Eur J Cancer, Vol. 29A, No. 8, pp. 1133–1140, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Treatment of FIGO (1971) Stage I Endometrial Carcinoma with Intensive Surgery, Radiotherapy and Hormonotherapy According to Pathological Prognostic Groups. Long-term Results of a Randomised Multicentre Study

Giuseppe De Palo, Costantino Mangioni, Piero Periti, Marcella Del Vecchio and Ettore Marubini

A multicentre trial on patients with apparent stage I endometrial carcinoma was conducted with the aims of defining a treatment plan on the basis of the pathological disease extension and of evaluating the effectiveness of adjuvant medroxyprogesterone acetate (MPA). After surgery, patients with disease limited to the endometrium did not receive any further treatment. Patients with inner myometrial invasion and well or moderate differentiation were randomised to no further treatment vs. MPA 100 mg orally twice a day for 12 months; patients with moderate or deep myometrial invasion or undifferentiated grade were randomised to radiotherapy on pelvis vs. radiotherapy plus MPA, and patients with node-positive disease (N+) were submitted to radiotherapy on pelvis and para-aortic nodes vs. radiotherapy plus MPA. At 84 months, analysis as intention to treat on 856 patients shows a high relapse-free survival, whereas it did not show any significant difference between the MPA-treated and untreated groups. The study indicates that relapse-free survival is influenced by a treatment based on the pathological extension of the disease and that adjuvant hormonotherapy does not improve the cure rate.
Eur J Cancer, Vol. 29A, No. 8, pp. 1133–1140, 1993.

INTRODUCTION

ENDOMETRIAL CARCINOMA is at present one of the most frequent neoplastic diseases in women. As about 90% of the cases are diagnosed at stage I, endometrial carcinoma is considered as the gynaecological tumour with the most favourable prognosis and the highest survival rate. Control of stage I endometrial carcinoma varies from 100% in selected series characterised by tumour limited to the endometrium with a high grade of differentiation and treated with adequate surgery [1, 2], to 70% in series with involvement of the adnexae. This percentage drops to 40% in women with a high operative risk in whom only radiotherapy can be performed [1].

The possibility of cure of stage I endometrial carcinoma depends, therefore, on the limits of FIGO classification and on the existence of pathological prognostic factors such as histological grade, myometrial invasion and retroperitoneal lymph node involvement.

The presence of deep myometrial invasion, lymph node metastases or undifferentiated histological grade defines a high-risk group, while the absence of these features indicated a low-risk group with a favourable prognosis. Primary surgical approach is, thus, necessary not only to establish the number of cases in which the tumour is beyond the limit of the corpus uteri, e.g. occult involvement of the endocervix, diffusion to the adnexae and/or serosa, but also to determine the pathological prognostic factors.

Correspondence to G. De Palo.
The authors are at the Istituto Nazionale Tumori, Via Venezian 1-20133 Milan, Italy.
Revised 7 Dec. 1992; accepted 15 Dec. 1992.

In December 1979, the subproject Clinical Multimodality Therapies of the special project Control of Neoplastic Growth of the Consiglio Nazionale delle Ricerche-CNR (National Research Council, Italy) was implemented. This endometrial carcinoma programme was carried out on a multicentre basis with the following aims: (1) to prospectively register all patients with FIGO (1971) stage I endometrial carcinoma observed at the participating operative units; (2) to evaluate a surgical pathological staging system; (3) to define a treatment plan based on the pathological extension of the disease and (4) to test the effect of adjuvant medroxyprogesterone acetate treatment administered at low doses orally for 1 year in a randomised clinical trial.

The aim of this paper is to report the results of the last two objectives. The results of the first two aims have been previously reported [3].

PATIENTS AND METHODS

Between 1 February 1980 and 31 December 1983, all patients with histologically proven FIGO (1971) stage I endometrial carcinoma diagnosed by D and C at the participating institutions (see Appendix) were considered eligible if they fulfilled the following criteria: age <75; no previous or synchronous neoplastic disease; no previous therapy; no neuropsychiatric disorders, severe disease or high surgical risk; geographic accessibility to follow-up; willingness to undergo therapy and follow-up; adequate staging.

Initial work-up included chest X-ray, intravenous urography, lymphography, X-ray of the pelvic bones, rectosigmoidoscopy or double contrast enema. Surgical staging included inspection of omentum and abdominal viscera with biopsies on suspicious lesions; lymph node sampling on pelvic and para-aortic nodes in

the presence of abnormal (positive or doubtful) lymphography or palpable, firm or enlarged anatomosurgical nodes or presence of clear extrauterine diffusion. However, after about 2 years from the start of the study, lymphadenectomy was performed upon clinical judgement. Peritoneal cytology (free fluid or washing) was optional. Surgical treatment consisted of total abdominal hysterectomy (TAH), bilateral salpingoovariectomy (BSO), and colpectomy of the superior third of the vagina. Pathological staging was performed on three sections of the ovaries, three sections of the tubes (intramural tract, isthmus, ampulla), one transverse section about 2 cm above the internal uterine orifice, three longitudinal sections of the upper two-thirds (anterior and posterior) and three longitudinal sections of the lower third of the corpus uteri and the cervix (anterior and posterior aspects).

