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LOCAL HYPERTHERMIA IN THE TREATMENT OF MALIGNANT TUMOURS — TECHNICAL POSSIBILITIES AND FIRST CLINICAL EXPERIENCES AT THE INSTITUTE OF ONCOLOGY IN LJUBLJANA (PART II)

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Abstract — A low-cost water circulating heating device has been constructed for interstitial hyperthermia treatment. Seventeen patients with 23 residual, recurrent or locally advanced malignant tumours were treated. All of them had previously received some kind of treatment, except a patient with locally advanced malignant tumour which was believed not to be controllable by conventional treatment modalities. The treatment consisted of interstitial hyperthermia — 42.5°C — 48°C for 45—60 minutes, followed in most cases by immediate afterloading with Ir-192 wires (8—64 Gy, dose rates ranging from 30—108 TDF). Response achieved in the 23 treated lesions was as follows: complete response 7/23 (30%), partial response 14/23 (61%), and no response 2/23 (9%). The homogeneity of heat distribution within the tumour was satisfactory and normal-tissue adverse reactions tolerable. The technique of implantation, temperature control and required technical improvements are discussed.

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Introduction — The control of locally advanced, residual or recurrent accessible malignant tumours still remains a significant problem in modern radiation oncology. The use of hyperthermia may have some additional potential for killing those radioresistant tumour cells which often present the basic population leading to recurrence after radiation therapy (4). There are several reports in recent literature suggesting that a combination of interstitial hyperthermia and brachytherapy provides the best clinical results (2, 6, 8).

Good control of heat distribution within the tumor, sparing of the surrounding normal tissuse and overlying skin, and the possibility of combination with brachyradiotherapy are perhaps the greatest advantages of interstitial hyperthermia. In the reported clinical studies on interstitial hyperthermia mostly radiofrequency and microwave units were used (2, 3, 5).

In our presentation the clinical use of heating device constructed on the principle of circulating heated water is reported.

Material and methods — Patients: seventeen patients (13 males and 4 females) with 23 tumour lesions were treated by interstitial thermoradiotherapy at the University Clinic for Radiotherapy and Radiobiology A-1090 Vienna, Austria, and at the Institute of Oncology, Ljubljana, Yugoslavia in the period from May 1986 to February 1987. Their age ranged from 47—84 years. Table 1 shows the distribution of patients and the number of tumour lesions treated by thermoradiotherapy.

Histologically, the treated tumours were squamous cell carcinomas (14), adenocarcinomas (5), anaplastic cell carcinomas (3), and malignant pleomorphic adenoma (1).

Before thermoradiotherapy all patients except one received some kind of antitumour treatment. Table 2 shows the distribution of patients according to previous treatment and indications for thermoradiotherapy.

Parameters of observation: tumour size was estimated in three largest perpendicular diameters by inspection, palpation, ultrasonography or CT scan. Patients were followe up in monthly intervals. The changes in tumour size and treated normal tissue were recorded.

Clinical disappearance of the tumour was considered as complete response (CR). Tumour volume reduction 50% or more was regarded as partial response (PR), whereas a less than 50% reduction indicated no response (NR). Follow up of the patients lasted 3—11 months.

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Tumor site	No. of patients	No. of treated tumour lesions
Head and neck		
— floor of the mouth	3	3
— mobile tongue	2	2
— parotid gland	1	1
— neck metastasis	4	8
Rectum	2	3
Anus	2	3
Prostate	3	3
Total	17	23

Table 1 — Distribution of patients according to the number of treated tumour lesions

Previous treatment	No. of patients	Indications for thermoradiotherapy
SRG + RT	9	recurrence*
SRG + RT + CT	1	residual tumour
RT	3	unresponsive tumour
RT + CT	3	unresponsive tumour
No treatment	1	locally advanced tumour
Total	17	

* One patient developed a new primary 5 years after the successful treatment of carcinoma in the same site.
SRG — surgery, RT — radiotherapy, CT — chemotherapy

Table 2 — Distribution of patients according to previous treatment and indications for thermoradiotherapy.

Tumour site	No. of treated lesions	Treatment response CR	PR	NR
Head and neck				
— floor of the mouth	3		2	1
— mobile tongue	2	1	1	
— parotid gland	1	1		
— neck metastasis	8	1	6	1
Rectum	3	1	2	
Anus	3	2	1	
Prostate	3	1	2	
Total	23	7	14	2

Table 3 — Treatment response according to the tumour site

The unit: for hyperthermia treatment the unit KHS-9/W 18 developed and constructed at the University Clinic for Radiotherapy and Radiobiology in Vienna, Austria, was used. The unit was designed in such a way that the circulation of heated water through the applicators was maintained by means of pressure and suction pump. The temperature of the circulating water was controlled by the thermostat. Water was driven to the applicators through silicon tubes which in turn were connected with two manifolds at the pressure and suction side of the unit (Fig. 1). Both the temperature and the flow rate could be modified manually or by computer according to the needs of heating.

