Vaccine Therapy For Colon Cancer.

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Vaccine Therapy for Colon Cancer

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A native Kansan, Dr. Hoover received his MD from the University of Kansas School of Medicine in 1970. He received his surgical training at Massachusetts General Hospital between 1970 and 1978, with a surgical oncology fellowship in the surgery branch of the National Cancer Institute, National Institutes of Health, Bethesda, MD, from 1972 to 1974. From 1978 to 1983, he was assistant and associate professor of surgery and oncology at the Johns Hopkins School of Medicine, and then served as chief of the Division of Surgical Oncology at the State University of New York at Stony Brook from 1983 to 1986. In that year, Dr. Hoover returned to Massachusetts General Hospital as chief of surgical oncology research, and as associate professor of surgery at Harvard Medical School, where he remained until assuming his present position in 1995.

Dr. Hoover's research interests focus primarily on experimental and clinical immunotherapy, and the development of human monoclonal antibodies. His clinical practice is broad in the area of surgical oncology, with special emphasis on tumors of the gastrointestinal tract.

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Of the approximately 224,000 gastrointestinal malignancies diagnosed in the United States each year, colorectal cancer has the highest incidence, with approximately 135,000 new cases annually (Table 1). Gastrointestinal malignancies account for approximately 16% of all new cancers diagnosed, and 23% of cancer deaths. Since the introduction of ether anesthesia in 1846 and antiseptic techniques in 1867, surgical resection of gastrointestinal malignancies has become the mainstay of therapy. As Table 2 depicts, other approaches, including radiation and chemotherapy, have been of more recent origin. In the 1980s, biological therapies, such as vaccines for colon cancer, began to emerge.

Over the past 20 years, we have developed a vaccine approach, called active specific immunotherapy. This therapy presumes that there are distinct tumor antigens within each patient's primary tumor that are likely to be those represented in any subclinical metastatic sites. Each vaccine is made from the individual patient's own tumor with an immune adjuvant, such as bacillus Calmette-Guérin (BCG), to increase the tumor cell's immunogenicity in order to elicit a distinct immune response in the host.

Experimental model

The impetus for this work was the development and biological characterization of an experimental model that determined the requirements for effective immunotherapy of established tumors. A series of studies in the guinea pig line 10 hepatocarcinoma model [1–6] demonstrated that BCG mixed with autologous tumor cells can induce systemic immunity capable of eliminating a limited disseminated tumor burden when the vaccine is carefully controlled for quality variables. These include the number of tumor cells, ratio of viable BCG organisms to tumor cells, viability of the tumor cells, and the vaccination regimen.

The need to start these trials in colorectal cancer in the late 1970s was strengthened by the fact that no adjuvant therapy for this common disease had been proven effective. Treatment protocols were translated as exactly as possible from the relevant animal model into trials in patients with colon and rectal cancer. Important components for a successful vaccine were demonstrated in the guinea pig model [6]. In that model, tumor cell viability was found to be extremely critical as dead cells failed to elicit a clinical response. The number of tumor cells was also crucial in that 10^7 tumor cells plus 10^7 BCG were necessary for each vaccine. Other important findings in the guinea pig model were that intact draining lymph nodes were essential. The vaccines were given intradermally so that drainage was into the lymph nodes, where the important antigenic processing occurs. The dermis is very rich in dendritic cells, the ultimate antigen-presenting cells. The antigen-presenting cells pick up the tumor and BCG antigens and deliver them to the relevant lymph nodes for sensitization of T cells and production of lymphokines. These lymphokines and specifically sensitized T cells then can circulate throughout the body for tumor killing.

Table 1. Milestones in cancer therapy

Era	Event
1846–1940	Resection of solid tumors Ether (1846) Antiseptics (1867)
1940–1950	Radiation therapy (RT)
1950s	Chemotherapy (CTX)
1960s	Adjuvant CTX and RT
1980s	Biological therapies

Table 2. Gastrointestinal malignancies

Location	Number per Year
Colorectal	135,000
Pancreas	26,000
Gastric	23,000
Esophagus	12,300
Liver and biliary	19,900
Small intestine	2600
Other	3100
Total	223,900

Human studies

In 1980, a five-patient pilot study at Johns Hopkins Hospital demonstrated that human colorectal cancers could be successfully dissociated into viable cell preparations and that the toxicity associated with administration of the tumor cell-BCG vaccine was minimal. The principles and procedures of active specific immunotherapy, as learned in the guinea pig hepatocarcinoma model, were then applied in a series of prospective, randomized, controlled trials of patients with colorectal cancer. In 1981, the first trial was launched and addressed two simple questions: 1) Can colorectal cancer patients' reactivity to their tumors be enhanced by active specific immunotherapy? and 2) Will increased tumor immunity be translated into improved survival in colorectal cancer patients?