The histological grade was classified as follows: G1: high degree of differentiation; G2: moderate degree of differentiation; G3: low degree of differentiation or undifferentiated carcinoma. Invasion of the myometrium was graded as follows: M0: carcinoma confined to the endometrium; M1: tumour involving as much as one-third of the myometrium; M2: tumour involving as much as two-thirds of the myometrium; M3: tumour involving the whole thickness of the myometrium.

After pathological examination, patients were classified into five risk groups: R0: no myometrial invasion, any G; R1: one-third of the myometrium invaded (M1) and high (G1) or moderate differentiation (G2); R2: two-thirds (M2) or all (M3) of the myometrium invaded, G1 or G2, or M1-M2-M3 and low differentiation (G3); R3: retroperitoneal involvement, G1-G2-G3, M1-M2-M3; RE: pathological stage II (occult involvement of the cervix), stage III (involvement of the ovaries, the free tract of fallopian tubes, the pelvic peritoneum, the parametria, except retroperitoneal node involvement), stage IV (involvement beyond the true pelvis).

A total of 1120 patients with FIGO (1971) stage I endometrial carcinoma were eligible, of whom 1055 were evaluable. The clinical characteristics, the extent of the disease and the natural history of the 1055 patients have been reported in a previous study [3]. According to the above parameters, 163 belonged to the R0 group, 382 to R1, 341 to R2, 23 to R3 and 146 patients to the RE group.

Patients were treated according to the design of the study reported in Fig. 1. Patients with tumour outside the uterine corpus (RE group) received a personalised treatment. R0 patients did not receive any further treatment after surgery. R1 patients were randomised to no further treatment vs. medroxyprogesterone acetate (MPA). R2 patients were randomised to receive external high-voltage radiotherapy (50 Gy) on the pelvis vs. the same radiotherapy plus MPA. Finally, R3 patients were randomised in two groups: one treated with external high-voltage radiotherapy on the pelvis (50 Gy) and para-aortic nodes (45 Gy), and the other one treated with radiotherapy plus MPA. The study protocol was approved by the ethical committee of each participating institution. Patients were randomly assigned to MPA and control groups after oral informed consent.

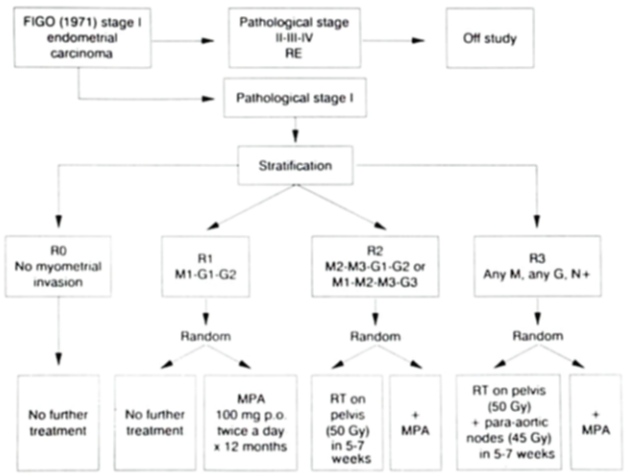

Fig. 1. Design of the study.

Radiotherapy

Postoperative radiotherapy was performed on the pelvic and the para-aortic nodes.

Treatment consisted of external beam radiotherapy (cobalt 60, betatrone, linear accelerator) through two opposed portals (anterior and posterior). Radiotherapy was started within 45 days of surgery.

In R2 patients, the pelvic area was irradiated. The pelvic target volume was shaped as follows: the lower limit was tangential to the caudal contour of the tuberosity of the ischium; the upper limit was tangential to the upper surface of L5, and the lateral limits were not less than 2 cm outside the ileopectineal line. Radiotherapy was administered in a single daily fraction of 1.7–2.0 Gy five times a week, up to a total focal dose of 50 Gy over 5–7 weeks. A boost of 10 Gy was administered to the sites of lymph node metastases where metallic clips were placed.

In the R3 category, the pelvic and the para-aortic nodes were irradiated. The pelvic area was irradiated as above. The target para-aortic volume was the following: the lower limit was defined by the upper limit of the pelvic field, the upper limit of the field was tangential to the upper surface of L1, and the lateral limits were the transverse apophysis of the lumbar vertebral bodies. The daily dose was 1.5–1.8 Gy for 5 days every week. The total focal dose was 45 Gy over 5–7 weeks. In these cases too, a boost of 5–10 Gy was given to the sites where lymph node metastases were detected.

Irradiation of the pelvis and para-aortic area was generally carried out simultaneously.

Hormonotherapy

MPA was administered at the dose of 100 mg twice a day orally for 1 year. This dose was chosen on the basis of the data of Sall *et al.* [4] and on the data of a pharmacokinetic study performed by one of the authors (P.P.) [5].

