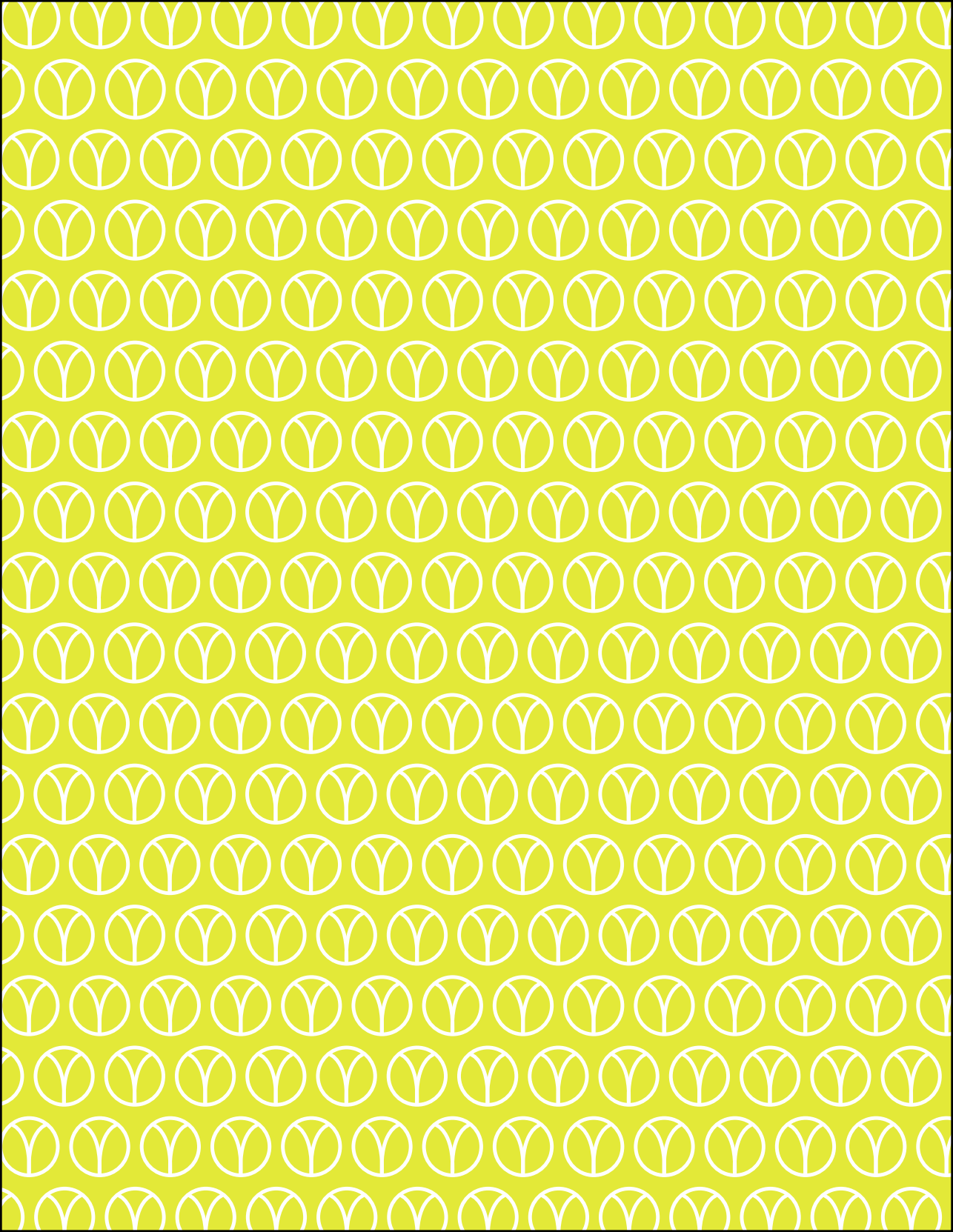
Advanced and Recurrent Endometrial Cancer

current concepts of treatment

Proefschrift Heidy van Wijk



Advanced and Recurrent Endometrial Cancer

current concepts of treatment

Proefschrift **Heidy van Wijk**

Advanced and Recurrent Endometrial Cancer; current concepts of treatment

Thesis, Erasmus University Rotterdam, The Netherlands

The work presented in this thesis was performed at the Department of Obstetrics and Gynecology, Erasmus MC, Rotterdam, The Netherlands and at the European Organisation for Research and Treatment of Cancer, for the Gynecological Cancer Group, Brussels, Belgium.

Financial support for the publication of this thesis was kindly provided by Abbott, Accenture, Amgen, Ferring, J.E. Jurriaanse Stichting, Medical Dynamics, Memidis Pharma, Olympus Nederland, Pentax Nederland/Lifecare, Teva Nederland and Wyeth Pharmaceuticals.

Design and layout by Communicatie & Onderneming, Bavel (Breda)
Printed by Letoprint, Roosendaal
ISBN: 9789056770471

Advanced and Recurrent Endometrial Cancer; current concepts of treatment

Hoogstadium en recidief endometriumkanker; huidige behandelingsstrategieën

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 4 juni 2008 om 15.45 uur

door

Flora Hermina van Wijk
geboren te Maurik

Promotiecommissie

Promotoren:	Prof.dr. C.W. Burger Prof.dr. I. Vergote
Overige leden:	Prof.dr. Th.J.M. Helmerhorst Prof.dr. G.G. Kenter Prof.dr. J. Verweij
Copromotor:	Dr. H.C. van Doorn

Table of contents

Chapter 1

Introduction and objectives

Epidemiology

Endometrial cancer is the most common gynecological malignancy in Western Countries. In the United States approximately 39,000 cases will be diagnosed in 2007 and 7,400 deaths will occur. Women have a 2.6% lifetime risk of developing endometrial cancer and it accounts for 6% of all cancers in women (1). The incidence of endometrial cancer rises from 2 per 100,000 women per year under the age of 40 years, to 40-50 per 100,000 women per year after the age of 60 (2). In the Netherlands, it is the fourth most common invasive tumor in women after breast, colorectal and lung cancer. Its incidence is still rising; 1,619 new cases of endometrial cancer were reported in the Netherlands in 2003, compared to 1,293 new cases in 1989 (www.ikcnet.nl). This increase is related not only to higher life expectancy but also to the exposure of the uterus to unopposed estrogens, either exogenous or endogenous as in obese patients.

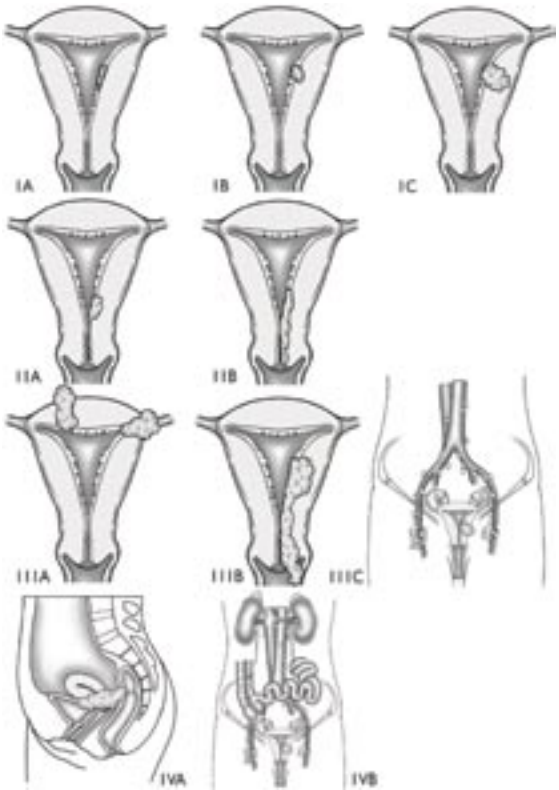
Table 1.1. Carcinoma of the Corpus Uteri: Surgical staging classification (International Federation of Gynecology and Obstetrics, FIGO nomenclature 1988, Annual Report, Vol. 26) and TNM classification (UICC, International Union Against Cancer, 2002, 6th edition).

FIGO STAGES	T	UICC N	M	
o	Tis	No	Mo	In situ
I				Tumor confined to the corpus
IA	T1a	No	Mo	Tumor limited to the endometrium
IB	T1b	No	Mo	Tumor invades up to less than one-half of the
IC	T1c	No	Mo	myometrium Tumor invades to more than one-half of the myometrium
II				Tumor invades cervix, but does not extend beyond uterus
IIA	T2a	No	Mo	Endocervical glandular involvement only
IIB	T2b	No	Mo	Cervical stromal invasion
III				Local and/or regional spread
IIIA	T3a	No	Mo	Tumor invades uterine serosal and/or adnexa and/or positive peritoneal cytology
IIIB	T3b	No	Mo	Vaginal involvement
IIIC	T1	N1	Mo	Metastasis to pelvic and/or para-aortic lymph nodes
	T2	N1	Mo	
	T3a	N1	Mo	
	T3b	N1	Mo	
IVA	T4	Any N	Mo	Tumor invades bladder mucosa and/or bowel mucosa
IVB	Any T	Any N	M1	Distant metastasis

Rules for classification

The Committee on Gynecologic Oncology of the International Federation of Gynecology and Obstetrics (FIGO), following its meeting in 1988, recommended surgical staging for endometrial cancer with histological verification of grading and extent of the tumor (3). In a small number of patients with endometrial cancer to be treated primarily with radiotherapy, the clinical staging adopted by FIGO in 1971 would still apply, but designation of that staging system would be noted. The staging classification is presented in Table 1.1 and Figure 1.1. Dissemination of the tumor takes place via the utero-ovarian (infundibulo-pelvic), parametrial, and presacral lymphatic trunks, which drain into the hypogastric, external iliac, common iliac, presacral and para-aortic nodes. The vagina and lungs are common metastatic sites.

Figure 1.1. Carcinoma of the Corpus Uteri. Staging uterine cancer. Primary tumor and metastases (FIGO). Adapted from Creasman et al (5).



Histopathology

In 1983, Bokhman was the first to describe two different types of endometrial carcinoma (4) (Table 1.2). Type I tumors are considered estrogen related, often preceded by a hyperplastic condition, and are typically low grade endometrioid tumors with positive hormone receptor status. They usually develop in an estrogen rich environment (obesity, pre-menopausal and peri-menopausal state). Patients with this type of tumor show a long treatment-free interval between initial diagnosis and subsequent development of metastatic disease, they do respond mostly to hormonal treatment and do generally have a good prognosis. On the other hand, type II tumors are unrelated to estrogen, mostly develop in atrophic endometrium and are most often higher-grade tumors or poorly prognostic cell types, such as papillary serous or clear cell tumors. They affect older women and usually have a poor clinical outcome. Patients with this type of tumor rarely respond to hormonal treatment.

According to the World Health Organization / International Society of Gynecological Pathology (WHO/ISGP) classification, the histopathologic types are classified as endometrioid carcinoma (further categorized into adenocarcinoma, adenoacanthoma, adenosquamous carcinoma), mucinous adenocarcnoma, papillary serous adenocarcinoma, clear cell adenocarcinoma, undifferentiated carcinoma and mixed carcinoma. Endometrioid carcinoma histopatholgical type is present in 84% of the patients. Poor prognostic cell types, such as

Table 1.2. Predominant features of pathogenetic type I and II endometrial carcinoma. Adapted from Bokhman (4).

TUMOR CHARACTERISTICS	TYPE I	TYPE II
Duration of symptoms	Usually long	Usually short
Degree of tumor differentiation	Highly or moderately differentiated (more frequent G1 or G2)	Poorly differentiated (more frequent G3)
Depth of invasion in the myometrium	Frequent prevalence of superficial invasion	Frequent prevalence of deep invasion
Potentiality for lymphogenic metastatic spread	Not high	High
Sensitivity to progestagens	High	Low
Prognosis	Favorable	Doubtful

Table 1.3. Carcinoma of the Corpus Uteri. Patients treated in 1999-2001. Survival by FIGO surgical stage, n=7990. Adapted from Creasman et al (5).

STAGE	PATIENTS (N)	MEAN AGE (YEARS)	OVERALL SURVIVAL (%) AT					HAZARDS RATIO[a] (95% CI)
			1 YEAR	2 YEARS	3 YEARS	4 YEARS	5 YEARS	
IA	1,054	59.0	98.2	96.6	95.3	93.7	90.8	Reference
IB	2,833	62.1	98.7	96.6	94.6	92.5	91.1	0.9 (0.7-1.2)
IC	1,426	66.2	97.5	93.7	89.7	87.2	85.4	1.4 (1.1-1.8)
IIA	430	63.8	95.2	93.2	89.0	86.0	83.3	1.8 (1.3-2.5)
IIB	543	63.8	93.5	85.3	80.3	76.7	74.2	2.8 (2.1-3.7)
IIIA	612	63.0	89.0	79.9	73.3	69.4	66.2	4.4 (3.4-5.8)
IIIB	80	67.0	73.5	61.6	56.7	52.7	49.9	7.3 (4.8-10.9)
IIIC	356	61.6	89.9	74.5	66.3	61.5	57.3	6.2 (4.7-8.2)
IVA	49	64.5	63.4	46.7	34.4	29.1	25.5	14.0 (9.2-21.2)
IVB	206	63.9	59.5	37.0	29.0	22.3	20.1	16.1 (12.2-21.3)

[a] Hazards ratio and 95% CI obtained from a COX model adjusted for age, stage and country.

papillary serous and clear cell carcinoma, represent only 6% of surgically staged patients. Of the endometrioid types, 86% are early stage (stage I or II) at presentation compared with 59% for papillary serous and 67% for clear cell types. Of all patients with stages I and II, papillary serous and clear cell represent only 4% of cases, while 14% of the patients with stages III and IV have these histopathologic types.

Cases of carcinoma of the corpus should be grouped as follows (depending on the degree of differentiation of the adenocarcinoma): G1: ≤ 5% of a nonsquamous or nonmorular solid growth pattern, G2: 6-50% of a nonsquamous or nonmorular solid growth pattern, G3: ≥ 50% of a nonsquamous or nonmorular solid growth pattern. Notable nuclear atypia raises the grade of a Grade 1 or 2 tumor by 1 (5).

Survival and prognostic factors

As endometrial cancer often causes abnormal uterine bleeding at an early stage, the majority of patients are diagnosed during the early stage of the disease (defined as FIGO stages I and II) and only a small proportion of patients are diagnosed during an advanced stage of the disease (defined as FIGO stages III and IV). As depicted in Table 1.3, survival is

obviously stage related: the 5-year survival rate declines from 91% for patients with stage IA disease, to 20% for patients with stage IVB disease. Another important prognostic factor is the histopathologic type of endometrial cancer. Endometrioid tumors of all stages have a 5-year survival rate of 83% compared to 62% for clear cell and 53% for papillary carcinomas. This is to a certain extent related to the fact that these histopathologic types are present in a more advanced stage of the disease. However, early stage endometrioid tumors do actually have a better prognosis than early stage clear cell and papillary carcinomas. Grade and depth of invasion within a given stage are prognostically important. It appears that grade and depth of invasion are independently important yet complementary to each other. Within each given stage, age continues to be an important prognostic factor in multivariate analysis. The prognosis for patients over 80 years of age is considerably worse (5).

Management of endometrial cancer

Surgery

The FIGO system changed in 1988 from a clinical to surgical staging procedure of endometrial cancer. Primary treatment should commence with surgery in all cases, as written in the staging classification and clinical practice guidelines of gynecologic cancers (3). An exception can be made for patients with stage IIIB disease (i.e. with vaginal involvement) who are best treated by pelvic irradiation (after an adnexal mass or adnexal involvement is excluded during the metastatic work-up) and followed by exploratory laparotomy if the disease seems to be resectable (3). Although it was described in the staging classification and clinical practice guidelines, in practice the few patients who present with stage IIIB disease are most often staged and treated by primary surgery. Since the staging procedure was changed, considerable debate has ensued as to what constitutes an acceptable surgical approach (6-8). The FIGO Committee on Gynecologic Oncology described a general recommended protocol in their staging booklet (3). To summarize: surgery should start with a vertical midline abdominal incision and collection of ascites or peritoneal lavage fluid for cytological evaluation, followed by exploration of the intra-abdominal contents (examination of the omentum, liver, peritoneal cul-de-sac and adnexal surfaces for possible metastases, and palpation for suspicious or enlarged nodes in the aortic and pelvic nodal areas). The standard surgical procedure includes an extrafascial total hysterectomy with bilateral salpingo-oophorectomy. If cervical stroma is involved, a radical hysterectomy is often the procedure of choice. Currently the role of pelvic and para-aortic lymphadenectomy or lymph node sampling is still being debated (9, 10). The following guidelines are recommended by the FIGO: 'Any deeply invasive tumor or radiological suggestion of positive nodes are definitely indications for retroperitoneal lymph node evaluation with removal of any enlarged or suspicious lymph nodes. If these nodes are positive on frozen section, further node dissection may be unnecessary unless clinically positive nodes can be excised with minimal

risk to the patient. Indication for aortic node sampling would include suspicious aortic or common iliac nodes, grossly positive adnexa, grossly positive pelvic nodes and high grade tumors showing full thickness myometrial invasion.' Despite the potential adverse consequences of not detecting metastatic disease, a systematic lymphadenectomy is not routinely performed at all centers. The arguments used for omitting lymphadenectomy are that the occurrence of involved nodes is low (≤ 20%) and that an extended procedure increases the risk of developing lymph edema. Some series showed a survival benefit related to the performance of a lymphadenectomy (11-13) and data from the Surveillance Epidemiology and End Results (SEER) registry, evaluating 12,333 patients, support the view that a survival benefit is gained by a more extensive lymph node dissection (14). On the other hand, other series did not detect a difference in survival between patients who underwent a pelvic lymphadenectomy and those who did not (15, 16). A few series suggest a potential therapeutic role for para-aortic lymphadenectomy in patients with positive pelvic lymph nodes (17, 18). The varying results of these studies could be explained by the selection bias of the retrospective studies, stage migration and identification of patients with nodal metastases potentially curable with adjuvant treatment. In conclusion, there continues to be controversy about which approach is preferable, which in turn has led to two approaches of management: broader application of more extensive nodal sampling versus more frequent utilization of adjuvant therapy in patients where complete staging information is missing (19).

Nowadays routine lymphadenectomy is utilized more frequently in the United States than in Western European Centers (20, 21). In the Netherlands, it is optional to perform a lymphadenectomy in patients with endometrial cancer. However, in patients with stage IIB disease, a pelvic lymphadenectomy is strongly advised. A para-aortic lymph node sampling is indicated in case of suspicious para-aortic lymph nodes or adnexal involvement (www.oncoline.nl). In clinical practice, most endometrial cancer patients in the Netherlands do not undergo a lymphadenectomy.

Radiotherapy

After the surgical staging procedure, further treatment with radiation might be indicated based on the pathologic staging information. Radiotherapy can be administered locally to the vagina (brachytherapy), to the pelvis (external irradiation with or without brachytherapy) or to the whole abdomen (external irradiaton (WART) or radiation with intraperitoneal P-32). Some patients for whom surgery is contraindicated due to severe co-morbidity (such as cardiopulmonary disease and morbid obesity) are clinically staged and radical radiotherapy is used based on patient and tumor characteristics (22). The practice of preoperative radiotherapy has been abandoned because it interferes with the surgical staging procedure and there is no proven benefit over postoperative radiotherapy (23). According to the FIGO staging guidelines, patients with stage IIIB should be the only exception to this (3).

In patients with stage I endometrial cancer and multiple high risk factors, including deep myometrial invasion and grade 3 tumors, there was a trend towards a survival benefit with adjuvant external beam radiotherapy. For patients with only one risk factor no definite conclusion can be made as data from ongoing studies are still to be made known (24).

Systemic treatment

The majority of patients with endometrial cancer is identified with early stage disease and can be cured by surgery with or without adjuvant radiotherapy. Less than ten percent of the patients present with distant disease at time of diagnosis (25) and 13% of all patients develop recurrent disease (26). Therefore, only a small number of patients are treated with systemic treatment and clinical studies on systemic treatment will take many years to accrue. In order to ensure adequate sample sizes to detect treatment related differences, most studies and randomized trials were designed to include patients with either advanced or recurrent disease. This has created an obvious complexity in terms of evaluating the clinical relevance of the findings of these studies and trials. Clinicians recognize that these two patient populations (advanced and recurrent) are different; not only in terms of their presenting symptoms but also in terms of the number of distribution sites and the biology of the disease itself. Another drawback of numerous systemic treatment trials on endometrial cancer is the fact that patients with different histopathological types such as endometrioid adenocarcinoma, papillary serous and clear cell carcinomas are included. As previously mentioned, papillary serous and clear cell carcinomas represent highly aggressive tumors with a poor prognosis (27). These histopathological types should be considered as another entity and consequently treatment of these patients requires a different approach than patients with endometrioid tumors. Furthermore, responsiveness to chemotherapy may also be influenced by prior treatment, particularly radiotherapy and chemotherapy. Thus, there is considerable heterogeneity in the patient populations that comprise the systemic treatment studies and trials and consequently make them difficult to interpret. For that reason, pooling of data for statistical analysis was not deemed appropriate by systematic reviews (28-31).

Advanced and recurrent endometrial cancer

A growing interest in endometrial cancer can be observed during recent decades. The increasing incidence of this disease, better understanding of prognostic important factors and improved treatment approaches are the main reasons. The overall 5-year survival rates of endometrial cancer patients have improved during the last two decades from 65.1% to 80.0% (5). The majority of patients are diagnosed with early stage endometrial cancer which has a favorable prognosis. The management of endometrial cancer is reviewed in several papers (7, 9, 23, 32-37) and focuses mainly on patients with early stage disease. Advanced stage disease is defined as FIGO stages III and IV, which includes patients with local and/or

regional spread to the uterine serosa, adnexa, vagina, lymph nodes, bladder or bowel and patients with tumor-positive peritoneal cytology or with distant metastases. Recurrences are classified according to their site of disease: local, regional or distant. As only a small proportion of the patients present with advanced or recurrent disease, treatment modalities for these patients tend to evolve slowly and treatment is frequently individualized since limited evidence is available. Of all endometrial cancer patients, the population of patients with advanced and recurrent disease are most frequently treated with chemotherapy, and therefore seen as a similar group of patients. Nevertheless, it is important to recognize that the patient population with advanced disease is different from the patient population with recurrent disease. Identifying differences in terms of their presenting symptoms, sites of disease, prior treatment and the biology of the advanced versus recurrent disease itself are important elements for defining the optimal treatment for these patients. In this patient population of elderly patients with significant co-morbidity it is important to develop less toxic, yet effective, chemotherapeutic regimens. As only a small number of endometrial cancer patients is treated with chemotherapy, it is therefore important to evaluate new regimens in international multi-centre trials to ensure adequate sample sizes.

Aim of the thesis

The aim of this thesis is to critically evaluate and discuss the available evidence and to make recommendations for treatment of patients with the different stages of advanced disease and different sites of recurrent disease. Firstly, we shall analyze our clinical experience of patients with advanced and recurrent endometrial cancer in the Erasmus MC in Rotterdam. Secondly, we wish to evaluate different chemotherapy regimens in two multi-centre clinical trials in patients with advanced and recurrent endometrial cancer. Thirdly, we aim to assess the current status of the management of advanced endometrial cancer in literature, focusing on patients with histopathologic endometrioid type of tumors resulting in a treatment management proposal for these patients. Finally, an overview of treatment options for patients with recurrent endometrial cancer will be given and a management schedule per site of recurrent disease will be presented.

Outline of the thesis

In Chapters 2 and 3, a retrospective analysis over a 20-year period of patients with advanced and recurrent endometrial cancer in the Erasmus MC in Rotterdam, The Netherlands, is presented. The importance of positive peritoneal cytology and optimal surgical cytoreduction in patients with advanced endometrial cancer and the value of follow-up after treatment for endometrial cancer are discussed.

In Chapter 4, two multi-centre clinical trials evaluating different chemotherapeutic regimens in patients with advanced or recurrent endometrial cancer will be discussed. The

first, presented in Chapter 4.1, is a phase II study evaluating single agent carboplatin. The second, presented in Chapter 4.2, is a randomized trial comparing single agent doxorubicin with the combination treatment of doxorubicin and cisplatin.

An overview of the management of advanced and recurrent endometrial cancer is presented in Chapter 5, focusing on patients with histopathologic endometrioid type of tumors. In Chapter 5.1 the management of advanced endometrial cancer is described according to recent literature and in Chapter 5.2 the management of recurrent endometrial cancer is presented. Recommendations for treatment of patients with advanced and recurrent endometrial cancer are given and management schedules for these patients will be proposed.

Lastly, in Chapter 6, general conclusions regarding the optimal treatment for patients with advanced or recurrent endometrial cancer will be drawn and indications for further research will be provided.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007 Jan-Feb;57(1):43-66.
2. Benedet JL, Ngan HY, Hacker NF. Staging classification and clinical practice guidelines of gynecologic cancers.http://www.figo.org/docs/staging_booklet.pdf Reprinted from the International Journal of Gynecology and Obstetrics, 70(2000):207-312.
3. Benedet JL, Bender H, Jones H, 3rd, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet. 2000 Aug;70(2):209-62.
4. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983 Feb;15(1):10-7.
5. Creasman W, Odicino F, Maisonneuve P, Quinn M, Beller U, Benedet J, et al. Carcinoma of the corpus uteri. Int J Gynaecol Obstet. 2006 Nov;95 Suppl 1: S105-43.
6. Bremond A, Bataillard A, Thomas L, Achard JL, Fervers B, Fondrinier E, et al. [Standards, Options and Recommendations for the surgical management of carcinoma of the endometrium]. Bull Cancer. 2001 Feb;88(2):181-98.
7. Santin AD, Bellone S, O'Brien TJ, Pecorelli S, Cannon MJ, Roman JJ. Current treatment options for endometrial cancer. Expert Rev Anticancer Ther. 2004 Aug;4(4):679-89.
8. Boronow RC. Surgical staging of endometrial cancer: evolution, evaluation, and responsible challenge--a personal perspective. Gynecol Oncol. 1997 Aug;66(2):179-89.
9. Kitchener H. Management of endometrial cancer. Eur J Surg Oncol. 2006 Oct;32(8):838-43.
10. Irvin WP, Rice LW, Berkowitz RS. Advances in the management of endometrial adenocarcinoma. A review. J Reprod Med. 2002 Mar;47(3):173-89; discussion 89-90.
11. Kilgore LC, Partridge EE, Alvarez RD, Austin JM, Shingleton HM, Noojin F, 3rd, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol. 1995 Jan;56(1):29-33.
12. Orr JW, Jr., Holimon JL, Orr PF. Stage I corpus cancer: is teletherapy necessary? Am J Obstet Gynecol. 1997 Apr;176(4):777-88; discussion 88-9.
13. Barnes MN, Kilgore LC. Complete surgical staging of early endometrial adenocarcinoma: optimizing patient outcomes. Semin Radiat Oncol. 2000 Jan;10(1):3-7.
14. Chan JK, Cheung MK, Huh WK, Osann K, Husain A, Teng NN, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. Cancer. 2006 Oct 15;107(8):1823-30.
15. Candiani GB, Belloni C, Maggi R, Colombo G, Frigoli A, Carinelli SG. Evaluation of different surgical approaches in the treatment of endometrial cancer at FIGO stage I. Gynecol Oncol. 1990 Apr;37(1):6-8.
16. Massi G, Savino L, Susini T. Vaginal hysterectomy versus abdominal hysterectomy for the treatment of stage I endometrial adenocarcinoma. Am J Obstet Gynecol. 1996 Apr;174(4):1320-6.
17. Onda T, Yoshikawa H, Mizutani K, Mishima M, Yokota H, Nagano H, et al. Treatment of node-positive endometrial cancer with complete node dissection, chemotherapy and radiation therapy. Br J Cancer. 1997;75(12):1836-41.
18. Mariani A, Webb MJ, Galli L, Podratz KC. Potential therapeutic role of para-aortic lymphadenectomy in node-positive endometrial cancer. Gynecol Oncol.

2000 Mar;76(3):348-56.

19. Aalders JG, Thomas G. Endometrial cancer--revisiting the importance of pelvic and para aortic lymph nodes. Gynecol Oncol. 2007 Jan;104(1):222-31.
20. Maggino T, Romagnolo C, Landoni F, Sartori E, Zola P, Gadducci A. An analysis of approaches to the management of endometrial cancer in North America: a CTF study. Gynecol Oncol. 1998 Mar;68(3):274-9.
21. Maggino T, Romagnolo C, Zola P, Sartori E, Landoni F, Gadducci A. An analysis of approaches to the treatment of endometrial cancer in western Europe: a CTF study. Eur J Cancer. 1995 Nov;31A(12):1993-7.
22. Einhorn N, Trope C, Ridderheim M, Boman K, Sorbe B, Cavallin-Stahl E. A systematic overview of radiation therapy effects in uterine cancer (corpus uteri). Acta Oncol. 2003;42(5-6):557-61.
23. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet. 2005 Aug 6-12;366(9484):491-505.
24. Kong A, Johnson N, Cornes P, Simera I, Collingwood M, Williams C, et al. Adjuvant radiotherapy for stage I endometrial cancer. Cochrane Database Syst Rev. 2007(2):CD003916.
25. Ries L, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2001, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2001/. 2004.
26. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006 Jun;101(3):520-9.
27. Boruta DM, 2nd, Gehrig PA, Groben PA, Bae-Jump V, Boggess JF, Fowler WC, Jr., et al. Uterine serous and grade 3 endometrioid carcinomas: is there a survival difference? Cancer. 2004 Nov 15;101(10):2214-21.
28. Humber C, Tierney J, Symonds R, Collingwood M, Kirwan J, Williams C, et al. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Ann Oncol. 2007 Mar;18(3):409-20.
29. Carey MS, Gawlik C, Fung-Kee-Fung M, Chambers A, Oliver T. Systematic review of systemic therapy for advanced or recurrent endometrial cancer. Gynecol Oncol. 2006 Apr;101(1):158-67.
30. Pectasides D, Pectasides E, Economopoulos T. Systemic therapy in metastatic or recurrent endometrial cancer. Cancer Treat Rev. 2007 Apr;33(2):177-90.
31. Fleming GF. Systemic chemotherapy for uterine carcinoma: metastatic and adjuvant. J Clin Oncol. 2007 Jul 10;25(20):2983-90.
32. Barakat RR. Contemporary issues in the management of endometrial cancer. CA Cancer J Clin. 1998 Sep-Oct;48(5):299-314.
33. Creasman WT. Endometrial cancer: incidence, prognostic factors, diagnosis, and treatment. Semin Oncol. 1997 Feb;24(1 Suppl 1):S1-140-S1-50.
34. Ball HG, Elkadry EA. Endometrial cancer: current concepts and management. Surg Oncol Clin N Am. 1998 Apr;7(2):271-84.
35. Elit L. Endometrial cancer. Prevention, detection, management, and follow up. Can Fam Physician. 2000 Apr;46(4):887-92.
36. Levine DA, Hoskins WJ. Update in the management of endometrial cancer. Cancer J. 2002 May-Jun;8 Suppl 1:S31-40.
37. Kim RY, Omura GA, Alvarez RD. Advances in the treatment of gynecologic malignancies. Part 2: Cancers of the uterine corpus and ovary. Oncology (Huntingt). 2002 Dec;16(12):1669-78; discussion 78-80.

Chapter 2

Stage III and IV endometrial cancer; a 20 year review of patients

Stage III and IV endometrial cancer; a 20 year review of patients
F.H. van Wijk, F.J. Huikeshoven, L. Abdulkadir, P.C. Ewing, C.W. Burger
International Journal of Gynecological Cancer 2006; 16: 1648-1655.

Abstract

Background: In advanced endometrial cancer the importance of peritoneal cytology and optimal surgical cytoreduction remain subjects of discussion.

Methods: We evaluated our clinical experience of 67 patients with FIGO stage III and IV endometrial cancer treated in the Erasmus MC in Rotterdam over a 20 year period with an emphasis on stage IIIA disease based on positive cytology only and optimal cytoreduction. Lymphadenectomy was not routinely performed and peritoneal cytology was examined in 74% of the patients.

Results: Stage IIIA disease was found in 33 patients, 10 of whom had positive cytology only. Analysis showed that incidence of recurrence and survival rates of patients with stage IIIA disease based on positive cytology only were comparable with stage IIIA disease based on other factors.

In 50 patients it proved possible to remove all macroscopic tumor while for 17 patients an optimal cytoreduction was not achievable. The 2- and 5-year survival rates after optimal cytoreduction were 82.2% and 65.6%; where this could not be achieved these figures were 50.8% and 40.6%.

Conclusions: In advanced endometrial cancer patients positive peritoneal cytology seems an important prognostic factor in stage IIIA disease if lymph node status is unknown. Survival is improved if optimal surgical cytoreduction is achievable.

Introduction

Cancer of the uterine corpus is the most common gynecological malignancy and the fourth most common cancer in women in the United States. In the Netherlands, the incidence of endometrial cancer for 2000 was 1,457 cases, compared with 1,116 for ovarian cancer and 677 for cervical cancer (1). The majority of patients present with disease confined to the uterus at the time of diagnosis and this is associated with a relatively favorable 5-year survival rate of 86% (2). However, 15 to 25% of patients present with advanced stage disease with a 5-year survival rate varying from 40 to 79% for FIGO stage III (2-6) and 0 to 24% for FIGO stage IV disease (2, 7, 8).

In the FIGO surgical staging system for endometrial cancer, introduced in 1988, the finding of positive peritoneal cytology upstages a clinical stage I or II tumor to stage IIIA (9). The importance of positive peritoneal cytology remains subject of discussion (5, 6, 10-13).

Several retrospective studies describing the role of cytoreductive surgery in advanced endometrial cancer have been published and suggest that optimal tumor cytoreduction may improve survival (3, 4, 7, 8, 14).

We reviewed all patients with stage III and IV endometrial cancer treated at the Erasmus MC over a 20 year period. Emphasis is placed on the evaluation of a subgroup of patients with stage IIIA disease who had positive peritoneal cytology only and on the impact on survival of optimal surgical cytoreduction.

Patients and methods

We reviewed the medical files of patients with advanced endometrial cancer treated at Erasmus MC in Rotterdam between 1984 and 2003. Erasmus MC is the largest university medical centre in the Netherlands and includes the Erasmus MC Daniel den Hoed Cancer Center. Advanced endometrial cancer was defined as FIGO stage IIIA or more, independent of the grade of the tumor (9). Patients were identified using the databases of the hospital and of the Comprehensive Cancer Centre Rotterdam. All patient records were reviewed retrospectively. Clinical data, details of treatment and follow-up information were recorded. Lymphadenectomy is not routinely performed in The Netherlands. Optimal surgical cytoreduction was defined as removal of all macroscopic tumor including retroperitoneal tumor. Treatment toxicity was assessed according to WHO criteria.

Histopathological features, lymph nodes status and presence of positive peritoneal washings were noted. At the time of diagnosis all histological specimens were evaluated according to the World Health Organization / International Society of Gynecological Pathology classification and reported by pathologists experienced in gynecologic pathology. Pathological reports were reviewed; tumors reported to contain serous, adenosquamous, clear-cell components, or with unclear tumor type, were re-evaluated. We excluded patients with uterine sarcomas or mixed müllerian tumors. Patients who received their complete treatment

elsewhere were excluded.

Response to treatment was defined as a clinically complete response. Recurrent disease was defined as histopathologically confirmed disease after a clinically complete response to primary therapy. Two categories of recurrent disease were identified: local recurrences included recurrent disease confined to the true pelvis, and distant recurrences were defined as any extra-pelvic recurrent disease. The survival, time to recurrent disease or time to death were calculated starting at date of primary surgery or date of start treatment for primary disease. The overall survival was analyzed with a Kaplan-Meier curve. When appropriated, differences in survival curves were tested with the logrank test.

Results

Patient characteristics

Sixty-seven patients with advanced endometrial cancer were included in this study. Median age at primary disease was 63 years (range 32-84). Nineteen patients were nulliparous, 52 were postmenopausal. In 58 patients diagnosis of endometrial cancer was made after presentation with vaginal bleeding or pain. In seven patients endometrial cancer was a chance finding; four patients had undergone surgery because of suspicion of ovarian pathology, two because of uterine leiomyomata and in one patient diagnosis was made during investigation for infertility. Hormone replacement therapy and oral contraceptive use was not documented. Co-morbidity was found in 26 patients; diabetes was present in eight patients, hypertension in 22 patients and a secondary malignancy in eight patients.

Histopathological features

The histological tumor type was endometrioid adenocarcinoma in 85% of the 62 patients operated on for primary disease and serous carcinoma in 5% of the patients. Thirty-one percent of the patients had poorly differentiated tumors. Peritoneal cytology was examined in 74% of the patients.

FIGO stage

The FIGO stages at time of primary surgery are shown in Table 2.1. Five patients were not primarily surgically staged, in these cases the FIGO clinical staging adopted in 1971 was applied, as advised in such cases. Stage IIIA disease was diagnosed on the following histological characteristics: in ten patients because of only positive cytology, in 11 patients because of adnexal involvement, in five patients because of both positive cytology and adnexal involvement and in seven patients because of invasion of the serosa. Of the ten patients with stage IIIA disease based on only positive cytology, two patients underwent a bilateral pelvic lymph node sampling and one a bilateral pelvic lymph node dissection, in the other seven patients were no pelvic lymph nodes removed.

Table 2.1. FIGO stage.

FIGO STAGE	N
III	51
III (clinical stage)	1
IIIA	33
IIIB	2
IIIC	15
IV	16
IVA	5
IVB	11

Primary treatment

Table 2.2 summarizes the initial method of treatment with reference to the different FIGO stages.

Surgery

Where surgery was performed this consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy. Prior to the diagnosis two patients underwent a subtotal hysterectomy for benign disease and the endometrial carcinoma originated in the residual part of the uterus. Three patients underwent an uni- or bilateral salpingo-oophorectomy for benign disease prior to diagnosis of carcinoma. In 12 patients an additional partial or complete omentectomy was performed. Intestinal surgery was necessary in two patients with stage IVA

Table 2.2. Initial treatment of primary endometrial cancer according to FIGO stage.

FIGO STAGE	INITIAL TREATMENT N							TOTAL N
	S[a]	S + RT [b]	S + CT[c]	S + HT[d]	S + RT + CT	RT	RT + CT	
III	0	0	0	0	0	1	0	1
IIIA	4	28	1	0	0	0	0	33
IIIB	1	0	0	0	0	1	0	2
IIIC	1	12	0	0	2	0	0	15
IVA	0	3	0	0	2	0	0	5
IVB	2	1	3	1	1	1	2	11
Total	8	44	4	1	5	3	2	67

[a] S=surgery. [b] RT=radiotherapy. [c] CT=chemotherapy. [d] HT=hormonal treatment.

disease and consisted of a proximal rectum amputation or partial ileal resection.

Lymphadenectomy was not routinely performed. In eight patients a complete pelvic lymphadenectomy was performed, one of whom also underwent unilateral para-aortic lymph node sampling. In one patient a complete para-aortic lymphadenectomy was performed. In 14 patients a pelvic or para-aortic lymph node sampling or removal of suspicious lymph nodes took place.

In 50 patients macroscopic complete removal of the tumor was possible. Twelve patients underwent a cytoreduction that was macroscopically irradical, thus defined as not optimal. Along with five patients who were not operated on, these formed a group of 17 patients where cytoreduction was not optimal who were then analyzed further. Retroperitoneal debulking was performed in six patients.

One patient with stage IVB disease died two weeks postoperatively. Four patients underwent a relaparotomy and three patients developed a thrombosis or embolism.

Radiotherapy

The type of radiotherapy used varied among the patients. Ten patients received postoperative external pelvic irradiation and additional brachytherapy, 37 patients received postoperative external pelvic irradiation only, one patient with stage IIIA disease received postoperative brachytherapy and in one patient the type of postoperative radiotherapy was unknown. In total three patients refused postoperative radiotherapy; two patients with stage IIIA disease and one with stage IIIB disease. One patient did not receive postoperative radiotherapy due to patient delay. Two patients were treated with primary radiotherapy consisting of external irradiation and brachytherapy, one of these was not operated on because she refused blood transfusion. All patients with stage IIIA based on positive cytology only were treated with surgery and postoperative radiotherapy. One patient with stage IVB was treated with primary radiotherapy, she also underwent a non-radical excision of unilateral enlarged inguinal lymph nodes. Two patients with staged IVB disease were treated with chemotherapy and external radiotherapy.

During radiotherapy, sepsis occurred in one patient and two patients suffered severe nausea and vomiting. Treatment was seriously complicated in two patients by radiation-enteritis, in two patients by sigmoid-perforation and in one patient by a rectal fistula.

Chemotherapy

None of the patients was treated with chemotherapy only. In total eleven patients received 59 courses of combination chemotherapy. Five patients received a combination of cyclophosphamide, doxorubicin and cisplatin; five patients received cisplatin in combination with doxorubicin, cyclophosphamide, taxol or etoposide. One patient with stage IIIA endometrial cancer was initially diagnosed as having ovarian cancer and treated with surgery and chemotherapy.

Seven courses were delayed and two doses were reduced due to toxicity. Severe nausea

occurred in one patient; severe leucopenia, neutropenia and anemia in respectively two, one and one patient.

Hormonal treatment

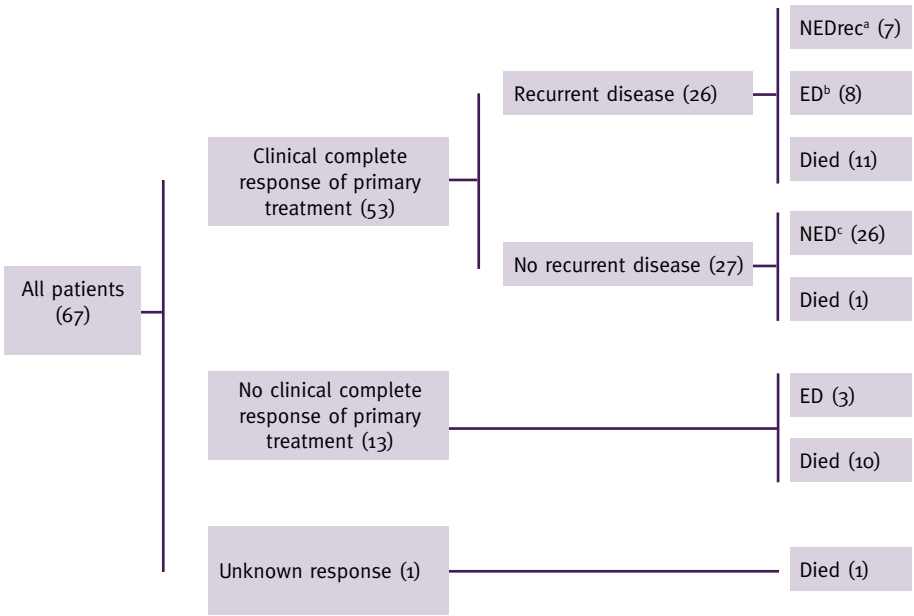
No patient received primary hormonal treatment. One patient with stage IVB disease received postoperative hormonal treatment.