Two types of applicators were used:

a) plastic or metal tubes permitting the flow of water through the tube (Fig. 2);
b) double-tubed metal needles with sealed points permitting the inflow and outflow of water at the proximal side (Fig. 3). This type was used for heating of the tumours accessible from one side only.

After hyperthermia treatment the same applicators were loaded with Ir-192 wires.

The interstitial thermoradio - therapy: under general anesthesia, metal needles or plastic tubes were placed in the tissue parallel to each other, 10—15 mm apart. It was attempted

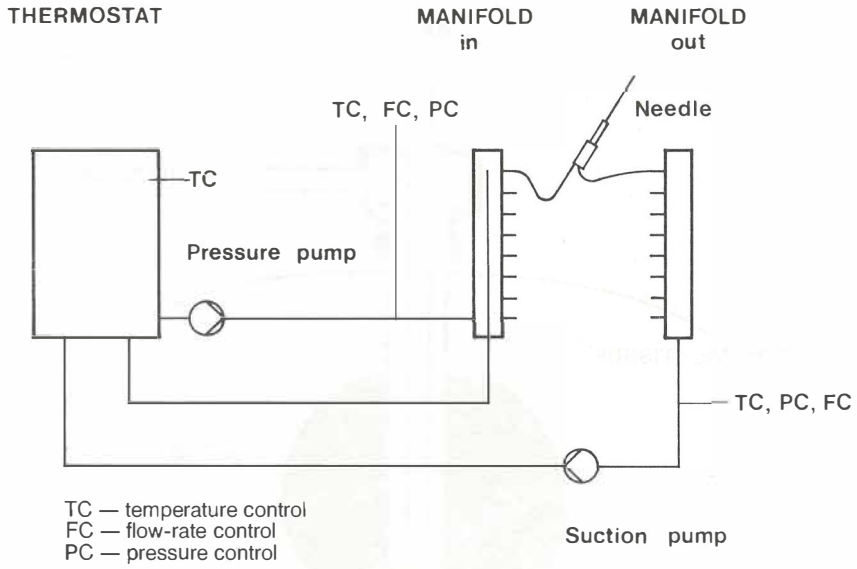

Fig. 1 — Schematic presentation of the KHS-9/W 18 hyperthermia unit

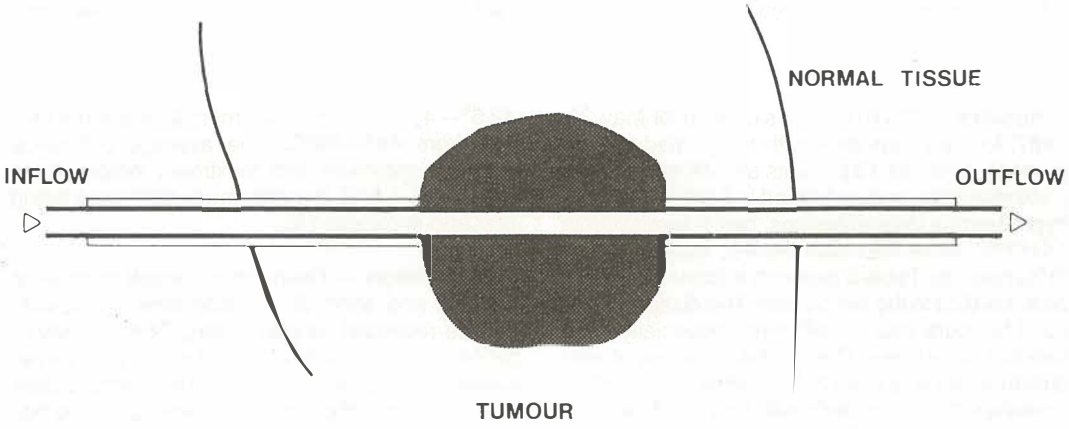

Fig. 2 — Scheme of the applicator which permits heated water flow through the implanted area

that by encompassing the tumour borders into the implant a sufficiently uniform heat distribution as well as radiation dose distribution would be achieved. The estimated mean implant volmue was 100 ± 80 ccm (1).

The temperature was measured with a 5-point thermocouple probe which was placed obliquely or perpendicularly to the direction of the needles, directly into the tumour tissue; in some cases it was being moved through a plastic tube which was for this purpose inserted through the centre of the implant (Fig. 4). The minimum temperature of 42.5°—43°C was selected as the starting point of the hyperthermia treatment. The maximum temperature up to 48°C was reached in the course of treatment. The heating time was 45—60 minutes. The Ir-192 wires were loaded immediately after the completion of heating, except in three cases where post-treatment edema distorted the geometry of the implant. In these patients the afterloading was postponed for 1—2 days. The irradiation tumour dose ranged from 8—64 Gy (given in various doserates) or expressed in time-dose factors (TDF) (7) — 30—108 TDF, depending on previous irradiation treatment.

