge, England. He described a case with a primary lesion on the abdominal skin originating from a pre-existing mole. Later on, the patient died as a result of metastatic disease. Norris performed the autopsy himself and found metastases throughout the inner organs; the lumbar glands were also "in a shockingly morbid condition". Norris was the first author who advocated wide local excision of the tumour and surrounding "healthy parts" reporting an 8-year survival with this treatment.

Robert Carswell was the first to use the term *melanoma* as a synonym for melanosis in 1834. There were also other original descriptions of melanoma on the nineteenth century published by such pioneers as Jean Cruveilier, David Williams, Isaac Parrish, Samuel Cooper, James Paget, Oliver Pemberton and Jonathan Hutchinson. In 1840, Samuel Cooper reported that "no remedy is known for melanosis. The only chance for benefit depends upon the early removal of the disease by operation". In 2008, 168 years later, this understanding is still valid.

The discussion, whether lymph node dissection should be performed in melanoma, was first initiated over a century ago. Herbert Snow, a London surgeon with a particular interest in melanoma, stated in the journal Lancet in 1892 that "We further see the paramount importance of securing, whenever possible, the perfect eradication of those lymph glands which will necessarily be first infected." This fundamental recommendation for routine elective lymph node dissection (ELND) was based on the concept that melanoma progresses sequentially from the primary site to the regional lymph nodes and then to more distant sites; logically, early removal of these nodes would interrupt the metastatic cascade. Later, in 1907, William Handley also recommended wide local excision, regional lymph node dissection, and amputation in selected cases. This surgical approach remained as standard of care until extensive excision margins and the therapeutic benefit of ELND began to be questioned.

In summary, the early literature confirmed that localized melanoma can be cured by surgery, but occult metastases are associated with poor prognosis. This understanding highlights the importance of further investigations with intention to find more accurate staging methods and effective treatment modalities.

(McLeod et al., 2003; Neuhaus et al., 2004)

2.2 Epidemiology and global trends

For several decades, age-adjusted incidence rates for cutaneous melanoma have been increasing steadily among most fair skinned populations. The annual increase in the incidence rate varies between populations depending on the skin type and latitude, but it has been 3–7 % in recent decades (Marks, 2000). The increasing incidence rates within the Scandinavian countries are presumably associated with the lighter skin type combined with changes in lifestyle and affluence, enabling the people to travel to sunny Mediterranean or subtropical regions where they may expose themselves intensively and intermittently to amounts of sun that their skin is not used to (de Vries and Coebergh, 2004).

Although an increase of melanoma incidence is still occurring, there is evidence that the overall increases have recently begun to level off (Lens and Dawes, 2004). Coory et al. (2006) analyzed the trends in Queensland, Australia, between 1982 and 2002 on 33 393 melanoma patients and found that the largest increase in incidence rates remained among older men, but the rates became more stable among younger birth cohorts. Also in Northern Europe, where the incidence rates came very high during the 1980s, a similar levelling off has also been observed, starting in the younger groups (de Vries et al., 2003). This birth cohort effect has been suggested to be due to improved awareness and sun exposure behaviour among these age groups. During the last decades in Sweden, the increase of the melanoma incidence has been associated mainly with thin tumours and melanoma in situ (Månsson-Brahme et al., 2002).

Finland has followed these global trends. A time trend analysis of melanoma incidence was carried out on the whole population of Finland with 16 414 cases from 1953 through 2003 based on the database of the Finnish Cancer Registry (Stang et al., 2006). The investigators found a steady increase of melanoma incidence since 1953. The estimated annual percentage increase was about 5 % among both men and women, until the mid 1980s. Thereafter, the incidence increase levelled off. Among men, the authors identified a watershed in 1987 and among women, five years earlier. After these time points the annual percentage increase of the incidence was 1.2 % from 1987 through 2003 in men and 1.4 from 1982 through 2003 in female. In future, however, the crude incidence rate remains high because of the elderly population in society. According to the latest statistics, the age-standardized incidence of melanoma was 11.7 per 100 000 (491 new cases) among males and 9.4 (435 new cases) among females in Finland in 2006 (Finnish Cancer Registry). The corresponding mortality rates were 2.6 in males

and 1.2 in females. Skin melanoma was the ninth most common cancer in men and eleventh most common cancer in women in 2006. The survival of melanoma patients has continuously improved in Finland (Ilmonen et al., 2002).

2.3 Pathogenesis and risk factors

2.3.1 Environmental factors

Sunlight is the major principal environmental risk factor for melanoma. Solar ultraviolet radiation promotes malignant change in the skin by having direct mutagenic effects on DNA. Ultraviolet B radiation is overwhelmingly responsible for sunburn and the formation of the principal DNA lesions, the incorrect repair of which leads to the selection for genetic mutations that allow the aspects of the malignant phenotype, including stimulation of blood vessel growth, evasion of the immune response, tumour invasion and metastatic spreading (Satyamoorthy and Herlyn, 2002; Thompson et al., 2005). The pathogenesis is associated with the intermittent exposure hypothesis: unlike the non-melanosytic skin cancers which are associated with total cumulative exposure to UV radiation over a lifetime, melanomas are associated with intense intermittent exposure and repetitive sunburns (Elwood, 1992). There has also been evidence for the speculation that exposure to high levels of sunlight in childhood is a strong determinant of melanoma risk (Whiteman et al. 2001). Indeed, the peak melanocytic activity occurs in early life and for this reason there is an important correlation between intermittent intense sun exposure and the development of melanocytic nevi and freckles in exposed areas (Green et al., 1985). Freckles are thought to represent clones of mutated melanocytes and their precence is associated with an increased risk of melanoma (Gilchrest et al., 1999).

2.3.2 Host factors

Nevi and phenotype. The historically classic risk factors for cutaneous melanoma, including fair or red hair, blue eyes and fair type I skin, are surrogates for the tendency to develop nevi, freckles, and sunburn. 20 % to 30 % of skin melanomas derive from benign nevus melanocytes, whereas 70 % arise from epidermal melanocytes de novo (Kanzler and Mraz-Gernhard, 2001). The number of nevi correlates with the risk of melanoma (Green et al., 1985; Grob et al.,1990). Hereditary susceptibility is an important determinant of nevus phenotype and one particular melanocytic lesion, the dysplastic nevus, is a potential determinant of melanoma risk (Greene 1999). Familial dysplastic nevus syndrome is characterized by the familial occurrence of cutaneous melanoma in combination with multiple atypical precursor nevi (Greene et al., 1987). In addition, individuals with rare congenital melanocytic giant nevi are also at high risk of developing melanoma and in such a situation, exceptionally, the melanomas may develop in childhood. The lifetime risk of malignant transformation in patients with large congenital nevi has been estimated to be between 5 % and 20 % (Kanzler and Mraz-Gernhard, 2001). This increased risk has been shown for those patients with

large nevi of 20 cm or greater, whereas medium size congenital nevi have not shown the same risk (Sahin et al., 1998).

Genetic factors. The risk for an individual developing a melanoma is greatly increased if there is a family history of the disease. Among high-incidence populations, about 5 % to 12 % of cutaneous melanomas develop in individuals with at least one affected first-degree relative (Gerstenblith et al., 2007). However, most melanomas arise as a result of a combination of environmental and sporadic factors that cause mutations and are not part of a hereditary syndrome. In general, melanoma is genetically very heterogeneous (Hayward, 2003). Sporadic mutations are associated with the pathogenesis of melanoma in about 90 % and about 10 % of cases represent familiar clusters, of which about 60 % are due to unknown gene mutations (Hansen et al., 2004). Less than 2 % of all melanomas are due to the presence of identifiable, heritable mutations in highly penetrant genes (Thompson et al., 2005). The genes known to function this way are CDKN2A, located on chromosome 9p21 (Cannon-Albright et al., 1992; Hussussian et al., 1994; Kamb et al., 1994) and rarely CDK4, located on chromosome 12q14 (Wölfel et al., 1995; Zuo et al., 1996). In clinical practice, the risks and benefits of genetic testing for CDKN2A mutations have not been completely delineated at this time and therefore, predictive genetic testing outside of research settings is not currently recommended by most research groups (Gerstenblith, 2007).

2.4 Prevention and screening

2.4.1 Primary prevention

Public education and physical protection from exposure to sunlight are the most important elements of melanoma risk reduction. Australia, with the world´s highest rates of skin cancer, has been at the forefront of these preventive activities. The primary prevention programs have been largely based on state government and non-governmental organizations such as Cancer Councils. The Australian public health program entitled Slip!Slop!Slap! advised people to “slip on a shirt, slop on sunscreen, and slap on a hat” when they go out into the sun in order to prevent skin cancer. The Victoria Anti-Cancer Council has been running Australia´s most recognisable sun protection programs for nearly 30 years directed especially at children (Montague et al., 2001). This kind of program emphasizes the importance of photoprotection, including the use of broad-spectrum suncreens, wearing sun-protective clothing when outdoors, and avoiding the sun in the middle of the day when UV radiation is the strongest. Despite these efforts, Australian adolescents seem to be more resistant to sunlight protection programs than children (McCarthy, 2004). Tanning is gaining in popularity as an aesthetic value and this group as a whole has little or no interest in sunlight avoidance. Unfortunately, the same attitude is seen among adolescents in Europe (de Vries et al., 2006).

2.4.2 Secondary prevention

Whereas primary prevention has an influence on melanoma incidence, the purpose of secondary prevention is to improve disease survival by means of early diagnosis. Individuals should be taught to recognize their own nevi and to watch for their change in shape, size, and colour. However, public education and melanoma awareness has been mostly focused on superficial spreading melanoma. Indeed, there has been a significant increase in the proportion of thin, good prognosis lesions and that is felt to be the principal reason for the current overall improvement in melanoma survival. In contrast, according to the Scottish Melanoma Group data, the absolute number of thick, poor prognosis melanomas has not significantly altered (Murray et al., 2005). Thick melanomas are characterized by an increasingly older age group and male gender (McHenry et al., 1992). If the lesion is of nodular type, secondary prevention with early self-detection of those lesions is less effective, since the rapidly growing nodular tumours do not always fit the typical ABCD criteria (Asymmetry, Border irregularity, Colour variegation, large Diameter) (Chamberlain et al., 2003). Amelanotic nodular lesions may be particularly challenging even for physicians. Elderly men are resistant to awareness campaigns and on public skin cancer screening days, the elderly individuals who are attending, tend to be predominantly women (Holme et al., 2001). Thus, alternative preventive strategies are clearly needed and education needs to be directed, not only at elderly people, but also at those who care for them (McHenry et al., 1992).

2.4.3 Screening

To date, no population-based randomized trials have addressed whether early detection via screening asymptomatic persons with whole-body exams by physicians is effective in reducing mortality or morbidity from skin cancer (Geller et al., 2007). However, there are many evaluations of the results of skin cancer screening campaigns, in which free skin inspection has been offered to volunteers. Overall, there is a significant heterogeneity considering both the attendees and the examination methods in such studies. A Finnish study on this subject was recently published (Oivanen et al., 2008). A total of 10 187 patients were analyzed, of whom 5903 had made a campaign and 4284 a routine visit as their first contact. The authors found a higher specificity (79 % vs. 49 %), but a lower sensitivity (59 % vs. 82 %) for campaign attendees versus routine visitors regarding overall skin cancer detection.

In general, media campaigns also have educational purposes with a view to improving public awareness. While organized whole population-based skin cancer screening remains controversial, major efforts should be focused on patients with high and moderate risk of developing melanoma: patients with giant congenital pigmented nevi, dysplastic nevus syndrome, a strong family history or previous melanoma (Thompson et al., 2005). Regular full-body examinations performed by a dermatologist should be considered especially when multiple atypical nevi are present. These selected high or moderate risk patients should be examined by dermatologists, because their practice

setting is an ideal place for this kind of screening. New technologies including dermatoscopy and follow-up photography have resulted in earlier detection of melanomas (Kittler et al., 2002; Feit et al., 2004).

In Germany, from the first of July, 2008, a new skin cancer screening programme has been available. Beginning from the age of 35, everyone with compulsory health insurance will be entitled to receive a clinical examination for skin cancer every two years (hautkrebs-screening).

2.5 Diagnosis

2.5.1 Clinical detection based on morphological subtypes

In most cases, melanoma is diagnosed by primary care physicians. In clinical diagnosis, the recognition of the morphological subtypes of melanoma and their variants is crucial for the physician to avoid certain pitfalls.

Superficial spreading melanoma (SSM) is the most common form of cutaneous melanoma constituting 50–70 % of all lesions (Figure 1). Clinically, an initially slow growing, variably pigmented plaque with irregular and often notched border is seen, ranging from a few millimetres to several centimetres; shades of tan-brown to jet-black, and from red to blue, are also seen in these lesions (Swetter, 2003). Unlike most other subtypes, SSM often arises in a precursor nevus. A clinical differentiation between SSM and dysplastic nevus is challenging.

***N**odular melanoma* is the second most common subtype and accounts for 10 % to 15 % of all melanomas (Figure 2). It is more rapidly growing, typically a darkly pigmented nodule or papule, although amelanotic lesions also occur. Chamberlain et al. (2003) found that more than 50 % of the nodular melanomas were predominantly amelanotic, red or pink. The nodules may be polypoid or pedunculated. Unlike SSMs, nodular melanomas are more often symmetric and uniform in colour and that is why the ABCD diagnostic criteria of early melanoma do not apply well for nodular melanoma. In the case of amelanotic nodular melanoma, there may be a clinical suspicion of basal cell carcinoma, pyogenic granuloma, hemangioma or Spitz nevus (Grant-Kels et al., 1999).

Lentigo maligna melanoma arises on chronically sun-exposed sites in older individuals and presents as a freckle-like lesion (Figure 3). Calculated as density per skin area, lentigo maligna melanoma is 74 times more common in the face compared to the skin outside the head and neck (Gillgren et al., 1999). The lesion begins as an irregular flat, variably pigmented, tan-brown patch which gradually grows and develops darker, asymmetric flecks in areas (Swetter, 2003). Partial regression may be present. During transformation to invasive melanoma palpaple induration or nodules may develop.

Acral lentiginous melanoma is the rarest type of melanoma among white-skinned populations, but the most common form among populations with Fitzpatrick type V-VI skin (Figure 4). It arises on palmar, plantar and subungual surfaces as dark brown to black, irregular, unevenly pigmented patches (Swetter, 2003). Acral lentigious melanomas of the soles may be misdiagnosed as a foot ulcer, particularly in a diabetic. They may also be hidden by a thickened layer of keratin, appearing as a callus. The classical subungual melanoma in the hand or foot arises as a narrow pigmented band in the nail, which slowly widens and produces a mass under the nail. This form of melanoma is very easy to misdiagnose, commonly as a fungal infection or a pyogenic granuloma (Grant-Kels et al., 1999). Grant-Kels et al. (1999) listed almost 50 skin conditions, which may appear as clinical simulators of melanoma. Conversely, melanomas can also masquerade them. The diagnostic pitfalls are frequently associated with amelanotic lesions, because any of the four subtypes can occur as a nonpigmented variant (Koch and Lange, 2000). Sometimes, however, a tiny peripheral rim of pigment may provide a crucial diagnostic clue (Chamberlain et al., 2003). The red flags, associated with any suspicious skin lesions, are bleeding and ulceration.

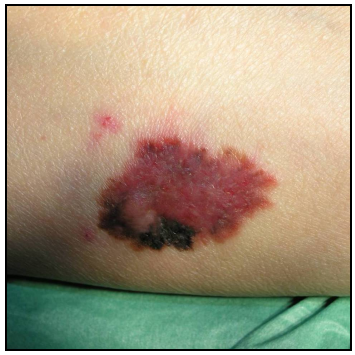

Figure 1. Superficial spreading melanoma.

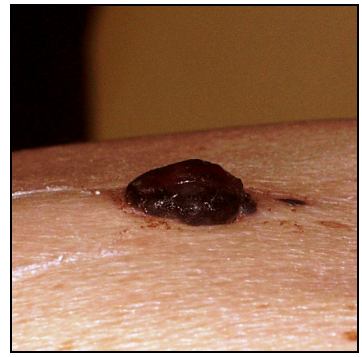

Figure 2. Nodular melanoma.

(© *Doc. Olli Saksela)*

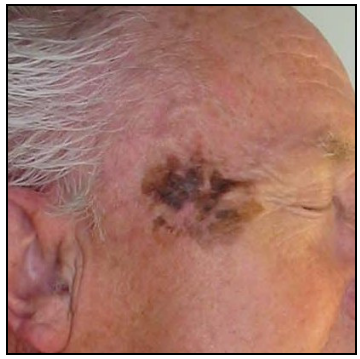

Figure 3. Lentigo maligna melanoma.

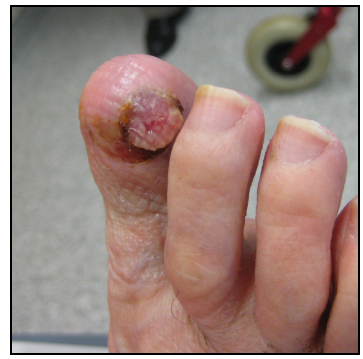

Figure 4. Acral lentigious melanoma.

2.5.2 Biopsy

Because of the diagnostic pitfalls, a low threshold for biopsy is critical in making the diagnosis of cutaneous melanoma. Whenever possible, the whole lesion should be excised with narrow skin margins laterally and with a cuff of subdermal fat (Sober et al., 2001; Tsao et al., 2004; Bishop et al., 2002). If the clinical suspicion for melanoma is low or if the lesion is too large, an incisional or punch biopsy is appropriate as long as the sample is representative of the entire process. There is strong evidence that such biopsy does not adversely affect prognosis in terms of local recurrence and mortality (Lees and Briggs, 1991; Bong et al., 2002). When a punch is used, its blade should be 4–6 mm in diameter. A tangential shave biopsy is not appropriate when invasive melanoma is suspected, because such an approach results in incomplete Breslow depth measurement (Tsao et al., 2004).

2.6 Prognostic factors

2.6.1 Demographic factors

Increasing patient age is an independent prognostic factor with respect to the overall survival rate within all thickness subgroups (Balch et al., 2001b). Male gender is also associated with worse prognosis than female gender (Balch et al., 2001b). In addition to age and sex, the anatomic site correlates significantly with survival: trunk, head and neck sites with worse prognosis than extremities (Balch et al., 2001b).

2.6.2 Pathologic factors

Horizontal versus vertical growth phase. The pathology of primary melanoma provides diagnostic data, offers prognostic information and, to large extent, directs the treatment of the patient (Liu and Mihm, 2003). The basic delineation can be made between preinvasive melanoma in situ and invasive melanoma. Melanoma in situ is an intraepidermal lesion at a pure radial growth phase without any metastatic potential. If a vertical component is present and the tumour cells have broken through the basement membrane into the papillary dermis, melanoma is defined as invasive. This concept of distinct radial and vertical growth phases is also associated with the subtypes of melanoma. SSM is thought to grow mainly by radial growth pattern at the initial stage, whereas nodular melanoma lacks a radial growth phase and grows vertically. Because of this feature, nodular melanomas tend to be more advanced at diagnosis and have worse prognosis. The prognosis of melanoma is strongly associated with its vertical invasion in depth, not with its visible size, i.e. diameter in radial dimension. However, when other risk factors such as tumour thickness are equal, the subtype is not an independent prognostic factor for survival (Clark et al., 1989).

Clark´s level of invasion. Wallace Clark (1924-1997), a skin pathologist from Boston, Massachusetts, U.S.A., established a five-levelled scale of melanoma according to the

depth of microscopic invasion of the tumour cells and demonstrated its correlation with survival (Clark et al., 1969). This classification system is highly reproducible for pathologists and it has been a valuable tool for melanoma researchers giving them a standard vocabulary for sharing information from studies.

Clark´s levels are defined as follows according to the anatomic compartment of invasion:
Level I: Intraepidermal in situ melanoma
Level II: Invasion through the basement membrane into the papillary dermis
Level III: Invasion into the interface between papillary and reticular dermis
Level IV: Invasion into the reticular dermis
Level V: Invasion through the entire skin into the subcutaneous fat tissue

To date, Clark´s level is still valid and widely used in routine pathology reports. Level of invasion is highly associated with survival when considered as a single variable. However, Balch et al. (2001b) found in a multivariate analysis of 17 600 melanoma patients that the Clark´s level of invasion is an independent predictive feature of thin T1 melanoma, but not for thicker lesions. As a result, the level of invasion was incorporated only into the staging definitions of T1 melanomas in the revised American Joint Committee on Cancer (AJCC) 2002 classification system.

