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Dr. T. de Roo, Central Hospital, Alkmaar, The Netherlands

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Current Status of Endolymphatic Therapy with Radionuclides

P.E. Peters, H. Weissleder

The Wiesbaden workshop was initiated to exchange experience and to discuss values and limitations of endolymphatic radiotherapy (ELRT).

The limitations due to the many variations of lymphatic anatomy were demonstrated by *Kubik* (Zurich). Restricting his presentation to the lower limb lymphatic system, he recalled the fact that certain groups of lymph nodes are not visualized by conventional foot lymphangiography (e.g. the internal iliac and external gluteal nodes). Consequently these will not be reached by intralymphatically infused radionuclides. Thus, the primary regions of lymphogenic spread of tumors of all pelvic organs – except ovaries and testes – are excluded from this therapeutic approach. Further limitations of endolymphatic radiotherapy from an anatomical viewpoint are:

- 1) the possibility of "by passing" nodes,
- 2) the preferential segmental filling lymphnodes which can be incomplete, and
- 3) the lack of lymph channels in metastatic tissue.

The latter phenomenon leads to the well known sharply defined filling defects in lymphangiography which are diagnostic for metastatic involvement.

The anatomical findings are taken into consideration as *Weissleder* (Wiesbaden) pointed out. Currently most centers are performing endolymphatic radiotherapy only in patients with malignant melanoma or other radioresistant tumors of the extremities without clinical evidence of lymph node metastases. The rationale of this policy is to treat micrometastases which have been proven to be present in a high percentage of malignant melanoma stage I.

Since endolymphatic radiotherapy is performed with labeled contrast medium ($^{32}\text{P}/^{131}\text{I}$ -Lipiodol UF) it also provides diagnostic information. Almost one third of 57 patients in a joint study (Berlin, Essen, Wiesbaden), presenting with malignant melanoma stage I, had to be reclassified because of metastatic disease in lymphangiogram (*Peters*).

Due to the limited penetration of the ^{32}P beta radiation (max. range 0.8 cm) patients with positive findings in lymphogram are subjected to surgical lymph node dissection. According to *Pfannenstiel* (Wiesbaden) the operation should be carried out about 14 days after endolymphatic radiotherapy. At this time the radiation dose to the hands of the surgeon is negligible (ca. 2-3 rads/hour per lymphnode).

Radiation dosimetry of ELRT depends heavily upon the assessment of the weight of the lymph nodes. *Pfannenstiel* utilizes a formula based on the assumption that the lymph nodes are three dimensional and ellipsoidal in shape. By taking measurements of length and width of every node from the x-ray the calculated mean weight was 20.6 g in 32 patients, resulting in a mean radiation dosage of ca. 100,000 rads to the retroperitoneal lymphatic system. This figure was considered rather high by other participants of the workshop (*Zum Winkel und Harbst*, Berlin). They regard the lymph nodes as being essentially flat and by employing a different formula they obtained weights which are about three times higher. The radiation dosage at the retroperitoneal lymphatic system thus was assumed to be in the range of 30,000 rads.

Whatever calculation is correct, the fact remains that the delivered radiation dosage of ELRT is considerably higher than what can be obtained by external radiation. Furthermore, the limited range of the beta-rays render it a highly selective radiation dose without damage to adjacent structures. For this reason *Zum Winkel und Harbst* are using ELRT occasionally in systemic diseases, like malignant lymphoma stage II or III, in order to reduce the volume of external radiation therapy.

A similar approach was chosen by *Uslenghi et coll.* (Milano) who from 1961 to 1969 treated 426 malignant lymphoma patients with intralymphatic application of radionuclides. Even though ELRT was in most cases combined with other means of treatment (e.g. chemotherapy and/or percutaneous radiotherapy), the authors reported fewer recurrences in patients with negative lymphograms following ELRT as compared to a similar group of patients without ELRT.

The main indication, however, for endolymphatic radiotherapy remains malignant melanoma.

Mlig (Gießen) gave a succinct review of current concepts of diagnosis and therapy of this disease. Statistically between 24 and 37% of malignant melanomas are located at the lower limb. The tumor is known to metastasize early, probably into the lymph vessels as well as into the blood stream. The slower flow in the lymphatic system and the barrier function of the lymph nodes seem to facilitate the growth of metastases while hematogenous spread occurs rather late.

Histological findings of the different types of malignant melanoma according to *Clark's* classification were demonstrated by *Paul* (Gießen) who also developed a method to test the viability of metastatic tissue from malignant melanoma.

At the Wiesbaden workshop more than 500 cases of malignant melanoma were presented by various groups:

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|--|---------|
| <i>Edwards</i> (London) | n = 189 |
| <i>Makoski and Scherer</i> (Essen) | n = 98 |
| <i>Gehring and Baumeister</i> (Freiburg) | n = 67 |
| <i>Kokoschka and Wolf</i> (Vienna) | n = 65 |
| <i>Zum Winkel and Harbst</i> (Berlin) | n = 41 |
| <i>Weissleder, Peters and Pfannenstiel</i> (Wiesbaden) | n = 32 |
| <i>Capello</i> (Ottawa) | n = 31 |

Except for *Capello* (Ottawa) who prefers radioactive gold for ELRT all other contributors are using either pure ^{32}P -Lipiodol UF (tri-n-octylphosphate ^{32}P , Amersham) or $^{32}\text{P}/^{131}\text{I}$ -Lipiodol UF where a small amount of ^{131}I -triolein is added for scanning purposes and dosimetry.

