Urol Res (1988) 16:1–7

Urological Research

Local Microwave Hyperthermia in Treatment of Advanced Prostatic Adenocarcinoma

S. Szmigielski[1], H. Zielinski[2], B. Stawarz[2], J. Gil[2], J. Sobczynski[2], G. Sokolska[1], J. Jeljaszewicz[3], and G. Pulverer[4]

[1] Center for Radiobiology,
[2] Department of Clinical Urology, MMA Postgraduate Medical School,
[3] National Institute of Hygiene, Warsaw, Poland, and
[4] Institute of Hygiene, University of Cologne, Cologne, Federal Republic of Germany

Accepted: July 1, 1987

Summary. Fifteen patients with advanced (T_{3-4}, N_{x-2}, M_{0-1}) prostatic adenocarcinoma were treated with local microwave hyperthermia (LMwH) applied as the sole method of therapy (automatically controlled set generating 2,450 MHz microwaves with intrarectal applicator). All patients were monitored with a battery of tests, including USG image and volumetry of prostate, bone scintigraphy, serum alkaline phosphatase and serum level of PAP. LMwH sessions were well tolerated and did not cause pain except a moderate sensation of heating in the pelvic region. 8 of these 15 patients responded to the therapy (3x complete remission and 5x partial remission). Involution of the prostatic tumor in responders was accompanied by improvement of the general clinical and urological state. In two responders bone metastases, documented scintigraphically before therapy, disappeared. 7 patients did not respond to LMwH, mostly patients with very large primary tumors.

Key words: Prostate cancer – Hyperthermia – Microwaves

Introduction

Selective heating of neoplastic cells to 43–45 °C causes all deaths without a significant damage of the surrounding normal tissues (for most recent monographs and reviews, see [2, 10, 18, 25]). The differences in thermal sensitivity between normal and neoplastic cells are in fact small [14], but the more sluggish blood supply of most neplastic tumors and their weaker thermoregulation allow the heating of tumorous tissues to temperatures exceeding 3–6 °C of those obtained in surrounding areas [10, 11]. Clinical benefits arising from local microwave hyperthermia (LMwH) of solid tumors are at present well established [2, 15, 16, 20] and only the technical problems associated with controlled heating of deeply located tumors limit the wider use of hyperthermic techniques in clinical oncology [3]. Therefore, the use of LMwH is restricted to superficially located tumors [1, 6] and most of the valid clinical trials with LMwH are directed towards the treatment of locoregionally advanced or recurrent breast cancer, tumors of the neck region and skin neoplasms, including melanoma [1, 13, 25]. The recent introduction of intracavity applicators matched for certain microwave frequencies (mainly for 2,450 MHz, 915 MHz or 434 MHz [6, 7, 13, 17]) allows their intrarectal or intravaginal introduction and interstitial heating of colorectal, prostatic and cervical neoplasms. Surprisingly, in the literature available we could not find references on the use of LMwH in the treatment of advanced prostatic neoplasms [5], except of preliminary data of Yerushalmi et al. [26] claiming encouraging results after intrarectal heating with a 915 MHz radiation.

We describe the effects of LMwH treatment in 15 patients with very advanced prostatic adenocarcinoma, in a Phase I clinical study. For intrarectal interstitial LMwH of the prostate we designed and constructed an original applicator matched for 2,450 MHz microwave radiation [7, 8]. After successful tests with intrarectal heating in pigs reaching temperatures of 47–48 °C at the surface of rectal musa [21, 22] the applicator was employed for preliminary clinical studies in patients with rectal adenocarcinoma. Because of good tolerance and absence of side-effects in this pilot group of patients, the applicator was used for LMwH in patients with advanced prostatic adenocarcinoma. LMwH applied alone is of limited value in the treatment of advanced neplasms [15], therefore this technique should always be combined with other forms of anticancer therapy, as reported with radiotherapy [1, 11, 33]. Nevertheless, before the trials on combined treatment it seemed desirable to test the safety and efficacy of LMwH in patients with prostatic neoplasms.

