

# Cancer Outcomes at the Hufeland (Complementary/Alternative Medicine) Klinik: A Best-Case Series Review

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**Purpose:** A best-case series review is an efficient tool with which to screen complex complementary and alternative treatments for cancer as candidates for further study. **Study Design:** The National Cancer Institute and other agencies have adopted the best-case series method to evaluate cancer treatments involving complementary and alternative medicine (CAM) for further study. The authors conducted a best-case series review of the Hufeland Klinik. Established in 1985 in Bad Mergentheim, Germany, this facility treats more than 500 cancer patients per year. Hufeland treatment includes dietary modification, injections, ozone therapy, active fever therapy, psychotherapy, and sometimes hormone therapy and/or low-dose chemotherapy. The goal of the treatment is to prolong survival and to maintain good quality of life. **Methods:** The clinic provided summaries of 27 cases in which patients with longer than expected survival had agreed to make their medical records available for review. The review involved pathologic confirmation of disease and radiologic confirmation of complete response (CR) or partial response (PR) not attributable to conventional treatment. **Results:** Based on the summaries and an exhaustive 2-year search for medical records, slides, and imaging data, 12 of 27 cases were selected for full review, and 5 (3 CRs and 2 PRs) were judged best cases. **Conclusion:** Most patients with common cancers receive conventional treatment before coming to Hufeland, and many are treated with chemotherapy and/or hormonal therapy while there. Hence, only a few could be considered for review. **With 5 of 12 patients showing a treatment response, the authors conclude that the Hufeland treatment merits further study.** They also recommend the development of criteria with which to evaluate best-case series reviews of complex CAM treatments for patients with advanced cancer.

**Keywords:** cancer; best-case series; complementary; alternative; holistic; complete response; partial response; survival

In the past decade, support for research on complementary and alternative medicine (CAM) for cancer has grown dramatically, and numerous clinical trials of

herbal agents and specific CAM procedures have been undertaken or completed. The most successful candidates for research funds have been investigators who proposed studies of standardized single-modality interventions for which conventional research methods are well suited. Claims regarding the benefits of complex treatments customized to each patient are more difficult to evaluate. Many cancer clinics outside the United States provide such treatments, especially to patients who have failed to benefit from conventional treatment.

Few providers at CAM cancer clinics have research training or even a reliable charting system,<sup>2</sup> but some are willing to allow outside investigators to study their treatments and results. Because conventional clinical research methods cannot be readily applied to the assessment of most CAM cancer clinics, the best-case series method has come into use to identify those facilities whose patients might have fared better than expected and to evaluate them as candidates for further study.<sup>3</sup>

First proposed by the Office of Technology Assessment in 1990, the best-case series method was adopted by the National Cancer Institute (NCI) in 1991 for preliminary evaluation of complex CAM cancer therapies for which claims of efficacy were made. The NCI Office of Cancer Complementary and Alternative Medicine Web site publishes the guidelines "The Preparation of Best Case Series and the Conduct of Pilot Clinical Trials Using CAM Modalities."<sup>4</sup> The

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guidelines allow practitioners to select for review any cases that exemplify what their treatment can do for cancer patients and specify that every **best case must meet the following 4 entry criteria:**

- The diagnosis of cancer must be well documented.
- There must be evidence that cancer was present at the time the unconventional treatment was started.
- The patient must have received the unconventional treatment according to the alternative practitioner's regimen.
- The patient must not have received, recently or concurrently, another therapy with the potential to affect the disease.

**Best cases also must fulfill at least 1 of the following outcome criteria:**

- Complete response (CR): complete disappearance of all evidence of tumor for a set number of weeks.
- Partial response (PR): decrease by  $\geq 50\%$  in the sum of the products of the perpendicular diameters of all measured lesions in the absence of progression of any sites or the appearance of any new lesions for a set number of weeks.

Many cases proposed for a best-case series are those involving longer than expected survival based on data for age and stage from the medical literature or a population-based registry, such as the NCI's Surveillance, Epidemiology, and End Results database. However, although survival with good quality of life is the primary aim of cancer treatment, it is not interpretable as evidence of efficacy in an uncontrolled case series.<sup>5</sup>

In this report, we describe the results of our assessment of a best-case series submitted by Wolfgang Woepfel, MD, founder and director of the Hufeland Klinik in Bad Mergentheim, Germany, to the National Foundation for Alternative Medicine (NFAM). Since 1998, NFAM has been visiting clinics that use CAM and inviting them to submit best cases. Of some 60 clinics reviewed in the first 2 years of this program, the Hufeland Klinik was found to be the most rigorous in its record keeping. Hufeland also has an international reputation that draws patients from the United States as well as other countries. For those reasons, it was selected for review.