Figure 1 illustrates the preparation of tumor vaccines. The schema includes collecting the colon cancer in the operating room, and subsequent mechanical and enzymatic dissociation into a single cell suspension, which is then cryopreserved using a liquid nitrogen system for later use as a vaccine and for delayed cutaneous hypersensitivity (DCH) testing. Figures 2 and 3 give the schema and protocol of postoperative adjuvant active specific immunotherapy in colon and rectal cancer (concurrent parallel studies). In 1984, we published data that showed we were able to immunize patients to their tumors as measured by DCH to autologous tumor cells (Fig. 4) [7].

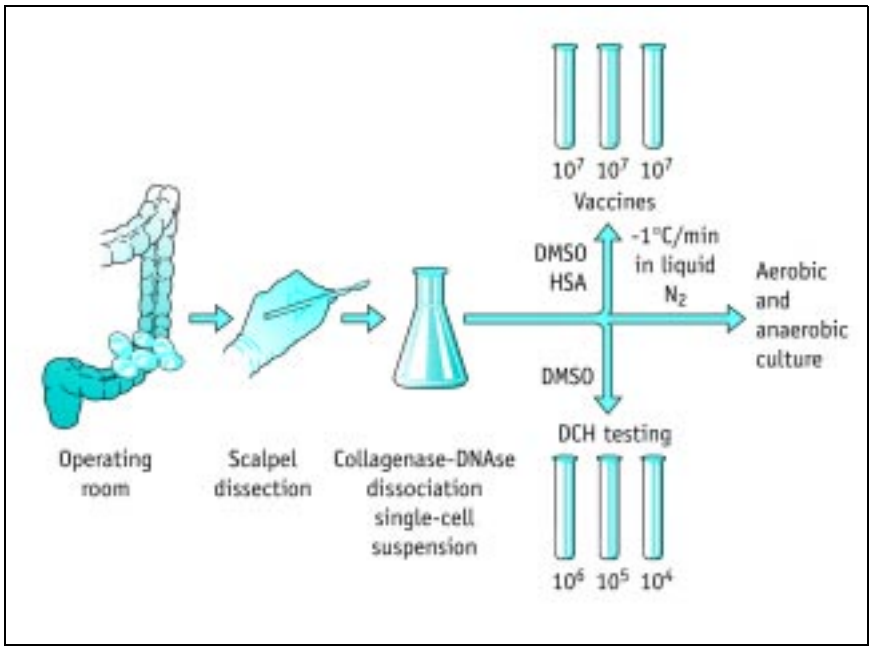

Figure 1. Preparation of tumor vaccine and DCH test. DCH=delayed cutaneous hypersensitivity; DMSO=dimethyl sulfoxide; HSA=human serum albumin; OR=operating room. (*From* Hoover HC Jr, Surdyke M, Dangel R, *et al*. [7]); with permission.