Table 1. The scales for evaluation of general clinical state and urological state of patients

Grade	Karnovsky-Index	Criteria
General clinical state		
0	> 90	Excellent clinical condition, no complaints, normal body weight, no pain, normal test results
1	70–90	Good condition, temporary local (limited to tumor region) pain without need for analgesics, body weight normal or slightly (5–10%) lowered, normal or slightly changed results of laboratory tests
2	60–80	Weakness, frequent pain with temporary need for analgesics, lower (10–15%) body weight, slight anemia, abnormal laboratory tests without marked hypoproteinemia
3	50–70	Marked weakness with only temporary improvement, progressive loss of weight, markedly lowered (25–30%) body weight, frequent pain with permanent need for analgesics, anemia, abnormal laberatory tests with hypoproteinemia and increased serum alkaline phosphatase
4	< 50	Cancerous cachexia, no apetite, strong and very frequent pain with continous need for analgesics, highly elevated serum alkaline phosphatase, blood protein and ion abnormalities
Urological state		
0		No urologic complaints
1		Periodic, transient dysuria, frequent urination without symptoms of residual urine
2		Permanent dysuria, intensified frequent urination during day and night, need for periodic catheterization of urinary bladder, residual urine in bladder
3		Urinary retention, permanent catherization, symptoms of upper tract obstruction

Materials and Methods

Patients

15 patients, aged 58–78 years, hospitalized at the Department of Clinical Urology MMA Postgraduate Medical School in Warsaw, were selected for this study. 2 to 3 years earlier prostatic adenocarcinoma was diagnosed in all patients and proved histologically they were treated with adenomectomy/electroresection, orchiectomy, hormonotherapy or cryosurgery, according to indications. Three patients with very advanced neoplasms were qualified for LMwH without any former therapy. In all cases former therapy was completed at least 6 months before LMwH and clinically the disease was diagnosed as progressing. All patients were acquinted with principles, risks and possible benefits of LMwH therapy and volunteered for the treatment.

Evaluation of Local and General Clinical State

Before LMwH all patients were monitored. Similar criteria were later used for the monitoring of effects of this therapy. General clinical and urological states were evaluated according to arbitrary 5-grade and 4-grade scales being in use at the Department of Clinical Urology (see Table 1).

Urological Symptoms (Table 1) included difficulties in urination, frequent urination, the need for catheterization and residual urine in bladder and upper tract dilatation were taken into consideration, giving a reasonably good picture of the local acvancement of prostatic adenocarcinoma.

USG images of prostate were analysed in all patients and in most of them tumor volume was determined. For USG investigations the device type 1846 (Bruel and Kjaer, Denmark), operating in the real time system, was used. The rotatory applicator generating 4 MHz at 90° was introduced intrarectally. Volume of prostate was computerized as a sum of volumes of serial 5 mm layers of the prostate. Serum prostate acid phosphatase (PAP) levels were evaluated with RIA kits (ABBOTT, FRG). Normal PAP-levels were established on the base of data in healthy persons for 2 mg/l, results exceeding this limits by at least 15–20% were counted as elevated. For alkaline phosphatase "normal" level was accepted as being below 85 IU/ml. In all patients scintigraphy of skeleton was performed for the diagnosis of bone metastases.

Hyperthermic Devices

LMwH sessions were performed with automatically controlled set generating 2,450 MHz microwaves and with original intrarectal applicators matched for this frequency. The technical details of this equipment are described elsewhere [7, 8]. Technical diagram of the set is presented on Fig. 1 and a general view of applicator and the whole set on Fig. 2.

Briefly, the applicator radiates 2,450 MHz microwaves only from a 4-cm distant part and special chokes protect against leakage of radiation from other parts of the applicator. Microwaves may be emitted from the distant part either circularly or sectorally (90 or 180°), depending on the type of applicator. This allows the heating of either the whole material (tissues) surrounding the applicator or of only one side (e.g. the side directed towards prostate). The applicator is connected to a generator producing continuous waves (CW) of 2.450 MHz via a matching regulator and power indicator (to measure power generated and power reflected). Miniature thermistors YSI400 (needle-shaped) are introduced into the heated area (e.g. in the prostatic tumor) and the temperature is fixed for a predicted level (43.5 °C). The generator is switched on, microwaves are radiated from the applicator and heating of tissue starts. As soon as the predicted temperature is reached and registered by the thermistor the power is automatically switched off until the temperature decreases by 0.1–0.2 °C, when power is again generated to heat the