Follow-up

A standardised follow-up programme was set up. Patients were followed-up every 3 months during the first and second year; every 6 months from the third to the fifth year and every 12 months thereafter. At each control, physical and gynaecological examinations were carried out, as well as a Pap test on the vaginal cuff, while performance status and body weight were registered. Chest X-ray, X-ray of the pelvis and laboratory values were taken every 12 months. Liver echography, endoscopy, etc. were carried out in the case of a clinical doubt. Relapses were classified as local when they occurred in the vagina or central pelvis, regional in the case of relapse in the lateral pelvis or retroperitoneal nodes, and distant when distant sites were involved. Inguinal nodes were considered as extraregional nodes.

In the case of side-effects, the principal investigator of the operative unit had the option either to continue or to stop MPA treatment according to the severity of the side-effects. In the case of treatment discontinuation, follow-up had to be continued.

Data quality control

Randomisation was peripheral. Quality control of data was performed at a centralised data centre through a specific programme which was the same for all studies of the subproject Clinical Multimodality Therapies.

Whereas histopathological diagnosis as well as radiological diagnosis were not centralised, a specific programme of interactive validation provided monthly reports on the layout of all new cases registered, as well as on the treatment in progress or terminated. Meetings with the participating centres were held every 6 months in order to discuss, exclude or classify specific situations.

Statistical evaluation

As previously stated, the accrual period lasted from February 1980 to December 1983. Follow-up was planned for another 5 years. Unfortunately, due to a lack of funds, some operative units had to close to follow-up in December 1984. For each operative unit, a censoring date was chosen such that the percentage of patients lost to follow-up was less than 25% (median 17% and first quartile 13%). Two operative units were excluded from the analysis due to inadequacy of the follow-up procedure. These units had recruited 53 patients (R0: 25 cases, R1: 15 cases; R2: 13 cases, R3: 0 case). Therefore, the analysis was performed on 856 patients. Events which appeared after the censoring date were not taken into consideration; in other words, patients who relapsed or died after this date were considered as no evidence of disease (NED) and alive.

The analysis was carried out in terms of intention to treat. Cumulative incidence of relapse (CIR) and overall cumulative mortality (OCM) were measured from the date of surgery and computed by means of the product-limit method according to Kaplan–Meier [6]. Local, regional and distant relapses were taken as end points of CIR. Death from all causes was taken as the end point of OCM. Patients with second primary tumour were included in the analysis of CIR and treated as withdrawals at the time the second primary was diagnosed. Statistical comparison of different treatments in terms of CIR and OCM was performed by log-rank test.

RESULTS

The distribution of the 856 patients according to the risk groups is the following: R0, 138 patients; R1, 367 patients; R2, 328 patients and R3, 23 patients. The main characteristics of the 856 patients are reported in Table 1.

MPA treatment was assigned to 348 patients. For 21 of them, there was no information concerning treatment administration. Furthermore, MPA treatment was discontinued within 1 year for adverse effects in 17 cases, for early relapse in 6, for early or late refusal in 11 and for intercurrent events in 6 cases. These patients were, however, included in the analysis. 327 patients completed treatment with or without dose reduction or interruption (Table 2).

Frequency and site of the first unfavourable event are reported in Table 3. A total of 58 patients relapsed. Local relapses occurred in 19 patients (33%), distant relapses in 25 (43%), local plus distant and regional relapses in 5 (8.6%) patients,

Table 1. Characteristics of 856 patients

	R0	R1 (n = 367)		R2 (n = 328)		R3 (n = 23)	
	(n = 138)	MPA (n = 175)	No MPA (n = 192)	MPA (n = 162)	No MPA (n = 166)	MPA (n = 11)	No MPA (n = 12)
Age							
≤40	4	4	3	—	3	1	—
41–50	28	18	18	6	10	—	—
51–60	63	88	89	75	65	7	7
61–70	37	56	72	60	67	3	4
>70	6	9	10	21	21	—	1
Median age (years)	56	58	59	60	61	59	59
Histological type							
Adenocarcinoma	81	150	164	133	135	8	11
Adenoacanthoma	11	20	22	21	15	1	1
Clear cell	—	—	—	3	1	—	—
Adenosquamous	—	5	6	4	12	2	—
Undifferentiated	—	—	—	1	3	—	—
No tumour in the specimen	46	—	—	—	—	—	—
Histological grade							
G1	71	128	137	58	64	3	—
G2	18	47	55	72	66	4	10
G3/undifferentiated	2	—	—	32	36	4	2
Gx	47						
Myometrial invasion							
M1	—	175	192	14	12	5	1
M2	—	—	—	91	95	2	4
M3	—	—	—	57	59	4	7
M0	138	—	—	—	—	—	—

