

gold grain implant. Complete resolution of primary and secondary lesions occurred in 94% of cases, and the survival rate after three years was 54%. Retrospective study of comparable series revealed 62.5% resolution rate, and 29% survival after treatment with hyperbaric oxygen and cobalt, while after conventional supervoltage therapy, the resolution rate was 36.5%, and only 19% survived for three years.

THE FIRST International Symposium on Hyperthermia in Washington, in 1975, brought together much laboratory, experimental and clinical evidence that hyperthermia is more lethal to malignant cells than to normal cells. Examples in the clinical scene are Henderson and Pettigrew's use of wax-bath whole body heating,¹ and the work of Leveen *et alii* who heated tumours preferentially by short-wave electric currents,² each obtaining striking regressions of tumour masses. Henderson and Pettigrew's work has been duplicated and confirmed by ourselves in the Radiotherapy Department at the Royal Perth Hospital in 1974, by treating a series of 11 cases of advanced cancer.

Many reports have been published on the use of heat over the last two decades. These were summarized by Crile in his own contribution,³ and, more recently, by Hahn.⁴ Cater *et alii* demonstrated 13 years ago a marked synergism by means of deep X-ray therapy and microwave heating in the treatment of rat hepatoma.⁵ In subsequent years, this synergism has been confirmed and measured. At the second International Conference on Hyperthermia and Radiation in Essen, in 1977, the use of heat as an adjuvant to radiotherapy was emphasized and received close study.

In 1975, Kim and Hahn demonstrated that hypoxic cancer cells exhibited enhanced sensitivity to the lethal effects of heat, these being the very cells which are so radioresistant in large bulky tumours.⁶ Robinson and Wisenburg undertook detailed studies of the effect of temperature on the sensitivity to radiation of Chinese hamster cells.⁷ They found that heat of a few degrees applied for a relatively short time would confer on a cell a very marked increase of radiosensitivity which would persist for about half an hour. We used a clinical technique based qualitatively on this work. Overgaard and Overgaard clearly showed that large discrete animal tumours are readily heated by microwave, but that diffuse or small tumours exhibit only small rises in temperature.⁸ The difference depends on the ability of the blood supply to conduct the heat away from the tumour. These scientific facts led us to consider the treatment of tumours of the head and neck.

These tumours are frequently inoperable, and patients present with bulky masses which have a poor blood supply and contain many anoxic cells and areas of necrosis. They are not treated satisfactorily by conventional radiotherapy, and the outstanding problem is that of local control. The slow rate of distant dissemination, however, makes cure a possibility. The region is one where a successful adjuvant to radiotherapy could greatly enhance the cure rate.

For this reason, hyperbaric oxygen therapy was introduced in the Royal Perth Hospital in 1970, with immediately improved results. In 1974, a few of such patients were exposed to 434-MHz electromagnetic radiation. Striking immediate regressions were noticed. No local cures could be obtained by this microwave hyperthermia alone, but where radiation was added, a marked sensitivity was seen, and certain apparently hopeless cases of maxillary and pyriform fossa cancer were completely healed. So a trial for two years of treatment by a combined method was carried out.

COMBINED MICROWAVE THERAPY

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Fifty-two cases of advanced head and neck cancer were treated by 434-MHz radiowave hyperthermia which was combined with cobalt radiotherapy and/or radioactive

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PATIENTS AND METHODS

Fifty-two patients with cancers of the head and neck were treated over a two-year period, mainly at our private radiotherapy centre, using daily cobalt-60 radiotherapy with standard planning. Microwave radiation was applied two or three times a week, 20 minutes before the ionizing radiation. The average dose given was 4600 rads in eight weeks, the range being 1500 rads to 6000 rads. In two cases, cobalt-60 was not used, because the dramatic resolution after hyperthermia made a radioactive gold-grain implant sufficient for the local cure. In five of these patients and also in two of the patients who were treated conventionally, the cobalt-60 therapy was interrupted prematurely, and treatment was completed by an implant, a technique which is often used here. One year after the trial closed, the series was analysed for initial complete healing of primary and secondary lesions, for survival after one, two, and three years, and for subsequent recurrences at the primary site.

For comparison, two similar series of patients were selected. One series comprised the first 52 patients, who were treated by radiotherapy with hyperbaric oxygen therapy over a two-year period. This series was then analysed as above. Unfortunately for these patients, these simple parameters are quite sufficient to show up most of the natural history of this gruesome disease. The patients received an average of 3500 rads at an oxygen pressure of 303 kPa in seven fractions given twice a week, the range being 3000 rads to 3850 rads.

