RADIOSENSITIZATION OF ENDOMETRIAL ADENOCARCINOMA BY MEANS OF MEDROXYPROGESTERONE

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Hormone dependency and radiosensitivity of endometrial adenocarcinoma are studied. Pathologic data are compared for hysterectomy or curettement specimens obtained after curietherapy, only after curietherapy is preceded by administration of medroxyprogesterone. Destruction of adenocarcinoma by curietherapy seems to be enhanced by means of medroxyprogesterone. These data suggest phenomena of radiosensitization characterized by definite histologic transformations.

ALTHOUGH THE TREATMENT OF ENDOMETRIAL adrenocarcinoma seems to be primarily a surgical problem, curietherapy has an important place in the therapeutic scheme. Indeed, intra-uterine radium application is an excellent method to "sterilize" the cancer focus prior to the operative procedure and, in this way, minimizes the danger of dissemination.[1, 4, 6, 7, 10] Moreover, many patients with endometrial adenocarcinoma are poor operative risks or present other contraindications for surgery. In these instances, curietherapy remains the only available therapeutic procedure.

In our experience, many patients present residual, apparently viable cancer tissue after curietherapy, performed according to generally accepted standards and under dosimetrically valuable conditions.[3, 5, 8, 9, 11] Two solutions are at hand to control this situation—either to correct the curietherapeutic procedure or to enhance the radiosensitivity of the adenocarcinoma.

Of all curietherapeutic procedures, radium-packing by the Stockholm method seems, in our experience, most effective in destroying completely an adenocarcinoma focus in the uterine corpus.

However, because endometrial adenocarcinoma could be characterized by some degree of radioresistance,[2] chemotherapeutic sensitization prior to radiumtherapy should be attempted. In view of the hormone dependence of endometrial adenocarcinoma, it seems logical to attempt this preparation with hormonal chemotherapeutics, in particular with progestogens.

MATERIALS AND METHODS

A prospective study was done on 2 groups of patients—each composed of 20 women and statistically comparable as to clinical condition and histologic aspect of the endometrial adenocarcinoma.

The control group included 20 women suffering from an endometrial adenocarcinoma strictly confined to the uterine cavity, 10 of which were a well-differentiated type, the others poorly or nondifferentiated. The treatment was started by standardized intra-uterine curietherapy. This curietherapeutic procedure consisted in maintaining 5 tubes each containing 10 mg radium-element, and one tube containing 5 mg radium-element disposed in a fork-shaped applicator within the uterine cavity for 96 hours (Figs. 1, 2). In order to prove the value of the used radiotherapeutic procedure, a dosimetric study on the patient was made by means of an intravesical and intrarectal probe connected to an isodose plotter. Five weeks after curietherapy, a careful anatomicopathologic exploration of the uterine cavity was performed, either by complete curettement or directly on the operative specimen.

The experimental group was composed of 10 patients with a well-differentiated adenocarcinoma and 10 patients presenting a poorly or nondifferentiated tumor. During the 4 weeks preceding radium application, 1