Table 2. Adjuvant treatment with MPA

No. patients randomised for MPA treatment	348	
No. cases with missing information	21	
No. treated patients	327	
Treatment without interruption or dose reduction	247	(76%)
Treatment with interruption or dose reduction	40	(12%)
Treatment discontinued	40	(12%)
Toxicity	17	
Relapse during treatment	6	
Early refusal	4	
Refusal	7	
Intercurrent events	6	
Viral hepatitis	2	
Ocular diseases	2	
Hemiparesis	1	
Post radiotherapy ileitis	1	

respectively. In 4 cases there was no information on the site of relapse. Thus, about 50% of failures occurred in distant sites. In patients with distant failures, the sites most involved were the abdomen, lung and extraregional lymph-nodes. Relapses occurred in 6 out of 23 patients (26%) with retroperitoneal node involvement, in 6 out of 138 patients (4.3%) with tumour confined to the endometrium, and in 46 out of 695 patients (6.6%) with myometrial invasion. Out of the 58 patients who relapsed, 19 had G1 tumour (33%), 23 G2 tumour (40%) and 15 G3 tumour (26%). One of these 58 patients belonged to the Gx group. Relapse was as frequent in patients treated with MPA as in those treated without MPA (29 relapses in each group), whereas distant or distant plus local relapses occurred in 20 patients treated with MPA and in 10 who did not receive MPA treatment. The association between histological grade and MPA treatment showed no difference in the incidence of relapse: relapses occurred in 10 G1-treated patients and in 9 G1-untreated patients, in 12 G2-treated cases and in 11 G2-untreated cases, in 7 G3-treated and in 8 G3-untreated patients.

Second primary tumours were observed in 19 patients with the following histopathological diagnosis: breast cancer, 11; colorectal cancer, 2; lung cancer, 4; liver cancer, 1; skin cancer, 1. The causes of death are reported in Table 4. In addition to the 47 patients who died from endometrial cancer, 24 patients died as a result of another disease without relapse of the primary tumour.

There were only a few mild to moderate adverse effects induced by MPA treatment. A total of 38 patients experienced adverse effects (11.6%), the most common being nausea, dyspeptic syndrome, overweight and phlebitis. In 17 patients MPA treatment had to be stopped for toxicity (Table 5).

In the R1 group, CIR at 84 months was 5.4% in patients treated with MPA and 4.2% in patients not treated with MPA (Fig. 2). In the R2 group these figures were 12 and 8%, respectively (Fig. 3), and finally, in the R3 group, CIR reached 18.2% in MPA-treated and 33.4% in MPA-untreated patients. No statistically significant difference between the two arms was attained in the R1 and R2 groups. Owing to the small size in R3 group the pertinent log-rank test was not performed.

Figure 4 shows the product limit estimates of CIR in the four risk categories. At 84 months, CIR was 4% in the R0 group, 4.8% in the R1 group, 10.4% in the R2 group, and 26.8% in the R3 group. No patient of the R0 and R3 groups relapsed after 42 months whereas the last relapse of the R1 group was at 84 months and at 66 months in the R2 group.

Finally, Fig. 5 reports the overall cumulative mortality which is of 6% for patients with tumour limited to the endometrium only (R0 group), 7.8% for patients who had inner myometrial invasion and well or moderate differentiation (R1 group), 18.1% for patients with deep myometrial invasion or undifferentiated grade (R2 group) and 27.2% for patients with retroperitoneal node involvement (R3 group).

DISCUSSION

It is common opinion that combined surgery and radiotherapy allows for the control of local disease. Surgery consists of total abdominal hysterectomy with bilateral salpingo-oophorectomy plus colpectomy of the superior third of the vagina; the last being performed so as to assure the correct excision of the cervix. Adequate irradiation of the vaginal vault, by means of intracavitary radium techniques, and the addition of external beam therapy reduced the incidence of vaginal [7, 8] and pelvic recurrences [7, 9, 10]. The latter data have been recently confirmed by Morrow *et al.* [11]. Nevertheless, the 5-year survival

Table 3. Site of first unfavourable event

	R0	R1		R2		R3		Total
		MPA	No MPA	MPA	No MPA	MPA	No MPA	
	$n = 138$	$n = 175$	$n = 192$	$n = 162$	$n = 166$	$n = 11$	$n = 12$	$n = 856$
Local relapse								
Vagina cuff	1	2	3	2	3	—	—	11
Vagina medium third	—	—	1	—	2	—	—	3
Vagina inferior third	—	—	—	—	1	—	—	1
Pelvis	2	—	1	—	—	—	1	4
Regional relapse	—	1	1	—	1	1	1	5
Distant relapse	2	3	2	11	4	1	2	25
Local + distant relapse	—	3	—	2	—	—	—	5
ED unknown site	1	—	—	3	—	—	—	4
Total number of relapses	6	9	8	18	11	2	4	58
Second primary tumour	2	1	7	4	5	—	—	19

ED = evidence of disease.

Table 4. Causes of death

	R0	R1		R2		R3		Total
		MPA	No MPA	MPA	No MPA	MPA	No MPA	
	n = 138	n = 175	n = 192	n = 162	n = 166	n = 11	n = 12	n = 856
Endometrial cancer	4	6	4	17	10	2	4	47
Other neoplastic disease	1	—	1	1	3	—	—	6
Complication of treatment	—	—	—	2	—	—	—	2
Other disease in patients with NEED	—	3	9	5	2	—	—	19
Myocardial infarction		1	3	3	1	—	—	8
Heart failure		—	2	—	1	—	—	3
Stroke		1	2	2	—	—	—	5
Thromboembolism		1	1	—	—	—	—	2
Cirrhosis		—	1	—	—	—	—	1
Other disease in patients with EED	—	1	—	—	—	—	—	1
Unknown causes in NEED	—	1	1	1	2	—	—	5
Unknown causes in EED	1	—	—	—	—	—	—	1
Total patients who died	6	11	15	26	17	2	4	81

NEED = no evidence of endometrial disease; EED = evidence of endometrial disease.

rate was not improved by external irradiation for systemic dissemination [9, 10] which represents a cause of failure in some risk group patients receiving adequate local treatment.