Breslow thickness. One year after Wallace Clark´s landmark study, Alexander Breslow (1928-1980), a professor of pathology at George Washington University Medical Center, Washington, U.S.A., published his retrospective study on only 98 patients (Breslow, 1970). Breslow found by careful analysis that both tumour thickness and the stage of invasion were of value in assessing prognosis. Later on, with a larger study population Breslow reported that the incidence of metastatic disease is directly proportional to the tumour thickness (Breslow, 1975). Breslow suggested that "these criteria may be of value in selecting patients for prophylactic lymph node dissection". Because of this significance, Breslow depth is the single most important parameter of localized melanoma in the AJCC classification. Unlike Clark´s qualitative classification, the Breslow thickness measurement assesses the depth of melanoma as a quantitative parameter, measured from the top of the granular cell layer of epidermis to the deepest point of invasion. Breslow thickness is the most powerful independent factor for prediction of lymph node metastasis and survival (Balch et al., 2001b). Among pathologists, there is also good agreement of the reproducibility of tumour thickness (Scolyer et al., 2003).

Ulceration. In 1953, Sophie Spitz (1910-1956) and Arthur Allen (1910-1994), pathologists at Memorial Hospital, New York, published a study on 934 patients regarding the clinicopathological analysis of the criteria for diagnosis and prognosis of malignant melanoma (Allen and Spitz, 1953). In their extensive article in the journal Cancer, they were the first to establish the clinical significance of ulceration as a major prognostic factor. They noticed a significant association between the incidence of ulceration and mortality. Ulceration is defined as the absence of an intact epidermis over-

lying a major portion of the primary melanoma based on microscopic examination (McGovern et al., 1982; Balch et al., 1978). The distinction between traumatic or artificial disruption of the epidermis and spontaneous ulceration is essential. An ulcerated melanoma is associated with aggressive metastatic behaviour and, analogiously, such lesions should be considered in the same category as any poorly differentiated or locally advanced cancer (Balch et al., 1980). Ulceration is one of the most reproducible of all the major histopathologic features of melanoma (Corona et al., 1996).

Mitotic rate. Tumour mitotic rate was originally classified as the average number of mitoses per 10 high power fields (HPF) (McGovern et al., 1973). In the later revised recommendation, mitotic rate was determined as the number of mitoses per mm^2 (McGovern et al., 1986). Tumour mitotic rate has been confirmed to be an important independent predictor of survival for melanoma patients (Azzola et al., 2003; Francken et al., 2004). Despite this significance, mitotic rate was considered to be too interpretive as a parameter and therefore it would have been difficult to include it into the latest AJCC 2002 classification system (Balch et al., 2004).

Regression. Primary cutaneous melanoma has a tendency to disappear spontaneously. Histologically, the active phase is characterized by a dense infiltrate of lymphocytes similar to that seen in spontaneously disappearing naevi. The regression process may continue until the tumour has been completely destroyed, or it may cease when only a part of the tumour has been destroyed (McGovern, 1975). The larger size of the regression area is associated with a worse prognosis, particularly in thin melanomas (Ronan et al., 1987; Guitart et al., 2002). Completely regressed melanomas have not been documented but probably some of the occult primary lesions, when only metastases have been found, are associated with this event. It has been speculated that regression may cause underestimation of the tumour depth resulting in a determination of "false-thin" melanoma (Liu and Mihm, 2003). Regression has, however, been defined differently in various studies, and the reproducibility of the classification of regression has been considered low (Elder et al., 2005).

Microsatellites. Satellites are discrete tumour nests, separated from the main body of the tumour by normal reticular dermal collagen or subcutaneous fat, and considered to most likely represent locoregional metastases (Day et al., 1981). Satellites appear to be associated with increased risk for local recurrence, even after a formal wide excision has been completed (Elder et al., 2005). The distinction between satellites and in-transit metastases is unclear from the biological point of view. The latest AJCC 2002 classification system merges them into a single staging entity that is grouped under stage N2c disease (Balch et al., 2000).

Angiolymphatic invasion. Vascular invasion has been considered as closely related to tumour satellites, as most of them presumambly occur as a result of angiolymphatic invasion (Elder et al., 2005). In general, the distinction between blood vessel and lymphatic vessel invasion is not possible. Angiolymphatic invasion, however, is likely to be associated with poor prognosis (Kashani-Sabet et al., 2001).

Taken together, the pathology report should accurately include all this information of the primary lesion, which is important for rational and effective clinical management of the patient. Diagnostic difficulties may occur, particularly for pathologists who are not experienced in assessing and reporting melanocytic lesions (Veenhuizen et al., 1997). For this reason, pathologists should be encouraged to seek second and third opinions when there is uncertainty, as many already do (Thompson et. al, 2005).

2.6.3 Nodal status

Because of the high number of characteristics, there are many computer-based prognostic models for cutaneous melanoma. In clinical practice, however, the prognosis for an individual patient with melanoma simply depends mainly on two factors: the thickness of the primary tumour and the presence or absence of metastasis to regional lymph nodes (Thompson et al., 2005). Stage III disease, defined as presence of regional lymph node metastasis, is associated with a dramatic deterioration of prognosis. Nodal status is the most important independent predictive factor for survival (Balch et al., 2001a). In a multivariate analysis of 1201 patients with nodal metastases, the following three factors were significant prognostic factors: the number of metastatic nodes, the tumour burden at the time of staging (i.e. clinically occult vs. clinically apparent) and the presence of ulceration of the primary lesion (Balch et al., 2001b). This finding is the basis of the N classification in the AJCC 2002 melanoma staging system.

2.7 Classification and staging

2.7.1 AJCC Staging system

The tumour-node-metastasis (TNM) staging of cancer is a shorthand system for describing the extent of disease, typically including three major categories of disease: localized disease (stage I-II), disease with regional lymph node metastases (stage III), and disease with distant metastases (stage IV). A new AJCC staging system for melanoma was introduced in 2002 and it is now in the international use. The classification is based on the details of 17 600 patients from 13 melanoma treatment centres and their prospective databases in the U.S.A, Australia and Europe. A subcommittee of six experienced clinical statisticans participated in the analysis (Balch et al., 2001a). The AJCC 2002 staging system and the estimated 10-year survival rates in each category are presented in Table 1.

In this classification system, stage I-II melanoma is defined as localized disease. In contrast, stage III signifies nodal involvement, either microscopic or macroscopic. A microscopic metastasis is defined as a metastasis not detectable by clinical or radiological examination but pathologically detected (Balch et al., 2001a). In the study population of the AJCC database, the microscopic tumour burden had been identified

by either sentinel or elective node dissection for patients with clinically localized melanoma (Balch et al., 2001a).

Table 1. AJCC 2002 staging system with corresponding 10-year survival rates (Balch et al., 2001a)

Stage	*Definition*	*10-year survival (%)*
IA	Thickness ≤1.0mm, no ulceration, Clark level II-III	87.9
IB	Thickness ≤1.0mm, with ulceration or Clark level IV-V	83.1
	Thickness 1.01-2.0mm, no ulceration	79.2
IIA	Thickness 1.01-2.0mm, with ulceration	64.4
	Thickness 2.01-4.0mm, no ulceration	63.8
IIB	Thickness 2.01-4.0mm, with ulceration	50.8
	Thickness >4.0mm, no ulceration	53.9
IIC	Thickness >4.0mm, with ulceration	32.3
IIIA	1-3 nodes with micrometastasis, no ulceration	56.9 – 63.0
IIIB	1-3 nodes with micrometastasis, with ulceration	35.9 – 47.7
	1-3 nodes with macrometastasis, no ulceration	
	Satellites or intransit metastases, no nodal metastases	
IIIC	Macrometastases with ulceration or intransit metastases	15.0 – 24.0
	or satellites, or any metastases in 4 or more nodes	
IV	Distant metastases	2.5 – 15.7

2.8 Surgical management of the primary melanoma

2.8.1 Primary excision

Most cases of cutaneous melanoma are cured by the excision of the primary tumour alone. Inadequate excision margins may increase the risk of local recurrence and decreased survival but, in contrast, overtreatment is associated with increased morbidity. This topic has been investigated by five prospective randomized trials of good quality (Veronesi et al., 1988; Balch et al., 1993; Ringborg et al., 1996; Khayat et al., 2003; Thomas, et. al 2004). Three of them have also reported follow-up studies (Veronesi and Cascinelli, 1991; Balch et al., 2001c; Cohn-Cedermark et al., 2000). They all compared the results of narrow excision margins (1 to 2 cm) to wide excision margins (3 to 5 cm), but there was significant clinical heterogeneity between the trials. Trials in-

cluded patients with different stages of disease and the definitions of narrow versus wide excision margins were different. The data of these trials comprising a total of 3313 participants have been analyzed by two meta-analyses (Haigh et al., 2003; Lens et al., 2007). These meta-analyses concluded that there was no statistically significant difference in overall mortality or local recurrence rate between patients treated with wide excision margins versus those treated with narrow excision margins. Only Thomas and co-workes (2004) showed a borderline statistically significant increased risk of locoregional recurrence in patients treated with narrow excision margins, if the Breslow thickness of the lesion was 2 mm or greater. From the results of these analyses, however, it is difficult to recommend the minimum excision margins required. A 1 cm margin is widely accepted as adequate for thin melanomas, but there is still debate about the safety of 1-cm margins for melanomas with a thickness of 1 to 4 mm, because a 1-cm margin has never been tested against a 2-cm margin in any randomized trial. In this category, the recommended maximum margin is 2 cm according to most guidelines. Minimum margins necessary for thick melanomas (>4 mm) remain unclear, because current published data including the meta-analyses provide insufficient evidence to recommend optimal surgical treatment (Veronesi et al., 1988; Balch et al., 1993; Ringborg et al., 1996; Khayat et al., 2003; Thomas, et. al 2004; Lens et al., 2007). In general, local failure may result from both the biology of the primary tumour and the extent of excision.

2.8.2 Reconstruction

In most cases, the wound can be closed directly by means of narrow excision margins (1 to 2 cm). However, the recommendations for excision margins are based primarily on data from melanomas of the trunk and extremities. Melanomas in hands, feet or in the face are less well studied and they pose a surgical challenge. Nonetheless, oncologic principles and adequate margins should not be compromised for aesthetic or functional concerns with potentially curable melanoma. A well-planned reconstructive procedure is preferred to a suboptimal surgical excision (van Aalst et al., 2003). A variety of options exists for reconstruction instead of primary closure: skin grafting, local skin flaps, regional muscle or fasciocutaneous flaps or, rarely, microvascular free flaps. These techniques allow for closure of most defects.

Subungual melanomas are often associated with delayed diagnosis and present with deep primary lesions (Cohen et al., 2008). A history of anamnestic nail trauma is not uncommon (Möhrle and Häfner, 2002), which may lead to a misdiagnosis of subungual haematoma. The treatment should be planned according to the Breslow thickness, but digital amputation is frequently needed because of the paucity of soft tissue between the tumour and the bone beneath the nail even in patients with thin melanoma (Cohen et al., 2008). Finger amputation may be performed as distal or proximal interphalangeal level amputation, depending on appropiate cutaneous margins (van Aalst et. al, 2003). In the foot or heel, extensive resections of plantar weight-bearing areas may require flap reconstruction, either with a local or free flap. Fasciocutaneous free flaps,

such as the radial forearm flap, are preferred alternatives in such situations (van Aalst et al. 2003).

2.9 Lymphatic mapping and sentinel lymph node biopsy

2.9.1 Preliminary studies on the lymphatic system

Bartholin was the first to notice the existence of the lymphatic system in 1653. A comprehensive systematic mapping of the lymphatic anatomy of skin was done in the 19th century by Marie Sappey, a French anatomist. His atlas of the lymphatic anatomy included the classic watershed concept, an assumption that lymphatic vessels drain towards the axilla above a horizontal line and towards groin below it (Sappey, 1874). In the 1950s, the lymphatic system was studied with lymphangiography. The lymphatic trunks were made visible to the naked eye by subcutaneous injection of a diffusible blue dye (Patent blue V) so that watery radio-opaque solution could be injected directly into them through a small needle (Kinmonth et al., 1955). In the 1960s, there were attempts to use lymphangiography in the detection of clinically occult lymph node metastases in patients with melanoma. Filling defects in the x-rays of regional lymph nodes was thought to determine the presence of metastasis. However, this method was not found to be reliable, particularly when the nodal metastases were microscopic (McPeak and Constantinides, 1964). Because of the high rate of both false positive and false negative findings, the value of lymphangiography in guiding clinical decisions on melanoma patient management was nullified (Cox et al., 1966).

Before the era of sentinel lymph node biopsy, elective lymph node dissection was widely used in melanoma patients with the purpose to improve survival and local disease control. There was an obvious difficulty, particularly in axial trunk melanomas, to determine which lymph node basins were the potential sites of occult metastases and candidates for surgical removal. The conventional concept was based on Sappey´s anatomical guidelines. At that time, lymphoscintigraphy (LS) studies questioned the lymphatic watershed concept of Sappey in many cases. As the lymphatic pathways vary for every individual, they may lead to unpredictable or multiple lymph node basins. LS was a reliable technique to visualize this complex system and it was easier to perform and less invasive than lymphography. The preliminary study was reported on patients with trunk melanoma and whose evaluation was performed by colloidal gold radionucleotide 198Au scanning (Fee et al., 1978). Nine of the 27 patients had nodal metastases in the area of nucleotide uptake and there were no recurrence in those basins which did not show preoperative gold uptake. Two pioneer studies were performed in Scandinavia. Swedish investigators reported an evaluation on 32 melanoma patients and 239 removed lymph nodes (Bergqvist et al., 1984). They concluded that LS was of great importance visualizing lymph flow directions when prophylactic lymph node dissection was planned. During follow-up, no recurrences were found in areas other than those indicated by the LS. Interestingly, increased radioactivity was found in tumour-involved lymph nodes. This was speculated by the authors to be due to an increased

function of the phagocytes during the early phase of metastatic spread. These nodes were probably radioactive because they were the sentinel nodes. Another study from Denmark found that 48 % of truncal melanomas had a multidirectional lymph flow from the tumour site, which did not agree with the classic assumption as to the direction of lymph flow (Lock-Andersen et al., 1989). The simple drawings in this paper demonstrated very elegantly the unpredictable variations of lymphatic routes to regional lymph node basins and there is an interesting similarity between these drawings and recently published three-dimensional, computer-based, colour-coded heat maps, which were based on over 5000 lymphoscintigrams performed in the Sydney Melanoma Unit in the past 10 years (Reynolds et al., 2007). Both of these studies confirm that the traditional Sappey´s lines are not effective in predicting lymphatic drainage.

2.9.2 The sentinel node concept

The first clinical observation of the sentinel node, i.e. the first draining node, was reported by Ernest Gould and his co-workers (1960). Their observations were based on the constant location of a normal lymph node at the junction of the anterior and posterior facial vein during the operation of parotid gland cancer. This normal-appearing node was sent to the pathologist for frozen section study and "to the surprise of the surgeon, the report was lymph node with metastatic tumour". Thereafter, radical neck dissection was performed. Based on 28 further similar operations, Gould stated that sentinel node status may guide the surgeon in the justification of radical neck dissection. This finding formulates the basis of the sentinel node concept: the status of the sentinel node is predictive for the status of the entire nodal basin.

The next step on the development of the sentinel lymph node biopsy (SLNB) was the pilot study by Ramon Cabañas (1977) on 46 patients with penile carcinoma. The lymphangiography technique was used for the detection of the sentinel node. Cabañas demonstrated lymphatic drainage from the penis into "a specific lymph node center, the so-called sentinel lymph node". The sentinel node was found to be the first filter in the penile lymphatic pathway and in 80 % of the metastatic cases, no other lymph nodes were positive. Cabañas concluded that if SLNBs are negative for metastases, no further surgical therapy is immediately indicated. However, some later reports found this method unreliable (Perinetti et al., 1980; Wespes et al., 1986). In addition, penile cancer is a rare disease and the number of cases for individual urologists would have been insufficient for the challenging approach (Busby and Pettaway, 2005). This resulted in a 15-year long silent period which ended in the return of the SLNB concept in patients with melanoma and breast cancer.

Finally, the concept was outlined by Donald Morton and co-workers in patients with melanoma (Morton et al., 1992). Their publication "Technical details of intraoperative lymphatic mapping for early stage melanoma" consists of two parts: first, there was a feline study to determine the ideal dyes and technique for identifying the regional lymphatics, and secondly, a clinical study on 223 melanoma patients. The feline study was

also reported elsewhere in detail (Wong et al., 1991). Morton, who operated most of the patients himself, used patent blue-V or isosulfan blue for intraoperative mapping of the lymphatics (Morton et al., 1992). LS was used selectively only in 14 patients to identify the lymphatic drainage for melanomas located in ambiguous sites, such as the midline of the trunk. By meticulously dissecting along the blue-stained lymphatic ducts, the first draining lymph nodes were identified and removed. At least one sentinel node was identified in 82 % of the procedures and metastatic tumour cells were detected in 21 % of them. The false-negative rate was 1 % and no severe complications were reported (Morton et al., 1992).

2.9.3 Technical details of sentinel lymph node biopsy

Blue dye

In their feline studies, Morton and co-workers examined a variety of mapping substances for their potential utility as tracking dyes in the lymphatics (Morton et al., 1992). These included methylene blue, isosulfan blue, patent blue-V, Cyalume and fluerescein dye, which were injected intradermally in adult cats to determine whether the anatomic site of injection had a predictable pattern of drainage to a particular lymph node. Among these substances, Patent blue-V and isosulfan blue provided the best results in mapping the regional lymphatics. When injected intradermally, they rapidly entered the lymphatics and were associated with minimal diffusion into the surrounding soft tissue. The bright blue coloration of these dyes was clearly visible and allowed easy identification of the afferent lymphatic channel. In his first human study, Morton also found Patent blue-V to enable the best viewing of the draining lymphatics and the brightest staining of the sentinel nodes. Injection of the dye intradermally was considered as critical and only a small volume of dye (0.5 to 1.0 ml) was needed. The dye was injected at the site of melanoma, or if the primary lesion had been removed by excisional biopsy, intradermally on either side of the incision scar. The injection site was gently massaged to promote the passage of dye along the lymphatics. Morton learned that the dye passed rapidly to the sentinel node and then to secondary nodes causing a risk for false-negative result. Therefore, the injections were repeated every 20 minutes during the procedure.

Preoperative lymphoscintigraphy

A surgeon always needs a roadmap. If only blue dye is used, the surgeon cannot know precisely where the blue-stained sentinel nodes are located and considerable dissection is often required to find the node. By lymphoscintigraphy the tumour´s specific individual drainage routes are visualized, providing the roadmap of the lymphatic highways for the surgeon. The Sydney Melanoma Unit started the practice of preoperative LS in high-risk trunk melanomas in 1986 and the results were published some years later (Uren et al., 1993). Uren and his working group used technetium-99^{m}-antimony sulphide colloid (^{99m} Tc-Sb2S3) and the particle size of the tracer varied from 3 to 12

nanometers. Multiple small-volume (0.1 ml) intradermal injections were used to surround the biopsy excision site or the primary lesion and the radioactivity of the dose varied from 50-70 MBq/ml. The studies were performed prior to wide local excision. The scanning using a large gamma camera was commenced immediately and each scan view was collected over 10 minutes. LS had a sensitivity of 94 % in detecting draining sites that contained metastases. Most patients showed lymph drainage to one or two nodal basins and most of them also had multiple draining lymph channels. Unusual drainage patterns were frequently seen, for example deeply to the para-aortic nodes. Aberrant sentinel nodes outside the regional basins are also common. During the last six months of this preliminary study Uren also marked the sentinel node in each draining node group. Uren stated that the sentinel node concept has proved to be one of the most useful aspects of LS (Uren et al., 1994). A preoperative lymphoscintigraphy is presented in Figure 5.