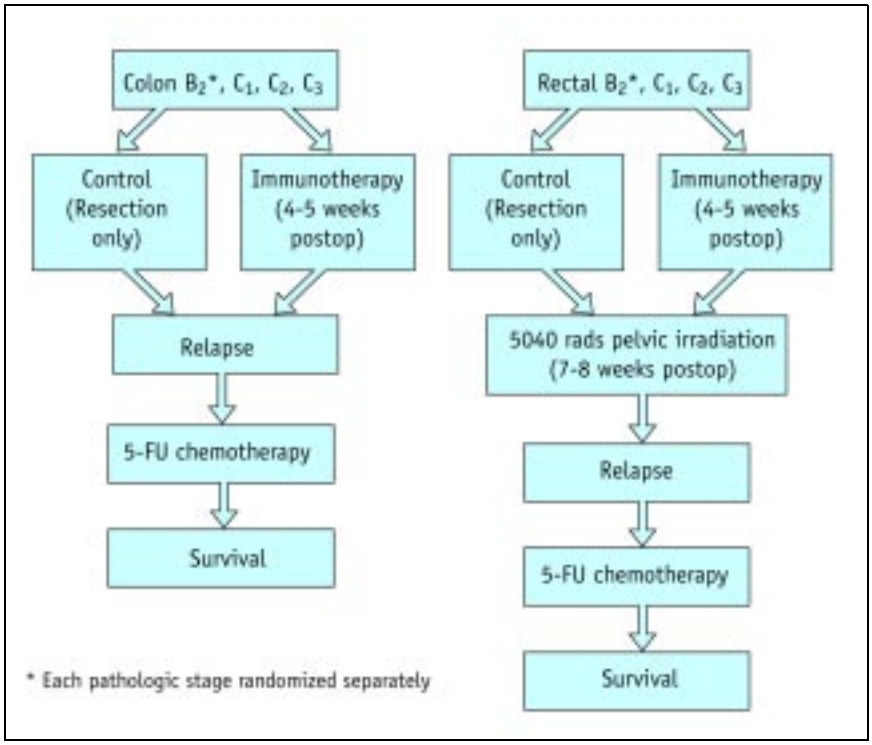

Figure 2. Schema for postoperative adjuvant active specific immunotherapy for colorectal cancer.

Weeks on study	Treatment
– 4	Resection
– 1	Recall antigen testing (C/M/P/T)
– 1	DCH pretest 10^4, 10^5, 10^6, mucosa 10^4, 10^5, 10^6, tumor
0	Vaccine #1 10^7, BCG + 10^7 TC
1	Vaccine #2 10^7, BCG + 10^7 TC
2	Vaccine #3 10^7 TC
6	DCH testing 10^4, 10^5, 10^6, mucosa 10^4, 10^5, 10^6, TC
3 months	Recall antigen testing (C/M/P/T)
6 months	DCH testing 10^4, 10^5, 10^6, mucosa 10^4, 10^5, 10^6, TC
1 year	DCH testing 10^4, 10^5, 10^6, mucosa 10^4, 10^5, 10^6, TC

Figure 3. Protocol for colorectal cancer immunotherapy.

There were 80 patients randomized in the original pilot trial. The data, published in 1993 with a 6.5-year median follow-up, did not show a statistically significant difference in survival or disease-free survival [8]. That study, however, included both rectal cancer patients who received post-immunotherapy radiation and colon cancer patients who received surgery alone. With a median follow-up of 93 months, there was a significant improvement in survival (two-sided P =0.02, hazards ratio 3.97) and disease-free survival (two-sided P =0.039, hazards ratio 2.67) in all eligible colon cancer patients who received active specific immunotherapy. Rectal cancer patients received no benefit.

Phase III trials

That randomized controlled pilot trial led to two phase III trials of active specific immunotherapy in colon cancer. In 1986, the Eastern Cooperative Oncology Group (ECOG) began a larger randomized trial of active specific immunotherapy in patients with stages II and III colon cancer [9]. Patients in this trial received either no further therapy, or three vaccinations after surgical resection. An intent-to-treat analysis of 412 patients showed no significant differences in benefits between groups. However, in a subset of 307 patients who were immunized with vaccines that met quality control specifications and who had a substantial immune response (DCH to the third vaccine more than 5 mm), active specific immunotherapy improved overall survival. Also, the magnitude of the DCH response correlated with improved prognosis. The 5-year survival rate was 84.6% for those with indurations over 10 mm compared with 45.0% for those with indurations under 5 mm (Figs. 5, 6).