It is now widely accepted that the incidence of relapse depends on the presence of pelvic lymph node involvement, the depth of myometrial invasion and on the severity of histological grade [3, 12, 13].

Two points were particularly controversial in the 1970s: the necessity of postsurgical radiotherapy in all patients with endometrial carcinoma stage I, and the usefulness of adjuvant progestin therapy which resulted in an overall response rate of 30–40% in advanced cases [14, 15].

As regards the first question, the results of our study showed that patients with tumour limited to the endometrium and patients who had inner myometrial invasion and a well or moderate grade of differentiation should be treated with surgery alone. Low CIR and OCM justify the therapeutic approach without postsurgical radiotherapy. On the other hand, patients with pelvic and/or para-aortic node involvement need further treatment after radiotherapy. This clearly appears from our series in which CIR of patients treated with surgery and radiotherapy with or without MPA was 27%. The need for postsurgical radiotherapy in patients with moderate or deep myometrial invasion and well or moderate differentiation, as well as the treatment of patients with undifferentiated grade and any grade of myometrial invasion, is less clear because these patients were classified in one single risk group and there was no control group. As reported in a companion paper [3], the relapse-free survival (RFS) according to histological grade was 94.8, 90.3 and 78.5% in G1, G2 and G3, respectively. As the difference between G1/G2 (RFS = 93%) vs. G3 patients (RFS = 78.5%) was statistically significant, we think that patients with undifferentiated grade need not only radiotherapy but also further

Table 5. Adverse effects of MPA

Patients evaluable	327	
Patients without adverse effects	289	
Patients with adverse effects	38	(11.6%)
Patients with treatment interruption for adverse effects	17	
Nausea	7	(2)
Allergy	1	(1)
Urticaria	2	(2)
Phlebitis	5	(3)
Pruritus	1	(—)
Conjunctivitis	2	(—)
Oedema of the limbs	1	(1)
Overweight	6	(2)
Dyspeptic syndrome	6	(3*)
Hyperglycaemia	2	(1†)
Abnormal liver function tests	1	(—)
Phlebectasias	1	(1)
Hypertension	1	(1)
Paresthesias	1	(—)
Hirsutism	1	(—)

Number of cases with treatment interruption in parentheses.
*Patients with previous gastric ulcer, †in-patient with diabetes mellitus.

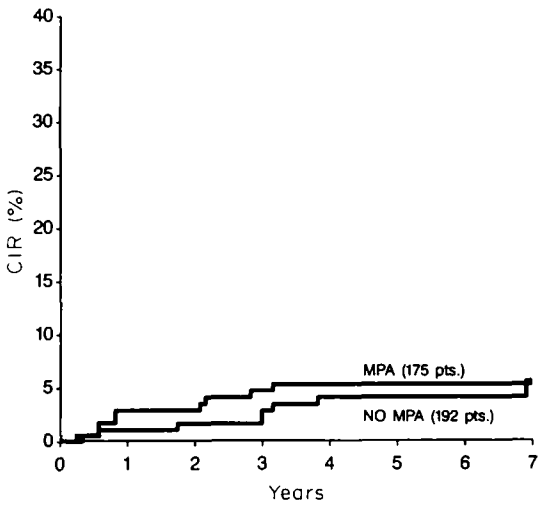

Fig. 2. Cumulative incidence of relapse (CIR) in R1 cases. CIR in MPA-treated patients is equal to 5.4% and in MPA untreated patients is 4.2%. Log-rank test: $P = 0.7170$.

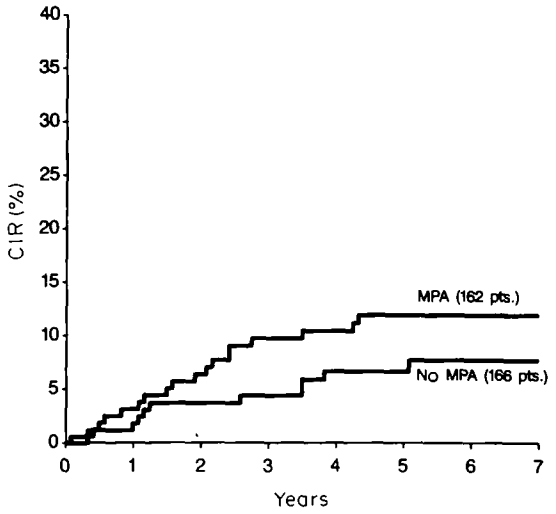

Fig. 3. Cumulative incidence of relapse (CIR) in R2 cases. CIR in MPA-treated patients is 12% and in MPA untreated patients is 8%. Log-rank test: $P = 0.1805$.