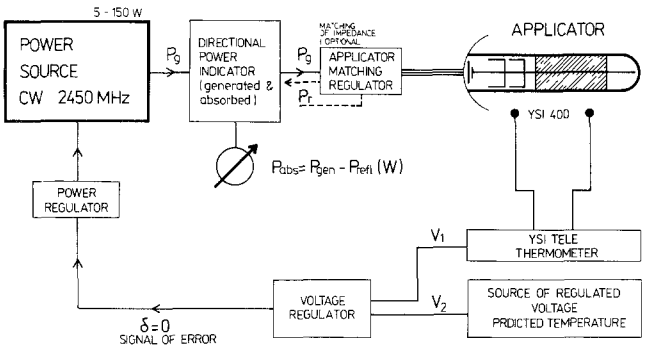

Fig. 1. Diagram of the automatic set for microwave hyperthermia of prostate. The 2,450 MHz set operates with the use of intrarectal applicators

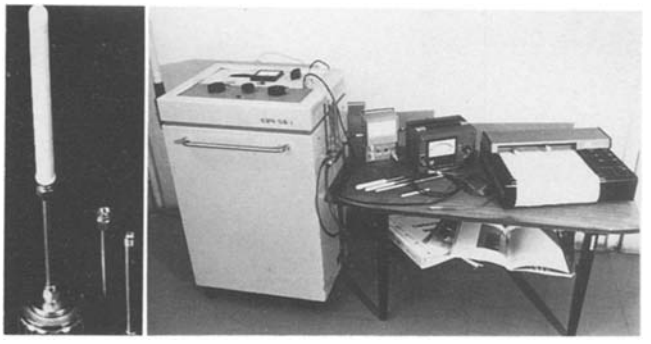

Fig. 2. Devices used for intrarectal hyperthermia of prostatic neoplasms. Note different sizes of intrarectal applicators (designed and constructed by Dr. P. Debicki, Department of Microwave Technics, University Technical School, Gdansk, Poland)

tissues up to the predicted temperature. In practice, the predicted temperature of 43.5 °C in prostatic tumor, where the leading thermistor was introduced, was reached in 1–2 min and later maintained automatically at this level for 30 min.

LMwH Session and Scheme of Therapy

For every LMwH session the patient was placed on a wooden table, a dorsal position with flexed legs. After intrarectal palpation of the tumor a needle thermistor was introduced into the tissue to be treated to a depth of 1–1.5 cm (marked on the thermistor). Next, the applicator was introduced intrarectally to face the thermistor. A second thermistor was introduced superficially in the rectal mucosa. A predicted temperature for the leading thermistor whithin the prostatic tumor) was fixed at 43.5 °C and the generator was switched on. From this moment the LMwH session run automatically for 30 min.

The scheme of therapy contained a total of 6 sessions of LMwH for each patient. The treatment was divided into two sets of three sessions each with a 4-week break between. In each set the LMwH sessions were applied every 3rd day (twice weekly) to avoid the phenomenon of thermotolerance [9, 19] which might lower the sensitivity of neoplastic cells to elevated temperatures.

Assessment of the response to LMwH therapy was based on reactions of the heated primary tumor (CR = complete remission; PR = partial remission, lowering of tumor size above 50%; SD = stable disease; PD = progressing disease), state of metastases (no metastases before and after therapy; stable metastases; spread or disappearance of metastases), improvement of clinical and urological symptoms and serum levels of phosphatases (Table 2). *Responders* to LMwH had an objective CR or PR with improvement of clinical and urological symptoms by at least one grade on the scales (Table 1) and no spread of metastases, *or* stable primary tumor with predomination of improvement of clinical and urological state and no spread of metastases during the whole period of observation. *Non-responders* did not have objective reactions from the heated primary tumor (e.g. stable primary tumor without detectable improvement of urologic state or progressing tumor) with stable or spreading metastases.

Results

General and Local State of Patients Before LMwH Therapy

All the data concerning general and local state, progression of disease and results of biochemical tests are presented in Table 2. Despite locally advanced prostatic cancer (10 patients with T_3 and 5 patients with T_4) the general clinical state was reasonably good and expressed as 2° or 3° at a 5-grade scale (60–80 Karnovsky index). The urologic state was established as 2–3 in a 4-grade scale. This means that all patients had continuous outflow symptoms or urinary retention requiring catheterization. Tumor (prostate) volume, evaluated from serial 5 mm USG images in 11 patients varied from 16.4 to 171.9 cm^3 with predominating values of 30–70 cm^3. Elevated PAP levels were found in 7 patients without relation to tumor volume or to the presence of metastases. Bone metastases were documented scintigraphically in 7 patients, while elevated levels of alkaline phosphatase in 9 cases.