## Methods

### Review Procedure

The study was approved by the Columbia Presbyterian Medical Center Institutional Review Board. Dr Woepfel selected the cases for review, obtained in-

formed consent and permission to obtain medical records from the participating patients, and provided a summary of each case. The reviewers eliminated cases that, based on the summary, did not fulfill best-case criteria. For the remainder, in addition to reviewing the records on file at the Hufeland Klinik, we requested medical records including pathology slides and radiologic examinations from all the other institutions where the patient had received diagnostic assessment or cancer treatment. After document texts were translated into English, the cases were reviewed by the investigative team, including oncologists, pathologists, and radiologists at the Herbert Irving Comprehensive Cancer Center of the College of Physicians and Surgeons, Columbia University. The purpose of the pathology review was to confirm the cancer diagnosis of each case. Radiologists reviewed imaging studies in various formats to assess patients' status before and after the Hufeland Klinik treatment. The team then identified those cases that fit the best-case criteria.

### The Practitioner

Wolfgang Woepfel, MD, graduated from the medical school at the University of Wuerzburg (Bavaria, Germany) in 1971. Board certified in internal medicine (1978) and naturopathy (1984), he also studied acupuncture and neural therapy. From 1976 to 1982, he was a senior physician in the Department of Internal Medicine at Mosbach Regional Hospital (Baden, Germany). From 1982 to 1984, he worked with Josef M. Issels, MD, who developed and practiced a holistic approach to cancer therapy, at the Ringberg Klinik in Tegernsee, in the Bavarian Alps of Germany.<sup>6</sup> Dr Issels's theories and methods have greatly influenced alternative cancer treatment programs in Europe and Mexico.'

### The Hufeland Klinik

Established by Dr Woepfel in 1985, the Hufeland Klinik has treated more than 3000 inpatients and 500 outpatients and currently treats about 500 inpatients and 120 outpatients per year. The Klinik is located in Bad Mergentheim, a well-known health resort area famous for its mineral springs, in southwestern Germany near Heidelberg, Frankfurt, and Nuremberg.

Most patients who come to Hufeland have cancer. Hufeland treats all malignant diseases except acute leukemias, regardless of stage and prognosis. The Klinik also treats patients with some other diseases; it treats adults and children older than 5 years.

### The Philosophy

According to theories first described by Alfred Pischinger,<sup>8</sup> the body's most important systems (eg, the autonomic nervous system, hormones, blood and

lymph vessels, and connective tissue) comprise an interdependent network. Dr Woepfel views cancer as involving both cells and their interaction with this network, which constitutes their environment. Under conditions such as infection and psychological distress, the environment may cease to prevent cancer cells from proliferating. Under more favorable conditions, the environment may become conducive to apoptosis or redifferentiation of cancer cells. Treatment at Hufeland, therefore, does not primarily target the tumor, as conventional cancer treatment does, but focuses on the tumor's environment.

### **The Treatment**

Upon admission, each patient is examined by a physician and has an electrocardiogram, ultrasound imaging, routine laboratory studies, and, in some cases, a chest x-ray. Depending on the results of these studies, patients may receive the basic treatment alone or with fever therapy or conventional treatment.

### **Basic Treatment**

Basic treatment consists of the following.

*Biological treatment.* All patients receive daily subcutaneous or intramuscular injections of homeopathic agents, vitamins, and herbal agents and nonspecific immune stimulators (echinacea, "mistletoe, fresh thymus," and microbial extracts). Proteolytic pancreatic enzymes; probiotics (symbiotic intestinal bacterial flora supplements); vitamins A, C, E; and selenium are administered orally. Twice a week, patients receive ozone therapy (autologous blood is incubated with a mixture of oxygen and ozone and/or irradiated by ultraviolet light and then reinfused)<sup>12</sup> followed by an intravenous infusion. The intravenous infusion contains trace elements (magnesium, selenium, zinc), homeopathics, high-dose vitamins, and plant- or microbial-derived agents intended to eliminate toxins, alter metabolism, and stimulate the nonspecific immune system.

The basic program also includes dental work to eliminate mucosal pockets; dead, root-filled, or impacted teeth; and, if possible, amalgams.<sup>13</sup> If tonsils show signs of chronic inflammation, tonsillectomy is recommended."

Patients are also offered enemas, lime-blossom and other herbal teas, and herbal and homeopathic remedies. Patients with constipation or digestive problems are encouraged to drink from Bad Mergentheim's healing springs to activate bile flow and/or stimulate bowel movements.<sup>15</sup>

*Diet.* All patients follow a low-fat lactovegetarian diet high in vegetables and whole grains, with some

fruit. They are allowed (but not encouraged) to eat 1 serving of meat or fish per week. Frequent small meals are recommended for seriously ill patients. Patients are encouraged to avoid tobacco, caffeine, and alcohol.

