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Survival after lymphadenectomy of nodal metastases from melanoma of unknown primary site

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ABSTRACT

Although the vast majority of melanomas have a primary site, 3%–4% of all melanomas in distant sites display no known primary site (MUP). This phenomenon is not fully understood and various hypotheses have been introduced. The prognostic significance of MUP has been unclear, with some studies showing no survival benefit while others find improved survival compared to stage-matched patients with melanoma of known primary site (MKP). Between 1997 and 2014, 864 patients underwent an en bloc resection of clinical nodal metastases at a referral centre for metastatic melanoma in Norway. The MUP ($n = 113$) and MKP ($n = 751$) patients were graded with stage III or IV. The overall survival (OS) was calculated with the Kaplan-Meier method, and multivariate analysis identified factors of significance for the two groups. A significant five-year OS emerged for stage III, MUP = 58% and 42% for MKP, but not for stage IV. The five-year relapse-free survival (RFS) was 41% and 31% for MUP and MKP respectively ($p = 0.049$). The statistically significant inter-group differences (MUP/MKP) were observed in the univariate and multivariate analyses of age, gender, number of affected nodes, tumour size and perinodal growth within stage III and tumour size within stage IV. After regional lymphadenectomy, MUP patients with clinical nodal metastases had a better outcome than MKP patients. This finding supports the theory that an endogenously mediated immune response may promote the regression of a cutaneous melanoma.

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Introduction

About 96–97% of all melanoma patients are diagnosed with a known primary site (MKP), most often involving the skin, less commonly present within the eye or mucous membranes [1]. In some patients with regional- or distant metastasis, no primary melanoma can be detected. These are referred to as melanoma of unknown primary site (MUP). Usually, these patients present with loco-regional disease in the lymph nodes, in the soft tissue or with disseminated disease. In 1963, Dasgupta originally defined MUP as melanoma discovered in subcutaneous tissue, lymph nodes (LN's) or visceral organs without a cutaneous, ocular or mucosal primary site [2]. The aetiology of MUP is not fully understood. Possible explanations are spontaneous regression of a cutaneous melanoma by an endogenously mediated immune response after the metastases have occurred, or malignant transformation of a melanocyte after migrating along the neural crest to lymph nodes or the viscera [3–5].

According to previous reports, MUP occurs more often in men in their fourth and fifth decades of life [6]. MUP may have a different biology than MKP and it resembles the genotype of cutaneous melanoma rather than that of mucosal melanoma [7]. The most common clinical presentation of MUP is lymph node disease and it occurs most commonly in the axillary-, (50%), cervical- (26%) and groin nodes (20%) [5].

The prognostic significance of MUP has been disputed. Some studies found similar or poorer outcome in MUP patients [8–10], whereas others found improved survival [6, 11–14].

In the new era of immune- and targeted therapy, which increases the repertoire of available treatments for melanoma, the analysis of the differences between MPK and MUP appears to be essential.

Aim of the study

The aim of this retrospective study was to evaluate our data in order to see if there is a difference in survival between a consecutive series of MUP and MKP patients following lymph node dissection in clinical nodal disease and also to identify possible prognostic factors.

Material AND methods

This survey took place in 2018. Patients treated for clinical stages III and IV melanoma, between 1997 and 2014, were identified from a prospective database which registered all melanoma patients who underwent surgery for clinical nodal disease at the plastic surgery unit at The Norwegian Radium Hospital (DNR), Oslo University Hospital, a referral centre for metastatic melanoma.

All patients fulfilled the following inclusion criteria:

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- Stage III or stage IV disease treated with lymphadenectomy
- No other oncological treatment for melanoma prior to surgery
- No other malignant disease
- All ages
- Clinically detectable nodal disease verified by fine needle aspiration cytology (FNAC), biopsy, node-picking or previous incomplete nodal dissection

The exclusion criteria were as follows:

- Patients with revised malignant outcome of previously removed presumed benign mole
- Patients who later were diagnosed with a new primary melanoma
- Patients who previously have removed a congenital nevi

Surgery

Surgery for all patients with clinical nodal disease has been consistent throughout the whole period.

- Neck: Selective nodal dissection as a standard and modified radical dissection with extensive disease. Superficial parotidectomy when the parotid gland or level II was affected.
- Axilla: Full en bloc dissection (level I-II-III). This involved complete clearance of the axillary content up to the apex of the axilla defined by the musculus subclavious tendon [15].
- Groin/Pelvis: Radical groin dissection with identification of Clocquet's node. Whenever suspicious or confirmed metastatic nodes were present in the pelvic area, an ilioinguinal dissection was performed.

