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USE OF RADIOACTIVE COLLOIDAL GOLD (AU198) IN TREATMENT OF CARCINOMA OF THE CERVIX

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Historical: In 1851, Charles C. Meigs[1] wrote that a diagnosis of cancer of the uterus was a prognosis of death. Even now, the state of our knowledge of the treatment of carcinoma of the cervix leaves much to be desired.

The first surgical approach in the treatment of this disease consisted of a simple vaginal operation. Complete abdominal hysterectomy at a later date failed to remove the disease except in very early cases. Wertheim[2] after performing 500 radical hysterectomies reported his results and established a standardized operative procedure. Mortality was high with 93 deaths, 39 of wich were attributed to peritonitis. With the advent of x-ray and radium, surgery with its high mortality was rejected by all but a few pioneers. With accumulation of experience and improvements in technique it was still apparent, however, that deep x-ray therapy did not eliminate distant metastases in the pelvis.

Roentgen, as a result of his research work in Wurzburg, Germany, discovered the x-ray in 1895. This was followed in 1898 with the discovery of radium by Mme Curie. In 1901, Becquerel placed a tube of radium in the pocket of his coat and a week or two later, a severe inflammation appeared in the skin beneath the radium. Besnier examined the dermatitis and suggested the use of radium as a therapeutic agent. In 1903, Morton in New York first reported the treatment of fibroids by x-ray.

Just prior to the first World War, announcements that radium would cure cancer encouraged several institutions to purchase large amounts of the element. The value of radium in the treatment of gynecological conditions was first fully realized by Kelly of Baltimore. In 1915 he reported a large series of cases treated with radium.

Progress in Surgery: Blood replacement, sulfonamide drugs and antibiotics encouraged Meigs[3] to re-explore the possibilities of radical hysterectomy. Taussig[4] emphasized that careful, nearly en bloc dissections of nodes of the pelvis should be made. Wertheim removed these lymph glands only if they were palpably involved, which in some instances resulted in cancer being left in the pelvis if metastases were minute or microscopic. Meigs[5] combined bilateral pelvic lymph node dissection with radical hysterectomy and in 1951 reported a series of 85 cases which stimulated interest again in the surgical approach to the problem. He cited the use of silver dura clips in node bearing areas as suggested by Dr. Langdon Parsons, and pointed out that effective radiation therapy was not being administered to the more distant nodal areas which were removed by surgery.

The occurrence of radioresistant tumors which extend locally prior to the development of distal metastases prompted Brunschwig[6] to effectively increase the extent of radical surgery. Many cases, however, which recur after radiation or radiation and surgery present widespread dissemination and are hopeless with any form of treatment.

Progress in Radiotherapy: Morris and Meigs[7] admitted that their results with radiation therapy were unsatisfactory even though they were comparable to the figures from

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other clinics. Studies with ionization chambers in the cervix revealed that the tumor dose of radiation was often far different from the calculated dosage in air. Calculations of isodose curves often showed that distal extensions of a tumor did not receive cancerocidal doses from the radium given. Increased accuracy of measurement of radiation in gamma roentgens at the periphery of the tumor is desired. It is a more accurate statement of effective dosage than measurement in milligram hours. Volume of tissue radiated, uniformity of the tissue radiation and physical distribution of the source together with improved methods for clinically determining the exact extent of the tumor are problems to be faced.

With an increase in the safety of radical surgery, ready access to lymph nodes of the pelvis has aided in the study of the effects of radiation. Reliable methods of quantitating the radiant energy delivered have aided in standardization of therapeutic schedules.

Recurrences after surgery or radiation are frequently found in the lateral pelvic wall suggesting that tumor cells were already outside the effective area of irradiation or operation at the time of treatment. Current thought is therefore being directed toward more efficient treatment of the lateral pelvic wall.

Results of Current Therapy: Complete hysterectomy will cure practically all cases of carcinoma in situ with no need for irradiation. In Stage I lesions a cure rate of 70 to 80 per cent is possible by either radiotherapy or surgical operation. The cure rate is about 50 per cent by either method of treatment when Stage II lesions are considered. With more extensive lesions, radiotherapy probably has more to offer. We are faced with the fact that two-thirds of all women presenting themselves for treatment of carcinoma of the cervix still die within five years from local extension of the tumor or distal metastases.

Radioactive Colloidal Gold (Au198): With the advent of the atomic age and the construction of the nuclear reactor pile, radioisotopes became available for clinical investigation.

Radioactive colloidal gold (Au198) is an isotope prepared by neutron bombardment of gold foil in a nuclear reactor pile. It is converted to gold chloride and is then reduced to metallic gold by ascorbic acid in the presence of excess gelatin. In this form, it is a stable colloid with deep cherry red color. With decay it is converted to the end product mercury (Hg198).