*Physical therapy.* Nearly every day, patients receive hydrotherapy (cold water treatments and hot showers),<sup>16</sup> reflexology,<sup>17</sup> massages,<sup>18</sup> or special treatments with electric fields.

*Oxygen therapy.* For at least 2 hours each day, most patients inhale oxygen; they continue to do so after discharge.<sup>19</sup>

*Psychotherapy.* Dr Woepfel states, "Anyone for whom life is unconsciously a burden logically has no real reason to get well, and his autonomic nervous system is programmed for death." Therefore, Hufeland offers patients a variety of approaches to help reduce the undesirable stress in their lives. Dr Woepfel conducts weekly group hypnosis sessions to influence the unconscious and to support the patient's will to get healthy again. A psychologist and an art therapist offer individual and group therapy sessions. Other modalities include deep relaxation exercises, respiratory biofeedback, imagery, color therapy, group singing, and walks and hikes.

*Pain relief.* Hufeland emphasizes the importance of complete pain relief. Conventional analgesics, as well as acupuncture, therapeutic local anesthesia, infrared (warming) therapy, subcutaneous carbon dioxide injections, and physical therapy are used for pain relief.

### **Fever Therapy**

Patients who have no serious comorbid conditions may receive active fever therapy, in which Coley's toxins (bacterial lipopolysaccharides and other agents) are injected intravenously. Patients usually experience chills, nausea, vomiting, or headache within about 20 minutes, along with a slow rise in body temperature. The temperature should remain at 40°C or higher for several hours."

### **Conventional Modalities**

In addition, patients without comorbid conditions may receive surgery, chemotherapy, radiation therapy, or hormonal therapy. The goal of such treatment is not so much to destroy the tumor as to suppress it enough to allow the host to keep it under control. Hence, patients who undergo chemotherapy at Hufeland usually receive lower doses or a shorter course of treatment than they would under a conven-

tional protocol. Some patients receive chemotherapy along with passive hyperthermia by pulsed electromagnetic field to about 43°C, applied either locally (eg, to treat liver metastases, prostate cancer, or abdominal tumors) or to the whole body. Most patients with breast cancer or prostate cancer receive hormonal therapy.

## Results

Initially, Dr Woepfel submitted reports of 27 cancer cases. Based on these reports, we selected 12 cases for review. Table 1 lists the 12 cases that were reviewed. Of these, 5 met the criteria for best cases.

### Pathology Review

Table 2 compares the original histologic interpretation to that of the reviewing pathologist for each of the 12 potential best cases. In 6 of the 12 cases, the reviewing pathologist confirmed the original interpretation. In colon cancer case 1, the pathology reviewer's diagnosis differed from that in the original report regarding tumor type, but the differences were not relevant to prognosis.<sup>21</sup> In ovarian cancer case 1, the reviewer's diagnosis differed from the original regarding the site of origin and was more consistent than the original with the indolent course of the disease. In mediastinum cancer case 1, the reviewer's diagnosis also differed slightly from that in the original report regarding tumor type, but the material was obtained by bronchoscopy and was too limited in quantity for a firm histologic diagnosis.

In 3 of 4 brain tumor cases, the histologic diagnosis differed. For this reason, the brain tumor cases were also reviewed separately by a pathologist at the NCI (Table 2). The NCI reviewer noted that prior treatment with chemotherapy and/or radiation therapy in cases 1 and 3 made firm histologic diagnoses difficult. The differences between the original pathologists and the reviewing pathologists did not appear to follow any specific pattern.

### Radiology Review

Table 3 shows the results of the radiology review of the available films and the radiologists' conclusions regarding tumor response. Three patients were judged to have a complete response and 3 to have a partial response. However, in 1 of the latter (brain cancer case 2), the patient had received radiation therapy (without evidence of benefit at the time) shortly before coming to Hufeland and was therefore not categorized as a best case.

Table 4 lists the 15 cases that were excluded from the best-case series review. Of these, 7 (3 colon cancer cases, 1 stage III and 2 stage IV; 2 sarcoma cases; 1 lung

cancer case; and 1 melanoma case) were excluded because the presence of malignant disease was not confirmed at the time treatment was initiated. Four cases (all 3 cases with advanced breast cancer and 1 with ovarian cancer) were excluded because they received conventional therapy (hormonal therapy or chemotherapy) shortly before or during treatment at Hufeland, 3 because of disease progression (an ovarian cancer case) or lack of a partial response to treatment (a stomach cancer case and a lung cancer case), and 1 (an ovarian cancer case) because slides were unavailable for pathology review. (In Germany, slides may be discarded after 10 years.)