Measures

Demographical- and treatment characteristics for each individual patient were extracted from the hospital's melanoma database. The quantity of removed metastatic lymph nodes and the tumour size were provided by the pathologist's report. Also the quantity of affected nodes from previous node-picking or incomplete nodal dissection was included in the final count. In large tumours, where the pathologist could not clearly distinguish between one solid tumour and several melted nodes, the entire tumour size was recorded. MUP patients had an extensive physical examination, which included the ano-genital-, naso-pharyngeal- and ocular area to search for a primary lesion prior to referral. All patients were screened for metastases with either CT-scan, FDG-PET or MRI and classified according to the American Joint Committee on Cancer (AJCC) recommendations in either stage III or stage IV [16]. MUP patients with metastases in the subcutaneous tissue or regional nodes were classified as stage III, while MUP patients presenting with metastases in visceral organs were classified as stage IV.

Statistics

Median and range were calculated from continuous variables with the Mann-Whitney U test assessing inter-group differences. The disparities between the categorical variables were evaluated by the chi-square test and the Kaplan-Meier method was used for survival analysis. In addition, hazard ratios (HR) and 95% confidence interval (CI) of several clinico-pathological variables for overall survival were calculated using uni- and multivariate analysis with a Cox proportional hazard model. A p-value of less than 0.05 was regarded as statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.).

Ethics

The study was approved by the Regional Ethical Committee of the South-Eastern Health Region of Norway (REC 2016/1672).

Results

A total of 864 patients with clinical nodal disease (males = 510, females = 354) was identified from the database, of which 720 were diagnosed with stage III (males = 421, females = 299) and 144 with stage IV (males = 55, females = 89). The MUP group consisted of 113 (13%) patients (males = 63, females = 50), where 93 were diagnosed with stage III (males = 52, females = 41) and 20 with stage IV (males = 11, females = 9). In the MKP group there were 751 patients (males = 447, females = 304), of which 627 had stage III (males = 369, females = 258) and 124 (males = 44, females = 80) had stage IV.

The MUP patients were similar to the MKP patients as to gender, age at surgery, BMI and surgery duration. Almost half of the patients (MUP = 54%, MKP = 45%) had an axillary site of nodal metastasis. In the MKP group the younger population and the male patients were more frequent. Pre-operative characteristics and diagnostics are listed in Table 1.

Table 1. Pre-operative characteristics ($n = 864$).

	MUP ($n = 113$)		MKP ($n = 627$)	
Characteristics	St III ($n = 93$)	St IV ($n = 20$)	St III ($n = 627$)	St IV ($n = 124$)
Gender				
Male	52 (56%)	11 (55%)	369 (59%)	44 (35%)
Female	41 (44%)	9 (45%)	258 (41%)	80 (65%)
Age at surgery, years	62 (25–90)	62 (37–83)	61 (13–95)	65 (30–93)
BMI[a]	26 (17–41)	24 (19–33)	26 (19–33)	25 (18–37)
Duration of surgery, minutes[a]	106 (60–240)	110 (66–260)	95 (30–540)	133 (55–252)
Nodal station				
Neck	9 (10%)	2 (10%)	73 (12%)	21 (17%)
Axilla	43 (46%)	15 (75%)	269 (43%)	56 (45%)
Groin	40 (43%)	3 (15%)	275 (44%)	46 (37%)
Pelvic	1 (1%)	0	7 (1%)	1 (1%)
Pre-op diagnosis				
US/FNAC	39 (42%)	7 (35%)	472 (75%)	81 (65%)
Biopsy	22 (24%)	7 (35%)	38 (6%)	9 (7%)
Node picking	28 (30%)	3 (15%)	98 (16%)	21 (17%)
Previously nodal dissection	4 (4%)	3 (15%)	19 (3%)	13 (11%)

[a]Median and range.

Table 2. Stage III, post-operative characteristics.