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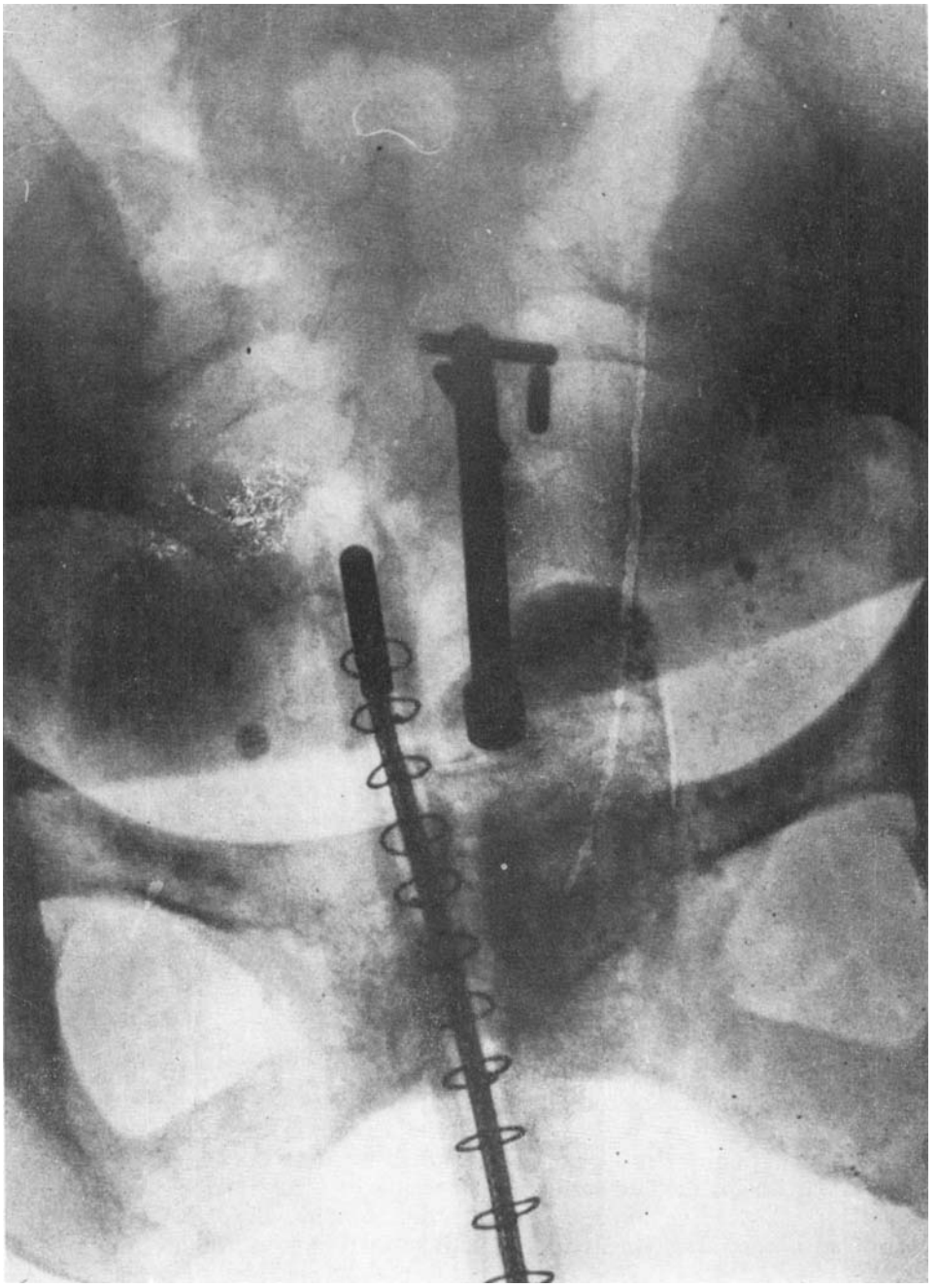

FIG. 1. Radiograph showing the "fork" shaped radium applicator within the uterine cavity and the dosimeter within the rectum.

g medroxyprogesterone (Depo-Provera, Upjohn) was administered weekly to these patients in 2 intramuscular injections. In order to discover possible histologic transformations induced by hormonal chemotherapy, an exploratory curettement was performed immediately before the described radium application. All histologic specimens were prepared by H.E.S. and P.A.S. staining.

RESULTS AND COMMENT

In 18 of 20 patients belonging to the control group, apparently viable cancer tissue was obtained from the uterine cavity 5 weeks

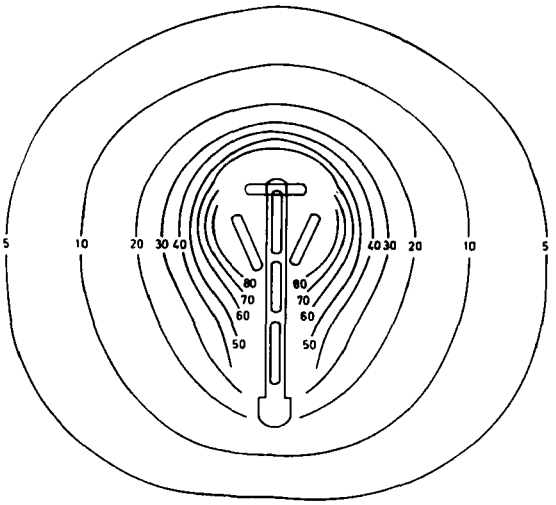

FIG. 2. Dosimetric study of the previous type of radium application, expressed in ry hour.

after curietherapy. These histologic data seem to prove a kind of radioresistance of endometrial adenocarcinoma against a generally accepted curietherapeutic procedure.

TABLE 1. Pathologic Data 5 Weeks after Curietherapy

ADENOCARCINOMA	PRETREATMENT WITH MEDROXYPROGESTERONE	NO PRETREATMENT
ABSENT	7	1
DEGENERATING	6	1
APPARENTLY VIABLE	7	18
TOTAL	20	20

Anatomicopathologic examination of the uterus 5 weeks after an identical curietherapeutic procedure preceded by hormonal treatment revealed residual, apparently viable cancer tissue in only 7 cases out of 20 (Table 1).

On a practical basis, these data could be interpreted as suggestive for phenomena of radiosensitization.