## Discussion

Since 1985, about 3000 individuals have been treated for cancer at Hufeland. Although some of these patients achieved remission and remain well, many, including all patients with metastatic breast cancer or prostate cancer, were ineligible for inclusion in the best-case series because they had received conventional and CAM treatment at Hufeland simultaneously. This exclusion limits best-case series review to patients who have cancers for which no conventional treatment is known, refuse conventional treatment, or wait a sufficient time after receiving conventional treatment for restaging to verify treatment failure. Yet many patients whose disease is spreading and not responding to treatment begin immediately to explore alternatives. Moreover, although potential best cases cannot be evaluated unless they have had repeat imaging just prior to starting the CAM treatment, complete restaging is not always performed at this time in clinical practice. The best-case series, therefore, shares many of the difficulties of any retrospective review. As Table 1 shows, even the patients whose cases we reviewed wasted little time between failing (or being failed by) conventional treatment and seeking treatment at Hufeland.

The best-case series approach to CAM treatments for cancer requires pathologic confirmation of the cancer diagnosis, evidence that cancer was present at the time the CAM treatment was initiated, no recent conventional treatment, and evidence of complete or partial response. These requirements are reasonable but not easy to fulfill. Old charts and scans are often difficult to find. Scans that are not necessary for the patient's treatment might not be covered by insurance. And few CAM practitioners, especially those who are not also conventional physicians, require patients to document their cancer diagnosis or interact routinely with the conventional physicians who treat their patients.<sup>2</sup>

**Table 1. Cases Reviewed for Best-Case Status**

<i>Primary Site and Case Number</i>	<i>Age at Diagnosis/ Gender</i>	<i>Date of Diagnosis</i>	<i>Conventional Treatment</i>	<i>Last Conventional Treatment</i>	<i>First Visit to Hufeland</i>	<i>Status at First Visit</i>	<i>Last Contact</i>	<i>Outcome/Status at Last Contact</i>
Best cases								
Melanoma 1 (skin of arm)	51/F	1985	Surgery: primary removed 1985, jejunal metastases resected Jun 1989 and Nov 1990	Nov 1990	Mar 1991	Unresectable pelvic mass, poor nutritional condition, pencil-thin stools, poor appetite, fatigue	Apr 1996	Condition improved, expired Apr 1997, PR
Brain 1	43/M	Oct 1987	2 subtotal resections, radiation therapy, BCNU	Second craniotomy, Aug 1988	Oct 1988	Poor short-term memory, disorientation, fatigue, difficulty writing, gait drift to left, seizures	Jul 1996	Initially condition improved, expired from stroke Jul 1996, PR
Urinary bladder 1	58/M	May 1989	None	NA	JUL1989	5-cm tumor in right side of bladder, right hydronephrosis, dilated right ureter	2002	Alive and well, CR
Melanoma 2 (skin of thigh)	35/M	Apr 1991	Surgery: multiple resections skin, SQ fat, regional lymph nodes	Mar 1992	Apr 1992	Palpable tumors close to scars of previous surgery	Feb 2002	Alive and well, working as engineer, CR
Colon 1	51/M	Jun 1994	Surgery, 5FU/leucovorin	Mar 1995	Apr 1995	Liver metastases, unresectable	Mar 2002	Alive and well, CR
Not best cases								
Brain 2 (pineal)	15/M	Sep 1982	Radiation therapy Sep- Dec 1982, drainage procedures to Jan 1983	Jan 1983	Jan 1983	Scan Jan 1983 showed tumor size doubled since Sep 1982, diplopia, trunk and extremity ataxia	Jun 2002	Alive, clinical improvement, MS diagnosed 1995; improvement might have been due to RT
Brain 3	52/F	Jan 1983	Surgery, preoperative radiation therapy, pre-/ postoperative BCNU	Nov 1983 (Ringberg) Nov 1983	Nov 1983	Tumor present on CT, paresthesias/dysesthesias left hand, abnormal reflexes, reduced general condition	Nov 1989	Clinical improvement, expired Nov 1989; no PR
Brain 4	3/M	Aug 1985	Subtotal resection, radiation therapy	RT Sep-Dec 1985	Mar 1986	Residual tumor by MRI Feb 28, 1986, poor condition	Apr 2001	Alive, vision impaired, mentally and physically in good condition; no PR