	Stage III					
Characteristics	MUP $n=93$	MKP $n=632$	Univariate HR (95% CI)	Univariate p Value	Multivariate HR (95% CI)	Multivariate p Value
Number of affected nodes[a]	1 (1–25)	2 (0–74)	1.72 (1.301–2.200)	$p<0.001$	1.69 (1.326–3.072)	$p<0.001$
Tumour size[a,b]	45 (11–140)	30 (7–150)	1.00 (1.000–1.011)	$p<0.001$	1.01 (1.001–1.009)	$p=0.040$
Perinodal growth						
Yes	29 (31%)	246 (39%)	0.55 (0.463–0.671)	$p<0.001$	0.69 (0.570–0.853)	$p<0.001$
No	63 (68%)	370 (58%)				
Unknown	1 (1%)	16 (3%)				
Affected nodal basins[c]						
1	73	512	0.97 (0.860–1.104)	$p=0.689$	0.88 (0.778–1.006)	$p=0.063$
2	18	106				
3	2	14				

[a]Median and range.
[b]Millimetres.
[c]Number of patient.
HR: Hazard Ratio; CI: Confidence Interval.

Table 3. Stage IV, post-operative characteristics.

	Stage IV					
Characteristics	MUP $n=20$	MKP $n=124$	Univariate HR (95% CI)	Univariate p Value	Multivariate HR (95% CI)	Multivariate p Value
Number of affected nodes	4 (1–60)	2 (1–50)	1.30 (0.728–2.351)	$p=0.380$	1.38 (0.691–1.984)	$p=0.288$
Tumour size[a,b]	44 (15–230)	41 (4–220)	1.00 (1.003–1.10)	$p<0.001$	1.00 (1.001–1.010)	$p<0.004$
Perinodal growth						
Yes	9 (45%9	71 (60%)	0.61 (0.427–0.880)	$p=0.008$	0.70 (0.472–1.053)	$p=0.088$
No	10 (50%)	40 (34%)				
Unknown	1 (5%)	8 (7%)				
Affected nodal basins[c]						
1	19	108	0.80 (0.540–1.212)	$p=0.306$	0.85 (0.536–1.361)	$p=0.509$
2	1	10				
3	0	1				

[a]Median and range.
[b]Millimetres.
[c]Number of patients.
HR: Hazard Ratio; CI: Confidence Interval.

The statistically significant inter-group differences came to light in the univariate and multivariate analyses of number of affected nodes, tumour size and perinodal growth within stage III (Table 2) and MKP patients also presented with more metastatic lymph nodes with perinodal growth and smaller tumours than MUP patients. These statistically significant inter-group differences did not apply in stage IV, except for tumour size in both univariate and multivariate analyses (bigger tumours in MUP group) and perinodal growth in univariate analysis (perinodal growth more frequent in MKP group) (Table 3).

Five-year survival for stage III was 58% and 42% for MUP and MKP respectively (the hazard ratio (HR)=1.29, $p=0.022$), (Figure 1). The ten-year survival was 40% and 34%, and the twenty-year survival was 24% and 20% for MUP and MKP respectively. For stage IV, the five-year survival was 16% and 10% for MUP and MKP respectively ($p=0.151$), (Figure 2). Five-year relapse-free survival (RFS) was 41% and 31% for MUP and MKP respectively ($p=0.049$), (Figure 3). The difference in RFS between MUP and MKP at ten and twenty years did not meet statistical significance.

The median follow-up for stage III was 47 months (4–236) for MUP and 35 months (1–241) for MKP and for stage IV 13 months (2-86) and 7 months (0–144) for MUP and MKP respectively.

BRAF and NRAS testing were introduced in 2010–2012, and immune therapy was introduced to stage IV patients from 2014 onwards. In this cohort of 864 patients, 250 (29%) were tested for BRAF V600E or V600K mutations and testing was evenly distributed between the MUP and MKP group. The remaining 71% in both groups have unknown BRAF status. 8/627 patients in the MKP group and 1/93 in the MUP group have been enrolled in an ongoing adjuvant stage III study (COMBI-AD) [17]. These patients are registered with a one-year treatment with BRAF/Mek inhibitor.

Discussion

Of the 864 melanoma patients diagnosed with clinical nodal disease at DNR between 1997 and 2014, 113 (13%) were identified as MUP. Within this group, we found a much higher number of patients with stage III compared to stage IV of the disease (93 and 20 patients respectively).

Following the national guidelines for melanoma treatment, the patients diagnosed at the local hospitals with "an unresectable stage IIIC or stage IV disease" were directly referred for radiotherapy or chemotherapy to the referral centre. The referred cohort also comprised MUP patients with a palpable nodal disease which was often incorrectly deemed as stage IV of metastatic melanoma. After adequate diagnostics at the referral centre, many of these patients were re-staged to resectable MUP stage III and subsequently operated with an en bloc nodal dissection. This may explain the considerable difference in numbers between stage III and stage IV in the MUP group.