Tolerance of LMwH Therapy

All in all 90 LMwH sessions were performed in 15 patients. The sessions were tolerated and did not cause pain, although a sensation of heating in the pelvic region was usual. There was no need to stop LMwH sessions because of discomfort and all patients received the scheduled 6 sessions. Routinely before and after every LMwH sessions a short endoscopic examination of the rectal mucosa was done. Out of 90 LMwH sessions only in three cases a moderate redness of the mucosa with mucous secretions over one to two days was seen, all the remaining sessions did not result in detectable changes of the mucosa. In these three cases of local overheating the rectal mucosa cured spontaneously before the next LMwH session (in 3–4 days).

Effects of LMwH Therapy

The observation period for seven patients lasted from 17 to 21 months, for three patients from 9 to 10 months and 6 months for five patients.

Table 2. Clinical state and effects of hyperthermic therapy in patients with advanced prostatic cancer

	Before hyperthermia								Effects of hyperthermic therapy										
											Oncologic evaluation[b]			PAP levels		Alkaline phosphatase		Bone[c] metastases		General evaluation
Patient No.	Initials	Age (years)	Clinical advancement	General clinical state[a]	Karnovsky index	Urological state[a]	Tumor volume (cm^3)	Period of observation (months)	Clinical improvement	Urological improvement	CR	PR	SD/PD	Before	After	Before	After	Before	After	Responders (+, ++) / Non-Responders (–)
1	AM	66	T_3 N_2 M_1	3	65	2	25,0	21	+++	++		+		37,9	1,1	178	104	++	–	+
2	KM	59	T_3 N_x M_1	2	75	2	38,5	18	++	++	+			1,5	0,8	95	101	++	–	++
3	HB	65	T_3 N_x M_0	2	70	3	28,9	19	++	++	+			2,4	0,6	118	88	–	–	++
4	JA	64	T_3 N_x M_0	2	75	2	16,4	18	++	++	+			1,4	0,7	64	45	–	–	++
5	JF	58	T_3 N_x M_0	2	80	2	17,5	18	+	+		+		1,0	1,4	58	106	–	–	+
6	SH	73	T_4 N_x M_0	3	55	3		9 (died)	0	0			++	0,8	3,5	305	480	–	+	–
7	ES	68	T_4 N_x M_0	3	65	3	49,2	17	+	+		+		15,5	7,6	208	246	++	++	+
8	JW	72	T_4 N_x M_1	2	75	3		19	+	+			+	2,4	15,4	276	420	+++	+++	–
9	AS	67	T_4 N_2 M_1	3	60	2	50,1	10	0	0			++	4,0	12,9	213	436	++	+++	–
10	KS	74	T_3 N_x M_1	3	60	3	70,0	9	0	+			+	18,0	12,4	296	360	++	++	–
11	BJ	78	T_3 N_x M_0	3	70	3	171,9	6	0	0			+	34,1	25,0	290	426	–	+	–
12	ZW	68	T_3 N_x M_0	2	80	3		6	0	0			+	3,6	2,4	168	128	–	–	–
13	ZM	65	T_3 N_x M_0	1	90	2		6	0	0			+	3,3	3,2	73	93	–	–	–
14	EZ	75	T_4 N_x M_1	3	65	3	65,3	6	+	+		+		2,5	2,3	79	75	+	+	+
15	JH	68	T_3 N_x M_0	2	75	1	32,5	6	0	+		+		0,5	0,6	81	101	–	–	+

[a] see Table 1 for the scales and grades

[b] CR = complete remission of the primary tumor; PR = partial remission, lowering of tumor mass by more than 50%; SD = stable tumor; PD = progressing disease

[c] – = no detectable metastases; + = single bone metastase; ++, +++ = multiple bone metastases