Ovary 1	52/F	Jan 1988	Surgery	Jan 1988	Jul 1988	Liver metastases	Jul 1999	Progressed; expired Jul 1999
Ovary 2	36/F	Apr 1996	Surgery, mitomycin, then	Aug 1996	Apr 1997	CA125 = 94.3 (elevated),	2002	Alive and well CA125 = 13.8; no
Mediastinum 1	52/M		stem-cell transplant			but no evidence of disease		evidence of disease at first visit
		Nov 1991	1 cycle epirubicin/cytoxan/	Mar 1992	Aug 1992	Unresectable mediastinal	2001	Clinical improvement, stable
Mesothelioma 1	54/M		Oncovin, radiation therapy			tumor		through 1999, expired 2001; no
(pleura)		Oct 1994	Surgery, 1 cycle ifosfamide,	Nov 1994	Jan 1995	Severe exertional dyspnea,	Apr 1998	PR
			talc pleurodesis			slight nonproductive		Clinical improvement, expired
						cough, postoperative		1998; no PR
						weight loss of about 5 kg		

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PR = partial response; BCNU = 1,3 bis(2-chloroethyl)-1-nitrosourea; NA = not applicable; CR = complete response; SQ = subcutaneous; MS = multiple sclerosis; RT = radiation therapy; CT = computed tomography; MRI = magnetic resonance imaging.

Table 2. Results of Pathology Review

Primary Site and Case Number	Original Histologic Diagnosis	Histologic Diagnosis on Review
Melanoma 1	Melanoma	Melanoma
Brain 1	Anaplastic gemistocytic astrocytoma	Anaplastic gemistocytic astrocytoma
Bladder 1	Transitional cell carcinoma	Transitional cell carcinoma
Melanoma 2	Melanoma	Melanoma
Colon 1	Adenosquamous carcinoma, poorly differentiated	Adenocarcinoma, poorly differentiated
Brain 2 (pineal)	Malignant glioma	Pilocytic astrocytoma
Brain 3	Malignant brain tumor	Anaplastic astrocytoma (grade III)
Brain 4	Kernohan astrocytoma grade II	Anaplastic astrocytoma (grade III)
Ovary 1	Cystic ovarian cancer at the base of a pseudomucinous cystoma with extensive peritoneal pseudomyxoma	Mucinous cystadenocarcinoma and appendiceal cystadenoma with rupture
Ovary 2	Papillary serous carcinoma	Papillary serous carcinoma
Mediastinum 1	Malignant mixed	Bronchogenic carcinoma in malignant mixed tumor
Mesothelioma 1	Mesothelioma	Mesothelioma

Brain cancer cases 1 through 4 were rereviewed by Martha Quezado, MD, National Cancer Institute pathologist. Her diagnoses were brain 1: residual tumor high grade with gemistocytic features; brain 2: pineal parenchymal tumor of intermediate differentiation; brain 3: radiation changes with residual tumor, most likely high grade; brain 4: pilocytic astrocytoma.

Due in part to legal and regulatory constraints on the provision of unconventional cancer treatments in the United States, many of the clinics that offer such treatments are based elsewhere. Linguistic and cultural differences add to the difficulty of obtaining documentation for a best-case series.

Staff and consultants at the NFAM selected the Hufeland Klinik for review in part because its medical records were far more complete and organized than those of most clinics they had visited. Dr Woeppel was also highly cooperative in providing additional records from Hufeland upon request. He obtained authorization from patients for retrieval of additional documents, histology, and imaging material and assisted in the retrieval process, which nonetheless took 2 years.

The most compelling candidates for a best-case series are patients who have survived for many years after their initial diagnosis. But for those patients, the documentation trail is often cold; specimens, slides, and films may have deteriorated or been lost; and treating physicians may have retired or relocated. In the Hufeland series, many of the computed tomography scans that were reviewed by our radiologists came from first-generation scanners and were of limited quality; the settings of images on some magnetic resonance imaging studies posed additional challenges for the reviewing radiologists. Some of the digital images derived from radiographic films for the best-case series review were also of poor quality.

Among the cases submitted by Dr Woeppel but either not considered best cases or excluded from the review, were many who had arguably longer survival than would be expected given their conventional treatment or their status at presentation.<sup>22,23</sup> The 5 best cases also improved clinically and survived longer

than would be expected for patients with the same disease and stage. However, they are not the only Hufeland patients with better than expected survival, and duration of survival is not a criterion for best-case status.

The best-case series methodology came into use as a tool for evaluating complex unconventional cancer therapies as candidates for further study. Ideally, such preliminary reviews should be reasonably quick and inexpensive. Our team took more than 2 years to assemble the case records and to complete the imaging and histology review. However, it is difficult to imagine how the Hufeland approach and that of other similar cancer clinics could be initially evaluated without such a case review.

A strength of the methodology is that it permits the evaluation of holistic, multimodality approaches. However, having participated in this best-case series review, Dr Woeppel has come to see some merit in developing an evidence-based standardized treatment that other cancer facilities could adopt.

