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Standard & non-standard applications of sentinel node (SN) guided melanoma (MM) surgery

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Purpose: Identification and histology of the SN is an acceptable guide for treating Intermediate Thickness MM (ITMM). This prospective open study widens the range of applications of the SN technique.

Methods: 77 MM pts with either ITMM or for whom standard surgical treatment could not be offered. We used preoperative lymphoscintigraphy in 46 pts. IOLM (Intra-operative lymphatic mapping) using Patent Blue® dye and surgery were performed. We used frozen section (FS) and total node processing (TNP)+ H&E staining. Whenever SN was not identified, elective lymph node dissection (ELND) was performed. Median follow-up was 16 (2–76) months. We defined four categories of patients that may benefit from IOLM: **A.** ITMM, **B.** MM 0.75–1.5 mm + risk factors, ie; satellites, ulceration, head & neck acral, two primaries, perineal, Clark/Breslow discordance, delayed referral, **C.** MM around 4 mm, and **D.** MM of undetermined thickness, i.e; regression, locally recurrent, technical pathological or surgical failure.

Results: IOLM successfully identified the SN in 91% of basins explored. F/S detected mets. in 8 SN. TNP added 3 metastatic SN. Twenty basins were formally dissected. **A** (n = 31, mean thickness 2.15 mm): Three of the 35 basins were SN+, 28 were SN−, and in 4 we failed technically. All 31 patients are NED median of 16 (3–30) months. **B** (n = 22, mean 1.26 mm): There were 24 SN−, and 0 SN+. Two of the 24 SN− recurred, and underwent therapeutic dissection 5 and 11 month later. All pts. are NED median of 12 (3–31) months. **C** (n = 9, mean 4.4 (4–6) mm): There were 4 SN+ who underwent LND, and are NED 12 to 31 months. Six SN− are NED median of 18 (5–24) months. **D** (n = 15): One SN+ and 14 SN− were detected, one exploration failed. All 15 pts are NED median of 14 (3–31) months.

Conclusion: In ITMM **(A)** 80% of LNDS were spared. Additionally, in thin MM with higher risk of failure **(B)**, IOLM is advantageous in more accurate staging, patient reassurance and guidance of treatment. For MM around 4 mm **(C)** we achieved earlier detection of regional mets. thus avoiding early failure while on adjuvant treatment. IOLM offers the only tool to guide surgical and adjuvant treatments in undetermined thickness MM **(D)**.

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Hyperthermic isolated limb perfusion (HILP) – A therapeutic concept in locoregional metastasized malignant melanoma – Experiences over 20 years

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Locoregional metastasized malignant melanoma, particularly multiple intransit metastases, is a widely accepted indication for HILP.

From 1975 to 1994 163 patients were treated with isolated perfusion in a therapeutic setting, i. e. because of manifest locoregional metastases of melanoma localized at the extremities at the Surgical Department of the University Hospital in Erlangen, Germany. The cytostatic drug used was a combination of Melphalan (L-PAM) and Actinomycin D. Simultaneously a regional lymph node dissection was performed.

The 10-year survival rate of all patients were 37%. Patients with intransit (n = 51) or lymph node metastases exclusively (n = 79) benefited mostly of the treatment with a 10-year survival rate of 41% and 40% (stage IIIA and IIIB according to M. D. Anderson classification). In case of simultaneous intransit and regional lymph node metastases (n = 33) according to stage IIIAB, prognosis significantly decreased to a 10-year rate of 26%. Since 1992 a further group of 20 patients was treated with a modified perfusion technique. On the basis of experimental data, perfusion time was prolonged to 90 minutes and the drug was continuously infused over 20 minutes. Our experiences showed an increase of complete remission rate to 85% similar to that with the application of TNFα in HILP.

HILP apparently is a suitable tool to control local tumor growth and improve prognosis of melanoma patients with intransit metastases. With respect to the high complete remission rates, the acceptable morbidity and low mortality we continue to follow our concept of modified perfusion technique using melphalan.

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A randomized trial of IFNα/IL-2 with or without CDDP in advanced melanoma: An EORTC melanoma cooperative group trial

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A randomized trial comparing immunotherapy with IFN-a and IL-2 versus chemo-immunotherapy with cisplatinum (CDDP) and IFN-α/IL-2 has been performed. Treatment consisted of 10 × 10^6 U/m^2/day IFNα (Roferon) days 1 to 5 and high dose IL-2 (Proleukin) starting on day 3 using a decrescendo regimen (1 mg/m^2 over 6 hours, followed by 1 mg/m^2 over 12 hours, 1 mg/m^2 over 24 hours, and a maintenance dose of 0.25 mg/m^2 over 24 hours for 3 × 24 hours) with (arm A) or without (arm B) 100 mg/m^2 CDDP on day 1. Cycles were to be repeated on day 28. 138 patients with predominantly visceral metastases (86%) were randomised. Toxicity (gastrointestinal, hematologic, renal, and liver) was more pronounced in arm A. Dose modifications were necessary in only 9% of treatment cycles. The response rate was 15% without and 36% with CDDP (p = 0.01). Median response duration was 17 months without CDDP and 7 months with CDDP. Overall survival was identical in both arms.