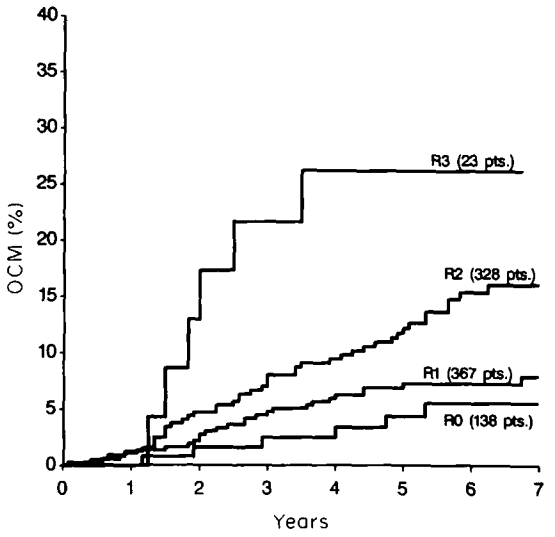

Fig. 5. Overall cumulative mortality in R0-R1-R2-R3 cases.

treatment. The same may be true for patients with moderate or deep myometrial invasion for the constant association between M and N as reported in our companion paper [3].

Finally, as regards the second question, although it has been suggested in the 1970s that progestins should be given to all patients with endometrial carcinoma as part of primary treatment [16], the use of progestins as adjuvant therapy was reported with contrasting results: it was favourably described in the series of Bonte *et al.* [14], unfavourably in the series of Malkasian and Decker [17] and without statistical significance in a small-scale study of the Istituto Nazionale Tumori of Milan [18] and in a large study reported by Lewis *et al.* [19].

The results of our study did not show any benefit in CIR at 84 months of observation from long-term adjuvant hormone treatment with MPA.

Three points would be questionable in the use of MPA: its route of administration, dose and compliance.

As regards the first point, Sall *et al.* [4] found that serum levels in patients treated with oral MPA (50 mg three times daily) were higher than those in patients treated with intramuscular MPA (300 mg weekly). As regards the second point, Kauppila [20] found in a retrospective analysis that the response rate for patients given intramuscular MPA was similar to that obtained in patients given oral MPA. Furthermore, Moore *et al.* [21], in an excellent review on systemic therapy of endometrial carcinoma, reported preliminary data of a randomised GOG trial in which high-dose MPA (1000 mg/day) was compared to moderate dose (200 mg/day) and no increase in response rate was observed in the group treated with high-dose MPA. Therefore, data from the most recent literature suggests that the route of administration of progestins, whether oral or intramuscular, does not influence the response rate, that adequate blood levels can be achieved with oral MPA, and that a high-dose progesterone therapy does not modify the response rate. Finally, it is well known that compliance is unknown in all studies with oral treatment. The difficulties in performing a multicentre study with long-term oral administration of a compound are highlighted in this trial by the fact that of the 348 randomised patients in the adjuvant group, 327 followed the given treatment, but only 247 completed the treatment without interruption or dose reduction.

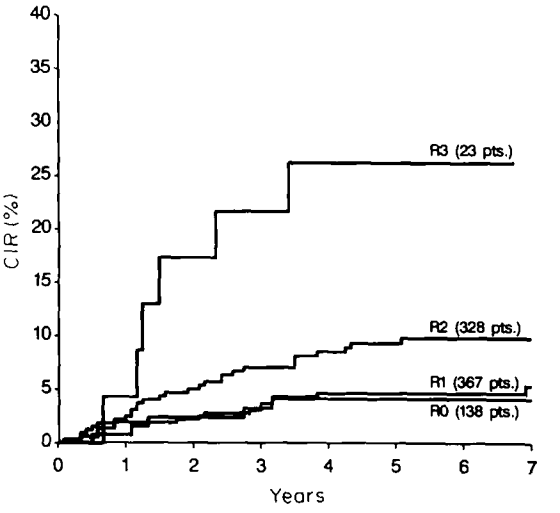

Fig. 4. Cumulative incidence of relapse (CIR) in R0-R1-R2-R3 cases.

Apart from these considerations, the study showed that adjuvant treatment with low prolonged oral doses of MPA did not reduce CIR.

Data of this study are in agreement with the results of a study conducted in the early 1970s [19] and with those of the British study [22]. The first study on 574 stage I patients reported a 4-year RFS for women given MPA (500 mg/week intramuscularly for 14 weeks) similar to that reported for women given placebo (87% in the MPA group vs. 93% in the placebo group). In the second trial, which was carried out simultaneously to our study, the 5-year survival rate for 429 patients with stage I-II-III endometrial carcinoma, after removal of withdrawals, was 73% in the MPA group, all stages, and 80% in the control group.

In conclusion, the following points are worth noting.

1. A treatment plan based on the pathological extension of the disease led to a CIR for stage I tumour confined to the endometrium equal to 4%, for stage I with myometrial invasion less than 10% and for retroperitoneal positive cases equal to 27%.
2. Since MPA, in addition to surgery and radiotherapy, does

not seem to reduce CIR, it should not be proposed as adjuvant treatment. Moreover, the literature [23–24] recently suggests that the response rate of progestational agents in patients with advanced endometrial carcinoma, reported by the authors of the 1960s-1970s and by Kauppila [20] in a retrospective analysis of 17 studies, was optimistic. Recent studies, in which standard criteria of response were used, reported a low level of effectiveness, approximately 15%, and it is well known that a drug may be used as adjuvant treatment when an overall response rate of 30–40% has been obtained in advanced disease.