Netherlands study

A third randomized study was initiated in The Netherlands in 1987. This study was in stage II and III colon cancer patients (n =254) and differed significantly from the other two studies in that four vaccinations were used instead of three, whereby the fourth vaccination (a booster vaccination) was given at 6 months after surgery [10]. The rationale for this was evident from the DCH

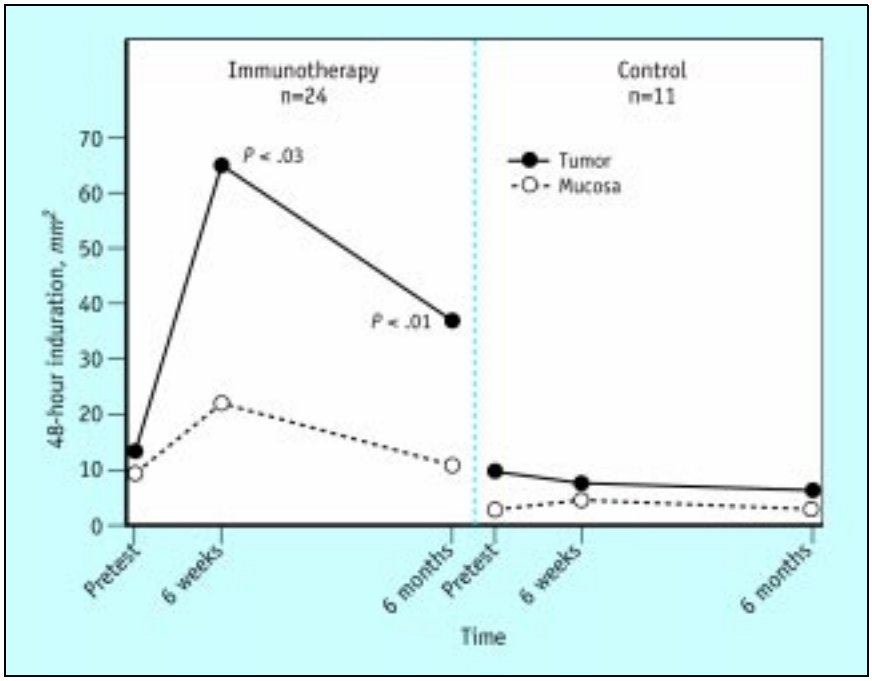

Figure 4. Delayed cutaneous hypersensitivity response to tumor and mucosa. (*From* Hoover HC Jr, Surdyke M, Dangel R, *et al*. [7]); with permission.

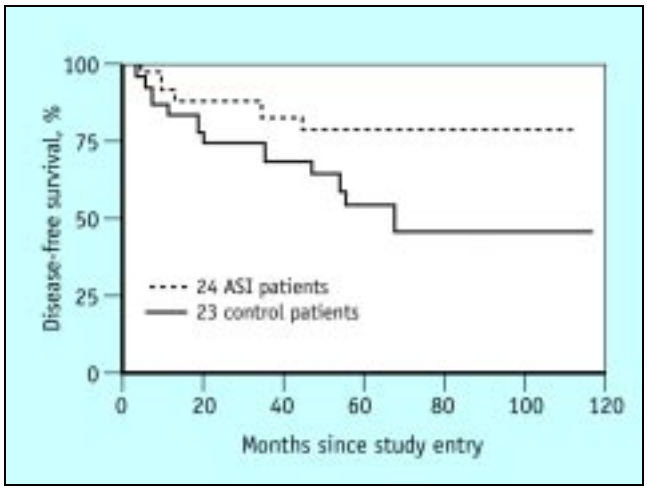

Figure 5. Disease-free survival in colon cancer patients. (*From* Hoover HC Jr, Brandhorst JS, Peters LC, *et al*. [8]); with permission.

data described above (Fig. 3). Moreover, vaccine preparation was centralized (performed in one laboratory) which assured high quality vaccines. This trial, also, had a positive outcome. The 5.3-year median follow-up (range 8 months to 8.9 years) showed a 44% risk reduction for recurrence in all patients receiving active specific immunotherapy (95% CI:7–66, P =0.023). Overall, there were 40 recurrences in the control group (n =126) and 25 in the group receiving active specific immunotherapy (n'128). Analysis by stage showed no significant benefit of active specific immunotherapy in stage III disease. The major impact of active specific immunotherapy was seen in patients with stage II disease, with a significantly longer recurrence-free period associated with a 61% risk reduction for recurrences (95% CI:18–81, P =0.011) (Fig. 7). Recurrence-free survival was significantly longer for patients receiving active specific immunotherapy (42% risk reduction for recurrence or death, 0–68, P =0.032), and there was a proportional improvement in overall survival.