Follow-up after treatment of advanced endometrial cancer

The follow-up of all patients treated for advanced endometrial cancer is showed in Figure 2.1. A detailed overview of all patients is presented in Table 2.3. Median duration of follow-up for all patients was 27 months (range 1-145).

Of the ten patients with stage IIIA based on positive cytology only, six developed recurrent cancer (including the patient with histological uncertainty if this recurrence originated from endometrial or breast cancer). Site of recurrent disease differed among these patients: two patients developed local recurrent disease, two distant diseases and two local and distant diseases together. Of the 11 patients with stage IIIA based on ovarian invasion only, five

Figure 2.1. Status at the end of follow-up of patients with advanced endometrial cancer.



[a] No evidence of disease after recurrent cancer treatment. [b] Evidence of disease. [c] No evidence of disease.

Table 2.3. Follow-up of patients treated for advanced endometrial cancer.

	AGE	FIGO STAGE[a]	PRIMARY TREAT MENT[b]	RESPONSE PRIMARY TREATMENT[c]	RECURRENCE	RECURRENCE SITE SPECIFIED	TREATMENT RECURRENCE	STATUS AT END OF FOLLOW-UP[d]	DURATION (MONTHS)[e]
1.	54	III	RT	CR	Local and distant	Central pelvis, lung, liver, para-aortic lymph node	CT	ED	75
2.	40	IIIA G1	S+RT	CR	No			NED	37
3.	54	IIIA G1	S+RT	CR	No			NED	34
4.	70	IIIA G1	S+RT	CR	No			NED	18
5.	74	IIIA G1	S+RT	CR	Distant	Liver, para-aortic lymph node	HT	Died of EC	20
6.	83	IIIA G1	S+RT	CR	No			NED	54
7.	45	IIIA G2	S+CT	CR	Distant	Para-aortic lymph node	S+CT	ED	117
8.	47	IIIA G2	S	CR	No			NED	63
9.	51	IIIA G2	S+RT	CR	No			NED	31
10.	51	IIIA G2	S+RT	CR	Distant	Peritoneum	HT	NED	27
11.	54	IIIA G2	S+RT	CR	No			NED	93
12.	55	IIIA G2	S+RT	CR	No			NED	67
13.	55	IIIA G2	S+RT	CR	Distant[f]	Bone	RT	Died EC or BC	10
14.	58	IIIA G2	S	CR	Local and distant	Bowels	S	NED	145
15.	60	IIIA G2	S+RT	CR	Local and distant	Central pelvis, lung	HT	Died of EC	29
16.	62	IIIA G2	S+RT	CR	Distant	Liver		Died of EC	9
17.	65	IIIA G2	S+RT	CR	Local and distant	Bowels, skin	S+HT	ED	115
18.	67	IIIA G2	S+RT	CR	No			Died of ID	104
19.	71	IIIA G2	S+RT	CR	No			NED	63
20.	73	IIIA G2	S+RT	CR	Local	Vagina	S+RT	Died of EC	51
21.	74	IIIA G2	S+RT	PD	No			ED	12
22.	75	IIIA G2	S+RT	CR	Local and distant	Vagina, axillary lymph node	S	Died of EC	15
23.	75	IIIA G2	S+RT	CR	Distant	Lung, bone	S+RT+HT	Died of EC	96
24.	76	IIIA G2	S+RT	CR	Local	Vagina	S	NED	109
25.	77	IIIA G2	S+RT	CR	Local	Vagina	RT	Died of EC	38
26.	78	IIIA G2	S+RT	CR	No			NED	10
27.	81	IIIA G2	S	CR	No			NED	13
28.	81	IIIA G2	S	CR	Local	Vagina	S+RT	NED	75
29.	52	IIIA G3	S+RT	CR	No			NED	34
30.	59	IIIA G3	S+RT	CR	Local and distant	Pelvis, abdomen	S+RT	NED	22
31.	63	IIIA G3	S+RT	CR	Distant	Bowels	S	ED	36
32.	64	IIIA G3	S+RT	CR	Distant	Bone	RT	Died of EC	27

[a] G=grade, mentioned if known. [b] S=surgery (optimal surgical cytoreduction), S[n]= surgery (not optimal surgical cytoreduced), RT=radiotherapy, CT=chemotherapy, HT=hormonal treatment. [c] CR=clinical complete response, PD=progressive disease, UNK=unknown. [d] ED=evidence of disease, NED=no evidence of disease, EC=endometrial cancer, ID=intercurrent disease, BC=breast cancer,

	AGE	FIGO STAGE[a]	PRIMARY TREATMENT[b]	RESPONSE PRIMARY TREATMENT[c]	RECURRENCE	RECURRENCE SITE SPECIFIED	TREATMENT RECURRENCE	STATUS AT END OF FOLLOW-UP[d]	DURATION (MONTHS)[e]
33.	68	IIIA G3	S+RT	CR	Distant	Lung, bone	RT	ED	20
34.	68	IIIA G3	S+RT	CR	Local and distant	Vagina, lung, peritoneum	CT	ED	21
35.	55	IIIB	RT	PD	No			Died of EC	6
36.	84	IIIB G3	S	CR	No			NED	3
37.	75	IIIC	S^n+RT	CR	Distant	Peritoneum	HT	ED	48
38.	50	IIIC G2	S+RT	CR	No			NED	135
39.	57	IIIC G2	S+RT+CT	CR	No			NED	9
40.	61	IIIC G2	S+RT	CR	Distant	Para-aortic lymph node	S+RT	NED	36
41.	71	IIIC G2	S+RT	CR	Distant	Lung	HT	ED	23
42.	71	IIIC G2	S+RT	CR	Local and distant	Vagina, peritoneum		Died of EC	23
43.	72	IIIC G2	S+RT	CR	No			NED	52
44.	45	IIIC G3	S+RT	CR	No			NED	27
45.	46	IIIC G3	S^n+RT+CT	PD	No			ED	4
46.	51	IIIC G3	S+RT	CR	Distant	Supraclavicular and para-aortic lymph node	RT+CT	NED	52
47.	52	IIIC G3	S+RT	CR	No			NED	131
48.	53	IIIC G3	S+RT	CR	No			NED	67
49.	54	IIIC G3	S+RT	PD	No			Died of EC	6
50.	57	IIIC G3	S+RT	CR	No			NED	26
51.	62	IIIC G3	S	CR[g]	No			NED	12
52.	60	IVA G2	S^n+RT+CT	CR	No			NED	33
53.	61	IVA G2	S^n+RT+CT	CR	No			NED	6
54.	80	IVA G2	S+RT	PD	No			Died of EC	6
55.	65	IVA G3	S^n+RT	CR	No			NED	23
56.	80	IVA G3	S^n+RT	PD	No			ED	6
57.	52	IVB	RT+CT	CR	No			NED	52
58.	64	IVB	RT+CT	PD	No			Died of EC	13
59.	32	IVB G2	S^n+CT	PD	No			Died of EC	6
60.	59	IVB G2	S^n	PD	No			Died of EC	1
61.	59	IVB G2	S^n+RT	CR	No			NED	114
62.	63	IVB G2	S+CT	PD	No			Died of EC	14
63.	72	IVB G2	S^n+CT	UNK	No			Died of UR	34
64.	77	IVB G2	S+HT	CR	Distant	Lung, supraclavicular lymph node	HT	Died of UR	27
65.	54	IVB G3	S^n+RT+CT	PD	No			Died of EC	8
66.	72	IVB G3	S^n	PD	No			Died of EC	15
67.	77	IVB G3	RT	PD	No			Died of EC	22

UR=unknown reason. [e] Duration=time from start primary treatment to last follow-up or death. [f] Recurrent disease in bone, unknown if primary tumor was endometrial or breast cancer. [g] Primary treatment resulted in PD, extended primary treatment with S and RT resulted in a CR.

patients developed recurrent disease. At the end of follow-up six of the patients with stage IIIA disease based on positive cytology only showed no evidence of disease and four had died. Of the patients with stage IIIA disease based on ovarian invasion only, seven showed no evidence of disease at the end of follow-up, two showed evidence of disease and two had died. After analyzing of subgroups of patients with stage IIIA disease, it can be concluded that the incidence of recurrence and the status at the end of follow-up among these subgroups is comparable.

All three patients with serous type carcinoma had died of endometrial cancer at the end of the observation period; one patient died of progressive disease within six months of primary diagnosis, the other two developed recurrent disease and died after 20 and 23 months.

Survival

The survival curves for patients with advanced stage endometrial cancer are shown in Figure 2.2. The 2- and 5-year survival rate for all patients with advanced endometrial cancer was 74.7% and 59.7%. For patients with FIGO stage IIIA based on only positive cytology the 2- and 5-year survival rates were 86.9% and 60.9%.The survival of patients with FIGO stage III or IV is significantly different ($p < 0.005$).

Figure 2.3 shows the survival curves for patients with advanced stage endometrial cancer treated with or without optimal surgical cytoreduction. The 2- and 5-year survival rates for patients treated with optimal surgical cytoreduction were 82.2% and 65.6%. The 2- and 5-year survival rates for patients who were not optimal surgical cytoreduced were 50.8% and 40.6%. This difference approaches significance ($p < 0.1$).

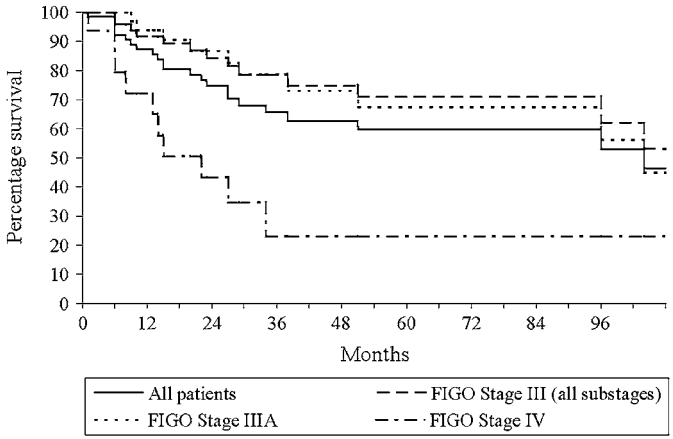
Two patients who underwent retroperitoneal debulking died, one after 6 months due to endometrial cancer, the other after 27 months of unknown reason. Three patients showed no evidence of disease after 26, 67 and 131 months of follow-up.

Discussion

Our data show similar survival rates and recurrence rates in the subgroup of patients with stage IIIA disease based on positive peritoneal cytology only as in patients with stage IIIA disease based on other factors.

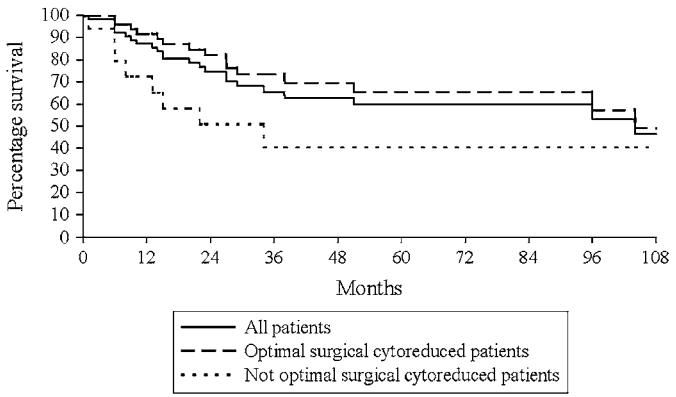
The prognostic significance of positive peritoneal cytology in endometrial carcinoma has led to the incorporation of peritoneal cytology into the current FIGO staging system. While cytology was shown to be prognostically relevant in patients with clinical stage II and III disease, conflicting data exists about its significance in patients who have been clinical stage I but were classified as surgical stage III solely and exclusively on the basis of positive peritoneal cytology. The purpose of taking peritoneal washings is to identify microscopic disease and peritoneal cytology is assumed to add information on the spread of occult

Figure 2.2. Kaplan-Meier survival curve for patients with advanced stage endometrial cancer.



peritoneal disease. While some studies report good correlation of peritoneal cytology with prognosis, other studies do not. It has been suggested that studies before 1990 merely reported peritoneal washings to be significantly associated with outcome (15, 16). More recent studies report different results of the prognostic value of positive peritoneal cytology in endometrial cancer. An overview of the most recent literature is shown in Table 2.4. So,

Figure 2.3. Kaplan-Meier survival curve according to optimal surgical cytoreduction.



results are conflicting and our series, in which relatively few lymph node dissections were performed, is in accordance with the studies showing a prognostic significance (11-13).

Optimal cytoreduction has a beneficial effect on survival of ovarian cancer patients (17), but it is not completely clear what role it plays in the treatment of endometrial cancer. Because of the pattern of dissemination, including the removal of retroperitoneal tumor to cytoreductive surgery, might be more important in endometrial cancer compared to ovarian cancer. In ovarian cancer surgery, optimal cytoreduction is usually defined as residual nodules ≤ 1 cm diameter. Several retrospective studies have evaluated the effect of surgical cytoreduction in endometrial cancer. Aalders et al. showed that surgical eradication of all macroscopic tumor was of major prognostic importance for patients with clinical stage III. Fourteen of 108 patients were treated with complete surgical eradication, resulting in an improvement in 5-year survival from 16 to 41% (3). Greven et al. showed in a study of 52 patients with clinical stage III disease that local control and survival was improved in patients undergoing surgical resection (4), with an improvement in survival rate from 36% to 48%. Goff et al. analyzed 47 patients treated for surgical stage IV endometrial cancer (7). Twenty-nine of these patients underwent explorative laparotomy with a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and cytoreduction, although the exact amount of residual disease after surgery was not recorded. Patients who underwent surgery, had a median survival of 18 months compared to 8 months in those who did not. Bristow et al. evaluated the role of optimal cytoreductive surgery defined as ≤ 1 cm maximal diameter of residual disease in patients with stage IVB endometrial carcinoma and concluded that the amount of residual disease after cytoreductive surgery was an important determinant of survival (8). They showed in their series of 65 patients a statistically significant difference in survival rate between patients undergoing optimal cytoreductive surgery and patients with > 1 cm of residual tumor: 34.3 months compared to 11.0 months. Chi et al. evaluated the impact of surgical cytoreduction in 55 patients with stage IV endometrial adenocarcinoma. They defined optimal surgical cytoreduction as residual tumor nodule ≤ 2 cm in diameter and suggested that aggressive tumor cytoreduction may improve survival (14). A drawback in this limited literature on surgical cytoreduction is the use of different definitions of optimal surgical cytoreduction. Nevertheless, optimal surgical cytoreduction or the fact that such surgery is achievable, improves the survival of patients with advanced endometrial cancer. Our series shows a similar advantage of optimal surgical cytoreduction on survival in patients with advanced endometrial cancer.

The current study has several characteristics that should be considered in interpreting the data. First, it is a relative shortcoming of our study that peritoneal cytology was not examined in all patients. Second, a particularity of this study is that lymphadenectomy was not routinely performed.

Keeping these characteristics in mind, it can be concluded that, in our experience,

Table 2.4. Association of positive cytology on outcome reported in literature.

REFERENCE	YEAR	NUMBER OF PATIENTS[a] A	B	C	OUTCOME	STUDY SHOWS PROGNOSTIC SIGNIFICANCE
Schorge et al (5)	1996	86	29	?	Positive cytology is not a prognostic factor in stage III patients	No
Zuna et al (11)	1996	135	17	11	5-year survival for patients with positive or negative cytology is 0% versus 84.3%	Yes
Kashimura et al (12)	1997	303	44	?	5-year survival for patients with positive or negative cytology is 80% versus 92%	Yes
Aoki et al (6)	2001	61	36	?	Positive cytology has no influence on disease-free survival in stage III patients	No
Hirai et al (10)	2001	448	50	34	Positive cytology without adnexal metastasis is not associated with intra-peritoneal recurrence	No
Obermair et al (13)	2001	369	13	13	Disease-free survival at 36 months for patients with positive or negative cytology is 67% versus 96%	Yes
Our series		67	26	10	Survival and recurrence rates of patients with stage IIIA based on positive cytology only are comparable with stage IIIA based on other factors	Yes

[a] A=all patients, B=all patients with positive cytology, C= patients with IIIA based on cytology only, ?=number of patients is unknown.

patients with advanced endometrial cancer based on positive peritoneal cytology only, have a recurrence rate comparable with other patients with stage III endometrial cancer. Therefore, positive peritoneal cytology is in our hands an important prognostic factor in endometrial cancer patients and may be particularly important in patients who did not undergo a lymphadenectomy. Advanced endometrial cancer based on positive peritoneal cytology only

does not act as local disease. These patients benefit by systemic treatment and such treatment should be studied.

Furthermore, we conclude that survival is influenced by optimal surgical cytoreduction and this should be the cornerstone of the treatment of choice in patients with advanced endometrial cancer. Where optimal surgical cytoreduction is not possible, treatment should be individualized.

References

1. Association of Comprehensive Cancer Centres. Incidence of cancer in the Netherlands 1999-2000: report of the Netherlands cancer registry. http://www.ikcnet.nl/uploaded/bibliotheek/document/VIKC-Inc-2000-81-webpdf. 2003.
2. FIGO. Annual Report. International Federation of Gynecology and Obstetrics. 1994.
3. Aalders JG, Abeler V, Kolstad P. Clinical (stage III) as compared to subclinical intrapelvic extrauterine tumor spread in endometrial carcinoma: a clinical and histopathological study of 175 patients. Gynecol Oncol. 1984 Jan;17(1):64-74.
4. Greven KM, Curran WJ, Jr., Whittington R, Fanning J, Randall ME, Wilder J, et al. Analysis of failure patterns in stage III endometrial carcinoma and therapeutic implications. Int J Radiat Oncol Biol Phys. 1989 Jul;17(1):35-9.
5. Schorge JO, Molpus KL, Goodman A, Nikrui N, Fuller AF, Jr. The effect of postsurgical therapy on stage III endometrial carcinoma. Gynecol Oncol. 1996 Oct;63(1):34-9.
6. Aoki Y, Kase H, Watanabe M, Sato T, Kurata H, Tanaka K. Stage III endometrial cancer: analysis of prognostic factors and failure patterns after adjuvant chemotherapy. Gynecol Oncol. 2001 Oct;83(1):1-5.
7. Goff BA, Goodman A, Muntz HG, Fuller AF, Jr., Nikrui N, Rice LW. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol. 1994 Feb;52(2):237-40.
8. Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol. 2000 Aug;78(2):85-91.
9. Mikuta JJ. International Federation of Gynecology and Obstetrics staging of endometrial cancer 1988. Cancer. 1993 Feb 15;71(4 Suppl):1460-3.
10. Hirai Y, Takeshima N, Kato T, Hasumi K. Malignant potential of positive peritoneal cytology in endometrial cancer. Obstet Gynecol. 2001 May;97(5 Pt 1):725-8.
11. Zuna RE, Behrens A. Peritoneal washing cytology in gynecologic cancers: long-term follow-up of 355 patients. J Natl Cancer Inst. 1996 Jul 17;88(14):980-7.
12. Kashimura M, Sugihara K, Toki N, Matsuura Y, Kawagoe T, Kamura T, et al. The significance of peritoneal cytology in uterine cervix and endometrial cancer. Gynecol Oncol. 1997 Dec;67(3):285-90.
13. Obermair A, Geramou M, Tripcony L, Nicklin JL, Perrin L, Crandon AJ. Peritoneal cytology: impact on disease-free survival in clinical stage I endometrioid adenocarcinoma of the uterus. Cancer Lett. 2001 Mar 10;164(1):105-10.
14. Chi DS, Welshinger M, Venkatraman ES, Barakat RR. The role of surgical cytoreduction in Stage IV endometrial carcinoma. Gynecol Oncol. 1997 Oct;67(1):56-60.
15. Mazurka JL, Krepart GV, Lotocki RJ. Prognostic significance of positive peritoneal cytology in endometrial carcinoma. Am J Obstet Gynecol. 1988 Feb;158(2):303-6.
16. Turner DA, Gershenson DM, Atkinson N, Sneige N, Wharton AT. The prognostic significance of peritoneal cytology for stage I endometrial cancer. Obstet Gynecol. 1989 Nov;74(5):775-80.
17. Hacker NF, van der Burg ME. Advanced ovarian cancer. Debulking and intervention surgery. Ann Oncol. 1993;4 Suppl 4:17-22.

Chapter 3

Recurrent endometrial cancer: a retrospective study

Recurrent endometrial cancer: a retrospective study
F.H. van Wijk, F.J. Huikeshoven, L. Abdulkadir, P.C. Ewing, C.W. Burger
European Journal of Obstetrics & Gynecology and Reproductive Biology 2007; 130: 114-120.

Abstract

Background: The value of follow-up after treatment for endometrial cancer will be discussed.

Methods: We evaluated our clinical experience, including mode of detection, of patients with recurrent endometrial cancer treated in the Erasmus MC in Rotterdam over a 20 year period. Clinical data and histopathological features from 64 patients were analyzed. Survival was analyzed with a Kaplan-Meier curve.

Results: Twenty-two patients had a local recurrence, 30 had a distant recurrence and 12 had simultaneous local and distant recurrent disease. Ninety-five percent of the local recurrences and 67% of the distant recurrences were detected within three years. Twenty-seven patients had a screen-detected recurrence, 34 had an interval screening recurrence and two had a chance finding recurrence. The overall survival rate at two years was 70% and at five years 53%. Patients with a screen-detected recurrence had a 5-year survival rate of 62%, while patients with interval screening and chance finding recurrences had a 5-year survival rate of 47%.

Conclusions: A follow-up program in the first three years after primary treatment of endometrial cancer is useful in detecting recurrent disease. We have no reason to use a different program of follow-up in patients with low risk primary disease.

Introduction

Cancer of the uterine corpus is the most common gynecological malignancy and the fourth most common cancer in women in the United States. The incidence rises from 2 per 100,000 women per year under the age of 40 years to 40-50 per 100,000 women per year in the sixth, seventh and eighth life decades (1). In the Netherlands, the number of case for endometrial cancer in 2000 was 1,457, compared to 1,116 for ovarian cancer and 677 for cervical cancer (2). Approximately 77% of patients with endometrial cancer have disease confined to the uterus at the time of diagnosis associated with a favorable 5-year survival rate (3). Five-year survival rates decline from 86% for FIGO stage I disease to 16% for FIGO stage IV disease (4). Recurrences occur after all stages of initial disease, and are uniformly associated with poor survival (5).

It is common clinical practice to follow patients who have been treated for cancer for several years after their primary treatment. Despite this widespread practice there is considerable controversy about how often patients should be seen, what tests should be performed and whether these varying strategies have any significant impact on patient outcomes. Follow-up may lead not only to early detection of recurrent disease, but also to a survival benefit.

Recently, Tjalma et al. published an overview of the available retrospective studies on routine follow-up management of patients after treatment for endometrial cancer (6). They concluded that the sensitivity of routine follow-up schemes appeared very low and that there is little or no value in routine follow-up in terms of improving survival rates in endometrial cancer. Early detection of recurrent disease appeared not to be beneficial in terms of improving outcome or reducing morbidity.

The value of follow-up after treatment for cancer is still the subject of discussion. In this study we evaluated our clinical experience and mode of detection of patients with recurrent endometrial cancer treated in the Erasmus MC over a 20-year period, in terms of disease free interval, mode of treatment and survival.

Patients and methods

We reviewed the tumor files of patients with recurrent endometrial cancer treated between 1984 and 2003 at Erasmus MC in Rotterdam. This is the largest university medical centre in The Netherlands and includes the Erasmus MC Daniel den Hoed Cancer Center. Patients were identified using the databases of medical registration of the hospital and of the Comprehensive Cancer Centre Rotterdam. All patients' records of these cases were reviewed retrospectively. Clinical data and histopathological features were noted. At the time of diagnosis all histological specimens had been evaluated according to the WHO/ISGP classification and reported by pathologists experienced in gynecologic pathology. Pathological reports were reviewed; tumors reported to contain serous or adenosquamous components or where the tumor type

was unclear were re-evaluated. We excluded patients with tumors of mesodermal origin – uterine sarcomas and mixed müllerian tumors – since they have different biological behavior. Also patients who received their complete treatment elsewhere were excluded. All tumors were staged retrospectively according to the International Federation of Gynecology and Obstetrics (FIGO) surgical staging criteria from 1988 (7).

Recurrent disease was defined as histopathologically confirmed disease after a clinically complete response to primary therapy. The time to recurrence was defined as time between date of primary diagnosis of endometrial cancer and date of histopathological confirmed recurrent disease. Patients with single recurrent disease confined to the true pelvis were said to have local recurrence, and those with any extra pelvic disease were said to have distant recurrence or a combination of both. The mode of detection of recurrent disease will be emphasized. Recurrences were considered symptomatic if the patient reported complaints prior to examination. The follow-up programs used varied owing to patients being followed up in different regional hospitals. Screen-detected recurrences were recurrences detected during standard follow-up in asymptomatic patients in whom the recurrence was detected by routine physical exam, cytology or chest X-ray. Interval screening recurrences were recurrences detected in symptomatic patients not during standard follow-up. Chance finding recurrences were recurrences detected during examinations not primarily initiated to detect recurrent disease.

The management of recurrent disease is described and the effectiveness of this management is evaluated. If the patient received treatment, the treatment of the first detected recurrent disease is evaluated. The survival, time to progression or time to death were calculated from the date of confirmed recurrent disease. The overall survival was analyzed with a Kaplan-Meier curve.

Results

Patient characteristics and histopathological features

Sixty-four patients with recurrent endometrial cancer are included in this study. Median age at primary disease was 66.5 years (range 45-82). Nineteen percent of the patients were nulliparous, 90% were postmenopausal. Use of hormone replacement therapy and oral contraception was not documented. Co-morbidity at time of recurrent disease was found in 34 patients; diabetes was present in 10 patients, hypertension in 22 patients and a secondary malignancy in 13 patients.

The histopathological details of patients operated for primary endometrial cancer are presented in Table 3.1. In three patients the surgical margins of the uterine specimen were not free of tumor; in two due to parametrial extension and in one patient tumor was left in the vagina. Extra pelvic disease was found in one patient, on the peritoneum and in a para-aortic lymph node.

Table 3.1. Histopathological details of patients operated for primary disease.

	N (%)
Number	63
Histopathologic type	
Endometrioid	53 (84)
Serous	7 (11)
Adenosquamous	2 (3)
Undifferentiated	1 (2)
Unknown	1 (2)
Grade	
1	11 (17)
2	37 (59)
3	12 (19)
Unknown	3 (5)
Myometrial invasion	
No	3 (5)
Yes, ‹ 1/2	24 (38)
Yes, › 1/2	36 (57)
Adnexa involved	
No	53 (84)
Yes	10 (16)
Cervical invasion	
No	43 (68)
Yes	19 (30)
Glandular	8 (13)
Stromal	10 (16)
Glandular or stromal	1 (2)
Unknown	1 (2)
Peritoneal cytology positive	
No	24 (38)
Yes	9 (14)
Unknown	30 (48)
Pelvic lymph node positive	
No	8 (13)
Yes	5 (8)
Unknown	50 (79)
Para-aortic lymph node positive	
No	1 (2)
Yes	1 (2)
Unknown	61 (97)
Margins free	
No	3 (5)
Yes	60 (95)
Extrapelvic disease	
No	62 (98)
Yes	1 (2)

Table 3.2. FIGO stage at primary diagnosis of patients with recurrent endometrial cancer.

FIGO STAGE	N	
I	29	
I A		3
I B		13
I C		13
II	10	
II A		5
II B		5
III	24	
III (clinical stage)		1
III A		18
III B		0
III C		5
IV	1	
IV A		0
IV B		1

The FIGO stages at time of primary surgery are shown in Table 3.2. One patient was not primarily surgically staged, in this case the FIGO clinical staging adopted in 1971 was applied, as advised in such cases. Stage IIIA disease was found in 18 patients, five patients had positive cytology, five patients had adnexal involvement, three patients had both positive cytology and adnexal involvement and in five invasion of the serosa was present. Nineteen patients had their primary treatment in the Erasmus MC, the remaining were primarily treated elsewhere in the Netherlands and referred later to our Cancer Center.

Primary treatment

Table 3.3 summarizes the initial method of treatment with reference to the different FIGO stages. If surgery was performed this was usually total abdominal hysterectomy and bilateral salpingo-oophorectomy. One patient with stage I disease was previously (37 years before diagnosis of endometrial cancer) treated with radiation for cervical cancer, therefore a supracervical hysterectomy was performed and additional hormonal therapy was prescribed. Lymphadenectomy is not routinely performed in The Netherlands. In only nine patients was a complete pelvic lymphadenectomy performed. In one of these patients a unilateral para-aortic lymph node sampling was also performed. In five patients a pelvic or para-aortic lymph node sampling or removal of suspected lymph nodes took place. The type of radiotherapy used varied among the patients. Twelve patients received postoperative external pelvic irradiation and additional brachytherapy, 24 patients received only postoperative external pelvic irradiation, and three patients received only postoperative brachytherapy. One patient

Table 3.3. Initial treatment of primary endometrial cancer according to FIGO stage.

FIGO STAGE	INITIAL TREATMENT N (%)					TOTAL N
	SURGERY ALONE	SURGERY + RADIO-THERAPY	SURGERY + HORMONAL THERAPY	SURGERY + CHEMO-THERAPY	PRIMARY RADIO-THERAPY	
I	17 (27)	11 (17)	1 (2)	0	0	29
II	2 (3)	8 (13)	0	0	0	10
III	2 (3)	20 (31)	0	1 (2)	1 (2)	24
IV	0	0	1 (2)	0	0	1
Total	21 (33)	39 (61)	2 (3)	1 (2)	1 (2)	64

was treated with primary radiotherapy consisting of external irradiation, brachytherapy and hyperthermia; she was not operated on because she refused blood transfusion. Two of the three patients who received postoperative brachytherapy had primary stage IIA disease. In total, four patients refused postoperative radiotherapy, three patients with stage I disease and one with stage III disease. One patient with stage III endometrial cancer was initially diagnosed as having ovarian cancer and treated with surgery and chemotherapy.

Mode of detection of recurrent disease

Thirty-four patients presented with symptoms in the outpatient clinic and an interval screening recurrence was detected. Pain was the most common complaint in patients with recurrent disease, followed by vaginal bleeding, general malaise, loss of weight and intestinal complaints. Twenty-nine patients had no symptoms of their recurrent disease. Twenty-seven patients had a screen-detected recurrence. In two patients recurrent disease was detected by chance during intestinal surgery for radio-enteritis or adhesive bowel obstruction.

Sites of recurrence

The various sites of recurrences in relation to primary FIGO stage are presented in Table 3.4. After primary higher stage disease, recurrences were detected more frequently in distant sites.

Nineteen patients had an isolated distant recurrence; six of the recurrences were located in the lungs, four in the para-aortic lymph nodes, two in the bowel, two in the peritoneum and one in each of bone, brain, liver, inguinal lymph node and abdominal wall.

Mode of detection related to sites of recurrences

The mode of detection related to the site of recurrence is presented in Table 3.5. Two symptomatic patients with recurrent disease in the lung presented with dyspnea or cough. Nine of the fifteen patients with recurrent disease in the lung were asymptomatic and the

Table 3.4. Sites of recurrence related to primary stage.

PRIMARY FIGO STAGE	SITES OF RECURRENCE		
	LOCAL	DISTANT	LOCAL AND DISTANT
I	16	11	2
II	2	6	2
III	4	12	8
IV	0	1	0
Total	22	30	12

recurrence was detected during routine follow-up. Five of these nine patients had isolated recurrent disease in the lung.

Interval between primary treatment and recurrence

Local recurrence was detected within one year after diagnosis of primary disease in 11 patients (48%) and distant recurrence in five patients (17%). Within three years 95% of the local recurrences (21 patients) and 67% of the distant recurrences (20 patients) were detected. In nine patients (14%) the recurrence appeared more than five years after primary diagnosis. The median interval to local recurrence was 13 months (range 2-79) and to distant recurrent disease was 23 months (range 3-102).

Management of recurrences and survival

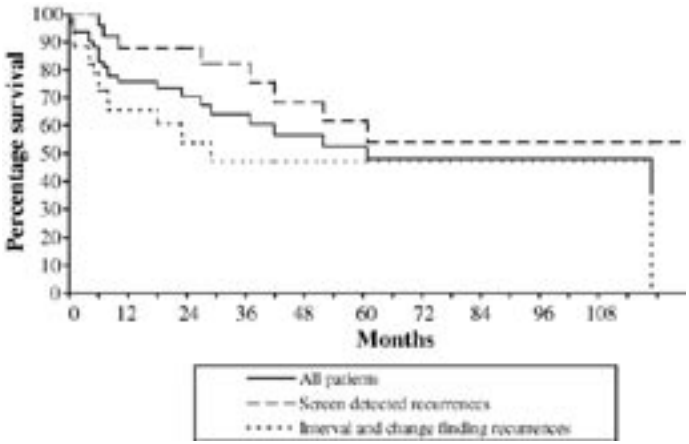
The overall survival of our endometrial cancer patients with recurrent disease is shown

Table 3.5. Mode of detection related to sites of recurrences.

MODE OF DETECTION	SITES OF RECURRENCE		
	LOCAL	DISTANT	LOCAL AND DISTANT
Complaints	7	19	8
Pain	2	10	4
Vaginal bleeding	5	0	2
Intestinal	0	4	1
General malaise	1	3	2
Loss of weight	0	5	1
Other [a]	0	11	4
Follow-up	14	9	4
By chance finding	0	2	0
Unknown	1	0	0

[a] Cough, dyspnea, fever, increased abdominal size, palpable abdominal tumor, palpable neck tumor, paraneoplastic dermatomyositis, pathological fracture, polyneuropathy, stroke of paralysis, rectovaginal fistula.

Figure 3.1. Kaplan-Meier survival curve for patients with recurrent endometrial cancer, according to mode of detection.



in Figure 3.1. By two years 70% of all patients were still alive and at five year their survival rate was 53%. Patients with screen-detected recurrences had a 5-year survival rate of 62%. Patients with interval screening recurrences or recurrences detected by chance had a 5-year survival rate of 47%. Evaluating the patients with an endometrioid type of tumor separately, the 5-year survival rate for patients with screen-detected recurrences is 68% and for patients with interval screening recurrences is 51%.

Forty patients (63%) were alive at the end of the observation period (median 2 years, ranging 0-16 years). Twenty-three of these patients showed no evidence of disease. Twenty-four patients were dead at the end of the observation period; eighteen due to their endometrial cancer and six of other causes. Two patients received no treatment; both died within two months from their recurrent endometrial cancer.

Taking all patients together, radiotherapy was the most common method of treatment, with 31 patients (48%) receiving radiotherapy for their recurrent disease. Twelve of these patients also underwent surgery, three patients received concomitant chemotherapy and three patients received concomitant hormonal treatment. The best results with radiotherapy were obtained in patients with local recurrent disease. Radiotherapy for previously non-irradiated patients with local recurrent disease resulted in a cure in ten out of 16 patients. At the end of the observation period, 11 patients treated with radiotherapy were dead, nine due to endometrial cancer and two to other causes.

Only six of our patients were treated with chemotherapy, in all cases a combination

Table 3.6. Status at the end of the observation period and the survival in relation to mode of detection of recurrent disease.

	MODE OF DETECTION OF RECURRENT DISEASE	
	FOLLOW-UP	OTHERWISE
Number	27	37
Status at end of observation period		
Dead	9	15
< 1 year	1	11
< 3 years	4	14
Due to endometrial cancer	6	12
No evidence of disease	12	11
Observation period > 3 years	7	3
Survival rate		
2-year	88	54
5-year	62	47

treatment. One patient was cured by chemotherapy. She received a combination of cyclophosphamide, doxorubicin and cisplatin and showed no evidence of disease after a follow up of 40 months.

The status at the end of the observation period and the survival of our patients with recurrent disease detected during follow-up and detected otherwise is shown in Table 3.6. Survival rates for patients with screen-detected recurrences were better than for patients with interval screening recurrences.

Women at low risk for recurrence were characterized by FIGO stage IA, grade 1 or 2 or stage IB grade 1 endometrioid adenocarcinoma. In our study group five patients had low risk primary disease. Recurrent disease was detected in four patients during follow-up, and one patient was symptomatic. Two patients died of their disease after 29 and 53 months. After treatment for their local recurrence, two of these patients showed no evidence of disease after an observation period of 101 and 195 months.

Discussion

Evidence from randomized clinical trials is needed before considering changing the standard practice of routine follow-up in endometrial cancer. Without this evidence we can conclude that a follow-up program in the first three years after primary treatment of endometrial cancer is useful in detecting recurrent disease. Most recurrences were diagnosed within the first three years after primary treatment in our population. The reported median intervals to local and distant recurrent disease in our population are consistent with those reported in the literature (8-11).

Most series in the literature focus on recurrent disease after stage I primary disease,

since most patients present with early stage disease (12). Aalders et al. found 28% of their population to have primary stage III or VI disease (10). While in the study of Burke et al. 13% of patients with recurrent disease had advanced stage primary disease (11). In our population, 39% of the patients had primary stage III or IV disease. However these three series are not directly comparable because the first two used the FIGO clinical staging system, while we adopted the surgical staging system from 1988 (7).

When compared to the study population of Aalders et al., a similar percentage (59%) of the patients in our group was primarily treated with surgery and radiotherapy. However a much lower percentage (13%) of the patients in the earlier series were treated with surgery alone; in the study population of Aalders et al. 27% of patients received primary radiotherapy alone, while in our group this was 2%. This difference may be explained by national differences in protocols and by the fact that their report describes a patient population treated two decades earlier than our patients. For patients who have evidence of metastatic disease at time of surgery, it is nowadays generally accepted that there is a survival benefit to be gained if all gross evidence of disease can be resected or at least debulked to leave small-volume residual disease (13).

There are limited published data analyzing site of recurrence. Aalders et al. reported an equal distribution of local and distant recurrences in their population (10). In a population where pelvic radiotherapy is applied to selected high risk patients, the local failure rate is usually one-fourth to one-third of the distant failure rate (14, 15). The local and distant failure rates of our patient population are comparable to those reported in the literature (6, 11, 14).

Aalders et al. and Burke et al. reported a salvage rate of respectively 12% and 18% of the local recurrences in their patient population (10, 11). In our series 68% of the patients with local recurrences showed no evidence of their disease at the end of the observation period with a median of four years (range 0-16 years). A possible explanation for this difference might be the fact that in our series a greater proportion of patients with local recurrent disease had not been primarily irradiated compared to the series of Aalders et al. and Burke et al.

In The Netherlands it is standard practice to follow patients after treatment for cancer. One valuable aspect of follow-up is the identification of treatment-related complications (16). Another important aspect of follow-up may be the psychological lift and reassurance that negative follow-up examinations provide for the cancer patient and her family (17). In some cases, routine follow-up may lead to a delay in diagnosis of recurrent disease, because a symptomatic patient sometimes delays seeking help until the scheduled visit (18). It is generally assumed that detecting recurrent cancer before symptoms develop should permit earlier treatment and may lead to improved survival. However, randomized controlled trials are needed to substantiate this.

Tjalma et al. recently published an overview of 11 retrospective studies (evaluating 2866 patients) addressing routine follow-up of endometrial cancer. In these studies symptomatic recurrences ranged between 41% and 81% (mean 65%) of all recurrences (6). In our population 53% of the patients were symptomatic. Tjalma et al. showed that there was no difference in survival between asymptomatic and symptomatic patients. They noted that because of a difference in survival between isolated vaginal recurrence and non-vaginal recurrences, 5-year survival respectively 50% and 6%, it is important to identify isolated vaginal recurrences early.

As the sensitivity of routine follow-up schemes appears very low, tailored follow-up protocols based on high risk and low risk for recurrence are suggested. Low risk patients are generally defined as patients with adenocarcinoma IA grade 1 or 2 or IB grade 1, with a recurrence rate of just under 4%, whereas high risk patients have a recurrence rate of around 23% (16). Salvesen et al. found no asymptomatic recurrences in his group of 160 low risk endometrial cancer patients, defined as women ≤ 60 years or with FIGO stage IA or IB disease. Therefore, they concluded that low risk patients should be considered for less frequent follow up (8). We reported five low risk patients with recurrent disease; of these patients only one patient, suffering from distant recurrent disease, was symptomatic. Without a follow-up program for patients with low risk endometrial cancer, recurrent disease would only have been detected after symptoms had developed in four of these five patients. Despite our low number of patients with low risk disease, we see no reason to use different follow-up scheme for these patients. Patients with low risk disease have a relatively increased risk of developing recurrent disease in the lungs. These patients would benefit by routine thoracic examinations, because of the good therapeutic options of these recurrences.

Two systematic reviews on follow-up strategies have been published. In colorectal cancer it has been suggested that there is an overall survival benefit after intensifying the follow-up of patients (19). This review underlined that it was not possible to estimate the potential harm or cost of intensifying follow-up for these patients in order to adopt a cost-effective approach in this clinical area. Rojas et al. concluded that in early breast cancer follow-up programs based on regular physical examinations and yearly mammography alone appeared to be just as effective as more intensive approaches in terms of timeliness of recurrence detection, overall survival and quality of life (20). One randomized controlled trial showed that follow up care in breast cancer patients performed by general practitioners was comparable in effectiveness to that delivered by hospital-based specialists in terms of quality of life and time to detection of distant metastases. Also, in endometrial cancer some authors are in favor of a shift to follow-up by general practitioners (21). It is argued that oncologists can then focus on newly diagnosed patients and thereby shorten waiting lists. Others think that post-treatment surveillance is best provided by the gynecologist or even gynecological oncologist or oncology nurse who has more experience of evaluating women with potential

recurrent cancer or therapy complications (12). Improving patient education so that early symptoms of recurrence are reported appears eminently sensible, but may serve also to heighten anxiety amongst the majority who will never develop recurrent disease (9).

We conclude that all patients should be thoroughly followed up irrespective of stage of primary disease. We found a survival advantage if the recurrence was detected during follow-up; this supports the benefit of a follow-up program. Randomized controlled trials are needed to obtain more evidence of the value of follow-up programs in endometrial cancer.

