CONCLUSION

In ovarian cancer and endometrial cancer the surgeon plays an important role in both the staging procedure and in the removal of as much tumour as possible. Although uniform treatment policies have not been developed, the better understanding of the pattern of spread in both tumours allows for accurate staging and can be of help in selecting patients for more extended treatment and saving others from unnecessary overtreatment.

1. Young RC, Decker DG, Wharton JT, *et al.* Staging laparotomy in early ovarian cancer. *JAMA* 1983, **250**, 3072–3076.
2. Helewa ME, Krepart GV, Lotocki R. Staging laparotomy in early epithelial ovarian carcinoma. *Am J Obstet Gynecol* 1986, **154**, 282–286.
3. Trimbos JB, Schueler JA, Van Lent M, Hermans J, Fleuren GJ. Reasons for incomplete surgical staging in early ovarian carcinoma. *Gynecol Oncol* 1990, **37**, 374–377.
4. Young RC. Initial therapy for early ovarian carcinoma. *Cancer* 1987, **60**, 2042–2049.
5. Guthrie D, Davy MLJ, Phillips PR. Study of 656 patients with "early" ovarian cancer. *Gynecol Oncol* 1983, **17**, 363.
6. Heintz APM, Van Oosterom AT, Baptist J, *et al.* The treatment of advanced ovarian carcinoma (1): clinical variables associated with prognosis. *Gynecol Oncol* 1988, **30**, 347–358.
7. Neijt JP, Ten Bokkel Huinink WW, Van der Burg MEL, *et al.* Randomised trial comparing two combination regimens (CHAP-5 v CP) in advanced ovarian carcinoma. *J Clin Oncol* 1987, 5, 1157–1168.
8. Griffith CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Int Monogr* 1975, **42**, 101–105.
9. Hacker NF. Controversial aspects of cytoreductive surgery in epithelial ovarian cancer. *Baillieres Clin Obstet Gynaecol* 1989, 3, 49–57.
10. Di Re F, Fontanelli R, Raspagliesi F Di Re E. Pelvic and para-aortic lymphadenectomy in cancer of the ovary. *Baillieres Clin Obstet Gynaecol* 1989, 3, 131–142.
11. Burghardt E, Lahousen M, Stettner H. The role of lymphadenectomy in ovarian cancer (chapter 42). In Sharp F, Mason WP, Leake RE, eds. *Ovarian Cancer, Biological and Therapeutic Challenges*. London, Chapman and Hall Medical, 1990, 425–433.
12. Kenemans P, Bast RC, Yedema CA, Price MR, Hilgers J. CA125 and polymorphic epithelial mucin as serum tumor markers. *Cancer Rev* 1988, **11**, 119–144.
13. Berek JS. Epithelial ovarian cancer. In Berek JS, Hacker NF, eds. *Practical Gynecologic Oncology*. Baltimore, Williams and Wilkins, 1990, 327–364.
14. Young RC. A second look at second-look laparotomy. *J Clin Oncol* 1987, 5, 1311–1313.
15. Jones HW. Treatment of adenocarcinoma of the endometrium. *Obstet Gynecol Survey* 1975, **30**, 147–169.
16. Aalders JG, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma. *Obstet Gynecol* 1980, **56**, 419.
17. Creasman WT, Morrow CP, Bundy L, *et al.* The surgical pathologic spread pattern of endometrial cancer. A Gynecologic Oncology Group study. *Cancer* 1987, **60**, 2035–2041.
18. Lotocki RJ, Copeland LJ, De Petrillo AD, Muirhead W. Stage I endometrial adenocarcinoma: treatment results in 835 patients. *Am J Obstet Gynecol* 1983, **146**, 141–145.
19. Piver MS, Yazigi R, Blumenson L, Tsukada Y. A prospective trial comparing hysterectomy, hysterectomy plus vaginal radium and uterine radium plus hysterectomy in stage I endometrial carcinoma. *Obstet Gynecol* 1979, **54**, 85–89.
20. Potish RA, Twiggs LB, Adcock LL, Savage JE, Levitt SH, Prem KA. Para-aortic lymph node radiotherapy in cancer of the uterine corpus. *Obstet Gynecol* 1985, **65**, 251–256.
21. Morrow CP, Di Saia PJ, Townsend DE. Current management of endometrial carcinoma. *Obstet Gynecol* 1973, **42**, 399–406.
22. Rutledge F. The role of radical hysterectomy in adenocarcinoma of the endometrium. *Gynecol Oncol* 1974, 2, 331–347.
23. Onsrud M, Aalders JG, Abeler V, Taylor P. Endometrial carcinoma with cervical involvement (stage II): prognostic factors and value of combined radiological–surgical treatment. *Gynecol Oncol* 1982, **13**, 76–86.
24. Aalders JG, Abeler V, Kolstad P. Clinical (stage III) as compared to subclinical intrapelvic extra-uterine tumor spread in endometrial carcinoma: A clinical and histo-pathological study of 175 patients. *Gynecol Oncol* 1984, **17**, 64–74.
25. Aalders JG, Abeler V, Kolstad P. Stage IV endometrial carcinoma. A clinical and histopathological study of 83 patients. *Gynecol Oncol* 1984, **17**, 75–89.