The third series was of 52 consecutive patients who were treated by supervoltage therapy alone, before 1970. In this series, the patients received an average 6000 rads in six weeks, the range being 4800 rads to 6600 rads.

In each of the series, there was one advanced case, where the patient became too ill to complete the planned course of treatment. Table 1 compares the anatomical site of the primary disease, and the clinical stages in the series treated by conventional supervoltage (SVT), hyperbaric oxygen and cobalt-60 (HBO), and very high frequency radiation and cobalt-60 (VHF). There is a disparity in the number of patients with pyriform fossa tumours, but the results of these cases were quite similar to those of the whole group. There is a slight disparity of gland involvement, which is related to the differences of site involvement. However, the classification into advanced group at the different times was performed by the same three senior radiotherapists.

TABLE 1
Composition of Three Series

Primary Site of Tumour	Number of Patients		
	SVT (n=52)	HBO (n=52)	VHF (n=52)
Salivary gland	2	4	1
Sinuses or ear	2	0	5
Nose or nasopharynx ..	4	3	2
Palate	2	6	6
Tonsil	9	5	9
Tongue	6	10	5
Mouth	4	4	5
Pharynx	8	6	10
Larynx	6	7	7
Pyriform fossa	9	7	2
Patients with involved glands	31	37	28
Advanced primary T2, T3, T4 or recurrent	49	49	49
T3 or T4 (primary) stage ..	26	23	26
N2 or N3 (glands) stage ..	23	26	20

The microwave apparatus which was used is described by Holt,⁹ but a single radiator was applied to some tumours directly. The electromagnetic field which is reflected from the twelve radiating aerials within the barrel-shaped head has been shown experimentally to heat a phantom composed of material equivalent in electrical properties to human tissue. The rise in temperature in a solid block, 12 cm in diameter, was uniformly distributed and was 4°C in 10 minutes. The absorption of energy depends on the dielectric coefficient of the absorber, and the amount absorbed varies greatly with particular different materials or tissues. The rise in temperature in human tumours has been measured with a specially designed thermocouple

probe, and up to 42.5°C has been recorded at the end of a treatment, and the cooling effect of the bloodstream was noted. No distressing effects or evidences of damage by hyperthermia occurred in this series of patients.

RESULTS

The results are interesting. According to every parameter, the combined microwave treatment was two or three times better than conventional treatment, and hyperbaric oxygen therapy was intermediate in value. Complete healing and disappearance of tumour masses occurred after treatment in 94% of VHF-treated, in 62.5% of HBO-treated, and in only 36.5% of SVT-treated patients. Over the first three years of the records of each series, 19 VHF-treated patients died, but 29 HBO-treated patients and 36 SVT-treated patients also died. It is significant that of the 19 VHF-treated patients who died, only five died from local disease, while 24 of HBO-treated patients and 31 of SVT-treated patients died from advance of uncontrolled local disease. Seven other VHF-treated patients died of metastases with local disease healed and seven died from unrelated causes. Two HBO-treated patients died of metastases and three of unrelated causes. For SVT-treated patients, these numbers were three and two respectively, and this illustrates again that far fewer patients have survived the malignant local effects of the cancer. The figures illustrate that the patients who were treated were suffering from a severe and advanced disease, and we are also reminded that local cure does not insure against later distant deposits.

When local recurrence occurred in any series, it was treated by the best salvage method available to a combined consultative unit, with some successes. However, the efficiency of the treatment of cancer of the neck by the initial method is demonstrated in Figure 1, which shows the percentage of cases becoming free of persistent disease and remaining free of any subsequent local recurrence at the end of each year. Thus, after one year, 79% of patients treated by VHF were still completely healed, but only 38.5% of HBO-treated and 21% of SVT-treated patients did not have persistent or recurrent disease. After three years, 60% of VHF-treated patients had remained free of disease, but only 8% of SVT-treated patients had not had

