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## **Combination of Progestogen Therapy with the Conventional Treatment of Endometrial Carcinoma**

T. LUUKKAINEN and O. KARJALAINEN

The frequency of endometrial carcinoma in relation to other female genital malignant tumors seems to be increasing as the average age of the female population increases. The ratio between the occurrence of carcinoma of the corpus uteri and of primary invasive carcinoma of the cervix was 1:2.4 in New South Wales (McGARRITY and SCOTT, 1968) and 1:2.3 in Finland as a whole (TIMONEN and OJANEN, 1967). The conventional treatment of endometrial carcinoma consists of the following methods: surgery alone, surgery combined with preoperative irradiation or postoperative irradiation, and irradiation alone. Even in the recent reports the effectiveness of these methods in the treatment of endometrial carcinoma has only been between 60% and 70% for the 5-year survival rate. Although high 5-year cure rates have been observed, when the carcinoma is confined to the corpus uteri (stage 1), the number of survivors reaching the fifth anniversary of this treatment is only 33% in stage 2 (McGARRITY and SCOTT, 1968) and very few having stage 3 or stage 4 will survive more than 5 years after the start of this treatment.

Other methods of treatment for advanced or recurrent endometrial carcinoma are therefore urgently needed. The poor results of the treatment of stage 2 with surgery or/and irradiation likewise indicate the need for a re-evaluation of the methods used.

It has been demonstrated during the last decade by several investigators that progestogen therapy causes objective and subjective improvement in patients with advanced or recurrent endometrial carcinoma (KELLEY and BAKER, 1961; KISTNER et al., 1961; STOLL, 1961; VARGA and HENRIKSEN, 1961; for further reports and more details see the recent review by NORDQVIST, 1969).

The effect of the progestogen treatment has been also demonstrated by giving progestogens before surgery or radiation to patients with a primary untreated endometrial carcinoma (VARGA and HENRIKSEN, 1961; KISTNER et al., 1965; BONTE et al., 1966; see also NORDQVIST, 1969). The progestogens have been used in these investigations mainly to study their effect in histologically different types of endometrial carcinoma and to study the dosage and nature of compounds needed for the beneficial effect.

KISTNER and co-workers (1965) describe a method of treatment in which progestogens are used as adjuvants to surgery and irradiation. Progestogens are given from the time of intracavitary radium and are continued until the time of surgery 3 weeks later or, if the cancer has spread beyond the uterus, X-ray therapy is given postoperatively in combination with progestin. The results of this treatment have not yet been published.

At our hospital since January 1, 1966, we have systematically treated all stages, excluding stage 0, of endometrial carcinoma with progestogen therapy combined with surgery and irradiation. Because the preliminary results seem to indicate improvement, especially in stages 2-4, the results of the treatment of patients who have been followed 1-3 years are reported here.

#### *Material and methods*

This study is based upon an analysis of the records of patients having endometrial carcinoma and treated during the years 1966 and 1967 and followed to April 1, 1969. The stage grouping of the patients has been done according the recommendations of the Third Congress of the International Federation of Gynecologists and Obstetricians in Vienna in 1961.

There were altogether 81 patients, when stage 0 was excluded. Of this group 65 patients were treated by operation, progestogen and irradiation, and 16 patients with progestogen and irradiation alone. Surgery was contraindicated in these patients, because of poor physical condition and/or advanced age.

The distribution of the patients according to stage in the operative series was as follows: 46% of cases in stage 1, 38.5% in stage 2, 12.4% in stage 3 and 3.1% in stage 4. In the radiologically treated series the respective percentages were 44%, 19%, 6% and 31%. The high percentage of cases more advanced than stage 1 demonstrated that stage 1 is treated in the local hospitals in Finland, while complicated and more advanced cases are remitted to the University Hospital. In the large series from New South Wales, stage 2 included 9.2% of cases and 1% were in stage 3 and stage 4 (McGARRITY and SCOTT, 1968).

#### *Treatment*

The method of treatment depends upon the extent of the disease as follows:

*Stage 1.* Each patient was given one preoperative irradiation, which consisted of the intracervical implantation of 75 mg radium source and an 80 mg radium source vaginally packed against the cervix, the average tumor dose being 3000 r. After three weeks abdominal hysterectomy with bilateral salpingo-oophorectomy and excision of the upper third of the vagina was performed. Progestogen therapy is given from the day of operation by injecting 50 mg medroxyprogesterone acetate (Depo-Provera, The Upjohn Company, Kalamazoo, Mich., USA) intramuscularly daily for one week. Then progestogen is continued orally by giving megestrol acetate (Niagestin, Novo Industri A/S, København, Denmark) 20 mg daily for six months and 10 mg daily for a further six months.

*Stage 2.* Preoperative irradiation is given as in stage 1. After three weeks the patients are subjected to radical hysterectomy with node dissection. Progestogen therapy is the same as in stage 1, but if the nodes are affected, then the loading dose with medroxyprogesterone acetate is 100 mg daily for 10 days. Six weeks after operation the patients are exposed to external irradiation.

*Stage 3:* The treatment is the same as in stage 2 but the surgery may be extended, depending on the case, to remove metastases, whenever possible, in the abdominal cavity.