In our treatment schedule hyperthermia was used in all patients before brachytherapy and was not repeated afterwards.

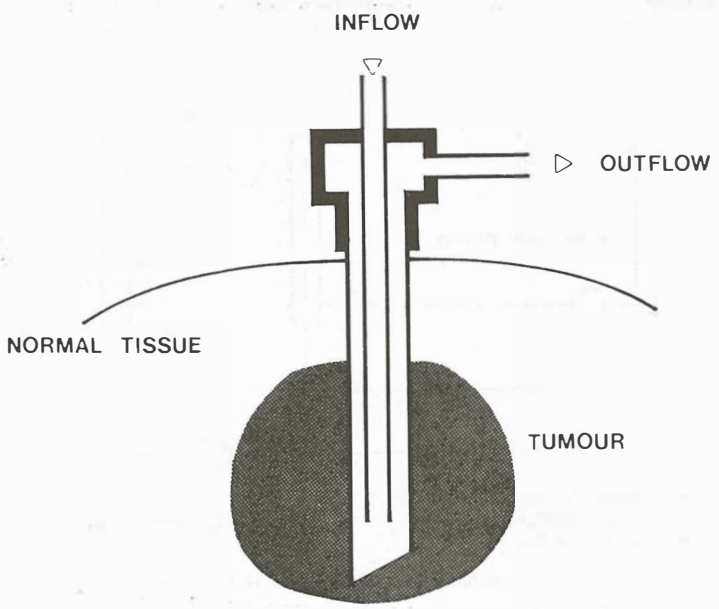

Fig. 3 — Scheme of double-tubed metal needles used for heating of the tumours accessible from one side only

Results — Clinical results: until May 30, 1987, four patients died with the treated tumour present, whereas 13 patients are still alive. Complete remission was achieved in 7 (30%) of the 23 hyperthermia treated lesions, partial remission in 14 (61%), while the treatment was ineffective in 2 (9%) patients. Table 3 presents treatment response according to the tumour site. The disappearance of tumours was usually slow, especially if the tumours were bulky. The aspiration biopsy of residual tumours was done 2—4 months after thermoradiotherapy in 5 patients with head and neck tumours. Only necrotic material without viable malignant cells was found. Later on, one of this tumours has regressed completely while other still persist, their size slowly decreasing.

Early complications comprised edema lasting 1—3 days (5 treatments) and superficial skin damage of small size (2 treatments). Late complications were: induration of the peritumoural soft tissue lasting 2—6 months (3 treatments of carcinoma of the floor of the mouth and tongue), and fibrosis causing inconvenience (2 patients). The patient who received total radiation dose by implant only (64 Gy/7 days = 108 TDF) developed a rather severe mucositis which persisted 5 months after treatment.

Homogeneity of heat distribution: the minimum tumour temperature ranged from 42.5°—43°C, and the maximum temperature ranged from 44°—49°C. The average difference between minimum and maximum temperatures was 3.2°—1.5°C, the maximum difference being 6°C and minimum 1°C.

Discussion — Owing to the small number of patients and short observation time our results can be regarded as preliminary. The majority of patients were treated by hyperthermia for their residual or recurrent tumours. The method was used in combination with brachyradiotherapy because the chances that a significant therapeutic effect could be achieved by brachytherapy alone were slim. In most cases the treated tumours were rather bulky; this, together with short observation time, probably explains why the complete remission rate in our patients (30%) was lower than that reported by some other authors (2). Nevertheless, the overall response rate (91%) is in appliance with the reported results (2, 6).

Most patients tolerated the treatment well. Three patients with carcinoma of the oral cavity developed acute edema after hyperthermia treatment, probably due to large treatment volume. In 2 patients small-sized superficial skin damage was caused by accidental overheating. The three late indurations in the submandibular region observed in patients with carcinoma of the oral cavity could