Bringing the Hufeland approach in its present form to the United States would not be easy. Some elements of the program are not available in the United States because of Food and Drug Administration regulations, physicians' lack of training in certain methods, and lack of insurance coverage for them.

The best-case methodology evaluates the success of a therapy in inducing a tumor response. But the Hufeland basic treatment program does not target the tumor and has no specific cytotoxic components. Tumor response is, from Hufeland's perspective, neither necessary nor sufficient; the Klinik's mission is to help patients to survive with good quality of life, and Dr Woeppel selected cases for review with that mission

**Table 3. Results of Radiology Review**

Primary Site and Case Number	Modality	Dates	Findings
Melanoma 1	Abdominal/pelvic CT without contrast	Mar 1991	Right pelvic mass ~5 cm, secondary moderate right hydronephrosis and mild right hydronephrosis
	Abdominal/pelvic CT with contrast	Jul 1994	Ill-defined mass ~2 cm, hydronephrosis and hydronephrosis unchanged
Brain 1	CT brain	Sep 1988	S/P subtotal resection, cannot exclude residual tumor
	CT brain	May 1996	Recent, evolving, right MCA infarct on CT; no evidence of tumor but no contrast; residual tumor not ruled out
Bladder 1	CT pelvis	May 1989	5-cm bladder mass, dilated R ureter and R hydronephrosis
	CT pelvis	Oct 1989	
	U/S pelvis	Oct 2001	R ureter questionably dilated distally, otherwise normal
Melanoma 2	MRI thigh	Oct 1992	Soft tissue masses in SQ down to muscle in right medial thigh
	MRI thigh	May 1993	Defects same location, postoperative changes, melanoma may still be present
	CT	Feb 2002	No evidence of malignancy chest, abdomen, pelvis; limited lung field evaluation due to data compression on transfer
Colon 1	CT abdomen	Mar 1995	Abdominal CT: 3 metastatic foci persist in liver
		Jun 200	Abdominal CT: no evidence of metastatic disease
Brain 2	CT without contrast	Jan 1983	Pineal tumor doubled in size involving adjoining structures, extending into thalamus
	MRI	Jun 1999	Pineal gland smaller, less enhancement; white matter lesions noted consistent with multiple sclerosis
Brain 3	CT with contrast	Dec 1983	R frontal large enhancing tumor
		Aug 1987	Minimal rim enhancement, moderate white matter edema
Brain 4	CT brain	Feb 1986	Tumor in lateral thalamus, chiasm, and optic tracts
	MRI brain	Feb 1995	Residual tumor optic chiasm and tracts but less compared with Jul 1987
Ovary 1	NA	NA	No imaging review because of clinical progression in indolent tumor
Ovary 2	CT	Aug 1996	3-mm round peripheral juxtapleural opacity, not solid; unclear if inflammatory or neoplastic
	MRI	May 1998	Unchanged on MRI
Mediastinum 1	Chest x-ray	NA	Not reviewed here because x-ray reports indicate no PR
Mesothelioma 1	Chest x-ray	Oct 1994	Cannot distinguish 3 cm x 2 cm pleural-based mass-like opacity R midlung from loculated effusion postop
	Chest x-ray	Dec 1995	
	Chest x-ray	Mar 1998	New medial pleural mass, 2 right midlung zone masses: progression

CT = computed tomography; S/P = status post; MCA = middle cerebral artery; U/S = ultrasound; MRI = magnetic resonance imaging; SQ = subcutaneous; NA = not applicable; PR = partial response; R = right.

in mind. However, he understood the requirements of the review and accepted them.

The 27 cases that he selected were those in which patients survived longer than expected and agreed to provide access to their conventional medical records. The 12 cases that we reviewed were those that appeared to meet the NCI best-case series criteria based on the case summary. Where necessary, we then sought additional documentation. (We excluded only 1 case for lack of such documentation.)

Best-case series are not designed to permit calculation of a response rate. A recent report of 2 best-case series prepared for the Agency for Healthcare

Research and Quality did not present response rates but recommended consideration of further study of both modalities. For 1 modality, 9 of 30 cases were judged to meet the criteria; for the other, 3 of 21 were similarly judged. In both reviews, the cases involved cancers of several different organ/sites and a lengthy effort to obtain medical records.<sup>24</sup>

To calculate a response rate in our study, we would have had to review the charts of all 3000 cancer patients seen at Hufeland since 1985, to eliminate all those with recent or concurrent potentially curative conventional treatment, to document the status of the cancer at the time the patient first came to Hufeland,