References

1. Benedet JL, Bender H, Jones H, 3rd, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2000;70(2):209-62.
2. Association of Comprehensive Cancer Centres. Incidence of cancer in the Netherlands 1999-2000: report of the Netherlands cancer registry. http://www.ikcnet.nl/uploaded/bibliotheek/document/VIKC-Inc-2000-81-web.pdf 2003.
3. Jemal A, RC Tiwari, T Murray, A Ghafoor, A Samuels, E Ward, EJ Feuer, MJ Thun. Cancer Statistics, 2004. CA Cancer J Clin 2004;54(1):8-29.
4. International Federation of Gynecology and Obstetrics. Annual Report. 1994.
5. Campagnutta E, Giorda G, De Piero G, Sopracordevole F, Visentin MC, Martella L, et al. Surgical treatment of recurrent endometrial carcinoma. Cancer 2004;100(1):89-96.
6. Tjalma WA, van Dam PA, Makar AP, Cruickshank DJ. The clinical value and the cost-effectiveness of follow-up in endometrial cancer patients. Int J Gynecol Cancer 2004;14(5):931-7.
7. Mikuta JJ. International Federation of Gynecology and Obstetrics staging of endometrial cancer 1988. Cancer 1993;71(4 Suppl):1460-3.
8. Salvesen HB, Akslen LA, Iversen T, Iversen OE. Recurrence of endometrial carcinoma and the value of routine follow up. Br J Obstet Gynaecol 1997;104(11):1302-7.
9. Owen P, Duncan ID. Is there any value in the long term follow up of women treated for endometrial cancer? Br J Obstet Gynaecol 1996;103(7):710-3.
10. Aalders JG, Abeler V, Kolstad P. Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. Gynecol Oncol 1984;17(1):85-103.
11. Burke TW, Heller PB, Woodward JE, Davidson SA, Hoskins WJ, Park RC. Treatment failure in endometrial carcinoma. Obstet Gynecol 1990;75(1):96-101.
12. Gadducci A, Cosio S, Fanucchi A, Cristofani R, Genazzani AR. An intensive follow-up does not change survival of patients with clinical stage I endometrial cancer. Anticancer Res 2000;20(3B):1977-84.
13. Chi DS, Barakat RR. Surgical management of advanced or recurrent endometrial cancer. Surg Clin North Am 2001;81(4):885-96.
14. Reddoch JM, Burke TW, Morris M, Tornos C, Levenback C, Gershenson DM. Surveillance for recurrent endometrial carcinoma: development of a follow-up scheme. Gynecol Oncol 1995;59(2):221-5.
15. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355(9213):1404-11.
16. Shumsky AG, Brasher PM, Stuart GC, Nation JG. Risk-specific follow-up for endometrial carcinoma patients. Gynecol Oncol 1997;65(3):379-82.
17. Berchuck A, Anspach C, Evans AC, Soper JT, Rodriguez GC, Dodge R, et al. Postsurgical surveillance of patients with FIGO stage I/II endometrial adenocarcinoma. Gynecol Oncol 1995;59(1):20-4.
18. Olaitan A, Murdoch J, Anderson R, James J, Graham J, Barley V. A critical evaluation of current protocols for the follow-up of women treated for gynecological malignancies: a pilot study. Int J Gynecol Cancer 2001;11(5):349-53.

19. Jeffery GM, Hickey BE, Hider P. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 2002(1): CD002200.
20. Rojas MP, Telaro E, Russo A, Fossati R, Confalonieri C, Liberati A. Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev 2000(4):CD001768.
21. Allsop JR, Preston J, Crocker S. Is there any value in the long-term follow up of women treated for endometrial cancer? Br J Obstet Gynaecol 1997;104(1):122.

Chapter 4

Chemo-therapeutic treatment of advanced and recurrent endometrial cancer

Chapter 4.1

Phase II study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the EORTC Gynecological Cancer Group

Phase II study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the EORTC Gynecological Cancer Group
F.H. van Wijk, C. Lhommé, G. Bolis, V. Scotto di Palumbo, S. Tumolo, M. Nooij, C.F. de Oliveira, J.B. Vermorken
European Journal of Cancer 2003: 39: 78-85.

Abstract

Background: The aim of this study was to investigate the efficacy and toxicity of carboplatin in monotherapy in endometrial adenocarcinoma. Cisplatin is one of the most active drugs in gynecological cancer types, but at the cost of high toxicity. In this high-risk population of endometrial cancer patients it is necessary to have chemotherapy regimens with low toxicity.

Methods: Patients eligible for this study were those with histological confirmed endometrial adenocarcinoma with evidence of recurrent and/or metastatic disease. Carboplatin was administered every four weeks as a first (dose: 400 mg/m^2) or second (dose: 300 mg/m^2) line chemotherapy.

Results: Of the 64 patients who entered the trial, 60 were eligible, 53 patients were evaluable for toxicity and 47 for efficacy. A total of 169 cycles of carboplatin was given with a median of 2 cycles per patient (range 1-11) to a median cumulative dose of 798 mg/m^2 (range 290-3,879). No grade 4 or toxic death occurred. WBC toxicity grade 3 was noted five times, mainly in the radiotherapy pre-treated patients. Grade 3 non-hematological toxicity consisted mainly of nausea and vomiting (21%). There were a total of eight responses (3 CR and 5 PR) with an overall 13% response rate (95% CI 6-25). No responses occurred in patients with prior chemotherapy. In evaluable patients, overall response rate in all (n=47) and in first line chemotherapy (n=33) were respectively 17% (95% CI 8-31) and 24% (95% CI 11-42). After a median follow-up of 379 days, median duration of response was 488 days (range 141-5,303) with two very long responses in patients with complete response.

Conclusions: Carboplatin has low toxicity and is active in chemotherapy naïve advanced endometrial carcinoma. These results lead to propose it in association in first line chemotherapy in recurrent or advanced endometrial carcinoma. The choice of the initial dose can be done according to prior or no prior radiotherapy treatment.

Introduction

Endometrial cancer is the most common genital tract malignancy in women. While most patients are cured with surgery and/or radiotherapy alone (1), systemic therapy (hormonal therapy or chemotherapy) is required in cases of initial advanced disease and at time of relapse. At the time of this trial, prior phase II trials have identified in endometrial adenocarcinoma several chemotherapeutic single agents with demonstrable objective response in at least 20% of patients, including cyclophosphamide, anthracycline, 5-fluorouracil (2) and hexamethylmelamine (3).

Cisplatin is one of the most active drugs in other gynecological cancer types (4, 5) and so platinum containing regimens have also been studied in endometrial cancer. With single agent cisplatin in first line chemotherapy Tropé (6) reported in 1980, Deppe (7) also in 1980, and Seski (8) in 1982, respectively a 36, 31 and 42% response rate. In association, Turbow (9) reported a 47% overall response rate to cisplatin, adriamycin and cyclophosphamide (PAC) in 19 patients at the cost of moderate to severe toxicity, Tropé (10) a 60% response rate to cisplatin and adriamycin in 19 patients and Bayer (11) achieved a 27 CR rate in 11 patients with the combination of cisplatin, cyclophosphamide and 5-fluorouracil.

In these studies median duration of response is short and most patients experience moderate to severe toxicity. In this high risk population of patients, often old and in poor general condition, it is necessary to have chemotherapy regimens with low toxicity. Cisplatin and carboplatin have the same activity in ovarian carcinoma. Carboplatin is less nephrotoxic, less neurotoxic and induces less gastrointestinal toxicity allowing a better quality of life. Therefore, it was decided in 1985 to test the efficacy and toxicity of carboplatin in endometrial adenocarcinoma as a first or second line chemotherapy treatment.

Patients and Methods

Trial design

This protocol was designed to determine the objective response rate, time to response, duration of response and tolerance of carboplatin in monotherapy in endometrial cancer.

Eligibility

Patients eligible for this study were those with histological confirmed endometrial Aden carcinoma with evidence of recurrent and/or metastasis disease. Carboplatin was administered as a first or second line treatment after anthracycline based chemotherapy. Patients had to have measurable lesions outside previously irradiated areas, age < 75 years, life expectancy > 2 months, WHO performance ≤ 2, white blood cell count (WBC) ≥ $4.0x10^9$/l, platelet count ≥ $120x10^9$/l, blood urea ≤ 8.0 mmol/l and/or serum creatinine ≤ 120 µmol/l and/or creatinine clearance ≥ 60ml/min/1.73 m^2 and bilirubin ≤ 50 µmol/l. All patients entering the study had to give their oral informed consent.

Excluded were those who had received prior radiotherapy, hormone therapy or chemotherapy within 4 weeks, had a concomitant or prior second cancer (except basal cell carcinoma of the skin), brain involvement or leptomeningeal disease, poor medical risk due to non-malignant disease or uncontrolled infection, bone lesions or serous effusions as single tumor response parameter and expected difficulty with follow-up.

Investigations at baseline included a medical history and physical gynecological examination, assessment of performance status, laboratory profile, urinalysis, electrocardiograph, measurement of indicator lesion(s), whether clinically or by X-ray, CT scan, ultrasound, endoscopy or bone scan (if indicated).

Treatment and Dose Adjustments

Treatment consisted of a 30-minute intravenous administration of carboplatin (Paraplatin) every four weeks, 400 mg/m^2 for patients who had not received prior chemotherapy and 300 mg/m^2 for patients who had received prior chemotherapy. Ancillary treatment was given as medically indicated. Radiotherapy was allowed concomitantly for control of bone pain, provided that all evaluable lesions were not included in the irradiated field.

The dose schedule was modified as follows: drug administration was delayed, up to two weeks, if the WBC < 3.0x10^9/l or the platelet count < 120x10^9/l. If six weeks after the last dose of carboplatin recovery had not occurred to this extent, dose adjustments were made. The dose was reduced to 75% if WBC 2.0-3.0x10^9/l or platelet count 100-120x10^9/l and to 50% if WBC 1.5-1.9x10^9/l or platelet count 75-99x10^9/l. Patients went off study if WBC < 1.5x10^9/l or the platelet count < 75x10^9/l. Dose adjustments were also made according to nadir values in the previous course as measured by weekly blood counts. Adjustments to 75% if WBC < 1.5x10^9/l or platelet count < 75x10^9/l and to 50% if WBC ≤ 1.0x10^9/l or platelet count ≤ 50x10^9/l. No dose-modifications were required for renal or gastrointestinal dysfunction. Treatment had to be continued in case of objective response or stable disease. Treatment had to be stopped on evidence of disease progression, unacceptable toxicity or patient refusal.

Response Evaluation

The state of measurable disease was assessed before treatment and every two cycles. To be evaluable for response, patients should have had at least two cycles of chemotherapy and the second and following treatment cycles should not have been postponed for more than two weeks. Objective evidence of response was documented on the basis of measurement of clinical palpable lesions (to be confirmed by CT scan or ultrasound) or measurements of lesions detectable by X-rays, CT scan or ultrasound. Changes in liver function and carcinoembryonic antigen levels had to be confirmed by other examinations. A complete response (CR) was defined as a complete disappearance of all clinically detectable tumors together with a return of relevant blood chemistries to normal values for at least four weeks.

A partial response (PR) consisted of a 50% or more decrease in total tumor size of the measured lesions, being confirmed by a further observation no less than four weeks later, without any new lesions. Bone lesions should partially decrease in size or recalcification of lytic lesions should occur for at least four weeks. No change (NC) was defined as a change of less than 50% reduction or less than 25% increase in the size of one or more measurable lesions after at least eight weeks from start of therapy. Progression of disease (PD) represented an increase greater than 25% in the size of one or more measurable lesions or the appearance of new lesions. Early progressive disease was defined as progression that occurred after one cycle of carboplatin. Early tumor death was defined as death occurring during the first eight weeks due to tumor progression and early toxic death was defined as death occurring in the first eight weeks due to toxicity. The duration of response and stable disease dated from commencement of treatment until documentation of progression. The duration of CR dated from the moment complete remission was first recorded until documentation of progression. Survival and time to progression will be dated from the commencement of treatment.

Toxicity Evaluation

Hematological and non-hematological toxicity due to the carboplatin regimen were evaluated and documented using WHO criteria. Patients were evaluable for toxicity if they had received at least one cycle of carboplatin.

Statistical Consideration

Gehan's sequential two step statistical test was used to define the number of patients required to detect activity of the treatment. The lowest limit of therapeutic activity considered to be of interest is a response rate of 20%. Patients who had received previous chemotherapy or radiotherapy and those who had not were registered and evaluated in two separate groups. The Kaplan-Meier method was used to analyze the median follow-up time, Time To Progression (TTP) and the Overall Survival (OS).

Results

Patient characteristics

Between October 1985 and August 1988, 64 patients with histological confirmed endometrial adenocarcinoma and evidence of advanced or recurrent disease were entered into this trial. Four patients were found to be ineligible, two patients because of presence of all lesions in prior irradiated area, one because of receiving cancer treatment within four weeks prior to registration and one because of absence of measurable lesions. In the 60 eligible patients, seven patients were inevaluable for all analyses, two because of inadequate dosage and five for inadequate follow-up. Seven patients were evaluable only for efficacy,

Table 4.1. Pre-treatment characteristics of the eligible patients.

	N
Number	60
Median age in years (range)	70 (52-84)
Performance status	
WHO 0	23
WHO 1	18
WHO 2	17
Unknown	2
FIGO classification	
I	29
II	7
III	11
IV	11
Unknown	2
Extent of disease at registration	
Primary tumor	4
Loco-regional recurrent	9
Metastatic disease	26
Primary not excised and metastatic	3
Loco-regional recurrent and metastatic	16
Unknown	2
Prior treatment	
Surgery	53
Radiotherapy	38
Chemotherapy	17
Hormonotherapy	15

due to protocol violations (6 patients), incomplete data (2 patients) and/or intercurrent disease (1 patient). One of these patients is evaluable for response but not for duration of response. Therefore, in total 53 patients were evaluable for toxicity and 47 for efficacy.

Characteristics of all eligible patients are shown in Table 4.1. Mean age of the eligible patients was 70 years (range 52-84). Treatment received prior to carboplatin administration included surgery for 53 patients, radiotherapy for 38 patients, hormonotherapy for 15 patients, of which two patients had a response, and anthracycline-based chemotherapy for 17 patients, of which one in adjuvant setting. Of the other 16 patients, 4 patients received monotherapy (mitoxantrone) and 12 polychemotherapy (mainly CAP protocol, 9 patients), 7 patients experienced a response, of which 5 with the CAP protocol.

Extent of Exposure

A total of 169 cycles of carboplatin was given to the 53 evaluable patients, with a median

Table 4.2. Hematological toxicity grade 3 and 4.

NUMBER OF PATIENTS[a]		WBC[b]		PLT[c]	
		GRADE 3	GRADE 4	GRADE 3	GRADE 4
Total		5	0	6	0
Prior treatment					
Prior radiotherapy	No	1		3	
	Yes	4		3	
Prior chemotherapy	No	4		3	
	Yes	1		3	

[a] 53 patients evaluable for toxicity. [b] White blood cells. [c] Platelets.

of 2 cycles per patient (range 1-11) to a median cumulative dose of 798 mg/m^2 (range 290-3,879). The median number of cycles was also 2 in both groups, with a maximum of 11 cycles for the non-chemotherapy pre-treated patients (n=38) and 6 for patients pre-treated with chemotherapy (n=15). The median total dose administered was 789 mg/m^2 in the non-chemotherapy pre-treated and 588 mg/m^2 in the chemotherapy pre-treated patients. The treatment was delayed in 16 patients (30%), mainly in the non-chemotherapy pre-treated patients (88%). Twelve patients (23%) required at least one dose reduction. The median relative dose intensity was 90% (range 43-104) in the non-chemotherapy pre-treated patients and 100% (range 73-102) in the chemotherapy pre-treated group.

Toxicity

The hematological toxicity was acceptable, as presented in Table 4.2. The median WBC count nadir for all cycles was 3.4x10^9/l (range 1.2-12.1), and the median platelet count nadir was 120x10^9/l (range 26-413). WBC toxicity grade 3 was noted five times only during the first two courses and mainly in the radiotherapy pre-treated patients (80%). Antibiotics were administered once during the last cycle to three radiotherapy pre-treated patients (5%).

Thrombocytopenia grade 3 was mentioned 11 times in six patients, as often in the radiotherapy pre-treated or chemotherapy pre-treated patients, but more frequent in the first group. A blood transfusion was required for nine patients, during more than one cycle for three patients. Five out of nine patients (56%) were pre-treated with radiotherapy, and two (22%) were pre-treated with chemotherapy. For most of the patients the first transfusion was administered during the first cycle (67%).

The analysis of the non-hematological toxicity among all patients evaluable for toxicity is presented In Table 4.3. In one patient (2%), aged 74 years, consciousness toxicity grade 3 was reported during the treatment and the use of neuroleptics. The only other grade 3 non-hematological toxicity consisted of nausea and vomiting (21%) mainly in the non-chemotherapy

Table 4.3. Non-hematological toxicity during treatment[a].

TOXIC EFFECT	WHO GRADING		
	1	2	3
Nausea/vomiting	14	20	11
Consciousness	1	0	1
Diarrhea	10	1	0
Alopecia[b]	3	1	0
Peripheral neuropathy	2	1	0
Drug fever	2	0	0
Pulmonary	1	0	0
Drug fever	2	0	0
Cutaneous	1	0	0
Local	1	0	0
Oral	1	0	0
Allergy	1	0	0
Other	3	2	0

[a] 53 evaluable patients. [b] 3 patients suffered from alopecia due to prior chemotherapy.

Table 4.4. Response rate (intent to treat basis) (60 eligible patients).

WHO[a] RESPONSE	TOTAL (N=60)[b]		CHEMOTHERAPY PRE-TREATED (N=17)		RADIOTHERAPY PRE-TREATED (N=38)		HORMONOTHERAPY PRE-TREATED (N=15)	
	N	(%)	N	(%)	N	(%)	N	(%)
CR[c]	3	(5)	0	(0)	0	(0)	0	(0)
PR[d]	5	(8)	0	(0)	1	(3)	1	(7)
SD[e]	7	(12)	3	(18)	7	(18)	4	(27)
PD[f] and early PD	28	(47)	10	(59)	20	(53)	5	(33)
Early death (malignant disease)	2	(3)	1	(6)	1	(3)	1	(7)
Early death (other cause)	1	(2)	0	(0)	1	(3)	0	(0)
Not assessable	14	(23)	3	(18)	8	(21)	4	(27)
Overall response rate (%)								
Eligible patients (n=60)							13 (95% CI 6-25)[g]	
Patients assessable for response (n=47)							17 (95% CI 8-31)	
Non chemotherapy pre-treated patients assessable for response (n=33)							24 (95% CI 11-42)	

[a] World Health Organization. [b] Pre-treatment unknown in two patients and hormonotherapy unknown in three patients. [c] Complete response. [d] Partial response. [e] Stable disease. [f] Progressive disease. [g] 95% Confidence Interval.

pre-treated patients (24 vs. 13%). Anti-emetic therapy was used in 34 patients (64%). Diarrhea grade 1 and 2 occurred in 11 patients (seven with prior radiotherapy), one patient with diarrhea before carboplatin. Two grade 1 or one grade 2 peripheral neuropathies were reported (all in patients without prior cisplatin chemotherapy). No renal, grade 4 hematological or non-hematological toxicity or toxic deaths occurred.

Response

All 60 eligible patients were analyzed for response (Table 4.4). Eight patients achieved an objective response to therapy, with three of these achieving a complete response. Thus, there was a 13% Overall Response Rate (ORR) (95% CI 6-25). Among the 17 patients pre-treated with chemotherapy there were no objective responses. One PR was observed in the radiotherapy pre-treated (no prior hormonotherapy) and one PR in the hormonotherapy pre-treated patients (no prior radiotherapy). Thus patients in the no prior chemotherapy group (n=41) responded significantly better than those with prior chemotherapy (p=0.05), like those with no prior radiotherapy (p=0.002). Response analysis showed an ORR of 17% (95% CI 8-31) in the evaluable patients (n=47) and of 24% (95% CI 11-42) in the evaluable patients not pre-treated with chemotherapy (n=33). The maximum time to response was 296 days, with a median of 66 days. The median duration of follow-up was 379 days. Median TTP was 84 days (95% CI 58-171) and median duration of responses 488 days (range 141 to 5,303). Duration of the three complete responses was 77, 4,347, and 5,007 days. Median OS of all patients was 261 days (95% CI 151-440) and 1,013 days for responders. Two patients with CR were still alive without evidence of disease 11+ and 14+ years respectively after the start of carboplatin treatment. Both patients did not receive prior radiotherapy, chemotherapy nor hormonotherapy and the tumor sites were the regional and metastatic nodes for the first patient and the primary tumor for the second.

Discussion

Our study indicates that carboplatin is safe and active in advanced endometrial cancer. Nevertheless, as shown in Table 4.5, our ORR of 17% in evaluable patients is lower compared to ORRs reported by Long (12), Green (13) and Burke (14) (respectively 28%, 30% and 33%). The main difference in patient population is the difference in prior treatments. No patients received prior chemotherapy in the other studies. In this study, 41 patients received carboplatin as first line chemotherapy and four patients had only received mitoxantrone, which is now known to be inefficient in endometrial cancer (one PR in 51 evaluable patients included in three studies (15-17)). So, 12 patients (20%) had received carboplatin in second line after anthracycline and mainly cisplatin (nine patients) based polychemotherapy, including four patients after failure of cisplatin. As none of our chemotherapy pre-treated patients showed any response, the administration of carboplatin in second line, even after failure of cisplatin,

Table 4.5. Single agent carboplatin in endometrial carcinoma.

REFERENCE	N[a]	PRIOR TREATMENT (%)[b]			STARTING DOSE IN mg/m² (IF RT PRE-TREATED)	CR (N)	PR (N)	ORR[g] (%)
		RT[c]	CT[d]	HT[e]				
Burke	33 (27)	67	0	21	360 (270)	3	6	33
Long	26 (25)	80	0	76	400 (300)	0	7	28
Green	32 (23)	78	0	43	400 (400)	2	5	30
Present study	64 (47)	66	30	23	400 (400)[f]	3	5	17[h]

[a] Number of patients entered (number of evaluable patients). [b] % of evaluable patients (for Burke % of entered patients). [c] Radiotherapy. [d] Chemotherapy. [e] Hormonotherapy. [f] 300 if chemotherapy pre-treated. [g] Overall response rate of the evaluable patients. [h] 24% in the 33 evaluable patients naïve of chemotherapy.

might be a reliable explanation for the difference in ORR. Prior radiotherapy in our eligible population (63%) is comparable to the three published studies (Table 4.5). Prior hormonotherapy percentages are comparable except a higher percentage in the Long study. Thus, in our study 21 patients (35%) were treated after first-line chemotherapy and/or hormonotherapy. Horton (18, 19) demonstrated that responding or failing to prior progestagen therapy had a significant influence on the outcome of subsequent chemotherapy trials, the results being worse in patients who failed to respond to progestagen. He showed that this proved to be true for both trials with single agent chemotherapy and combination chemotherapy. This appeared to be true in our population also, where no response to carboplatin was observed among the 11 patients who did not respond to prior hormonotherapy. The second main difference with the other studies is the adjustment of initial dosage of carboplatin according to prior treatment, none in one study (13) or a decrease of 25% in case of prior radiotherapy in the two others (12, 14). In our study, we chose to decrease the initial dose only in cases of prior chemotherapy. It is not possible to assess the impact on the efficacy taking the initial dose into account: in the three prior studies (similar percentages of patients with prior radiotherapy), ORR's are similar with or without dose adjustments and dose effect relationship for platinum has never been demonstrated in endometrial cancer. Only Long reported ORR according to prior radiotherapy. The ORR is lower in patients pre-treated with radiotherapy (20% vs. 60%), but this lower response rate is possibly due to tumoral biological resistance in the irradiated area.

As expected, toxicity was acceptable for patients treated with carboplatin. It consisted mainly of grade 3 hematological toxicity among the radiotherapy pre-treated patients. In this group of patients, more blood transfusions were required. The toxicity level was not higher

among the chemotherapy pre-treated patients. It is not possible to assess whether it was due to the absence of impact of the dose or due to the initial dose reduction. In recent studies, doses of carboplatin were determined according to Area Under the Curve (AUC). This seems better than according to Body Surface Area, as in older studies, because in this older population of patients often with renal insufficiency and with increased hematological toxicity.

In endometrial cancer the response rate seems to be heightened with the use of cisplatin (6-8) compared to carboplatin, but at the cost of considerable toxicity resulting in poorer quality of life. Green (13) showed a long duration of response to carboplatin up to 814+ days, as did our trial, with a maximum duration of 5,303 days. Pending the demonstration of agents capable of inducing more prolonged responses, the simplicity of outpatient treatment and limited toxicity make carboplatin a good current choice for frontline therapy (14).

Paclitaxel seems to be a good candidate for endometrial cancer treatment (ORR 36 and 37%) (20, 21). Data concerning its association with cisplatin and carboplatin are shown in Table 4.6. Combination with cisplatin appears active, but caused an unacceptable incidence of neurotoxicity (22). Main toxicity observed with the combination of carboplatin and paclitaxel was grade 3 or 4 hematological toxicity, which did not require hospitalization (23, 24). In combination with carboplatin and amifostine, six-month PFS and OS compare very favorably with historical benchmark of cisplatin and doxorubicin chemotherapy, with favorable toxicity profile (25). According to all these data, it needs now to be demonstrated that this combination has an advantage for the patient, concerning not only response rate but also improvement of survival and quality of life. One ongoing French randomized phase II study is comparing carboplatin plus paclitaxel with cisplatin plus doxorubicin.

Our publication shows the results of an old phase II trial with carboplatin in endometrial cancer. The number of included and evaluable patients is the highest of the previous published studies. Its importance is still high because only a few phase II trials with a low number of patients in each have been carried out. This is the only study including patients receiving carboplatin in second line. Responses were observed in chemotherapy naïve patients and this leads to propose it as first line treatment. Toxicity was mild, but more transfusions were required after radiotherapy. The choice of the initial dose can be done according to prior or no prior radiotherapy treatment.

So, carboplatin is a good candidate in polychemotherapy in first line and/or in front-line therapy in endometrial cancer.

Table 4.6. Platinum and paclitaxel in endometrial carcinoma.

REFERENCE	DRUG COMBINATION (DOSE IN mg/m²)	N[a]	TOXICITY	GRADING[b] (% PATIENTS[c]) 2	3	4	CR (N)	PR (N)	RR[c] (%)
Dimopoulos	Cisplatin (75)[d] Paclitaxel (175/3h)	24					7	9	67
			Granulocytopenia	13	13	9			
			Alopecia	9	91	0			
			Nausea/emesis	48	9	0			
			Neurotoxicity	13	9	0			
Price	Carboplatin (AUC 5) Paclitaxel (135-175/3h)	20					0	5	63
			Leukopenia	11	32	47			
			Thrombocytopenia	0	0	5			
			Alopecia	100	0	0			
			Nausea	0	0	0			
			Numbness/tingling	5	5	0			
Hoskins[e]	Carboplatin (AUC 5-7) Paclitaxel (175/3h)	22							55
			Neutrophil nadir	$0{,}9 \times 10^9$/l					
			Platelet nadir	143×10^9/l					
			Febrile neutropenia	3%					
Scudder	Carboplatin (AUC 5) Paclitaxel (175/3h) Amifostine (740)	57					6 month PFS 78% 6 month OS 86% (estimated)		
			Neutropenia Lymphopenia Pain Anemia		41	33			

[a] Number of patients entered. [b] WHO criteria used by Dimopoulos, and NCI criteria used by Price. [c] % of the evaluable patients. [d] Together with G-CSF support. [e] Toxicity among all patients with and without irradiation.

Acknowledgement

This study was supported by the Pharmaceutical Research and Development Division of Bristol Myers Company, Brussels, Belgium.

We thank the following physicians from the following Institutes who treated the patients in the present cohort:
M.S. Aapro, Hopital Cantonal Universitaire de Geneve, Geneve, Switzerland (current hospital: Clinique de Genolier, Centre Anticancéreux, Genolier, Switzerland); L.V.A. Beex, St Radboud University Hospital, Nijmegen, The Netherlands; J.P. Guastalla, Centre Leon Berard, Lyon, France; A. Herruzo, Hospital Virgen de las Nievas Granada, Spain; P. Kerbrat, Centre Eugene Marquis, Rennes, France; A.J. Lacave, Hospital General de Asturias, Oviedo, Spain; C. Mangioni, Ospedale San Gerardo, Monza, Italy; J.P. Neijt, University Medical Centre Utrecht, The Netherlands; T. Osario, Insituto Portugues de Oncologia do Porto, Portugal; S. Pecorelli, Universita di Brescia, Italy; M. Piccart, Institut Jules Bordet, Brussels, Belgium; W. ten Bokkel Huinink, Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, The Netherlands; M.E.L. van der Burg, Erasmus MC, Rotterdam, The Netherlands; P.H.B. Willemse, Academic Hospital Groningen, The Netherlands; J. Wils, St. Laurentius Hospital, Roermond, The Netherlands; P. Zola, Clinica Universita Torino, Italy (current hospital: Ospedale Mauriziano Umberto I, Torino, Italy).

References

1. Glassburn JR. Carcinoma of the endometrium. Cancer. 1981 Jul 15;48(2 Suppl):575-81.
2. Deppe G. Chemotherapeutic treatment of endometrial carcinoma. Clin Obstet Gynecol. 1982 Mar;25(1):93-9.
3. Seski JC, Edwards CL, Copeland LJ, Gershenson DM. Hexamethylmelamine chemotherapy for disseminated endometrial cancer. Obstet Gynecol. 1981 Sep;58(3):361-3.
4. Thigpen T, Shingleton H, Homesley H, Lagasse L, Blessing J. Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Cancer. 1981 Aug 15;48(4):899-903.
5. Thigpen T, Blessing JA. Current therapy of ovarian carcinoma: an overview. Semin Oncol. 1985 Sep;12(3 Suppl 4):47-52.
6. Trope C, Grundsell H, Johnsson JE, Cavallin-Stahl E. A phase II study of Cis-platinum for recurrent corpus cancer. Eur J Cancer. 1980 Aug;16(8):1025-6.
7. Deppe G, Cohen CJ, Bruckner HW. Treatment of advanced endometrial adenocarcinoma with cis-dichlorodiammine platinum (II) after intensive prior therapy. Gynecol Oncol. 1980 Aug;10(1):51-4.
8. Seski JC, Edwards CL, Herson J, Rutledge FN. Cisplatin chemotherapy for disseminated endometrial cancer. Obstet Gynecol. 1982 Feb;59(2):225-8.
9. Turbow MM, Ballon SC, Sikic BI, Koretz MM. Cisplatin, doxorubicin, and cyclophosphamide chemotherapy for advanced endometrial carcinoma. Cancer Treat Rep. 1985 May;69(5):465-7.
10. Trope C, Johnsson JE, Simonsen E, Christiansen H, Cavallin-Stahl E, Horvath G. Treatment of recurrent endometrial adenocarcinoma with a combination of doxorubicin and cisplatin. Am J Obstet Gynecol. 1984 Jun 15;149(4):379-81.
11. Bayer GK, Koch PD. High response rate with combination chemotherapy for advanced endometrial cancer. Proc Am Ass Cancer Research. 1982;1:121.
12. Long HJ, Pfeifle DM, Wieand HS, Krook JE, Edmonson JH, Buckner JC. Phase II evaluation of carboplatin in advanced endometrial carcinoma. J Natl Cancer Inst. 1988 Apr 20;80(4):276-8.
13. Green JB, 3rd, Green S, Alberts DS, O'Toole R, Surwit EA, Noltimier JW. Carboplatin therapy in advanced endometrial cancer. Obstet Gynecol. 1990 Apr;75(4):696-700.
14. Burke TW, Munkarah A, Kavanagh JJ, Morris M, Levenback C, Tornos C, et al. Treatment of advanced or recurrent endometrial carcinoma with single-agent carboplatin. Gynecol Oncol. 1993 Dec;51(3):397-400.
15. Hilgers RD, Von Hoff DD, Stephens RL, Boutselis JG, Rivkin SE. Mitoxantrone in adenocarcinoma of the endometrium: a Southwest Oncology Group Study. Cancer Treat Rep. 1985 Nov;69(11):1329-30.
16. Muss HB, Bundy BN, DiSaia PJ, Ehrlich CE. Mitoxantrone for carcinoma of the endometrium: a phase II trial of the Gynecologic Oncology Group. Cancer Treat Rep. 1987 Feb;71(2):217-8.
17. Veenhof KH, George M, Forni M, Tumolo S, Rotmensz N, Vermorken JB. Mitoxantrone in advanced and/or recurrent endometrial carcinoma. Eur J Cancer. 1990;26(5):650.
18. Horton J, Begg CB, Arseneault J, Bruckner H, Creech R, Hahn RG. Comparison of adriamycin with cyclophosphamide in patients with advanced endometrial cancer. Cancer Treat Rep. 1978 Jan;62(1):159-61.
19. Horton J, Elson P, Gordon P, Hahn R, Creech R. Combination chemotherapy for advanced

endometrial cancer. An evaluation of three regimens. Cancer. 1982 Jun 15;49(12):2441-5.

20. Ball HG, Blessing JA, Lentz SS, Mutch DG. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1996 Aug;62(2):278-81.
21. Lissoni A, Zanetta G, Losa G, Gabriele A, Parma G, Mangioni C. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. Ann Oncol. 1996 Oct;7(8):861-3.
22. Dimopoulos MA, Papadimitriou CA, Georgoulias V, Moulopoulos LA, Aravantinos G, Gika D, et al. Paclitaxel and cisplatin in advanced or recurrent carcinoma of the endometrium: long-term results of a phase II multicenter study. Gynecol Oncol. 2000 Jul;78(1):52-7.
23. Price FV, Edwards RP, Kelley JL, Kunschner AJ, Hart LA. A trial of outpatient paclitaxel and carboplatin for advanced, recurrent, and histologic high-risk endometrial carcinoma: preliminary report. Semin Oncol. 1997 Oct;24(5 Suppl 15):S15-78-S15-82.
24. Hoskins P, Swenerton K, Pike J. Carboplatin paclitaxel +- irradiation for advanced or recurrent endometrial cancer. Proc Am Soc Clin Oncol. 2001;20:206a.
25. Scudder SA, Liu PY, Smith HO. Paclitaxel (PCT) and carboplatin (C) with amifostine (A) in advanced or recurrent endometrial cancer: a Southwest Oncology Group Trial (9720). Proc Am Soc Clin Oncol. 2001;20:205a.

Chapter 4.2

Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomized study (55872) by the EORTC Gynecological Cancer Group

Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomized study (55872) by the EORTC Gynecological Cancer Group

F.H. van Wijk, M.S. Aapro, G. Bolis, B. Chevallier, M.E.L. van der Burg, A. Poveda, C.F. de Oliveira, S. Tumolo, V. Scotto di Palumbo, M. Piccart, M. Franchi, F. Zanaboni, A.J. Lacave, R. Fontanelli, G. Favalli, P. Zola, J.P. Guastalla, R. Rosso, C. Marth, M. Nooij, M. Presti, C. Scarabelli, T.A.W. Splinter, E. Ploch, L.V.A. Beex, W. ten Bokkel Huinink, M. Forni, M. Melpignano, P. Blake, P. Kerbrat, C. Mendiola, A. Cervantes, A. Goupil, P.G. Harper, C. Madronal, M. Namer, G. Scarfone, J.E.G.M. Stoot, I Teodorovic, C. Coens, I. Vergote, J.B. Vermorken. On behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Gynecological Cancer Group

Annals of Oncology 2003; 14: 441-448 & 811.

Abstract

Background: Combination chemotherapy yields better response rates which do not always lead to a survival advantage. The aim of this study was to investigate whether the reported differences in the efficacy and toxicity of monotherapy with doxorubicin (DOX) versus combination therapy with cisplatin (CDDP) in endometrial adenocarcinoma lead to significant advantage in favor of the combination.

Methods: Eligible patients had histological-proven advanced and/or recurrent endometrial adenocarcinoma and were chemo-naïve. Treatment consisted of either DOX 60 mg/m^2 alone or CDDP 50 mg/m^2 added to DOX 60 mg/m^2, every four weeks.

Results: A total of 177 patients were entered and median follow-up is 7.1 years. The combination DOX&CDDP was more toxic than DOX alone. Hematological toxicity consisted mainly of WBC toxicity grade 3 and 4 (55% vs. 30%). Non-hematological toxicity consisted mainly of grade 3 and 4 alopecia (72% vs. 65%) and nausea/vomiting (36% vs. 12%). The combination DOX&CDDP provided a significantly higher response rate than single agent DOX ($p < 0.001$). Thirty-nine patients (43%) responded on DOX&CDDP (13 CR and 26 PR), versus 15 patients (17%) on DOX alone (8 CR and 7 PR). The median overall survival (OS) was 9 months in the DOX&CDDP arm versus 7 months in the DOX alone arm Wilcoxon $p=0.0654$). Regression analysis showed that WHO performance status was statistically significant as a prognostic factor for survival and stratifying for this factor, treatment effect reaches significance (Hazard ratio = 1.46, 95% CI 1.05-2.03, $p=0.024$).

Conclusions: In comparison to single agent DOX, the combination of DOX&CDDP results in higher but acceptable toxicity. The response rate produced is significantly higher, and a modest survival benefit is achieved with this combination regime, especially in patients with a good performance status.

Introduction

Endometrial cancer remains one of the commonest gynecological malignancies. Whilst many patients with early stage disease are cured by either surgery or radiotherapy, or a combination of the two (1), 40% of patients are either not amenable to such treatment due to metastatic disease, or subsequently relapse following primary treatment. Such patients require systemic therapy in the form of either hormonal or cytotoxic therapy (2-6). Although the latter has been less extensively studied in endometrial cancer, it is has been shown that response rates with single agent chemotherapy are comparable to those observed following hormonal treatment, and response duration is generally longer. Thus there is a need to define the optimal chemotherapy regime. Whilst several phase II trials have identified chemotherapeutic single agents with demonstrable objective response in endometrial adenocarcinoma, of which doxorubicin and cisplatin seem to be the most active single agents (2-6), the reported series are small and include patients with widely-varying pre-treatment conditions, together with variable response criteria.

As the combination of doxorubicin and cisplatin has been shown to be of benefit in treating other gynecological malignancies (7), the current study, a multi-centre prospective randomized trial, was designed to compare combination therapy with doxorubicin and cisplatin versus doxorubicin alone in endometrial carcinoma.

Patients and Methods

Trial design

This protocol was designed as a randomized phase II/III study to determine the anti-tumor activity of combination doxorubicin and cisplatin (DOX&CDDP), versus single agent doxorubicin, in patients with advanced primary endometrial cancer (i.e. beyond the stage of local treatment), and in those with recurrent disease. The second objective was to determine the toxicity of both treatment arms in comparable patients.

Eligibility

Patients eligible for this study were those with histological-proven advanced and/or recurrent adenocarcinoma of the corpus uteri, all of whom were first considered for radiotherapy and all of those with well differentiated tumors for hormone therapy. Eligibility criteria were: measurable or evaluable lesions outside previously irradiated areas, with documented progression; age ≤ 75 years; life expectancy ≥ 3 months; WHO performance ≤ 2; and adequate bone marrow, renal and liver function. All patients gave informed consent.

Excluded patients were those with the following: prior chemotherapy, radiotherapy or hormone therapy within 4 weeks of trial entry; unresolved toxic manifestations of their prior treatment; a concomitant or prior second cancer, other than adequately-treated basal or squamous cell carcinoma of the skin; brain or leptomeningeal involvement; pleural effusion,

ascites, bone lesions detectable only by bone scan or sclerotic bone metastases as the single tumor response parameter; poor medical risk due to non-malignant disease, such as active bacterial or other infection, heart failure, or uncontrolled hypertension; and expected difficulty with follow-up.

Baseline investigations included a medical history and physical gynecological examination, assessment of performance status, laboratory profile, urinalysis, electrocardiograph, clinical and/or radiological measurement of indicator lesion(s), CT scan, ultrasound, and cystoscopy or proctoscopy.

Treatment and Dose Adjustments

Treatment consisted of doxorubicin (DOX) 60 mg/m^2 and cisplatin (CDDP) 50 mg/m^2 or DOX 60 mg/m^2 every four weeks. CDDP was only given after adequate diuresis had been obtained with prehydration. Ancillary treatment was given as medically indicated. Radiotherapy was allowed concomitantly for control of bone pain or other reasons, provided that all evaluable lesions were not included in the irradiated field.

The drug cycle was delayed by one week if toxicity persisted at the day of the next cycle. If the treatment had to be delayed for two consecutive weeks, the following dose adjustments were made: if the white blood cell count (WBC) was 2.0-2.9x10^9/l or the platelet count 50-99x10^9/l, the DOX dose was reduced to 50% and the CDDP dose remained 100%; patients went off study if the WBC was < 2.0x10^9/l and/or the platelet count was < 50x10^9/l after two weeks delay. DOX dose adjustments according to hematological and hepatic toxicity were made as follows: according to nadir values on day 15, adjustment to 50% was made if the WBC was 1.0-1.9x10^9/l and/or the platelet count was 50-74x10^9/l; to 25% if the WBC was ≤ 1.0x10^9/l and/or the platelet count was ≤ 50x10^9/l; to 50% if the bilirubin was > 25 µmol/l; and to 25% if the bilirubin was > 50 µmol/l. In the case of mucositis, the DOX dosage was reduced to 50%. Dose adjustments of CDDP were made according to renal and neurological toxicity: if the creatinine value rose above 125% of baseline values, or the creatinine clearance decreased similarly, half the dose was administered. CDDP was discontinued completely in patients developing World Health Organization (WHO) grade II paresthesia and/or muscle weakness. Clinical evidence of hearing loss was also a reason to discard CDDP. Anti-emetics were used according to local treatment protocol if gastrointestinal toxicity developed.

A total of at least two courses were given, unless this was not in the best interest of the patient. The combination treatment was stopped on evidence of disease progression after two courses, or of rapid progression (> 50% increase in volume or new lesions). If remission of the disease was achieved, treatment was continued until either severe disease progression or severe toxicity developed. DOX was discontinued after seven courses (cumulative dose of 420 mg/m^2) regardless of the response. Complete responders in the combination arm then continued the treatment with CDDP alone for up to four months from the moment of complete

response. Treatment at disease progression was not defined per protocol.

Toxicity and Response Evaluation

The overall assessment of response involved all parameters including uni-dimensional (evaluable) and bi-dimensional measurable lesions, and non-measurable manifestations. Lesions that could be measured by CT scan or ultrasound were considered suitable for assessment of response provided that they were measurable with one or two diameters, had a minimal diameter of 5 cm, and were proven to be malignant disease. Evaluation was performed after eight weeks of treatment, or after at least two courses of treatment. Toxicity was assessed according to WHO criteria. Patients were evaluable for toxicity if they had received at least one cycle of treatment, and evaluable for overall response after they had received at least two cycles of chemotherapy, with the second and following treatment cycles not having been postponed for more than two weeks. The duration of overall response was dated from commencement of treatment until documentation of progression, and the duration of complete response (CR) from the moment complete remission was first recorded until documentation of progression. Survival will be dated from commencement of treatment.