*Stage 4.* These patients are treated primarily by giving progestogens. Progestogen therapy consists of intramuscular medroxyprogesterone acetate 50–100 mg daily for three weeks, and thereafter megestrol acetate 30 mg daily orally, a dosage which is maintained continuously. Patients who are found to gain from the operation (pyometra, large necrotic but mobile corpus uteri) are treated by hysterectomy with salpingo-oophorectomy. Otherwise the patients are treated with external irradiation in the addition to the progestogen therapy.

The patients treated with irradiation and progestogen therapy have been subjected from the time of the first intracavitary radium application to the same progestogen treatment, depending on the stages as described for the patients treated by surgery. The irradiation therapy consisted of three intracavitary implantations of radium, each of which consisted of five 50 mg radium sources or an equivalent amount of <sup>60</sup>Co, and after these three applications external irradiation was given. Three patients in stage 4 were treated with external irradiation only in addition to the progestogen therapy.

### Results

The mortality during the first and second years and the cumulative number of recurrences and deaths in the two groups of patients are shown in Table I. It should be stressed that the results are only preliminary even for the second year of observation, because only 62.5% of the cases have been observed for 2 years, but all for over 15 months, and the first for 3

Table I

Distribution according to stage of carcinoma corporis uteri, number of deaths and cumulative number of recurrences and deaths during the 1st and 2nd year after therapy with surgery and irradiation combined with progestogen (Group A) and irradiation combined with progestogen (Group B)

	Number of patients	Mortality during		Cumulative number of recurrences and deaths	
		1st year	2nd year	1st year	2nd year
<i>Group A:</i>					
Stage 1	30	—	—	—	—
Stage 2	25	1	—	1	1
Stage 3	8	2	—	3	3
Stage 4	2	1	—	1	1
Total	65	4	—	5	5
<i>Group B:</i>					
Stage 1	7	—	—	—	—
Stage 2	3	—	1	—	1
Stage 3	1	1	—	1	1
Stage 4	2	1	—	1	1
Palliative irradiation	3	2	—	2	2
Total	16	4	1	4	5

years up to now. On the other hand, there has been no mortality after the first year of observation in the group of patients operated on, irradiated and treated with progestogen, and no further recurrence of the disease either. In the group of patients treated with irradiation and progestogen there was one death during the second year. This latter group is small and unfavourable owing to the primary selection, high age and poor physical condition. Therefore, stages 2-4 combined give only a 30% survival rate for two years if one more death is to be expected.

In the group of 65 patients treated with surgery, irradiation and progestogen, the survival rate of the whole group for one year is 94%, and if one death is expected to occur during this year, 92% to two years, although 54% of patients were in stage 2-4. The salvage rates for stages 2, 3 and 4 were 94, 75 and 50% respectively, and these rates are valid for the second year at present, the patients in the group having been followed from 15 months to 3 years. The series reported by McGARRITY and SCOTT (1968) had a survival rate of 50% for stage 2 for two years.

#### *Comment*

It seems that the preliminary results presented strongly suggest that the combination of progestogen therapy with conventional methods of treatment improve the survival rate in stages 2-4. The results in stage 1 in both groups treated are good for almost two years, showing 100% survival at the present.

It has recently been demonstrated in the tissue cultures that the effect of progestogen on endometrial carcinoma depends on the concentration, but extremely high concentrations are needed to produce toxic effects on tumor tissue (NORDQVIST, 1964, 1969; KAHORN and TCHAO, 1968). These concentrations are not likely to be reached by parenteral administration. Only local administration by the method of KISTNER et al. (1965) can give this concentration on the surface of the endometrium. Until the results of determinations of tissue and plasma concentrations of progestogens given in vivo are available, it seems safer to use a loading dosage higher than in our series. We have given 350 mg of medroxyprogesterone acetate intramuscularly per week in stage 1 and 350-700 mg in more advanced stages. It has been reported that the optimum dosage of medroxyprogesterone acetate would be 600 mg per week during the first 5 to 6 weeks (ANDERSON, 1965). It seems that in stages 1 and 2 1000-1500 mg during the first 10 days from the day of the operation would be sufficient, and thereafter therapy could be continued with oral megestrol or medroxyprogesterone acetate.

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### Discussion

J. NEVINNY-STICKEL: We also have some experience in the treatment of endometrial carcinoma with progestogens. We used chlormadinone acetate. We treated some cases together with Prof. HAMMERSTEIN. There were mostly cases with metastasis, but also some cases without metastasis but with a bad risk for operation or irradiation. We have the impression that the success depends on the histological type of the endometrial carcinoma, i.e. that a mature carcinoma is well reacting and that from the other one which has solid parts in the histology and where the differentiation is lost there is not a good reaction to the therapy with progestagens. Two of our cases with two mature endometrial carcinoma are very interesting which we decided to treat with progestogens only. There was a bad risk to operate them. One of these cases has been for two years in treatment now, and the other one more than one year. We performed a curettage of the cavum uteri again and did not find any more carcinoma.

T. LUUKKAINEN: We all know that quite many clinics have been treating stage 3 and 4 with good results but I wanted to make it clear that one should also treat stage 1 and 2. I cannot say anything about the histology because the number of patients is quite small, and as you know it has been demonstrated in many reports that the effect of progestogen therapy is related to the histological picture.