PAP = serum prostate acid phosphatase

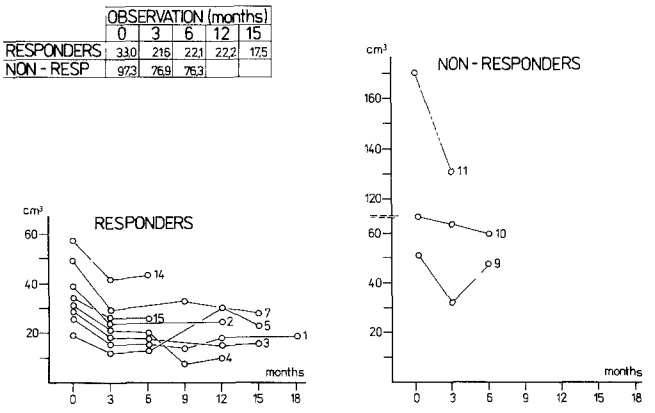

Fig. 3. Tumor (prostate) volumes in patients responding and non-responding to local microwave hyperthermia. Measurements of prostate serial (0.5 cm) USG images from the device type 1846 (Bruel and Kjær, Denmark)

Table 3. Serum prostate acid phosphatase (PAP) levels before and after hyperthermic therapy of advanced prostatic cancer

Serum PAP levels		Responders (n = 8)	Non-responders (n = 7)
before therapy	after therapy		
Elevated (above 2 mg/l)	Normal (below 2 mg/l)	2	0
Elevated	Elevated	2	6
Normal	Elevated	0	1
Normal	Normal	4	0

Table 4. Metastazing of advanced prostatic cancer treated with local microwave hyperthermia

	Responders 8 cases N° 1, 2, 3, 4, 5, 7, 14, 15	Non-responders 7 cases N° 6, 8, 9, 10, 11, 12, 13
Disappearence of bone metastases	2 (1, 2)	0
Stable metastases	2 (7, 14)	2 (8, 10)
Spread of metastases	0	3 (6, 9, 11)
No metastases before and after	4 (3, 4, 5, 15)	2 (12, 13)
Total	8	7

One patient (No. 6, Table 2) died 9 months after completing LMwH therapy because of progressing disease and spread of metastases, the remaining 14 patients are still alive. Analysis of final results (Table 2) and kinetics of the response to LMwH therapy (Fig. 3, Tables 3, 4) revealed that the 15 patients treated with LMwH therapy can be divided into responders (8 cases) and non-responders (7 cases). Tumor volume (Fig. 3) diminished during the first 3 months after completion of LMwH therapy in all responders and in three of 7 non-responders (temporary). It should be noted that responders had initially smaller tumors (mean volume 33 cm^3), while non-responders showed a much larger prostatic volume (mean 97,3 cm^3) (Fig. 3).

Serum levels of PAP were not very valuable for the assessment of tumor response in this group of patients (Table 2). As it was mentioned before, most of our patients had initial PAP levels close to normal values and only in 4 patients (Nos. 1, 7, 10 and 11) were the PAP values very high. After LMwH therapy in the group of responders (8 cases) in two patients elevated PAP decreased to normal value. On the other side, among non-responders normalization of initially elevated PAP levels were not found (Table 3). The results of scintigraphic evaluation of bone metastases before and after LMwH therapy are presented in Table 4. Among the 8 responders in two cases (patients No. 1 and 2) metastases, documented prior to LMwH, disappeared after 12 and 18 months, respectively. In two patients (Nos. 7 and 14) stable metastases were observed 12 and 6 months after completing LMwH therapy, while in the remaining four responders no metastases could be diagnosed before and after LMwH (Table 4). Among the 7 non-responders in three cases a spread of metastases was observed.

Discussion

The introduction of intrarectal applicators (matched for certain microwave frequencies) allows interstitial heating and the application of LMwH in the therapy of advanced prostatic neoplasms. We used 2,450 MHz microwaves as a source of thermal energy [3]. 2,450 MHz penetrate biological tissues only to a depth of 3–4 cm, where an effective and relatively uniform heating is possible. In our hands LMwH using 2,450 MHz microwaves was safe which was well tolerated by patients. LMwH therapy resulted in positive responses in 8 out of 15 patients, the remaining seven cases demonstrated no measurable improvement. It may be significant that non-responders had larger tumors than did the responders. The limited penetration of 2,450 MHz microwaves prevents the effective heating of the periphery of large tumors. Thus, in patients with large prostatic tumors only those tumor parts, which are close to the radiating applicator, can be heated to the predicted temperature of 43–44 °C, while in parts further from the applicator temperatures below 42 °C, which is a critical temperature for thermal destruction of neoplastic cells will occur. This problem can be theoretically solved by the use of lower frequencies of microwaves, e.g. 434 MHz, which penetrate deeper into biological tissues and can provide an effective heating at a depth of 10–15 cm [3]. However, the construction of intracavital applicators at 434 MHz for intrarectal introduction is much more complicated technically at 434 MHz and no good model exists which is applicable for LMwH. At the present state of technical advancement