A CR was defined as disappearance of all known disease, determined by two observations not less than four weeks apart. A partial response (PR) was defined as at least 50% decrease in the sum of the product of the largest perpendicular diameters of all measurable lesions, plus the sum of the diameter of all evaluable lesions, as determined by two observations not less than four weeks apart, without any progressed or new lesions. There also had to be an objective improvement in non-evaluable but clinically evident malignant disease, and no increase of any manifestations of malignant disease. No change (NC) was defined as less than 50% reduction, or less than 25% increase, in the size of one or more measurable lesions, without evidence of either new lesions or an increase in any manifestation of malignant disease, until the first evaluation date. Progression of disease (PD) was defined as an increase of greater than 25% in the size of one or more measurable lesions, or the appearance of a new lesion, and also by the occurrence of positive cytology of pleural effusion or ascitic fluid. Early progressive disease was defined as progression that occurred after one cycle. Early tumor death was defined as death occurring during the first eight weeks due to tumor progression, whilst toxic death was defined as death to which drug toxicity was thought to have a major contribution.

Statistical Considerations

The trial was designed as a randomized phase II to be extended into a comparative phase III trial in the case of sufficient responses. The phase II part required a minimum of 20 patients in each arm, with five patients to be added per each response observed during the first step. With respect to the comparative phase III part of the trial, it was assumed that the

median duration of survival in the control (DOX) arm would be 8 months, and the addition of CDDP would be justified if it could increase the median duration of survival to one year. A total of 192 deaths were required to detect such a difference, with a two-sided type I error of 0.05 and a power of 80% (8). During randomization, patients were stratified according to institution, degree of differentiation (well vs. moderate/poor), type of disease (locally advanced vs. recurrent), and performance status, using the minimization technique (9). Survival curves were estimated using the Kaplan-Meier technique (10). Duration of survival, time to progression (TTP), and progression-free survival (PFS), were compared between both treatment arms using a two-sided logrank test (11). Cox's proportional hazards model was used, retrospectively stratified for differentiation, type of disease, and performance status (12). Response rates were compared using Chi-square tests; the percentages in the tables are exact, whilst those in the text are rounded for clarity.

Results

Patient characteristics

Between September 1988 and June 1994, 177 patients with advanced inoperable or recurrent endometrial cancer were randomized by 35 institutions, with 90 patients in the DOX&CDDP combination arm and 87 in the single agent DOX arm. The study was stopped early as recruitment decreased dramatically after the publication of the GOG results in 1993. Five patients had no follow-up data (3 DOX&CDDP and 2 DOX). Twelve patients were found to be ineligible either due to inadequate disease stage (2 DOX&CDDP and 2 DOX), absence of measurable lesions (1 DOX&CDDP and 3 DOX), the lesions all being in a prior irradiated area (1 DOX&CDDP and 1 DOX), bad physical condition (1 DOX&CDDP), or prior treatment (1 DOX).

Baseline characteristics of all patients are shown in Table 4.7; these were similar in both treatment arms. The median age was 63 years (range 40-76), and 79% of all patients had a WHO performance status of 0-1. The FIGO stage at the initial diagnosis was stage IV in 25% of the patients. The tumor was well differentiated in 19% of the patients, and 59% had recurrent disease. Treatment received prior to this protocol included surgery in 85% of the patients, radiotherapy in 50% (23% of patients had had a response), hormone therapy in 23%, and chemotherapy in 1%.

Extent of Exposure

A total of 790 cycles was given to all patients, with 480 to patients in the DOX&CDDP arm, with a median of 6 cycles (range 0-15), and 310 to patients in the DOX arm, with a median of 3 (range 0-7). DOX was given in 740 cycles: 430 in the combination arm and 310 in the single agent arm. DOX was delayed in 25 cycles (6%) in the combination arm, and in 13 cycles (4%) in the single agent arm. DOX reductions were mainly made in the combination

Table 4.7. Baseline characteristics.

	TREATMENT		
	DOX & CDDP	DOX	TOTAL
Number	90	87	177
Median age in years (range)	63 (40-76)	63 (41-76)	63 (40-76)
Performance status			
WHO 0	29	39	68
WHO 1	42	29	71
WHO 2	15	17	32
Unknown	4	2	6
FIGO classification			
I	37	24	61
II	15	17	32
III	13	17	30
IV	19	25	44
Unknown	6	4	10
Type of disease			
Advanced primary	36	36	72
Recurrent	54	51	105
Tumor differentiation			
Well	18	16	34
Moderately/poorly	72	71	143
Extent of disease at registration			
Primary tumor	1	3	4
Loco-regional recurrent	9	10	19
Metastatic disease	46	31	77
Primary not excised and metastatic	9	15	24
Loco-regional recurrent and metastatic	21	25	46
Unknown	4	3	7
Prior treatment			
Surgery	79	73	151
Radiotherapy	40	48	88
Chemotherapy	0	1	1
Hormonotherapy	25	15	40

arm (13% vs. 5%). CDDP was given in 480 cycles, with a delay reported in 33 cycles (7%) and a dose reduction in 12 cycles (3%). In a single instance, the DOX and CDDP doses were both escalated in the combination arm, with no escalation reported in the single agent DOX arm.

Toxicity

The toxicity evaluation was based on the 165 patients (83 DOX&CDDP and 82 DOX) who received at least one cycle. The combination DOX&CDDP was more toxic than DOX alone. The

Table 4.8. Hematological toxicity grade 3 & 4[a].

TOXICITY		TREATMENT	
		DC[b] N (%)	D[c] N (%)
WBC	Grade 3	37 (44.6)	14 (17.1)
	Grade 4	9 (10.8)	11 (13.4)
Platelets	Grade 3	9 (10.8)	4 (4.9)
	Grade 4	2 (2.4)	0 (0.0)

[a] 165 evaluable patients. [b] Doxorubicin and cisplatin. [c] Doxorubicin.

hematological toxicity is presented in Table 4.8. The median WBC nadir was 1.9x10^3/mm^3 (range 0.2-17.7) in the DOX&CDDP arm, and 2.6x10^3/mm^3 (range 0.1-10.2) in the DOX arm. The median platelet count nadir was 147x10^3/mm^3 (range 11-720) in the DOX&CDDP arm, and 232x10^3/mm^3 (range 26-538) in the DOX arm. WBC toxicity grade 3 and 4 was noted in 55% of the DOX&CDDP patients and in 30% of the DOX patients. Antibiotics were administered to nine patients: five in the combination arm and four in the single DOX arm. In 13% of the DOX&CDDP patients, thrombocytopenia grade 3 and 4 was reported. Grade 3 thrombocytopenia

Table 4.9. Non-hematological toxicity during treatment[a].

TOXIC EFFECT	WHO GRADING							
	1		2		3		4	
	DC[b] N	D[c] N	DC N	D N	DC N	D N	DC N	D N
Alopecia	1	5	14	15	59	50	1	3
Nausea/vomiting	9	28	34	29	29	10	1	0
Infection	7	4	6	1	0	1	2	0
Oral	18	16	7	7	5	0	0	0
Cardiac	5	1	1	0	1	1	0	0
Consciousness	4	0	0	1	0	1	0	0
Diarrhea	15	3	7	4	0	0	0	0
Peripheral neuropathy	18	2	3	1	0	0	0	0
Drug fever	3	3	4	0	0	0	0	0
Pulmonary	4	0	0	1	0	0	0	0
Cutaneous	2	2	1	0	0	0	0	0
Local	6	1	0	0	0	0	0	0
Allergy	1	2	0	0	0	0	0	0
Other	14	7	6	3	1	1	0	0

[a] 165 evaluable patients. [b] Doxorubicin and cisplatin. [c] Doxorubicin.

was reported in 5% of the DOX patients; no grade 4 thrombocytopenia occurred in this arm. Six patients required a blood transfusion, five of whom had received the combination treatment. The hematological toxicity occurred mainly among the radiotherapy pre-treated patients, being WBC grade 3 and 4 in 50% vs. 32%, and thrombocytopenia grade 3 and 4 in 11% vs. 6%. This toxicity was not found to be cumulative by increasing the number of cycles.

The analysis of the non-hematological toxicity is presented in Table 4.9. The frequency of grade 3 or 4 non-hematological toxicity in the combination arm compared to the single agent arm was alopecia (72% vs. 65%), nausea/vomiting (36% vs. 12%), oral (6% vs. 0%), infection (2% vs. 1%), cardiac (1% vs. 1%) and level of consciousness (0% vs. 1%). Anti-emetic therapy was used in 431 cycles (90%) of the combination treatment and in 226 (73%) of the DOX alone. No diarrhea of grade 3 or 4 was noted. Almost all grade 1 and 2 diarrhea occurred in the radiotherapy pre-treated patients, expect for two patients in the DOX arm. Only grade 1 and 2 neuropathies were reported, mainly in the combination arm (25% vs. 4%). The non-hematological toxicity was also found not to be cumulative.

Extensive toxicity was more often the reason for stopping treatment in the DOX&CDDP arm than in the single DOX arm (10% vs. 2%). One patient in the DOX&CDDP arm died of toxicity two weeks after the start of the first cycle, the cause of death being pneumonia, despite treatment with antibiotics. Myelosuppression due to toxicity could not be excluded as cause of death, despite the WBC count not being excessively low ($0.8x10^3/mm^3$). No fatal toxicities were reported in the DOX arm.

Efficacy evaluation

Efficacy analysis was performed on all randomized patients (n=177). Eight patients had no response assessed due to early death (4 on the DOX&CDDP arm and 4 on the DOX arm). Response to treatment is summarized in Table 4.10. The combination of DOX&CDDP provided a significantly higher response rate than the single agent DOX arm ($p < 0.001$). Thirty-nine patients (43%) responded to DOX&CDDP (95% CI 33-54), of which 13 had a complete response and 26 a partial response, versus 15 patients (17%) on DOX (95% CI 3-15), of which 8 had a complete and 7 a partial response (Table 4.10). With respect to the type of disease, 29% had advanced and 31% recurrent disease. As the distribution of the type of disease among the responders was also broadly equal in both arms, no correlation was seen between the type of disease and the response rate. Prior radiotherapy and hormonotherapy did not seem to influence the response rate in either arm, and there were no major differences in the response rate of the various tumor sites between the treatment arms.

After a median follow-up of 86 months, 82 patients (91%) treated with DOX&CDDP had died compared to 78 patients (90%) treated with DOX. Of the patients in the combination arm, 73 had died because of malignant disease, 1 of toxicity, 4 of cardiovascular disease, 1

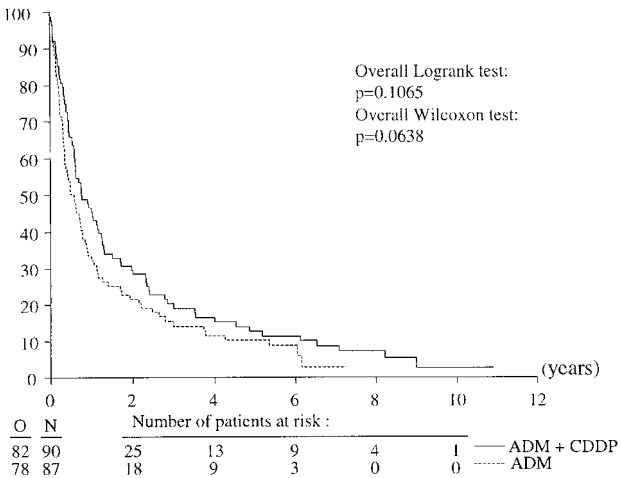
Table 4.10. Response rate (intent to treat basis) (177 patients).

WHO[a] RESPONSE	TOTAL (N=177)		DC[b]		D[c]	
	N	(%)	N	(%)	N	(%)
CR[d]	21	(11.9)	13	(14.4)	8	(9.2)
PR[e]	33	(18.6)	26	(28.9)	7	(8.0)
SD[f]	41	(23.2)	21	(23.3)	20	(23.0)
PD[g] and early PD	45	(25.4)	13	(14.4)	32	(36.8)
Early death (malignant disease)	5	(2.8)	2	(2.2)	3	(3.4)
Early death (toxicity)	1	(0.6)	1	(1.1)	0	(0.0)
Early death (other cause)	2	(1.1)	1	(1.1)	1	(1.1)
Insufficient data	27	(15.3)	12	(13.3)	15	(17.2)
Unknown	2	(1.1)	1	(1.1)	1	(1.1)

of another chronic disease, and 3 for unknown reasons. In the single treatment arm, 73 had died because of malignant disease, 3 of cardiovascular disease, and 2 for other reasons.

The Kaplan-Meier curves that illustrate overall survival (OS), TTP and duration of response are shown in Figures 4.1, 4.2 and 4.3. The median OS was 9 months (95% CI 7-14) in the DOX&CDDP versus 7 months (95% CI 4-9) in DOX arm. The Kaplan-Meier curve reveals no significant difference in survival between the two treatment arms (logrank p=0.107, Wilcoxon p=0.064). The overall median TTP for all treated patients was 8 months (95% CI 7-11) in the DOX&CDDP arm and 7 months (95% CI 6-10) in the DOX arm. The estimated median PFS was

Figure 4.1. Kaplan-Meier plot for overall survival according to the treatment arm.



8 months (95% CI 7-11) in the DOX&CDDP arm and 7 months (95% CI 6-10) in the DOX arm. The median duration of response was 9 months in the DOX&CDDP arm versus 24 months in the DOX arm (p=0.008). Forty-three of the 54 responders (34 of 39 in the DOX&CDDP arm and 9 of 15 in the DOX arm) had progressed at the cut-off date.

Figure 4.2. Kaplan-Meier plot for time to progression according to the treatment arm.

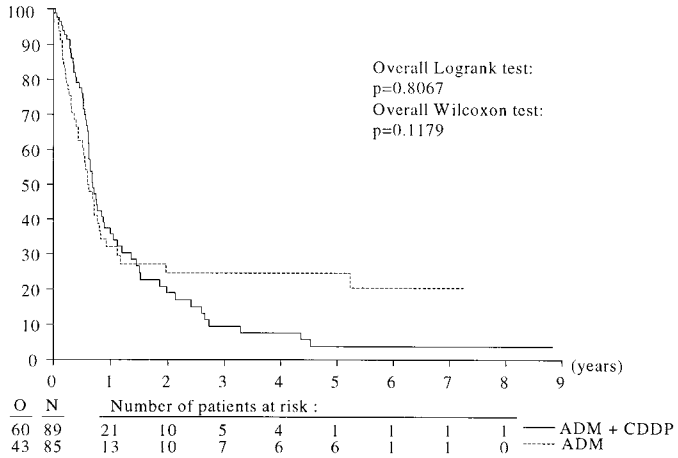
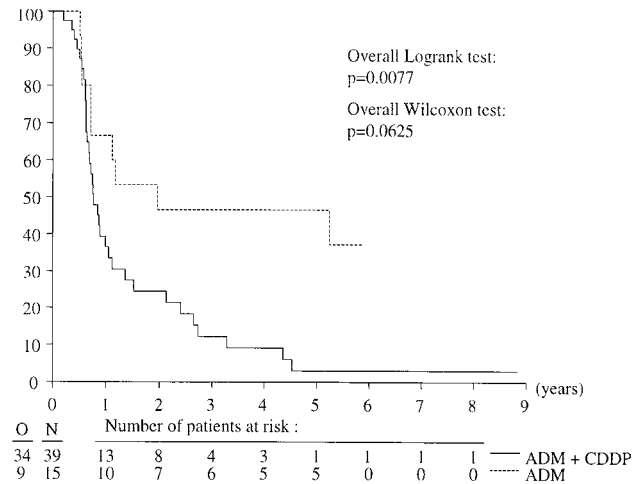


Figure 4.3. Kaplan-Meier plot for duration of response according to the treatment arm.



A Cox regression analysis was performed to identify prognostic factors for survival. After taking account of age, WHO performance status, FIGO stage, extent of disease and degree of differentiation, only WHO performance status appeared to be statistically significant. Stratifying only for this variable, the treatment effect increased, reaching significant difference in favor of the combination arm (p=0.024, Hazard ratio=1.46, 95% CI 1.05-2.03).

Discussion

Treatment of advanced or recurrent endometrial cancer with progestagens yields an overall response rate of 30%, with a higher response in patients with well differentiated tumors and in those with long time intervals before relapse (3). However, as hormone receptors predict well for response to hormonal treatment, it is imperative to find effective cytotoxic agents for the initial management of those patients who are receptor negative.

Since 1950, phase II trials have identified several chemotherapeutic agents with a demonstrable objective response in endometrial adenocarcinoma, including anthracycline, carboplatin, cisplatin, cyclophosphamide, 5-fluorouracil and hexamethylmelamine (5, 6, 13-15). Experience with single agent chemotherapy has identified doxorubicin and cisplatin to be the most consistently active agents investigated. Single agent doxorubicin was utilized in four trials with overall response rates of 19 to 37%, as summarized in two articles (5, 6). Since 1975, single agent cisplatin has been used in endometrial cancer, with reported response rates between 4 and 100% (5, 6, 14). The large range in response rate of the different trials can be explained by the difference in patient population. Most trials including chemotherapy pre-treated and chemotherapy-naïve patients showed a significant difference in response rate, being worse in patients who received prior cytotoxic therapy. Therefore, these results of previous studies suggest that cisplatin is only of use as a first-line agent in endometrial carcinoma, as in breast cancer (16).

The combination of doxorubicin and cisplatin in endometrial cancer has been evaluated in seven trials since 1984 (17-23). Most of these reports describe small trials without a control arm. In these trials, response rates of 33 to 82% were reported in the 93 evaluated patients. Seltzer (18) showed in his trial that this drug combination did not appear to be effective in the treatment of recurrent endometrial cancer, although in contrast, our trial has not shown any difference in response rate among primary advanced and recurrent disease. In a trial of the Gynecologic Oncology Group, Thigpen used single agent doxorubicin as a control arm (22), whilst Long compared the use of methotrexate, vinblastine, doxorubicin and cisplatin to doxorubicin and cisplatin (23), the latter showing a response rate of 26% with the combination of DOX&CDDP in only 15 patients. Thigpen showed a response rate of 45% with the combination treatment and a 27% response rate in the single agent arm among 223 evaluable patients, although there was no overall survival benefit of the combination treatment in his cohort (22).

An initial analysis performed on 113 evaluable patients from our trial showed a difference in the duration of survival between both treatment arms in favor of the combination arm (12.4 to 7.6 months) (24). However, the final analysis has shown a smaller difference, with some evidence of an early separation followed by a convergence in the survival curve. There is also evidence that the duration of response may be longer on the DOX arm for the few responding patients, as shown in Figure 4.3. This long duration of remission can be due to chance alone, to possible influence of prior hormonal therapy (some patients could have had a non-documented estrogen withdrawal) or demonstrate a subgroup of patients with highly doxorubicin-sensitive tumors. Although the median number of cycles in the DOX&CDDP arm was higher than in the DOX arm, explained by the fact that CDDP alone was continued in responding patients in the combination arm, no major differences were noted between the treatment arms in the response of the various tumor sites, and therefore the addition of CDDP does not seem to influence the response of specific sites.

Combination treatment was more toxic than DOX alone, with observed toxicity being mainly primarily hematological and gastro-intestinal. However, in general, this was acceptable, and similar to that observed in earlier trials.

Thus, overall, our randomized controlled trial shows that in comparison to single agent DOX, the combination of DOX&CDDP results in higher toxicity, but also a significantly higher response rate, and overall provides a moderate benefit in survival in patients with a good performance status.

Acknowledgements

We thank Dr. Anne Appleton of the Institut Multi-disciplinaire d'Oncologie (IMO), Clinique de Genolier, Switzerland, for assistance with editing of the manuscript.

References

1. Glassburn JR. Carcinoma of the endometrium. Cancer. 1981 Jul 15;48(2 Suppl):575-81.
2. Kelly RM, Baker WH. Progestational agents in the treatment of carcinoma of the endometrium. N Engl J Med. 1961;264:216.
3. Donovan JF. Nonhormonal chemotherapy of endometrial adenocarcinoma: a review. Cancer. 1974 Nov;34(5):1587-92.
4. Carbone PP, Carter SK. Endometrial cancer: approach to development of effective chemotherapy. Gynecol Oncol. 1974 Aug;2(2-3):348-53.
5. Deppe G. Chemotherapeutic treatment of endometrial carcinoma. Clin Obstet Gynecol. 1982 Mar;25(1):93-9.
6. Cohen CJ. Cytotoxic chemotherapy for patients with endometrial carcinoma. Clin Obstet Gynaecol. 1986 Dec;13(4):811-24.
7. Bruckner HW, Cohen CJ, Goldberg JD, Kabakow B, Wallach RC, Deppe G, et al. Improved chemotherapy for ovarian cancer with cis-diamminedichloroplatinum and adriamycin. Cancer. 1981 May 1;47(9):2288-94.
8. George SL, Desu MM. Planning the size and duration of a clinical trial studying the time to some critical event. J Chronic Dis. 1974 Feb;27(1):15-24.
9. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975 Mar;31(1):103-15.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-81.
11. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep. 1966 Mar;50(3):163-70.
12. Cox DR. Regression models and life-tables. J R Stat Soc B. 1972;34:187-202.
13. Thigpen JT, Blessing JA, Ball H, Hanjani P, Manetta A, Homesley H. Hexamethylmelamine as first-line chemotherapy in the treatment of advanced or recurrent carcinoma of the endometrium: a phase II trial of the Gynecologic Oncology Group. Gynecol Oncol. 1988 Nov;31(3):435-8.
14. Burke TW, Munkarah A, Kavanagh JJ, Morris M, Levenback C, Tornos C, et al. Treatment of advanced or recurrent endometrial carcinoma with single-agent carboplatin. Gynecol Oncol. 1993 Dec;51(3):397-400.
15. Thigpen JT, Blessing JA, Homesley H, Creasman WT, Sutton G. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 1989 Apr;33(1):68-70.
16. Martin M. Platinum compounds in the treatment of advanced breast cancer. Clin Breast Cancer. 2001 Oct;2(3):190-208; discussion 9.
17. Deppe G, Malviya VK, Malone JM, Christensen CW, Saunders D. Treatment of recurrent and metastatic endometrial carcinoma with cisplatin and doxorubicin. Eur J Gynaecol Oncol. 1994;15(4):263-6.
18. Seltzer V, Vogl SE, Kaplan BH. Adriamycin and cis-diamminedichloroplatinum in the treatment of metastatic endometrial adenocarcinoma. Gynecol Oncol. 1984 Nov;19(3):308-13.
19. Trope C, Johnsson JE, Simonsen E, Christiansen H, Cavallin-Stahl E, Horvath G. Treatment of recurrent endometrial adenocarcinoma with a combination of doxorubicin and cisplatin. Am J Obstet Gynecol. 1984 Jun 15;149(4):379-81.
20. Pasmantier MW, Coleman M, Silver RT, Mamaril AP, Quiguyan CC, Galindo A, Jr. Treatment of

advanced endometrial carcinoma with doxorubicin and cisplatin: effects on both untreated and previously treated patients. Cancer Treat Rep. 1985 May;69(5):539-42.

21. Barrett RJ, Blessing JA, Homesley HD, Twiggs L, Webster KD. Circadian-timed combination doxorubicin-cisplatin chemotherapy for advanced endometrial carcinoma. A phase II study of the Gynecologic Oncology Group. Am J Clin Oncol. 1993 Dec;16(6):494-6.
22. Thigpen JT, Blessing JA, Homesley H. Phase III trial of doxorubicin +/- cisplatin in advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group (GOG) study. Proc Am Soc Clin Oncol. 1993;12:261.
23. Long HJ, Nelimark RA, Cha SS. Comparison of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) vs doxorubicin and cisplatin (AC) in advanced endometrial carcinoma. Proc Am Soc Clin Oncol. 1995;14:282.
24. Aapro M, Bolis G, Chevallier B. Doxorubicin vs doxorubicin + cisplatin in endometrial carcinoma: A randomized study of the EORTC Gynecological Cancer Cooperative Group (GCCG) (Meeting abstract). Ann Oncol. 1994;5(Suppl 8):98.

Chapter 5

Management of advanced and recurrent endometrial cancer

Chapter 5.1

Management of surgical stage III and IV endometrioid endometrial carcinoma: an overview

Management of surgical stage III and IV endometrioid endometrial carcinoma: an overview
F.H. van Wijk, M.E.L. van der Burg, C.W. Burger, I. Vergote, H.C. van Doorn
Submitted.

Abstract

This paper covers an overview of the literature on the management of advanced endometrial cancer, concentrating on patients with histopathologic endometrioid type of tumors. The different treatment modalities are described and management recommendations are proposed.

The standard surgical procedure includes an extrafacial total hysterectomy with bilateral salpingo-oophorectomy, collection of peritoneal washings for cytology and exploration of the intra-abdominal contents. In cases of extensive disease in the abdomen, an optimal surgical cytoreduction is associated with improved survival. Further treatment with radiotherapy may be indicated based on the pathological staging information to improve loco-regional control. Primary radiotherapy is indicated in cases where surgery is contraindicated. Systemic treatment can either be hormone therapy or chemotherapy. Progesterons are the cornerstone of hormone therapy. Prognostic factors for response are the presence of high levels of progesterone and estrogen receptors and low grade histology. Paclitaxel is the most active single agent drug. The combination therapy with paclitaxel and carboplatin is adopted as first choice in patients with endometrial cancer, due to the efficacy and low toxicity, although not proven in a randomized trial.

The literature on the management of patients with advanced endometrial cancer is discussed in detail. Each stage of advanced disease is presented separately and management recommendations are proposed and alternative approaches are given.

Ongoing clinical trials are described and the focuses of ongoing research are mentioned.

Introduction

Endometrial cancer is the most common gynecological malignancy in Western Countries. In the United States; approximately 39.000 cases will be diagnosed in 2007 and 7400 deaths will occur. Women have a 2.6% lifetime risk of developing endometrial cancer and it accounts for 6% of all cancers in women (1). In the Netherlands, it is the fourth most common invasive tumor in women after breast, colorectal and lung cancer (www.ikcnet.nl). The overall incidence in developed countries has risen in recent years, partly related to increasing life expectancy but also to the exposure of the uterus to endogenous estrogens due to obesity. The death rate, around 20% overall, is lower than that of other gynecological cancers, principally due to early presentation by abnormal vaginal bleeding (2). However the belief that endometrial cancer is a disease which is not dangerous is erroneous; advanced endometrial cancer is as difficult to cure as advanced ovarian cancer.

The staging classification of endometrial cancer is presented in Table 5.1 and Figure 1.1. Most patients with endometrial cancer have stage I disease (71%), and only a small proportion

Table 5.1. Carcinoma of the Corpus Uteri: Surgical staging classification (International Federation of Gynecology and Obstetrics, FIGO nomenclature 1988, Annual Report, Vol. 26) and TNM classification (UICC, International Union Against Cancer, 2002, 6th edition).

FIGO STAGES	T	UICC N	M	
0	Tis	No	Mo	In situ
I				Tumor confined to the corpus
IA	T1a	No	Mo	Tumor limited to the endometrium
IB	T1b	No	Mo	Tumor invades up to less than one-half of the myometrium
IC	T1c	No	Mo	Tumor invades to more than one-half of the myometrium
II				Tumor invades cervix, but does not extend beyond uterus
IIA	T2a	No	Mo	Endocervical glandular involvement only
IIB	T2b	No	Mo	Cervical stromal invasion
III				Local and/or regional spread
IIIA	T3a	No	Mo	Tumor invades uterine serosal and/or adnexa and/or positive peritoneal cytology
IIIB	T3b	No	Mo	Vaginal involvement
IIIC	T1	N1	Mo	Metastasis to pelvic and/or para-aortic lymph nodes
	T2	N1	Mo	
	T3a	N1	Mo	
	T3b	N1	Mo	
IVA	T4	Any N	Mo	Tumor invades bladder mucosa and/or bowel mucosa
IVB	Any T	Any N	M1	Distant metastasis

of patients present with advanced stage disease (3). Advanced stage disease is defined as FIGO stage III and IV, which includes patients with local and/or regional spread to the serosa, adnexa, positive peritoneal cytology, spread to the vagina, lymph nodes, bladder or bowel and patients with distant metastases. The histopathologic type of endometrial cancers consists in 84% of all patients of endometrioid carcinoma, in 4% of papillary serous carcinoma and in 2% of clear cell carcinomas. Papillary serous and clear cell carcinomas commonly present at a more advanced stage; these tumors represent 14% of cases in stage III and IV, compared to 4% in stage I and II. Both tumors are highly aggressive and confer a poorer prognosis than endometrioid tumors (3, 4). Therefore, these histopathological types should be considered as another prognostic factor and consequently treatment of patients with papillary serous or clear cell tumors requires another approach than patients with endometrioid tumors.

Treatment of endometrial cancer has remained relatively unchanged over the last 40 years relying principally on surgery to achieve cure. During the past decade interest in endometrial cancer has increased considerably and research on treatment comprised among other things the optimal use of adjuvant radiotherapy and the role of systemic treatment in early and advanced stages. The management of endometrial cancer is reviewed in several papers (2, 5-12). The main focus of these papers concerns management of endometrial cancer in patients with early stage disease, in line with the most common clinical presentation. As of today, management of patients with advanced endometrial cancer is frequently individualized, as limited evidence is available how to manage these tumors.

This overview focuses on patients with advanced endometrial cancer with endometrioid type of tumors. The first part describes the different treatment modalities used to manage these patients. In the second part management recommendation for the different stages of advanced disease are proposed, based on the evidence using a Level of Evidence rating system (Appendix A).

Treatment modalities

Surgery

The FIGO system changed in 1988 from a clinical to a surgical staging procedure. In all cases with no firm contra-indication for surgery primary treatment should start with surgery, except in patients with vaginal involvement (i.e. stage IIIB disease) or distant metastases (i.e. stage IVB disease). Pre-operatively are chest X-ray (or more recently a CT-scan), full biochemistry, CA 125 and blood count routinely performed. A preoperative CT-scan of the abdomen is recommended, at least in patients with a raised serum CA-125 or abnormal liver function tests and also when particular clinical findings are present, such as parametrial or vaginal tumor extension or ascites. Evaluation of bladder or rectum is indicated if direct extension to these organs is suspected. The FIGO Committee on Gynecologic Oncology

described a general recommended protocol in their staging booklet (13). In summary: surgery should start with a vertical midline abdominal incision and collection of ascites or peritoneal washings for cytological evaluation, followed by exploration of the intra-abdominal contents (examination of the omentum, liver, cul-de-sac and adnexal surfaces for possible metastases, and palpation for suspicious or enlarged nodes in the aortic and pelvic nodal areas). The standard surgical procedure includes an extrafascial total hysterectomy with bilateral salpingo-oophorectomy. If the cervical stroma is involved, a radical hysterectomy is often the procedure of choice. Indications for retroperitoneal lymph node evaluation with resection of any enlarged or suspicious lymph nodes are tumor infiltration in more than half the myometrium or radiological suggestion of positive nodes. If these nodes are positive on frozen section, further node dissection might be omitted if this can not be carried out without minimal risk for the patient. Indication for aortic node sampling include high grade tumors showing full thickness myometrial invasion, grossly metastatic aortic or pelvic nodes and/or grossly pathologic adnexa (13). Although the FIGO recommendations are highly accepted other strategies are recommended by others, such as performing a pelvic and/or para-aortic lymphadenectomy in all grade 1 and 2 tumors larger than 2 cm, even when they are not deeply invasive (12, 14). As of today, the role of routine pelvic and para-aortic lymphadenectomy or lymph node sampling is still being debated (2, 15, 16), but not discussed in this paper since the treatment of endometrial cancer is described after identification of advanced disease.

For patients with macroscopic tumor outside the uterus, it is debated if optimal surgical cytoreduction is warranted. Several retrospective studies have evaluated the effect of surgical cytoreduction in advanced endometrial cancer (17-23). These studies are presented in Table

Appendix A. Levels of evidence; recommended by the National Health and Medical Research Council (NHMRC). http://www.nhmrc.gov.au/consult/_files/levels_grades05.pdf

Level I	Evidence obtained from a systematic review of all relevant randomized controlled trials
Level II	Evidence obtained from at least one properly designed randomized controlled trial
Level III-1	Evidence obtained from well-designed pseudo-randomized controlled trials
Level III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort-series), case-control studies, or interrupted time series with a control group
Level III-3	Evidence obtained from comparative studies with a histological control, two or more single-arm studies, or interrupted time series without a parallel control group
Level IV	Evidence obtained from case series, either post-test or pre-test and post-test

5.2. A drawback of these studies is the relative small number of included patients, different stages of advanced disease and the use of different definitions of surgical cytoreduction. Consequently, it is difficult to compare these studies. However, the available data suggest in general that optimal surgical cytoreduction in patients with advanced endometrial cancer is associated with improved survival. However, no randomized trial has been carried out to confirm the beneficial effect on survival; let alone the beneficial effect of interval debulking.

Radiotherapy

After the surgical staging procedure, additional treatment with radiotherapy might be indicated based on the pathological staging information to prevent local and/or lymph node metastases. Radiotherapy can be administered locally to the vagina (brachytherapy), to the pelvis (external irradiation with or without brachytherapy) or to the whole abdomen (external irradiaton(WART) or with the use of intraperitoneal P-32). Brachytherapy is targeted on the proximal vagina and is either given with ovoids or with a vaginal cylinder. The target volume of the external pelvic irradiation consists of the proximal vagina, the previous site of the uterus, the parametrial tissues and the iliac lymph node regions up to L4. In patients with

Table 5.2. The effect of surgical cytoreduction in endometrial cancer.

AUTHORS (REFERENCE)	YEAR	N	FIGO STAGE	DEFINITION OF SURGICAL CYTOREDUCTION	OUTCOME
Aalders et al (17)	1984	108	III[a]	Surgical resection of all macroscopic tumor	5-year survival[b]: 41% vs 11%
Greven et al (18)	1989	52	III[a]	Surgical resection not further specified	5-year survival[b]: 48% vs 36%
Goff et al (19)	1994	47	IV	Leaving no bulky disease; tumor residuum not stated	Median survival[b]: 18 vs 8 months*
Chi et al (20)	1997	55	IV	Optimal cytoreduction defined as largest tumor nodule ≤ 2 cm residual disease	Median survival[c]: 31 months vs 12 months*
Bristow et al (21)	2000	65	IVB	Optimal cytoreduction defined as largest residual tumor ≤ 1 cm	Median survival[c]: 34 months vs 11 months*
Ayhan et al (22)	2002	37	IVB	Optimal cytoreduction defined as largest residual tumor ≤ 1 cm	Median survival[c]: 25 months vs 10 months*
Van Wijk et al (23)	2006	67	III or IV	Optimal cytoreduction defined as macroscopic removal of all tumor	5-year survival[c]: 66% vs 41%

[a] Clinical stage. [b] Cytoreduction versus no cytoreduction. [c] Optimal cytoreduction versus not optimal cytoreduction. * Statistical significant.

para-aortic and common iliac lymph nodes metastases the field is extended up to Th12-L1. The standard dose is 46-50 Gray in 23-25 fractions and the technique used is a four-field box technique or use of three-dimensional treatment planning by CT-scanning.

Some patients in whom surgery is contraindicated due to severe co-morbidity, as cardiopulmonary disease and morbid obesity, are clinically staged and curative radiotherapy is used based on patient and tumor characteristics (24). The practice of preoperative radiotherapy has been abandoned (with the exception for stage IIIB disease) because it interferes with the surgical staging procedure and there is no proven benefit over postoperative radiotherapy (12, 13).

Systemic treatment

In 1983, Bokhman was the first to describe two different types of endometrial carcinoma (25) (Table 5.3). Type I tumors are estrogen related, often preceded by a hyperplastic condition sometimes in combination with atypia, and are typically low grade endometrioid tumors with positive hormone receptor status. They usually develop in an estrogen rich environment (obesity, pre- and perimenopausal state). Patients with this type of tumor show a long treatment-free interval between initial diagnosis and subsequent development of metastatic disease, are sensitive to progestagens and in general have a good prognosis. On the other hand, type II tumors are unrelated to estrogen, mostly develop in atrophic endometrium, are most often higher grade tumors or consist of poor prognostic cell types, such as papillary serous or clear cell tumors. They affect older women and usually have a poor clinical outcome

Table 5.3. Predominant features of pathogenetic type I and II endometrial carcinoma. Adapted from Bokhman (25) and Kurman (26).

TUMOR CHARACTERISTICS	TYPE I	TYPE II
Duration of symptoms	Usually long	Usually short
Histopathological type	Endometrioid carcinoma	Non-endometrioid carcinoma (papillary serous, clear cell tumors)
Degree of tumor differentiation	Highly or moderately differentiated (more frequent G1 or G2)	Poorly differentiated (more frequent G3)
Depth of invasion in the myometrium	Frequent prevalence of superficial invasion	Frequent prevalence of deep invasion
Potentiality for lymphogenic metastatic spread	Low	High
Sensitivity to progestagens	High	Low
Prognosis	Favorable	Doubtful

(26). Patients with this type of tumor are rarely sensitive to progestagens, but may respond to chemotherapy.

Clinical studies investigating the use of systemic treatment are not easy to conclude on due to the limited number of patients, differences in patient characteristics as advanced or recurrent disease, previous radiotherapy or systemic treatment, and in- or exclusion of different histological subtypes. Recently, several systematic reviews on systemic treatment with hormone therapy and chemotherapy have been published (27-31), but due to the heterogeneity of the literature, results of clinical trials could not be pooled.

Hormone therapy

Primary hormone therapy for patients with advanced endometrial cancer can be considered in patients who are not eligible for curative surgical treatment and/or radiotherapy due to severe co-morbidity or extended disease. Important positive predictive factors for response and selection criteria for hormone therapy are presence of high levels of progesterone and estrogen receptors and low grade histology (25).

Progestagens have been the cornerstone of the hormone therapy of endometrial cancer and are most extensively tested as last resort therapy. Several progestagens (e.g. medroxyprogesterone acetate, megestrol acetate, hydroxyprogesterone caproate) are used in the treatment of endometrial cancer, but not one agent have showed a significant higher response rate or better survival (32, 33). Nowadays, the ideal dose considered is 200 mg of medroxyprogesterone acetate, as this dose is equally effective but less toxic than the 1000 mg dose (34). In patients with grade 1 or 2 tumors, the response rate for progestagens as primary treatment is 11-56% and the progression-free survival is 2.5-14 months. The highest response rates are seen in progesterone receptor positive patients (27). Relative contra-indications to progestagens are prior or current thrombo-embolic disease, severe heart disease or inability of the patient to tolerate progestagens. Compared to cytotoxic chemotherapy, progestagens have a relative lack of side effects (grade 3 and 4 toxicity in less than 5% of the patients), although fluid retention, weight gain and dyspnea can be a problem in some patients (27) and may lead to discontinuation of treatment. Other hormone therapies as anti-estrogens, GnRH analogues and aromatase inhibitors are mainly tested as second line therapy or in patients with recurrent disease; these agents will be discussed in Chapter 5.2.

Progestagens as adjuvant treatment after curative treatment with surgery with or without radiotherapy do not have a beneficial effect. In a meta-analysis of six randomized trials, involving 4,351 patients with primarily stage I disease, no difference was observed in reduction of relapse or death from endometrial cancer. The overall survival was not improved with adjuvant hormonal treatment and non-endometrial cancer related deaths were more common in the adjuvant arm (35). In these studies, however, not only patients with low grade and hormone receptor positive tumors but also patients with high grade tumors and unknown hormone receptor levels were included, which might have influenced the results.

Table 5.4. Single agent chemotherapy in endometrial cancer.

AUTHORS (REFERENCE)	YEAR	N[a]	ORR[b] (%)	MEDIAN PFS[c] (MONTHS)	MEDIAN OS[d] (MONTHS)
Doxorubicin					
Horton et al[f] (36)	1978	21	19	NS[e]	NS
Thigpen et al (37)	1979	43	37	NS	6.8
Thigpen et al[f] (38)	1994	132	22	3.2	6.9
Van Wijk et al[f] (39)	2003	87	17	7	7
Thigpen et al[f] (40)	2004	150	25	5.7	9.0
Hexamethylmelamine					
Seski et al (41)	1981	20	30	NS	NS
Thigpen et al (42)	1988	34	9	NS	NS
Cisplatin					
Seski et al (43)	1982	26	42	5	NS
Thigpen et al (44)	1984	25	4	NS	NS
Edmonson et al[f] (45)	1987	14	21	1.8	4.1
Thigpen et al (46)	1989	49	20	2.9	8.2
Carboplatin					
Long et al (47)	1988	25	28	3.8	7.1
Green et al (48)	1990	23	30	NS	9.3
Burke et al (49)	1993	27	33	4-5	8-10
Van Wijk et al (50)	2003	47	17	2.8	8.6
Ifosfamide					
Barton et al (51)	1990	16	13	NS	5
Sutton et al (52)	1994	40	15	NS	NS
Sutton et al (53)	1996	33	24	NS	NS
Pawinski et al[f] (54)	1999	16	25	1.8	NS
Paclitaxel					
Ball et al (55)	1996	28	36	3.8	9.5
Lissoni et al (56)	1996	19	37	NS	NS
Ramondetta et al (57)	2001	13	77	NS	NS

[a] Number of patients with evaluable disease (i.e. not based on 'intention to treat' principle).
[b] Overall response rate. [c] Progression free survival. [d] Overall survival. [e] Not stated, [f] Randomized trial.

Table 5.5. Phase II studies with the CAP regimen in endometrial cancer.

AUTHORS (REFERENCE)	YEAR	DRUGS**	N[a]	ORR[b] (%)	MEDIAN PFS[c] (MONTHS)	MEDIAN OS[d] (MONTHS)
Lovecchio et al (58)	1984	CTX/DOX/CDDP/MEG	15	60	NS[e]	12
Turbow et al (59)	1985	CTX/DOX/CDDP	19	47	NS	10
Hancock et al (60)	1986	CTX/DOX/CDDP	18	56	NS	16
Edmonson et al[f] (45)	1987	CTX/DOX/CDDP	16	31	NS	6.6
Hoffman et al (61)	1989	CTX/DOX/CDDP/MEG	15	33	4	9
Burke et al (62)	1991	CTX/DOX/CDDP	87	45	6	10.5/50[g]

[a] Number of patients with evaluable disease (i.e. not based on 'intention to treat' principle). [b] Overall response rate. [c] Progression free survival. [d] Overall survival. [e] Not stated. [f] Randomized trial. [g] Patients with advanced / recurrent disease.

** Abbreviations of drugs:
CDDP=cisplatin
CTX=cyclophosphamide
DOX=doxorubicin
MEG=megestrol

Chemotherapy

In endometrial cancer, chemotherapy may be administered as adjuvant therapy, primary systemic therapy and more recently as neo-adjuvant therapy, induction therapy or as radio-sensitizer.