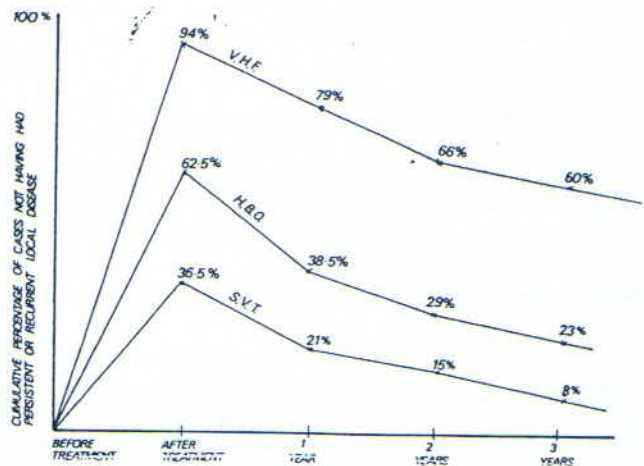


FIGURE 1

persistent or recurrent local disease. The cases are scored on this graph by the appearance of disease, irrespective of whether they subsequently died or were successfully salvaged. During the third year after treatment, there were four local recurrences in SVT-treated patients and three in HBO-treated patients. By

this time, there were roughly equal numbers at risk but only one recurrence occurred in a VHF-treated patient.

The crude survival is demonstrated year by year in Figure 2. At two years, 64% of VHF-treated, 36.5% of HBO-treated, and only 29% of SVT-treated patients were alive. The ultimate fate of nearly all SVT-treated and HBO-treated patients is known, but the VHF series is more recent. All 52 patients

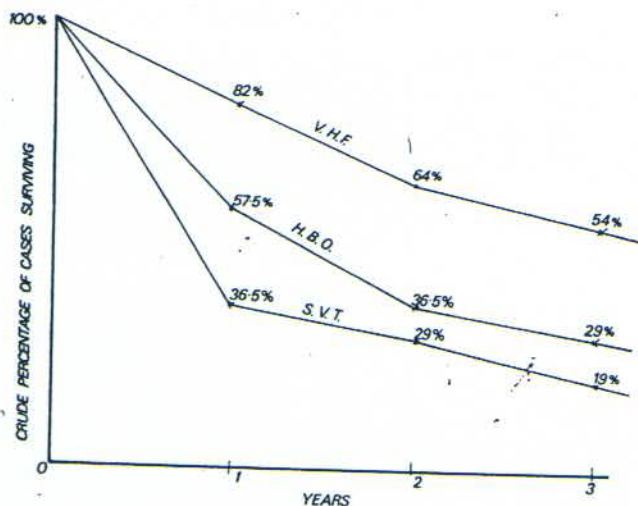


FIGURE 2

were followed up for the one year survival rate, and 39 patients were available at two years. So these results are quite reliable. Eleven of VHF-treated patients were followed up at three years. Six of them are alive and well, and five are dead. We consider that the comparison of three-year survival of 54% VHF-treated, 29% HBO-treated, and 19% SVT-treated patients is valid, because the curves of all graphs are consistent and, moreover, the present clinical status of those patients who have not yet reached the three-year review date is remarkably healthy. Even if one-third of them die this year, the figure will be unchanged, and it will remain about double or triple the survival rate of the other two series. In these particular diseases, to be able to survive the first year is quite an achievement for the patient. The one-year survival rate was 82% for VHF-treated, 57.5% for HBO-treated, and 36.5% for SVT-treated patients, an advantage factor of 2.3 times for the combined microwave treatment.

Elimination of non-cancer deaths would make an even greater contrast in the survival rates at each stage. We find these differences quite striking and significant. Microwave hyperthermia appears to be a superior and effective adjuvant to treatment with ionizing radiation for advanced cancer of the ear, nose and throat group. The results would justify a planned prospective trial. For this purpose, the clinical problems in the use of hyperthermia were recently reviewed by Nelson and Holt.¹⁰ Theoretical aspects of microwave and, in particular, the place of 434-MHz radiation have been presented by Holt.¹¹ The design of any trial should be to test the adjuvant effects to conventional therapy by 434-MHz radiation.

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ADDENDUM

Since the submission of this paper, 48 further cases have been treated. In 95 out of the 100 cases there has been complete disappearance of the primary and secondary glands at the end of treatment. One third of these cases were massive recurrences from previous surgery or radiotherapy. The rate of survival of the patients treated by combined microwave therapy seems to have been maintained. Our case histories have recently been examined by Professor Caldwell from Madison University, Wisconsin, who personally examined most of the 32 patients who still remain alive from the 52 patients quoted in our article.