**Table 4. Cases Excluded From Best-Case Series Review**

<i>Primary site/Diagnosis</i>	<i>Age at Diagnosis/ Gender</i>	<i>Date of Diagnosis</i>	<i>Conventional Treatment</i>	<i>First Visit to Hufeland</i>	<i>Status at First Visit</i>	<i>Status at Last Contact/Date</i>	<i>Reason for Exclusion From Review</i>
Breast 1, infiltrating papillary, pTxPNO/9,MO, receptor status unknown	41/F	1985	Apr 1985 mastectomy; Sep 1988 and Dec 1988 resection of chest wall recurrences, Sep 1989 resection lymph node metastases; Oct-Nov 1989 radiation therapy; Oct 1989-Oct 1991 Zoladex; Dec 1991 resection lymph node metastases; Jan-May 1992, cyclophosphamide/methotrexate/5FU (CMF); Jun 1992-Jan 1994 tamoxifen; Feb 1994 radiation therapy; Feb 1995 and Jul 1995 lymph node resection; Sep 1995 skin biopsy, Oct-Nov 1995 RT skin metastases	Aug 1996	Extensive skin metastases, palpable lymph node metastases	Alive and well, working Sep 1999	Chemotherapy (low-dose Ixoten) at Hufeland
Breast 2, invasive ductal, ER+	51/F	1991	Oct 1991 left mastectomy, Nov 1991-1995 tamoxifen, Jan-Nov 1995 CMF, 5FU/epirubicin/cyclophosphamide (FEC), velban/mitomycin/prednisone (VMP)	May 1996	Lung metastases, malignant pleural effusion, skin metastases, left arm lymph edema	Alive and well Mar 1999	Chemotherapy (low-dose Ixoten) and hormonal therapy (Lentaron) at Hufeland
Breast 3, invasive ductal, ER+, PR+	35/F	1996	Jun 1996 mastectomy, Jun-Nov 1996 4X EC, 3X CMF, Jul 1987 chest CT: lung metastases, Aug-Dec 1997 paclitaxel	Jan 1998	Lung metastases on chest CT, patient refuses high-dose chemotherapy	Alive and well Jan 1999	Hormonal therapy (Zoladex and tamoxifen) at Hufeland
Ovary 3, adeno-papillary with peritoneal carcinomatosis	25/F	1968	Nov 1968 total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO), cyclophosphamide X 10; Jun 1982 cyclophosphamide; Oct 1984 platinum/adriamycin/cyclophosphamide (PAC); Apr 1985 radiation therapy to entire abdomen for tumor cells in peritoneal fluid	Mar 1987	Peritoneal metastases on laparoscopic biopsy Dec 1986	Kidney cancer Jan 1999, pancreatic cancer Apr 1999, expired Aug 1999	Histology slides unobtainable
Ovary 4, papillary cystadenocarcinoma invading myometrium and omentum	56/F	1982	Feb 1982 TAHBSO, omentum resection, Mar 1982 chemotherapy; Jan 1989 abdominal wall metastasis; Feb-May 1989 chemotherapy 5 cycles; Nov 1991 extirpation of abdominal wall and pubic bone metastases	Sep 1989	Abdominal wall metastases, tumor size unchanged on CT Sep 1989	Alive and well Feb 1999	Progression and surgery after Hufeland treatment started
Ovary 5, cystadenocarcinoma, endometrioid	36/F	1987	Jul 1987 surgery, Jul-Oct 1987 CMF chemotherapy, Oct 1987 laparoscopy: biopsy positive carcinomatosis, Oct 1987 PAC chemotherapy 1 cycle	Nov 1987	Status post 1 cycle PAC for carcinomatosis	Alive and well May 1997	PAC 26 days before start at Hufeland
Lung 1, small-cell carcinoma with mediastinal lymph node metastases, pT3,pN2,pM0pG3	68/M	1989	Nov 1989 left pneumonectomy, Nov 1989-Feb 1990 adriamycin/cyclophosphamide/vincristine (ACO) 3 X, Jul 1990 radiation therapy for brain metastasis	Mar 1990	General weakness, heartburn, left shoulder discomfort	Alive and well Feb 1998	No evidence of disease at first visit; progression after Hufeland treatment started