3. Due to the high CIR of patients with lymph node metastases treated with radiotherapy after surgery, there is no doubt that a programme of combination chemotherapy should be explored through a controlled clinical trial.

1. Nolan JF, Huen H. Prognosis in endometrial cancer. *Gynecol Oncol* 1976, **4**, 384–390.
2. Green N, Melbye RW, Kernen J. Stage I well differentiated adenocarcinoma of the endometrium. *Am J Obstet Gynecol* 1975, **123**, 563–566.
3. Mangioni C, De Palo G, Marubini E, Del Vecchio M. Surgical pathologic staging in apparent stage I endometrial carcinoma. *Int J Gynecol Cancer* (submitted).
4. Sall S, DiSaia P, Morrow CP, *et al.* A comparison of medroxyprogesterone serum concentrations by the oral or intramuscular route in patients with persistent or recurrent endometrial carcinoma. *Am J Obstet Gynecol* 1979, **135**, 647–650.
5. Periti P, Ciuffi M, Mazzei T. Pharmacokinetics of oral medroxyprogesterone acetate at moderate doses in a long-term study. In Campio L, Robustelli della Cuna G and Taylor RW, eds. *Role of Medroxyprogesterone in Endocrine-related Tumors*, Volume II. New York, Raven Press, 1983.
6. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
7. Joslin CA, Vaishampayan GV, Mallik A. The treatment of early cancer of the corpus uteri. *Br J Radiol* 1977, **50**, 38–45.
8. De Palo G, Kenda R, Andreola S, Luciani L, Musumeci R, Rilke F. Endometrial carcinoma: stage I. A retrospective analysis of 262 patients. *Obstet Gynecol* 1982, **60**, 225–231.
9. Onsrud M, Kolstad P, Normann T. Postoperative external pelvic irradiation in carcinoma of the corpus stage I: a controlled clinical trial. *Gynecol Oncol* 1976, **4**, 222–231.
10. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma. *Obstet Gynecol* 1980, **56**, 419–426.
11. Morrow CP, Bundy BN, Kurman RJ, *et al.* Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group Study. *Gynecol Oncol* 1991, **40**, 55–65.
12. DiSaia PJ, Creasman WT, Boronow MD, Blessing JA. Risk factors and recurrent patterns in stage I endometrial cancer. *Am J Obstet Gynecol* 1985, **151**, 1009–1015.
13. DiSaia PJ. Management of early adenocarcinoma of the endometrium with surgical staging followed by tailored adjuvant radiation therapy. In Bulletti C, Gurpide E, eds. *The Primate Endometrium. Ann NY Acad Sci* 1991, **622**, 488–495.
14. Bonte J, Decoster JM, Ide P, Billiet G. Hormonoprophylaxis and hormonotherapy in the treatment of endometrial adenocarcinoma by means of medroxyprogesterone acetate. *Gynecol Oncol* 1978, **6**, 60–75.
15. Taylor RW. Hormone therapy in gynaecological cancer. In Brush MG, Taylor RW, eds. *Gynaecological Malignancy, Clinical and Experimental Studies*. London, Baillière Tindall, 1975, 212–221.
16. Taylor RW. Gynaecological malignancy. *Practitioner* 1979, **222**, 195–201.
17. Malkasian GD, Decker DG. Adjuvant progesterone therapy for stage I endometrial carcinoma. *Int J Gynaecol* 1978, **16**, 48–49.
18. De Palo G, Spatti GB, Bandieramonte G, Luciani L. Pilot study with adjuvant hormone therapy in FIGO stage I endometrial carcinoma with myometrial invasion. *Tumori* 1983, **69**, 65–67.
19. Lewis GC, Slack NH, Mortel R, Bross IDJ. Adjuvant progestogen therapy in primary definitive treatment of endometrial cancer. *Gynecol Oncol* 1974, **2**, 368–376.
20. Kauppila A. Progestin therapy of endometrial, breast and ovarian carcinoma. *Acta Obstet Gynecol Scand* 1984, **63**, 441–450.
21. Moore TD, Phillips PH, Nerenstone SR, Cheson BD. Systemic treatment of advanced and recurrent endometrial carcinoma: current status and future directions. *J Clin Oncol* 1991, **9**, 1071–1088.
22. Macdonald RR, Thorogood J, Mason MK. A randomised trial of progestogens in the primary treatment of endometrial carcinoma. *Br J Obstet Gynaecol* 1988, **95**, 166–174.
23. Thigpen T, Blessing J, DiSaia PhJ, Ehrlich C. Oral medroxyprogesterone acetate in advanced or recurrent endometrial carcinoma: results of therapy and correlation with estrogen and progesterone receptor levels. The Gynecologic Oncology Group experience. In Baulieu EE, Iacobelli S, McGuire WL, eds. *Endocrinology and Malignancy. Proceedings of the First International Congress on Cancer and Hormones*. Park Ridge, NJ, Parthenon, 1986, 446–454.
24. Podratz KC, O'Brien PC, Malkasian GD, Decker DG, Jefferies JA, Edmonson JH. Effects of progestational agents in treatment of endometrial carcinoma. *Obset Gynecol* 1985, **66**, 106–110.