Previous publications report that MUP more frequently appears in patients in their fourth and fifth decades of life as well as in male patients [10, 18]. In our study, the median age at surgery time was 62 years for both MUP and MKP patients and men were more frequently represented in the MUP group than women. 74%

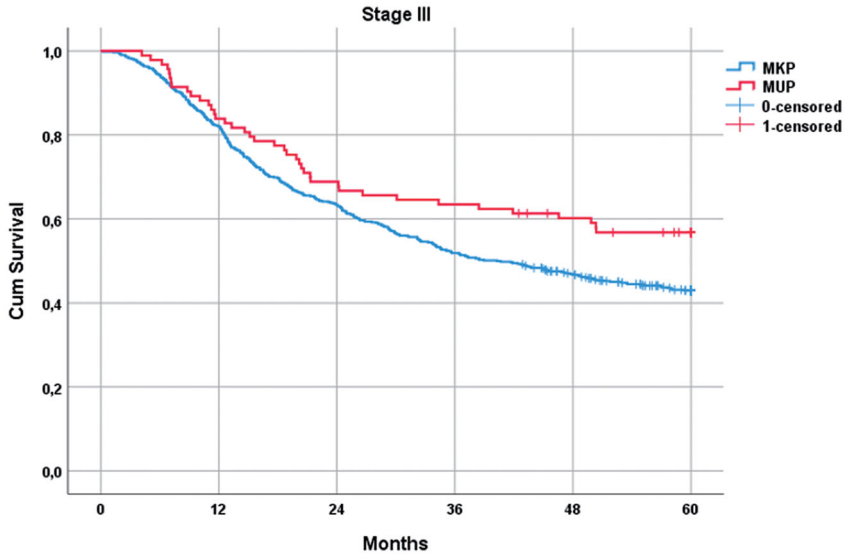

Figure 1. Five-year survival for stage III for MUP and MKP ($p = 0.022$).

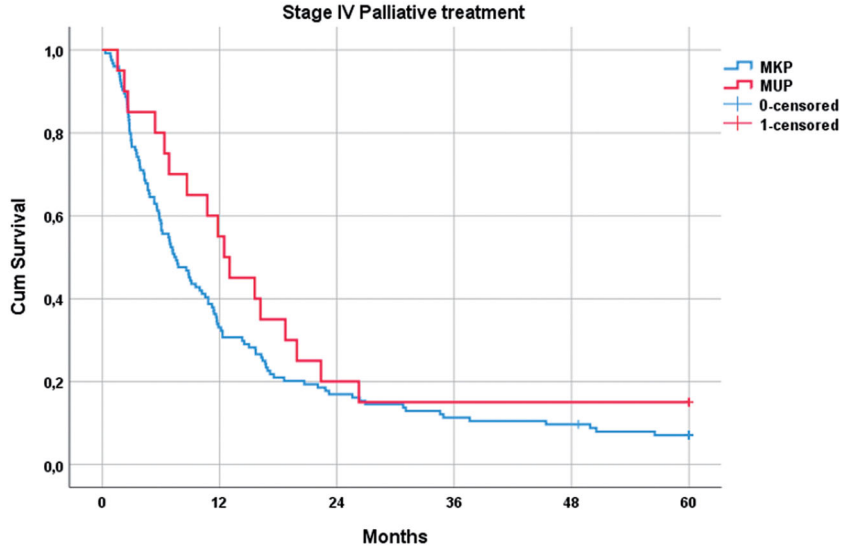

Figure 2. Five-year survival for stage IV for MUP and MKP ($p = 0.151$).

of the patients in the MKP group were diagnosed by means of FNAC, while 54% in the MUP group were diagnosed by means of biopsy/node-picking. The difference in the diagnostic between the two groups shows that the MUP patients were mostly diagnosed at the local hospitals prior to being referred to DNR, while the MKP patients were directly diagnosed at DNR using US/FNAC.