of hyperthermic techniques, the interstitial heating of prostatic tumors using intrarectal applicators matched for 2,450 or 915 MHz microwaves offers the best possibility for an effective LMwH therapy. In the present study we have established the scheme for LMwH therapy in two sets of three sessions of LMwH lasting 30 min each with a 4-week break between. Single LMwH sessions in the set were applied every 3rd day (twice weekly). The applied scheme of therapy is similar to those used by other authors for the therapy of superficially located tumors [1, 6, 10, 16] and was established to avoid the phenomenon of thermotolerance [9, 19]. The phenomenon of thermotolerance is transient, its maximum occurs between one and two days and disappears in a few days [9].

However, the kinetics of thermotolerance depend on the thermal load applied for the initial treatment [19]. These observations lead to the practical conclusion that a time interval of 72–96 h should be taken between LMwH sessions and thus, in clinical practice the hyperthermia sessions should be routinely run twice weekly with a total number of sessions not exceeding 3–4 in one set.

Analysing the results obtained after the application of LMwH therapy in patients with advanced prostatic adenocarcinoma, one should remember that treatment in advanced, metastatic neoplasms is still directed towards prolonged survival and not towards a total cure. In this context, three out of 15 patients treated with LMwH with a complete remission lasting for at least 1.5 years and with disappearance of bone metastases in two cases look encouraging. More than half of these patients benefited from the improvement in general clinical state, the disappearance of pain and relief of bladder outflow obstruction. These results strongly suggest that LMwH may be useful in palliative treatment of advanced prostatic cancer, where other forms of therapy have already failed. It is at present well established that hyperthermic treatment enhances the sensitivity of neoplastic cells to X-rays [11, 18] and may help to kill parts of neoplastic cells which are relatively resistant to ionizing radiation, e.g. hypoxic cells or cells existing in low pH or nutrient-deficient environment [2, 10]. LMwH is a safe procedure and it may be combined with radiotherapy for the treatment of T_1–T_2 prostatic adenocarcinoma [2]. LMwH of prostatic cancer may also be combined with other anticancer modalities, for example with immunomodulating substances [23, 24]. Modern strategies for the treatment of advanced neoplasms should combine the application of different cytoreductive modalities with a variety of immunomodifyers (e.g. thymomimetic substances, antisuppressor therapy, non-specific and specific immunotherapy) [4, 12]. Recently our group has started a clinical trial (Phase I/II) in combining LMwH with a potent macrophage-activator and interferon-inducer – *Propionibacterium granulosum* KP-45 [23]. One group of patients with advanced prostatic carcinoma was treated with LMwH applied alone, as in the present study, while in the other group LMwH was combined with intratumor injections of *P. granulosum* KP-45 (thermoimmunotherapy). The number of responders was higher in patients treated with thermoimmunotherapy as compared to those treated with LMwH alone. These findings suggest that a proper combination of LMwH with other anticancer modalities may significantly increase the chance of complete remission in patients suffering from advanced prostatic neoplasms, but further investigations and a wider use of hyperthermic techniques in urological oncology are still needed.

Acknowledgements. The present authors highly appreciate the cooperation of Dr. Piotr Debicki and his team of the Department Microwave Technics, Technical University School in Gdańsk, who designed and constructed the applicators and hyperthermia set applied in this study.

This work was supported by the Research Grant CPBR 11.5.23 from the National Oncological Center in Warsaw, Poland.