Particle size of the gold in suspension varies from 0.001 to 0.003 microns. The suspension of colloidal gold contains 10 trillion particles in 50 mc with each particle acting as a source of radiation. It has a half life of 2.7 days which allows about 95 per cent of the radiation dose to be delivered in 11 days. The radioactivity is due essentially to a 0.97 mev beta ray which has a maximum range of only 3.8 mm. in water and a 0.411 mev gamma component. It is reasonably heat stable.

Early Observations: In 1946, Sheppard and Hahn[8] called attention to the fact that radioactive isotopes were of most therapeutic value when there was some selectivity of uptake by the tissues. This selectivity is shown by the uptake of radioactive iodine

by the thyroid and by the uptake of radioactive strontium by growing bone tissue similar to its uptake of calcium. In addition to this natural selectivity, uptake by the tissues is also determined by the method of preparation, and the route of administration.

Drinker and Shaw[9] found that as much as 90 per cent of particles almost colloidal in size were taken up by phagocytic cells of the liver when the preparation was given intravenously.

Colloidal sols of radioactive manganese (Mn52) and gold (Au198) were studied by Sheppard, Wells, Hahn and Goodell[10]. These isotopes were given by cubital vein to several patients whose disease terminated fatally. Radioactivity of various tissues at autopsy was measured and compared. The liver and spleen contained a high concentration of radioactive gold with an intermediate concentration in the kidney and a low concentration in other organs.

Radioactive colloidal gold emits a gamma ray which makes it possible to determine the distribution of the injected material with a collimated counter. By the use of a directional type of counter, Jones, Wrobel, and Lyons[11] found that radioactive material remained in the tissues in which it had been deposited for as long as measurements could be made. Insolubility of gold colloids in body fluids suggested that they could be used for direct infiltration of neoplastic tissues[12]. Lymphomas and carcinomatous tumors in human subjects were treated by injections of radioactive gold directly into the tumors.

Some tumor tissue was so friable that it would not retain even small amounts of fluid. Other tumors were so vascular that local injection was tantamount to intravenous infusion.

Injection of tumors deep in the body precludes the need of excessive radiation of normal tissues to obtain an effective dose in the tumor. After injection of the tumor, the greatest intensity of radiation is within the tumor, decreasing toward the normal tissue in the periphery.

The radiation effect produced in tissues is almost entirely due to the beta emission. Because of a short half life of 2.7 days, it is unnecessary to remove the applicator supplying the source of radiation as is the case with radium.

Insolubility of radioactive colloidal gold which exists in metallic form renders it chemically and biologically inert. It has none of the toxicity of gold salts.

Animal Experiments: Sherman, Nolan, and Allen[13] conducted experiments in mice to determine the effectiveness of radioactive gold in the treatment of squamous cell carcinoma by direct injection. They found that colloidal gold leaked from puncture points in the skin and that it was absorbed into the general circulation from injection sites. To overcome this, the gold was suspended in a solution of pectin and dextrose. It was found that these tumors in mice could be cured with high survival rates when 200 to 300 microcuries per cc. of tumor tissue were injected. One to 25 millicuries of radioactive colloidal gold in pectin solution were injected under direct vision into the parametria of rabbits through an abdominal incision. At reoperation, 72 hours later, it was found that lymphatic channels were increased in number and were filled

with phagocytic cells. Gold particles were contained in the cytoplasm of the scavenger cells. Seven days after injection, considerable amounts of gold were found in the iliac lymph nodes accompanied by marked radiation damage. The injected area at three months showed marked fibrosis and atrophy of the normal cellular structures. Lymphatic channels were lined with gold particles and were involved in the fibrotic process.

In a study of tissue tolerance to radioactive gold, injection of graded doses from 0.25 to 3.5 millicuries per cc. of parametrial tissue was made. There were no injurious effects to normal structures at therapeutic levels. A study of general and local tolerance levels for radioactive colloidal gold injected into the parametrium of the monkey was made by Nolan, Jones, and Neil[14]. They concluded that limitations imposed by necrosis at the site of injection rather than liver injury was the decisive factor in arriving at the proper dosage for the human subject. They inferred that if 25 to 50 millicuries were injected into each parametrium, there would be sufficient spread through the parametrium and pelvic lymph nodes to cause sclerosis without extensive necrosis.

Clinical Experiments: In consideration of the above results, Sherman, Bonebrake, and Allen, in 1951,[15] were encouraged to continue the experiments at a clinical level. They found with cadavers that 50 to 60 cc. of material could be injected easily into each parametrium through the vagina. A technique was devised which resembled the insertion of radium needles into the parametrium. With sterile precautions, a 22 gauge spinal needle was inserted laterally through the mucosa and Mackenrodt's ligaments. The needle was advanced and angled 20 to 30 degrees from the midline to approximate the pelvic wall. Once in position, the stylet was removed and gold was injected as the needle was slowly withdrawn to prevent pooling. Three sites were usually injected in each parametrium to give a uniform dispersion of the gold throughout the area to be treated.

