Melanoma surgery and the impact of sentinel node biopsy

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SUMMARY AND CONCLUSIONS

This thesis evaluates the sentinel node procedure in melanoma surgery and analyzes cervical lymph drainage from primary cutaneous melanomas. Chapter one contains the outline of this thesis, a brief introduction concerning melanoma, the sentinel node procedure and the lymphatic drainage patterns of head and neck melanomas.

EVALUATION OF THE SENTINEL NODE PROCEDURE IN MELANOMA SURGERY

In 2002, we noticed a potential downside of the sentinel node procedure in melanoma surgery. The rate of in-transit metastases in our sentinel node positive patients was found to be 23%, substantially higher than the 8.3% in patients with palpable lymph node metastases.[1] The question arose whether sentinel lymph node biopsy could perhaps induce the development of in-transit metastases. The main aims of the study described in chapter two were to compare the occurrence of the various forms of local-regional recurrence in patients who underwent lymph node dissection for either a positive sentinel node or for palpable nodal metastases. The results show that the rate of local-regional metastases in these two latter groups is similar, which refutes the suggestion that a positive sentinel node predisposes for the development of in-transit metastases.

The sentinel node biopsy is a diagnostic procedure to detect lymphatic dissemination early and it improves staging.[2] Unfortunately, false-negative percentages from eight to 32 have been reported from renowned melanoma institutes (see chapter four). In chapter three, the percentage of false-negative sentinel node procedures in 708 melanoma patients was determined. The time cohort of these recurrences and their cause were also investigated. Sentinel node biopsy was positive in 164 patients (23%) and false-negative in ten (1.4%), which results in a false negative rate of 5.7%. Half of the false-negative biopsies occurred in the first year after the procedure was introduced, illustrating the existence of a learning period. The cause of these false-negative procedures could be attributed to the nuclear medicine physician once, to the surgeon once and to the pathologist twice. Chapter four is an editorial about false-negative sentinel node biopsy in melanoma patients. The definition of a false-negative result, potential reasons for false-negative procedures and a comparison with other cancers are elaborated in this chapter.
Lymphoscintigraphy has evolved in the past few years. The recently introduced single photon emission computed tomography with computed tomography (SPECT/CT) maybe helpful in detecting more sentinel nodes, which may decrease the percentage of false-negative procedures.\[3,4\] The objective of the study presented in chapter five was to investigate whether SPECT/CT is of additional value compared to conventional lymphoscintigraphy in routine lymphatic mapping in patients with melanoma. SPECT/CT depicted the same 69 sentinel nodes as conventional lymphoscintigraphy in 35 patients plus eight additional sentinel nodes in seven of these patients (20%). In two of these patients (5.7%), an additional nodal basin was explored to find the extra sentinel nodes. SPECT/CT provided additional anatomic information that was helpful to the surgeon in 11 patients (31%) and led to an adjustment of the surgical approach in 10 patients (29%).

Since the introduction of lymphatic mapping, the need for completion lymph node dissection in case of a tumor-positive sentinel node is being challenged, particularly when a minimal tumor burden is found.\[5-12\] Other experts believe that tumor burden should not yet determine treatment and that completion node dissection is still required.\[13\] Chapter six examines the incidence of lymph node recurrence in sixteen melanoma patients with a minimal metastasis (Starz level I) in a sentinel node in whom a completion lymph node dissection was omitted. No lymph node recurrences occurred during a median follow up of 60 months. This result suggests that the risk of refraining from node dissection in such patients is so small that this option can be considered.