Acknowledgements—We are grateful to Miss Patrizia Di Donato for secretarial assistance. The study was supported by a grant from the National Research Council of Italy. Presented in part to the American Society of Clinical Oncology, 1985.

APPENDIX
ENDOMETRIAL CANCER PROGRAMME OF THE ITALIAN NATIONAL RESEARCH COUNCIL: PARTICIPATING INSTITUTIONS

Institutions	Investigators
University of Bari	
Dept. Gynecology and Obstetrics	G. Cagnazzo, A. Restaino
Institute of Radiotherapy	P. Garriba
Institute of Pathology	A. Cimino
University of Bologna	
1st Dept. Gynecology and Obstetrics	G. Sani, G. Gentile
2nd Dept. Gynecology and Obstetrics	C. Orlandi, A. Marabini
Institute of Radiotherapy	L. Babini
Institute of Pathology	G. Martinelli
University of Brescia	U. Bianchi, S. Sartori
Dept. Gynecology and Obstetrics	L. Magno
Institute of Radiotherapy	M. Falchetti
Institute of Pathology	
University of Catania	
Dept. Gynecology and Obstetrics	S. Di Leo, S. Caschetto
Institute of Radiotherapy	S. Greco
Institute of Pathology	G. Nuciforo
University of Ferrara	
Dept. Gynecology and Obstetrics	G. Mollica, A. Bianchi
Institute of Radiotherapy	G. Magnoni
Institute of Pathology	I. Nenci

University of Firenze	
Dept. Gynecology and Obstetrics	G.B. Massi, L. Savino
Dept. of Pharmacology	P. Periti, T. Mazzei
Institute of Radiotherapy	A. Cionini
Institute of Pathology	M. Colafranceschi, G. Taddei
University of Genova	
Dept. Gynecology and Obstetrics	G. Pescetto, N. Ragni
Institute of Pathology	A. Badini
University of Milano	
Dept. Gynecology and Obstetrics	C. Mangioni, F. Landoni, A. Lissoni
Institute of Radiotherapy	A. Colombo
Institute of Pathology	G. Bratina
University of Milano	
Dept. Gynecology and Obstetrics	M. Vignali, M. Luerti
Institute of Radiotherapy	M. Boturri
Institute of Pathology	M.C. Antonacci
University of Milano	
Dept. Gynecology and Obstetrics "Mangiagalli"	C. Belloni
Institute of Radiotherapy	F. Rossi
Institute of Pathology	S. Carinelli
University of Milano*	
Dept. Gynecology and Obstetrics	G. Bolis, E. Saraceno
Institute of Pathology	S. Carinelli
University of Pavia*	
Dept. Gynecology and Obstetrics	P.F. Bolis, M. Franchi
Institute of Pathology	P. Tenti
University of Padova	
Dept. Gynecology and Obstetrics	A. Onnis, T. Maggino
Division of Radiotherapy and Nuclear Medicine-General Hospital	S. Maluta
Institute of Pathology	A. Piazza
University of Pisa	
Dept. Gynecology and Obstetrics	P. Fioretti, A. Gadducci
Institute of Radiotherapy	F. Ducci
Institute of Pathology	U. Urbano
University of Roma "La Sapienza"	
1st Dept. Gynecology and Obstetrics	L. Carenza, C. Villani
Institute of Radiotherapy	A. Loasses
Institute of Pathology	A. Vecchione
University of Roma "Cattolica"	
Dept. Gynecology and Obstetrics	S. Dell'Acqua, P.A. Margariti
Institute of Radiotherapy	N. Cellini
Institute of Pathology	M.A. Dina
University of Torino	
1st Dept. Gynecology and Obstetrics	P. Sismondi, R. Barengo
2nd Dept. Gynecology and Obstetrics	R. Monti, S. Danese
Institute of Radiotherapy	P. Rotta, M. Sacco
Division of Radiotherapy, P. Pinto Hospital	G. Sinistrero
Division of Pathology S. Anna Hospital	R. Arisio
Hospital of Como "Valduce"*	
Division of Gynecology	C. Meroni
Division of Pathology	G.C. Butti
Istituto Tumori "Regina Elena"—Roma	
Division of Gynecology	G. Atlante, M. Pozzi
Division of Radiotherapy	V. Le Pera
Division of Pathology	A. Bigotti
Statisticians	E. Marubini, M. Del Vecchio
Data Managers	M. Merson, F. Falcetta
Director of the subproject, Clinical Multimodality Therapies, of the special project, Control of Neoplastic Growth, supported by the National Research Council of Italy and coordinated at the Istituto Nazionale Tumori, Milano	G. De Palo

*Patients were treated at the Institute of Radiotherapy of Brescia.