Conclusion: The addition of CDDP to IFN-α/IL-2 is feasible, increases response rate, but does not increase survival. In a subsequent randomized trial we currently evaluate the impact of IL-2 on survival.

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Primary anorectal melanoma: Abdominoperineal resection or local resection?

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Purpose: This retrospective study presents prognostic factors of primary anorectal melanoma, and proposes guidelines for surgical treatment.

Methods: Between 1975 and 1995, 14 women and 5 men (59.6 years) with primary anorectal melanoma were treated. Lesions ranged from 12 mm from the anal verge, mean diameter was 45.2 mm, and mean thickness was 21.6 mm. At diagnosis, 5 patients had visceral metastases, 2 had suspicious inguinal lymph nodes, and one had direct vaginal extension. Six patients had an abdominoperineal resection, and 8 had a local resection with curative intent. Two patients had a therapeutic dissection of inguinal lymph nodes. Survival analysis was calculated with Kaplan-Meier, and statistical significance between 2 proportions was calculated with the chi-square test.

Results: Overall five-year survival was 21%, and 2 patients were disease-free at 85 months, and at 48 months. No patients with lymph nodes invasion (pelvic or inguinal) survived longer than 24 months after diagnosis. Univariate analysis showed a significantly poorer prognosis when lymph nodes were invaded (= 0.001), when surgical margins were positive (p = 0.003), when there were metastases (p = 0.01), and when the lesion was thicker than 20 mm (p = 0.01). Prognosis was not altered by type of surgical resection.

Conclusion: Surgical local resection is the first choice whenever negative surgical margins are obtained. Abdominoperineal resection should be reserved for localized large tumors, not amenable to local resection. Dissection of inguinal lymph nodes should be resorted to only when therapeutically necessary.

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Treatment of gutaneous Kaposi's sarcoma with tin ethyl etiopurpurin (SnET2) photodynamic therapy

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Purpose: Kaposi's Sarcoma (KS) lesions in immunocompromised individuals are often physiologically and psychologically distressing. The multifocal nature of these lesions makes local treatments (i.e. surgery, radiation) difficult and time consuming. Further, cosmetic outcomes are generally poor. Photodynamic Therapy (PDT) can overcome some of these negative outcomes in a single treatment session and as such may be of benefit to these patients.

Methods: SnET2 PDT was performed on 9 pts. with known KS lesions. The total number of lesions treated was 121. All patients were HIV positive.

The drug SnET2 was intravenously injected and subsequently activated, 24 hours post-injection, by 665 nm light delivered via fiberoptic from a diode laser light source. The total light dose delivered was 300 J/sq.cm at a power density of 150 mW/sq.cm. Response rates were assessed by serial follow-up and patient subjective satisfaction rates were recorded.

Results: Subjectively each patient was satisfied with the cosmetic outcome of treatment. Of 8 evaluable patients with 116 lesions objective response rates were: (CR 75%; PR 19%; NR 0%; 6% of lesions were of indeterminate status at follow-up). Follow-up ranged from 1–9 months. Adverse experiences were mild to moderate of which 100% were due to sun exposure and did not require treatment.

Conclusions: PDT is a well tolerated procedure that produces excellent subjective and objective responses. The patient is treated in a single session on an outpatient basis. PR and new or recurrent lesions can be retreated with PDT without complications or the development of resistance to therapy.

1162 POSTER

Optimized detection of 5-S-cysteinyldopa (5-S-CD) in serum of melanoma patients: A new marker of metastatic melanoma

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Purpose: It has been tried for years to establish a specific prognostic serum marker of malignant melanoma, which correlates with the clinical aspect of the patients. The routine use of 5-S-CD as a marker of melanoma progression, has been discussed controversially in the literature.

Methods: We investigated 58 melanoma patients (22 females, 36 males) with a total number of 77 serum samples. The patients were in different clinical stages (I–IV): primary tumors (I/II; n = 20); locoregional metastasis (III; n = 14); as well as advanced metastatic disease (IV; n = 21). 5-S-CD was collected under special antioxidative conditions, measured by a new optimized HPLC-analysis which makes the test useful for routine diagnosis.

Results: In healthy controls as well as in patients with other tumor entities, 5-S-CD remained within the normal range (< 1.6 μg/l). 5-S-CD serum level >1.6 μg/l could be detected in 35.6% of our patients in stage III and 87% in stage IV. We found clearly positive values for 5-S-CD (>3.2 μg/l) in stage I+II = 5%; stage III = 21.4%; stage IV = 57.1%. Increased levels of 5-S-CD correlate with the tumor mass and location of the metastases (visceral vs. non-visceral).

Conclusion: This new optimized HPLC-method to detect serum levels of 5-S-CD enables us to establish a promising tumor marker for the clinical state of melanoma patients. Our testsystem provided to be of high specificity and sensitivity and could be useful in the routine diagnosis and therapy monitoring.