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Systemic Treatment in Disseminated Endometrial Cancer

J.P. Neijt

Both hormonal agents and chemotherapy are of value in the treatment of selected patients with endometrial cancer. In unselected patients with advanced disease about 25% respond to progestational agents and 40% to combination chemotherapy. The choice between the two treatments is made on the basis of a number of prognostic factors, such as receptor status, tumour grade, performance status and tumour burden. Further improvement of treatment outcome is to be expected from new agents such as gonadotrophin releasing hormone analogues, taxol and modulation of 5-fluorouracil.
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INTRODUCTION

DURING THE past decades the incidence of endometrium cancer has tended to increase in most European countries as well as in the United States of America. The increased prevalence may be related to the aging of the population combined with exogenous factors. Most cases are diagnosed in older patients with diabetes, hypertension, or obesity, which complicates treatment. It is to be expected that one-third of the patients with endometrial cancer will require treatment for widespread or recurrent disease.

Table 1. Results of progestational agents in advanced or recurrent endometrial cancer before and after 1980

Agent	No. of patients	Response rate	Reference
Before 1980			
Medroxyprogesterone	151	34	2
Megestrol acetate	125	33	2
Medrogestrone	56	30	3
After 1980			
Progestogens	155	11	4
Depo-provera	114	16	5
MPA, oral	494	15	6

The overall 5-year survival rates indicate that endometrial cancer is a serious disease. Despite adequate treatment in stages I (cancer confined to the corpus) and II (extension to cervix only), only 75 and 50% of the patients, respectively, enjoy long-term survival. Those patients in stages I and II with positive periaortic nodes, deep myometrial invasion, and poorly differentiated tumours, represent a subgroup with a poor outlook. Approximately 50–60% of this subcategory will relapse within 3 years. In the advanced stages the survival rate at 5 years is roughly 25% for FIGO stage III (clinically extension of the tumour outside the uterus, but confined to the true pelvis) and only 5–10% in FIGO stage IV (extension beyond the true pelvis, or invading bladder or rectum with or without distant metastases).

The therapeutic approach to endometrial cancer is determined by prognostic factors such as the spread of the tumour, the size of the primary, the degree of differentiation, and the patient's performance status. This paper summarises the possibilities for systemic treatment, hormonal or cytotoxic, for patients in whom surgery and irradiation are of no benefit.

HORMONAL THERAPY

Hormonal therapy has been the most commonly used form of systemic treatment in recurrent and advanced cases of endometrial cancer. The most widely used progestogens are megestrol acetate, medroxy progesterone acetate, and hydroxyprogesterone acetate. The popularity of these drugs is caused by their lack of toxicity and easy administration. There is no significant advantage for any of these agents and neither route of administration nor the use of high dosages seem to influence the end results [1].

According to the older literature, progestational agents produce response rates of 30–50%, but this is probably too optimistic. Most of the recent reports in which more stringent objective response criteria were applied, mention lower response rates around 15% (see Table 1). Both survival and disease-free survival are brief after treatment with progestins. In the experience of the Mayo Clinics, 40% of patients are alive at 12 months, 19% at 2 years and 8% at 5 years [4].