Ten patients with carcinoma of the cervix were injected with radioactive colloidal gold in amounts sufficient only to be traced and located at operation. The parametrial areas, showed definite radiation effects with cellular destruction and accompanying fibrosis. There was a marked increase in lymphatics which were engorged with phagocytes containing gold particles. The blood vessels showed typical radiation effects of endarteritis. Definite localized radiation effects were present in the lymph nodes. Two cases were found to have cancer cells far out in the parametrial tissues. However, they were encircled by radioactive gold and showed the usual disintegrating changes associated with irradiation.

In 24 patients, Allen, Sherman, and Arneson[16] determined the amount of irradiation received by various lymph nodes removed at operation. Gamma radioactivity was measured with a scintillation counter and the total amount of beta irradiation was calculated. It was evident that most of the nodes removed received more irradiation than do those treated by present day x-ray and radium.

Diodrast was added to the radioactive solution. X-rays made after injections of 30 to 40 cc. in each side showed diffuse infiltration of the parametrium. Scintoscanner measurements made during a two week period after injection showed that radioactivity was unchanged except for anticipated decay.

Allen, Sherman, and Arneson[16,17] reported the clinical use of radioactive colloidal gold and seemed to have better results than in comparable cases treated with x-ray and radium. Veldhuis, Swinehart, and Preuss[18] also reported a series of cases with favorable results.

Toxic Effects: The use of radioactive colloidal gold is not innocuous. This is attested by an increasing number of reports of toxic effects in the literature. In laboratory animals liver damage[19], hepatomas[20], and cirrhosis with ascites[21] have been produced by radioactive gold administration. Weight loss, anorexia and pleural effusions with varying degrees of bone marrow hypoplasia and anemia occurred in dogs after intraperitoneal administration of radioactive colloidal gold.

In three clinical cases treated with transvaginal injections of radioactive gold, a skin rash was noticed. This was attributed to sensitivity to pectin contained in the solution[15].

Radiation sickness with nausea and vomiting has been reported. Intratumoral injection is accompanied by less radiation sickness than with the use of x-ray or radium because there is less radiation of normal tissues[22]. This may well be true with interstitial injection if vascular tissues are avoided.

Schoolman and Schwartz[23] reported a case of aplastic anemia following intravenous therapy with radiogold. Hypoplasia of bone marrow was reported by Botsford et al[24] in four patients who received a dose of more than 50 millicuries. Gold was present in bone marrow following intraperitoneal or intratumoral injections.

Any patient who has received injections of radioactive gold must be considered a hazard to attendants[25]. Excreta of patients following intratumoral injections have never shown any appreciable radioactivity.

Genitourinary fistulas were noted in three patients treated by transvaginal injection of radioactive gold[16]. These patients also received radium and radical surgery. No serious complications of this nature followed the use of radioactive gold and operation or radioactive gold and radium. A patient who developed an abdominal fistula after intraperitoneal injection of radioactive gold has been reported[26].

Paralysis may occur when radioactive gold is injected into or in close proximity to nerves[27].

COMMENT

The ultimate value of irradiation of pelvic lymph nodes has not been proven. Whether metastatic carcinoma in the pelvic lymph nodes may be destroyed by radiation or whether it is peculiarly resistant to this form of treatment is debatable. However, there is strong suggestive evidence that irradiation of pelvic lymph nodes is a worthwhile procedure in terms of five year survival of patients[28].

Extension of tumor from the cervix is usually by direct or lymphatic extension laterally along the uterine vessels and Mackenrodt's ligaments. Radioactive colloidal gold is injected parametrially anticipating that it will be carried by phagocytes along

the same lymphatic channels as the tumor cells. Once the lymphatic channels are blocked with tumor cells, phagocytes containing radioactive gold may be shunted through other channels. A cancerocidal dose of radiation may never reach the lymph nodes that are already engorged with tumor cells.

Clinical observations indicate that there are marked variations in radiosensitivity of cervical cancer. Early recognition of radioresistant tumors is desirable so that surgery can be recommended. Radiation-sensitivity testing has been studied with conventional histologic techniques[29], by cytologic changes[30] and by radioactive tracer methods[31].

Although there are undoubtedly relative degrees of radiation sensitivity, it is very likely that only a small percentage of cervical cancers are highly resistant. Central cervical cancer is usually well healed after x-ray or radium therapy even in patients who succumb from metastases. Even though intensive focal radiation of pelvic lymph nodes is possible after injection of radioactive gold, there undoubtedly will be some resistant tumors that will fail to respond to treatment.

The final appraisal of the clinical use of radioactive gold must await further observations of large groups of cases with adequate controls.

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