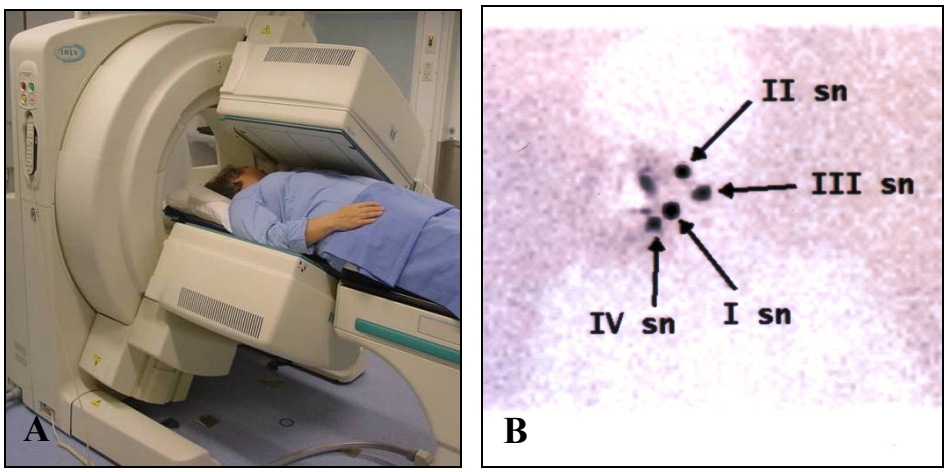

Figure 5. A. Preoperative scintigraphy with a gamma camera. **B.** A lymphoscintigraphy of a patient with a melanoma in the left cheek indicates the locations of four sentinel nodes (sn). Sn II was located and later excised in the parotid gland.

Most reports refer to sentinel nodes situated in the classic and anatomically well-defined lymph node basins: mainly the cervical, axillary, and groin. However, patterns of lymphatic drainage from the skin are not clinically predictable (Uren, 2004). LS studies have demonstrated that sentinel nodes are sometimes situated outside the familiar regional lymphatic basins. The incidence of such aberrant or interval sentinel nodes is between 4 % and 5 % (Matter et al., 2007; Roozendaal GK et al., 2001). These aberrant sentinel nodes are at the same metastatic risk as are sentinel nodes in the usual classic areas and should therefore be excised.

Intraoperative mapping and combined technique

The use of an intraoperative scintillation probe to detect deposits of radiolabelled tissue was described in 1948: an intraoperative Geiger-Müller counter was used to detect brain tumours radiolabelled with intravenously administered phosphorus-32 (Selverstone et al., 1948). After numerous intermittent experimental works, this approach made a come-back within the sentinel node concept. Using first a feline model, Alex and Krag (1993) reported that intradermally injected technetium-99^{m}-labeled sulphur colloid enters the same lymphatic pathways and labels the same lymph nodes as does the blue dye. In this animal model and in the following pilot series of melanoma patients (Alex et al., 1993; Krag et al., 1995), the radiolabeled sentinel nodes were found to be detectable with a handheld gamma detector. The sentinel nodes identified by the gamma probe on the skin surface were same as the hot spots in the preoperative mapping. This improved localization made it possible to remove the sentinel node faster and through a small incision. For this reason, SLNB was suggested to be done in an outpatient setting with local anaesthesia minimizing the time, cost and morbidity of the procedure. Technetium-99^{m} was stated to be the radionuclitide of choice. Its optimal gamma-ray energy and short half life (6 hours) minimize radiation exposure and makes sequential studies possible. In addition, it is inexpensive and readily available. This technique is also able to detect the residual gamma emissions in the lymphatic bed after the removal of the radiolabelled node, indicating the presence of additional nodes. Removal of lymph nodes until the bed count is 10 % of the hottest lymph node will remove 98 % of positive sentinel nodes (Carlson et al. 2002). It soon became clear that the identification of the sentinel node was most accurate if the combined triple method was used: preoperative lymphoscintigraphy with skin markings, blue dye injection and the use of hand-held gamma probe intraoperatively (van der Veen et al., 1994). There are many important variables within the procedure; such as the timing and the type of the lymphoscintigraphy (static vs. dynamic); and the type, the amount and the number of radiocolloidal tracer. Most importantly, however, the SLNB procedure is very much a team work with involvement of multiple disciplines including surgery, pathology, and nuclear medicine. The SLNB procedure is presented in Figure 6.

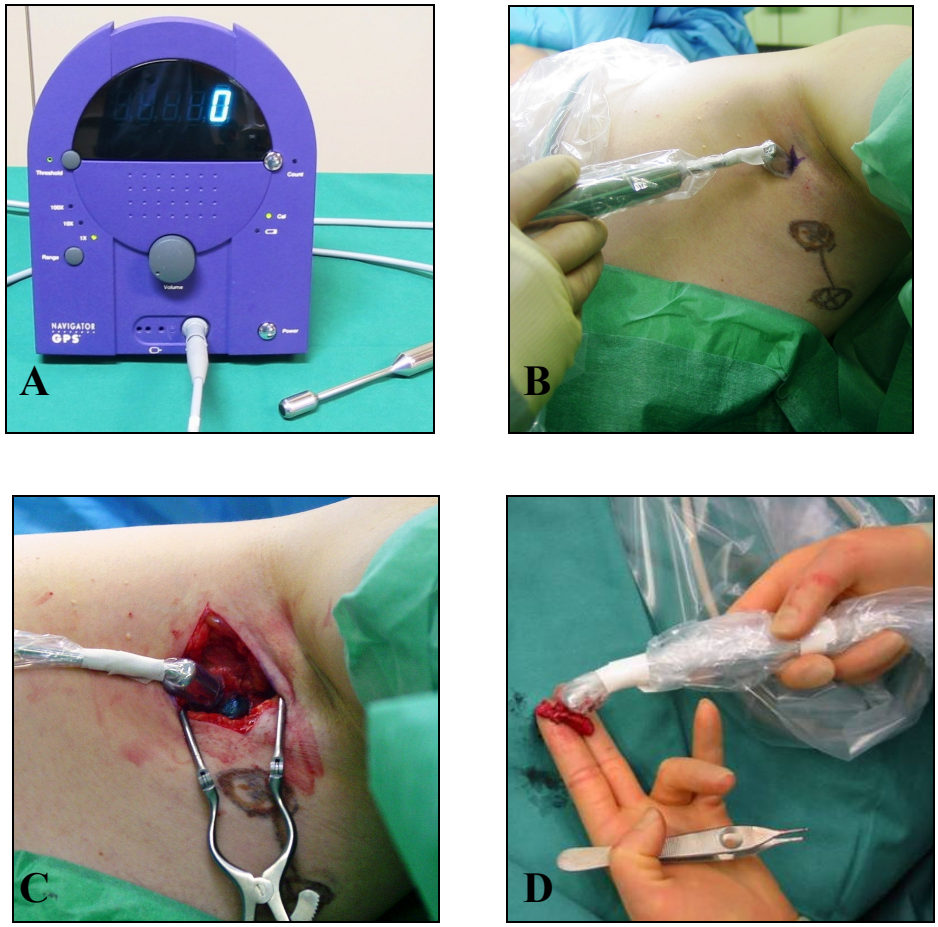

Figure 6. Sentinel lymph node biopsy: **A**. Gamma detecting probe. **B**. Radioactive focus in the right axilla, dorsally to the lymphoscintigraphy skin markings. **C**. Blue and hot node is found. **D**. Ex vivo radioactivity counted from the hot node.

2.9.4 Histopathological analysis of the sentinel node

Accurate pathologic evaluation is a key component in the sentinel node concept. As the surgeon has to perform a reliable SLNB procedure, the main task for the pathologist is to screen the sentinel nodes for possible metastases. This screening has to be done more meticulously than usual because a false negative assessment may lead to untreatable local tumour outgrowth in tumour-bearing lymph nodes that have remained (van Diest et al., 1999). The sentinel node concept has reduced the number of lymph nodes that need to be evaluated, allowing pathologists to focus their efforts (Cochran et al., 2000a). In the preliminary SLNB studies of melanoma, intra-operative frozen section analysis was used so that a completion lymph node dissection could have been performed during the same operation if the sentinel node contained micrometastasis. Cur-

rently, this one-step approach is still advocated in breast cancer whereas intraoperative frozen section analysis is strongly discouraged in melanoma patients due to the risk of interpretative errors (Cochran et al., 2000a). Evaluations are recommended to be made on formalin fixed, paraffin embedded sections for two reasons: first, to minimize the loss of limited diagnostic tissue, and secondly, to provide high quality sections that provide optimum cellular morphology for analysis of H&E-stained and immunostained preparations. In addition, the frozen section analysis is associated with poor sensitivity (Koopal et al., 2000). The standard protocol of histopathological investigation thus consists of haematoxylin and eosin (H&E) stained sections and immunohistochemistry. Excised and formaldehyde-fixed sentinel nodes are first cut coarsely into slices of 1-2 mm in thickness; the slices are embedded in paraffin, sectioned, and stained with H&E. Because melanomas metastasize first to the subcapsular sinus in the plane of entry of the relevant afferent lymphatic, the sentinel node should be sected through its longest meridian (Cochran et al., 2004a).

If no metastatic melanoma cells are identified in the H&E sections, further sections are cut and immunohistochemical staining is performed. Without immunohistochemistry, approximately 12 % of metastatic sentinel nodes would be miscategorized as tumour negative (Cochran et al., 2000b). Monoclonal antibodies as S-100 (Gaynor R et al., 1980, 1981) and HMB 45 (Gown et al., 1986) have been commonly used as diagnostic reagents in the immunohistochemical analyses of the sentinel nodes. The S-100 protein is most used in this regard, staining virtually 100 % of melanomas, but the disadvantage is that it is not specific; it also stains dendritic leukocytes of the paracortex, the Schwann cells of node-associated nerves (Cochran et al., 1984) and the intranodal nevi (Carson et al., 1996). HMB-45 is more specific, but up to 25 % of melanomas do not express the relevant epitope (Cochran et al., 2004a). Furthermore, MART-1 (Kawakami et al., 1994) and Melan-A (Coulie et al., 1994), synonyms for the same protein antigene discovered by two groups of researchers who independently sequenced the gene for this protein, suffer from the same limitation as HMB-45 in that some melanomas do not stain with this reagent (Cochran, 2000). Some investigators have suggested higher diagnostic accuracy with Melan-A and MART-1 compared to S-100 and HMB-45 (Shidham et al., 2001). A Melan-A-positive micrometastasis in a sentinel lymph node is presented in Figure 7.

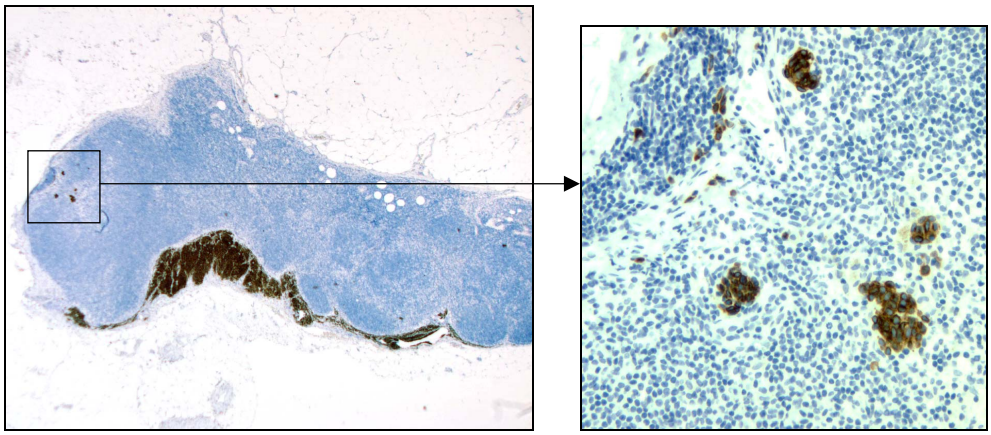

Figure 7. A micrometastasis of melanoma in a sentinel node (Melan-A stain).

In the sentinel node, the tumour cells are usually relative few in number and dispersed singly or as microcolonies in subcapsular sinuses (Cochran et al., 2004a). However, the histopathological findings cover a broad spectrum ranging from isolated tumour cells to complete replacement of lymph node tissue by melanoma cells (Satzger et al., 2007). The tumour burden or tumour disposition predicts the status of nonsentinel nodes, disease recurrence and death from melanoma (Carlson et al., 2003b; Cochran et al., 2008). There are several micromorphometric methods for measuring the tumour dimensions in a lymph node, such as tumour centripetal depth (Figure 8) (Starz et al., 2001), tumour area (Cochran et al., 1993), maximal size of the deposit (Wagner et al., 1999) or the microanatomic location of the tumour within the sentinel node (Dewar et al., 2004).

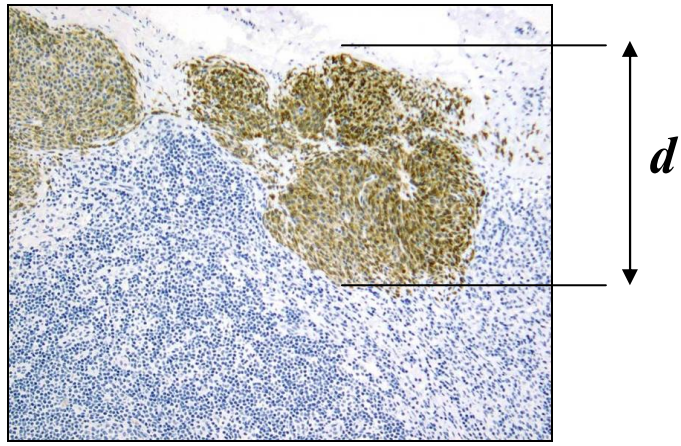

Figure 8. A subcapsular micrometastasis of 1.1 mm in tumour penetrative depth (*d*).

2.9.5 Molecular analysis of the sentinel nodes

Routine histopathological examination of sentinel nodes may underestimate the number of patients with melanoma who have occult nodal metastases. This is the rationale behind the molecular ultrastaging of the sentinel nodes in an attempt to improve the sensitivity of the SLNB procedure. The search for more accurate and sensitive staging has led to techniques, which are based on molecular detection of melanoma cells in peripherial blood or sentinel nodes (Palmieri et al., 2007). This type of detection utilizes the reverse transcriptase-polymerase chain reaction (RT-PCR) technique. The target for RT-PCR is tyrosinase messenger RNA (mRNA). Tyrosinase, the key enzyme in melanin synthesis, is tissue-specific and is actively expressed only by melanocytes and melanoma cells. The role of tyrosinase as a molecular marker was initially reported in the early 1990s and since then interest has been increasing (Smith et al., 1991). Recently, the data of 22 published studies on a large pool of 4019 patients underwent a systematic review and meta-analysis (Mocellin et al., 2007). Pooled data revealed a histology-based sentinel positivity rate of 20.3 %, whereas the mean RT-PCR positivity rate was 51.4 %, with a broad range between 12.1 % and 74.0 %. The meta-analysis indicated that RT-PCR status is a significant meta-risk for both overall survival and disease-free survival. However, there was significant heterogeneity between the trials. The main reason for the conflicting results was caused by the largest and most important trial: the Sunbelt Melanoma Trial, which is a prospective randomized trial involving 79 institutions (Scoggins et al., 2006). A total of 1446 patients with histologically negative sentinel nodes underwent RT-PCR analysis. 42.9 % of the patients were RT-PCR positive but there was no difference in disease-free survival or overall survival between the RT-PCR positive and negative patients and RT-PCR analysis of the sentinel nodes demonstrated no additional prognostic information beyond standard histopathological analysis. Thus, RT-PCR remains investigational and should not be used to direct any standard therapy.

2.9.6 Validation of the sentinel node concept

Within three years of the landmark publication by Morton (Morton et al., 1992), the validity of the SLNB concept in patients with melanoma was confirmed by two studies (Reintgen et al., 1994; Thompson et al., 1995). The aim of these studies was to confirm that metastatic melanoma cells travelling in lymphatics do not bypass the sentinel node, because such skip metastases would cause an increased false-negative rate and thus decreased sensitivity of the SLNB procedure. In these studies, both SLNB and immediate ELND of the relevant lymph node basin were undertaken and it was thereby confirmed that the sentinel node status accurately reflected the status of the entire nodal basin. Several other investigators subsequently also verified the accuracy of SLNB (Krag et al., 1995; Albertini et al., 1996; Leong et al., 1997). In these five preliminary studies the sentinel node identification rate varied between 87 % and 100 % and the sentinel positivity rate between 15 % and 21 %. In a review of 12 studies containing 4218 patients with stage I-II melanoma, 17.8 % (95 % CI; 16.7-19.0)

of patients were sentinel-positive (Lens et al., 2002). Breslow thickness predicted sentinel-positivity being 1.0 % for lesions of ≤ 0.75 mm, 8.3 % for 0.76-1.50 mm, 22.7 % for 1.51-4.0 mm, and 35.5 % for more than 4.0 mm.

The initial purpose of the development of the SLNB concept was to replace ELND. The available evidence overwhelmingly supports sentinel node status as the most powerful independent factor predicting recurrence and survival indicating that SLNB provides the highest sensitivity and specificity of any nodal staging method currently available (Gershenwald et al., 1999; Cascinelli et al., 2000; Jansen et al., 2000; Statius Müller et al., 2001; Kettlewell et al., 2006). In terms of this accuracy, SLNB is superior to ELND (Doubrovsky et al., 2004).

2.9.7 Complications of sentinel lymph node biopsy

The SLNB procedure is not complication-free. A study on 250 SLNB patients reported an overall complication rate of 20 % (Wasserberg et al., 2004). The wound complications were predominantly associated with the inguinal dissection. However, a publication from the Sunbelt Melanoma Trial Study Group reported a significantly lower complication rate of 4.6 % on a cohort of 2120 SLNB patients (Wrightson et al., 2003). Risks include wound separation (0.2 % to 1.2 %), seroma or hematoma (2.3 % to 5.5 %), wound infection (1.1 % to 4.6 %), and lymphedema (0.6 % to 0.7 %) (Morton et al., 2005; Wrightson et al., 2003). In general, SLNB alone entails significantly lower morbidity compared with a combination of SLNB and CLND.

2.9.8 Patient selection and special indications

Thin melanoma

There is a linear correlation between Breslow thickness and mortality and for this reason, thin T1 melanomas (Breslow thickness of ≤ 1 mm) have in general excellent prognosis. However, a small fraction of patients with thin melanoma will develop recurrence and die of disseminated disease. Any invasive melanoma may carry such potential risk and there is no thickness-related biological cut-off point regarding metastasis. According to extensive population-based studies, the 5-year-survival rate for patients with thin T1 melanoma is 98 % and the 10-year survival rate is 95 % (Lindholm et al., 2004; Gimotty et al., 2007). According to the statistics of the AJCC database, pathologic nodal status was present in 4.5 % of the 731 patients with thin melanoma (Balch et al., 2001a). Several single-institution SLNB studies have shown a wide variation in the percentage of patients who are found to have positive sentinel nodes. Ten such studies are presented in Table 2. Pooled data show an overall sentinel positivity rate of 5.0 %. In some of these studies, there have been attempts to find parameters that would predict the sentinel node positivity.

Table 2. Results of sentinel lymph node biopsy in thin T1 melanoma

Study	*n*	*Positive SNs*	*Predictors of SN-positivity*
Bleicher et al. (2003)	272	8 (2.9 %)	Not found
Wong et al. (2006a)	223	8 (3.6 %)	Not found
Ranieri et al. (2006)	184	12 (6.5 %)	Clark level, mitogenicity
Stitzenberg et al. (2004)	146	6 (4.1 %)	Not found
Starz and Balda (2007)	87	10 (11.5%)	Not reported
Oliveira Filho et al. (2003)	77	6 (7.8 %)	Ulceration, mitogenicity, VGP
Bedrosian et al. (2000)	71	4 (5.6 %)	VGP (all patients)
Jacobs et al. (2003)	65	2 (3.1 %)	Not reported
Hershko et al. (2006)	64	5 (7.8 %)	Younger age
Cecchi et al. (2007)	50	2 (4.0 %)	Not reported
Pooled data	**1249**	**63 (5.0 %)**	

VGP, vertical growth phase. SN, sentinel node.

