Regional metastatic melanoma. Aspects of treatment and prognostic factors

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Chapter I

Introduction and outline of the thesis
1. **MELANOMA, INCIDENCE AND STAGING**

The incidence of melanoma has doubled in the United States between 1989 and 1998. It was estimated that 44,200 new cases of melanoma would be detected in 1999. In the Netherlands, the increase in incidence was around ten percent between 1989 and 1995, with some 1,859 new cases in 1995. However, the mortality / incidence ratio for melanoma is 0.21, this is almost the lowest rate for all invasive malignancies and this ratio is decreasing. In Scotland survival rates improved by 12% over the period 1979-1994. This is mainly due to diagnosis of the primary melanoma at an earlier stage.

For staging melanoma the fourth edition (1992) of the TNM classification of malignant tumours was used. The 1997 edition remained unchanged with regard to melanoma. However, changes in the classification are expected to be effectuated in 2001.

2 **DISSEMINATED MELANOMA**

The risk of developing metastatic melanoma depends mainly on the Breslow thickness of the primary tumour, measured in millimeters. Other determinants are Clark level, site of the primary tumour, ulceration of the primary tumour and sex. The presence of tumour-positive lymph nodes found at sentinel lymph node biopsy further predicts the occurrence of distant metastases and consequently suggests a reduced chance of survival of the patient. This finding illustrates the importance of regional metastases in the staging of melanoma.

Cutaneous and subcutaneous metastases between the primary tumour location and the regional nodal basin are characteristic manifestations of regional metastases in melanoma. These (sub)cutaneous loco-regional recurrences have been termed satellites or in-transit metastases depending on the distance from the primary melanoma. This terminology, however, does not reflect a difference in biological behaviour and the term 'in-transit' will be used in this text to refer to both entities. Proliferation of tumour emboli in the (sub)cutaneous lymphatic vessels between the primary melanoma and the regional lymph node basin lies at the basis of this typical pattern of metastasis. In-transit metastases occur in about 2-5% of patients and the optimal treatment has to be determined on an individual basis. In addition to the potentially life-threatening aspect that all metastases have
in common, in-transit metastases are ever-present visual reminders of the activity of the cancer to the individual patient.

Metastases in the regional lymph nodes are seen in approximately 18 - 24% of the patients with a melanoma with a Breslow thickness of more than 0.76 mm. \textsuperscript{17} \textsuperscript{18} In surgery for solid tumours, lymph node removal has been considered mainly a staging procedure and a means to enhance loco-regional disease control. In addition to these goals, however, regional treatment strategies are also aimed at cure if distant metastases are absent. Five-year survival rates of 36 - 50% have been reported after surgical or multimodality treatment of stage III melanoma. \textsuperscript{19} \textsuperscript{20}

Surgical removal of all detectable tumour is important in melanoma because of the absence of non-surgical therapeutic modalities with proven efficacy. \textsuperscript{21} \textsuperscript{22} \textsuperscript{23} In spite of massive efforts put in fundamental and clinical research, little or no progress - in terms of survival - is made in the field of chemotherapy, immunotherapy or a combination for patients with metastatic melanoma. \textsuperscript{24} \textsuperscript{25} \textsuperscript{26}

3 THERAPEUTIC STRATEGIES FOR IN-TRANSIT METASTASES

In-transit metastases can be very embarrassing for both the patient and the treating physician. The therapy will be directed primarily at relief of symptoms like pain, ulceration and visible tumour growth. Prevention of further metastases and possible cure should be pursued. When the metastases are confined to an extremity and due to their multitude not amenable to excisional surgery, isolated limb perfusion is the therapy of choice. \textsuperscript{27} In-transit metastases on the trunk or on the head and neck region and recurrent (sub)cutaneous metastasis refractory to isolated limb perfusion pose therapeutic problems. Surgery is an option as long as the number of lesions is limited. Optimistic reports in literature advocated the use of carbon dioxide laser vaporisation of superficial localised melanoma metastases when other treatment modalities had failed or even as a primary treatment.\textsuperscript{28} \textsuperscript{29} \textsuperscript{30} \textsuperscript{31} \textsuperscript{32} We decided to familiarise ourselves with the technique and to set up a prospective registration of the results and failures of the laser treatment. In Chapter II we describe our experiences and try to put the different treatment modalities for in-transit metastases in perspective. Aspects of patient acceptance and of disease control are both taken into account.

Immunotherapy has received a lot of attention in the treatment of metastatic melanoma and still more in the scope of adjuvant treatment of high risk patients. \textsuperscript{26} \textsuperscript{33} \textsuperscript{34} Immunotherapy has been used as monotherapy in the form of vaccines,
intralesional injections or systemic drugs. It has also been used in combination with otherwise not very effective systemic chemotherapy in an effort to amplify the effect of that chemotherapy. From 1979 on, the combination of dinitrochlorobenzene (DNCB) and dacarbazine (DTIC) has been used at The Netherlands Cancer Institute following some reports on the activity of topical DNCB and the effects of immunotherapy. In Chapter III, we summarise our experiences with the combined immuno-chemotherapeutic approach of patients with the combination of in-transit metastases and systemic metastases.