In 1972 a joint working group of ELRT in malignant melanoma was founded in Germany with participants in Austria and Switzerland. In this group the endolymphatic radiotherapy is standardized including dosimetry and follow up examinations. A central registrar exists in Wiesbaden where data on primary treatment and follow up examinations are collected. In less than one year (Jan. to Nov., 73), 106 patients have been reported, most of them being malignant melanomas. The results of the joint study are going to be compared to another group of patients with malignant melanoma collected at ten different departments of dermatology which were treated by conventional methods.

Side effects are also reported to the central registrar. There were no serious complications in the first 106 patients. Since introducing smaller volumes of radioactive material the radiation dosage delivered to the lungs has been consistently lower than in previous reports. According to the recommendations of the joint working group the following doses are currently used:

- 1) unilateral application – lower limb:
5 mCi ^{32}P 1.2 mCi ^{131}I in 3.5 ml volume
- 2) bilateral application – lower limb:
2 mCi ^{32}P 0.5 mCi ^{131}I in 3.5 ml volume each side
- 3) unilateral application – upper limb:
2 mCi ^{32}P 0.5 mCi ^{131}I in 2.0 ml volume.

With these volumes injected the mean radiation dose to the lungs was calculated to be 247 rads based on a lung volume of 1000 ml (*Pfannenstiel*, Wiesbaden).

Stauch and Heissen (Essen) using a whole body counter with special shielding devices obtained a mean dosage of 164 rads to the lungs. In the experimental animal, however, the radiating particles were not equally distributed within the lungs resulting in "hot spots" with doses up to 6000 rads.

Encouraging results were presented by *Edwards* (London) who found a 5-year survival rate of 80% for stage I malignant melanoma and 21.4% for stage II. In these cases endolymphatic radiotherapy was performed following wide excision of the primary lesion. In general anesthesia the lymph vessels draining the operation site were cannulated and the radioactive substance was slowly infused. A comparable group of patients treated at the same hospital by surgical methods alone revealed 5-year survival rates of 58.9%

for stage I and 12.5% for stage II. In Great Britain a controlled clinical trial under the guidance of the Medical Research Council was set up seven years ago to study further the value of ELRT in malignant melanoma of the lower limb. This trial is still in progress. Preliminary results indicate a significantly lower rate of recurrences in lymph nodes (2,3%) in the ELRT-group as compared to 19% in the conventionally treated group, while recurrence in skin was seen more often in endolymphatically treated patients (16%) than in the comparable group (6%). Unfortunately, a number of institutions are participating in the trial which according to *Edwards* have limited experience in endolymphatic radiotherapy. The preliminary analysis of data suggests that unsatisfactory treatment by ELRT seems to pave the way for a more serious prognosis.

In the final round table discussion the attempt was made to evaluate the role of endolymphatic radiotherapy with respect to the immune response of the body. It was felt that the unilateral application of the radioactive substance is sufficient to achieve the goal of destroying micrometastases. By this approach less lymphatic tissue is irradiated leaving the immunological system relatively undisturbed.

In conclusion, endolymphatic radiotherapy in malignant melanoma as an adjunct to adequate surgery seems to improve the prognosis of the disease. Controlled trials are under way in Great Britain and Germany to further evaluate its efficiency.

Dr. P.E. Peters, Radiologische Universitätsklinik, 4400 Münster
Prof. Dr. H. Weissleder, Deutsche Klinik für Diagnostik, 6200 Wiesbaden,
Aukammallee 33

FORTHCOMING CONVENTIONS

9th International Congress of Angiology, April 3 to 7, 1974, Florence, Italy.

Information: Prof. *F. Pratesi*, Via della Robbia 5, I-50132 Florence.

5th International Congress of Cytology, May 29 to June 2, 1974, Bal Harbor, Miami, USA.

Information: Prof. *A. Meisels*, Univ. Laval, 1050 Chemin Ste-Foy, Quebec 6, Canada.

2nd International Congress of Immunology, July 21 to 26, 1974, Brighton, U.K.

Information: Dr. *G.L. Asherson*, Clinical Research Centre, Watford Rd., Harrow, Middlesex, HAI 3UJ, U.K.

5th International Congress of the Transplantation Society, September 1974, Jerusalem, Israel.

Information: Dr. *M. Schlesinger*, Experimental Med. and Cancer Res., Hadassah Medical School, P.O.B. 1172, Jerusalem, Israel.

INTERNATIONAL SOCIETY OF LYMPHOLOGY

Next Congress:

The date of the "Fifth International Congress of Lymphology" in Buenos Aires and Rio de Janeiro has been changed to March 23-29, 1975. For further information please contact the chairmen

C.M. Grandval
 Austria 2626, Buenos Aires, Argentina
 Deadline for abstracts September 30, 1974.

R.C. Mayall
 C.L. 1822-ZC.00, Rio de Janeiro, Brasil.