Thick melanoma

The optimal candidate for SLNB is a patient with an intermediate-thickness melanoma. In patients with thick T4 melanoma (Breslow thickness of >4 mm), it has been thought that the risk of occult distant metastases is so high that it may negate any potentially curative benefit of regional surgery. The SLNB concept, again, offers an alternative approach to assess disease in the regional nodal basin. In a retrospective study of 131 patients with thick melanoma, SLNB detected nodal disease in 39 % of the patients and this result provided essential prognostic information: compared with a positive SLNB, a negative SLNB was associated with 42 % and 35 % increases in 3-year disease-free and overall survival, respectively (Gershenwald et al., 2000b). Thus, as with thin T1 melanomas, thick T4 melanomas also represent a prognostically very heterogeneous population. Currently, a clinically localized thick melanoma is an accepted indication for SLNB in routine clinical practice (Carlson et al., 2003a).

Childhood melanoma

Malignant melanoma in childhood is extremely rare, and therefore, the biology and natural history of melanoma in this age group are poorly understood (Mehregan and Mehregan, 1993). A particular problem is the persistent confusion of Spitz nevi with atypical features with melanoma and lack of specific criteria for their distinction (Barnhill et al., 1995). In recent years, despite only a limited number of reported cases,

available data strongly support a role for SLNB in the identification of metastatic melanoma in pediatric and young patients (Livestro et al., 2007). In pediatric melanoma, SLNB has two special features. First, pediatric patients seem to have a higher sentinel positivity rate than adults yet have a lower incidence of recurrence (Roaten et al., 2005). Secondly, SLNB has been advocated as a diagnostic tool in distinguishing Spitz nevus-like malignant melanoma from atypical Spitz nevus; detection of melanoma cells in the sentinel node confirms the diagnosis of metastatic melanoma (Lohmann et al., 2002). However, there is also risk for more diagnostic confusion for a pathologist, because the sentinel node may contain benign spitzoid nevus cells (Busam and Pulitzer, 2008). The treatment of pediatric melanoma is thus generally administered on the basis of algorithms for adults. Currently, evidence of melanoma cells in sentinel nodes warrants offering a completion lymph node dissection (Downard et al., 2007). No serious complications have been reported from pediatric SLNB (Toro et al., 2003).

Elderly patients

SLNB is underused in the elderly (Cormier et al., 2005). Higher age alone should not be a contraindication to SLNB. Even if the natural life expectancy is decreased among the elderly, the option for accurate staging and better local control are still valuable aims. Lymph node status is the most important prognostic factor in older patients, not age alone (Chang et al., 2003). SLNB is a minimally invasive and safe procedure, which can in most cases, be performed under local anaesthesia. Poor health is not a contraindication to SLNB in general, but if such a patient is sentinel-positive, the decision of the second stage CLND should be considered individually. After positive SLNB, there remains approximately a 20 % risk for nodal recurrence due to nonsentinel metastases, and in some cases, that risk may be more preferable than the risk of operative mortality. However, age is also an independent prognostic factor for overall survival for patients with melanoma (Balch et al., 2001b). In addition, some other independent poor prognostic factors such as Breslow thickness, the presence of ulceration and male gender are significantly associated with increasing age (Chao et al., 2004; Caracò et al., 2006).

2.9.9 Contraindications of sentinel lymph node biopsy

Pregnancy

SLNB during pregnancy has not been systematically evaluated, but it is not considered as an absolute contraindication to SLNB. The estimated Tc99 dose to the fetus has been estimated to be low; the maximum dose of 4.3 mGy calculated for the worst-case scenario is well below the 50 mGy that is believed to be the threshold absorbed dose for adverse effects (Keleher et al., 2004). If melanoma is diagnosed during the first trimester and the radiocolloid injection site and the draining nodal basin are located in the pelvic region, there is no standard rule to guide the treatment decision. Some au-

thors advise not offering SLNB to women at the time of the most critical period of fetal organogenesis of less than 30 weeks gestation (Lloyd et al., 2004).

Hypersensitivity to blue dye

Some patients may carry a risk having a hypersensitivity or anaphylactic reaction to blue dye, a triphenylmethane dye, a well-known dye in the food industry. Such adverse reactions have been described as anecdotal studies (Beenen and Zuidewijn, 2005). Three decades ago, such reactions were common due to lymhangiography studies. At that time, a Finnish study group performed a prospective skin-prick testing on 435 patients undergoing lymphography and on 566 controls; positive reactions were seen in 2.8 % of the lymphography patients and in 2.7 % of the controls (Kalimo et al., 1981). Only four patients with positive patent blue test had a history of adverse reactions to blue dye. Thus, the adverse reactions are usually unpredictable in SLNB. If such an allergy is known in advance, SLNB should be performed without blue dye.

2.10 Lymph node dissection

Elective lymph node dissection

Historically, elective lymph node dissection (ELND) was developed for the surgical removal of an entire regional lymph node basin in patient with clinically localized (AJCC stage I-II) melanoma. In the pre-SLNB era, ELND was the only method to identify occult nodal micrometastases. However, four prospective randomized studies of ELND have not demonstrated any overall survival benefit (Veronesi et al., 1982; Sim et al., 1986; Cascinelli et al., 1998; Balch et al., 1996). Furthermore, the morbidity of ELND is substantial particularly considering that approximately 80 % of the patients cannot benefit from it because they have no nodal metastases.

Completion lymph node dissection

It should be stressed that completion lymph node dissection (CLND) is not the same procedure as ELND. Whereas ELND is a blind procedure, CLND is selective, because it is focused only on the specific lymph node basin, which is known to contain metastasis. The purpose of CLND is to remove potential additional nodal metastases beyond the sentinel nodes. Many research groups have attempted to find such features that could predict the likelihood of further nodal involvement in CLND specimens. If the patient is sentinel-positive, the overall risk of nonsentinel metastases is between 15 % and 24 %; the factors predictive of tumour-positive nonsentinel lymph nodes have been found to be Breslow thickness, ulceration and the number of tumour-positive sentinel nodes and, particularly, their tumour burden (Reeves et al., 2003; Scolyer et al., 2004a; Lee et al., 2004; Cascinelli et al., 2006; Rossi et al., 2008). The density of paracortical dendritic leukocytes in the sentinel node, as an index of immune modulation, has also

been evaluated to predict individuals likely to have a tumour in the nonsentinel nodes (Cochran et al., 2001; Cochran et al., 2004b; Cochran et al., 2006). Wong and coworkers (2006b) examined the survival of 134 melanoma patients who did not undergo CLND after positive SLNB; there was a nodal recurrence rate of 15 % at a median follow-up of 20 months, a similar to rate of nonsentinel node involvement in a contemporary cohort of patients who underwent CLND after positive SLNB.

2.11 Adjuvant treatment

To date, no adjuvant therapy has resulted in significant improvement in long-term overall survival in melanoma patients (Vihinen et al., 2003; Shah and Chapman, 2007). Only one adjuvant therapy has stood the test of time: high dose interferon-α (IFNα) has been shown to increase disease-free survival (DFS) in patients with high-risk melanoma and it is the only adjuvant treatment approved by the U.S. Food and Drug Administration (FDA) (Kirkwood et al. 1996, 2000, 2001, 2004). A meta-analysis comprising twelve IFNα trials confirmed the reductions in recurrence, about 10 % at five years, but it is unclear whether this translates into significant differences in overall survival (Wheatley et al., 2003). A recent study on 486 patients with AJCC stage III melanoma found that in multivariate analysis, IFNα increased DFS only in patients with stage IIIA disease, not in patients with stage IIIB or stage IIIC disease (Anaya et al., 2008). This study was a retrospective analysis but it nevertheless demonstrates clearly that the SLNB technique is needed for accurate nodal staging in adjuvant therapy trials. However, taken together, adjuvant IFNα therapy should not be considered standard care for patients with melanoma (Lens, 2006).

Melanoma has historically been considered to be relatively radio-resistent and therefore the mainstay of treatment has been surgery. Adjuvant radiotherapy is not routinely indicated in patients with localized stage I-II or micrometastatic stage III melanoma but rarely, in selected cases, postoperative radiotherapy may improve locoregional control; this would include patients at high risk for disease recurrence after surgery such as patients with positive surgical margins at the primary site who are not suitable for reexcision as well as those with multiple positive lymph nodes or extensive extracapsular extension after CLND (Mendenhall et al., 2008; Burmeister et al., 2006; Ballo et al., 2003).

2.12 Positron emission tomography

Otto Warburg (1883-1970), a German cell biologist and Nobel laureate, found that rapidly dividing tumour cancer cells have a higher rate of glucose utilization than normal tissues. This is due primarily to the increased activity of glucose membrane transporters, intracellular hexokinase, phosphofructokinase, and pyruvate dehydrogenase (Warburg et al., 1930). In cancer cells, the increased utilization of glucose is associated with an accumulation of 2-deoxyglucose, a molecule structurally analogous to glucose. 2-

deoxyglucose is phosphorylated and cannot be further metabolized and therefore becomes trapped. When labelled by radioisotope, 2-deoxyglucose has been shown to accumulate in tumours to such an extent as to allow imaging. Thus, such an imaging is based on abnormal cellular metabolic activity rather than on anatomical structural changes.

Whole body positron emission tomography (PET) is a non-invasive, high-resolution molecular imaging that can detect metastases of malignancies based on abnormal cellular glucose uptake. PET was developed in the early 1970s soon after CT and at about the same time as MRI (Phelps et al., 1975). The radiopharmaceutical that has had the most impact on clinical PET imaging is [^{18}F] fluorodeoxyglucose (FDG), which was first described in the late 1970s (Gallagher et al., 1978). FDG is a non-specific metabolic agent that reflects increased glucose metabolism regardless of the underlying cause. Therefore, it can be concentrated in any cell with increased glucose utilization (Lindholm et al., 1993). Gritters and co-workers (1993) imaged patients with melanoma in their initial study and found a 92 % sensitivity and 100 % specificity in the detection of lymph node and visceral metastases. Several investigators have reported that FDG PET is more sensitive and specific than conventional imaging studies, such as CT, in detecting melanoma metastases (Rinne et al., 1998; Holder et al., 1998; Swetter et al., 2002; Brady et al., 2006). A systematic review showed that the overall sensitivity and specificity of FDG PET were 74 % to 100 % and 67 % to 100 %, respectively (Prichard et al., 2002).

2.13 Surgical management of recurrent melanoma

Recurrent melanoma can occur in almost every organ and tissue in the body. The type of first recurrence may be local or intransit (21 % to 23 %), regional nodal (34 % to 56 %) or direct distant (22 % to 44 %) (Dicker et al., 1999; Francken et al., 2008; Meier et al., 2002). This kind of distribution, however, is mainly based on historical patient populations from the pre-SLNB era. In the past, the regional lymph node basin was the most common site of first recurrence in the orderly progression of cutaneous melanoma and the most common surgical management of recurrent melanoma was lymph node dissection. However, SLNB changes the pattern of recurrence and reduces the rate of nodal recurrence (Gershenwald et al., 2000a; Statius Müller et al., 2002; Fincher et al., 2003; Gutzmer et al., 2005). The site of the first recurrence is an important predictor of survival (Allen and Coit, 2002). Patients undergoing excision of local recurrence or therapeutic lymph node dissection due to a recurrent stage III disease have a better prognosis than those whose disease recurs at distant sites. Most patients with recurrent stage IV disease are not candidates for surgery and are treated with chemotherapy, immunotherapy, or radiotherapy. Once melanoma has metastasized to distant sites, median survival is 7 to 8 months and 5-year survival rate is less than 5 % (Essner et al., 2004). Of the modalities of therapy given, only radical surgery can significantly prolong survival (Brand et al., 1997; Ollila et al., 1999b).

3 AIMS OF THE STUDY

The aim of this study was to investigate the utility of sentinel lymph node biopsy and whole body positron emission tomography in the detection of occult metastases in patients with cutaneous melanoma.

The specific aims of this study were as follows:

I To investigate the changes in surgical management and prognosis in patients with clinical stage I–II cutaneous melanoma in South-Western Finland between 1983 and 2007.

II To compare the results of sentinel lymph node biopsy and immediate completion lymphadenectomy to the results of observation and delayed lymphadenectomy in patients with clinical stage I–II melanoma.

III To investigate the utility of sentinel lymph node biopsy in patients with thin T1 melanoma and to evaluate prognostic factors which could sensitively predict the sentinel node status in this population.

IV To investigate the utility of sentinel lymph node biopsy in patients with head and neck melanoma.

V After sentinel lymph node biopsy, to investigate the utility of whole body positron emission tomography in detecting occult metastases in patients with AJCC stage IIB–IIIC high-risk melanoma.

4 PATIENTS AND METHODS

4.1 Patients

Study I (Surgical treatment and prognosis)
This series comprised 1255 patients with clinical stage I–II invasive cutaneous melanoma (T1-T4N0M0) operated on in Turku University Hospital between 1983 and 2007. Medical records of 921 patients operated on between 1983 and 2001 were studied retrospectively. From 2001 to 2007, 334 patients undergoing SLNB were enrolled onto a prospective database. All of the 1255 patients had been followed up at the Department of Oncology and Radiotherapy at Turku University Hospital or at Satakunta Central Hospital. The most recent follow-up information of the patients was updated from the electronic patient records of Turku University Hospital or from the medical records of the Satakunta Central Hospital. The final follow-up date of each patient was defined as the date of the most recent hospital call or the date of death. The cause and time of death were obtained from patient records, autopsy reports or from Statistics Finland´s Archive of Death Certificates.

Study II (Sentinel lymph node biopsy)
This was a case-control study with ratio of 1:2 with the aim of comparing 305 patients who underwent SLNB with 616 historic control patients who had not undergone any invasive nodal staging. All patients had clinical stage I–II invasive melanoma (T1-T4N0M0). Patients who had undergone ELND or who had a primary lesion with undetermined Breslow thickness were not included in the control group. The follow-up data were obtained as described in Study I.

Study III (Thin melanoma)
To investigate the utility of SLNB in thin melanoma, we analyzed a subgroup of 155 patients with thin melanoma (T1N0M0). The follow-up data were obtained as described in Study I.

Study IV (Head and neck melanoma)
To investigate the utility of SLNB in head and neck melanoma, we analyzed a subgroup of 146 patients with head and neck melanoma; 121 historic control patients and 25 patients who had undergone SLNB. Of the 121 controls, 29 patients had undergone ELND and 92 patients had not undergone any invasive nodal staging at the time of initial surgery. Only patients with a primary lesion with a Breslow thickness of over 1.0 mm were included (T2-T4N0M0). The follow-up data were obtained as described in Study I.

Study V (FDG PET)
To investigate the utility of whole body FDG PET, we prospectively enrolled 30 voluntary postoperative patients with stage IIB–IIIC melanoma. The patients were selected consecutively from the prospective melanoma database of SLNB patients. Each patient

had undergone lymphatic mapping with an attempt for SLNB; 15 patients had positive sentinel nodes (Stage III, T1-T4N1-N2M0) and 15 patients had either negative sentinel nodes or unsuccessful lymphatic mapping (stage IIB-IIC, T3b-T4bN0M0). All patients were free of any clinical signs of disease at the time of study inclusion. None of the patients refused to participate in the study. A whole body FDG PET scanning was performed between 6 and 24 months after the primary surgery, independently from the regular follow-up schedule. The follow-up data were obtained as described in Study I.

The patients of Studies I-V are summarized in Table 3.

Table 3. Number of the patients of Studies I-V

	Study I	***Study II***	***Study III***	***Study IV***	***Study V***
Prospective patients (SLNB)	334	305	155	25	30
Retrospective patients (pre-SLNB)	921	616	-	121	-
Total	**1255**	**921**	**155**	**146**	**30**

4.2 Methods

4.2.1 Management of the primary lesion

After the histological confirmation of invasive melanoma, the primary melanoma or the biopsy scar was excised according to the thickness and anatomic location of the melanoma. The wound was closed directly, by the use of a local flap, by skin grafting or by digital amputation or ear lobe resection.

4.2.2 Sentinel lymph node biopsy

A total of 334 patients underwent lymphatic mapping before the surgical procedure. Technetium-99^{m}-labeled colloidal albumin (Albures®, from October 2001 to August 2004; Nanocoll®, from August 2004 to February 2007) was injected intradermally at two to four points at the margins of the primary melanoma or the biopsy scar. The injected dose was approximately 70 MBq in the volume of 0.2 to 0.3 ml. After 20 minutes to 2 hours, static images (40 kcts/image) were obtained with the gamma camera to visualize radioactive lymph nodes in different projections (anterior, lateral, oblique and posterior if needed). The sentinel node sites were marked on the skin of

the patient. After lymphoscintigraphy, SLNB was performed within 20 hours at the same time with the excision of the primary lesion or the biopsy scar. For the localization of the sentinel node a preoperative blue dye injection (Patent blue V) and intraoperative use of a gamma detecting probe (Navigator GPS, Tyco Health Care, Norwalk, CT, U.S.A.) were used. All bluestained and radioactive lymph nodes were excised. The lymph node was regarded as a sentinel node if the ex vivo count exceeded 10 % of the count of the most radioactive node or if it was blue.

Excised and formalin-fixed sentinel nodes were first cut coarsely into slices; the slices were embedded in paraffin, sectioned and stained with hematoxylin and eosin (HE). If no metastatic melanoma cells were identified in the HE-stained sections, further sections were cut and immunohistochemical staining with Melan-A and/or S-100 or antibodies was performed. The tumour burden of each micrometastasis was classified by Starz's centripetal thickness, i.e. tumour penetrative depth of the metastatic deposits (*d*), measured as the maximum distance of the tumour cells from the interior margin of the lymph node capsule.

The S-classification was determined for each patient:
S0 no micrometastasis
SI $d \leq 0.3$mm
SII 0.3mm $< d \leq 1.0$mm
SIII d > 1.0mm

Patients who were found to have micrometastasis in their sentinel nodes underwent completion lymph node dissection (CLND) of the entire regional nodal basin within 2-3 weeks. If the metastatic sentinel node was located only on an intransit field, the need for CLND was considered individually. The sentinel-positive patients, who had melanoma in the head and neck region, underwent selective, modified radical or radical neck dissection.

Management of lymph nodes in the control group

In the retrospectively collected control group, no invasive nodal staging had been performed on 710 patients (Studies I, II, IV) whereas elective lymph node dissection had been performed on 211 patients (Studies I, IV) at the same time with the excision of the primary melanoma or the biopsy scar. If nodal recurrence occurred during the follow-up, a therapeutic lymph node dissection had been performed in most cases if no distant metastases were present.

4.2.3 Positron emission tomography

Whole body FDG PET scanning was performed 7–24 months after the primary surgery, independently from the regular follow-up schedule. Computed tomography (CT) and physical examination were performed concurrently with FDG PET and the median

interval between FDG PET and CT was 35 days (range, 1–145 days), and CT was performed prior to FDG PET in most cases. The last three scans were performed with the new PET/CT hybrid camera. A CT scan covered the same body level as FDG PET in each case. Patients fasted at least 6 hours before entering Turku PET Centre, where all studies were performed. The imaging device was a GE Advance (General Electric Medical Systems, Milwaukee, WI, U.S.A.) or CTI ECAT HR+ (Siemens Medical Systems, Knoxville, TN, U.S.A.) PET scanner which both operated in 2D mode. The GE Advance and HR+ scanners consist of 18 and 32 rings of bismuth germanate detectors (BGO) yielding 35 and 63 transverse slices spaced by 4.25 mm and 2.46 mm, respectively. The imaging field of view is 55 cm in diameter in both scanners and 15,2 cm (GE Advance) and 15.5 cm (HR+) in axial length. A bolus of approximately 370 MBq of FDG was injected through a venous catheter which was flushed with saline after tracer injection. Blood glucose was evaluated routinely with HaemoGlucotest®. After a waiting period when physical activity was minimized the patients were placed supine on a scanner couch with arms downwards. Static PET imaging covering the entire body in case of lower extremity primary or the upper torso from eyebrows to mid thighs in case of abdominal, thoracic, head and neck, and upper extremity primaries started 50 min after FDG injection (5 minutes emission scan/position). To correct for photon attenuation a 2 min post-emission transmission scan was performed with robotically operated ^{68}Ge rods. Image analysis was performed by a certified nuclear medicine physician with experience in FDG PET. All images were analyzed visually and any abnormal focal FDG activity was considered as positive for tumour if physiologic uptake could be ruled out. In challenging cases, consensus reading was performed by two physicians and only lesions deemed as suspicious for tumour were classified as positive. Anatomical reference CT images were used to define the exact site of pathologic accumulation before final scan interpretation.