One of the most important predictive factors for the efficacy of progestational agents is the receptor status. Table 2 summarises the results of series which report the response to progestational agents in relation to the receptor status in advanced diseases. Of the total of 135 patients in Table 2, 46 were receptor positive (34%). This rate is much lower than the overall positive receptor status in early stages (roughly 70%) [7]. The overall response rate of 25% (34 out of 135 patients) holds, as could be expected for unselected cases (15–34% in Table 1). In a selected subgroup of receptor-positive patients a mean response rate of 57% is established which is in contrast to the 9% response rate in receptor-negative patients. From the data in Table 2 it can be concluded that the receptor status is of value for the prediction of the response to hormone therapy. Therefore, a receptor assay is useful in all patients with advanced or recurrent cancer. Tissue for this assay can sometimes be obtained by needle biopsy, and immunohistochemical analysis of the tissue sections [14]. A major problem that limits the use of the receptor is the lack of consensus about what can be considered as receptor positive and also the absence of a standardised assay [15].

Several reports have mentioned the relationship between progesterone receptor activity and histological grade. Most data concern the earlier stages of the disease. Analysis of 258 early cases showed that the progesterone receptor was present in 33% of the undifferentiated, 56% of the moderately differentiated, and 81% of the well-differentiated tumours [7]. Overall, 62% of the samples were positive for progesterone receptors. In patients with advanced primary or recurrent disease Podratz found a 40% response rate among well-differentiated, but not a single response among 27 patients with an undifferentiated tumour [4]. A similar experience has been reported by the Gynecological Oncology Group: 20% of grade 1 lesions responded but no responses were seen in 12 patients with grade 3 disease [16]. Unfortunately, most patients in stage III and IV have undifferentiated, receptor-negative tumours. One of the reasons being the fact that well-differentiated grade I tumours are less likely to recur. The above indicates that only a small subset of patients with advanced disease and with well-differentiated, hormone receptor-positive tumours are likely to benefit from treatment with progestins.

The poor results with progestational agents had led to the use of other hormone active drugs like tamoxifen and analogues of gonadotrophin releasing hormone (GnRH). Tamoxifen is known to increase the progesterone receptor content [17, 18] and also may have a direct effect on the tumour proliferation by blocking the binding of oestradiol to the oestrogen receptor. Results of clinical trials using tamoxifen in a dose of 20–40 mg daily led to

Table 2. The relationship between progesterone receptor and response to therapy in series reported in 1980 or later

Reference	Response in receptor-positive patients No. (%)	Response in receptor-negative patients No. (%)	Response in all patients No. (%)
8	5/6 (83)	2/7 (29)	7/13 (54)
6	4/10 (40)	3/25 (12)	7/35 (20)
9	7/8 (88)	1/16 (7)	8/24 (33)
10	3/5 (60)	1/8 (12)	4/13 (31)
11	2/4 (50)	1/17 (9)	3/21 (14)
12	2/3 (30)	0/3 (0)	2/6 (33)
13	3/10 (30)	0/13 (0)	3/23 (13)
Total	26/46 (57)	8/89 (9)	34/135 (25)

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response rates varying between 0 and 53% (mean 22%) [1]. It is suggested that women with well-differentiated tumours, and those who previously responded to progesterone are most likely to benefit from treatment with tamoxifen.

A new treatment for endometrial cancer may consist of the use of GnRH analogues. GnRH analogues may have a direct effect on endometrial cancer through a receptor for GnRH. However, several other mechanisms of action might affect the tumour. To test the antitumour effect of a GnRH analogue in recurrent endometrial cancer an open phase II trial was performed at The Royal London, Royal Marsden and St. Bartholomew's hospitals. 17 patients with endometrial cancer which had recurred after surgery, radiotherapy and progesterone treatment were treated monthly with a subcutaneous injection of zoladex 3.6 mg. 6 out of 17 patients (35%) achieved a remission which continued for a median of 20 months with no adverse effects. The group concluded that GnRH analogues have a significant antitumour effect in recurrent endometrial cancer which warrants further examination and comparison with progestogens [19].

NON-HORMONAL CHEMOTHERAPY

After hormonal treatment fails, cytotoxic agents have been used in endometrial cancer either alone (see Table 3) or in combinations (Table 4). Most of the phase-2 data on single drugs concern older series in which less stringent objective response criteria were used than has been the case in the past decade, which means that the response rates may have been exaggerated. The response rate for cytotoxic agents is also influenced by the site of the metastases. In the experience of the EORTC, an increased responsiveness of vaginal metastases, lung metastases, and lymph nodes was found, whereas the primary tumour in the pelvis and the abdominal masses were less likely to respond. A major factor with a negative influence on the likelihood to response is prior radiotherapy. In a series of 25 previously irradiated patients studied by the Gynecologic Oncology Group, cisplatin in a dosage of 50 mg/m^2 led to only one remission, whereas in another group comprising 39 non-irradiated patients the same dose of cisplatin led to 10 remissions [20].