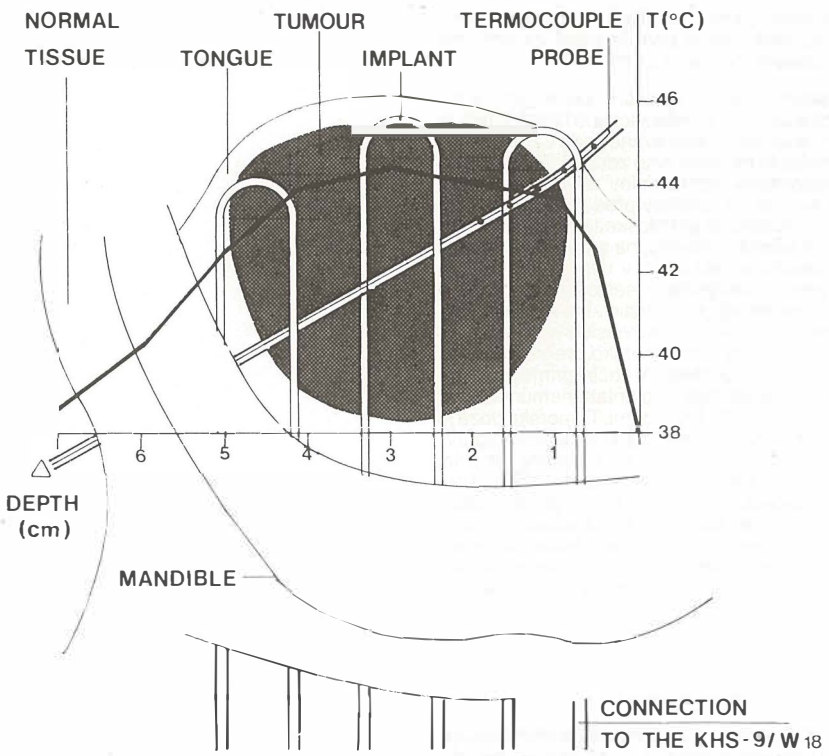

Fig. 4 — Schematic presentation of tumor implant in the mobile tongue. There is a plastic tube inserted obliquely through the tumour centre used for passing of the movable termister probe. The arrow indicates the movement direction. Superposed graph shows the temperatures measured in that region.

be prevented by reducing the heat transfer to the implanted normal tissue; this could be achieved by increasing the wall thickness in the corresponding part of the tube (by inserting a smaller tube), or by using tubes made of two materials with different heat transfer (metal-plastic tubes). It was assumed that the thermal effect of temperature 46°—48°C achieved in most tumours was not only synergistic to irradiation, but also directly cytotoxic. This was the reason for only one hyperthermia application per radiation treatment being used.

The homogeneity of heat distribution was better in smaller treatment volumes. In these cases we found that the measurements made by thermocouple inserted directly into the tumour tissue were sufficiently good. In larger tumours a better orientation of heat distribution was obtained if the thermocouple was moved through a plastic tube implanted for this purpose through the centre of the tumour.

From our experience it appears that the good geometry of the implant is of prime importance for good heat distribution. The proper position of the thermocouple is mandatory for proper measurements. In small accessible tumours the good geometry and proper position of the thermocouple were easier to achieve, and therefore, the differences between minimum and maximum tumour temperatures were less pronounced than in big tumours.

The KHS-9/W 18 hyperthermia unit is an efficient versatile device which is mobile and easy to handle. The flow-rate and temperature control are simple. There are many fail-safe mechanisms to prevent undesirable overheating.

Povzetek

Lokalna hipertermija pri zdravljenju malignih tumorjev — tehnične možnosti in prve klinične izkušnje na Onkološkem inštitutu v Ljubljani (II. del)

Na onkološkem inštitutu v Ljubljani uporabljamo v klinične namene aparaturo za intersticialno hipertermijo, ki deluje na osnovi kroženja segrevane vode v zaprtem sistemu. S pomočjo te naprave smo zdravili 17 bolnikov z lokalno napredovalimi, rezidualnimi ali recidivantnimi tumorji. Med njimi je 16 bolnikov pred tem prejelo vsaj eno vrsto konvencionalne onkološke terapije, pri enem od bolnikov, vključenih v študijo, pa zaradi razsežnosti primarnega tumorja ni bilo upati v uspeh standardnih metod zdravljenja. Zdravljenje se sestoji iz kombinirane intersticialne hipertermije in intersticialne brahiradioterapije. Implantat iz plastičnih ali kovinskih vodil je bil priključen na aparaturo za intratumorsko pregrevanje (od 42,5°C—48°C) za 45—60 minut. V večini primerov so bila ista vodila intersticialnega implantata nemudoma po pregrevanju polnjenja z Ir-192 žicami. Tumorska doza je variirala od 8—64 Gy oz. 30—108 TDF. Učinek zdravljenja 23 tumorskih lokalizacij je bil naslednji: popolni odgovor (CR) 7/23 (30%), delni odgovor (PR) 14/23 (61%) in brez odgovora 2/23 (9%). Homogenost toplotne razporeditve znotraj tumorja je bila zadovoljiva, poškodbe zdravega tkiva pa sprejemljive. Avtorji v članku razpravljajo o tehniki implantiranja, merjenju intratumorskih temperatur in o potrebnih dodatnih izboljšavah.

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