1163 POSTER

Essential factors in hyperthermic isolated limb perfusion (HILP) – Experimental results of in-vitro and in-vivo studies

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HILP for regionally metastasizing malignant melanoma of the extremities is a complex method of treatment influenced by multiple factors like temperature, drugs, drug administration modes, duration of perfusion etc. Several of these parameters were investigated in different experimental models.

Temperature-dependent intracellular uptake of melphalan (L-PAM) in a human melanoma cell line (SK-MEL-24) was measured by high-performance liquid chromatography (HPLC). A temperature rise from 37 to 41.5°C increased cellular melphalan uptake 16-fold. Further enhancement of temperature from 42 to 43°C decreased the cell-associated melphalan to the level at 37° indicating a carrier-mediated melphalan uptake also in melanoma cells. Additive effects of melphalan and hyperthermia seemed evident.

Using a miniature equipment for the perfusion of rat limbs we examined the impact of temperature, duration of perfusion and drug administration on tissue uptake of L-PAM. The highest tissue concentrations, measured by HPLC, were observed when perfusion was performed over 90 minutes with temperatures between 40.5°C and 41.5°C and the drug administered continuously into the arterial line within 20 minutes.

Since experimental in vitro- and nude mice studies showed an excellent effect of vinblastine on human melanoma it was considered for experimental extremity perfusion. Normothermic (37°C–38°C) vinblastine perfusions were performed on melanoma bearing nude rats (SK-MEL-3). HPLC-analysis of vinblastine concentrations in tissues (skin, muscle, tumor) demonstrated an increasing uptake of the drug during the course of perfusion. After microsurgical restoration of the vessels complete tumor regression was observed in single surviving animals.

These results suggest that experimental studies can help to clarify essential factors in HPLC. Potential consequences for clinical HILP are addressed.

1164 POSTER

Soluble VCAM-1 as predictor of survival in patients with advanced malignant melanoma

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Very rapid progression of disease with a median of 6 to 9 months is a common feature of metastatic malignant melanoma. Nevertheless, substantial variability of survival suggests that metastatic malignant melanoma can be divided into several biologic subgroups. We evaluated serum levels of soluble adhesion molecules (soluble vascular cell adhesion molecule-1 = sVCAM-1; soluble intercellular cell adhesion molecule-1 = sICAM-1; soluble endothelial leukocyte adhesion molecule-1 = sE-Selectin) and various clinical parameters (e.g., sex, visceral metastases, liver metastases, lactate dehydrogenase, erythrocyte sedimantation rate, C-reactive protein) in 97 consecutive patients with metastatic malignant melanoma seen at our institution between May 1990 and April 1996 and assesed their prognostic value. For statistical analysis, we used both univariate and multivariate Cox proportional-hazards models. Elevated serum levels of sVCAM-1 ($p = 0.02$) and of lactate dehydrogenase ($p = 0.0002$) were rendered statistically independent and were significantly associated with unfavourable outcome. Patients were assigned to one of three risk categories according to a cumulative risk score defined as the function of the sum of these two variables. There were significant differences in overall survival ($p < 0.0001$) between low (n = 53; median survival of 17 months), intermediate (n = 29; median survival of 6 months) and high risk (n = 15; median survival of 4 months) patients. Elevated serum levels of sVCAM-1 and of lactate dehydrogenase correlate with poor outcome in metastatic malignant melanoma. These data support risk stratification for future therapeutic trials, and identify factors which may influence decision making in palliative management of patients with disseminated malignant melanoma.

1165 POSTER

Treatment of metastatic melanoma with a combination of carmustine, dacarbazine, cisplatin, tamoxifen and interferon alpha

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Purpose: The combination of carmustine, cisplatin, dacarbazine and low-dose tamoxifen (20 mg/day) is widely used in metastatic melanoma (MM), and was originally reported to induce 55% objective response (OR) rate and 20% complete response (CR) rate (Cancer Treat Rep 68:1403, 1984). We evaluted a similiar combination but one to which interferon alpha (INF) was added.

Methods: INF 6×10^6 units/m^2/day was given subcutaneously on days 4–8 and 17–21 every 3 weeks. The other drugs were given as originally described. Eligibility criteria included WHO PS 0–3 and measurable disease.

Results: 30 patients (pts) were entered in the study. Among 29 evaluable pts, OR was seen in 15 (52%) and CR in 5 (17%). Median duration of partial response was 4 mo (range, 1–12+ mo) and of CR was 8 mo (range, 2–14+ mo). CR continues in 2 pts with lung metastases at 10+ and 14+ mo. Median survival time was 8.7 mo. Median WBC nadir was 2,050/mm^3 and median platelets nadir was 29,000 mm^3. Neutropenic fever developed in 4 (13%) and platelets transfusions were required in 5 (17%). One patient died with neutropenia and sepsis. Due to thrombocytopenia, the median interval between the first 2 courses was 4 weeks (instead of 3 weeks) and drug doses were reduced in the second course in 8/26 (31%).

Conclusion: The above-noted drug comination is active in MM and may induce durable remission. However, due to severe thrombocytopenia, a reduction of carmustine dose is recommended.