Table 3. Published data of phase-2 studies with single-agent chemotherapy in endometrial cancer (modified and updated from Thigpen et al.[20])

Drugs	Total no. of patients collected	No. of responders	Response rate
Cisplatin	128	33	26
Doxorubicin	179	49	27
Cyclophosphamide	33	7	21
Epirubicin	24	6	25
Hexamethylmelamine	20	6	30
VP-16	29	1	3
Vinblastine	34	4	12
Bleomycin	8	3	37
5-Fluorouracil	43	10	23
Carboplatin	25	7	28
Ifosfamide	16	2	12
Vinblastine (c.i.)	14	0	0
Mitoxantrone	15	0	0

c.i. = Continuous infusion.

Table 4. Activity of combination chemotherapy in endometrial cancer published after 1980

Combination	No. of patients	No. of responses (%)	Year of publication	Reference
MF + MPA	77	29 (38)	1984	25
CAF + MPA	78	28 (36)	1984	25
AC	105	34 (32)	1985	24
CAP	87	39 (45)	1991	26
CAP	16	5 (31)	1987	27
CAP	26	17 (65)	1986	28
CAP	18	10 (56)	1986	29
CAP	19	9 (47)	1985	30
APV	42	13 (31)	1987	31
AP	20	12 (60)	1984	32
Total	401	157 (39)		

C = Cyclophosphamide, A = doxorubicin, F = 5-fluorouracil, MPA = medroxyprogesterone acetate, M = melphalan, P = cisplatin, V = vinblastine.

Cisplatin and doxorubicin have proven to have activity in endometrial cancer in more than 100 patients (see Table 3). The less toxic analogues epirubicin [21, 22] and carboplatin [23] appear to possess equal antitumour activity. However, the use of carboplatin is associated with myelotoxicity and this may limit combination with other agents such as doxorubicin. Of the other drugs mentioned in Table 3 the results are less consistent and additional data are needed before these agents can be accepted as active in endometrial cancer [1].

Because the combination of drugs has been successful for the other types of cancer, a variety of combinations with or without progestagens have been tested in endometrial cancer (Table 4). The overall cumulative response rate of the combinations in Table 4 is about 39%, which is higher than the best response rates achieved with single drugs. The duration of these responses lies in the 5–8 months range and long-term survivors have only been reported occasionally. Because most combination chemotherapy trials have been uncontrolled, definite conclusions about the value of such combinations cannot be drawn. One comparative phase-3 study on doxorubicin vs. doxorubicin plus cyclophosphamide in 202 patients (refractory for medroxyprogesterone acetate as initial treatment) did not reveal any difference between the two regimens [24].

Among the combinations that have been used in endometrial cancer, those including cisplatin and doxorubicin seem most promising. In a small series Chauvergne treated 10 and 11 patients with doxorubicin alone or doxorubicin plus cisplatin, respectively. Twenty per cent of the patients responded to doxorubicin and 45% to the combination [33]. The difference, however, is not statistically significant. A frequently used combination is the CAP regimen including cyclophosphamide, doxorubicin and cisplatin. The response rates obtained with this three-drug combination range between 30 and 60%. One of the largest studies treated 102 patients with advanced primary (n= 42) or recurrent (n=60) endometrial carcinoma with cisplatin (50 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) (PAC) monthly. Of the 87 patients with measurable disease, 12 had a complete clinical response, while 27 had a partial clinical response. No differences in response rates between primary and recurrent disease patients were noted. Median time to response was 2.5 months with a median response

duration of 4.8 months. Median progression-free survival for all patients was 6 months. The authors concluded that endometrial cancer is significantly responsive to PAC but that enthusiasm for this regimen should be tempered by the limited duration of response and substantial treatment toxicity [26].