Doxorubicin, hexamethylmelamine, cisplatin, carboplatin, ifosfamide and paclitaxel are effective single agents in endometrial cancer, with response rates varying from 4-42% for non-paclitaxel agents (Table 5.4) (36-57). Reported response rates of paclitaxel on contrary vary from 36-77%, which makes this drug the most active single agent (55-57). The most effective agents have been combined to increase the efficacy. Since 1984, the combination cyclophosphamide, doxorubicin and cisplatin (CAP regimen) has been evaluated in advanced and recurrent endometrial cancer patients in several trials and showed response rates from 31-60% (Table 5.5) (45, 58-62). Enthusiasm for the CAP regimen is tempered by the limited duration of the response of 2.9-8 months, limited median survival of 7-16 months and substantial treatment toxicity mainly including nephro- and neurotoxicity, myelosuppression, gastro-intestinal toxicity and alopecia. In Table 5.6 randomized trials with more than 100 patients treated with combination chemotherapy are presented in chronological order (38-40,

Table 5.6. Randomized trials of chemotherapy in endometrial cancer (> 100 patients).

AUTHORS (REFERENCE)	YEAR	DRUG(S)**	NUMBER PATIENTS	ORR[a] (%)	MEDIAN PFS[b] (MONTHS)	MEDIAN OS[c] (MONTHS)
Horton et al (63)	1982	DOX/CTX/MEG	64	23°	NS[d]	6.3
		DOX/CTX/5FU/MEG	67	13°	NS	6.3
Cohen et al (64)	1984	5FU/MEL/MEG	146	20	6.1	10.6
		DOX/CTX/5FU/MEG	149	19	5.2	10.1
Thigpen et al (38)	1994	DOX	169	17	3.2	6.9
		DOX/CTX	90	30	3.9	7.3
Gallion et al (65)	2003	DOX/CDDP (standard timed)	175	44	6.5	11.2
		DOX/CDDP (circadian timed)	177	48	5.9	13.2
Van Wijk et al (39)	2003	DOX	87	17	7	7
		DOX/CDDP	90	43*	8	9
Thigpen et al (40)	2004	DOX	150	25°	3.8	9.2
		DOX/CDDP	131	42°*	5.7*	9.0
Fleming et al (66)	2004	DOX/CDDP	160	40°	7.2	12.6
		DOX/TAX/FIL	168	43°	6.0	13.6
Fleming et al (67)	2004	DOX/CDDP	136	34°	5.3	12.3
		DOX/CDDP/TAX/FIL	137	57°*	8.3*	15.3*

[a] Objective response rate based on 'intention to treat' principle. ° If not calculated based on 'intention to treat'. * Statistical significant. [b] Progression free survival. [c] Overall survival. [d] Not stated.

** Abbreviations of drugs:
CDDP=cisplatin
CTX=cyclophosphamide
DOX=doxorubicin
FIL=filgrastim
5FU=fluorouracil
MEG=megestrol
MEL=melphalan
TAX=paclitaxel

63-67). The combination of doxorubin with cisplatin showed a remarkably consistent response rate, progression free survival and overall survival in the different trials (respectively 34-48%; 5.3-8 months; 9.0-13.2 months). After adding paclitaxel, this combination of paclitaxel, doxorubicin and cisplatin (TAC) is the most effective chemotherapy regimen for these patients with a significant longer progression free survival and overall survival over the combination of doxorubicin and cisplatin (67). However, toxicity is significantly higher with this three-drug combination; in addition five treatment-related deaths are reported among 137 patients and neurotoxicity occurred in 39% of the patients. Regarding the toxicity of the three drug combination therapy and the favorable results of the combination therapy of paclitaxel and carboplatin in ovarian cancer trials (68, 69), phase II studies in endometrial

Table 5.7. Platinum in combination with paclitaxel in endometrial cancer.

AUTHORS (REFERENCE)	YEAR	DRUGS**	N[a]	ORR[b] (%)	MEDIAN PFS[c] (MONTHS)	MEDIAN OS[d] (MONTHS)
Dimopoulos et al (70)	2000	CDDP/TAX	24	67	8.4[e]	17.6
Lissoni et al (71)	1997	CDDP/TAX/EPI	30	73	NS[f]	NS
Price et al (72)	1997	CAR/TAX	8	63	NS	NS
Nakamura et al (73)	2000	CAR/TAX	11	73	NS	NS
Hoskins et al (119)	2001	CAR/TAX ± radiotherapy	21[g]	78	NS	NS
Scudder et al (74)	2005	CAR/TAX/AMI	47	40	7	14
Arimoto et al (120)	2006	CAR/TAX ± radiotherapy	37	61	NS	NS
Lupe et al (118)	2006	CAR/TAX + radiotherapy	33	NS	2-y PFS: 55%	2-y OS: 55%

[a] Number of patients with evaluable disease (i.e. not based on 'intention to treat' principle). [b] Overall response rate. [c] Progression free survival. [d] Overall survival. [e] Time to progression. [f] Not stated. [g] Patients with advanced endometioid tumors.

** Abbreviations of drugs:
AMI=amifostine
CAR=carboplatin
CDDP=cisplatin
EPI=epirubicin
TAX=paclitaxel

cancer have also concentrated on the use of the combination of paclitaxel and carboplatin (Table 5.7) (70-74). The high response rates (40-73%), low toxicity and advantage of outpatient therapy, have led to the evaluation of the combination paclitaxel carboplatin in phase III trials. Two trials randomizing doxorubicin, cisplatin and paclitaxel versus paclitaxel carboplatin are planned and one trial is already activated (Table 5.8). Although these results have to be awaited, the combination therapy paclitaxel carboplatin is more and more adopted in clinical practice as first choice for patients with endometrial cancer due to the high response rate, significantly less toxicity, better tolerance and out-patient treatment compared to three drug TAC regimen.

Radiotherapy versus systemic treatment

Four randomized trials compared radiotherapy with systemic therapy with or without radiotherapy in endometrial cancer patients with different stages of disease (75-77). These

Table 5.8. Ongoing randomized trials in advanced endometrial cancer.

TRIAL GROUP	NUMBER	TREATMENT ARMS*	ELIGIBLE PATIENTS
EORTC[a]	55984	CDDP/DOX CDDP/DOX/TAX	Advanced or recurrent disease
GOG	0209	CDDP/DOX/TAX CAR/TAX	Advanced or recurrent disease, no prior chemotherapy
JGOG[b]	2041	CDDP/DOC CAR/DOC CAR/TAX	Intermediate and advanced disease
JGOG[b]	2043	CDDP/DOX CDDP/DOC CAR/TAX	Intermediate and advanced disease
Adjuvant treatment			
GOG[a]	184	CDDP/DOX CDDP/DOX/TAX	Stage III disease, following radiotherapy
PORTEC-3	III	Chemoradiation (CDDP) followed by CAR/TAX Pelvic radiotherapy	High-risk stage IB-III

[a] Recently closed. [b] Planned.

* Abbreviations of drugs:
CAR=carboplatin
CDDP=cisplatin
DOC=docetaxel
DOX=doxorubicin
TAX=paclitaxel

trials are presented in Table 5.9. One trial compared the CAP regimen to whole pelvic radiotherapy and showed no differences between the two treatment arms, although the subgroup of women with stage IIIA based on positive peritoneal cytology had significantly better outcome with chemotherapy (5-year overall survival 80.3% versus 97.5%; p=0.019) (76). Another trial comparing the CAP regimen versus external radiotherapy in high-risk (low stage) endometrial carcinoma failed to show any difference in survival of patients treated with chemotherapy or radiotherapy (77). Radiotherapy might delay local relapses (12% versus 16% in respectively radiotherapy and chemotherapy group) and chemotherapy might delay metastases (27% versus 20% in respectively radiotherapy and chemotherapy group), however both differences were without statistical significance. A randomized GOG trial, comparing chemotherapy (cisplatin with doxorubicin) with whole abdominal irradiation in patients with advanced endometrial cancer, reported superiority of chemotherapy in terms of improving progression-free and overall survival (p=0.007 and p=0.004) (78). In this GOG trial, all patients had advanced stage disease and 25% of the patients had more aggressive pathologic types as serous and clear-cell tumor. The first two trials included patients with less advanced disease but with intermediate and high risk disease and mainly endometrioid type of tumor.

Table 5.9. Radiotherapy versus systemic treatment (with or without radiotherapy) in endometrial cancer .

AUTHORS (REFERENCE)	YEAR	TREATMENT ARMS**	PATIENT SELECTION	N	5-YEAR PFS[a]	5-YEAR OS[b]
Hogberg et al (75)	2007	External radiotherapy (± brachytherapy)	2% advanced stage	196	72%	74%
		External radiotherapy (± brachytherapy) + adjuvant chemotherapy		186	79%*	82%
Sagae et al (76)	2005	Whole pelvic radiotherapy	25% advanced stage	193	84%	86%
		CDDP/DOX/CTX		192	82%	87%
Maggi et al (77)	2006	External radiotherapy	64% advanced stage	166	63%	69%
		CDDP/DOX/CTX		174	63%	66%
Randall et al (78)	2006	Whole abdominal radiotherapy	100% advanced stage	202	38%	42%
		CDDP/DOX		194	50%*	55%*

[a] Progression free survival. [b] Overall survival. * Statistical significant.

** Abbreviations of drugs:
CDDP=cisplatin
CTX=cyclophosphamide
DOX=doxorubicin

The chemotherapy schedule in the GOG trial consisted of a higher doxorubicin dose (60mg/m^2 versus 45 or 40mg/m^2) and 3-weekly courses versus 4-weekly courses in the other two trials. The patient selection and the more aggressive chemotherapy schedule might be responsible for the superiority of systemic treatment in the GOG trial.

Recently, the results of the EORTC/NSGO 55991 trial comparing postoperative external radiotherapy to the combination of postoperative radiotherapy and adjuvant chemotherapy were presented. In this trial combination therapy of postoperative external radiotherapy and adjuvant chemotherapy showed to be superior in terms of progression free survival (79% versus 72%, p-value=0.03) over radiotherapy alone (75). It should however be noted that this trial included patients with early stage high risk disease.

Although evidence is scarce and most studies focus on early stage high risk patients it is expected that high stage patients will benefit from chemotherapy, considering their increased risk for metastatic disease, and poor outcome with localized treatment only.

Management of different stages of advanced disease

Stage IIIA based on positive peritoneal cytology only

Adjuvant treatment for stage IIIA based on positive peritoneal cytology only, further referred to as stage IIIA-P is, as of today, controversial, due to the fact that the prognostic value of positive peritoneal cytology is not clear. There are two different opinions of positive peritoneal cytology: it has no prognostic value by itself and positive peritoneal cytology itself is a significant prognostic factor.

If positive peritoneal cytology has no prognostic value by itself, the prognosis will be determined by other prognostic factors as age, myometrial invasion, tumor grade and lymph vascular space involvement (79-82). Therefore, in the presence of any of these prognostic factors patients are considered at risk for local recurrence, and are treated with adjuvant pelvic radiotherapy (www.nccn.org) or further staged with pelvic lymphadenectomy (12). In the Netherlands patients with stage III-P are treated with pelvic radiotherapy if two of the following risk factors are present: age 60 years and older, deep myometrial invasion or high tumor grade (83) (www.oncoline.nl). In contrast, subsequent staging, with extensive lymphadenectomy is practiced in other institutions all over the world. The recently closed trial of the National Cancer Institute of Canada Clinical Trials Group (NCT00002807) may clarify if patients with stage IIIA-P will benefit from postoperative irradiation for local control.

Others consider positive peritoneal cytology itself as a significant prognostic factor and as an indication for systemic disease (84-86), since distant recurrences are observed in 33% up to 66% of these stage IIIA-P patients (23, 86). Adjuvant chemotherapy might reduce the distant metastases rate by eliminating micro-metastases. The previously mentioned randomized trial which evaluated adjuvant CAP chemotherapy against whole pelvic radiotherapy, showed that in a subgroup of 74 women with stage II or IIIA-P a significantly better outcome was found in the group treated with adjuvant chemotherapy (5-year overall survival 80.3% versus 97.5%; p=0.019) (Table 5.9) (76).

In stage IIIA-P patients with hormone receptor positive tumors, systemic hormonal therapy might be considered as long disease free periods are reported with progestagen therapy (87, 88).

Based on the concept of high risk of systemic disease in stage IIIA-P disease, and focused on the risk of intra-abdominal disease, radioactive intraperitoneal phosphate (32P) (89, 90) and whole abdominal radiotherapy (91, 92) have been used in the past. Both treatment modalities were involved with high unacceptable bowel complication rates. In a randomized setting, whole abdominal radiotherapy showed efficacy, but worse survival compared to chemotherapy (78).

In patients with stage IIIA-P and the presence of risk factors for both local and systemic disease, treatment with pelvic radiotherapy and adjuvant systemic chemotherapy might be

necessary as shown in the EORTC/NSGO trial in patients with early stage high risk disease (75). Combined treatment with chemoradiation and adjuvant chemotherapy versus pelvic chemotherapy is currently under study in the PORTEC-3 trial in patients with high risk stage IB-III disease (Table 5.8).

In conclusion, based on the presence of unfavorable prognostic factors for local recurrence patients with stage IIIA-P are treated with adjuvant pelvic radiotherapy or further staged with pelvic lymphadenectomy (Level of Evidence IV). The value of adjuvant chemotherapy in addition to pelvic radiotherapy in patients with a high risk of distant metastases is not known in advanced stage disease, patients with stage IIIA-P should preferably be treated in international studies encompassing study arms with chemotherapy.

Stage IIIA based on involvement of the adnex or serosa

Pelvic radiotherapy with or without vaginal cuff brachytherapy improves local control for patients with adnex or serosa involvement (93, 94), and this management is standard in the Netherlands (www.oncoline.nl). However, radiotherapy does not improve overall survival (83, 95, 96) and is hence not accepted in other countries (14, 97-99).

The high rate of distant recurrences in stage IIIA based on involvement of the serosa, or adnex, further referred to as stage IIIA-SA, ranging from 76-90% (18, 23, 79), reflects the high risk of sub-clinical systemic disease. Therefore, administration of systemic therapy with or without local radiotherapy might be considered in this patient population (www.nccn.org). In a phase II study 46 patients with mainly stage IIIA disease were treated with postoperative concurrent chemoradiation with cisplatin followed by systemic paclitaxel cisplatin therapy (100) (Table 5.7). In this study deep myometrial invasion was present in 64% and the tumor was poorly differentiated in 39% of the patients. At four years one pelvic, one regional and nine distant recurrences were reported. The 4-year survival rate for all stage III patients was 77%. Because of the small number of patients and the risk of selection bias in this study, the conclusions from this study have to be taken with precaution. Although the local-regional control was good, distant metastases did still occur. As presented in Table 5.9, chemotherapy showed to be superior over radiotherapy in pure advanced stage patients and the combination of postoperative external radiotherapy and adjuvant chemotherapy showed to be superior in early stage high risk patients (75-77, 101).

In conclusion, pelvic radiotherapy with or without vaginal cuff brachytherapy improves local control but does not improve survival. Chemotherapy with or without radiotherapy seems appropriate postoperative treatment for patients with stage IIIA-SA disease. To answer the question whether chemoradiation and adjuvant systemic treatment improve clinical outcome, and particularly reduce distant recurrences, itnecessitates studies like PORTEC-3 (Level of evidence IV).

Stage IIIB

Stage IIIB disease (i.e. vaginal involvement) is rare and the prognosis seems to be poor. The standard treatment according to the FIGO guidelines is primary pelvic irradiation followed by exploratory laparotomy, if disease seems to be resectable (13) (Level of Evidence IV).

In clinical practice, stage IIIB is often detected coincidentally at surgery. In these cases, postoperative radiotherapy (consisting of external pelvic irradiation and brachytherapy) is indicated (www.oncoline.nl) (94) with or without chemotherapy (www.nccn.org) (Level of Evidence IV). The optimal treatment regimen for this patient population is difficult to describe, as the largest series reported in literature included only 14 patients. In this study with individualized primary treatment regimens the recurrence rate was 78% (102).

In conclusion, primary pelvic irradiation followed by exploratory laparotomy is recommended for patients with stage IIIB disease (Level of Evidence IV). However, since most patients are diagnosed at or after surgery, postoperative pelvic radiotherapy and brachytherapy is indicated with or without chemotherapy (Level of Evidence IV).

Stage IIIC

Stage IIIC disease is defined as metastasis to pelvic and/or para-aortic lymph nodes. Survival rates vary between 60% and 77% (103-105). Although the definition is clear, one should keep in mind that stage IIIC endometrial cancer is a very heterogeneous group of patients. This stage encompasses patients with (microscopic) lymph node metastases found after a staging procedure, which in itself varies between random lymph node sampling and complete dissection of pelvic and para-aortic lymph nodes. Moreover, stage IIIC consists of patients in whom suspicious or enlarged lymph nodes are diagnosed prior, or during surgery, with an optimal or incomplete dissection. Subsequently, after surgery different situations can be encountered; i.e. patients in whom all lymph nodes are removed and patients with positive lymph nodes detected at lymph node sampling or resection of enlarged lymph nodes, in whom still microscopic tumor is present in the remaining lymph nodes. As a result of the heterogeneity of this patient population, literature on the treatment after the different post-surgical situations is scarce and is often influenced by selection bias.

After complete lymph node dissection, post-operative radiotherapy showed a reduction in pelvic side wall recurrences from 57% to 10%, compared with patients who had incomplete node dissection, no radiotherapy or both (106) and a median overall survival of more than 60 months (107). Larson et al. treated similar patients by complete pelvic and para-aortic lymphadenectomy and postoperative chemotherapy without radiotherapy. None of the 18 patients had a recurrence (108).

Patients with positive lymph nodes, who did not undergo complete lymph node dissection treated with adjuvant radiotherapy (with or without brachytherapy or extended field radiotherapy) had a 5-year survival of 56% (109). Recurrent disease occurred in 53% of the

patients; in 40% at distant sites and in 13% loco-regional; adjuvant brachytherapy reduced the vaginal recurrence rate from 20% to zero.

In general, as described before, radiotherapy will be administered to the pelvis up to L3 L4 (with or without brachytherapy). Because of the high risk of significant small bowel complications extended field radiotherapy to the para-aortic region should be reserved for patients with histological evidence of para-aortic and/or and common iliac lymph node metastases. Prophylactic para-aortic irradiation is not recommended. Long-term disease free survival has been reported in women with positive para-aortic nodes who received extended field radiotherapy (79, 110, 111). Quite a few series point to the fact that survival is better if pathologic para-aortic lymph nodes are removed prior to para-aortic radiotherapy (110-113).

According to the FIGO guidelines primary surgery remains the cornerstone of therapy for patients with (pre-operative) suspected node involvement, if deemed resectable (114). This is in accordance with the survival benefit as shown in retrospective series (Table 5.2) (17, 18, 23). Although additional adjuvant treatment, is recommended after resection (www.nccn.org), several studies showed that isolated pelvic recurrences were rare in patients who underwent complete lymphadenectomy not treated with external radiotherapy or with brachytherapy only (97, 103, 108, 115, 116). In patients with pre-operative enlarged lymph nodes induction chemotherapy (for irresectable nodes) or neo-adjuvant chemotherapy might be applied to reduce the tumor load of affected nodes, to increase the efficacy of the subsequent surgery and/or radiotherapy.

The optimal treatment to prevent recurrent disease in stage IIIC patients is still controversial. Although radiotherapy decreases the incidence of local recurrences, it has no role in preventing distant metastases. A comparison of post-operative chemotherapy (cisplatin with doxorubicin) with whole abdominal irradiation in patients with predominantly stage IIIC disease showed the superiority of chemotherapy in terms of increased progression-free and overall survival ($p=0.007$ and $p=0.004$, respectively) (78). These results are not consistent with the findings of Maggi et al., probably because in this trial one third of the patients had low stage (stage I and II) disease (75, 77). Whether low stage disease and high stage disease patients benefit analogous from chemotherapy seems questionable. However, the EORTC/NSGO trial which only included patients with high risk early stage disease, reported a superior effect of the combination of postoperative radiotherapy and adjuvant chemotherapy over radiotherapy alone (75) (Table 5.9).

In patients with positive pelvic lymph nodes, concurrent positive peritoneal cytology and/or involvement of the adnexa increases the risk of distant recurrent disease, and deteriorates the prognosis (104, 111, 117). Particularly in these patients adjuvant systemic treatment seems indicated to improve tumor control and prolong survival. A small feasibility study ($n=33$) with adjuvant chemotherapy paclitaxel carboplatin and sequential pelvic radiotherapy showed that this combined treatment was well tolerated. The pelvic relapse rate

was only 3% and the 2-year overall survival rate was 55% (118). In two other studies, with primarily advanced endometrial cancer patients, the combination paclitaxel carboplatin, followed by radiotherapy showed response rates of 67% and 75%, and 3-year overall survival rates of 62% and 77% (119, 120). Interpretation of these results is difficult due to the small number of patients (41 and 34) and selection bias. A randomized phase III study showed that, even in patients with early stage high risk disease, combination therapy of post-operative external radiotherapy and adjuvant chemotherapy (AC, TP, TAC, TEP) showed to be superior to radiotherapy only in terms of progression free survival and (cancer-specific) overall survival (EORTC/NSGO 55991) (75). Future research to optimize the therapy for stage IIIC patients should focus on optimizing local control, by induction/neo-adjuvant chemotherapy and (chemo)radiotherapy schedules, and reducing distant metastases.

In conclusion, currently postoperative external pelvic radiotherapy is the standard treatment for patients with stage IIIC disease. Only in patients with histological evidence of common iliac or para-aortic node metastases extended field radiotherapy to the para-aortic region is indicated. Superior survival of postoperative chemotherapy over whole abdominal irradiation is shown in IIIC advanced stage disease (Level of evidence II). Sequential radiotherapy and chemotherapy (or chemotherapy and radiotherapy) is feasible and might be indicated for the patients with a high risk of distant metastases, but this is not proven yet in this patient population. Neo-adjuvant or induction chemotherapy should be considered in patients with primary inoperable nodal disease (Level of evidence IV).

Stage IVA

Stage IVA disease, defined as involvement of the bladder or rectum, is diagnosed during surgery or pre-operatively. In case bladder or rectum involvement is found during surgery, there are three treatment options: the procedure could be abandoned, the surgical procedure is continued and all macroscopic tumor is resected or a radical surgery with an exenteration is performed. Retrospective data reported a beneficial effect of cytoreductive surgery on survival (Table 5.2) (19, 20, 23). Whether this cytoreductive surgery should encompass pelvic exenteration can be deliberated upon; as this procedure is only described in a few small series and some case reports. (121-128). It is presumed that stopping surgical treatment could decrease the chance of cure compared with primary exenteration (129). This is explained by the (theoretical) risk for intra-abdominal tumor dissemination at surgery and the risk that by omitting exenteration the surgical margins will not be tumor free. Moreover, the effective local treatment (radiotherapy or a combination of chemotherapy and radiotherapy) is delayed since the patient has to recover from the extensive surgery. On the other hand, patients are unprepared about the consequences of pelvic exenteration, the morbidity rate is high (45-77%) and the complications are severe including urinary/intestinal tract fistulas and obstructions, abscesses, hemorrhages, septicemias, renal failures, pulmonary embolisms and

cerebrovascular accidents (121, 122, 124). The use of exenterative surgery for palliation is controversial due to the associated morbidity, complications, risk of death, and long hospitalization. Therefore, in general this procedure should be avoided in these cases (123, 130).

Post-operative radiotherapy is common practice, but for macroscopic residual disease, chemotherapy followed by radiotherapy is an option. The only randomized trial that included also patients with stage IVA disease, reported superiority of chemotherapy over whole abdominal radiotherapy in terms of increased progression-free and overall survival (p=0.007 and p=0.004) (Table 5.9) (78). It should be noted that in this trial not only patients with endometrioid type of tumor are included, but also patients with more poor prognostic histopathologic tumor types were included.

In case of Stage IVA disease diagnosed pre-operatively, several approaches may be considered, but none has been proven superior. Neo-adjuvant or induction chemotherapy may be considered, aiming to improve the chance of an optimal cytoreductive surgery, a less mutilating surgery and more effective radiotherapy. If response occurs, subsequent cytoreductive surgery and/or radiotherapy will be a consequence. One small series including 16 patients with stage IVA disease, evaluated induction chemotherapy with paclitaxel carboplatin followed by radiotherapy, and reported an encouraging 3-year overall survival of 62% (119).

The other approach is a primary pelvic exenteration. Although there is limited evidence of a beneficial effect of this procedure in this patient population, the procedure can be discussed and weighted against alternative strategies in pre-operatively well-informed patients in a good performance status.

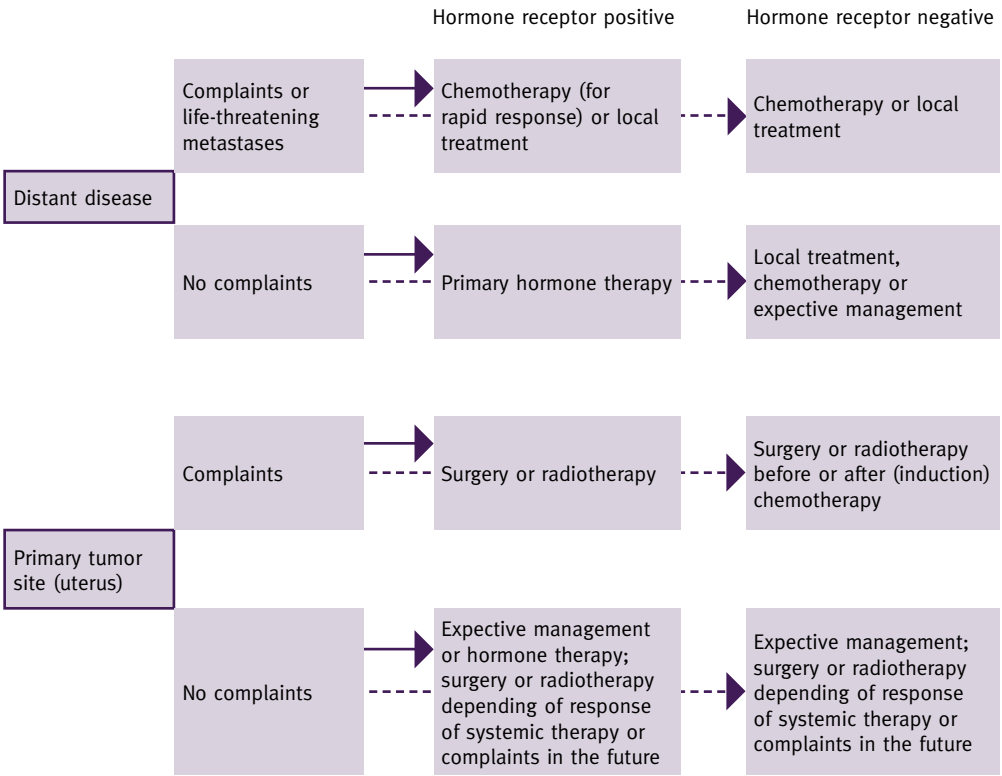
The precise value of post-operative chemotherapy or radiotherapy and the place of neo-adjuvant or induction chemotherapy in this patient population need clarification in further trials.

In conclusion, if bladder or rectum involvement is found during surgery, the procedure might be abandoned, or surgery could be continued for optimal cytoreduction. Whether this should encompass pelvic exenteration is debatable. Post-operative radiotherapy is common practice, but for macroscopic residual disease chemotherapy followed by radiotherapy might be indicated (Level of evidence IV). If involvement of the bladder or rectum is identified pre-operatively, neo-adjuvant or induction chemotherapy followed by cytoreductive surgery and/or radiotherapy might be considered. In a well-informed patient primary pelvic exenteration can be an alternative after extensive screening for distant metastases (Level of evidence IV).

Stage IVB

Diagnosis of stage IVB disease is based on either intra-abdominal or distant metastases.

Figure 5.1. Treatment algorithm for patients with stage IVB endometrial cancer based on distant metastases.



In case of pre-operatively suspicion of intra-abdominal disease a CT scan or MR scan is indicated. Intra-abdominal spread of disease warrants optimal cytoreduction if possible (Table 5.2) (21, 22) (www.nccn.org).

In patients with distant disease, treatment focuses primarily on the distant metastatic disease, as this influences the prognosis of the patient. However, in case of complaints the patients may also need treatment for local disease (i.e. uterus). A treatment algorithm for these patients is depicted in Figure 5.1. As shown in this algorithm, treatment depends on presence of complaints, site of distant disease and whether the tumor is hormone receptor positive or negative. In general, if systemic therapy is warranted: hormone therapy is indicated in patients with hormone receptor positive tumors minimal symptoms and non-life threatening

disease. Chemotherapy is indicated in patients with hormone receptor negative tumors and patients with serious complaints or life-threatening disease.

Besides systemic treatment, local treatment of distant metastases with surgery or radiotherapy can be considered. A review of the published literature regarding surgical management of metastatic disease in patients with gynecological cancer concluded that favorable prognostic factors for a prolonged survival were good performance status, absence of other systemic disease, and the resectability, preferably with tumor negative margins (131). However, as literature on metastasectomy is very limited, treatment should be individualized. The potential for long-term survival and the probability of improvement with systemic therapy should be weighted.

If local treatment of the primary tumor (i.e. uterus) is considered in patients treated with systemic therapy for distant metastasis, response to systemic therapy should be awaited. The first evaluation of response to hormone therapy is performed after three months and to chemotherapy after the first three (or two) cycles. If response is unsatisfactory, local therapy with surgery or radiotherapy can be considered for palliation.

The primary objective of treatment of stage IVB patients is to cure and/or prolong progression free and overall survival. However, some patients present with incurable tumors due to tumor characteristics, or adequate treatment cannot be administered due to bad performance status or serious cardiac and/or pulmonary co-morbidity. For these patients treatment should have palliative intention rather than curative. The team is challenged to achieve the best possible quality of life by relieving suffering, controlling symptoms, and restoring functional capacity. Treatment should be individualized and might encompass surgery, radiotherapy, hormone therapy or chemotherapy.

For patients with large volume disease in the pelvis, external beam radiotherapy is the palliation of choice. For patients with small volume disease, who did not underwent the usual surgical procedure because of co-morbidity or metastases outside the abdomen, palliative radiation therapy might be administered with an intracavitary implant or external field radiotherapy (93). Spanos et al. have reported a safe and effective accelerated, hyperfractionated pelvic irradiation schedule for patients with a life expectancy less than one year (132).

Most endometrial cancers are radiosensitive (133). If the metastatic site is accessible to radiotherapy, palliative radiotherapy can produce rapid amelioration of symptoms. The main indications for radiotherapy are bone metastases that are frequently painful or cause significant dysfunction and local disease causing vaginal bleeding. Other common sites of symptomatic metastasis outside the pelvis are lung, brain and lymph nodes (93).

In conclusion, for patients with stage IVB disease based on intra-abdominal spread of tumor, cytoreductive surgery and individualized (induction or postoperative) chemotherapy and/or radiotherapy is indicated (Level of Evidence IV). For patients with stage IVB disease

based on distant metastasis, therapy is individualized and recommended as depicted in Figure 5.1 (Level of Evidence IV).

Conclusions and further research

Treatment of advanced endometrial cancer is complex and necessitates the cooperation of many specialists. Treatment should preferably be given in clinical trials and patients should be encouraged to participate. In Table 5.10, we propose a management schedule for patients with advanced endometrial cancer of endometrioid histological type, based on sometimes scarce evidence from the literature, combined with experience of clinical practice.

The research in advanced endometrial cancer is focusing on the development of new agents, optimal chemotherapeutic regimens and combination treatment modalities. Several randomized trials are currently accruing patients to evaluate the optimal treatment regimen consisting of different chemotherapy and radiotherapy regimens and a combination of both. These trials are presented in Table 5.8. Other investigations focus on better understanding of the signal transduction pathways that are deregulated in endometrial carcinogenesis and to identify novel biological targets suitable for tailored therapy. Interesting fields of research are represented by the newer investigational agents directed against specific intracellular pathways involved in the proliferation, invasion and metastatic spread of endometrial cancer (134). It is likely that these therapies need to be combined with chemotherapy to assess their synergy and improve outcome (30, 134, 135). Targets of current interest include epidermal growth factor receptor (EGFR), mTOR, PI-3K, Akt inhibitors, vascular endothelial growth factor (VEGF), mutation of PTEN tumor suppressor gene, HER-2/neu, Clostridium perfringens enterotoxin (CPE) and many others.

Table 5.10. Management of advanced endometrial cancer.

FIGO STAGE	RECOMMENDATION	ALTERNATIVE APPROACHES
IIIA based on positive peritoneal cytology only	**A: Unfavorable factors[a] present:** Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with adjuvant pelvic radiotherapy (± brachytherapy) or total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with pelvic lymphadenectomy **B: No unfavorable factors present:** Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings	**A: Unfavorable factors[a] present:** Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with adjuvant pelvic radiotherapy (± brachytherapy) or chemoradiation with adjuvant systemic therapy in international trial **B: No unfavorable factors present:** Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with adjuvant systemic therapy
IIIA based on adnex or serosa involvement	Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with chemotherapy with or without adjuvant pelvic radiotherapy (± brachytherapy)	Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with adjuvant pelvic radiotherapy (± brachytherapy) or chemoradiation with adjuvant systemic therapy in international trial
IIIB	Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with adjuvant pelvic radiotherapy and brachytherapy with or without chemotherapy	Primary pelvic irradiation followed by exploratory laparotomy if disease seems to be resectable
IIIC	Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with resection of enlarged lymph nodes (or preferably complete lymph node dissection) with adjuvant pelvic radiotherapy (± brachytherapy)	Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with adjuvant systemic therapy with or without adjuvant pelvic radiotherapy
IIIC pre-operatively diagnosed with positive pelvic lymph nodes	Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with resection of enlarged lymph nodes (or preferably complete lymph node dissection) followed by pelvic radiotherapy (± brachytherapy)	Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with resection of enlarged lymph nodes (or preferably complete lymph node dissection) followed by pelvic radiotherapy (± brachytherapy) and/or systemic therapy, preferably in international trial Neo-adjuvant or induction chemotherapy followed by complete surgical cytoreduction and/or pelvic radiotherapy (if response occurs)

FIGO STAGE	RECOMMENDATION	ALTERNATIVE APPROACHES
IIIC with positive para-aortic lymph nodes	Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with resection of enlarged lymph nodes (or preferably complete pelvic and para-aortic lymph node dissection) followed by extended field radiotherapy (± brachytherapy)	Total hysterectomy + bilateral salpingo-oophorectomy + peritoneal washings with resection of enlarged lymph nodes (or preferably complete pelvic and para-aortic lymph node dissection) followed by extended field radiotherapy (± brachytherapy) and/or systemic therapy, preferably in international trial Neo-adjuvant or induction chemotherapy followed by complete surgical cytoreduction and/or extended field radiotherapy (if response occurs)
IVA diagnosed during surgery	Complete surgical cytoreduction with post-operative pelvic radiotherapy and/or chemotherapy	Pelvic exenteration with or without post-operative pelvic radiotherapy and/or chemotherapy
IVA pre-operatively diagnosed	Neo-adjuvant or induction chemotherapy followed by surgical cytoreduction (if response occurs) and/or radiotherapy	Pelvic exenteration with or without post-operative pelvic radiotherapy and/or chemotherapy
IVB based on intra-abdominal spread of tumor	Cytoreductive surgery followed by chemotherapy and/or radiotherapy on individual basis	Neo-adjuvant or induction chemotherapy followed by cytoreductive surgery (if response) and radiotherapy on individual basis
IVB based on distant metastasis	See algorithm in Figure 5.1	

[a] Unfavorable factors: age > 60 years, deep myometrial invasion, grade 3 tumor, lymph vascular space involvement.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007 Jan-Feb;57(1):43-66.
2. Kitchener H. Management of endometrial cancer. Eur J Surg Oncol. 2006 Oct;32(8):838-43.
3. Creasman W, Odicino F, Maisonneuve P, Quinn M, Beller U, Benedet J, et al. Carcinoma of the corpus uteri. Int J Gynaecol Obstet. 2006 Nov;95 Suppl 1: S105-43.
4. Boruta DM, 2nd, Gehrig PA, Groben PA, Bae-Jump V, Boggess JF, Fowler WC, Jr., et al. Uterine serous and grade 3 endometrioid carcinomas: is there a survival difference? Cancer. 2004 Nov 15;101(10):2214-21.
5. Barakat RR. Contemporary issues in the management of endometrial cancer. CA Cancer J Clin. 1998 Sep-Oct;48(5):299-314.
6. Creasman WT. Endometrial cancer: incidence, prognostic factors, diagnosis, and treatment. Semin Oncol. 1997 Feb;24(1 Suppl 1):S1-140-S1-50.
7. Ball HG, Elkadry EA. Endometrial cancer: current concepts and management. Surg Oncol Clin N Am. 1998 Apr;7(2):271-84.
8. Elit L. Endometrial cancer. Prevention, detection, management, and follow up. Can Fam Physician. 2000 Apr;46(4):887-92.
9. Levine DA, Hoskins WJ. Update in the management of endometrial cancer. Cancer J. 2002 May-Jun;8 Suppl 1:S31-40.
10. Kim RY, Omura GA, Alvarez RD. Advances in the treatment of gynecologic malignancies. Part 2: Cancers of the uterine corpus and ovary. Oncology (Huntingt). 2002 Dec;16(12):1669-78; discussion 78-80.
11. Santin AD, Bellone S, O'Brien TJ, Pecorelli S, Cannon MJ, Roman JJ. Current treatment options for endometrial cancer. Expert Rev Anticancer Ther. 2004 Aug;4(4):679-89.
12. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet. 2005 Aug 6-12;366(9484):491-505.
13. Benedet JL, Ngan HY, Hacker NF. Staging classification and clinical practice guidelines of gynecologic cancers.http://www.figo.org/docs/staging_booklet.pdf Reprinted from the International Journal of Gynecology and Obstetrics, 70(2000):207-312.
14. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol. 2000 Jun;182(6):1506-19.
15. Irvin WP, Rice LW, Berkowitz RS. Advances in the management of endometrial adenocarcinoma. A review. J Reprod Med. 2002 Mar;47(3):173-89; discussion 89-90.
16. Aalders JG, Thomas G. Endometrial cancer--revisiting the importance of pelvic and para aortic lymph nodes. Gynecol Oncol. 2007 Jan;104(1):222-31.
17. Aalders JG, Abeler V, Kolstad P. Clinical (stage III) as compared to subclinical intrapelvic extrauterine tumor spread in endometrial carcinoma: a clinical and histopathological study of 175 patients. Gynecol Oncol. 1984 Jan;17(1):64-74.
18. Greven KM, Curran WJ, Jr., Whittington R, Fanning J, Randall ME, Wilder J, et al. Analysis of failure patterns in stage III endometrial carcinoma and therapeutic implications. Int J Radiat Oncol Biol Phys. 1989 Jul;17(1):35-9.
19. Goff BA, Goodman A, Muntz HG, Fuller AF, Jr., Nikrui N, Rice LW. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol. 1994 Feb;52(2):237-40.

20. Chi DS, Welshinger M, Venkatraman ES, Barakat RR. The role of surgical cytoreduction in Stage IV endometrial carcinoma. Gynecol Oncol. 1997 Oct;67(1):56-60.
21. Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol. 2000 Aug;78(2):85-91.
22. Ayhan A, Taskiran C, Celik C, Yuce K, Kucukali T. The influence of cytoreductive surgery on survival and morbidity in stage IVB endometrial cancer. Int J Gynecol Cancer. 2002 Sep-Oct;12(5):448-53.
23. van Wijk FH, Huikeshoven FJ, Abdulkadir L, Ewing PC, Burger CW. Stage III and IV endometrial cancer: a 20-year review of patients. Int J Gynecol Cancer. 2006 Jul-Aug;16(4):1648-55.
24. Einhorn N, Trope C, Ridderheim M, Boman K, Sorbe B, Cavallin-Stahl E. A systematic overview of radiation therapy effects in uterine cancer (corpus uteri). Acta Oncol. 2003;42(5-6):557-61.
25. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983 Feb;15(1):10-7.
26. Kurman RJ. Endometrial Carcinoma. In: Kurman RJ, editor Blaustein's Pathology of the Female Genital Tract (4th edition) New York, Springer-Verslag 1994:439-86.
27. Decruze SB, Green JA. Hormone therapy in advanced and recurrent endometrial cancer: a systematic review. Int J Gynecol Cancer. 2007 Apr 18.
28. Humber C, Tierney J, Symonds P, Collingwood M, Kirwan J, Williams C, et al. Chemotherapy for advanced, recurrent or metastatic endometrial carcinoma. Cochrane Database Syst Rev. 2005(4): CD003915.
29. Carey MS, Gawlik C, Fung-Kee-Fung M, Chambers A, Oliver T. Systematic review of systemic therapy for advanced or recurrent endometrial cancer. Gynecol Oncol. 2006 Apr;101(1):158-67.
30. Pectasides D, Pectasides E, Economopoulos T. Systemic therapy in metastatic or recurrent endometrial cancer. Cancer Treat Rev. 2007 Apr;33(2):177-90.
31. Fleming GF. Systemic chemotherapy for uterine carcinoma: metastatic and adjuvant. J Clin Oncol. 2007 Jul 10;25(20):2983-90.
32. Piver MS, Barlow JJ, Lurain JR, Blumenson LE. Medroxyprogesterone acetate (Depo-Provera) vs. hydroxyprogesterone caproate (Delalutin) in women with metastatic endometrial adenocarcinoma. Cancer. 1980 Jan 15;45(2):268-72.
33. Podratz KC, O'Brien PC, Malkasian GD, Jr., Decker DG, Jefferies JA, Edmonson JH. Effects of progestational agents in treatment of endometrial carcinoma. Obstet Gynecol. 1985 Jul;66(1):106-10.
34. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol. 1999 Jun;17(6):1736-44.
35. Martin-Hirsch PL, Jarvis G, Kitchener H, Lilford R. Progestagens for endometrial cancer. Cochrane Database Syst Rev. 2000(2):CD001040.
36. Horton J, Begg CB, Arseneault J, Bruckner H, Creech R, Hahn RG. Comparison of adriamycin with cyclophosphamide in patients with advanced endometrial cancer. Cancer Treat Rep. 1978 Jan;62(1):159-61.
37. Thigpen JT, Buchsbaum HJ, Mangan C, Blessing JA. Phase II trial of adriamycin in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Cancer Treat

Rep. 1979 Jan;63(1):21-7.