4.2.4 Follow-up

All patients were referred for further follow-up to the Department of Oncology and Radiotherapy, Turku University Hospital. No routine adjuvant therapy was used. The regular follow-up schedule consisted of initial staging by whole body computed tomography and clinical examination every 3-6 months during the first five years. Routine chest-X-ray and blood tests including liver chemistry were performed annually. Recurrence was defined according to the site of the first recurrence. Local and intransit recurrences were defined as locoregional recurrences and were distinguished from regional nodal recurrences. If distant dissemination was detected within four weeks after locoregional or nodal recurrence, the recurrence was coded as distant. Most patients with recurrent and inoperable stage IV disease received chemotherapy and recombinant IFNα and/or radiotherapy.

4.2.5 Statistical analyses

Categorical variables were analyzed by the χ^2-square test and continuous data by Student's T test or by non-parametric Mann-Whitney's U test. Disease recurrence and disease-specific survival curves were constructed by the Kaplan-Meier method and group differences were analyzed by the log rank test. The ticks along the curves in the survival plots represent censored observations. Deaths from other causes or unknown outcome were categorized as censored observations. Univariate and multivariate survival analyses were performed using Cox's proportional hazards regression model. Results were quantified using hazard ratios (HR) with their 95 % confidence intervals (CI). The starting point for all survival analyses was the initial melanoma treatment. A *p* value of less than 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 14.0 (SPSS Inc., Chicago, IL, U.S.A.) software.

5 RESULTS

5.1 Study I (Surgical treatment and prognosis)

Of the 1255 patients, 605 (48.2 %) were male and 650 (51.8 %) were female. Patient characteristics between the sexes are summarized in Table 4.

Table 4. Clinical and histopathological characteristics of the study patients

	All patients (n=1255)	***Gender***	
		Male (n=605)	**Female (n=650)**
Age, years			
median	59	59	58
mean	57.6	57.8	57.4
range	10-92	10-92	11-92
Anatomic location (%)			
trunk	525 (41.4)	343 (56.7)	182 (28.0)
upper extrmities	237 (18.9)	102 (16.9)	135 (20.8)
lower extremities	295 (23.5)	73 (12.1)	222 (34.2)
head and neck	198 (15.8)	87 (14.4)	111 (17.1)
Breslow (mm)			
median	1.2	1.5	1.1
mean	2.1	2.3	1.9
range	0.1-20.0	0.1-20.0	0.1-15.0
Clark level (%)			
II	336 (27.7)	146 (25.0)	190 (30.1)
III	508 (41.8)	259 (44.3)	249 (39.5)
IV	310 (25.5)	154 (26.4)	156 (24.7)
V	61 (5.0)	25 (4.3)	36 (5.7)
Ulceration present (%)	268 (21.4)	161 (26.7)	107 (16.5)
AJCC stage (%)			
IA	424 (38.6)	169 (32.3)	255 (44.4)
IB	262 (23.9)	125 (23.9)	137 (23.9)
IIA	148 (13.5)	77 (14.7)	71 (12.4)
IIB	129 (11.7)	72 (13.7)	57 (9.9)
IIC	58 (5.3)	33 (6.3)	25 (4.4)
III	77 (7.0)	48 (9.2)	29 (5.1)

AJCC, American Joint Committee on Cancer (given if Breslow depth determined)
NS, not significant

The mean follow-up time of the entire population was 6.7 years (median, 5.0 years; range, 0.1–24.2 years). During the follow-up, there was recurrent disease in 281 patients (22.4 %). The mean disease-free time was 33 months (median, 19 months; range, 0.2–19.3 years). Of the recurrences, 14 % were of local or intransit, 41 % were of nodal, and 41 % were of distant type, defined as the first site of recurrence. A new primary melanoma was detected in 14 patients (1.1 %). Most of the recurrences were treated by chemotherapy, interferon or radiotherapy. 157 patients were operated due to recurrent melanoma: 86 patients with recurrence of regional lymph nodes, 41 patients with recurrence of skin or soft tissue, 11 patients with pulmonary metastasis, 7 patients with brain metastasis, and 3 patients with intra-abdominal metastases. In 1255 study patients, there were 222 melanoma-related deaths (17.7 %) and 191 melanoma-unrelated deaths (15.2 %).The mean time to death after the first recurrence was 18 months (median, 10 months). According to time-dependent survival analysis, the disease-specific overall survival rate was 84.4 % at five years and 76.6 % at ten years. There was a significant difference between sexes ($p<0,001$): the disease-specific overall survival rate at five years was 79.9 % in male and 88.8 % in female; the corresponding rates at ten years were 68.9 % and 83.9 %, respectively (Figure 9). The distribution of AJCC stages between sexes is presented in Figure 10. Breslow thickness was a statistically significant predictor for disease-specific death. At ten years, the melanoma-specific OS rate was 94.5 % in T1 lesions, 73.8 % in T2 lesions, 67.0 % in T3 lesions, and 41.0 % in T4 lesions (Figure 11).

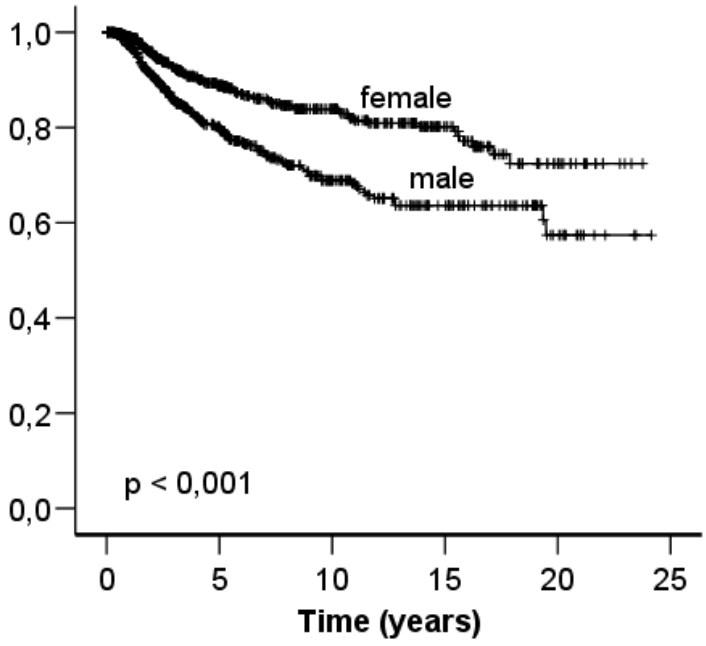

Figure 9. Melanoma-specific overall survival between sexes.
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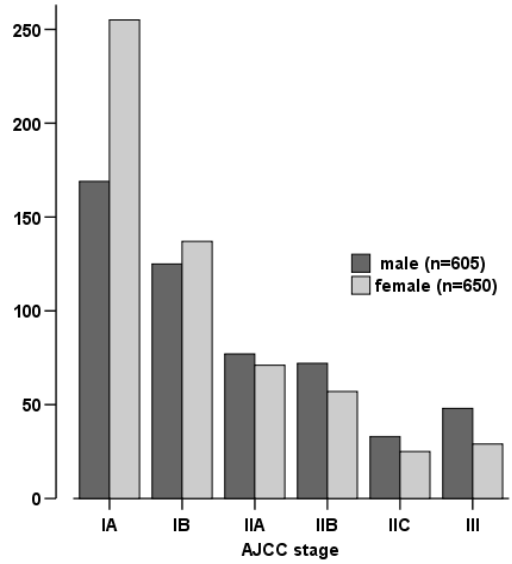

Figure 10. Distribution of AJCC stages between sexes.
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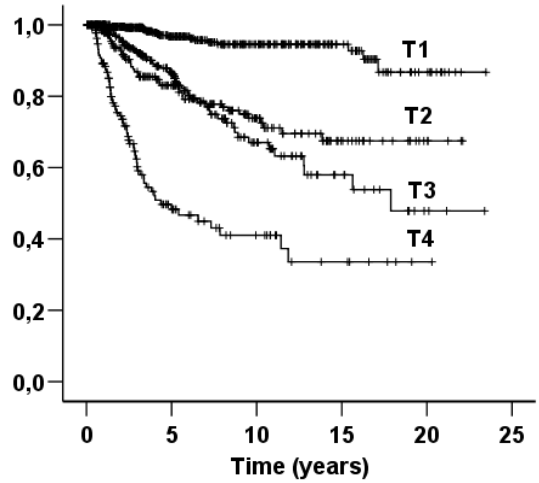

Figure 11. Melanoma-specific overall survival according to the tumour depth.
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The study population was divided into three time periods according to the time point of diagnosis: 1983–1992 (460 retrospective patients), 1992–2001 (461 retrospective patients), and 2001–2007 (334 prospective patients including all SLNB patients). The corresponding data between these subgroups are presented in Table 5.

Table 5. Surgical management and outcome of the patients between time periods

	1983-1992 (n=460)	*1992-2001 (n=461)*	*2001-2007 (n=334)*	*P*
Median age, years	57	59	60	NS
Breslow thickness, mm				NS
median	1.4	1.4	1.1	
mean	2.1	2.1	2.0	
Width of excision margin, cm				<0.001
median	4.0	2.0	1.5	
mean	3.9	2.2	1.5	
Reconstruction (%)				
direct closure	123 (26.7)	218 (47.3)	248 (74.3)	
local flap	124 (27.0)	119 (25.8)	48 (14.4)	
skin grafting	188 (40.9)	111 (24.1)	31 (9.3)	
other (e.g. digital amputation)	15 (3.3)	7 (1.5)	7 (2.1)	
Lymph node surgery (%)				
ELND	173 (37.6)	38 (8.2)	0	
SLNB / CLND [1]	0	0	328 (97.3)	
TLND	33 (7.2)	51 (11.1)	4 (1.2)	
Median follow-up time, years	10.8	5.6	2.1	
Locoregional recurrence (%)	11 (2.4)	16 (3.4)	6 (1.8)	NS
Nodal recurrence (%)	53 (11.5)	62 (13.4)	6 (1.8)	<0.001
Melanoma-specific OS rate [2]				
at 3 years	90.4 %	86.2 %	93.2 % [3]	
at 5 years	86.1 %	81.7 %	-	
at 10 years	79.9 %	71.2 %	-	
at 20 years	68.5 %	-	-	

ELND, elective (immediate) lymph node dissection. SLNB, sentinel lymph node biopsy. CLND, completion (immediate) lymph node dissection. TLND, therapeutic (delayed) lymph node dissection. OS, overall survival. NS, not significant.
[1] 54 patients underwent CLND due to positive sentinel node
[2] Log rank test; A vs. B significant (p = 0.014), A vs. C not significant, B vs. C not significant.
[3] 104 patients remaining in the SLNB group at 3 years.

In disease-specific overall survival, there was a significant difference between patients operated 1983–1992 and 1992–2001 according to the log rank test. When the same comparison was performed between the subgroups according to the lymph node operation (SLNB vs. ELND vs. observation), there were no significant differences in disease-specific overall survival, disease-free survival, locoregional disease-free survival or distant disease-free survival. Only in nodal disease-free survival, was there a significant difference between SLNB and ELND (log rank test, p=0.01) and between SLNB and observation (log rank test, p<0.001). There was no significant difference between ELND and observation in terms of nodal disease-free survival. The Cox proportional hazard model of prognostic factors for disease-specific overall survival is presented in Table 6.

Table 6. Cox's proportional hazard model of clinical and pathological factors for melanoma-specific overall survival of 1255 study patients

Factor	***Univariate***		***Multivariate***	
	HR (95 % CI)	**P [a]**	**HR (95 % CI)**	**P [a]**
Gender				
Female	1.00		1.00	
Male	1.90 (1.45-2.49)	< 0.001	1.58 (1.12-2.25)	0.010
Age, years				
- 44	1.00		1.00	
45-59	1.50 (0.96-2.37)	NS	1.40 (0.80-2.44)	NS
60-74	2.49 (1.65-3.76)	< 0.001	2.14 (1.28-3.55)	0.003
75-	4.08 (2.57-6.47)	< 0.001	2.70 (1.52-4.82)	0.001
Primary tumour site				
Trunk	1.00		1.00	
Upper extremity	0.63 (0.41-0.96)	0.032	0.84 (0.52-1.36)	NS
Lower extremity	0.83 (0.59-1.17)	NS	1.00 (0.65-1.54)	NS
Head and neck	1.50 (1.06-2.11)	0.020	0.92 (0.57-1.48)	NS
Tumour thickness				
≤ 1.00 mm	1.00		1.00	
1.01 – 2.00 mm	5.06 (2.92-8.77)	< 0.001	3.86 (2.01-7.40)	< 0.001
2.01 – 4.00 mm	7.03 (4,03-12.26)	< 0.001	4.36 (2.16-8.80)	< 0.001
> 4.00 mm	19.91 (11.62-34.14)	< 0.001	9.20 (4.37-19.36)	< 0.001
Clark level				
II	1.00		1.00	
III	3.92 (2.26-6.79)	< 0.001	1.40 (0.69-2.86)	NS
IV	7.54 (4.34-13.09)	< 0.001	1.39 (0.65-2.99)	NS
V	26.52 (14.10-49.88)	< 0.001	2.95 (1.18-7.40)	0.21
Ulceration present	2.71 (2.06-3.56)	< 0.001	1.36 (0.97-1.91)	0.07 (NS)

HR, hazard ratio. CI, confidence interval. NS, not significant. [a] Wald test.

5.2 Study II (Sentinel lymph node biopsy)

Sentinel lymph node biopsy

Of 305 patients, sentinel lymph node identification and biopsy were successful in 297 patients (97.4 %). In eight patients (2.6 %), the lymphoscintigraphy did not reveal any sentinel nodes. A total of 718 sentinel lymph nodes were excised (mean, 2.4 per patient). Histopathologically, 50 patients (16.4 %) had metastases in the sentinel nodes (sentinel-positive) and 247 patients (81.0 %) did not (sentinel-negative). A total of 49 of the sentinel node-positive patients underwent CLND and 9 of them (18 %) had additional micrometastases in the nonsentinel lymph nodes. There were 15 patients with a micrometastasis only in a single sentinel node (30 % of sentinel-positive patients). During follow-up there were five same-basin nodal recurrences after SLNB, which yielded a failure rate of 1.6 %, a false negative rate of 9.1 %, a sensitivity of 90.9 %, and a negative predictive value of 98.0 %. All nodal recurrences occurred in sentinel-negative patients. None of the micrometastases was regarded as falsely positive.

According to the AJCC classification of tumour thickness, 5 sentinel-positive patients (3.5 %) were of category T1 (≤ 1.00 mm), 12 (17.1 %) of category T2 (1.01 mm to 2.00 mm), 17 (31.5 %) of category T3 (2.01 mm to 4.00 mm) and 16 (37.1 %) of category T4 (> 4.00 mm).

The tumour burden of each micrometastasis was classified by Starz's centripetal thickness, i.e. tumour penetrative depth of the metastatic deposits (*d*), measured as the maximum distance of the tumour cells from the interior margin of the lymph node capsule. The S-classification was S0 (no micrometastasis) in 255 patients, SI ($d \leq 0.3$mm) in 9 patients, SII ($0.3\text{mm} < d \leq 1.0\text{mm}$) in 16 patients and SIII ($d > 1.0$mm) in 24 patients. In one patient, the S-level was undetermined.

Comparison between study groups

Patient characteristics are compared in Table 7. The median follow-up was 16 months in the SLNB group (mean, 21 months; range, 2–63 months) and 74 months in the control group (mean, 87 months; range, 2–281 months) including censored cases. The follow-up events are presented in Table 8.

Table 7. Comparison between the clinical characteristics of SLNB patients and control patients

Characteristic	***SLNB (n=305)***	***Control (n=616)***	***P***
Age, years			0.085 [a]
Median	60	58	
Mean	59.6	57.7	
Range	11-91	16-92	
Gender, n (%)			0.671 [b]
Male	145 (47.5)	302 (49.0)	
Female	160 (52.5)	314 (51.0)	
Primary tumour site, n (%)			0.093 [b]
Trunk	142 (46.6)	270 (43.8)	
Upper extremity	63 (20.7)	105 (17.0)	
Lower extremity	65 (21.3)	134 (21.8)	
Head and neck	35 (11.5)	107 (17.4)	
Tumour thickness			0.897 [c]
Median, mm	1.1	1.2	
Mean, mm	2.0	2.0	
Range, mm	0.1-18.0	0.1-15.0	
≤ 1,00mm, n (%)	141 (46.2)	292 (47.4)	
1,01-2,00mm, n (%)	70 (23.0)	154 (25.0)	
2,01-4,00mm, n (%)	54 (17.7)	95 (15.4)	
> 4,00 mm, n (%)	35 (11.5)	75 (12.2)	
Undetermined, n	5	0	
Clark level, n (%)			0.001 [b]
II	67 (22.0)	208 (33.8)	
III	131 (43.0)	252 (40.7)	
IV	86 (28.2)	120 (19.5)	
V	17 (5.6)	25 (4.2)	
Unknown	4 (1.3)	11 (1.8)	
Ulceration, n (%)			0.065 [a]
Present	75 (24.6)	119 (19.3)	
Absent or unknown	230 (75.4)	497 (80.7)	

[a] Student´s T test. [b] χ^2-square test. [c] Mann-Whitney's U test.

Table 8. Follow-up events

Event	*SLNB (n=305)*	*Control (n=616)*
Recurrences, n (%) [a]		
Locoregional	8 (26.7)	18 (11.2)
Nodal	5 (16.7)	72 (45.0)
Distant	14 (46.7)	61 (38.1)
New primary melanoma	3 (10.0)	9 (5.6)
Total	30	160
Surgery after recurrence, n (%)		
Local excision	9 (3.0)	17 (2.8)
Lymph node dissection	4 (1.3)	67 (10.9)
Distant metastasectomy	1 (0.3)	18 (2.9)
Death, n (%)		
Melanoma-related	14 (4.6)	119 (19.3)
Melanoma-unrelated	14 (4.6)	118 (19.2)
Total	28 (9.2)	237 (38.5)

[a] Percentage of recurrences.

There were no statistically significant differences in melanoma-specific overall survival (OS) (Figure 12A) or disease-free survival (DFS) (Figure 12B) when using Kaplan-Meier analysis. At 5 years, the melanoma-specific OS was 87.8 % in the SLNB group and 85.2 % in the control group (hazard ratio, 0.88; 95 % CI, 0.49-1.56; p = 0.66); the corresponding DFS was 85.1 % in the SLNB group and 79.0 % in the control group and (hazard ratio, 0.84; 95 % CI, 0.55-1.28; p = 0.415).

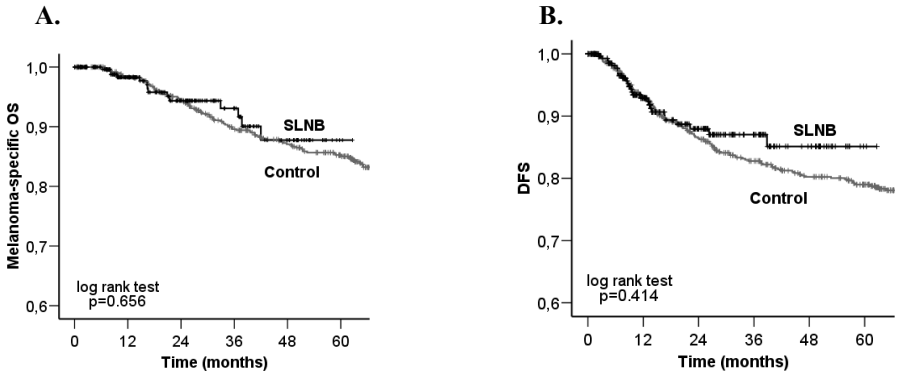

Figure 12. A. Melanoma-specific overall survival between the study groups. **B.** Disease-free survival between the study groups. (*Reprinted with the permission of the copyright holders*)

There were no significant differences in locoregional DFS between the groups (Figure 13A), but the nodal DFS was significantly higher among the SLNB group than among the controls (Figure 13B). The first recurrence type was nodal in 72 patients (45 % of all recurrences) in the control group and in five patients (17 %) in the SLNB-group. In the control group, 67 patients (11 %) had undergone TLND as a result of nodal recurrence and the median time from the initial surgery to the delayed lymphadenectomy was 14.7 months (mean, 23.2 months; range, 2.5–86.2 months).