CERVICAL LYMPH NODE DRAINAGE FROM CUTANEOUS MELANOMAS

Completion lymph node dissection is the currently recommended management of a patient with a tumor-positive sentinel node in the neck, but the extent of neck surgery is still a matter of debate. In 1995, O’Brien investigated a consecutive series of 92 parotidectomies and 183 neck dissection specimens and described the classic drainage patterns of cutaneous head and neck melanoma.\[14,15\] Based on these findings, potential metastatic sites in patients with head or neck melanoma can be predicted.\[15\] This map is widely used for planning (selective) therapeutic neck dissections. Lymph drainage is classified by the location of the primary tumor in relation to the so-called vertical watershed line that distinguishes anterior and posterior lesions. Chapter seven evaluates the sentinel node locations in 65 patients with head and neck cutaneous melanoma using dynamic and planar lymphoscintigraphy and SPECT/CT. The
drainage patterns were compared to “O’Brien's map” and to the treatment guidelines at The Netherlands Cancer Institute, and the incidence of discordant sentinel nodes was determined. O’Brien advocates a level I-III dissection and parotidectomy for primary skin lesions anterior to the watershed, level I-IV dissection and parotidectomy for anterior upper neck tumors (level V is included for coronal scalp and ear lesions), level III-V dissection for malignancies in the anterior, coronal or posterior lower neck and level II-V dissection with the suboccipital area for tumors posterior to the watershed and the ones located in the posterior upper neck. At The Netherlands Cancer institute, this guideline was modified resulting in the following treatment protocol. A (modified) radical neck dissection with parotidectomy is carried out in patients with a tumor-positive sentinel node derived from a primary melanoma anterior to the watershed line, on the coronal scalp, in the upper neck or on the ear. A level II-V dissection with extension to the suboccipital region is done for malignancies posterior to the watershed line or in the posterior neck, a level I-V dissection for anterior upper neck lesions and a level II-V dissection for tumors in the anterior or coronal lower neck.

The study showed that twenty-three percent of the harvested sentinel nodes were outside the area that O’Brien’s map indicates, while 14% were outside the dissection levels advocated by The Netherlands Cancer Institute. Dissections based on the latter map contained significantly more sentinel nodes. It was concluded that almost a quarter of head and neck melanomas metastasize outside clinically predicted neck levels and that the surgery guidelines of The Netherlands Cancer Institute result in the removal of significantly more potential tumor bearing lymph nodes than O’Brien’s recommendation. With our more extensive dissections we try to reduce the number of missed lymph nodes to a minimum. Our protocol has not been modified yet but a future goal is to operate more selectively, based on the individual lymph drainage pattern. The extent of the neck dissection could perhaps be guided by the location of the second-echelon nodes, in analogy to superficial or deep groin dissection.

In this study of 65 patients with a head and neck melanoma, 10% of the sentinel nodes were found in the suboccipital region, which is a remarkably high number. Familiarity with the surgical anatomy of this area is limited because, to our knowledge, no literature data is available on the number and exact locations of these lymph nodes. The main aim of chapter eight was to provide surgeons with solid landmarks for dissection of the occipital region based on the locations of its lymph nodes. The anatomy of the suboccipital region was studied in five human cadaver heads and necks (nine sides). A total of 32 lymph nodes were retrieved from the suboccipital region in the nine specimens, with a mean number of four lymph nodes per specimen (range: 2 - 7). The mean diameter of these nodes was 3 mm, with a range of 1 to
6 mm. Twenty-four of these lymph nodes (76%) were located in the subcutaneous tissue with an average distance of 7 mm (4 mm - 14 mm) from the epidermis and eight lymph nodes (24%) were situated between the fascia of the trapezius muscle and the muscle itself. These findings lead to recommendations for the extent of the suboccipital node dissection.

The lymphatic drainage of melanomas located on the upper trunk is often complex and may follow an unexpected pattern.[16,17] Sometimes lymphatic drainage from such lesions occurs directly to cervical lymph nodes, particularly from the sternal region.[18] Chapter nine describes three patients with a primary melanoma in the sternal region and cervical lymph node drainage. SPECT/CT was found to be helpful in visualizing these patterns.

Following this case series, a study was designed to determine the incidence and pattern of cervical lymph node drainage in patients with a melanoma located on the shoulder or trunk, and to evaluate our current neck dissection protocol for these patients with an involved sentinel node. The results of this study are presented in chapter ten. Thirty-nine patients with lymph drainage to a cervical node were identified among 631 patients (6.2%) with a melanoma on the shoulder or trunk. Sentinel nodes were excised from level IV or Vb in 34 of these 39 patients (87%), and in 30 of them (77%) from the axilla as well. In the remaining five patients (13%), sentinel nodes were harvested from level IIb, III or from the suboccipital region and none from the axilla. All harvested sentinel nodes were located in the clinically predicted lymph node basins level II-V. It was concluded that only a minority of upper limb or trunk melanomas drain to a cervical node, with preferential drainage to level IV and Vb. Our current neck dissection protocol (dissection of the levels II-V, with or without extension to the suboccipital region) in case of a tumor-positive cervical sentinel node derived from a melanoma on the shoulder or upper trunk appears to be adequate.