Large randomised studies evaluating the value of CAP to doxorubicin and cisplatin or cisplatin alone are lacking. In the Mayo Clinics a randomised phase-2 trial was performed to compare cisplatin and CAP in patients with progestin-refractory advanced endometrial cancer. 3 of 14 and 5 out of 16 patients responded in these two groups, respectively. Survival was better with CAP treatment (median 6.7 months for CAP vs. 4.2 months for cisplatin), but the difference was not significant in this small group of patients [27]. One of the highest response rates obtained with the CAP combination was reported by the EORTC. The Gynecological Cooperative Group accepted prior radiotherapy as one of their patients' entry criteria, but the lesions used as a parameter for response assessment were all non-irradiated. This is why their response rate of 65% is so high compared with those of other series [28]. A similar experience with respect to irradiated lesions was published by Turbow [32]. In his small but well-documented series of patients treated with CAP, all non-irradiated patients responded vs. 5/15 (33%) in the group with previous irradiation.

The role of cyclophosphamide in the combination remains questionable. Single-agent studies have not been conclusive about the value of this drug. In one study of 19 patients no responses were seen [34]. This led the EORTC to initiate a randomised phase-2 study comparing doxorubicin alone with cisplatin plus doxorubicin.

DISCUSSION

Both hormonal agents and cytotoxic drugs can be of clinical value in selected patients with endometrial cancer. In view of the factors that predict a response to progestational agents, it can be argued that patients with a progesterone receptor-positive tumour (a receptor concentration of more than 10 fmol/mg cytosol protein) [15] should be given first-line treatment with medroxy-progesterone acetate. If the receptor status is unknown but the original tumour is well differentiated (grade 1), or the interval from initial diagnoses and recurrence is more than 1 year, the treatment of choice is again hormonal. Because at least 3 months must elapse before the results of hormonal treatment can be evaluated, the selected patient must have a life expectancy of at least 4 months. The role of GnRH analogues has to be determined in future clinical trials. Because this drug can affect the tumour in several ways it can be considered as an alternative in patients who relapse after initial response to progestins. About the role of this drug as initial treatment in receptor-negative patients one can only speculate and it is definitely too early to use GnRH analogues in previously untreated patients outside a clinical trial.

For patients whose profile indicates a decreased likelihood of response to progestins (negative receptor status, poor condition, undifferentiated tumour) or when the tumour load does not allow delay to await the results of hormonal manipulation, the use of cytotoxic drugs can be considered as initial treatment. Although it is not entirely certain that combinations are more effective than single agents, combinations including both doxorubicin and cisplatin seem to improve the initial likelihood to respond.

However, for palliation both hormonal and chemotherapy may be useful in a subset of patients as indicated above. Further improvement of systemic treatment can be expected from optimising current treatment with new drugs such as taxol and new treatment strategies, such as modulation of 5-fluorouracil. Because only a limited number of patients are available for clinical trials in single institutions, cooperative efforts are needed to determine the optimal treatment for patients with advanced endometrial cancer.