Patient tolerance

One of the most appealing aspects of active specific immunotherapy in the adjuvant setting is the patient's tolerance to this treatment. There were no serious side effects in this outpatient treatment program. Although most of the vaccine preparations contained a limited bioburden of normal gastrointestinal flora, there were no systemic infections. Local ulceration at the first two vaccination sites occurred in nearly all patients. Some regional lymph node swelling occurred in about 65% of patients. Systemic reactions, such as fever and chills or both in the first 24 hours, occurred in a small proportion of patients. These reactions, however, were generally mild and have not been a reason for treatment refusal by any of the patients. This is in striking contrast to experience with adjuvant chemotherapy and may be particularly relevant for patients with stage II disease in whom the usefulness of chemotherapy is debatable [11–13].

Conclusions

A meta-analysis of all three trials with 723 patients has been concluded, and is currently being submitted for publication. Our conclusions at this point are that the data are sufficiently compelling to suggest that active specific immunotherapy with an autologous tumor

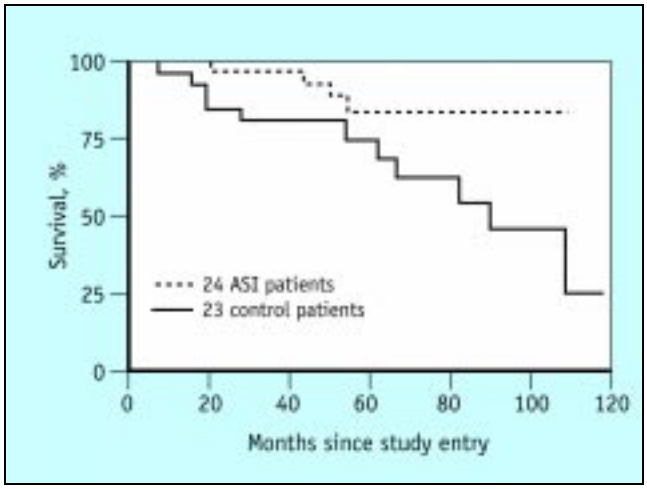

Figure 6. Months to death in patients with colon cancer. (*From* Hoover HC Jr, Brandhorst JS, Peters LC, *et al*. [8]); with permission.

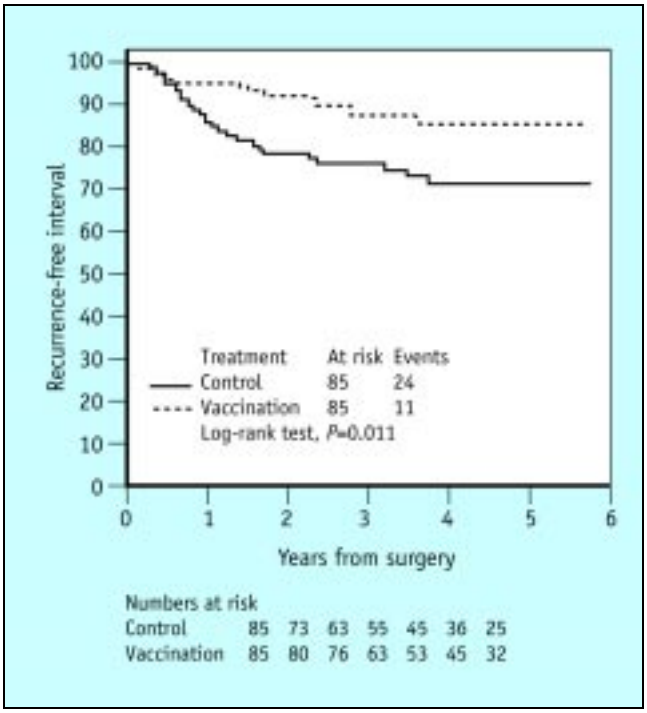

Figure 7. Recurrence-free interval for patients with stage II colon cancer. (*From* Vermorken JB, Claessen AME, van Tinteren H, *et al*. [10]); with permission.

cell plus BCG vaccine should be considered as a standard therapy for patients with stage II colon cancer. A phase III trial in Stage III colon cancer comparing surgical resection followed by six months of 5-FU/leucovorin chemotherapy followed by a fourth vaccine boost at 6 months versus surgical resection alone, is being started in Europe and the United States.

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