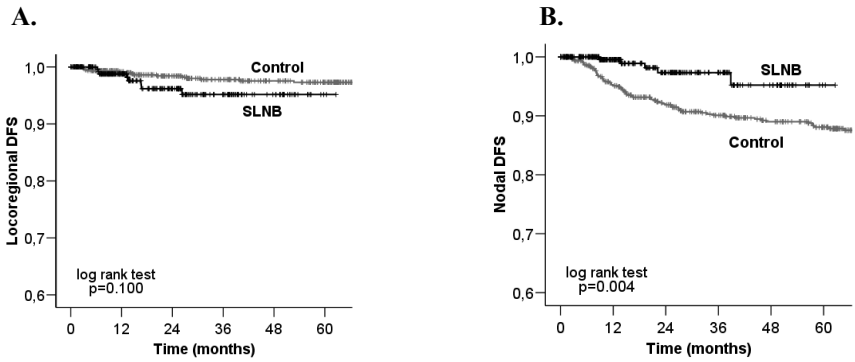

Figure 13. A. Locoregional disease-free survival between the study groups. **B.** Nodal disease-free survival between the study groups.
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There was a statistically significant difference regarding the disease-specific OS between sentinel-positive and sentinel-negative patients and the controls when using log rank analysis (Figure 14A). The differences in melanoma-specific OS between the S-subcategories according to the tumour burden of the micrometastases were also statistically significant (Figure 14B). The control patients had better OS than SII–SIII patients, but worse survival than S0–SI patients.

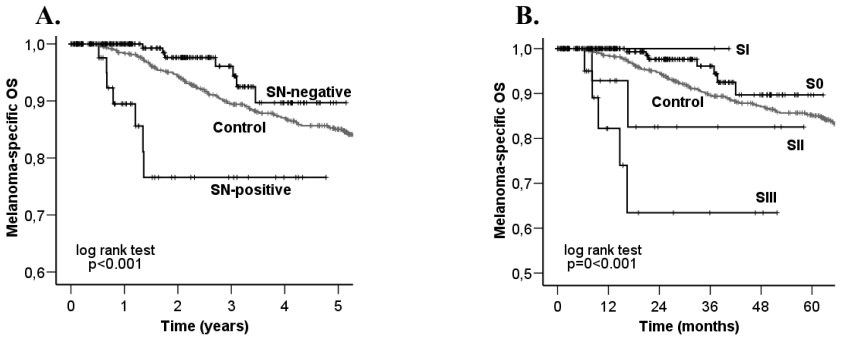

Figure 14. A. Melanoma-specific overall survival according to the sentinel node status. **B.** Melanoma-specific overall survival according to the tumour burden (S-classification).

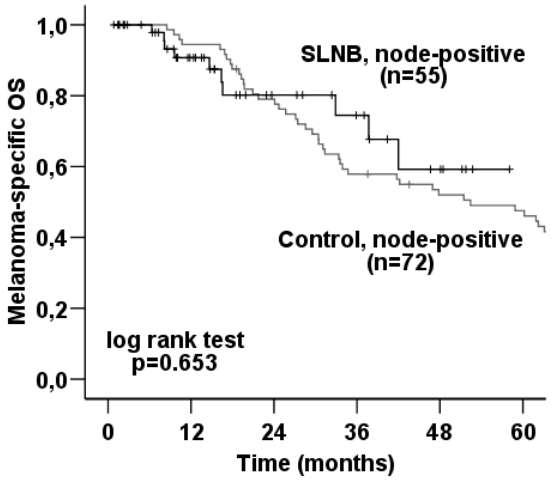

Figure 15. Melanoma-specific overall survival between 55 node-positive SLNB patients and node-positive 72 control patients (patients with nodal recurrences).

A stratified Kaplan-Meier analysis was performed between 55 node-positive SLNB patients (false-negative cases included) and 72 control patients, who had undergone delayed lymph node dissection due to nodal relapse. In the log rank test, there was no statistically significant difference between these subgroups (Figure 15).

5.3 Study III (Thin melanoma)

Of the 334 patients who underwent SLNB, 155 (46 %) had thin (T1) primary melanoma, i.e. lesion of ≤ 1.0 mm in Breslow depth. Seven patients with a thin primary melanoma had a micrometastasis in their sentinel nodes constituting 4.5 % of all T1-patients and 12.5 % of all sentinel-positive patients. The characteristics of these patients are presented in Table 9.

Table 9. Characteristics of seven sentinel-positive patients with thin melanoma

Patient Nr	***1***	***2***	***3***	***4***	***5***	***6***	***7***
Gender	male	male	female	male	female	female	female
Age, years	57	55	43	41	79	52	25
Location of melanoma	trunk	trunk	trunk	upper extrimity	upper extrimity	lower extremity	upper extremity
Breslow depth, mm	0.9	0.5	0.5	0.5	1.0	1.0	0.9
Clark level	III	II	III	III	III	IV	III
Ulceration	present	absent	absent	absent	absent	absent	absent
TNM classification	T1bN1a M0 (IIIB)	T1aN1a M0 (IIIA)	T1aN1a M0 (IIIA)	T1aN1a M0 (IIIA)	T1aN2a M0 (IIIA)	T1aN1a M0 (IIIA)	T1aN1a M0 (IIIA)
Regression	absent	absent	absent	absent	absent	absent	absent
Lympho-vascular invasion	absent	absent	absent	absent	absent	absent	absent
Mitotic rate / 10 HPF	1	1	2	1	9	1	5
Microsatel-lites	absent	absent	absent	absent	absent	absent	absent
Location of sentinel nodes	axilla	axilla	axilla	axilla	axilla	groin	axilla
Number of metastatic lymph nodes	1	1	1	1	3	1	1
***d*, mm**	0.7	0.3	1.1	0.1	0.7	0.2	0.2
Follow-up, years	4.2	5.2	4.6	2.5	1.9	1.3	1.2
Final status	Disease-free, dead[1]	Disease-free	Disease-free	Disease-free	Disease-free	Disease-free	Disease-free

HPF, high power field
d, Tumour penetrative thickness of the micrometastasis under the capsule of the sentinel node.
[1] Melanoma-unrelated death

5.4 Study IV (Head and neck melanoma)

A total of 146 patients with head and neck (H&N) melanoma were evaluated in this study. There were 69 male (47 %) and 77 female (53 %). The median age of the patients was 72 years (mean, 67 years; range, 10–92 years). The median Breslow depth was 3.0 mm (mean, 3.6 mm; range, 1.1–20.0 mm). The primary lesion was located in the face in 83 patients (57 %), in the scalp in 20 patients (14 %), in the ear in 21 patients (14 %), and in the neck in 22 patients (15 %). The wound was closed directly in 55 patients (38 %), by the use of a local flap in 70 patients (48 %), and by skin grafting in 21 patients (14 %).

SLNB group

Of the 146 patients, 25 underwent SLNB. Four patients were sentinel-positive (16 %) and 18 patients were sentinel-negative (72 %). Lymphatic mapping was unsuccessful and no sentinel nodes were indentified in three patients (12 %). A total of 48 sentinel nodes were excised. The distribution of the excised sentinel nodes between regional nodal basins, according to the location of the primary lesion, is presented in Table 10. In six patients, sentinel nodes were excised from the parotid gland and an intraparotid micrometastasis was found in one patient. This patient underwent subsequent superficial parotidectomy and a selective neck dissection of levels II–III in the second stage operation.

Table 10. Distribution of sentinel nodes according to the location of the primary lesion in 25 SLNB patients (n = number of sentinel nodes)

	I	***II***	***III***	***IV***	***V***	***VI***	***Parotis***	***Retroauricular***	***Other***	***Total***
Face	0	13	0	2	0	0	5	0	0	20
Scalp	0	2	2	0	3	0	0	7	0	14
Ear	0	7	0	0	0	0	0	0	0	7
Neck	0	0	3	2	0	0	1	0	1	7
Total	**0**	**22**	**5**	**4**	**3**	**0**	**6**	**7**	**1**	**48**

I-VI, indicates neck levels

ELND group

Of the 146 patients, 29 had undergone ELND. Nodal micrometastases were detected in four patients (16 %).

Nodal recurrences

During follow-up, there was one nodal recurrence in the SLNB group; this patient was initially sentinel-positive and additional nonsentinel metastases were also detected in the subsequent neck dissection. There were no false negative results of SLNB. In the ELND group, there were six nodal recurrences, of which two patients were node-positive and four patients node-negative, i.e. false negative results of ELND. In the entire cohort, nodal involvement, including both initial micrometastases and clinically detected late recurrences, was detected in a total of 37 nodal basins. The distribution of all metastatic nodal basins according to the location of the primary lesion is presented in Table 11.

Table 11. Distribution of metastatic lymph node basins according to the location of primary lesion in the entire study cohort of 146 patients (n = number of metastatic nodal basins)

	I	***II***	***III***	***IV***	***V***	***VI***	***Parotis***	***Retroauricular***	***Other***	***Total***
Face	0	8	0	0	0	0	4	0	0	12
Scalp	0	3	1	2	1	0	4	3	1	15
Ear	0	3	0	0	0	0	0	0	1	4
Neck	0	1	0	2	0	0	0	0	3	6
Total	**0**	**22**	**1**	**4**	**1**	**0**	**8**	**3**	**5**	37

I-VI, indicates neck levels

Follow-up

The median follow-up time was 27 months in the SLNB group (range, 8–65 months), 38 months in the ELND group (range, 6–218 months), and 46 months in the observation group (range, 1–260 months). In the SLNB group, there were 7 recurrences (28 %) in 25 patients: 3 of local, 1 of nodal and 3 of distant type. In the ELND group there were 11 recurrences (38 % of the ELND patients): 1 of local, 6 of nodal and 4 of distant type. In the observation group there were 35 recurrences (38 % of the observation group patients): 3 of local, 11 of nodal and 12 of distant type. The number of melanoma-related deaths was 3 in the SLNB group (12 %), 9 in the ELND group (31 %) and 33 in the observation group (36 %).

Using Kaplan-Meier analysis, the disease-specific OS was 67.1 % at 5 years and 61.9 % at 10 years for the entire H&N melanoma group. There was a significant difference between sexes: the male were associated with a significantly worse prognosis than the female. At 5 years, the disease-specific survival rate was 59.2 % in male and 74.8 % in female; at 10 years, the corresponding rates were 49.4 % in male and 74.8 %

in female The Kaplan-Meier analysis by anatomic subsites indicate that patients with scalp melanomas had worse disease-specific OS rates compared with patients with face, neck and ear melanomas (Figure 16). In contrast, there were no statistically significant differences between the treatment groups (SLNB vs. ELND vs. observation).

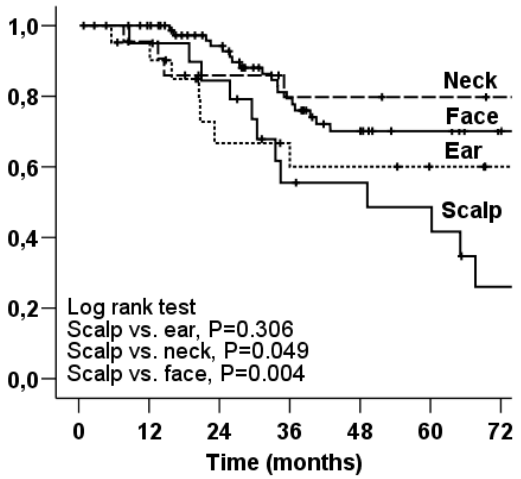

Figure 16. Melanoma-specific overall survival according to the anatomic location. (*Reprinted with the permission of the copyright holders*)

5.5 Study V (Positron emission tomography)

Among the 30 patients who underwent whole body FDG PET, there were originally seven recurrences (23 %). Six (20 %) of them were detected by FDG PET and one patient presented with a negative finding at the first scanning, but positive finding in a repeated scan after manifestation of palpable mass in the axilla. This case is regarded as a false negative while six others were true positive on baseline FDG PET. The anatomic localisation of metastases was subsequently verified by CT in every case. Histological confirmation of melanoma recurrence was obtained in three cases, and in the remaining cases metastatic disease was judged by subsequent clinical disease progression with the appearance of concurrent findings on a CT scan. The recurrence had influence on the treatment strategy in all patients. Three patients underwent surgery with a curative intent. An obese patient with no palpable disease had a subcutaneus intransit metastasis of the trunk on FDG PET (Figure 17) and underwent wide soft tissue excision with local flap reconstruction. The second patient underwent thoracotomy and lobectomy because of a bifocal lung metastasis. The third patient underwent axillary clearance because of nodal metastases. Four patients with inoperable recurrent disease received chemotherapy and/or interferon.

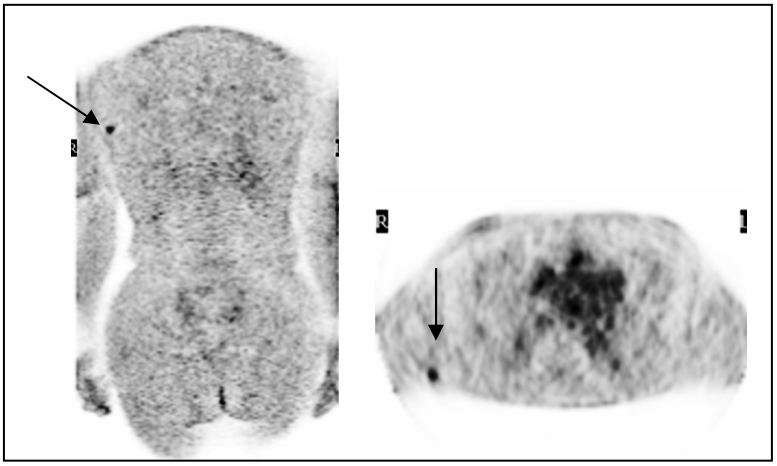

Figure 17. A 60-year-old male operated previously due to melanoma Stage IIB in the back. FDG-PET coronal slice and transaxial slice revealed a FDG-avid, unpalpable, lesion near the right axilla (arrow). Histological study confirmed a melanoma metastase. The patient has remained disease-free 2 years after the metastasectomy.
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One patient had bifocal hypermetabolic activity in the mediastinum, but there was no progression of this equivocal finding in the repeated PET scans after 3 and 6 months. CT results were also normal and the PET finding justified the benign underlying cause. This case was regarded as the only falsely positive FDG PET finding in this study. The data on these seven recurrences are summarized in Table 12. The entire study profile with recent updated data is summarized in Figure 18.

Table 12. Seven patients with recurrent disease

Patient Nr	*Age, years*	*Gender*	*Initial AJCC Stage*	*Time from surgery to PET, months*	*First PET finding*	*Recurrence site*	*Treatment*
1	68	female	IIIC	7	positive	lungs	medical therapy
2	60	male	IIB	14	positive	trunk	surgery
3	65	female	IIB	12	positive	lung	surgery+medical therapy
4	74	female	IIIC	7	positive	abdominal cavity	medical therapy
5	51	female	IIB	7	negative	axillary lymph nodes	surgery
6	49	female	IIC	8	positive	lungs	medical therapy
7	64	male	IIIC	7	positive	lungs	medical therapy

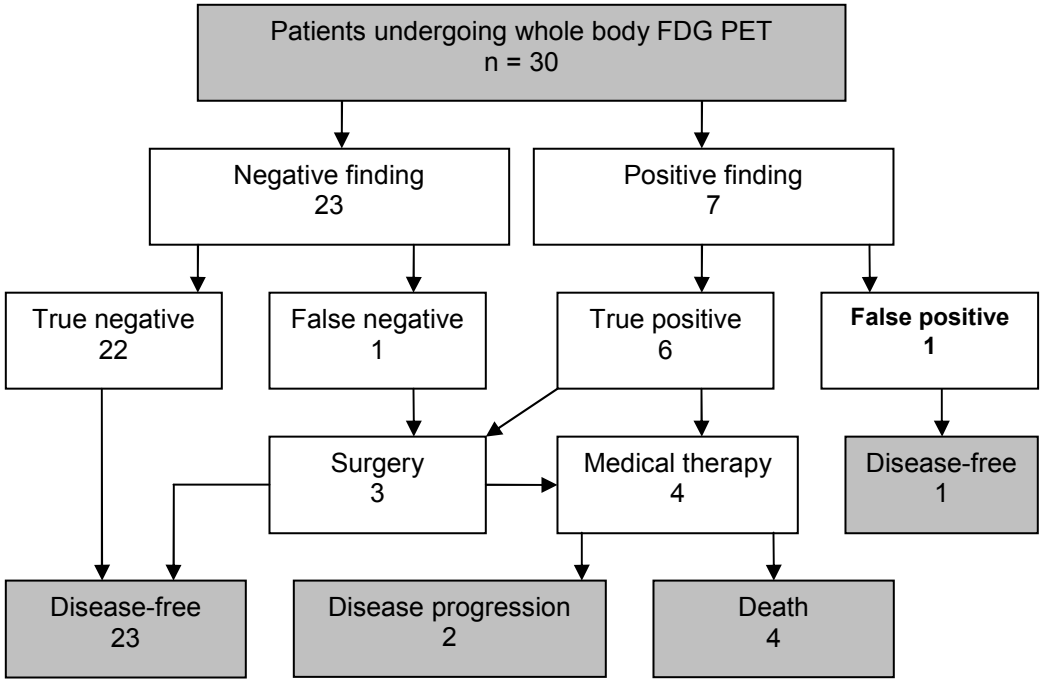

Figure 18. Summary of Study V.
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6 DISCUSSION

6.1 Surgical management and prognosis of cutaneous melanoma

Cutaneous melanoma is the most dangerous type of the common skin cancers and approximately 20 % of the patients will develop metastatic disease, which is lethal in most cases. Melanoma is thus responsible for most skin cancer deaths. The globally rising incidence rates of melanoma are alarming and more effective diagnostic and therapeutic modalities are strongly warranted. In South-Western Finland, the incidence is following global trends. During the 25-year-period of this study, the incidence rate has more than doubled. In 2006, the age-adjusted incidence rate per 100 000 was 12.8 in men and 12.5 in women (Finnish Cancer Registry). In Finland, the prognosis of primary melanoma, however, has continuously improved in the last decades being in line with the global tendency (Ilmonen et al., 2002). The improved prognosis correlates with the increasing proportion of thin melanomas and early diagnosis. The incidence rate of melanoma has always been higher in South-Western Finland than in eastern or northern parts of the country. Since the early 1970s, the treatment and follow-up of melanoma patients have been centred in Turku University Hospital.

During the 25-year period of this study, surgical treatment has become less invasive. The median width of the excision margin of the primary lesion has declined from 4 cm to 1.5 cm, but this reduction has not influenced local recurrence rate or overall survival. On the positive side, because of less extensive surgery, the need for flap reconstructions and skin graftings has declined from 68 % to 24 %. As a result of this trend in most cases, the patients can be managed in day surgery. The functional and aesthetic result is also better when surgery is less extensive.

In the 1980s and early 1990s, elective lymph node dissection was commonly performed in patients with clinically localized melanoma located in the extremities or in the head and neck. Occult nodal metastases were detected in 10 % of these cases, thus, less frequently than in the SLNB era. In cases with ELND, the histopathological evaluation of lymphadenectomy specimen was different than the current approach with the sentinel lymph nodes. The sentinel node concept has reduced the number of lymph nodes that need to be evaluated, allowing pathologists to focus their efforts (Cochran et al., 2000a). In the ELND era, such a meticulous evaluation with multiple serial sectioning and immunohistochemistry would have been impractical and exhausting for the pathologist. In the historic cohort of this study, a majority of the patients underwent no invasive nodal staging at the time of initial surgery and 12 % of these patients developed nodal recurrence during the follow-up resulting in therapeutic lymphadenectomy in most cases. Between our study cohorts, the surgical procedures were performed during different time periods and the follow-up times are different. Nevertheless, the type or timing of surgery itself does not seem to affect overall survival. Because of improved sensitivity and minimal invasiveness, SLNB is superior to ELND in terms of

nodal staging in patients with clinically localized melanoma. In general, the most essential factor for improving prognosis is an early diagnosis.