References

1. Arcangeli G, Guerra A, Lovisolo G, Cividalli A, Marin C, Mauro F (1985) Tumor response to heat and radiation – prognostic variables in the treatment of neck node metastases from head and neck cancer. Int J Hyperthermia 1:207–211
2. Anghileri NJ, Robert J (1986) In: Hyperthermia in cancer treatment, vols 1–3. CRC Press Inc, New York
3. Cheun A, Samaras G (1981) Hyperthermia for cancer therapy. J Microwave Power 16:85–106
4. Chirigos MA, Talmadge JE (1985) Immunotherapeutic agents: their role in cellular immunity and their therapeutic potential. Springer Semin Immunopathol 8:327–341
5. Chisholm GD (1985) Treatment of advanced cancer of the prostate. Semin Surg Oncol 1:38–49
6. Cosset JM (1985) Interstitial techniques. In: Overgaard J (ed) Hyperthermic oncology, vol 2. Taylor and Francis, London Philadelphia, pp 309–326
7. Dębicki P, Holowacz J (1984) Intracavital applicators for 2,450 MHz microwave interstitial hyperthermia-theory, construction and biological tests. Technical Report 03/84, Departments of Microwave Technics, University Technical School, Gdańsk, Poland, pp 1–62
8. Dębicki P, Holowacz J (1985) Automatic set for 2,450 MHz hyperthermia (ZUHM-1) using intracavital applicators for interstitial heating of prostatic and rectal tumors – technical data, construction, instruction for users. Technical Report 05/85, Department of Microwave Technics, University Technical School, Gdańsk, Poland, pp 1–36
9. Field SB, Anderson RL (1982) Thermotolerance: a review of observations and possible mechanisms. Natl Cancer Inst Monogr 61:193–196
10. Gerweck LE (1985) Hyperthermia in cancer therapy. The biological basis and unresolved questions. Cancer Res 45:3029–3032
11. Gillette EL (1984) Clinical use of thermal enhancement and therapeutic gain for hyperthermia combined with radiation or drugs. Cancer Res 44:4836–4841
12. Hadden JW, Spreafico F (1985) New strategies of immunotherapy. Springer Semin Immunopathol 8:321–333
13. Hand JW, Hind AJ, Cheetham JL (1985) Multielement microwave array applicators for localized hyperthermia. Strahlentherapie 161:535–539
14. Jung J (1986) A generalized concept for cell killing by heat. Radiat Res 106:56–59
15. Meyer JL (1984) The clinical efficacy of localized hyperthermia. Cancer Res 44:4745–4748

16. Nussbaum GM (1984) Quality assessment and assurance in clinical hyperthermia: requirements and procedures. Cancer Res 44:4811–4815
17. Oshiumi Y (1984) Intrarectal hyperthermia of circumferential rectal cancer – report of 2 cases. Radiat Med 2:265–268
18. Overgaard J (1985) Hyperthermic oncology, vols 1 and 2, Taylor and Francis, London Philadelphia
19. Overgaard J, Nielsen OS (1983) The importance of thermotolerance for the clinical treatment with hyperthermia. Radiother Oncol 1:167–171
20. Suit HD (1982) Potential for improving survival rates for the cancer patient by increasing the efficacy of treatment of the primary lesion. Cancer 42:453–458
21. Szmigielski S (1985) Biological testing in pigs and preliminary tests of clinical tolerance of intrarectal hyperthermia using prototypes of intracavital applicators and the automatic set for 2,450 MHz microwaves. Final Report of Research Project PR-6-2122, National Institute of Oncology, Warsaw, Poland, pp 1–46
22. Szmigielski S, Dębicki P, Sokolska G (1984) Intracavital applicator for 2,450 MHz hyperthermia of prostatic and colorectal tumors. Abstracts, Sanrocco 1984, International Symposium "Hyperthermia in Cancer Treatment", Como-Menaggio, Italy, 8–13 April, pp 18–19
23. Szmigielski S, Jeljaszewicz J, Pulverer G (1987) Thermoimimmunotherapy of advanced neoplasms – a concept and preliminary results. Biomed Pharmacother 41:132–138
24. Szmigielski S, Zaboklicki S, Gil J, Jeljaszewicz J, Pulverer G (1984) Inhibition of Lewis lung carcinoma in mice by local microwave hyperthermia combined with immunomodulating Propionibacterium granulosum KP-45. Cancer Immunol Immunother 16:151–156
25. Vaeth JM (1984) Hyperthermia and radiation therapy/chemotherapy in the treatment of cancer. Karger, Basel New York
26. Yerushalmi A, Fischelovitz Y, Singer D, Reiner I, Shani A (1985) Localized deep microwave hyperthermia in the treatment of poor operative risk patients with benign prostatic hyperplasia. J Urol 133:873–879

Prof. Dr. Stanislaw Szmigielski
Department of Biological Effects of Non-Ionizing Radiations
Center for Radiobiology and Radiation Safety
128 Szaserow
PL-00909 Warsaw 60
Poland