CONCLUSIONS, IMPLICATIONS AND FUTURE DEVELOPMENTS

This thesis shows that sentinel node biopsy in patients with melanoma is a useful and fairly accurate tool for early detection of nodal dissemination and that lymphoscintigraphy helps us to analyse the lymphatic drainage pattern in the head and neck region. The 29% false-negative rate in our first year shows that there is a learning curve (chapter 3 of this thesis). The false-negative rate is decreased and the sensitivity of this procedure in the last four years rose above 98%. The advantages of the sentinel node biopsy justify offering this procedure for the detection of occult lymph node metastases. In the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) of Morton et al, 2001 melanoma patients were randomized between sentinel
node biopsy and observation.[19] Therapeutic lymph node dissection followed in case of a tumor-positive sentinel node. In patients who were observed, therapeutic lymph node dissection was performed when lymph node metastases became palpable. The prognostic value of the procedure was confirmed by the finding of a five-year survival of 72.3% in patients with a tumor-positive sentinel node while this was 90.2% in those with a negative sentinel node. The study did not show a significant difference in the five-year melanoma-related survival between the two main groups (87.1% and 86.6%, respectively). The most important purpose of sentinel node biopsy is to identify patients with early lymph node metastases so that they can undergo timely treatment with an improved chance to survive. The fourth interim analysis after a median follow up of 8.2 years for the patients who were still alive revealed that in the patients with a melanoma with a Breslow thickness between 1.2 and 3.5 mm the ten-year melanoma-specific survival was 60.9% in the sentinel node-positive patients and 41.8% in the patients who developed overt metastases in the wide excision only group (p=0.01). The forthcoming final conclusions of this study can eradicate lingering doubts about the increased survival in patients who underwent sentinel node biopsy. We conclude that the procedure improves survival in the target population of people with early nodal involvement.

Completion lymph node dissection is routinely recommended if sentinel node involvement is found but less than 20% of these patients will have additional lymph node metastases identified in the dissection specimen.[20-23] Regional lymph node dissection is a procedure with substantial morbidity.[24] Therefore, it is necessary to determine whether patients with metastasis in the sentinel node benefit from completion lymph node dissection in terms of survival and quality of life. This thesis suggests that the risk of refraining from node dissection in patients with a minimal tumor burden (Starz level 1) in the sentinel node is small and that this option can be considered. It will be interesting to see if this suggestion is confirmed by the ongoing MSLT-II study. In this study of Morton et al, patients with a tumor-positive sentinel node are randomised for either completion lymph node dissection or a wait and see policy.

A significant part of this thesis concerns head and neck melanoma. We mapped the lymph drainage patterns based on the sentinel node locations. A small fraction of the sentinel nodes were found outside the recommended neck dissection regions and the current neck dissection protocol is therefore justified. Comprehensive coverage is not feasible because the individual lymph drainage patterns are so diverse.

The suboccipital lymph node dissection was refined. Dissection of a skin flap with a minimum of subcutaneous tissue and removal of the underlying muscular fascia of the trapezius muscle are essential, because this thesis showed that suboccipital nodes may be
located in the subcutaneous tissue with a minimal depth of 4 mm from the epidermis or just underneath this fascia.

Innovative technologies like the intra-operative gamma camera, fluorescent tracers and freehand SPECT may lead to a higher sensitivity of the sentinel node procedure.[25-27] Although completion selective neck dissections according to strict guidelines are now performed after retrieval of a tumor-positive sentinel node, the attempt to limit the extent of completion node dissection will meet with new challenges. In order to create a more patient-tailored treatment and to minimize postoperative morbidity further research on reducing the extent of therapeutic neck surgery is needed. Perhaps analysis of the location of second-echelon nodes may guide the extent of neck dissection in analogy to the management of patients with a positive sentinel node in the groin.[28]

Nowadays, genetic analysis of the primary tumor is a new and hot topic. Perhaps the gene expression pattern of the primary melanoma may reliably indicate the presence of lymph node metastases and determine the need for additional treatment.[29] In fact, it has been predicted that within a year gene analysis will tell which primary melanomas will generate lymph node metastases and which melanomas will not do so.[30]
REFERENCES

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