38. Thigpen JT, Blessing JA, DiSaia PJ, Yordan E, Carson LF, Evers C. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. J Clin Oncol. 1994 Jul;12(7):1408-14.
39. Van Wijk FH, Aapro MS, Bolis G, Chevallier B, Van Der Burg ME, Poveda A, et al. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. Ann Oncol. 2003 Mar;14(3):441-8.
40. Thigpen JT, Brady MF, Homesley HD, Malfetano J, DuBeshter B, Burger RA, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. J Clin Oncol. 2004 Oct 1;22(19):3902-8.
41. Seski JC, Edwards CL, Copeland LJ, Gershenson DM. Hexamethylmelamine chemotherapy for disseminated endometrial cancer. Obstet Gynecol. 1981 Sep;58(3):361-3.
42. Thigpen JT, Blessing JA, Ball H, Hanjani P, Manetta A, Homesley H. Hexamethylmelamine as first-line chemotherapy in the treatment of advanced or recurrent carcinoma of the endometrium: a phase II trial of the Gynecologic Oncology Group. Gynecol Oncol. 1988 Nov;31(3):435-8.
43. Seski JC, Edwards CL, Herson J, Rutledge FN. Cisplatin chemotherapy for disseminated endometrial cancer. Obstet Gynecol. 1982 Feb;59(2):225-8.
44. Thigpen JT, Blessing JA, Lagasse LD, DiSaia PJ, Homesley HD. Phase II trial of cisplatin as second-line chemotherapy in patients with advanced or recurrent endometrial carcinoma. A Gynecologic Oncology Group study. Am J Clin Oncol. 1984 Jun;7(3):253-6.
45. Edmonson JH, Krook JE, Hilton JF, Malkasian GD, Everson LK, Jefferies JA, 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 Sep;28(1):20-4.
46. Thigpen JT, Blessing JA, Homesley H, Creasman WT, Sutton G. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 1989 Apr;33(1):68-70.
47. Long HJ, Pfeifle DM, Wieand HS, Krook JE, Edmonson JH, Buckner JC. Phase II evaluation of carboplatin in advanced endometrial carcinoma. J Natl Cancer Inst. 1988 Apr 20;80(4):276-8.
48. Green JB, 3rd, Green S, Alberts DS, O'Toole R, Surwit EA, Noltimier JW. Carboplatin therapy in advanced endometrial cancer. Obstet Gynecol. 1990 Apr;75(4):696-700.
49. Burke TW, Munkarah A, Kavanagh JJ, Morris M, Levenback C, Tornos C, et al. Treatment of advanced or recurrent endometrial carcinoma with single-agent carboplatin. Gynecol Oncol. 1993 Dec;51(3):397-400.
50. Van Wijk FH, Lhomme C, Bolis G, Scotto di Palumbo V, Tumolo S, Nooij M, et al. Phase II study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the EORTC Gynaecological Cancer Group. Eur J Cancer. 2003 Jan;39(1):78-85.
51. Barton C, Buxton EJ, Blackledge G, Mould JJ, Meanwell CA. A phase II study of ifosfamide in endometrial cancer. Cancer Chemother Pharmacol.

1990;26 Suppl:S4-6.

52. Sutton GP, Blessing JA, Homesley HD, McGuire WP, Adcock L. Phase II study of ifosfamide and mesna in refractory adenocarcinoma of the endometrium. A Gynecologic Oncology Group study. Cancer. 1994 Mar 1;73(5):1453-5.
53. Sutton GP, Blessing JA, DeMars LR, Moore D, Burke TW, Grendys EC. A phase II Gynecologic Oncology Group trial of ifosfamide and mesna in advanced or recurrent adenocarcinoma of the endometrium. Gynecol Oncol. 1996 Oct;63(1):25-7.
54. Pawinski A, Tumolo S, Hoesel G, Cervantes A, van Oosterom AT, Boes GH, et al. Cyclophosphamide or ifosfamide in patients with advanced and/or recurrent endometrial carcinoma: a randomized phase II study of the EORTC Gynecological Cancer Cooperative Group. Eur J Obstet Gynecol Reprod Biol. 1999 Oct;86(2):179-83.
55. Ball HG, Blessing JA, Lentz SS, Mutch DG. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1996 Aug;62(2):278-81.
56. Lissoni A, Zanetta G, Losa G, Gabriele A, Parma G, Mangioni C. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. Ann Oncol. 1996 Oct;7(8):861-3.
57. Ramondetta L, Burke TW, Levenback C, Bevers M, Bodurka-Bevers D, Gershenson DM. Treatment of uterine papillary serous carcinoma with paclitaxel. Gynecol Oncol. 2001 Jul;82(1):156-61.
58. Lovecchio JL, Averette HE, Lichtinger M, Townsend PA, Girtanner RW, Fenton AN. Treatment of advanced or recurrent endometrial adenocarcinoma with cyclophosphamide, doxorubicin, cis-Platinum, and megestrol acetate. Obstet Gynecol. 1984 Apr;63(4):557-60.
59. Turbow MM, Ballon SC, Sikic BI, Koretz MM. Cisplatin, doxorubicin, and cyclophosphamide chemotherapy for advanced endometrial carcinoma. Cancer Treat Rep. 1985 May;69(5):465-7.
60. 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 Jun;70(6):789-91.
61. Hoffman MS, Roberts WS, Cavanagh D, Praphat H, Solomon P, Lyman GH. Treatment of recurrent and metastatic endometrial cancer with cisplatin, doxorubicin, cyclophosphamide, and megestrol acetate. Gynecol Oncol. 1989 Oct;35(1):75-7.
62. Burke TW, Stringer CA, Morris M, Freedman RS, Gershenson DM, Kavanagh JJ, et al. Prospective treatment of advanced or recurrent endometrial carcinoma with cisplatin, doxorubicin, and cyclophosphamide. Gynecol Oncol. 1991 Mar;40(3):264-7.
63. Horton J, Elson P, Gordon P, Hahn R, Creech R. Combination chemotherapy for advanced endometrial cancer. An evaluation of three regimens. Cancer. 1982 Jun 15;49(12):2441-5.
64. Cohen CJ, Bruckner HW, Deppe G, Blessing JA, Homesley H, Lee JH, et al. Multidrug treatment of advanced and recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Obstet Gynecol. 1984 May;63(5):719-26.
65. Gallion HH, Brunetto VL, Cibull M, Lentz SS, Reid G, Soper JT, et al. Randomized phase III trial of standard timed doxorubicin plus cisplatin versus circadian timed doxorubicin plus cisplatin in stage III and IV or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol.

2003 Oct 15;21(20):3808-13.

66. Fleming GF, Filiaci VL, Bentley RC, Herzog T, Sorosky J, Vaccarello L, et al. Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study. Ann Oncol. 2004 Aug;15(8):1173-8.
67. Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2004 Jun 1;22(11):2159-66.
68. du Bois A, Weber B, Rochon J, Meier W, Goupil A, Olbricht S, et al. Addition of epirubicin as a third drug to carboplatin-paclitaxel in first-line treatment of advanced ovarian cancer: a prospectively randomized gynecologic cancer intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. J Clin Oncol. 2006 Mar 1;24(7):1127-35.
69. Kristensen GB, Vergote I, Stuart G, Del Campo JM, Kaern J, Lopez AB, et al. First-line treatment of ovarian cancer FIGO stages IIb-IV with paclitaxel/epirubicin/carboplatin versus paclitaxel/carboplatin. Int J Gynecol Cancer. 2003 Nov-Dec;13 Suppl 2:172-7.
70. Dimopoulos MA, Papadimitriou CA, Georgoulias V, Moulopoulos LA, Aravantinos G, Gika D, et al. Paclitaxel and cisplatin in advanced or recurrent carcinoma of the endometrium: long-term results of a phase II multicenter study. Gynecol Oncol. 2000 Jul;78(1):52-7.
71. Lissoni A, Gabriele A, Gorga G, Tumolo S, Landoni F, Mangioni C, et al. Cisplatin-, epirubicin- and paclitaxel-containing chemotherapy in uterine adenocarcinoma. Ann Oncol. 1997 Oct;8(10):969-72.
72. Price FV, Edwards RP, Kelley JL, Kunschner AJ, Hart LA. A trial of outpatient paclitaxel and carboplatin for advanced, recurrent, and histologic high-risk endometrial carcinoma: preliminary report. Semin Oncol. 1997 Oct;24(5 Suppl 15):S15-78-S15-82.
73. Nakamura T, Onishi Y, Yamamoto F, Kouno S, Maeda Y, Hatae M. [Evaluation of paclitaxel and carboplatin in patients with endometrial cancer]. Gan To Kagaku Ryoho. 2000 Feb;27(2):257-62.
74. Scudder SA, Liu PY, Wilczynski SP, Smith HO, Jiang C, Hallum AV, 3rd, et al. Paclitaxel and carboplatin with amifostine in advanced, recurrent, or refractory endometrial adenocarcinoma: a phase II study of the Southwest Oncology Group. Gynecol Oncol. 2005 Mar;96(3):610-5.
75. Hogberg T, Rosenberg P, Kristensen G, de Oliveira CF, de Pont Christensen R, Sorbe B, et al. A randomized phase-III study on adjuvant treatment with radiation (RT) ± chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991). Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. 2007;25(18S (June 20 Supplement)):5503.
76. Sagae S, Udagawa Y, Susumu N, Niwa K, Kudo R, Nozawa S, et al. JGOG2033: Randomized phase III trial of Whole pelvic radiotherapy vs cisplatin-based chemotherapy in patients with intermediate risk endometrial carcinoma. J Clin Oncol. 2005;23:455s.
77. Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer. 2006 Aug

7;95(3):266-71.

78. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2006 Jan 1;24(1):36-44.
79. Schorge JO, Molpus KL, Goodman A, Nikrui N, Fuller AF, Jr. The effect of postsurgical therapy on stage III endometrial carcinoma. Gynecol Oncol. 1996 Oct;63(1):34-9.
80. Kadar N, Homesley HD, Malfetano JH. Positive peritoneal cytology is an adverse factor in endometrial carcinoma only if there is other evidence of extrauterine disease. Gynecol Oncol. 1992 Aug;46(2):145-9.
81. Aoki Y, Kase H, Watanabe M, Sato T, Kurata H, Tanaka K. Stage III endometrial cancer: analysis of prognostic factors and failure patterns after adjuvant chemotherapy. Gynecol Oncol. 2001 Oct;83(1):1-5.
82. Hirai Y, Takeshima N, Kato T, Hasumi K. Malignant potential of positive peritoneal cytology in endometrial cancer. Obstet Gynecol. 2001 May;97(5 Pt 1):725-8.
83. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000 Apr 22;355(9213):1404-11.
84. Zuna RE, Behrens A. Peritoneal washing cytology in gynecologic cancers: long-term follow-up of 355 patients. J Natl Cancer Inst. 1996 Jul 17;88(14):980-7.
85. Kashimura M, Sugihara K, Toki N, Matsuura Y, Kawagoe T, Kamura T, et al. The significance of peritoneal cytology in uterine cervix and endometrial cancer. Gynecol Oncol. 1997 Dec;67(3):285-90.
86. Obermair A, Geramou M, Tripcony L, Nicklin JL, Perrin L, Crandon AJ. Peritoneal cytology: impact on disease-free survival in clinical stage I endometrioid adenocarcinoma of the uterus. Cancer Lett. 2001 Mar 10;164(1):105-10.
87. Piver MS. Progesterone therapy for malignant peritoneal cytology surgical stage I endometrial adenocarcinoma. Semin Oncol. 1988 Apr;15(2 Suppl 1):50-2.
88. Piver MS, Recio FO, Baker TR, Hempling RE. A prospective trial of progesterone therapy for malignant peritoneal cytology in patients with endometrial carcinoma. Gynecol Oncol. 1992 Dec;47(3):373-6.
89. Soper JT, Creasman WT, Clarke-Pearson DL, Sullivan DC, Vergadoro F, Johnston WW. Intraperitoneal chromic phosphate P 32 suspension therapy of malignant peritoneal cytology in endometrial carcinoma. Am J Obstet Gynecol. 1985 Sep 15;153(2):191-6.
90. Heath R, Rosenman J, Varia M, Walton L. Peritoneal fluid cytology in endometrial cancer: its significance and the role of chromic phosphate (32P) therapy. Int J Radiat Oncol Biol Phys. 1988 Oct;15(4):815-22.
91. Potish RA. Abdominal radiotherapy for cancer of the uterine cervix and endometrium. Int J Radiat Oncol Biol Phys. 1989 Jun;16(6):1453-8.
92. Greer BE, Hamberger AD. Treatment of intraperitoneal metastatic adenocarcinoma of the endometrium by the whole-abdomen moving-strip technique and pelvic boost irradiation. Gynecol Oncol. 1983 Dec;16(3):365-73.
93. Grigsby PW. Update on radiation therapy for

endometrial cancer. Oncology (Huntingt). 2002 Jun;16(6):777-86, 90; discussion 91, 94-5.

94. Jereczek-Fossa BA. Postoperative irradiation in endometrial cancer: still a matter of controversy. Cancer Treat Rev. 2001 Feb;27(1):19-33.
95. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004 Mar;92(3):744-51.
96. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol. 1980 Oct;56(4):419-27.
97. Kalogiannidis I, Lambrechts S, Amant F, Neven P, E VANL, Vergote I. Role of lymphadenectomy and pelvic radiotherapy in patients with clinical FIGO stage I endometrial adenocarcinoma: An analysis of 208 patients. Int J Gynecol Cancer. 2006 Sep-Oct;16(5):1885-93.
98. Papanikolaou A, Kalogiannidis I, Goutzioulis M, Misailidou D, Makedos A, Vergote I, et al. Pelvic lymphadenectomy as alternative to postoperative radiotherapy in high risk early stage endometrial cancer. Arch Gynecol Obstet. 2006 May;274(2):91-6.
99. Lo KW, Cheung TH, Yu MY, Yim SF, Chung TK. The value of pelvic and para-aortic lymphadenectomy in endometrial cancer to avoid unnecessary radiotherapy. Int J Gynecol Cancer. 2003 Nov-Dec;13(6):863-9.
100. Greven K, Winter K, Underhill K, Fontenesci J, Cooper J, Burke T. Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. Gynecol Oncol. 2006 Oct;103(1):155-9.
101. Ma BB, Oza A, Eisenhauer E, Stanimir G, Carey M, Chapman W, et al. The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers--a study of the National Cancer Institute of Canada Clinical Trials Group. Int J Gynecol Cancer. 2004 Jul-Aug;14(4):650-8.
102. Nicklin JL, Petersen RW. Stage 3B adenocarcinoma of the endometrium: a clinicopathologic study. Gynecol Oncol. 2000 Aug;78(2):203-7.
103. Mariani A, Webb MJ, Keeney GL, Haddock MG, Aletti G, Podratz KC. Stage IIIC Endometrioid Corpus Cancer Includes Distinct Subgroups. Gynecol Oncol. 2002 Oct;87(1):112-7.
104. Nelson G, Randall M, Sutton G, Moore D, Hurteau J, Look K. FIGO stage IIIC endometrial carcinoma with metastases confined to pelvic lymph nodes: analysis of treatment outcomes, prognostic variables, and failure patterns following adjuvant radiation therapy. Gynecol Oncol. 1999 Nov;75(2):211-4.
105. McMeekin DS, Lashbrook D, Gold M, Scribner DR, Kamelle S, Tillmanns TD, et al. Nodal distribution and its significance in FIGO stage IIIc endometrial cancer. Gynecol Oncol. 2001 Aug;82(2):375-9.
106. Mariani A, Dowdy SC, Cliby WA, Haddock MG, Keeney GL, Lesnick TG, et al. Efficacy of systematic lymphadenectomy and adjuvant radiotherapy in node-positive endometrial cancer patients. Gynecol Oncol. 2006 May;101(2):200-8.
107. Katz LA, Andrews SJ, Fanning J. Survival after multimodality treatment for stage IIIC endometrial cancer. Am J Obstet Gynecol. 2001 May;184(6):1071-3.
108. Larson DM, Broste SK, Krawisz BR. Surgery without radiotherapy for primary treatment of endometrial

cancer. Obstet Gynecol. 1998 Mar;91(3):355-9.

109. Mundt AJ, Murphy KT, Rotmensch J, Waggoner SE, Yamada SD, Connell PP. Surgery and postoperative radiation therapy in FIGO Stage IIIC endometrial carcinoma. Int J Radiat Oncol Biol Phys. 2001 Aug 1;50(5):1154-60.
110. Rose PG, Cha SD, Tak WK, Fitzgerald T, Reale F, Hunter RE. Radiation therapy for surgically proven para-aortic node metastasis in endometrial carcinoma. Int J Radiat Oncol Biol Phys. 1992;24(2):229-33.
111. Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD, 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 Jan;40(1):55-65.
112. Potish RA, Twiggs LB, Adcock LL, Savage JE, Levitt SH, Prem KA. Paraaortic lymph node radiotherapy in cancer of the uterine corpus. Obstet Gynecol. 1985 Feb;65(2):251-6.
113. Mariani A, Webb MJ, Galli L, Podratz KC. Potential therapeutic role of para-aortic lymphadenectomy in node-positive endometrial cancer. Gynecol Oncol. 2000 Mar;76(3):348-56.
114. Benedet JL, Bender H, Jones H, 3rd, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet. 2000 Aug;70(2):209-62.
115. Rittenberg PV, Lotocki RJ, Heywood MS, Jones KD, Krepart GV. High-risk surgical stage 1 endometrial cancer: outcomes with vault brachytherapy alone. Gynecol Oncol. 2003 May;89(2):288-94.
116. Fanning J. Long-term survival of intermediate risk endometrial cancer (stage IG3, IC, II) treated with full lymphadenectomy and brachytherapy without teletherapy. Gynecol Oncol. 2001 Aug;82(2):371-4.
117. McMeekin DS, Lashbrook D, Gold M, Johnson G, Walker JL, Mannel R. Analysis of FIGO Stage IIIc endometrial cancer patients. Gynecol Oncol. 2001 May;81(2):273-8.
118. Lupe K, Kwon J, D'Souza D, Gawlik C, Stitt L, Whiston F, et al. Adjuvant paclitaxel and carboplatin chemotherapy with involved field radiation in advanced endometrial cancer: A sequential approach. Int J Radiat Oncol Biol Phys. 2006 Nov 1.
119. Hoskins PJ, Swenerton KD, Pike JA, Wong F, Lim P, Acquino-Parsons C, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. J Clin Oncol. 2001 Oct 15;19(20):4048-53.
120. Arimoto T, Nakagawa S, Yasugi T, Yoshikawa H, Kawana K, Yano T, et al. Treatment with paclitaxel plus carboplatin, alone or with irradiation, of advanced or recurrent endometrial carcinoma. Gynecol Oncol. 2006 Sep 20.
121. Lopez MJ, Standiford SB, Skibba JL. Total pelvic exenteration. A 50-year experience at the Ellis Fischel Cancer Center. Arch Surg. 1994 Apr;129(4):390-5; discussion 5-6.
122. Jakowatz JG, Porudominsky D, Riihimaki DU, Kemeny M, Kokal WA, Braly PS, et al. Complications of pelvic exenteration. Arch Surg. 1985 Nov;120(11):1261-5.
123. McCullough WM, Nahhas WA. Palliative pelvic exenteration--futility revisited. Gynecol Oncol. 1987 May;27(1):97-103.
124. Mirhashemi R, Averette HE, Estape R, Angioli R, Mahran R, Mendez L, et al. Low colorectal anastomosis after radical pelvic surgery: a risk factor analysis. Am J Obstet Gynecol. 2000 Dec;183(6):1375-9; discussion 9-80.

125. Morley GW, Hopkins MP, Lindenauer SM, Roberts JA. Pelvic exenteration, University of Michigan: 100 patients at 5 years. Obstet Gynecol. 1989 Dec;74(6):934-43.
126. Endometrial carcinoma treated by pelvic exenteration; cholecystectomy followed by shock, chest pain, urinary tract infection and convulsions. Am J Med. 1967 Mar;42(3):423-34.
127. Robertson G, Lopes A, Beynon G, Monaghan JM. Pelvic exenteration: a review of the Gateshead experience 1974-1992. Br J Obstet Gynaecol. 1994 Jun;101(6):529-31.
128. Kraybill WG, Lopez MJ, Bricker EM. Total pelvic exenteration as a therapeutic option in advanced malignant disease of the pelvis. Surg Gynecol Obstet. 1988 Mar;166(3):259-63.
129. Hockel M, Dornhofer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. Lancet Oncol. 2006 Oct;7(10):837-47.
130. Murphy KJ, Depetrillo AD. Pelvic exenteration. Baillieres Clin Obstet Gynaecol. 1987 Jun;1(2):383-92.
131. Tangjitgamol S, Levenback CF, Beller U, Kavanagh JJ. Role of surgical resection for lung, liver, and central nervous system metastases in patients with gynecological cancer: a literature review. Int J Gynecol Cancer. 2004 May-Jun;14(3):399-422.
132. Spanos WJ, Jr., Perez CA, Marcus S, Poulter CA, Doggett RL, Steinfeld AD, et al. Effect of rest interval on tumor and normal tissue response--a report of phase III study of accelerated split course palliative radiation for advanced pelvic malignancies (RTOG-8502). Int J Radiat Oncol Biol Phys. 1993 Feb 15;25(3):399-403.
133. Southcott BM. Carcinoma of the endometrium. Drugs. 2001;61(10):1395-405.
134. Gadducci A, Cosio S, Genazzani AR. Old and new perspectives in the pharmacological treatment of advanced or recurrent endometrial cancer: Hormonal therapy, chemotherapy and molecularly targeted therapies. Crit Rev Oncol Hematol. 2006 Jun;58(3):242-56.
135. Kieser K, Oza AM. What's new in systemic therapy for endometrial cancer. Curr Opin Oncol. 2005 Sep;17(5):500-4.

Chapter 5.2

Management of recurrent endometrioid endometrial carcinoma: an overview

Management of recurrent endometrioid endometrial carcinoma: an overview
F.H. van Wijk, M.E.L. van der Burg, C.W. Burger, I. Vergote, H.C. van Doorn
Submitted.

Abstract

In this paper an overview of the literature on the management of recurrent endometrial cancer is presented, focusing on patients with histopathologic endometrioid type of tumors. The different treatment modalities are described and a management recommendation scheme is presented.

Indications for surgical treatment depend on resectability, site and size of the tumor and performance status of the patient. Indications for radiotherapy depend on the site of the recurrence and also on the initial therapy received. When considering systemic treatment for patients with recurrent endometrial cancer, it is important to take into account the general health status and condition of the patient as well as which prior therapy the patient has received. The treatment of choice for patients with hormone sensitive tumors (positive receptor levels, low-grade tumors and long disease free interval) are progestagens as first-line treatment and tamoxifen as second-line treatment. Patients with high grade tumors, negative hormone receptor levels and short treatment-free interval are best treated with chemotherapy. The combination therapy with paclitaxel and carboplatin is adopted unofficially as standard therapy.

The literature on the management of patients with recurrent endometrial cancer is discussed in detail. The different sites of recurrent disease (i.e. local, regional and/or distant) are evaluated separately; management recommendations are proposed and alternative approaches are given.

Introduction

Most endometrial cancers are diagnosed in early stage, and as result of the effective surgery with or without adjuvant radiotherapy the failure rate is low. Only about 13% of all patients with endometrial cancer develop recurrent disease (1). More than half of the recurrences develop within two years and about three fourths occur within three years after initial treatment. Patients with recurrent endometrial cancer represent a heterogeneous group of patients with difference in histological types and grade, stage and treatment of primary tumor, diverse interval between primary tumor and recurrence and various sites of recurrent disease. Depending upon prior therapy and the nature and site of the recurrence, patients may be treated with a curative or a palliative intent. In general, patients with an isolated vaginal recurrence have a higher chance of cure than those with pelvic or abdominal recurrences, who in turn do better than those with distant metastases.

In this overview the management of patients with recurrent endometrial cancer is reviewed. The first part describes the different treatment modalities of patients with recurrent endometrial cancer. After reviewing the literature, management recommendation for patients with local, regional and distant recurrent endometrial cancer are proposed in the last part, based on the evidence using a Level of Evidence rating system (Appendix A).

Treatment modalities

Surgery

In general, indications for surgery of recurrent endometrial cancer depend on resectability, site and size of the tumor and performance status of the patient. Indications for surgical cytoreduction and metastasectomy will be discussed in the sections per site of recurrent disease.

Radiotherapy

Long-term survival rates in patients who undergo radiotherapy after relapse range from 25% to 75%, with most reported 5-year survival rates between 40-55% (2-8). Favorable prognostic factors of relapse are isolated vaginal recurrence, no prior radiotherapy, long relapse-free interval, low-grade histology and endometrioid adenocarcinoma (5, 7, 9-13). The indications of radiotherapy for recurrent endometrial cancer depend not only on the site of the recurrence but also whether the tumor is located in prior irradiated area. Patients with a history of prior radiotherapy are at highest risk for severe treatment-related sequelae (2, 14).

Radiotherapy can be administered, depending on the site of recurrent lesions, as brachytherapy (locally to the vagina) or as teletherapy (external irradiation to the site of recurrent disease). More recently, radiotherapy can be administered as stereotactic radiotherapy, with the advantage of treating inaccessible or multiple lesions without damaging the surrounding tissue.

Systemic treatment

When considering systemic treatment for patients with recurrent endometrial cancer it is important to take into account the general health status and condition of the patient. The choice of systemic treatment depends on the type of tumor, the condition of the patient and prior therapy. Patients with low grade endometrioid tumors with positive hormone receptor levels and long treatment-free intervals respond mostly to hormonal treatment. Patients with high grade tumors, poor prognostic histopathologic types serous and clear cell tumors, negative hormone receptors and a short treatment-free interval do respond rarely to hormonal treatment and are best treated with chemotherapy. Although prior treatment is not always documented in clinical studies, it is important to take into consideration which prior therapy patients received, because this might influence the response to systemic treatment.

Hormone therapy

The overall response rate to hormone therapy is 15% to 30% in contrast to a response rate up to 65% in hormone sensitive tumors (15-26). Important positive prognostic factors for response to hormone therapy are presence of high levels of progesterone and/or estrogen receptors, low-grade histology, long treatment-free interval between initial diagnosis and recurrence and minimal tumor burden (≤ 10 cm^3) (22, 27). These prognostic factors are often simultaneously present in these patients. The response to hormone therapy takes more time than to chemotherapy. The response to hormone therapy should therefore be evaluated after an interval of three months. Particularly patients with minimal symptoms or non-life threatening disease are candidates for hormone therapy; in these patients the effect of hormonal treatment can be awaited. Patients with serious complaints or life-threatening disease, on contrary, might benefit more (quicker) from chemotherapy.

Progestagens

The best response rate to progestagens is reported in patients with recurrent disease after more than five years of initial treatment (response rate of 65%); the response rate of patients with a time to recurrence of less than six months was only 6% (28). Response rates in patients with high progesterone receptor levels are significantly higher compared to patients with low levels (37% versus 8%); response rates are also significantly higher in patients with grade 1 tumors compared to patients with grade 3 tumors (37% and 9% respectively) (20). The reported progression-free survival varies from 2.5 to 14 months (29). Several progestagens (e.g. medroxyprogesterone acetate, megestrol acetate, hydroxyprogesterone caproate) are used in the treatment of endometrial cancer, but not one agent have shown a significant higher response rate or better survival (22, 23), neither did high dose medroxyprogesterone acetate. In one trial high dose medroxyprogesterone acetate (1000 mg/day) demonstrated no superiority over standard dose therapy (medroxyprogesterone acetate 200 mg/day) in terms of response rate (25% versus 15%) or survival (11.1 versus 7.0 months) ($p=0.93$), the number of adverse effects consisting of thrombophlebitis, anemia and

pulmonary emboli were comparable in both arms (20).

Anti-estrogens

The pooled response rates of tamoxifen of several small phase II trials with a total of 257 patients was 22% (16). In second line therapy, about half of the patients who previously responded to progestagen therapy did respond to tamoxifen (response rates of 53% and 57%) (30, 31), this in contrast to none of the patients who were refractory to progesterone (32, 33). In hormone-naïve patients response to tamoxifen was observed in 10% and 21% of the patients (32, 34).

Based on the hypothesis that tamoxifen might induce sensitivity to further progestagen therapy due to stimulation of both estrogen and progesterone receptor synthesis, tamoxifen was combined with megestrol acetate or medroxyprogesterone acetate and showed response rates of respectively 27% and 33% (35, 36). These combinations are not compared with single agent tamoxifen therapy in a randomized trial.

GnRH analogues

The response rate of leuprorelin and goserelin in recurrent endometrial cancer was respectively 28% and 35% (37, 38). After prior progestin treatment, the response rates was low (0-11%) (39-41).

Aromatase inhibitors

Anastrozole and letrozole showed only limited activity in patients with advanced or recurrent endometrial cancer (response rates of 8.7% to 9.4%) (42, 43). The role of aromatase inhibitors in patients with hormone-receptor-positive tumors is not clear.

Conclusion hormone therapy

In conclusion, the treatment of choice for patients with recurrent endometrial cancer with hormone sensitive tumors (positive receptor levels, low-grade tumors and long disease free interval) are progestagens in first-line therapy and tamoxifen in second-line therapy, after prior response to progestagens.

Chemotherapy

The optimal chemotherapeutic agents in endometrial cancer are discussed in chapter 5.1. The most active single agent in endometrial cancer is paclitaxel (44-46). Paclitaxel, doxorubicin and cisplatin is the most active combination therapy for these patients, but with significant toxicity (47). The combination of paclitaxel and carboplatin seems to be as effective but significant less toxic and is an out-patient therapy (48-52). Although the results of the randomized trials with the combination therapy of paclitaxel doxorubicin and cisplatin versus paclitaxel and carboplatin have to be awaited, the combination therapy with paclitaxel and carboplatin is adopted unofficially as standard therapy outside studies.

In patients with recurrent endometrial cancer it is important to take into account the prior treatment. In general, responses to chemotherapy are higher in chemotherapy-naïve patients compared to those who received prior chemotherapy. Response rates to cisplatin in mainly

chemotherapy-naïve patients ranged from 20% to 42% (53-55); patients who had received prior chemotherapy showed a response rate of only 4% (56). Paclitaxel showed a response rate of 37% as second-line therapy (45), while other phase II studies reported the response rates up to 77% in chemotherapy-naïve patients (44, 46). Prior response to hormone therapy reflects the chance for response to chemotherapy; the responses are worse in patients who failed to respond to progestagens (57, 58).

Lower response rates to chemotherapy are observed of tumors in irradiated areas compared to tumors outside irradiated areas, possibly due to biological resistance of the tumor in the irradiated area, diminished blood supply and necessary dose reductions due to increased myelosuppression as a result of prior radiotherapy (59, 60).

Management of recurrent endometrial cancer according to the site of recurrence

Local recurrence

Patients with local recurrences should be evaluated for surgical extirpation and/or radiotherapy. Other sites of recurrent disease must be excluded by radiological imaging. Local recurrence should be divided in a recurrence in radiotherapy-naïve area and in a recurrence in irradiated area. Five-year survival rates between 10% and 43% have been reported in patients with a vaginal relapse in prior irradiated area (5, 61, 62) versus 65% in patients without prior radiotherapy, which is well illustrated by the results of the PORTEC-1 trial that included low stage endometrial cancer patient and randomized between adjuvant radiotherapy or conservative treatment (62).

In irradiated area

Surgical management is the best treatment for patients with an isolated vaginal recurrence in a previously irradiated field if the patient is in a good condition and the tumor is resectable. This procedure, however, is rarely indicated, because of the high radio-sensitivity of endometrial cancer, patients with a central pelvic recurrence are therefore uncommon after prior radiotherapy.

In retrospective studies, complete cytoreductive surgery for recurrent endometrial cancer in irradiated area showed in selected patients a long recurrence-free survival. The potential benefit of complete cytoreduction was illustrated in a study of 35 patients undergoing surgery for recurrent endometrial cancer in irradiated area (63). Twenty-three patients who underwent a complete cytoreduction had a median survival of 39 months, significantly longer than patients with gross residual disease (13.5 months). At 40 months post treatment, 54% of the patients who underwent complete cytoreduction were alive versus none in the other group. Although cytoreductive surgery seems to be useful for recurrent disease in irradiated area, one must keep in mind that appropriate surgical indications and selection criteria for cytoreductive surgery in recurrent disease are not defined.

It is debatable whether surgery for an isolated (central) pelvic recurrence also should include a pelvic exenteration. One should keep in mind that pelvic exenteration is intended for curative treatment. It is associated with high postoperative morbidity and poor survival (64), but this procedure remains the only potentially curative option for the few patients with local central recurrence involving bladder and/or rectum following initial radiotherapy (with or without surgery). In general, for patients with cancer of the female genital tract, pelvic exenteration provides about 50% chance to save patients with this procedure given that the tumor diameter does not exceed 5 cm, there are no metastases or peritoneal tumor involvement is present, and resection of the pelvic tumor with clear resection margins is accomplished. Although treatment-related mortality has fallen greatly to less than 1% in recent series (65), severe morbidity is still present in more than half of the treated patients (66). In endometrial cancer patients, five-year survival rates after pelvic exenteration are between 17 and 62% (64, 67-69). Morris et al. showed a 5-year disease-free survival of 45% in highly selected patients with a local recurrence treated with pelvic exenteration after extensive prior treatment (70). Poor prognostic factors influencing survival in patients who had undergone exenteration were age older than 69 years, recurrence within 3 years of prior treatment, persistent recurrence (i.e. tumor left after surgery), and positive resection margins (71). Barakat et al. described a high operative morbidity and poor overall survival in a study of 44 patients treated with pelvic exenteration. Seven patients (16%) died intra- or postoperatively and only nine patients (20%) were long term survivors (64). Also other available data on exenteration for recurrent endometrial cancer show in general disappointing results (72, 73).

In an attempt to improve the potential for salvage therapy in patients who underwent surgical resection, intra-operative radiation therapy (IORT) may provide an adjunctive treatment to surgery in case of microscopically positive margins. In a cohort of 17 patients with recurrent gynecological tumors, of which seven patients with endometrial cancer, and six patients with a local recurrence, the 3-year local control rate was favorable in patients with complete gross resection compared to patients with gross residual disease (83% and 25% respectively) (74). The most common type of toxicity was a gastro-intestinal complication, which occurred in 24% of the patients; no life-threatening complications occurred.

If a patient with a local recurrence in an irradiated area is not a good candidate for surgical treatment, systemic treatment with hormone therapy or chemotherapy is advised (www.nccn.org). Nevertheless, so far, not one study has proven activity of systemic treatment in this patient population.

In conclusion, in patients with a local recurrence in a previously irradiated area is tumor resection with clear resection margins the first choice, even if this means an pelvic exenteration (Level of Evidence IV). In case of microscopically positive margins, intra-operative radiation therapy might be considered (Level of Evidence IV). Re-irradiation might be indicated for

palliative reasons, like abundant vaginal bleeding.

In radiotherapy-naïve area

Radiotherapy is the first choice of treatment for patients with an isolated vaginal recurrence in radiotherapy-naïve area. In patients with recurrent disease of initially early stage endometrial cancer, the cure rates after external radiotherapy and brachytherapy are high (5-year survival rates of 65-100% and 5-year local control rates of 75-81%) (4, 8, 62, 75-78).

A major determinant for local control is tumor size at the time of relapse (5, 6, 79). In the largest report of 58 radiotherapy-naïve patients with locoregional recurrent disease, the 5-year local control rates were significantly higher for tumors less than 2 cm compared to larger tumors (80% versus 54%) (6). As a consequence, in patients with tumors > 2 cm, surgical cytoreduction or neo-adjuvant chemotherapy followed by surgery and/or radiotherapy might be of preference over primary radiotherapy, although in literature randomized data are lacking.

In conclusion, local radiotherapy with brachytherapy with or without pelvic radiotherapy is the first choice for patients with a recurrence in radiotherapy naïve area. In patients with a recurrence larger than 2cm complete resection or neo-adjuvant chemotherapy followed by surgery and/or radiotherapy might be indicated. (Level of Evidence IV)

Regional recurrence

Many endometrial cancer recurrences occur at the pelvic sidewall or in the retro peritoneum as a result of lymphatic embolization. In general, 10-year survival rates drop from 50 to 24% if there is a pelvic recurrence compared to vaginal recurrent disease (78).

Pelvic lymph node recurrences are most frequently treated with pelvic radiotherapy with or without prior surgery. Metastases in para-aortic or common iliac lymph nodes can be treated with extended field radiotherapy, preceded by debulking surgery in case of large lymph nodes. For upper abdominal or peritoneal recurrences, systemic treatment with or without radiotherapy is recommended (www.nccn.org).

Limited experience is available using radiotherapy for the salvage of regional recurrences in radiotherapy-naïve patients. A retrospective series showed no survivors beyond 1.5 years among patients with pelvic recurrence treated with radiotherapy (80). After treatment in the PORTEC trial, seven of the 20 patients with pelvic recurrence were treated with radiotherapy with curative intent and only one survived at 3-years (62). In radiotherapy-naïve patients with unresectable isolated non-vaginal recurrent gynecologic malignancies, I^{125} implants followed by external beam radiotherapy was feasible and contributed occasionally to long-term disease-free survival (81).

Since curative re-radiation seems impossible, surgical resection is the best option for patients with a recurrence within a previously irradiated field. According to the literature the

most favorable results are observed in patients with a single site of recurrence. The amount of residual disease showed to be the most important factor associated with survival (63, 82-84). Ultra-radical compartmentalized pelvic surgery, which is multivisceral pelvic resection aiming a resection with microscopically tumor-free margins, was investigated in patients with pelvic side wall disease who were traditionally not considered for surgical therapy. These patients seemed to benefit from this procedure. In 72 of the 74 patients with recurrent gynecological cancers, of which five patients with endometrial cancer, it was possible to remove the tumor with microscopically tumor-free margins. The 5-year overall survival was 56% (85).

Alternative approaches are multi-modality treatments consisting of combined operative and radiotherapeutic treatment (CORT), radical resection in combination with intra-operative radiation therapy (IORT) or hyperthermic intraperitoneal chemotherapy (HIPEC) (74, 86-88). CORT was designed for the treatment of post-irradiation recurrence infiltrating the pelvic wall; total resection of the tumor with only a microscopic residual disease in the margins at the pelvic wall is mandatory with this procedure (86). In 48 patients with post-irradiation recurrent or persistent gynecologic malignancies infiltrating the pelvic wall the 5-year survival probability was 44%, the overall local control rate 68% and the severe complication rate was 33%. With an aggressive surgical approach including radical resection of the pelvic sidewall en bloc (obturator nerve; external iliac vein; psoas, iliacus, or obturator internus muscles; ureter; bony ileum; and/or exenteration) followed by intra-operative electron radiotherapy a 5-year survival rate of 53% was reported in a series of 25 women with recurrent endometrial cancer (87). Five-year survival was higher for patients with total resection of gross disease and free or close tumor-free margins as compared to those with microscopic residual disease (71% versus 40%). However, few women were candidates for such an aggressive procedure, with a high morbidity (64%). Another study evaluating this treatment approach in 17 patients with recurrent gynecologic tumors, of which seven patients with recurrent endometrial cancer, also showed the importance of complete tumor-free surgical resection (3-year local control rate 83% for patients with complete surgical resection versus 25% for patients with gross residual disease, $p < 0.01$) (74). The combination of surgical resection with HIPEC was evaluated in a cohort of 5 patients showed long survival (two patients with no evidence of disease a at 28 and 32 months, two with evidence of disease at 12 and 36 months and one died at three months without evidence of cancer). The treatment was relatively well tolerated (88).

In conclusion, the best treatment for radiotherapy-naïve patients with a recurrence in pelvic is pelvic radiotherapy with or without prior surgery aiming at optimal cytoreduction. Rare alternative approaches are combined operative and radiotherapeutic treatment (CORT), radical resection with or without intra-operative radiation therapy (IORT) or hyperthermic intraperitoneal chemotherapy (HIPEC). Systemic treatment with or without surgery is

recommended for upper abdominal or peritoneal recurrences (Level of Evidence IV).

Distant recurrence

Common sites of symptomatic metastasis are lymph nodes, bone, lung, and brain. Systemic treatment is indicated for most patients with distant recurrent disease. For asymptomatic patients with hormone receptor positive tumors, hormone therapy is the first choice. Especially in patients with pulmonary metastases, long responses are reported (89-91). Chemotherapy is indicated for receptor negative tumors, fast growing tumors and symptomatic recurrences requiring rapid relief, and for patients with progression during hormone therapy.

Surgical treatment might be the treatment of choice for an isolated metastasis. Successful surgical resections are reported for isolated recurrences in the lung, liver, brain, spleen and vulva (92-95). Favorable prognostic factors for a prolonged survival after metastatectomy are good performance status, long disease-free interval, absence of other systemic disease, and resectability with tumor-free margins (95). However, as literature on metastasectomy is very limited, a clinical judgment should be individualized, bearing in mind the potential for long-term survival and the probability of improvement of treatment with systemic therapy.

Radiotherapy can be administered to an isolated metastasis which cannot be resected or to symptomatic metastases, because radiotherapy will produce rapid responses with a quick amelioration of symptoms (96). The main indications for palliative radiotherapy are not only pelvic disease causing vaginal bleeding, but also symptomatic brain metastases, painful bone metastases and threatening bone fractures, which are frequently painful or causes significant dysfunction.

A new approach is the stereotactic radiotherapy. This is effective treatment for inaccessible or multiple lesions, and spares the surrounding tissue and needs a relatively short treatment time. In gynecological cancer, stereotactic radiotherapy is evaluated in the treatment of para-aortic lymph node metastases of cervical cancer (97, 98). Also for brain metastases, stereotactic radiotherapy showed to be a good alternative for whole brain radiotherapy, with less risk of neurocognitive damage (99, 100).

In conclusion, patients with distant recurrent disease are treated with systemic paclitaxel platinum based chemotherapy. Although literature on metastasectomy is very limited, good results are achieved in individual patients. If surgical metastatectomy is not possible, radiotherapy might be a good alternative. For patients with symptomatic disease radiotherapy can give a good and quick palliation. (Level of Evidence IV)

Conclusions

Our efforts should focus on defining the optimal treatment of primary endometrial cancer in order to prevent recurrences in the first place. Patients who develop recurrent disease,

Table 5.11. Management recurrent endometrioid endometrial carcinoma.

SITE OF RECURRENT DISEASE	RECOMMENDATION	ALTERNATIVE APPROACHES
Local	**In irradiated area:** Surgical cytoreduction (compromising pelvic exenteration) followed by radiotherapy on individual basis	**In irradiated area:** Surgical cytoreduction and in case of microscopically positive margins, combined with intra-operative radiotherapy Palliative re-irradiation
	In radiotherapy-naïve area: Pelvic radiotherapy and/or brachytherapy	**In radiotherapy-naïve area:** Surgical cytoreduction (compromising pelvic exenteration) followed by radiotherapy and/or systemic therapy on individual basis In cases of large primarily unresectable tumors: neo-adjuvant or induction chemotherapy followed by surgery and/or radiotherapy
Regional		
Pelvic recurrence	**In irradiated area:** Surgical cytoreduction if disease is completely resectable	
	In radiotherapy-naïve area: Pelvic radiotherapy with or without prior complete surgical cytoreduction	**In radiotherapy-naïve area:** Extensive surgical cytoreduction if disease seems completely resectable
Upper abdominal or peritoneal recurrence	Systemic therapy with or without debulking surgery and/or radiotherapy	Systemic therapy followed by surgery or radiotherapy Surgical cytoreduction with or without combined operative and radiotherapeutic treatment (CORT), intra-operative radiation therapy (IORT) or hyperthermic intraperitoneal chemotherapy (HIPEC)
Distant	Systemic therapy (chemotherapy or hormone therapy)	Metastasectomy or local radiotherapy with or without systemic therapy (chemotherapy or hormone therapy) Palliative radiotherapy

should be evaluated thoroughly to define the best treatment strategy with respect to site and extent of recurrent disease and prior treatment. Research should focus on developing new chemotherapeutic and biologic agents active against endometrial cancer.