A comparative study between the responsive and the nonresponsive series of the experimental group might perhaps elucidate

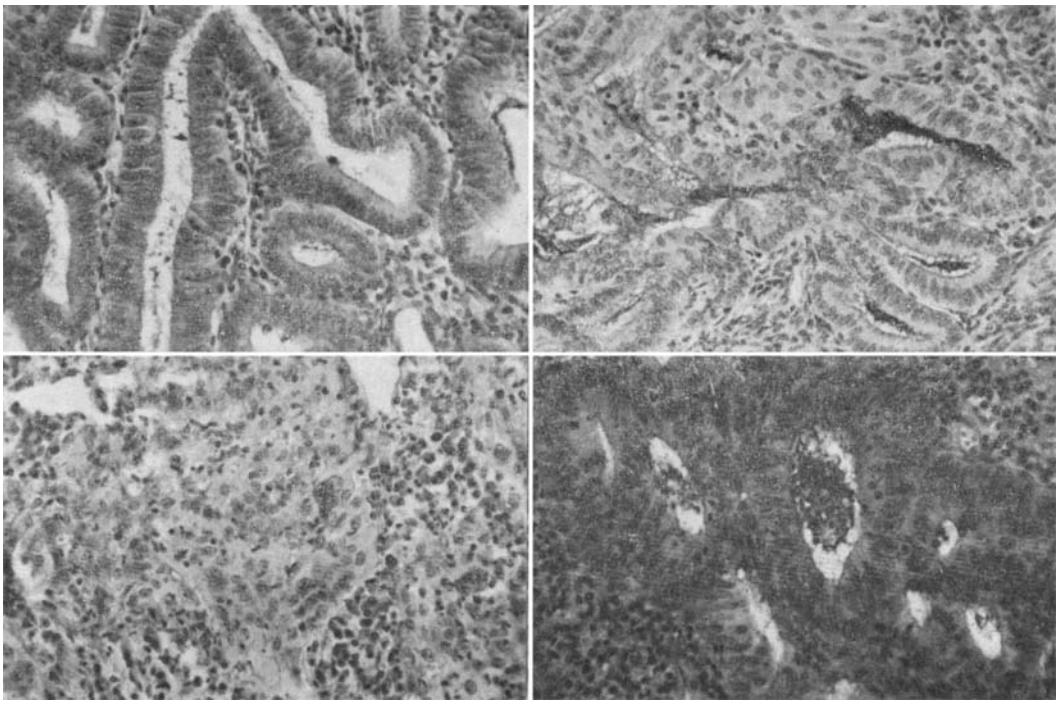

FIG. 3 *(top, left)*. Differentiated adenocarcinoma of the uterus—Curettement biopsy—P.A.S. staining.

FIG. 4 *(top, right)*. Same case after 5 weeks medroxyprogesterone treatment previous to curietherapy: evident phenomena of further maturation and stromal decidualization.

FIG. 5 *(bottom, left)*. Undifferentiated adenocarcinoma of the uterus—Curettement biopsy—P.A.S. staining.

FIG. 6 *(bottom, right)*. Same case after 5 weeks medroxyprogesterone treatment previous to curietherapy: evident phenomena of differentiation.

the mechanism of this hormonal radiosensitization by medroxyprogesterone.

The responsive and nonresponsive patients seem to present somewhat different characteristics. The responsive patients belong to the older postmenopausal group, they present a low parity and are sometimes unmarried and always obese. The nonresponsive patients are younger, sometimes in the premenopausal period, and present a higher parity.

The responsive adenocarcinomatous lesions are mostly localized within a more voluminous uterus; nonresponsive lesions seem concealed in a normal-sized uterus.

The histologic and histochemical characteristics of the adenocarcinoma might be important in determining hormone dependence of the lesion. In the responsive series, 9 of 13 are well-differentiated adenocarcinomata, 8 of them being charged with PAS-positive material. In the nonresponsive series, only one well-differentiated adenocarcinoma was found.

Furthermore, radiosensitization of the adenocarcinoma seems characterized by definite histologic and histochemical transformations (Figs. 3–6), namely, maturation, epithelial metaplasia, accumulation and redistribution of PAS-positive material. These morphological reactions to medroxyprogesterone found in most of responsive cases are quite absent in the nonresponsive series. These reactions of the adenocarcinomatous foci to parenteral hormonotherapy suggest a local mechanism in radiosensitization of endometrial adenocarcinoma by medroxyprogesterone. Instillation of 1 to 2 g medroxyprogesterone in the uterine cavity produces, within 10 days, the same morphological phenomena in the cancer tissue and provides further confirmation at the hypothesis of radiosensitization by local action.

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