6.2 Sentinel lymph node biopsy

We found that 16–17 % of the patients with clinically localized melanoma can be upstaged by SLNB. Our result is in concordance with that of other investigators (Gershenwald et al., 1999; Cascinelli et al., 2000; Jansen et al., 2000; Statius Müller et al., 2001; Lens et al., 2002; Kettlewell et al., 2006). Our sentinel node detection rate of 97 % was exactly the same as in a recent Swedish multicenter study (Mattsson et al., 2008). Furthermore, 18 % of our sentinel-positive patients had additional occult lymph node metastases detected by selective completion lymphadenectomy. Our sentinel-positive patients had significantly worse outcome than sentinel-negative patients (Figure 14A). Indeed, the sentinel node status is the single most important predictive factor for disease-specific survival. Our false negativity rate was 9 %, nearly the same as 8 % in the Danish study by Lock-Andersen and co-workers (2006).

However, despite the widespread agreement on the prognostic value of SLNB, there is no consensus concerning the advantage of hunting occult micrometastases in patients with clinically localized melanoma. In various scientific medical journals, recent opinions on the use of SLNB in cutaneous melanoma have been strikingly conflicting. The New England Journal of Medicine has stated that “sentinel node biopsy is a standard-of-care staging procedure and is justified in patients with melanoma with tumour thicknesses of 1.2 to 3.5 mm who have a sufficient risk of nodal metastases” (Balch and Cascinelli, 2006). In contrast, the British Journal of Surgery has cautioned that “there is no justification for performing SNB outside of a trial” (Thomas, 2006). In April, 2008, the British Medical Journal argued that “Sentinel lymph node biopsy in malignant melanoma is unnecessary as clinically important micrometastases can be identified by ultrasound” (Thomas, 2008b). Such journals as the British Journal of Dermatology, Archives of Dermatology, and Nature Clinical Practice Oncology have also published critical editorials on this topic (Russel-Jones, 2005; Kanzler, 2007; Rosenberg, 2008). To date, this debate is still continuing.

It has been argued that SLNB should not be standard of care in the treatment of melanoma because:
1. SLNB lacks therapeutic benefit
2. SLNB staging is useless because no effective adjuvant therapy exists
3. SLNB increases the risk of intransit metastases
4. SLNB is associated with false-negative findings
5. SLNB detects prognostically false-positive submicrometastases
6. SLNB can be replaced by ultrasound-guided fine needle aspiration biopsy

These arguments will now be discussed in detail.

Therapeutic benefit

The question regarding the therapeutic benefit of lymph node surgery in clinically localized melanoma is of great importance from a historic point of view. In 1892, Herbert Snow published "Abstract of a lecture on melanotic cancerous disease" describing the necessity of ELND for melanoma for curative intent (Neuhaus et al., 2004). Subsequently, ELND became one of the most debated controversies in surgical oncology for decades. In patients with clinically localized melanoma, ELND has been compared with nodal observation and delayed therapeutic lymph node dissection (TLND) in four prospective randomized trials (Veronesi et al., 1982; Sim et al., 1986; Cascinelli et al., 1998; Balch et al., 1996). In these studies, no statistically significant difference in melanoma-specific overall survival was provided to support ELND. However, these kinds of studies are statistically underpowered because approximately 80 % of patients with clinically localized melanoma do not have metastatic lymph nodes and cannot benefit from lymphadenectomy.

In 1992, 100 years after Herbert Snow´s historical statement, Donald Morton and colleagues published their landmark study on the SLNB concept (Morton et al., 1992). It was the final endpoint of traditional ELND. Thereafter, the discussion of the therapeutic benefit is focused on SLNB but the dilemma has persisted because SLNB trials suffer from the same statistical limitations as ELND trials. Currently, no definitive or high-level evidence exists that SLNB, with subsequent immediate CLND, could improve overall survival in patients with melanoma. The only prospective randomized trial designed to address the survival benefit of SLNB is the first Multicenter Selective Lymphadenectomy Trial (MSLT-1), which was initiated on January 4, 1994, and is directed by Donald Morton, John Wayne Cancer Institute, Santa Monica, U.S.A. (Morton et al., 1999). In this trial, 1347 patients were initially randomized in a 3:2 ratio to wide local excision (WLE) with concomitant SLNB versus WLE alone. The MSLT-1 trial included patients with clinically localized melanoma of over 1 mm in Beslow thickness (T2-T4). Patients with positive sentinel nodes underwent immediate lymphadenectomy whereas all other patients underwent delayed lymphadenectomy only if nodal recurrence occurred during the follow-up. In the third interim analysis of the MSLT-1 trial, which included only selected patients with intermediate-thickness melanoma (1.2 to 3.5 mm in Breslow thickness), the melanoma-specific overall survival was similar between the two study groups, but in a subanalysis among patients who had nodal metastases, the 5-year survival rate was higher in the SLNB group than in the observation group: 72.3 % ±4.6 % in patients with immediate lymphadenectomy versus 52.4 % ±5.9 % in those with delayed lymphadenectomy (hazard ratio, 0.51; 95 % CI, 0.32-0.81; p=0.004) (Morton et al., 2006). This subgroup analysis was a secondary objective but was prospectively incorporated into the design of the trial. In the control patients with nodal relapse, there were a greater number of metastatic lymph nodes than in the SLNB group (3.3 versus 1.4). This is also indirect evidence for the support of the therapeutic benefit of SLNB, because the number of metastatic nodes is most strongly associated with worse survival compared with all other prognostic factors (hazard ratio, 1.26; 95 % CI, 1.18-1.33; p<0.001) (Balch et al., 2001b).

There have been some European retrospective observational studies on this subject with conflicting results. Some studies have reported improved survival of SLNB patients in comparison with retrospective non-SLNB controls (Kretschmer et al., 2004; Starz et al. 2004) whereas some have not (Rutkowski et al. 2003; Möhrle et al., 2004; Gutzmer et al., 2005). Kretschmer and co-workers (2004) reported a study from five German centres and demonstrated a 5-year survival of 62.5 % in 314 SLNB patients versus 50.2 % in 623 historic non-SLNB controls. Similarly, another German study by Starz and co-workers (2004) also reported a significant improvement in overall survival between 324 SLNB patients and 274 pre-SLNB controls both in Kaplan-Meier analysis and in multivariate Cox regression.

In our retrospective case-control study (study II), we could not find any disease-specific overall survival benefit of SLNB in Kaplan-Meier analysis (Figure 12A). Our result is in concordance with that of the MSLT-1 trial (Morton et al., 2006). We also performed a subgroup analysis between sentinel-positive patients and node-positive controls but we could not find any significant difference in disease-specific survival either (Figure 15). On the other hand, we could demonstrate that the metastatic tumour burden of the sentinel node is a highly significant predictor for survival (Figure 14B). We used the S-classification as a parameter which is based on the tumour penetrative depth of the metastatic deposits, measured as the maximum distance of the tumour cells from the interior margin of the lymph node capsule (Starz, 2004). We consider the S-classification system very practical and have thus adopted it in routine clinical practice at our institution. However, while there is a strong correlation between metastatic tumour burden and survival, it seems paradoxical that an early sentinel node metastasectomy does not improve overall survival. We suggest an explanation could be the low number of such patients: in the SI- and SII-categories, we had only 25 patients constituting 8 % of all SLNB patients. We assume that some proportion of them may benefit from SLNB, but this effect does not significantly influence overall survival due to statistical dilution. In addition, we are aware of some other methodological limitations of this study. A major problem is the misbalance in follow-up time between prospective SLNB patients and historic controls. In our prospective SLNB study group, there were 104 patients remaining after a follow-up of three years and only seven patients at five years. The time-dependent statistical analyses cannot eliminate this misbalance and a longer follow-up is hence clearly needed to demonstrate any therapeutic advantage in our prospective cohort.

However, prolonged survival is not the only aim to perform SLNB. We found that the most obvious therapeutic advantage of SLNB is better regional disease control as a result of reduced nodal recurrence rate. There was regional lymph node recurrence in 1.6 % of the SLNB patients and 11.7 % in the retrospective controls. The follow-up time of SLNB patients is short but, nevertheless, using Kaplan Meier analysis, the difference in nodal disease-free survival was statistically significant (Figure 13B). Indeed, several studies have demonstrated that the SLNB procedure changes the pattern of recurrence and reduces the number regional nodal failures (Gershenwald et al., 2000a;

Statius Müller et al., 2002; Fincher et al., 2003; Gutzmer et al., 2005). Immediate and delayed lymphadenectomy are not the same, since stage III disease varies widely in terms of the number and the size of metastatic nodes: it is of immense importance if the nodal metastases are microscopic or macroscopic. The extent of surgery and its morbidity also reflect this heterogeneity (Sabel et al., 2007). An uncontrollable nodal recurrence with bulky mass can be a very distressing clinical problem because it causes pain and lymphoedema in the extremities, and is frequently associated with ulceration, infection or postoperative wound complications. Furthermore, the psychological aspects should be highlighted regarding comparison between early treatment and the watch-and-wait philosophy. Each melanoma patient has a subjective opinion, whether the prevention of lymph node recurrences is an advantage or not. Occasionally, a nodal relapse may follow a long disease-free period. In some cases this period may be as long as 10–20 years. Clearly, the opportunity to prevent such late disease failures must be regarded as an obvious therapeutic benefit in oncologic surgery. On the other hand, it seems paradoxical that better local control does not influence the final outcome. First, SLNB may reduce the rate of nodal recurrence principally at the expense of an increased rate of distant metastases (Russell-Jones, 2005). Secondly, a longer follow-up than presented in this study is needed to demonstrate any significant overall survival benefit.

It should be stressed that SLNB was originally developed for a staging procedure to identify clinically occult metastases in the draining basin (Morton and Cochran, 2004). SLNB should be more clearly distinguished from CLND, the purpose of which is the therapeutic excision of all nodes within that basin of a patient whose nodal metastases have already been identified by SLNB staging. SLNB improves the diagnostic advantage of the traditional ELND without its morbidity. Thus, the question about the potential survival advantage should be focused on selective CLND, not on SLNB alone, which is a minimally invasive diagnostic approach and widely accepted as such. After positive SLNB, however, only a minority of sentinel-positive patients have additional metastatic nodes in the sentinel node basin. Therefore, it has been questioned whether CLND could be avoided in selected patients (Morton et al., 2007). To date, the risk of nonsentinel node metastases cannot be sensitively predicted by using clinicopathological characteristics and CLND cannot be safely avoided in any subgroup of sentinel-positive patients (McMasters et al., 2002; Roka et al., 2008). Until ongoing second MSLT trial resolves the dilemma, all patients with positive sentinel nodes should undergo CLND as a standard of care (Henderson, 2006; Morton et al., 2007).

Staging

Opponents claim that SLNB-guided staging is of no use because no effective adjuvant therapy exists. Adjuvant therapy, however, is not the only aim of accurate staging. The patient with melanoma will be followed up for several years and the follow-up schedule should be tailored according to the individual prognosis of each patient, which is based on the result of SLNB. Because sentinel-positive patients have a high risk of recurrence, they should be referred for intensive specialist follow-up. On the other hand,

low-risk patients constitute the majority of the melanoma population, and if they are sentinel-negative and if they have had a thin primary lesion, this predicts complete remission. These patients do not require intensive follow-up and they may be followed by general practitioners. At our institution, approximately 60 % of melanoma patients are currently managed by this cost-effective approach. In addition, SLNB-staged patients are the best candidates for adjuvant therapy trials. In the future, if effective systemic adjuvant therapies are found, routine SLNB will be clearly needed to identify the high-risk patients at that moment.

Intransit metastases

Doubts about the increased risk of intransit metastases related to SLNB were raised by some European investigators (Estourgie et al., 2003; Estourgie et al., 2004; Thomas and Clark, 2004). An intransit metastasis is defined as a unique manifestation of intralymphatic tumour dissemination, characterized by the presence of melanoma in either cutaneous or subcutaneous tissue situated between the primary tumour (≥2 cm beyond) and the draining regional lymph node basin (Pawlik et al., 2005). An illustration of the lymphatic spreading of cutaneous melanoma is presented in Figure 19.

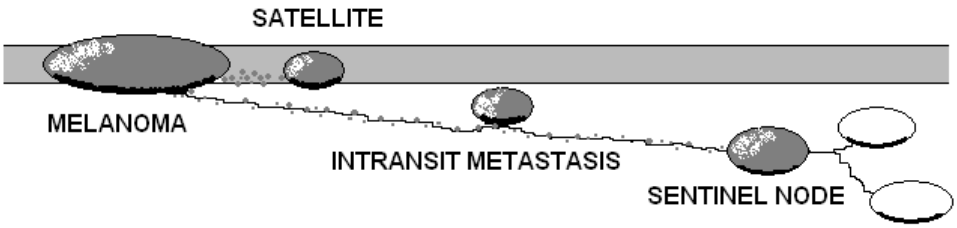

Figure 19. The lymphatic route from the primary lesion to the lymph node basin.

The AJCC classification system places the isolated intransit metastases, when nodal metastases are absent, into the stage IIIB (N2c) category, because they are associated with a worse prognosis equivalent to satellite metastases or multiple nodal metastases (Balch et al., 2001a). In the pre-SLNB era, the reported overall incidence of patients with intransit metastases ranged from 2.3 % to 14.3 % in stage I-II melanoma (Roses et al., 1983). Estourgie et al. (2003, 2004) reported a corresponding rate of 23 % among SLNB-positive patients. Due to this alarming result, a potentially increased risk of intransit metastases would be of particular concern as an adverse effect of SLNB. Intransit metastases are believed to develop as a result of tumour cells becoming entrapped in the lymphatic vessels. Theoretically, the excision of draining lymph nodes might cause mechanical disruption of the proximal nodal basin resulting in the entrapment of tumour cells in the afferent lymphatic. However, this argumentation against SLNB has been discredited by two extensive retrospective studies. A working group from Australia demonstrated on 2018 patients, subdivided in to three treatment protocols (SLNB,

ELND, observation), that the incidence of intransit metastases was 4.9 %, 3.6 %, and 5.7 %, respectively, and 10.8 % among sentinel-positive patients (van Poll et al., 2005). On multivariate analysis, primary tumour thickness and patient age predicted intransit metastases but the type of treatment did not. Another review from the John Wayne Cancer Institute, U.S.A, also compared the same treatment modalities and found that treatment groups matched by T stage or by age, sex, Breslow depth, and primary location, showed no significant differences in intransit metastasis incidences (Kang et al., 2005). In our study, the incidence of locoregional recurrences was slightly higher in the SLNB group than among the controls (Figure 13A), but the difference is not statistically significant, and hence the rate of local or in-transit recurrences cannot be regarded as a result of the SLNB procedure. Taken together, there is no relationship between SLNB and intransit metastases. The risk of intransit metastasis depends on tumour biology, not on the surgical approach to regional lymph nodes (Pawlik et al., 2005; van Poll et al., 2005).

False-negative results

Some proportion of the sentinel-negative patients may develop nodal recurrence within the draining lymph node basin during a long-term follow-up indicating that the sentinel nodes have been initially falsely negative. The false-negative rate of the SLNB procedure should be calculated as the rate of false-negative results over the group of node-positive patients (Nieweg and Estourgie, 2004). The corresponding rate over the entire study population, including node-negative cases, should be termed as the failure rate (Vuylsteke et al., 2003). According to this definition, the false-negative rate seems to be moderately high in some of the preliminary SLNB studies; the WHO Melanoma Program reported 40 regional nodal relapses in 181 nodal-positive patients giving thus a false-negative rate of 22 % (Cascinelli et al., 2000). In general, the false-negative rate has remained at an acceptable level of 10 % or less (Gershenwald et al., 1998; Essner et al., 1999; Wagner et al., 2003). In our study (Study II), the false-negative rate of SLNB was 9 %.

A false-negative finding is of great importance, because it challenges the validity of the sentinel node hypothesis. Current evidence suggests three main causes of false-negative findings: pathological failure, technical failure, and biological failure (Johnson et al., 2006). Pathological failure was investigated in a study on 1152 patients, who had undergone SLNB at the Sydney Melanoma Unit (Li et al., 2003). All false-negative sentinel nodes were re-evaluated and there were 26 regional lymph node recurrences among 957 patients with negative sentinel nodes by initial pathologic examination (false-negative rate 12 %, failure rate 2 %). In the re-examination, pathologic failure was demonstrated in 32 % of the cases by finding metastatic deposits in the original sentinel nodes. An extended or stepped histopathological evaluation has been shown to improve the detection rate of sentinel node micrometastases from 14–22 % to 28 % (Abrahamsen et al., 2004; Gietema et al., 2004), but there is no consensus between different studies as to how many sections exactly are needed (van Diest, 1999). For a pathologist, the sentinel node analysis involves a compromise between the

comprehensive examination of the entire sentinel node and practical considerations in routine practice (Scolyer et al., 2004b). A technical failure is associated either with methodological problems or with the inexperience of the surgeon. A biological failure may occur when the lymphatics are obstructed by melanoma cells resulting in the re-routing of the lymph flow; this type of failure is difficult to manage and is inevitable (Vuylsteke et al., 2003).

Taken together, the SLNB procedure requires a collaborative effort between the nuclear physician, the surgeon, and the pathologist. A failure in any of these components may result in an unsatisfactory outcome.

Prognostically false-positive micrometastases

SLNB is able to detect micrometastases of minimal tumour burden and even single isolated melanoma cells in the sentinel nodes. In this study, nine sentinel-positive patients had a micrometastasis in the sentinel node with a tumour penetrative thickness of less than 0.1 mm (S-class I) and all of these patients have remained completely disease-free. This excellent outcome may be associated with lead time bias, i.e. to the long, slow and natural progression of the disease. In contrast, SLNB opponents have suggested that the theory of prognostic false-positive sentinel nodes may result in incorrect upstaging of some patients and therefore cause a fundamental error in the survival comparisons (Thomas, 2008a). This concept is based on the hypothesis that not all metastatic lymph nodes will develop into clinically relevant nodal disease. It has been argued that these patients with prognostic false-positive sentinel nodes are given inaccurate prognostic information and they are undergoing unnecessary CLND or adjuvant therapy. Based on the analysis of 262 SLNB patients, a working group from the Netherlands suggested that patients with submicrometastases (tumour burden <0.1 mm) in the sentinel node should be judged as sentinel-negative (van Akkooi et al., 2006). The authors found no additional nonsentinel positivity for micrometastases <0.1 mm. However, another retrospective analysis was carried out on 1382 patients who underwent SLNB; 57 patients had metastases limited to isolated tumour cells and 12 % had additional nonsentinel metastases in CLND (Scheri et al., 2007). Patients with isolated tumour cells in their sentinel nodes also had a significantly higher risk of melanoma-specific death than those with tumour-negative sentinel nodes. An Australian working group identified a small number of melanoma patients, whose sentinel nodes were originally reported as pathologically negative, but who had subsequently developed regional nodal recurrence; subsequent more detailed pathologic reanalysis found very small, submicrometastatic, deposits in the subcapsular sinus region of the sentinel node (Scolyer et al., 2007). Thus, the picture is unclear and further studies are warranted on this subject. To date, no empirical studies have been carried out on detectable micrometastases in situ and true histological regression of nodal micrometastases has never been described. Currently, such a study is impossible because the detection of micrometastases is based on the excision of the metastatic sentinel node, which is also its treatment. Thus, the excellent outcome of patients with submicrometastases may also indicate a true survival benefit of SLNB in this small subgroup of patients with

minimal tumour burden, no nonsentinel metastases and no distant metastases. Without evidence-based data, no cancer metastases can be regarded as clinically unimportant or benign.