Lung 2, poorly differentiated adenocarcinoma, T4N2	64/M	1995	Feb-Mar 1996 radiation therapy (60 Gy)	Apr 1997	Suspicion of progression	Alive and well May 2000	No tumor response after Hufeland treatment started
Colon 2, moderately differentiated adenocarcinoma, pT3pN1Mx,G2	66/F	1988	Apr 1988 sigmoid resection, Oct 1988 liver metastases resected, Jun 1989 lung metastases resected	Jul 1989	No evidence of cancer	Alive and well Feb 1999	No evidence of disease at first visit
Colon 3, moderately differentiated nonmucinous adenocarcinoma, pT3,N0,M1	63/F	1991	Jan 1991 hemicolectomy and resection liver metastasis; Jan 1993 resection liver, gall bladder, diaphragm metastasis; Feb-Jul 1993 active-specific-immune therapy; Jan 1995 resection liver and diaphragm metastases	Apr 1995	No evidence of cancer, CEA 2.1	Alive and well Sep 1999	No evidence of disease at first visit
Colon 4, mucinous signet ring adenocarcinoma, pT4pN3MxR1	49/M	1993	Sep 1993 hemicolectomy, Oct 1993-May 1994 5FU/ergamisol	May 1994	No evidence of cancer	Alive and well Sep 1999	No evidence of disease at first visit
Ewing's sarcoma 1, right ischium and pubic bone	18/M	1988	Jun 1988 right pelvic resection and arthroplasty; Jul 1988-Apr 1999 CESS-86-system chemotherapy; Aug 1995 wedge resection lung metastases; patient refused radiation therapy and chemotherapy	Sep 1995	No evidence of cancer	Alive and well Sep 1999	No evidence of disease at first visit
Alveolar soft tissue sarcoma 2, thigh	17/F	1992	Apr 1992 tumor resection right thigh, Aug 1992 resection left lung, Mar 1993 resection right lung, Jul-Nov 1992 chemotherapy epirubicin/vincristine/ifosphamide	Jun 1993	Status postsurgery, chemotherapy	No further recurrences, alive and well Aug 1998	No evidence of disease at first visit
Melanoma 3, SQ tumor left leg, unknown primary tumor	42/F	1984	Jul 1984 resection SQ tumor left leg, Sep 1984 reexcision and Jan 1985 exploratory laparoscopy benign, Jan 1985 Melfalan hyperthermal perfusion leg, Feb 1985 resection local recurrence, Feb 1986 excision large left inguinal lymph node metastasis	Apr 1986	Status postresection	No further recurrences, alive and well Feb 1999	No evidence of disease at first
Stomach 1, signet ring/ Krukenberg	54/F	1996	Dec 1996 radiation therapy to rectal, pelvic metastases	May 1997	Gastric tumor, peritoneal carcinomatosis	Clinical improvement, then progression, expired Sep 2000	No PR

RT = radiation therapy; CT = computed tomography; TAHBSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy; SQ = subcutaneous; PR = partial response.

and to identify all the CRs and PRs. To assess survival as an outcome, we would need a comparison cohort of patients similar in cancer organ/site, age, stage, gender, date of diagnosis, and status of disease at the time the treatment group came to Hufeland but receiving only conventional treatment. A prospective study that purported to have such a comparison group collected data on the CAM cohort via interview and chart abstraction but used only chart review of the comparison group and was therefore seriously biased.<sup>25</sup> Appropriate comparison groups for prospective studies are hard to find. Most patients who present at an inpatient CAM clinic do so because they have reason to doubt that conventional treatment will cure them. Even matching on stage might not level the playing field unless additional markers and/or perceived risk of an adverse outcome are taken into account.

Clinics such as Hufeland clearly seek to provide comfort and hope to patients with advanced disease who are not ready for exclusively palliative care. The more established clinics do not guarantee to cure cancer; they offer, as Hufeland does, support for the immune system, spa services, and psychosocial programs in a setting of natural beauty, with an attentive staff and well-prepared meals. Although the treatment is not as gentle (eg, daily injections, enemas, and fever therapy) as is widely assumed, clinics such as Hufeland appear to offer something of value to cancer patients who have reached the end of the line in conventional medicine.

## Conclusions

Our best-case series review indicates that a handful of patients, treated at this facility and not expected to do well, experienced tumor regression. That kind of observation is all that the method can support. However, a new conventional treatment that achieved 3 CRs and 2 PRs in a similar series of 12 cases might well be described as a candidate for further study. We believe that that kind of reasoning was the basis for the recommendations of the RAND best-case series reviewers.<sup>24</sup> From that perspective, a phase II or prospective study of Hufeland patients with specific advanced cancers, such as melanomas or gliomas, seems worth proposing.

The RAND reviews and ours have highlighted the need for explicit criteria for the evaluation of both retrospective best-case series and prospective single-arm studies. As they do in phase II studies, investigators might select a priori a number or proportion of CRs and PRs (or other outcomes) required to justify further research. In reporting their results, they would describe this determination and the factors they took into consideration. Patients with advanced cancer

who use CAM are a heterogeneous group, and the claims made for treatments vary. Taking those and other relevant factors into account will not be easy, but the difficulty should not deter us from trying to standardize the preliminary evaluation of complex CAM treatments alleged to benefit cancer patients.

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