1. 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.
2. Kohorn E. Gestagens and endometrial carcinoma. *Gynecol Oncol* 1976, **4**, 398–411.
3. Bonte J, Decostu JM, Ide P, *et al.* Hormonoprophylaxis and monotherapy in the treatment of endometrial adenocarcinoma by means of medroxyprogesterone acetate. *Gynecol Oncol* 1978, **6**, 60–75.
4. Podratz KC, O'Brien PC, Malkasian GD, Decker DG, Jefferies JA, Edmonson JH. Effects of progestational agents in treatment of endometrial carcinoma. *Obstet Gynecol* 1985, **66**, 106–110.
5. Piver S, Barlow J, Lurain J, *et al.* Medroxyprogesterone acetate (Depo-Provera) vs hydroxyprogesterone caproate (Delalutin) in women with metastatic endometrial adenocarcinoma. *Cancer* 1980, **45**, 268–272.
6. Thigpen T, Blessing J, DiSaia P, Ehrlich C. Treatment of advanced or recurrent endometrial carcinoma with medroxy-progesterone acetate. *Gynecol Oncol* 1985, **20**, 250 (abstract).
7. Richardson GS, MacLaughlin DT. Hormonal receptors in endometrial and ovarian neoplasia. In Griffiths CT, Fuller AF, eds. *Gynecologic Oncology*. Boston, Martinus Nijhoff, 1983, 81–101.
8. Benraad T, Finberg L, Koenders A, *et al.* Do estrogen and progesterone receptors in metastasizing endometrial cancers predict to response to gestagen therapy? *Acta Obstet Gynecol Scand* 1980, **59**, 155–159.
9. Ehrlich C, Young P, Cleary R. Cytoplasmic progesterone and estradiol receptors in normal, hyperplastic, and carcinomatous endometria. Therapeutic implications. *Am J Obstet Gynecol* 1981, **141**, 539–546.
10. Creasman W, McCarty KSr, Barton T, *et al.* Clinical correlates of estrogen and progesterone binding proteins in human endometrial adenocarcinoma. *Obstet Gynecol* 1980, **55**, 363–370.
11. Kauppila AJI, Isotalo J, Kujansuru E, Vihko R. Clinical significance of female sex steroid hormone receptors in endometrial carcinoma treated with conventional methods and medroxyprogesterone acetate. In Carelli F, *et al.*, eds. *Proceedings of the International Symposium on Medroxyprogesterone Acetate* 1982. Amsterdam, Excerpta Medica, 350–359.
12. Carlson J, Allegra J, Day T, Wittliff J. Tamoxifen and endometrial carcinoma: alterations in estrogen and progesterone receptors in untreated patients and combination hormonal therapy in advanced neoplasia. *Am J Obstet Gynecol* 1984, **149**, 149–153.
13. Quinn MA, Cauchi M, Fortune D. Endometrial carcinoma: steroid receptors and response to medroxyprogesterone acetate. *Gynecol Oncol* 1985, **21**, 314–319.
14. Richardson GS, MacLaughlin DT. The status of receptors in the management of endometrial cancer. *Clin Obstet Gynecol* 1986, **29**, 628–637.
15. Ingram SS, Rosenman J, Heath R, *et al.* The predictive value of progesterone receptor levels in endometrial cancer. *Int J Radial Oncol Biol Phys* 1989, **17**, 21–27.
16. Thigpen T, Blessing J, Disaia P, *et al.* Oral medroxyprogesterone acetate in advanced and 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, NY, Parthenon, 1986, 446–454.
17. Oriana S, Raspagliesi F, Duca PG, *et al.* Changes in receptor status after treatment with tamoxifen in endometrial cancer. *Int J Biol Markers* 1988, **3**, 233–236.
18. Schwartz PE, Maclusky N, Naftolin F, *et al.* Tamoxifen-induced increase in cytosol progestin receptor levels in a case of metastatic endometrial cancer. *Gynecol Oncol* 1983, **16**, 41–48.
19. Gallagher CJ, Oliver RT, Oram DH, *et al.* A new treatment for

endometrial cancer with gonadotrophin releasing-hormone analogue. *Br J Obstet Gynaecol* 1991, **98**, 1037–1041.
20. Thigpen T, Vance R, Lambuth B, *et al.* Chemotherapy for advanced or recurrent gynecologic cancer. *Cancer* 1987, **60**, 2104–2116.
21. Calero F, Jimeno J, Rodriguez-Escudero F, *et al.* Epirubicin: clinical toxicity during the phase II program in endometrial and cervical cancer. *Eur J Gynaecol Oncol* 1992, **13**, 83–89.
22. Calero F, Rodriguez-Escudero F, Jimeno J, *et al.* Clinical evaluation of epirubicin in endometrial adenocarcinoma and uterine cervix carcinoma. *Proc Am Soc Clin Oncol* 1989, **8**, 156 (abstract).
23. Muggia FM, Gill I. Role of carboplatin in endometrial and cervical carcinomas. *Semin Oncol* 1992, **19**, 90–93.
24. Thigpen T, Blessing J, DiSaia P, *et al.* A randomized comparison of adriamycin with or without cyclophosphamide in the treatment of advanced or recurrent endometrial carcinoma. *Proc Am Soc Clin Oncol* 1985, **4**, 115 (abstract).
25. Cohen C, Bruckner H, Deppe G, *et al.* A randomized study comparing multi-drug chemotherapeutic regimens in the treatment of advanced and recurrent endometrial carcinoma. A Gynecologic Oncology Group study. *Obstet Gynecol* 1984, **63**, 719–726.
26. Burke TW, Stringer CA, Morris M, Freedman RS, Gershenson DM, Kavanagh JJ, Edwards CL. Prospective treatment of advanced or recurrent endometrial carcinoma with cisplatin, doxorubicin and cyclophosphamide. *Gynecol Oncol* 1991, **40**, 264–267.
27. Edmonson JH, Krook JE, *et al.* Randomized phase II studies of cisplatin and a combination of cyclophosphamide–doxorubicin–cisplatin (CAP) in patients with progestin-refractory advanced endometrial carcinoma. *Gynecol Oncol* 1987, **28**, 20–24.
28. De Oliveira CF, Burg v.d. MEL, Namer M, *et al.* Phase II study of cyclophosphamide (C), adriamycin (A), cisplatin (P) in recurrent or advanced endometrial cancer. *Proc ASCO* 1986, **5**, 123.
29. Hancock KC, Freedman RS, Edwards CL, Rutledge FN. Use of cisplatin, doxorubicin, and cyclophosphamide to treat advanced and recurrent adenocarcinoma of the endometrium. *Cancer Treat Rep* 1986, **70**, 789–791.
30. Turbow MM, Ballon SC, Sikic BI, Koretz MM. Cisplatin, doxorubicin, and cyclophosphamide chemotherapy for advanced endometrial carcinoma. *Cancer Treat Rep* 1985, **69**, 465–467.
31. Alberts DS,Mason NL, *et al.* Doxorubicin-cisplatin-vinblastine combination chemotherapy of advanced endometrial carcinoma: a Southwest Oncology Group Study. *Gynecologic Oncology* 1987, **26**, 193–201.
32. Tropé C, Johnsson J, Simonsen E, Christansen H, Cavallin-Stahl E, Horvath G. Treatment of recurrent endometrial adenocarcinoma with a combination of doxorubicin and cisplatin. *Am J Obstet Gynecol* 1984, **149**, 379–381.
33. Chauvergne J, Granger C, Mage Ph, Pigneux J, David M. Chimiothérapie palliative des cancers de l'endomètre. *Rev Fr Gynecol Obstet* 1986, **81**, 547–551.
34. Horton J, Bezz C, Arseneau J, *et al.* Comparison of adriamycin with cyclophosphamide in patients with advanced endometrial cancer. *Cancer Treat Rep* 1978, **62**, 159–161.