Ultrasonography and fine needle aspiration cytology

Ultrasonography-guided fine needle aspiration cytology has been suggested to replace SLNB for nodal staging (Thomas, 2008a). Currently, this is unrealistic and based on inconclusive and uncontrolled evidence. In our study, 25 of 49 sentinel-positive patients (51 %) had a micrometastasis of ≤1.0 mm in size. This is far below the detection level of ultrasonography, which is regarded to be between 4 and 5 mm in most melanoma centres (Starritt et al., 2005; Hafner et al., 2004; Sibon et al., 2007).

In summary, we suggest that there is sufficient scientific evidence and support for the routine use of SLNB in cutaneous melanoma. An option for SLNB should be provided for every patient with clinically localized cutaneous melanoma exceeding 1,0 mm in Breslow depth, because SLNB provides unique information for staging and better regional disease control. In Finland, a recommendation for this option is stated in the national guideline of care for cutaneous melanoma (Suominen et al., 2005). During this study, none of the 334 patients refused this option. It should be stressed that SLNB is a minimally invasive and safe procedure for the patient. In most cases, SLNB can be performed as day surgery, at the same time with the excision of the primary lesion or the biopsy scar. In our study, 84 % of the patients were sentinel-negative and were spared completion lymphadenectomy at the time of disease presentation. Only 2 % had nodal recurrence during the follow-up as result of false-negative SLNB.

6.3 Thin melanoma

We designed our study to include thin melanomas because this subgroup is of great clinical importance. This patient population is growing rapidly in incidence and there is no consensus considering the precise indications of SLNB in this category. Occult metastases in thin melanomas are rare but if melanoma is invasive, there is a potential risk of metastasis regardless of the Breslow thickness. There is no thickness-related biologic cutoff point regarding metastasis in patients with invasive melanoma. We found in our historic control patients that 15 (4.6 %) of 324 patients with thin T1 primary lesion had died of recurrent metastatic melanoma. In the SLNB group, an equal proportion, seven (4.5 %) of 155 patients with thin T1 melanoma had micrometastasis in the sentinel node. Each of these seven patients underwent CLND and one patient had additional nonsentinel micrometastases. Although the seven patients were upstaged as a result of the micrometastasis detected by SLNB, there were no recurrences after a mean follow-up time of 3.0 years. Similarly, in a German study on 87 patients with thin melanomas between 0.75 mm and 1.00 mm in Breslow thickness, 11.5 % of the patients were sentinel-positive and all of them remained disease-free after a median follow-up time of 74 months (Starz and Balda, 2007). We consider these results sug-

gestive of the potential survival benefit of SLNB in this subgroup of patients with a thin primary lesion and minimal risk for hematogenic spreading and dissemination in general.

The problem is the expanding T1 population. Thin melanomas account for the great majority of melanomas in most developed countries. Many authors consider it doubtful whether a 4-5 % sentinel positivity rate is enough to justify the use of SLNB in all thin melanomas since the therapeutic benefit is unclear. The cost-benefit is questionable since only a small number will have disease identified that will alter treatment (Agnese et al., 2003). Therefore, there is a clear need for non-invasive predictive indicators that would judge a precise indication for SLNB in thin melanomas. In the AJCC staging system, thin melanomas are divided into two prognostically different subgroups on the basis of ulceration and Clark level (Balch et al., 2001a). Some studies, however, have questioned the accuracy of the AJCC staging system for thin melanomas. In a large German cohort of 12 728 thin cutaneous melanomas, multivariate analysis showed that histological subtype, body site, sex and age were prognostic factors – not ulceration or Clark level (Leiter et al., 2004). In contrast, an Australian study on 18 088 patients demonstrated that ulceration, which is uncommon in thin melanomas confers a worse prognosis when present (McKinnon et al., 2003). Tumour cell mitotic rate has been identified as an independent prognostic factor in two important studies (Sondak et al., 2004; Gimotty et al., 2007). Mitotic index has been strongly suggested to be included in the next updated version of the AJCC classification system. Sondak and co-workers also found younger age as a predictor of sentinel positivity, whereas Gimotty and co-workers included sex in his classification scheme. This heterogeneity of prognostic variables, however, demonstrates that the histopathologic parameters of the primary tumour have relatively low sensitivity in predicting sentinel node status. As demonstrated in Table 2, there are several studies which have not been able to find such predictors.

The single most important parameter is the Breslow thickness itself. Some authors have suggested that all patients with thin melanomas between 0.75 and 1.00 mm could be appropriate candidates for SLNB after the giving of proper patient information (Puleo et al., 2005). Indeed, many melanoma centres consider SLNB for patients if Breslow thickness is over 0.75 mm, the Clark-level is over III, or if the primary lesion is ulcerated. Among our seven sentinel-positive patients with T1 melanoma, only one patient had an ulcerated melanoma, one patient had a melanoma with Clark-level IV, and three of seven patients had Breslow thickness of below 0.75 mm (Table 8). It is obvious that without performing SLNB on all patients with T1 melanoma, most of the micrometastases would remain unidentified. Currently at our institution, we offer our patients the option for SLNB if melanoma is histologically invasive and if the Breslow depth exceeds 0.5 mm. Most patients accept that option.

6.4 Head and neck melanoma

We detected occult nodal metastases in four (16 %) of 25 patients with H&N melanoma. Because only T2-T4-melanomas (Breslow thickness >1.0 mm) were evaluated, the relative sentinel-positivity rate is significantly lower than the corresponding rate in the trunk and extremities. Some other investigators have reported similar findings. The multi-institutional SLN Working Group published a report on 629 H&N melanoma patients, including thin melanomas, with a sentinel-positivity rate of 10 % (Leong et al., 2006). In another study on 321 H&N melanoma patients, there was a sentinel-positivity rate of 15 %, which was significantly less than the corresponding rates of 23 % and 20 % found in truncal and extremity melanomas, respectively (Chao et al., 2003). In general, H&N location is thought to be a negative prognostic factor for survival and this low sentinel-positivity rate therefore seems to be paradoxical. We suggest that this paradox could be age-related. Our H&N patients were approximately ten years older than the patients with melanoma in the trunk and extremities (mean, 66 years vs. 56 years; median 68 years vs. 57 years). Despite the age-related worse clinicopathologic profile and decreased melanoma-specific survival, older patients tend to have a significantly lower rate of nodal metastases detected by SLNB (Chao et al., 2004; Chagpar et al., 2007). Chao reported on 3076 SLNB patients that the overall sentinel positivity rate was 18.2 %, but only 14.4 % among the patients of older than 60 years. Several potential explanations exist for this age paradox: age-related changes in the lymphatic system could result in a decreased sensitivity of the SLNB procedure. Same changes may result in preferential metastatic spread via the hematogenous route. In younger patients, in contrast, a more competent immune system could eliminate some micrometastases (Carlson, 2004).

To date in our study, there have been no nodal recurrences in sentinel-negative patients with H&N melanoma after a median follow-up time of 2.2 years. A longer follow-up is needed to estimate the true false-negative rate. SLNB is more challenging in the head and neck (H&N) than in other body sites and this may result in an increased false-negative rate in the head and neck compared with trunk and extremity locations (Chao et al., 2003; de Wilt et al., 2004). The sentinel nodes are frequently located near the tracer injection site and the high background radioactivity may mask the hot spots of sentinel nodes. Moreover, the skin of the H&N region is associated with complex and unpredictable drainage patterns. Multiple drainage basins have been reported in approximately 40 % of cases (Wells et al., 1997; Carlson et al., 2005). Likewise, lymphoscintigrams in the H&N have been discordant with clinical predictions in 34-43 % of cases (O´Brien et al., 1995; Lin et al., 2006). In addition, the lymph nodes are often small and located in surgically demanding sites that are not easily accessible as in the parotid gland. SLNB in the parotid gland may present special problems and it is associated with a risk for facial nerve injury (Eicher et al., 2002). In our patients, 12 % of the sentinel nodes of H&N melanomas were located in the parotid gland. Nodal metastases, if present, were detected in 37 nodal basins and the metastatic site was the parotid gland in eight cases. There were no complications in these patients. In general,

the morbidity associated with SLNB of the parotid gland has been reported to be less than 4 % (Ollila et al., 1999a; Wagner et al., 2000; Loree et al., 2006). These results do not support the recommendations of some authors who have suggested that superficial parotidectomy should always be performed instead of parotid SLNB (Eicher et al., 2002). Nevertheless, such an approach would compromise the mini-invasiveness of SLNB which is the main advantage of the procedure.

We found that patients with scalp melanoma had poor prognosis (Figure 16). This finding is in accordance with other studies (Leong et al., 2006; O´Brien et al., 1991). We also found that scalp melanomas were frequently associated with male gender, higher age, high Breslow thickness and the presence of ulceration. In comparison between treatment modalities, i.e. elective neck dissection vs. SLNB vs. observation, there were no differences in disease-specific overall survival. It is important to note that there were different follow-up times between the cohorts and the surgical procedures were performed during different time periods. Nevertheless, because SLNB is found to be a reliable and mini-invasive approach for the nodal staging in the head and neck, traditional neck dissection is recommended only for therapeutic purposes in clinically node-positive or sentinel-positive patients.

6.5 Follow-up and positron emission tomography

After the initial surgery, a proportion of patients carry a risk for occult metastases, resulting in recurrent disease. Surgical treatment of advanced-stage metastatic melanoma is thought to be questionable in general, but we found that 56 % of patients with recurrent disease underwent surgical metastasectomy. It should be stressed that the majority of these operations were therapeutic lymph node dissections and, in the era of SLNB, the number of nodal recurrences and need for therapeutic lymphadenectomies is strongly reduced. However, an option for metastasectomy should be considered, particularly if the metastasis is single and isolated. The earlier the metastasis is detected, the more effective the treatment is likely to be; surgery being the only modality of therapy that significantly influences the prognosis in recurrent melanoma (Brand et al., 1997). In a retrospective study on 373 patients, a survival advantage was demonstrated in patients who were asymptomatic in comparison with symptomatic patients at the time of recurrence, suggesting that early detection of recurrent disease may improve overall survival (Poo-Hwu et al., 1999).

If surgical resection is considered, the goal of the operation may be palliative or curative. Careful patient selection is important and a thorough preoperative staging evaluation should be performed. In general, surgery is most effective in patients exhibiting advanced disease limited to a few sites with a limited number of metastases (Young et al., 2006). This benefit is particularly associated with pulmonary metastasectomy; a solitary metastasis and absence of extrapulmonary disease are predictive for improved survival (Neuman et al., 2007). In this study, we had 21 patients who had been operated because of visceral metastases and 11 of them underwent thoracotomy and pul-

monary metastasectomy. Overall, the mean survival time after the pulmonary metastasectomy was 24 months, which is six months longer than in patients with recurrent melanoma on average. In an extensive analysis on 1720 melanoma patients with pulmonary metastasis, the performance of pulmonary metastasectomy was associated with a survival advantage of 12 months for patients with a preceding disease-free interval longer than 5 years and 10 months for patients without extrathoracic metastasis (Petersen et al., 2007). A recent study on 873 patients with recurrent melanoma reported a better prognosis of lung metastases compared to other visceral recurrences (Francken et al., 2008).

In addition, metastases in the gastrointestinal tract are suitable for surgical resection and results have been reported to give some therapeutic benefit in terms of prolonged survival in patients rendered free of all identifiable disease (Agrawal et al., 1999). If the resection is not complete, operative intervention for bowel metastases is recommended for palliative reasons, in order to prevent bowel obstruction. In contrast, the resection of melanoma metastases in the liver remains controversial. Pawlik and coworkers reported a study on 40 patients with hepatic melanoma undergoing hepatic resection (Pawlik et al., 2006). The primary lesion had been cutaneous in 24 and ocular in 16 patients. The patients with primary skin melanoma had worse outcome than those with ocular tumours: among patients with cutaneous melanoma, the median time to recurrence after hepatic resection was 4.7 months and there were no 5-year survivors.

In asymptomatic patients, there is no consensus regarding the optimum frequency and length of follow-up but the follow-up schedule should be guided by the fact that the majority of the recurrences seem to occur within the first three years (Dicker et al., 1999; Poo-Hwu et al., 1999). The follow-up screening protocols for patients with melanoma vary from country to country with significant differences in expert opinion and practice. Almost all recommendations are based more on common-sense or historical practice than on evidence-based guidance (Francken et al., 2005). Only one prospective study from Germany has been published on this subject (Garbe et al., 2003). Garbe and co-workers reported that 71 % of all recurrences were primarily detected on scheduled follow-up examinations. In contrast, according to an extensive review of 72 selected articles, several investigators have found that most recurrences are detected by the patients themselves (Francken et al., 2005). For this reason, some authors do not support high-intensity routine follow-up investigations and only medical history and physical examination seem to be cost-effective.

Traditionally, imaging studies have played a prominent role in follow-up but the benefits of these studies are not entirely clear (Choi and Gershenwald, 2007). Chest radiography is often routinely used due to its low cost and relatively low inconvenience. However, with chest radiography alone, the detection rate of occult lung disease is low in asymptomatic patients and false-positive or equivocal findings are common (Wang et al., 2004; Gold et al., 2007). The initial chest radiograph may be useful as a baseline examination against which to compare future studies in evaluating clinical signs or symptoms. More advanced imaging techniques such as computed tomography (CT) or

magnetic resonance imaging (MRI) are more sensitive than the plain chest x-ray, but their efficacy in routine use has not been established (Choi and Gershenwald, 2007). Imaging of asymptomatic patients at the time of initial diagnosis, in general, is of low yield with a high false-positive rate and does not usually lead to upstaging or change in initial management (Yancovitz et al., 2007). More than screening asymptomatic patients, these imaging modalities should be used to address specific clinical questions. Compared with CT, MRI may be more sensitive in detecting metastases located in the brain, liver, spleen, subcutaneous tissues, muscle, and bone; in contrast, CT may detect more pulmonary disease than MRI (Müller-Horvat et al., 2006).

Whole body FDG PET is a new technique based on metabolic imaging of malignant tissue. There are three potential indications for the use of FDG PET in patients with melanoma: staging at the time of initial disease presentation, staging during follow-up, or restaging the patients with distant metastases in terms of treatment response. The use of FDG PET in the initial staging is considered to provide only limited value. At the time of initial diagnosis FDG PET has suboptimal sensitivity in detecting low tumour volume in patients with clinical stage I-II melanoma, because the lower limit of sensitivity for FDG PET detection is approximately 6 to 8 mm in tumour size, which is far above the size of micrometastases at that time (Wagner et al., 2001; Wagner et al., 2005). Therefore, FDG PET cannot replace lymph node staging with the SLNB at the time of initial diagnosis (Ackland et al., 2001; Belhocine et al., 2002; Havenga et al., 2003). For the same reason, distant micrometastases, if present, are undetectable at the initial stage. False positive or equivocal findings bring an additional problem. Non-specific FDG uptake is frequently seen with PET imaging in many benign conditions, such as inflammatory lesions, infections, reactive lymphadenopathy, recent surgical wounds, and benign tumours in a wide variety of tissues (Wagner, 2006). A high physiological cellular glucose metabolism can also limit the utility of FDG PET in the bowel, renal collecting systems, bladder, skeletal muscles, brain, and heart, although the use of integrated FDG PET/CT has markedly decreased the problem of interpretaion of these physiological uptakes (Ho Shon et al., 2008).

Compared with the use in primary staging, FDG PET may have a more valuable role later on during the follow up. FDG PET can detect or exclude the presence of occult disease in unsuspected sites and aid in the planning of surgical treatment. In a prospective study on 103 patients with high-risk melanoma, preoperative imaging, with either FDG PET alone or in combination with CT, led to a change in the clinical management in 35 % of the patients (Brady et al., 2006). The most common decision was to cancel the operation due to an unexpected metastatic finding. Tyler and co-workers (2000) reported on 95 patients with clinical stage III melanoma that FDG PET revealed unsuspected sites of metastases in 19.7 % of the scans, leading to a change in management in these patients. In a retrospective analysis of 257 Dutch melanoma patients undergoing FDG PET, overall, 21.8 % of the patients were upstaged as a result of PET and the treatment was changed in 17.1 % of the patients, most often from surgery to systemic treatment (Bastiaannet et al., 2006). Unexpected malignancies, such as colon cancer, were found in 4.3 % of the patients.

In this study, we investigated the use of whole body FDG PET in detecting occult metastases in asymptomatic patients with high risk of recurrence. We performed FDG PET prospectively in 30 voluntary patients with AJCC stage IIB to III melanoma between 6 and 24 months after the initial surgery. This resulted in a sensitivity and specificity for melanoma recurrence of 86 % and 96 %, respectively. The positive predictive value was 86 % and the negative predictive value was 96 %. We consider this result good, because FDG PET was performed as a one-time screening study in asymptomatic patients. We stress that this upstaging altered the clinical treatment in each patient. Three patients underwent surgery and four patients received medical therapy. A similar Danish study reported a sensitivity of 80 % and specificity of 88 % in 33 patients undergoing routine FDG PET after positive SLNB; the individual scan was judged as true negative if no recurrence occurred within six months after negative scanning (Horn et al., 2006).

The optimal length of the follow-up is not certain, since each patient carries an unpredictable and individual course of the disease progression. Therefore, intensive follow-up of the patients is important even if the FDG PET is negative, due to risk of late recurrence. When we updated the follow-up data, we found two additional recurrences in patients with negative baseline FDG PET result. In the first patient, intransit metastases were detected in the leg 14 months after negative FDG PET. She underwent repetitive surgical excisions, and currently, 35 months after the last operation, she is disease-free. In the second patient, a rapid distant dissemination was detected 36 months after negative FDG PET. To date, he is alive under disease progression. To date, the median follow-up time for the survivors is 3.9 years.

Currently at our institution, imaging with hybrid FDG PET/CT scanner has replaced traditional plain CT in the routine follow-up schedule of patients with high risk melanoma. FDG PET/CT is performed in patients with stage IIB-IIIC melanoma at six months postoperatively. In the follow-up of asymptomatic high-risk patients, this screening FDG PET/CT is a one-time examination but it is repeated if there is any clinical suspicion of recurrence or surgical metastasectomy is planned. In addition, because lymphoscintigraphy were unsuccessful in 3 % of our study patients undergoing SLNB, we suggest that a failed SLNB could constitute a special indication for FDG PET, particularly when the primary lesion is thick or of intermediate thickness with ulceration.

Taken together, SLNB is still the single most important tool for identifying patients with high risk for recurrency and this staging can be used in patient selection. Sentinel node status separates melanoma patients into high- and low-risk groups also providing a logical basis on which assessment of the need for follow-up schedule can be based. The intensity of clinical and technical examinations should be intensified among high risk patients. In contrast, low risk patients can be followed safely by more simple and lower-cost methods.

7 CONCLUSIONS

On the basis of the present study, the following conclusions can be made:

I In the last 25-years, melanoma surgery has become less invasive. This evolution has not influenced disease-specific overall survival. An early diagnosis of melanoma remains important in terms of improving prognosis. Sentinel lymph node biopsy is the method of choice for nodal staging.

II Compared with historic controls, SLNB did not significantly improve disease-free survival or disease-specific overall survival. In contrast, nodal disease-free survival was significantly higher among the SLNB patients and SLNB thus provides a better regional disease control. Metastatic tumour burden in the sentinel node was a highly significant predictor for survival.

III SLNB detected occult nodal metastases in 4.5 % of the patients with thin T1 melanoma. We could not identify any indicators that would have sensitively predicted the sentinel node positivity. Without SLNB, nodal micrometastases would remain undetected.

IV SLNB detected occult nodal metastases in 16 % of the patients with head and neck melanoma. SLNB is superior to traditional neck dissection in the staging of clinically node-negative patients. SLNB is more challenging in the head and neck than in other body sites.

V Whole body FDG PET detected occult distant metastases in six of 30 asymptomatic patients with high risk melanoma. This upstaging altered the treatment in each patient. A failed SLNB constitutes a special indication for FDG PET, particularly when the primary lesion is thick or of intermediate thickness or ulcerated.

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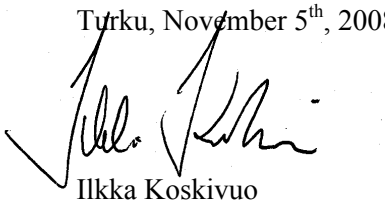

Ilkka Koskivuo

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