In Table 5.11 recommendations for the management of patients with recurrent endometrial cancer are proposed.

References

1. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006 Jun;101(3):520-9.
2. Lin LL, Grigsby PW, Powell MA, Mutch DG. Definitive radiotherapy in the management of isolated vaginal recurrences of endometrial cancer. Int J Radiat Oncol Biol Phys. 2005 Oct 1;63(2):500-4.
3. Pai HH, Souhami L, Clark BG, Roman T. Isolated vaginal recurrences in endometrial carcinoma: treatment results using high-dose-rate intracavitary brachytherapy and external beam radiotherapy. Gynecol Oncol. 1997 Aug;66(2):300-7.
4. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. Int J Radiat Oncol Biol Phys. 2003 Aug 1;56(5):1366-72.
5. Curran WJ, Jr., Whittington R, Peters AJ, Fanning J. Vaginal recurrences of endometrial carcinoma: the prognostic value of staging by a primary vaginal carcinoma system. Int J Radiat Oncol Biol Phys. 1988 Oct;15(4):803-8.
6. Wylie J, Irwin C, Pintilie M, Levin W, Manchul L, Milosevic M, et al. Results of radical radiotherapy for recurrent endometrial cancer. Gynecol Oncol. 2000 Apr;77(1):66-72.
7. Jereczek-Fossa B, Badzio A, Jassem J. Recurrent endometrial cancer after surgery alone: results of salvage radiotherapy. Int J Radiat Oncol Biol Phys. 2000 Sep 1;48(2):405-13.
8. Huh WK, Straughn JM, Jr., Mariani A, Podratz KC, Havrilesky LJ, Alvarez-Secord A, et al. Salvage of isolated vaginal recurrences in women with surgical stage I endometrial cancer: a multiinstitutional experience. Int J Gynecol Cancer. 2007 Feb 14.
9. Sears JD, Greven KM, Hoen HM, Randall ME. Prognostic factors and treatment outcome for patients with locally recurrent endometrial cancer. Cancer. 1994 Aug 15;74(4):1303-8.
10. Podczaski E, Kaminski P, Gurski K, MacNeill C, Stryker JA, Singapuri K, et al. Detection and patterns of treatment failure in 300 consecutive cases of “early” endometrial cancer after primary surgery. Gynecol Oncol. 1992 Dec;47(3):323-7.
11. Poulsen MG, Roberts SJ. Prognostic variables in endometrial carcinoma. Int J Radiat Oncol Biol Phys. 1987 Jul;13(7):1043-52.
12. Morgan JD, 3rd, Reddy S, Sarin P, Yordan E, DeGeest K, Hendrickson FR. Isolated vaginal recurrences of endometrial carcinoma. Radiology. 1993 Nov;189(2):609-13.
13. Hart KB, Han I, Shamsa F, Court WS, Chuba P, Deppe G, et al. Radiation therapy for endometrial cancer in patients treated for postoperative recurrence. Int J Radiat Oncol Biol Phys. 1998 Apr 1;41(1):7-11.
14. Tewari K, Cappuccini F, Brewster WR, DiSaia PJ, Berman ML, Manetta A, et al. Interstitial brachytherapy for vaginal recurrences of endometrial carcinoma. Gynecol Oncol. 1999 Sep;74(3):416-22.
15. Neijt JP. Systemic treatment in disseminated endometrial cancer. Eur J Cancer. 1993;29A(4):628-32.
16. 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 Jun;9(6):1071-88.
17. Elit L, Hirte H. Novel strategies for systemic treatment of endometrial cancer. Expert Opin Investig Drugs. 2000 Dec;9(12):2831-53.
18. Bridges J, Oram D. Management of advanced gynaecological malignancies. Br J Hosp Med. 1993 Feb 3-16;49(3):191-9.

19. Deppe G. Chemotherapeutic treatment of endometrial carcinoma. Clin Obstet Gynecol. 1982 Mar;25(1):93-9.
20. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol. 1999 Jun;17(6):1736-44.
21. Quinn MA, Cauchi M, Fortune D. Endometrial carcinoma: steroid receptors and response to medroxyprogesterone acetate. Gynecol Oncol. 1985 Jul;21(3):314-9.
22. Podratz KC, O'Brien PC, Malkasian GD, Jr., Decker DG, Jefferies JA, Edmonson JH. Effects of progestational agents in treatment of endometrial carcinoma. Obstet Gynecol. 1985 Jul;66(1):106-10.
23. Piver MS, Barlow JJ, Lurain JR, Blumenson LE. Medroxyprogesterone acetate (Depo-Provera) vs. hydroxyprogesterone caproate (Delalutin) in women with metastatic endometrial adenocarcinoma. Cancer. 1980 Jan 15;45(2):268-72.
24. Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 1996 Feb;14(2):357-61.
25. Pandya KJ, Yeap BY, Weiner LM, Krook JE, Erban JK, Schinella RA, et al. Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative Oncology Group Study (E4882). Am J Clin Oncol. 2001 Feb;24(1):43-6.
26. Emons G, Heyl W. Hormonal treatment of endometrial cancer. J Cancer Res Clin Oncol. 2000 Nov;126(11):619-23.
27. Markman M. Hormonal therapy of endometrial cancer. Eur J Cancer. 2005 Mar;41(5):673-5.
28. Reifenstein EC, Jr. The treatment of advanced endometrial cancer with hydroxyprogesterone caproate. Gynecol Oncol. 1974 Aug;2(2-3):377-414.
29. Decruze SB, Green JA. Hormone therapy in advanced and recurrent endometrial cancer: a systematic review. Int J Gynecol Cancer. 2007 Apr 18.
30. Bonte J, Ide P, Billiet G, Wynants P. Tamoxifen as a possible chemotherapeutic agent in endometrial adenocarcinoma. Gynecol Oncol. 1981 Apr;11(2):140-61.
31. Swenerton KD, White GW, Boyes DA. Treatment of advanced endometrial carcinoma with tamoxifen. N Engl J Med. 1979 Jul 12;301(2):105.
32. Edmonson JH, Krook JE, Hilton JF, Long HJ, 3rd, Cullinan SA, Everson LK, et al. Ineffectiveness of tamoxifen in advanced endometrial carcinoma after failure of progestin treatment. Cancer Treat Rep. 1986 Aug;70(8):1019-20.
33. Slavik M, Petty WM, Blessing JA, Creasman WT, Homesley HD. Phase II clinical study of tamoxifen in advanced endometrial adenocarcinoma: a Gynecologic Oncology Group study. Cancer Treat Rep. 1984 May;68(5):809-11.
34. Thigpen T, Brady MF, Homesley HD, Soper JT, Bell J. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2001 Jan 15;19(2):364-7.
35. Fiorica JV, Brunetto VL, Hanjani P, Lentz SS, Mannel R, Andersen W. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004 Jan;92(1):10-4.
36. Whitney CW, Brunetto VL, Zaino RJ, Lentz SS, Sorosky J, Armstrong DK, et al. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004

Jan;92(1):4-9.

37. Gallagher CJ, Oliver RT, Oram DH, Fowler CG, Blake PR, Mantell BS, et al. A new treatment for endometrial cancer with gonadotrophin releasing-hormone analogue. Br J Obstet Gynaecol. 1991 Oct;98(10):1037-41.
38. Jeyarajah AR, Gallagher CJ, Blake PR, Oram DH, Dowsett M, Fisher C, et al. Long-term follow-up of gonadotrophin-releasing hormone analog treatment for recurrent endometrial cancer. Gynecol Oncol. 1996 Oct;63(1):47-52.
39. Lhomme C, Vennin P, Callet N, Lesimple T, Achard JL, Chauvergne J, et al. A multicenter phase II study with triptorelin (sustained-release LHRH agonist) in advanced or recurrent endometrial carcinoma: a French anticancer federation study. Gynecol Oncol. 1999 Nov;75(2):187-93.
40. Asbury RF, Brunetto VL, Lee RB, Reid G, Rocereto TF. Goserelin acetate as treatment for recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Am J Clin Oncol. 2002 Dec;25(6):557-60.
41. Covens A, Thomas G, Shaw P, Ackerman I, Osborne R, Lukka H, et al. A phase II study of leuprolide in advanced/recurrent endometrial cancer. Gynecol Oncol. 1997 Jan;64(1):126-9.
42. Rose PG, Brunetto VL, VanLe L, Bell J, Walker JL, Lee RB. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2000 Aug;78(2):212-6.
43. Ma BB, Oza A, Eisenhauer E, Stanimir G, Carey M, Chapman W, et al. The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers--a study of the National Cancer Institute of Canada Clinical Trials Group. Int J Gynecol Cancer. 2004 Jul-Aug;14(4):650-8.
44. Ball HG, Blessing JA, Lentz SS, Mutch DG. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1996 Aug;62(2):278-81.
45. Lissoni A, Zanetta G, Losa G, Gabriele A, Parma G, Mangioni C. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. Ann Oncol. 1996 Oct;7(8):861-3.
46. Ramondetta L, Burke TW, Levenback C, Bevers M, Bodurka-Bevers D, Gershenson DM. Treatment of uterine papillary serous carcinoma with paclitaxel. Gynecol Oncol. 2001 Jul;82(1):156-61.
47. Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2004 Jun 1;22(11):2159-66.
48. Dimopoulos MA, Papadimitriou CA, Georgoulias V, Moulopoulos LA, Aravantinos G, Gika D, et al. Paclitaxel and cisplatin in advanced or recurrent carcinoma of the endometrium: long-term results of a phase II multicenter study. Gynecol Oncol. 2000 Jul;78(1):52-7.
49. Lissoni A, Gabriele A, Gorga G, Tumolo S, Landoni F, Mangioni C, et al. Cisplatin-, epirubicin- and paclitaxel-containing chemotherapy in uterine adenocarcinoma. Ann Oncol. 1997 Oct;8(10):969-72.
50. Price FV, Edwards RP, Kelley JL, Kunschner AJ, Hart LA. A trial of outpatient paclitaxel and carboplatin for advanced, recurrent, and histologic high-risk endometrial carcinoma: preliminary report. Semin Oncol. 1997 Oct;24(5 Suppl 15):S15-78-S15-82.
51. Nakamura T, Onishi Y, Yamamoto F, Kouno S,

Maeda Y, Hatae M. [Evaluation of paclitaxel and carboplatin in patients with endometrial cancer]. Gan To Kagaku Ryoho. 2000 Feb;27(2):257-62.

52. Scudder SA, Liu PY, Wilczynski SP, Smith HO, Jiang C, Hallum AV, 3rd, et al. Paclitaxel and carboplatin with amifostine in advanced, recurrent, or refractory endometrial adenocarcinoma: a phase II study of the Southwest Oncology Group. Gynecol Oncol. 2005 Mar;96(3):610-5.
53. Seski JC, Edwards CL, Herson J, Rutledge FN. Cisplatin chemotherapy for disseminated endometrial cancer. Obstet Gynecol. 1982 Feb;59(2):225-8.
54. Edmonson JH, Krook JE, Hilton JF, Malkasian GD, Everson LK, Jefferies JA, 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 Sep;28(1):20-4.
55. Thigpen JT, Blessing JA, Homesley H, Creasman WT, Sutton G. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 1989 Apr;33(1):68-70.
56. Thigpen JT, Blessing JA, Lagasse LD, DiSaia PJ, Homesley HD. Phase II trial of cisplatin as second-line chemotherapy in patients with advanced or recurrent endometrial carcinoma. A Gynecologic Oncology Group study. Am J Clin Oncol. 1984 Jun;7(3):253-6.
57. Horton J, Begg CB, Arseneault J, Bruckner H, Creech R, Hahn RG. Comparison of adriamycin with cyclophosphamide in patients with advanced endometrial cancer. Cancer Treat Rep. 1978 Jan;62(1):159-61.
58. Horton J, Elson P, Gordon P, Hahn R, Creech R. Combination chemotherapy for advanced endometrial cancer. An evaluation of three regimens. Cancer. 1982 Jun 15;49(12):2441-5.
59. Long HJ, Pfeifle DM, Wieand HS, Krook JE, Edmonson JH, Buckner JC. Phase II evaluation of carboplatin in advanced endometrial carcinoma. J Natl Cancer Inst. 1988 Apr 20;80(4):276-8.
60. Van Wijk FH, Lhomme C, Bolis G, Scotto di Palumbo V, Tumolo S, Nooij M, et al. Phase II study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the EORTC Gynaecological Cancer Group. Eur J Cancer. 2003 Jan;39(1):78-85.
61. Burke TW, Heller PB, Woodward JE, Davidson SA, Hoskins WJ, Park RC. Treatment failure in endometrial carcinoma. Obstet Gynecol. 1990 Jan;75(1):96-101.
62. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol. 2003 May;89(2):201-9.
63. Bristow RE, Santillan A, Zahurak ML, Gardner GJ, Giuntoli RL, 2nd, Armstrong DK. Salvage cytoreductive surgery for recurrent endometrial cancer. Gynecol Oncol. 2006 Oct;103(1):281-7.
64. Barakat RR, Goldman NA, Patel DA, Venkatraman ES, Curtin JP. Pelvic exenteration for recurrent endometrial cancer. Gynecol Oncol. 1999 Oct;75(1):99-102.
65. Fleisch MC, Pantke P, Beckmann MW, Schnuerch HG, Ackermann R, Grimm MO, et al. Predictors for long-term survival after interdisciplinary salvage surgery for advanced or recurrent gynecologic cancers. J Surg Oncol. 2007 May 1;95(6):476-84.

66. Hockel M, Dornhofer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. Lancet Oncol. 2006 Oct;7(10):837-47.
67. Morley GW, Hopkins MP, Lindenauer SM, Roberts JA. Pelvic exenteration, University of Michigan: 100 patients at 5 years. Obstet Gynecol. 1989 Dec;74(6):934-43.
68. Numa F, Ogata H, Suminami Y, Tsunaga N, Nakamura Y, Tamura H, et al. Pelvic exenteration for the treatment of gynecological malignancies. Arch Gynecol Obstet. 1997;259(3):133-8.
69. Berek JS, Howe C, Lagasse LD, Hacker NF. Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA. Gynecol Oncol. 2005 Oct;99(1):153-9.
70. Morris M, Alvarez RD, Kinney WK, Wilson TO. Treatment of recurrent adenocarcinoma of the endometrium with pelvic exenteration. Gynecol Oncol. 1996 Feb;60(2):288-91.
71. Shepherd JH, Ngan HY, Neven P, Fryatt I, Woodhouse CR, Hendry WF. Multivariate analysis of factors affecting survival in pelvic exenteration. Int J Gynecol Cancer. 1994 Nov;4(6):361-70.
72. Jakowatz JG, Porudominsky D, Riihimaki DU, Kemeny M, Kokal WA, Braly PS, et al. Complications of pelvic exenteration. Arch Surg. 1985 Nov;120(11):1261-5.
73. Lopez MJ, Standiford SB, Skibba JL. Total pelvic exenteration. A 50-year experience at the Ellis Fischel Cancer Center. Arch Surg. 1994 Apr;129(4):390-5; discussion 5-6.
74. Gemignani ML, Alektiar KM, Leitao M, Mychalczak B, Chi D, Venkatraman E, et al. Radical surgical resection and high-dose intraoperative radiation therapy (HDR-IORT) in patients with recurrent gynecologic cancers. Int J Radiat Oncol Biol Phys. 2001 Jul 1;50(3):687-94.
75. Nag S, Yacoub S, Copeland LJ, Fowler JM. Interstitial brachytherapy for salvage treatment of vaginal recurrences in previously unirradiated endometrial cancer patients. Int J Radiat Oncol Biol Phys. 2002 Nov 15;54(4):1153-9.
76. Mandell LR, Nori D, Hilaris B. Recurrent stage I endometrial carcinoma: results of treatment and prognostic factors. Int J Radiat Oncol Biol Phys. 1985 Jun;11(6):1103-9.
77. Kalogiannidis I, Lambrechts S, Amant F, Neven P, E VANL, Vergote I. Role of lymphadenectomy and pelvic radiotherapy in patients with clinical FIGO stage I endometrial adenocarcinoma: An analysis of 208 patients. Int J Gynecol Cancer. 2006 Sep-Oct;16(5):1885-93.
78. Poulsen MG, Roberts SJ. The salvage of recurrent endometrial carcinoma in the vagina and pelvis. Int J Radiat Oncol Biol Phys. 1988 Oct;15(4):809-13.
79. Hoekstra CJ, Koper PC, van Putten WL. Recurrent endometrial adenocarcinoma after surgery alone: prognostic factors and treatment. Radiother Oncol. 1993 May;27(2):164-6.
80. Kuten A, Grigsby PW, Perez CA, Fineberg B, Garcia DM, Simpson JR. Results of radiotherapy in recurrent endometrial carcinoma: a retrospective analysis of 51 patients. Int J Radiat Oncol Biol Phys. 1989 Jul;17(1):29-34.
81. Monk BJ, Tewari KS, Puthawala AA, Syed AM, Haugen JA, Burger RA. Treatment of recurrent gynecologic malignancies with iodine-125 permanent interstitial irradiation. Int J Radiat Oncol Biol Phys. 2002 Mar 1;52(3):806-15.
82. Campagnutta E, Giorda G, De Piero G, Sopracordevole F, Visentin MC, Martella L, et al. Surgical treatment

of recurrent endometrial carcinoma. Cancer. 2004 Jan 1;100(1):89-96.

83. Awtrey CS, Cadungog MG, Leitao MM, Alektiar KM, Aghajanian C, Hummer AJ, et al. Surgical resection of recurrent endometrial carcinoma. Gynecol Oncol. 2006 Sep;102(3):480-8.
84. Scarabelli C, Campagnutta E, Giorda G, DePiero G, Sopracordevole F, Quaranta M, et al. Maximal cytoreductive surgery as a reasonable therapeutic alternative for recurrent endometrial carcinoma. Gynecol Oncol. 1998 Jul;70(1):90-3.
85. Hockel M. Ultra-radical compartmentalized surgery in gynaecological oncology. Eur J Surg Oncol. 2006 Oct;32(8):859-65.
86. Hockel M, Sclenger K, Hamm H, Knapstein PG, Hohenfellner R, Rosler HP. Five-year experience with combined operative and radiotherapeutic treatment of recurrent gynecologic tumors infiltrating the pelvic wall. Cancer. 1996 May 1;77(9):1918-33.
87. Dowdy SC, Mariani A, Cliby WA, Haddock MG, Petersen IA, Sim FH, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: technique and analysis of outcomes. Gynecol Oncol. 2006 May;101(2):280-6.
88. Helm CW, Toler CR, Martin RS, 3rd, Gordinier ME, Parker LP, Metzinger DS, et al. Cytoreduction and intraperitoneal heated chemotherapy for the treatment of endometrial carcinoma recurrent within the peritoneal cavity. Int J Gynecol Cancer. 2007 Jan-Feb;17(1):204-9.
89. Aalders JG, Abeler V, Kolstad P. Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. Gynecol Oncol. 1984 Jan;17(1):85-103.
90. Crespo C, Gonzalez-Martin A, Lastra E, Garcia-Lopez J, Moyano A. Metastatic endometrial cancer in lung and liver: complete and prolonged response to hormonal therapy with progestins. Gynecol Oncol. 1999 Feb;72(2):250-5.
91. Dowdy SC, Mariani A, Bakkum JN, Cliby WA, Keeney GL, Podratz KC. Treatment of pulmonary recurrences in patients with endometrial cancer. Gynecol Oncol. 2007 Nov;107(2):242-7.
92. Hamy A, Letessier E, Guillard Y, Paineau J, Visset J. Splenectomy for isolated splenic metastasis from endometrial carcinoma. Acta Obstet Gynecol Scand. 1995 Oct;74(9):745-6.
93. Temkin SM, Hellman M, Lee YC, Abulafia O. Surgical resection of vulvar metastases of endometrial cancer: a presentation of two cases. J Low Genit Tract Dis. 2007 Apr;11(2):118-21.
94. Bindal RK, Sawaya R, Leavens ME, Lee JJ. Surgical treatment of multiple brain metastases. J Neurosurg. 1993 Aug;79(2):210-6.
95. Tangjitgamol S, Levenback CF, Beller U, Kavanagh JJ. Role of surgical resection for lung, liver, and central nervous system metastases in patients with gynecological cancer: a literature review. Int J Gynecol Cancer. 2004 May-Jun;14(3):399-422.
96. Southcott BM. Carcinoma of the endometrium. Drugs. 2001;61(10):1395-405.
97. Mutic S, Malyapa RS, Grigsby PW, Dehdashti F, Miller TR, Zoberi I, et al. PET-guided IMRT for cervical carcinoma with positive para-aortic lymph nodes-a dose-escalation treatment planning study. Int J Radiat Oncol Biol Phys. 2003 Jan 1;55(1):28-35.
98. Esthappan J, Mutic S, Malyapa RS, Grigsby PW, Zoberi I, Dehdashti F, et al. Treatment planning guidelines regarding the use of CT/PET-guided IMRT for cervical carcinoma with positive paraaortic lymph nodes. Int J Radiat Oncol Biol Phys. 2004 Mar 15;58(4):1289-97.

99. Sneed PK, Lamborn KR, Forstner JM, McDermott MW, Chang S, Park E, et al. Radiosurgery for brain metastases: is whole brain radiotherapy necessary? Int J Radiat Oncol Biol Phys. 1999 Feb 1;43(3):549-58.
100. Shiohara S, Ohara M, Itoh K, Shiozawa T, Konishi I. Successful treatment with stereotactic radiosurgery for brain metastases of endometrial carcinoma: a case report and review of the literature. Int J Gynecol Cancer. 2003 Jan-Feb;13(1):71-6.

Chapter 6

General discussion

Endometrial cancer has come a long way in the last 20 years. It used to be known as the 'Cinderella' of gynecological cancer because surgery was generally viewed as straightforward, adjuvant radiation was frequently used and survival rates were in general high. Recently, new insights from clinical trials have intensified the use of radiotherapy based on prognostic factors in high risk, low stage patients and have focused more on chemotherapy regimens. The new challenge is to focus on patients with advanced and recurrent disease. The aim of this thesis is to investigate the treatment of these groups of patients. In this chapter, notable clinical features of patients with advanced or recurrent endometrial cancer are discussed, special attention is given to clinical trials, treatment recommendations are considered and implications for future research are proposed.

Clinical features

Positive peritoneal cytology is incorporated in the current FIGO staging system of endometrial cancer. The purpose of taking peritoneal washings is to identify microscopic disease and peritoneal cytology is assumed to add information on occult peritoneal disease. Results from a questionnaire based on clinical practice among leading gynecological oncology centers reported that peritoneal cytology is not considered to be of any value either for prognosis or for treatment planning in 14% of the cases in the United States and in 20% of the cases in Western Europe in which peritoneal cytology is examined (1, 2). SGO members reported that patients with stage IIIA based on positive peritoneal cytology only, are less likely to be offered adjuvant therapy than those with stage IIIA who had serosal and/or adnexal involvement (3). However, in our series reported in Chapter 2, we show similar survival rates and recurrence rates in the subgroup of patients with stage IIIA disease based on positive peritoneal cytology only as in patients with stage IIIA disease based on other factors. Although our study only included a limited number of patients with stage IIIA based on peritoneal cytology only, positive peritoneal cytology seemed an important prognostic factor in our patients. Literature is not conclusive as different prognostic values of positive peritoneal cytology in endometrial cancer are reported (4-9). Since the true prognostic value of positive peritoneal cytology is unclear, we remain aware that advanced endometrial cancer based on positive peritoneal cytology only probably does not act as local disease. Patients with stage IIIA based on positive peritoneal cytology only may benefit from systemic treatment, and such treatment should be studied in this patient population.

A worrying fact is that in the evaluation of a patient with suspected endometrial cancer, invasive diagnostic procedures such as hysteroscopy or saline infused sonography may facilitate the dissemination of malignant cells through the fallopian tubes into the abdominal cavity by distension of the uterine cavity with fluid media (10-19). However, there have not been any long-term studies to demonstrate or rule out that this observed dissemination has an effect on long-term survival. To investigate the attributive effect of these diagnostic

procedures, prospective randomized trials (e.g. comparing endometrial biopsy versus hysteroscopy/curettage) with substantial numbers of patients are needed; obviously the ethical concerns of such trials should be taken into consideration.

Optimal surgical cytoreduction has a beneficial effect on the survival rate of ovarian cancer patients (20-22). Due to an analogous pattern of dissemination in endometrial cancer patients, optimal cytoreductive surgery might also be important in this population. In Chapter 2, we define optimal surgical cytoreduction as macroscopic complete removal of the tumor and describe the effect on survival of this procedure in our patient population with advanced endometrial cancer. We show that survival is improved if optimal surgical cytoreduction is achievable. Although different definitions of optimal surgical cytoreduction are used in literature, all studies report advantages of surgical cytoreduction on survival in patients with advanced endometrial cancer (23-28). Optimal surgical cytoreduction turned out to be the cornerstone of treatment in patients with advanced endometrial cancer. Cytoreductive surgery also has a beneficial effect on survival rates in patients with recurrent endometrial cancer (29-32). The outcome is most favorable in patients with an isolated vaginal recurrence, without retroperitoneal tumor or disease extension to the pelvic sidewall, who are able to undergo complete resection. Nevertheless, appropriate surgical indications and selection criteria for cytoreductive surgery in recurrent disease have not yet been defined.

In The Netherlands it is standard practice to offer patients post-treatment surveillance after treatment for cancer. The primary goal of this surveillance strategy is to facilitate the early detection of recurrent disease with the overall aim to improve survival, or decrease morbidity secondary to the recurrence. In addition, regular follow up aims to give psychological support and information as well as to identify and treat complications. In The Netherlands a regular follow up program is offered on an individual basis and focuses on complaints and physical examination of the patient, without routine laboratory or imaging tests (www.oncoline.nl). The specific surveillance guidelines recommended by the National Comprehensive Cancer Network (NCCN) include a much more intensive program (www.nccn.org): physical examination every three to six months for two years, then annually; vaginal cytology every six months for two years, then annually; measurement of serum CA-125 at each visit in patients whose initial level was elevated. However, there is no evidence from controlled clinical trials that any surveillance strategy in endometrial cancer patients is associated with an improved outcome. On the other hand, evidence is needed before considering changing the standard practice of routine follow-up in endometrial cancer. The issues associated with surveillance after treatment for cancer are: how intensively and for how long surveillance should be performed, which tests are appropriate, which patients should be followed and who should perform the follow-up.

In our series, as reported in Chapter 3, most recurrences were diagnosed within the first three years after primary treatment. This is in accordance with the literature reporting 68-100% of endometrial cancer recurrences occurring within the first three years after primary treatment (33), which supports the view that a follow-up program in the first three years after primary treatment of endometrial cancer is most useful in detecting recurrent disease. In literature, about 70% of recurrences are associated with symptoms (33) and this percentage is higher compared to our patient population, where 53% of the patients had an interval detected recurrence. These patients had a lower 5-year survival rate compared to those with a screen-detected recurrence (respectively 47% versus 62%, not significant). However, one must bear in mind that in our retrospective series, selection bias probably also influenced the results and that the number of patients is limited. Another shortcoming is the fact that the follow-up programs used are varied, due to patients being followed up in different regional hospitals. The follow-up schedules of other studies ranged from 8 to 15 visits, in general during a 5-year follow-up period (33).

Clinical follow-up generally focuses on signs or symptoms suggestive of recurrence: vaginal bleeding, abdominal or pelvic pain, persistent cough or unexplained weight loss. Most vaginal recurrences are symptomatic and can be visualized. Histological verification of the suspected lesions is needed to confirm diagnosis. Asymptomatic disease has been detected in a variety of ways. In a review of follow-up studies of endometrial cancer patients asymptomatic recurrences were detected by the following modalities: physical examination (5-33%), vaginal vault cytology (0-4%), chest x-ray (0-14%), abdominal ultrasound (4-13%) CT-scan (5-21%) and CA 125 (15% in selected patients in one study). There was no evidence to support the view that intensive follow-up schemes result in a survival benefit over non-intensive follow-up schedules in endometrial cancer patients (33). This supports the performance of physical examination during routine follow-up, whilst the cost-effectiveness of laboratory and imaging tests is questionable (34-36).

Approximately 40% of recurrent endometrial cancer occurs locally (vaginal vault, pelvis) and 60% occurs at distant sites (33). Of all recurrences, vaginal recurrences are particularly important to diagnose as these are mainly curable in radiotherapy-naïve patients. Radiotherapy is effective in these patients with an 89% complete response rate and a 5-year survival rate of 65%. In contrast, previously irradiated patients with a vaginal relapse showed a 5-year survival rate of 43% (37). A major determinant of local control is tumor size at the time of relapse (38-40). The largest report, of 58 radiotherapy-naïve patients with loco-regional recurrent disease, shows that 5-year local control rates were significantly higher for tumors 2 cm compared to larger ones (80% versus 54%) (39). If site (i.e. local disease) and extent of recurrence are prognostic for outcome, would this suggest a need for follow-up for those patients treated with surgery alone?

In breast cancer patients there is evidence that follow-up strategies performed by general

practitioners were comparable in effectiveness to those delivered by hospital-based specialists in terms of quality of life and time to detection of distant metastases (41). For endometrial cancer, it has also been suggested that after three to five recurrence free years, follow-up can be provided by the patient's general practitioner (33). Arguments for this strategy in endometrial cancer are that the risk of recurrence after three to five years is low and that oncologists can then focus on newly diagnosed patients and thereby shorten waiting lists. Improving patient education so that early symptoms of recurrence are reported appears extremely sensible, given a 70% symptomatic recurrence rate in literature, but on the other hand it may serve also to heighten anxiety amongst the majority who will never develop recurrent disease (42).

In conclusion, based on the results from our study and other retrospective studies, a reasonable surveillance strategy for endometrial cancer patients includes physical examination (without routine laboratory and imaging tests) in asymptomatic patients, targeted examination in symptomatic patients and counseling about the symptoms of recurrent disease and focus on any potential adverse effects of prior therapy. The choice of follow-up intervals could be decided by the individual patient's preference and their risk of developing potential curable recurrent disease and could be offered during three to five years by a specialist.

Clinical trials

In other gynecological cancers, cisplatin and carboplatin have equal therapeutic activity, but carboplatin is less toxic. The high risk population of endometrial cancer patients, often old and in poor clinical condition with co-morbidity, necessitates chemotherapy regimens with low toxicity. Therefore, carboplatin is tested in this patient population and this study is described in Chapter 4.1. As expected, toxicity levels were acceptable. It consisted mainly of grade 3 hematological toxicity among the radiotherapy pre-treated patients. The toxicity level was not higher among the chemotherapy pre-treated patients, due to the absence of impact of the dose or due to the initial dose reduction in this study. The overall response rate in our study of 17% is lower compared to the overall response rates in other studies (28%, 30% and 33% respectively) (43-45). The main difference in patient population among these studies is the difference in prior treatment. No patients received prior chemotherapy in the other studies, compared to 30% of the evaluable patients in our study. None of our chemotherapy pre-treated patients showed any response, and this might be a reliable explanation for the difference in overall response rates (response rate of first line chemotherapy in evaluable patients was 24%). The percentage of patients who received prior hormonal therapy is comparable with the other studies, except for a higher percentage in one study (43-45). Horton demonstrated that responding or failing to prior progestagen therapy had a significant influence on the outcome of subsequent chemotherapy trials, the influence being worse in patients who failed to respond to progestagen (46, 47). This appeared also to be true in our

population of 11 patients who did not respond to prior treatment (possibly due to tumor characteristics) and amongst whom no effects of carboplatin were observed.

Long term response to carboplatin is reported in both our study and one other report (up to 814+ days and 5303 days respectively) (44). Pending the demonstration of agents capable of inducing more prolonged responses, the simplicity of outpatient treatment and limited toxicity makes carboplatin a good choice for first line therapy, allowing a better quality of life.

To increase the efficacy, active chemotherapeutic agents against endometrial cancer have been combined. In Chapter 4.2, we evaluated whether the combination of cisplatin and doxorubicin yields better response rates and leads to a survival advantage in patients with endometrial cancer as compared to single agent doxorubicin. A total of 177 chemotherapy naïve patients were entered into the trial. The combination was more toxic than the single agent treatment, with observed toxicity being mainly primarily hematological and gastro-intestinal. A significantly higher response rate was provided by the combination compared to the single agent (43% and 17% respectively). Interestingly, in the patient population of endometrial cancer patients (with known high co-morbidity) performance status was statistically significant as a prognostic factor for survival. Both patients with advanced and recurrent disease were included in our trial. We did not show any difference in response rate among primary advanced and recurrent disease, in contrast to another trial which showed that the combination chemotherapy did not appear to be effective in the treatment of recurrent endometrial cancer, due to the fact that all of these recurrences were at least partially within the surgical and irradiated field (48).

As noticed in the study and trial reported in Chapters 4.1 and 4.2, a drawback of systemic therapy literature is the considerable heterogeneity in the patient populations. First of all, most studies and randomized trials were designed to include both patients with advanced and recurrent disease in order to ensure adequate sample sizes to detect treatment related differences. Another factor contributing to the heterogeneity is the fact that patients with different histopathological types representing variable prognosis are included simultaneously. Furthermore, prior treatment such as radiotherapy and chemotherapy differs among the populations yet these patients have been included in the same studies and trials. These differences of patient populations, included in the studies and trials that comprise the systemic treatments, make them difficult to interpret. For that reason, pooling of data for statistical analysis was not deemed appropriate by systematic reviews (49-52).

In future trials stratification or, better still, separate trials are needed with respect to disease status (advanced versus recurrent disease), histopathological type (endometrioid carcinoma versus non-endometrioid carcinoma), type of previous treatment (radiotherapy or

systemic treatment), and consequently the type of systemic treatment with response outcome to this treatment, site of advanced or recurrent disease (i.e. recurrent disease in or out irradiated field).

In developing new treatment regimens, it is important to consider that the population of endometrial cancer patients has extensive co-morbidity. Patients are often old, in poor general condition, obese and being treated for diabetes mellitus and hypertension. Therefore, it is necessary to have low toxic chemotherapy regimens. As shown in earlier studies and also in Chapter 4.1, carboplatin is less nephrotoxic, less neurotoxic and induces less gastrointestinal toxicity allowing a better quality of life when compared to cisplatin. This makes the drug a good candidate in combination therapy in endometrial cancer. Paclitaxel has proven to be the most active single agent in endometrial cancer, with reported response rates between 36-77% (53-55). Given the favorable results of the combination therapy of paclitaxel and carboplatin in ovarian cancer trials (56, 57), endometrial cancer studies have also evaluated this combination, with high response rates (40-73%) in phase II studies, low toxicity and advantage of outpatient therapy (58-62). Although evidence from randomized clinical trials is lacking, the combination of paclitaxel carboplatin has become first choice for patients with endometrial cancer in clinical practice nowadays. Currently, in ongoing randomized clinical trials, the standard arm is treatment with paclitaxel carboplatin. It might still be important to prove its place in the treatment of endometrial cancer patients in an observational study.

Treatment recommendations

The primary aim of treatment of patients with advanced and recurrent endometrial cancer is to cure and to prolong survival. However, some patients present with incurable tumors, and for these patients treatment should have palliative intention rather than curative. The team is faced with the challenge of achieving the best possible quality of life by relieving suffering, controlling symptoms and restoring functional capacity. In general, the patient population of advanced and recurrent endometrial cancer patients is a challenge in itself; most patients have significant cardiac or pulmonary co-morbidity and are of advanced age. Nevertheless, advanced age is not a contra-indication for treatment.

Hitherto, treatment of patients with advanced and recurrent endometrial cancer has been mostly individualized. After having evaluated the literature, we propose a management schedule for patients with advanced and recurrent endometrial cancer in Chapters 5.1 and 5.2. The recommended treatment approach is given and alternatives are discussed per stage of advanced disease, and per site of recurrent disease.

The patterns of dissemination of the primary tumor are important for defining optimal cancer treatment. It is assumed that dissemination of endometrial cancer takes place in

different ways: lymphatic, intra-abdominal and hematogenic. Compared to cervical cancer, the lymphatic drainage of the uterine corpus is much more complex, having a bipartite and bilateral drainage system. The lower uterine segment drains to the pelvic lymph nodes via the broad ligaments and the upper segment of the corpus drains into the para-aortic lymph nodes via the ovarian lymphatics (63). The treatment of choice for local control is radiotherapy. Endometrial cancer also disseminates intra-abdominal and hematogenic; to treat the intra-abdominal spread, surgical cytoreduction is important and systemic therapy is used in the treatment of endometrial cancer aimed at more distant control. As complete cytoreductive surgery shows a beneficial effect on survival in patients with advanced endometrial cancer, future studies should be initiated to evaluate the effect on survival of treatment with neo-adjuvant or induction chemotherapy followed by intervaldebulking in patients with advanced endometrial cancer, as compared to ovarian cancer patients (22).

A logical step in the treatment of advanced endometrial cancer is combining the therapy for local, intra-abdominal and distant control. The combined use of adjuvant chemotherapy and radiotherapy showed promising results, even with agents considered less superior than the current standard combination of paclitaxel carboplatin (64). Combined treatment with chemotherapy and radiotherapy is being investigated further in different regimens and patient populations. Studies defining the optimal therapy for high-risk endometrial cancer patients can also be of importance to pure advanced stage patients by better understanding of the disease. However, per stage and presentation of disease, a specific treatment approach should be applied.

Treatment recommendations for patients with stage IIIB endometrial cancer are discussed in more detail below. The FIGO has recommended treating these patients by pelvic irradiation followed by exploratory laparotomy if the disease seems to be resectable (65). It is remarkable that this recommendation is not supported by any clinical evidence. Moreover, this recommendation is not reasonable as this stage of disease is diagnosed in most cases postoperatively. Therefore, in clinical practice, the treatment of choice should be a standard surgical staging procedure and postoperative external radiotherapy and brachytherapy, with or without chemotherapy.

Future directions

Interesting fields of research are represented by investigational agents directed against specific intracellular signal transduction pathways involved in the proliferation, invasiveness and metastatic spread of endometrial cancer. In particular, mTOR inhibitors could represent a promising therapeutic option for endometrioid type carcinomas that are often characterized by loss of PTEN function.

Because of the need to improve chemotherapy for advanced and recurrent disease, there is now need for phase II studies to explore new combinations and phase III trials to compare such regimens with standard arms. Such trials are challenging because of the relatively small incidence of such tumors and limited life-expectancy. Inter-group trials involving international collaboration and incorporating translational elements are undoubtedly the way forward (66). Enrollment of patients with endometrial carcinoma on clinical trials, when available, must remain a priority so we can provide better informed recommendations to our future patients. Even if inclusion in a clinical trial is not possible, it is nevertheless important to collect the patient information because by doing so we can learn from our own experience and thus enhance treatment of future patients. To achieve this goal, and bearing in mind the relatively small incidence of advanced and recurrent disease, it might be appropriate to put our efforts into designing a national database of patients' characteristics, histopathology and treatment details. To create a successful national database, support from a multidisciplinary committee such as the Dutch Society of Gynecologic Oncology (Werkgroep Oncologische Gynaecologie) is essential.

In the light of the debate on the role of pelvic and para-aortic lymphadenectomy or lymph node sampling in endometrial cancer (66, 67), alternatives to identifying positive lymph nodes are currently being investigated. As in breast cancer and cutaneous malignant melanoma, and the gynaecological cancers of the vulva and more recently the cervix, the sentinel node concept is also being investigated in endometrial cancer (68). In endometrial cancer the sentinel node method seems difficult due to the complex lymphatic drainage, as well as the difficultly in injecting radioactive tracer preoperatively (63). Further studies should explore the feasibility and define clinical value in endometrial cancer patients. Perhaps, in the future, other alternative methods as positron emission tomography coupled with MRI/CT might be of help in identifying positive lymph nodes in patients who do not undergo routine lymphadenectomy (69).

Advances in treatment of recurrent endometrial cancer are expected with radiotherapy administered as stereotactic treatment. Inaccessible or multiple lesions can be treated by stereotactic radiotherapy with less damage to the surrounding tissue. Indications could be para-aortic lymph node metastases, analogue to patients with cervical cancer (70, 71) or brain metastases (72). Future research is needed to work out indications for stereotactic radiotherapy as well as when and how to combine this therapy with other treatment modalities in patients with endometrial cancer.

Conclusions

The main conclusions to be drawn from the studies described in this thesis are as

follows: since the true prognostic value of positive peritoneal cytology is still unclear, we remain aware that advanced endometrial cancer based on positive peritoneal cytology alone probably does not act as local disease. Future studies should be initiated to define the optimal treatment for these patients. Optimal surgical cytoreduction is advantageous for patients with advanced endometrial cancer and probably also for patients with recurrent disease; this treatment should be evaluated in combination with other treatment modalities. There is no evidence that any surveillance strategy in endometrial cancer patients is associated with improved outcome. The choice of follow-up intervals could be decided by an individual patient's preference and risk of developing potential curable recurrent disease (i.e. vaginal recurrence in radiotherapy naïve patients) during a three to five year (maximum) period. Systemic therapy with favorable toxicity profiles are needed in the patients' population of advanced and recurrent disease and should be evaluated in combinations with other treatment modalities. Nowadays, treatment for patients with advanced and recurrent endometrial cancer should not be individualized, but should be applied according to the stage of advanced disease and site of recurrent disease.