4 THERAPEUTIC STRATEGIES FOR REGIONAL LYMPH NODE METASTASES

Tumour spread to the regional lymph nodes is the most frequently encountered metastatic pattern in melanoma and these can be the only site of metastasis. If lymph node involvement is present, regional node dissection should be performed with curative intent. Review of the literature shows ensuing five- and ten-year survival of 37% and 32% respectively. The discussions regarding the role of elective lymph node dissection have almost been settled since the advent of the selective lymphadenectomy through sentinel node biopsy. While there is general agreement about the extent of the dissection of the axilla, the anatomy of the groin basin leaves room for discussion. The groin basin is divided in an inguino-femoral and a pelvic region, interconnected through a small string of lymphatic tissue in the femoral canal.

It is clear that a therapeutic inguinal dissection is mandatory in the presence of lymph node metastases in the inguino-femoral region. Dissenting views, however, exist on the desirability of an associated pelvic lymphadenectomy in the absence of clearly demonstrated pelvic node involvement. In Chapter IV we review the results of the policy of a standard combined groin dissection at The Netherlands Cancer Institute over a period of 34 years. In this study, the largest patient group in the literature with positive pelvic nodes and treated with curative intent is described. Survival, prognostic factors for survival, morbidity and regional tumour control are addressed.

The decision whether or not to operate the pelvic lymph node region in the presence of inguino-femoral lymph node metastases would be easier if criteria exist that reliably predict the tumour-status of the pelvic nodes. Coit published a decision tree mainly based on the presence or absence of tumour in the lymph node
of Cloquet,\textsuperscript{43} which is situated in the femoral canal. Other authors, however, could not reproduce the high negative predictive value of Cloquet's node.\textsuperscript{48,49} This was the reason for us to review our experience with the predictive value of Cloquet's node, as described in Chapter V. For this purpose, we conducted a prospective registration of the combined lymph node dissections, focusing on the predictive value of Cloquet's node and the number of involved inguino-femoral nodes.

Once we realised that the predictive value of Cloquet's node was less than optimal, the question arose why this is so. Classical surgical – anatomical studies taught that the lymph flowing from the skin of the trunk and the leg travels from the inguino-femoral region through Cloquet's node to the pelvic region.\textsuperscript{50,51} If all the lymph fluid were to follow that pathway, the negative predictive value of Cloquet's node should be 100 %. In Chapter VI, the pathways of the lymph fluid from the inguino-femoral to the pelvic basin are visualised in an in vivo model. For this purpose we applied the vital blue dye staining technique as described in the lymphatic mapping procedures.\textsuperscript{52,53,54} The observation of blue lymphatics bypassing Cloquet's node can explain its less than optimal predictive power regarding the tumour-status of the pelvic nodes.

5 Prognostic factors for survival after surgical therapy for stage III melanoma

For several reasons it is not only interesting but also necessary to gain insight in the long-term outcome and the factors governing survival following therapeutic lymph node dissection with curative intent. Survival is a means of evaluating the quality of care in an institution devoted to cancer treatment. Probably more important, however, is the possibility to enhance the quality of life by being able to provide patients with prognostic data and use these as a basis for making evidence-based choices from the therapeutic arsenal. This becomes more important as adjuvant treatment modalities may emerge in the context of a clinical trial.\textsuperscript{55,56} In addition, patients get more emancipated and likewise the demand for precise information and associated evidence-based counselling will grow.

Data on survival and regional recurrence after cervical node dissection for melanoma in the head and neck region vary considerably throughout the literature.\textsuperscript{57,58,59} It is in this perspective that we evaluated the outcome and the prognostic factors for these patients separately, as outlined in Chapter VII.
The aforementioned emerging adjuvant treatment modalities come at high costs, both in terms of morbidity and of finances. Moreover, only a limited percentage of the target population may experience a survival benefit. As a consequence, an important aspect of the evaluation of these therapies will be to find out which subgroup of patients will benefit from which kind of adjuvant treatment following a regional node dissection. One way to deal with patient selection and evaluation of therapies is to stratify the patients into risk groups deduced from prognostic factors for survival. Several authors already constructed prognostic formulas, none of which has been validated by using a different patient group than the one the formula was based on.\textsuperscript{60,61,62} The formula devised by Slingluff et al. was chosen to be validated and - if possible - improved through our patient group. In Chapter VIII we present the search for a prognostic formula for stage III patients based on readily available parameters and with optimal discriminating power.

In Chapter IX we summarise the results and conclusions and present a concise overview of the subject.
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Introduction


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