Comparing the MUP patients with the MKP patients at stage III, we found a five-year survival benefit of 58% compared to 42% in the respective groups. The difference in survival decreases over time and almost disappears at the twenty-year follow-up. In stage IV we observed a similar tendency; however, the results were not statistically significant. RFS for the stage III MUP patients compared to the MKP patients was of borderline significance, slightly favouring the MUP patients. A comparable observation has previously been reported by Lee *et al.* after analysing a much bigger patient cohort: 262 (MUP) and 1309 (MKP) [6]. He reports a five-year survival for MUP and MKP patients of 55% and 44% respectively, additionally finding a significant survival benefit for stage IV patients.

The origin of MUP is still not fully elucidated. One hypothesis is the spontaneous regression of a cutaneous melanoma by an endogenously mediated immune response [3]. The removal of clinically evident tumour (lymphadenectomy) may prevent further metastasising from the nodal station and would thus allow the MUP patient's already stimulated immune system to eradicate any residual occult disease. We believe that such a mechanism could be a potential explanation of the better survival outcome for the MUP patients.

This theory is supported by another observation we made, namely that there is no difference in OS between those MUP patients who operated one nodal station compared to those who have operated two or three nodal stations, all of which were identified as regional nodal stations.

The differences in tumour size between MUP and MKP within stage III and IV, where MUP tumours were larger, showed a statistical significance. We believe that the size of the tumours may correspond to local immune response, where the greater tumour volume may represent a neoplastic tissue surrounded by an

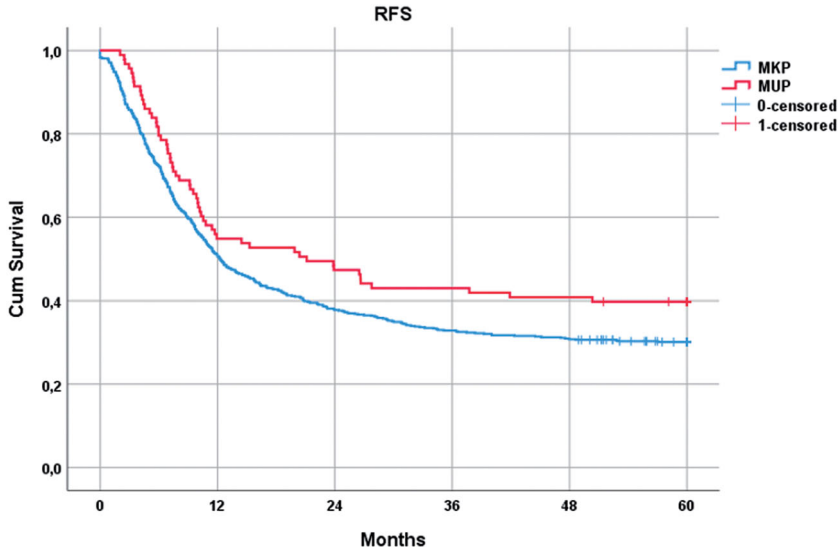

Figure 3. Five-year RFS for MUP and MKP ($p = 0.049$).

immune infiltrate. Rødgaard *et al.* found that 39.6% of MUP patients and 17.5% of MKP patients had an extra-capsular growth [9]. In this study, we found reversed figures, with 31% in the MUP group and 39% in the MKP group, and where MKP was characterised by a greater number of affected nodes. This may indicate that MUP has a more favourable biology than MKP, and at the same time supports the theory about endogenously mediated immune response.

Partial tumour regression has been reported in 9%–46% of primary melanomas, where the regression was more common in thin lesions than in thicker lesions [19]. This also coincides with Egbert's finding about MUP resembling the genotype of cutaneous melanomas rather than mucosal melanomas [7].

The reduced survival benefit from stage III to stage IV as noted in this study may also be explained by the spontaneous regression of a cutaneous melanoma and strongly suggests that the treatment of MUP with clinical nodal metastasis should be a regional lymphadenectomy.

Conclusion

Our study shows that the MUP patients had a better outcome than the MKP patients after regional lymphadenectomy, and it supports the theory that an endogenously mediated immune response may promote the regression of a cutaneous melanoma.

Strengths and limitations

The strength of this study is that all patients were operated at the same plastic surgery unit at DNR, a referral centre for metastasising melanoma. The entire cohort of MUP and MKP patients was operated according to the same pre- and per-operative guidelines. The study's main limitation is the relative low number of patients. The referral practice may also represent a certain selection bias that cannot be excluded.

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Disclosure statement

The authors declare no competing interests as defined by the journal or other interests that might be perceived to influence the results and discussion in this paper.

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