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Chemotherapy for Ovarian Cancer

S.B. Kaye

INTRODUCTION

POPULATION STUDIES have indicated that over the past 15–20 years, the overall mortality for ovarian cancer has improved, particularly for younger patients [1]. Since earlier diagnosis of the disease is most unlikely to have occurred, it is likely that these changes reflect improvements in management. Whether this involves changes in surgical practice or improvements in chemotherapy, e.g. the introduction of cisplatin, requires further study. Nevertheless, ovarian cancer remains the most lethal of the gynaecological cancers, and it represents a continuing challenge to both medical and gynaecological oncologists. Some of the main questions in treatment in 1993 are discussed in this review, the purpose of which is to examine these issues and offer some comments which might serve as a basis for continuing clinical research in these areas.

WHICH PATIENTS WITH EARLY DISEASE SHOULD RECEIVE CHEMOTHERAPY?

Some 20% of cases of ovarian cancer, after careful surgical staging, fall into the category of FIGO stage I, i.e. growth limited to one or both ovaries. A continuing dilemma for oncologists is whether or not such patients should receive additional treatment, the aim being to eradicate any microscopic metastatic disease.

Features which are frequently used to help in decisions over management include the histological grade of the tumour, the presence of tumour on the external surface, presence of an intact ovarian capsule, and the presence of adhesions within the pelvis, or of ascites containing malignant cells or positive peritoneal washings.

Although stage I patients with one or more of these adverse prognostic factors are often treated with chemotherapy (or intraperitoneal ^{32}P [2]), its use in the "adjuvant" setting has not yet been shown in controlled randomised trials to be of value.

A wide range of clinical practice can in fact be seen, and variations in surgical practice, particularly staging procedures, can add to the problem. Some investigators would routinely treat stage I patients with adverse prognostic features with cisplatin/carboplatin-containing chemotherapy, while others would consider no initial treatment as a valid option for patients with stage I and even completely resected stage III disease. Data recently presented from a large randomised trial which included the use of cisplatin for stages Ia and b disease showed no difference in survival compared with no treatment, although there was a difference in 5-year disease-free survival (76 vs. 58%, $P < 0.05$) [3]. Clearly, longer follow-up is required, and in addition, much larger randomised trials, such as that initiated by the MRC Gynaecological Cancer Subgroup (ICON-I) [4] are needed, in which a policy of observation is compared with initial cisplatin- or carboplatin-containing chemotherapy for patients whose disease has been completely resected.

In the future, analysis of tumour ploidy [5] and levels of expression of mutant p53 protein [6] may significantly help in decision-making in stage I disease.

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