References

1. Maggino T, Romagnolo C, Landoni F, Sartori E, Zola P, Gadducci A. An analysis of approaches to the management of endometrial cancer in North America: a CTF study. Gynecol Oncol. 1998 Mar;68(3):274-9.
2. Maggino T, Romagnolo C, Zola P, Sartori E, Landoni F, Gadducci A. An analysis of approaches to the treatment of endometrial cancer in western Europe: a CTF study. Eur J Cancer. 1995 Nov;31A(12):1993-7.
3. Lee CM, Slomovitz BM, Greer M, Sharma S, Gregurich MA, Burke T, et al. Practice patterns of SGO members for stage IIIA endometrial cancer. Gynecol Oncol. 2005 Jul;98(1):77-83.
4. Schorge JO, Molpus KL, Goodman A, Nikrui N, Fuller AF, Jr. The effect of postsurgical therapy on stage III endometrial carcinoma. Gynecol Oncol. 1996 Oct;63(1):34-9.
5. Aoki Y, Kase H, Watanabe M, Sato T, Kurata H, Tanaka K. Stage III endometrial cancer: analysis of prognostic factors and failure patterns after adjuvant chemotherapy. Gynecol Oncol. 2001 Oct;83(1):1-5.
6. Hirai Y, Takeshima N, Kato T, Hasumi K. Malignant potential of positive peritoneal cytology in endometrial cancer. Obstet Gynecol. 2001 May;97(5 Pt 1):725-8.
7. Zuna RE, Behrens A. Peritoneal washing cytology in gynecologic cancers: long-term follow-up of 355 patients. J Natl Cancer Inst. 1996 Jul 17;88(14):980-7.
8. Kashimura M, Sugihara K, Toki N, Matsuura Y, Kawagoe T, Kamura T, et al. The significance of peritoneal cytology in uterine cervix and endometrial cancer. Gynecol Oncol. 1997 Dec;67(3):285-90.
9. Obermair A, Geramou M, Tripcony L, Nicklin JL, Perrin L, Crandon AJ. Peritoneal cytology: impact on disease-free survival in clinical stage I endometrioid adenocarcinoma of the uterus. Cancer Lett. 2001 Mar 10;164(1):105-10.
10. Revel A, Tsafrir A, Anteby SO, Shushan A. Does hysteroscopy produce intraperitoneal spread of endometrial cancer cells? Obstet Gynecol Surv. 2004 Apr;59(4):280-4.
11. Selvaggi L, Cormio G, Ceci O, Loverro G, Cazzolla A, Bettocchi S. Hysteroscopy does not increase the risk of microscopic extrauterine spread in endometrial carcinoma. Int J Gynecol Cancer. 2003 Mar-Apr;13(2):223-7.
12. Gucer F, Sayin C, Tamussino K. Association between initial diagnostic procedure and hysteroscopy and abnormal peritoneal washing in patients with endometrial carcinoma. Cancer. 2002 Apr 25;96(2):123-4.
13. Kudela M, Pilka R. Is there a real risk in patients with endometrial carcinoma undergoing diagnostic hysteroscopy (HSC)? Eur J Gynaecol Oncol. 2001;22(5):342-4.
14. Biewenga P, de Blok S, Birnie E. Does diagnostic hysteroscopy in patients with stage I endometrial carcinoma cause positive peritoneal washings? Gynecol Oncol. 2004 Apr;93(1):194-8.
15. Kuzel D, Toth D, Kobilkova J, Dohnalova A. Peritoneal washing cytology on fluid hysteroscopy and after curettage in women with endometrial carcinoma. Acta Cytol. 2001 Nov-Dec;45(6):931-5.
16. Obermair A, Geramou M, Gucer F, Denison U, Graf AH, Kapshammer E, et al. Impact of hysteroscopy on disease-free survival in clinically stage I endometrial cancer patients. Int J Gynecol Cancer. 2000 Jul;10(4):275-9.
17. Zerbe MJ, Zhang J, Bristow RE, Grumbine FC, Abularach S, Montz FJ. Retrograde seeding of malignant cells during hysteroscopy in presumed

early endometrial cancer. Gynecol Oncol. 2000 Oct;79(1):55-8.

18. Takac I, Zegura B. Office hysteroscopy and the risk of microscopic extrauterine spread in endometrial cancer. Gynecol Oncol. 2007 Jul 2.
19. Alcazar JL, Errasti T, Zornoza A. Saline infusion sonohysterography in endometrial cancer: assessment of malignant cells dissemination risk. Acta Obstet Gynecol Scand. 2000 Apr;79(4):321-2.
20. Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM. Primary cytoreductive surgery for epithelial ovarian cancer. Obstet Gynecol. 1983 Apr;61(4):413-20.
21. Hacker NF, van der Burg ME. Advanced ovarian cancer. Debulking and intervention surgery. Ann Oncol. 1993;4 Suppl 4:17-22.
22. van der Burg ME, Vergote I. The role of interval debulking surgery in ovarian cancer. Curr Oncol Rep. 2003 Nov;5(6):473-81.
23. Aalders JG, Abeler V, Kolstad P. Clinical (stage III) as compared to subclinical intrapelvic extrauterine tumor spread in endometrial carcinoma: a clinical and histopathological study of 175 patients. Gynecol Oncol. 1984 Jan;17(1):64-74.
24. Greven KM, Curran WJ, Jr., Whittington R, Fanning J, Randall ME, Wilder J, et al. Analysis of failure patterns in stage III endometrial carcinoma and therapeutic implications. Int J Radiat Oncol Biol Phys. 1989 Jul;17(1):35-9.
25. Goff BA, Goodman A, Muntz HG, Fuller AF, Jr., Nikrui N, Rice LW. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol. 1994 Feb;52(2):237-40.
26. Chi DS, Welshinger M, Venkatraman ES, Barakat RR. The role of surgical cytoreduction in Stage IV endometrial carcinoma. Gynecol Oncol. 1997 Oct;67(1):56-60.
27. Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol. 2000 Aug;78(2):85-91.
28. Ayhan A, Taskiran C, Celik C, Yuce K, Kucukali T. The influence of cytoreductive surgery on survival and morbidity in stage IVB endometrial cancer. Int J Gynecol Cancer. 2002 Sep-Oct;12(5):448-53.
29. Campagnutta E, Giorda G, De Piero G, Sopracordevole F, Visentin MC, Martella L, et al. Surgical treatment of recurrent endometrial carcinoma. Cancer. 2004 Jan 1;100(1):89-96.
30. Awtrey CS, Cadungog MG, Leitao MM, Alektiar KM, Aghajanian C, Hummer AJ, et al. Surgical resection of recurrent endometrial carcinoma. Gynecol Oncol. 2006 Sep;102(3):480-8.
31. Bristow RE, Santillan A, Zahurak ML, Gardner GJ, Giuntoli RL, 2nd, Armstrong DK. Salvage cytoreductive surgery for recurrent endometrial cancer. Gynecol Oncol. 2006 Oct;103(1):281-7.
32. Scarabelli C, Campagnutta E, Giorda G, DePiero G, Sopracordevole F, Quaranta M, et al. Maximal cytoreductive surgery as a reasonable therapeutic alternative for recurrent endometrial carcinoma. Gynecol Oncol. 1998 Jul;70(1):90-3.
33. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006 Jun;101(3):520-9.
34. Cooper AL, Dornfeld-Finke JM, Banks HW, Davey DD, Modesitt SC. Is cytologic screening an effective surveillance method for detection of vaginal recurrence of uterine cancer? Obstet Gynecol. 2006 Jan;107(1):71-6.
35. Berchuck A, Anspach C, Evans AC, Soper JT,

Rodriguez GC, Dodge R, et al. Postsurgical surveillance of patients with FIGO stage I/II endometrial adenocarcinoma. Gynecol Oncol. 1995 Oct;59(1):20-4.

36. Bristow RE, Purinton SC, Santillan A, Diaz-Montes TP, Gardner GJ, Giuntoli RL, 2nd. Cost-effectiveness of routine vaginal cytology for endometrial cancer surveillance. Gynecol Oncol. 2006 Nov;103(2):709-13.
37. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol. 2003 May;89(2):201-9.
38. Curran WJ, Jr., Whittington R, Peters AJ, Fanning J. Vaginal recurrences of endometrial carcinoma: the prognostic value of staging by a primary vaginal carcinoma system. Int J Radiat Oncol Biol Phys. 1988 Oct;15(4):803-8.
39. Wylie J, Irwin C, Pintilie M, Levin W, Manchul L, Milosevic M, et al. Results of radical radiotherapy for recurrent endometrial cancer. Gynecol Oncol. 2000 Apr;77(1):66-72.
40. Hoekstra CJ, Koper PC, van Putten WL. Recurrent endometrial adenocarcinoma after surgery alone: prognostic factors and treatment. Radiother Oncol. 1993 May;27(2):164-6.
41. Grunfeld E, Mant D, Yudkin P, Adewuyi-Dalton R, Cole D, Stewart J, et al. Routine follow up of breast cancer in primary care: randomised trial. Bmj. 1996 Sep 14;313(7058):665-9.
42. Owen P, Duncan ID. Is there any value in the long term follow up of women treated for endometrial cancer? Br J Obstet Gynaecol. 1996 Jul;103(7):710-3.
43. Long HJ, Pfeifle DM, Wieand HS, Krook JE, Edmonson JH, Buckner JC. Phase II evaluation of carboplatin in advanced endometrial carcinoma. J Natl Cancer Inst. 1988 Apr 20;80(4):276-8.
44. Green JB, 3rd, Green S, Alberts DS, O'Toole R, Surwit EA, Noltimier JW. Carboplatin therapy in advanced endometrial cancer. Obstet Gynecol. 1990 Apr;75(4):696-700.
45. Burke TW, Munkarah A, Kavanagh JJ, Morris M, Levenback C, Tornos C, et al. Treatment of advanced or recurrent endometrial carcinoma with single-agent carboplatin. Gynecol Oncol. 1993 Dec;51(3):397-400.
46. Horton J, Begg CB, Arseneault J, Bruckner H, Creech R, Hahn RG. Comparison of adriamycin with cyclophosphamide in patients with advanced endometrial cancer. Cancer Treat Rep. 1978 Jan;62(1):159-61.
47. Horton J, Elson P, Gordon P, Hahn R, Creech R. Combination chemotherapy for advanced endometrial cancer. An evaluation of three regimens. Cancer. 1982 Jun 15;49(12):2441-5.
48. Seltzer V, Vogl SE, Kaplan BH. Adriamycin and cis-diamminedichloroplatinum in the treatment of metastatic endometrial adenocarcinoma. Gynecol Oncol. 1984 Nov;19(3):308-13.
49. Humber C, Tierney J, Symonds R, Collingwood M, Kirwan J, Williams C, et al. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Ann Oncol. 2007 Mar;18(3):409-20.
50. Carey MS, Gawlik C, Fung-Kee-Fung M, Chambers A, Oliver T. Systematic review of systemic therapy for advanced or recurrent endometrial cancer. Gynecol Oncol. 2006 Apr;101(1):158-67.
51. Pectasides D, Pectasides E, Economopoulos T. Systemic therapy in metastatic or recurrent endometrial cancer. Cancer Treat Rev. 2007 Apr;33(2):177-90.

52. Fleming GF. Systemic chemotherapy for uterine carcinoma: metastatic and adjuvant. J Clin Oncol. 2007 Jul 10;25(20):2983-90.
53. Ball HG, Blessing JA, Lentz SS, Mutch DG. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1996 Aug;62(2):278-81.
54. Lissoni A, Zanetta G, Losa G, Gabriele A, Parma G, Mangioni C. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. Ann Oncol. 1996 Oct;7(8):861-3.
55. Ramondetta L, Burke TW, Levenback C, Bevers M, Bodurka-Bevers D, Gershenson DM. Treatment of uterine papillary serous carcinoma with paclitaxel. Gynecol Oncol. 2001 Jul;82(1):156-61.
56. du Bois A, Weber B, Rochon J, Meier W, Goupil A, Olbricht S, et al. Addition of epirubicin as a third drug to carboplatin-paclitaxel in first-line treatment of advanced ovarian cancer: a prospectively randomized gynecologic cancer intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. J Clin Oncol. 2006 Mar 1;24(7):1127-35.
57. Kristensen GB, Vergote I, Stuart G, Del Campo JM, Kaern J, Lopez AB, et al. First-line treatment of ovarian cancer FIGO stages IIb-IV with paclitaxel/epirubicin/carboplatin versus paclitaxel/carboplatin. Int J Gynecol Cancer. 2003 Nov-Dec;13 Suppl 2:172-7.
58. Dimopoulos MA, Papadimitriou CA, Georgoulias V, Moulopoulos LA, Aravantinos G, Gika D, et al. Paclitaxel and cisplatin in advanced or recurrent carcinoma of the endometrium: long-term results of a phase II multicenter study. Gynecol Oncol. 2000 Jul;78(1):52-7.
59. Lissoni A, Gabriele A, Gorga G, Tumolo S, Landoni F, Mangioni C, et al. Cisplatin-, epirubicin- and paclitaxel-containing chemotherapy in uterine adenocarcinoma. Ann Oncol. 1997 Oct;8(10):969-72.
60. Price FV, Edwards RP, Kelley JL, Kunschner AJ, Hart LA. A trial of outpatient paclitaxel and carboplatin for advanced, recurrent, and histologic high-risk endometrial carcinoma: preliminary report. Semin Oncol. 1997 Oct;24(5 Suppl 15):S15-78-S15-82.
61. Nakamura T, Onishi Y, Yamamoto F, Kouno S, Maeda Y, Hatae M. [Evaluation of paclitaxel and carboplatin in patients with endometrial cancer]. Gan To Kagaku Ryoho. 2000 Feb;27(2):257-62.
62. Scudder SA, Liu PY, Wilczynski SP, Smith HO, Jiang C, Hallum AV, 3rd, et al. Paclitaxel and carboplatin with amifostine in advanced, recurrent, or refractory endometrial adenocarcinoma: a phase II study of the Southwest Oncology Group. Gynecol Oncol. 2005 Mar;96(3):610-5.
63. Balega J, Van Trappen PO. The sentinel node in gynaecological malignancies. Cancer Imaging. 2006;6:7-15.
64. Greven K, Winter K, Underhill K, Fontenesci J, Cooper J, Burke T. Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. Gynecol Oncol. 2006 Oct;103(1):155-9.
65. Benedet JL, Ngan HY, Hacker NF. Staging classification and clinical practice guidelines of gynecologic cancers.http://www.figo.org/docs/staging_booklet.pdf Reprinted from the International Journal of Gynecology and Obstetrics, 70(2000):207-312.

66. Kitchener H. Management of endometrial cancer. Eur J Surg Oncol. 2006 Oct;32(8):838-43.
67. Irvin WP, Rice LW, Berkowitz RS. Advances in the management of endometrial adenocarcinoma. A review. J Reprod Med. 2002 Mar;47(3):173-89; discussion 89-90.
68. Lopes LA, Nicolau SM, Baracat FF, Baracat EC, Goncalves WJ, Santos HV, et al. Sentinel lymph node in endometrial cancer. Int J Gynecol Cancer. 2007 Sep-Oct;17(5):1113-7.
69. Yen TC, Lai CH. Positron emission tomography in gynecologic cancer. Semin Nucl Med. 2006 Jan;36(1):93-104.
70. Mutic S, Malyapa RS, Grigsby PW, Dehdashti F, Miller TR, Zoberi I, et al. PET-guided IMRT for cervical carcinoma with positive para-aortic lymph nodes-a dose-escalation treatment planning study. Int J Radiat Oncol Biol Phys. 2003 Jan 1;55(1):28-35.
71. Esthappan J, Mutic S, Malyapa RS, Grigsby PW, Zoberi I, Dehdashti F, et al. Treatment planning guidelines regarding the use of CT/PET-guided IMRT for cervical carcinoma with positive paraaortic lymph nodes. Int J Radiat Oncol Biol Phys. 2004 Mar 15;58(4):1289-97.
72. Shiohara S, Ohara M, Itoh K, Shiozawa T, Konishi I. Successful treatment with stereotactic radiosurgery for brain metastases of endometrial carcinoma: a case report and review of the literature. Int J Gynecol Cancer. 2003 Jan-Feb;13(1):71-6.

Summary

The aim of this thesis is to critically evaluate and discuss the available evidence, as well as make recommendations for the treatment, of patients with the various stages of advanced endometrial cancer and different sites of recurrent endometrial cancer. In Chapter 1, a general introduction of endometrial cancer is given focusing on the patient population with advanced and recurrent endometrial cancer. An evaluation of our clinical experience of patients with advanced and recurrent endometrial cancer in the Erasmus MC in Rotterdam is presented in Chapters 2 and 3. The results of different chemotherapy regimens, as evaluated in two multi-centre clinical trials in patients with advanced and recurrent endometrial cancer, are presented in Chapter 4. Chapter 5 summarizes the current status of the management of patients with advanced and recurrent endometrial cancer with a histopathologic endometrioid type of tumor. A management schedule per stage of advanced disease and per site of recurrent disease is proposed. Chapter 6 contains a general discussion and recommendation for further research.

Chapter 1:

Introduction and objectives

Endometrial cancer is the most common gynecological malignancy in Western Countries and it accounts for 6% of all cancers in women. Its incidence is still rising; this is related not only to increasing life expectancy, but also to the exposure of the uterus to unopposed estrogens, either exogenous or endogenous as in obese patients. As endometrial cancer often causes abnormal uterine bleeding at an early stage, the majority of patients are diagnosed with early stage disease (defined as FIGO stages I and II). Only a small proportion of patients are diagnosed with advanced stage disease (defined as FIGO stages III and IV); this includes patients with local and/or regional spread to the uterine serosa, the adnex(a), vagina, bladder or bowel, lymph nodes, and patients with tumor-positive peritoneal cytology or with distant metastases. A growing interest in endometrial cancer has been observed in recent decades; the main reasons for this being the increasing incidence of the disease and a better understanding of prognostic important factors which leads to more tailored and less aggressive treatment approaches for patients with early stage disease. Since the majority of the patients is identified with endometrial cancer at an early stage of the disease, clinical studies mainly focus on these patients. Since only a small proportion of the patients present with advanced or recurrent disease, treatment modalities for these patients tend to evolve slowly, and treatment is frequently individualized as limited evidence is available. The objectives of this thesis involve analyzing the clinical experience and evaluating different chemotherapy regimens in patients with advanced and recurrent endometrial cancer, discussing the available evidence and making recommendations for treatment of patients with the different stages of advanced disease and different sites of recurrent disease.

Chapter 2:

Stages III and IV endometrial cancer; a 20 year review of patients

In this chapter we evaluate our clinical experience of 67 patients with FIGO stages III and IV endometrial cancer who were treated in the Erasmus MC in Rotterdam over a 20 year period. Special emphasis is given to the prognostic impact of stage IIIA based on positive peritoneal cytology only and the importance of optimal surgical cytoreduction in our series of patients.

Stage IIIA disease is found in 33 patients, of whom 10 have positive cytology only. In advanced endometrial cancer patients, positive peritoneal cytology is an important prognostic factor. Although our study only includes a limited number of patients with stage IIIA based on peritoneal cytology only, our analysis shows that incidence of recurrence and survival rates of patients with stage IIIA disease based on positive cytology only are comparable with stage IIIA disease based on other factors.

There is an improved survival rate in patients with advanced endometrial cancer where optimal surgical cytoreduction is achievable. In 50 patients all macroscopic tumor is removed, while for 17 patients an optimal surgical cytoreduction is not achievable. The 2- and 5-year survival rates after optimal surgical cytoreduction, with adjuvant radiotherapy and/or chemotherapy in most cases, are 82.2% and 65.6% respectively. Where optimal cytoreduction cannot be achieved these figures are 50.8% and 40.6% respectively. This difference approaches significance ($p < 0.1$).

Chapter 3:

Recurrent endometrial cancer; a retrospective study

The value of follow-up after treatment for endometrial cancer is discussed in this chapter. We evaluate our clinical experience (including time to recurrence, mode of detection and site of recurrence) of 64 patients with recurrent endometrial cancer treated in the Erasmus MC in Rotterdam over a 20 year period.

Of our patients, 22 patients have a local recurrence, 30 have a distant recurrence and 12 have simultaneous local and distant recurrent disease. Within three years, 95% of the local recurrences and 67% of the distant recurrences are detected. Twenty seven patients have a recurrence detected during follow-up without presenting symptoms (i.e. screen-detected recurrence), 34 have a recurrence detected due to symptoms (i.e. interval screening recurrence) and two have a recurrence detected during examinations not primarily initiated to detect recurrent disease (i.e. chance finding recurrence). The overall survival rate at two years is 70% and at five years 53%. Patients with a screen-detected recurrence have a 5-year survival rate of 62%, while patients with interval screening and chance finding recurrences have a 5-year survival rate of 47%. Five patients have low risk primary disease (FIGO stage IA grade 1 or 2, or stage IB grade 1 endometrioid adenocarcinoma) and recurrent disease is detected in

four of these patients during follow-up with one patient being symptomatic.

As reported in literature, the majority of recurrences in our series are also detected in the first three years after primary treatment of endometrial cancer. We think that a follow-up program in these first three years may be useful in detecting recurrent disease but a clear benefit on survival is not yet proven.

Chapter 4:

Chemotherapeutic treatment of advanced and recurrent endometrial cancer

4.1. Phase II study of carboplatin in patients with advanced or recurrent endometrial carcinoma: A trial of the EORTC Gynecological Cancer Group

In the population of endometrial cancer patients with significant co-morbidity it is necessary to have chemotherapy regimens with low toxicity. Cisplatin is one of the most active drugs in gynecological cancer types but at a cost of high toxicity. The profile of carboplatin in ovarian carcinoma patients is more favorable; similar activity; but less toxic when compared to cisplatin. Therefore, the efficacy and toxicity of single agent carboplatin in patients with endometrial adenocarcinoma is investigated in this multi-centre study of the European Organisation of Research and Treatment of Cancer (EORTC). Patients eligible for this study are those with histologically confirmed endometrial adenocarcinoma with evidence of recurrent and/or metastatic disease. The choice of the initial dose is based upon whether or not there had been prior radiotherapy treatment. Carboplatin is administered every four weeks as first (400 mg/m^2) or second (300 mg/m^2) line chemotherapy.

Of the 64 patients entered into the trial 60 are eligible, 53 patients are evaluable for toxicity and 47 for efficacy. A total of 169 cycles of carboplatin is given with a median of 2 cycles per patient (range 1-11) to a median cumulative dose of 798 mg/m^2 (range 290-3,879). No grade 4 toxicity or toxic death occurs. White blood cell toxicity grade 3 is noted five times mainly in the radiotherapy pre-treated patients. Grade 3 non-hematological toxicity consists mainly of nausea and vomiting (21%). There is a total of eight responses (3 complete and 5 partial responses) with an overall 13% response rate (95% CI 6–25). No response occurs in patients who had previously undergone chemotherapy. In evaluable patients, overall response rate in all (n=47) and in first line chemotherapy (n=33) are respectively 17% (95% CI 8-31) and 24% (95% CI 11-42). After a median follow-up of 379 days, median duration of response is 488 days (range 141-5,303) with two very long responses in patients with complete response.

Carboplatin has low toxicity and is active in chemotherapy naïve advanced or recurrent endometrial carcinoma. These results lead to the proposal of using carboplatin in combination chemotherapy as first line treatment in advanced or recurrent endometrial carcinoma.

4.2. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomized study (55872) by the EORTC Gynecological Cancer Group

Combination chemotherapy yields better response rates which do not always lead to a survival advantage. The aim of this trial is to compare single agent therapy with doxorubicin to the combination therapy of doxorubicin and cisplatin in terms of efficacy, toxicity and survival. Similar to the above mentioned study this trial is performed under the auspices of the EORTC. Eligible patients have histological-proven advanced and/or recurrent endometrial adenocarcinoma and are chemotherapy-naïve. Treatment consists of either doxorubicin (60 mg/m2) alone or cisplatin (50 mg/m^2) and doxorubicin (60 mg/m^2), administered every four weeks.

A total of 177 patients are entered; 41% of the patients have primary advanced disease and 59% have recurrent disease. The median follow-up is 7.1 years. The combination therapy is more toxic than the single agent therapy. Hematological toxicity consists mainly of white blood cell toxicity grades 3 and 4 (55% vs. 30%). Non-hematological toxicity consists mainly of grades 3 and 4 alopecia (72% vs. 65%) and nausea/vomiting (36% vs. 12%). The combination therapy provides a significantly higher response rate than the single agent therapy ($p < 0.001$). Thirty-nine patients (43%) respond on the combination arm (13 complete and 26 partial responses), versus 15 patients (17%) on the single agent arm (8 complete and 7 partial responses). Although the median overall survival is 9 months in the combination arm versus 7 months in the single agent arm, statistical significance is not met. Regression analysis shows that WHO performance status is statistically significant as a prognostic factor for survival and stratifying for this factor treatment effect is significant (Hazard ratio = 1.46, 95% CI 1.05-2.03, $p=0.024$).

When compared to single agent doxorubicin, the combination of doxorubicin and cisplatin results in higher (yet still acceptable) toxicity levels. The response rate produced is significantly higher and a modest survival benefit is achieved with the combination regime, especially in patients with a good performance status.

Chapter 5:

Management of advanced and recurrent endometrial cancer

5.1. Management of surgical stage III and IV endometrioid endometrial carcinoma: an overview

Chapter 5.1 covers an overview of the literature on the management of advanced endometrial cancer, concentrating on patients with histopathologic endometrioid type of tumors. The different treatment modalities are described and management recommendations are proposed.

Treatment modalities

The standard surgical procedure includes an extrafacial total hysterectomy with bilateral salpingo-oophorectomy, collection of peritoneal washings for cytology and exploration of the intra-abdominal contents. The role of routine pelvic and para-aortic lymphadenectomy or lymph node sampling is still being debated. In cases of endometrial cancer with tumour extension in upper abdomen and in cases with bulky nodes an optimal surgical cytoreduction is associated with improved survival, this has however not yet been proven in a randomized trial. Further treatment with radiotherapy may be indicated based on the pathological staging information to improve loco-regional control. Primary radiotherapy is indicated in cases where surgery is contraindicated. Systemic treatment can either be hormone therapy or chemotherapy. Primary hormone therapy can be considered in patients who were not eligible for surgery and/or radiotherapy. Progesterons are the cornerstone of hormone therapy. Prognostic factors for response are the presence of high levels of progesterone and estrogen receptors and low grade histology. In the treatment of advanced and recurrent endometrial cancer there is an increasing usage of chemotherapy, either as primary (stand alone), adjuvant, neo-adjuvant or induction therapy or in combination with radiotherapy as radiosensitizer. Paclitaxel is the most active single agent drug and the most active combination treatment is the combination of paclitaxel, doxorubicin and cisplatin, but, because of the high toxicity, this combination treatment is not the best choice. Although not proven in a randomized trial, combination therapy with paclitaxel and carboplatin is adopted as first choice in patients with endometrial cancer, due to the efficacy and low toxicity.

Management recommendations per stage

Stage IIIA based on positive peritoneal cytology only: based on the presence of unfavorable prognostic factors (i.e. tumor grade, myometrial invasion, age and lymph vascular space involvement), patients are treated with adjuvant pelvic radiotherapy or further staged with pelvic lymphadenectomy. Since the value of adjuvant chemotherapy in addition to pelvic radiotherapy in patients with a high risk of distant metastases is not known in advanced stage disease, these patients should preferably be treated in international studies encompassing study arms with chemotherapy.

Stage IIIA based on involvement of the serosa, or adnex(a): pelvic radiotherapy with or without vaginal cuff brachytherapy improves local control but does not improve survival. Chemotherapy with or without radiotherapy seems appropriate postoperative treatment for these patients. To answer the question whether chemoradiation and adjuvant systemic treatment improve clinical outcome, and particularly reduce distant recurrences, necessitates studies like PORTEC-3.

Stage IIIB: since most patients are diagnosed at or after surgery as stage IIIB, postoperative pelvic radiotherapy and brachytherapy are indicated in these patients with or without chemotherapy.

Stage IIIC: treatment should start with surgery including proper removal of the (affected) nodes and neo-adjuvant or induction chemotherapy should be considered in patients with primary inoperable nodal disease. Post-operative treatment can consist of external pelvic radiotherapy or chemotherapy. Extended field radiotherapy to the para-aortic region is only indicated in patients with histological evidence of common iliac or para-aortic node metastases. Sequential radiotherapy and chemotherapy is feasible and may be indicated for patients with a high risk of distant metastases, but this has not yet been proven in this patient population.

Stage IVA: if bladder or rectum involvement is found during surgery, and if the procedure is not abandoned, surgery should be aimed at cytoreduction. It is debatable whether or not this should encompass pelvic exenteration. Post-operative radiotherapy is common practice, but for macroscopic residual disease chemotherapy followed by radiotherapy may be indicated. If involvement of the bladder or rectum is identified pre-operatively, start of treatment with neo-adjuvant or induction chemotherapy can be considered, followed by cytoreductive surgery (and/or radiotherapy). Primary pelvic exenteration can be the treatment of choice in a well-informed patient. The precise value of post-operative chemotherapy or radiotherapy as well as the place of neo-adjuvant or induction chemotherapy in this patient population is not yet well defined.

Stage IVB: for patients with stage IVB disease based on intra-abdominal spread of tumor, cytoreductive surgery is indicated with individualized (induction or postoperative) chemotherapy and/or radiotherapy. For patients with stage IVB disease based on distant metastasis, treatment depends on presence of complaints, site of distant disease and whether the tumor is hormone receptor positive or negative. In patients with distant disease, systemic therapy is usually necessary: preferably hormone therapy in patients with hormone receptor positive tumors, and chemotherapy in patients in whom instant symptom relief is warranted (irrespective of hormone status) and in all hormone receptor negative tumors. The primary aim of treatment is to cure the patient. If cure is not achievable, due to tumor characteristics or co-morbidity of the patient, treatment should be palliative.

Ongoing research focuses on developing new agents, optimal chemotherapeutic regimens and multimodality strategies.

5.2. Management of recurrent endometrioid endometrial carcinoma: an overview

In Chapter 5.2 an overview of the literature on the management of recurrent endometrial cancer is presented, focusing on patients with histopathologic endometrioid type of tumors. The different treatment modalities are described and a management recommendation scheme is presented.

Treatment modalities

Indications for surgical treatment depend on resectability, site and size of the tumor and performance status of the patient. Indications for radiotherapy depend on the site of the recurrence and also on the initial therapy received. When considering systemic treatment for patients with recurrent endometrial cancer, it is important to take into account the general health status and condition of the patient as well as which prior therapy the patient has received. The choice of systemic treatment depends on the type of tumor. The treatment of choice for patients with recurrent endometrial cancer with hormone sensitive tumors (positive receptor levels, low-grade tumors and long disease free interval) are progestagens as first-line treatment and tamoxifen as second-line treatment, but only after prior response to progestagens. Patients with high grade tumors, negative hormone receptor levels and short treatment-free interval are best treated with chemotherapy. The combination therapy with paclitaxel and carboplatin is adopted unofficially as standard therapy.

Management recommendations per site of recurrent disease

Local recurrence: patients with a local recurrence in a previously irradiated area benefit most from surgery, consisting of the removal of all tumor with clear margins, which may encompass pelvic exenteration. In case of microscopically positive margins, intra-operative radiation therapy is considered. Patients with local recurrent disease who did not receive prior radiotherapy have a favorable prognosis after treatment with pelvic radiotherapy and brachytherapy. Another approach is surgery, aimed at the removal of all tumors with clear margins or neo-adjuvant chemotherapy followed by surgery and/or radiotherapy; this approach may be of preference in patients with large tumors.

Regional recurrence: radiotherapy-naïve patients with regional recurrence in pelvic lymph nodes are best treated with pelvic radiotherapy, with or without prior surgery, aimed at optimal cytoreduction. For upper abdominal or peritoneal recurrences systemic treatment, with or without radiotherapy, is recommended. Rare alternative approaches are combined operative and radiotherapeutic treatment (CORT), radical resection in combination with intra-operative radiation therapy (IORT) or hyperthermic intraperitoneal chemotherapy (HIPEC).

Distant recurrence: patients with distant recurrent disease are treated with systemic therapy. Although literature on metastasectomy is very limited, any clinical judgment would be individualized. Radiotherapy is indicated for palliation.

In patients with recurrent cancer, therapy should be given with regard to site and extension of the tumor and any prior treatment received.

Chapter 6:

General discussion

This thesis gives an insight into the current approach of patients with advanced and recurrent endometrial cancer. Hitherto, treatment was often individualized in these patients. In this chapter, notable clinical features of patients with advanced or recurrent endometrial cancer are discussed, attention is paid to clinical trials, treatment recommendations are discussed and implications for future research are proposed.

Samenvatting

Dit proefschrift richt zich op de behandeling van patiënten met hoogstadium en recidief endometriumcarcinomen. De beschikbare literatuur wordt kritisch geëvalueerd en besproken en aanbevelingen voor de behandeling van deze patiënten worden gegeven. In hoofdstuk 1 wordt een algemene introductie over endometriumkanker gegeven waarbij de nadruk wordt gelegd op patiënten met hoogstadium en recidiefziekte. In de hoofdstukken 2 en 3 wordt de klinische ervaring gepresenteerd van patiënten met een hoogstadium en recidief endmetriumcarcinomen die behandeld zijn in het Erasmus Medisch Centrum te Rotterdam. De resultaten van verschillende behandelingen met chemotherapie, die zijn geëvalueerd in twee multi-centrische klinische studies bij patiënten met hoogstadium en recidief endometriumcarcinomen, worden besproken in hoofdstuk 4. Hoofdstuk 5 geeft een samenvatting van de huidige stand van zaken betreffende de behandeling van patiënten met hoogstadium en recidief endometriumcarcinomen met histo-pathologisch endometrioide type tumoren. Voor alle hogere stadia endometriumcarcinomen en voor alle lokalisaties van recidiefziekte wordt een behandelingsschema voorgesteld. Hoofdstuk 6 bevat de algemene discussie en aanbevelingen voor toekomstig onderzoek.

Hoofdstuk 1:

Introductie en doelstellingen

Endometriumkanker is de meest voorkomende gynaecologische maligniteit in westerse landen en omvat 6% van alle kankers bij vrouwen. De incidentie neemt nog steeds toe; dit is niet alleen toe te schrijven aan de gestegen levensverwachting, maar ook aan de blootstelling van de uterus aan oestrogenen (zonder progestagenen), zowel exogeen als endogeen (in obese patiënten). Doordat endometriumkanker vaak in een vroeg stadium klachten van abnormaal vaginaal bloedverlies geeft, presenteert de meerderheid van de patiënten zich met laagstadium ziekte, gedefinieerd als FIGO stadium I en II. Slechts een klein deel van de patiënten presenteert zich met hoogstadiumziekte, gedefinieerd als FIGO stadium III en IV; dit zijn patiënten met lokale of regionale uitbreiding van de ziekte naar de serosa van de uterus, adnexa, vagina, lymfklieren, blaas of darm, en patiënten met positieve peritoneale cytologie of met metastasen op afstand. De laatste decennia staat endometriumkanker in toenemende belangstelling. De gestegen incidentie van de ziekte, beter inzicht in belangrijke prognostische factoren en verbeterde behandelingsmogelijkheden zijn de voornaamste oorzaken. Omdat de meeste patiënten zich met laagstadium ziekte presenteren, is de behandeling van endometriumkanker in de literatuur met name gericht op deze patiënten. De behandelingsmogelijkheden voor patiënten met hoogstadium- en recidiefziekte ontwikkelen zich langzaam en behandeling wordt vaak geïndividualiseerd. De doelstellingen van dit proefschrift zijn het analyseren van de klinische ervaring en het evalueren van verschillende chemotherapeutische behandelingen voor patiënten met hoogstadium en recidief endometriumkanker, het bespreken van de beschikbare literatuur en het geven van

aanbevelingen voor behandeling van patiënten met de verschillende stadia van hoogstadiumziekte en verschillende lokalisaties van recidiefziekte.

Hoofdstuk 2:

Patiënten met stadium III en IV endometriumcarcinoom; een evaluatie van 20 jaar

In dit hoofdstuk wordt de klinische ervaring geëvalueerd van 67 patiënten met een endometriumcarcinoom FIGO stadium III of IV, die gedurende een periode van 20 jaar zijn behandeld in het Erasmus Medisch Centrum te Rotterdam. De prognostische waarde van stadium IIIA gebaseerd op alleen de aanwezigheid van positieve peritoneale cytologie en het nut van optimale chirurgische cytoreductie zijn beide onderwerp van discussie en zijn benadrukt in deze patiëntengroep.

Bij 33 patiënten is stadium IIIA ziekte vastgesteld, waarvan bij 10 patiënten alleen op basis van positieve peritoneale cytologie. Onderzoek toont aan dat de incidentie van recidiefziekte en de overleving van patiënten met stadium IIIA ziekte alleen op basis van de aanwezigheid van positieve peritoneale cytologie gelijk zijn aan die van patiënten met stadium IIIA ziekte gebaseerd op andere factoren. In patiënten met een hoogstadium endometriumcarcinoom lijkt positieve peritoneale cytologie een belangrijke prognostische factor.

Bij 50 patiënten is een optimale chirurgische cytoreductie verricht, waarbij alle macroscopische tumor is verwijderd; bij 17 patiënten was dit niet mogelijk. De 2- en 5-jaars overleving na optimale chirurgische cytoreductie zijn respectievelijk 82,2% en 65,6%. Indien optimale chirurgische cytoreductie niet mogelijk is, zijn deze aantallen respectievelijk 50,8% en 40,6%. Bij patiënten met een hoogstadium endometriumcarcinoom is de overleving verbeterd door optimale chirurgische cytoreductie ($p < 0,1$).

Hoofdstuk 3:

Recidief endometriumkanker; een retrospectief onderzoek

Het nut van follow-up na behandeling van een endometriumkanker wordt in dit hoofdstuk besproken. Wij evalueren onze klinische ervaring, inclusief de wijze waarop de diagnose is gesteld, van 64 patiënten die gedurende een periode van 20 jaar vanwege een recidief endometriumcarcinoom in het Erasmus Medisch Centrum te Rotterdam zijn behandeld.

Van deze patiënten is bij 22 patiënten een lokaal recidief vastgesteld, bij 30 patiënten ziekte op afstand en bij 12 patiënten zowel een lokaal recidief als ziekte op afstand. Binnen drie jaar na behandeling van de primaire tumor zijn 95% van de lokale recidieven ontdekt en 67% van de recidieven op afstand. Bij 27 patiënten is het recidief tijdens de follow-up afspraken ontdekt, bij 34 patiënten tussen de follow-up afspraken in en bij twee patiënten is het recidief bij toeval ontdekt. De gemiddelde overleving van alle patiënten is na twee jaar 70% en na vijf jaar 53%. Bij patiënten met een recidief dat tijdens de follow-up is ontdekt, is

de 5-jaars overleving 62%, tegenover 47% bij patiënten met een recidief dat tussen de follow-up afspraken in of bij toeval is ontdekt. Bij vijf patiënten is er een laag risico primaire tumor aanwezig (FIGO stadium IA, graad 1 of 2 of stadium IB graad 1 endometrioide adenocarcinomen); bij vier van deze patiënten is het recidief tijdens de follow-up ontdekt en bij één patiënt naar aanleiding van symptomen.

De meerderheid van de recidieven is ontdekt in de eerste drie jaar na primaire behandeling van endometriumkanker, zoals ook wordt beschreven in de literatuur. Een follow-up programma tijdens de eerste drie jaar na primaire behandeling lijkt nuttig om recidiefziekte vast te stellen; een duidelijk voordeel op de overleving staat echter vooralsnog niet vast.

Hoofdstuk 4:

Behandeling van patiënten met een hoogstadium of recidief endometriumcarcinoom met chemotherapie

4.1. Een fase II studie naar de behandeling met carboplatine bij patiënten met een hoogstadium of recidief endometriumcarcinoom: Een studie van de EORTC Gynecological Cancer Group

In de hoog risico populatie van patiënten met een endometriumcarcinoom is chemotherapie nodig met lage toxiciteit. Cisplatine is een van de meest actieve middelen in de behandeling van gynaecologische kanker, echter met hoge toxiciteit. Cisplatine en carboplatine zijn even effectief in de behandeling van patiënten met ovariumcarcinomen; carboplatine geeft echter lagere toxiciteit. Daarom is in deze multi-centrische studie van de European Organisation of Research and Treatment of Cancer (EORTC) de activiteit en toxiciteit van carboplatine onderzocht bij patiënten met een adenocarcinoom uitgaande van het endometrium.

Patiënten met een histologisch bevestigd adenocarcinoom uitgaande van het endometrium met ziekte op afstand of recidiefziekte zijn in deze studie geïncludeerd. Carboplatine is elke vier weken toegediend als eerstelijns (in dosis van 400 mg/m^2) of tweedelijns (in dosis van 300 mg/m^2) chemotherapie.

Van de 64 patiënten die zijn geregistreerd in deze studie, voldoen 60 patiënten aan de inclusiecriteria, van 53 patiënten kan de toxiciteit worden geëvalueerd en van 47 patiënten de effectiviteit. In totaal zijn 169 kuren carboplatine toegediend met een mediaan van 2 kuren per patiënt (variërend van 1 tot 11) en een mediane cumulatieve dosis van 798 mg/m^2 (variërend van 290 tot 3.879). Graad 4 toxiciteit treedt niet op, en er treedt geen toxische dood op. Vijf maal treedt een graad 3 toxiciteit van de witte bloedcellen op, met name bij de met radiotherapie voorbehandelde patiënten. Niet-hematologische toxiciteit bestaat voornamelijk uit misselijkheid en braken (21%). In totaal zijn er acht patiënten met volledige of gedeeltelijke respons (3 patiënten met volledige respons en 5 met gedeeltelijke respons), dit geeft een respons ratio van 13 % (95% betrouwbaarheidsinterval 6-25). Er treedt geen

respons op onder patiënten die eerder met chemotherapie zijn behandeld. De respons ratio is 17% (95% betrouwbaarheidsinterval 8-31) in alle patiënten (n=47) bij wie de effectiviteit geëvalueerd is. De respons ratio is 24% (95% betrouwbaarheidsinterval 11-42) in patiënten die deze therapie als eerstelijns behandeling hebben ontvangen. Na een mediane follow-up periode van 379 dagen, is de mediane duur van respons 488 dagen (variërend van 141 tot 5.303) met een langdurige respons in twee patiënten bij wie een complete respons is opgetreden.

Carboplatine heeft een lage toxiciteit en is effectief bij de behandeling van chemotherapienaïeve endometriumcarcinoom patiënten. Deze resultaten hebben ertoe geleid dat carboplatine als eerstelijns behandeling in combinatietherapie getest kan worden in patiënten met een hoogstadium of recidief endometriumcarcinoom.

4.2. Doxorubicine versus doxorubicine met cisplatine in patiënten met een endometriumcarcinoom: definitieve resultaten van een gerandomiseerde studie (55872) van de EORTC Gynecological Cancer Group

Combinatiechemotherapie leidt tot betere respons ratios, maar niet altijd tot een voordeel op de overleving. Het doel van deze studie is om doxorubicine monotherapie te vergelijken met de combinatietherapie van doxorubicine met cisplatine wat betreft effectiviteit, toxiciteit en overleving. Ook deze studie is uitgevoerd onder auspiciën van de EORTC. Patiënten met een histologisch bevestigd adenocarcinoom uitgaande van het endometrium met ziekte op afstand of recidiefziekte, die niet eerder met chemotherapie zijn behandeld, zijn in deze studie geïncludeerd. De behandeling bestaat uit doxorubicine monotherapie (in dosis van 60 mg/m^2) of combinatie van cisplatine (in dosis van 50 mg/m^2) met doxorubicine (in dosis van 60 mg/m^2) eenmaal in de vier weken.

In totaal zijn 177 patiënten in deze studie geregistreerd, waarvan 41% met een hoogstadium en 59% met een recidief endometriumcarcinoom. De mediane follow-up periode is 7.1 jaar. De combinatietherapie is meer toxisch dan de monotherapie. Hematologische toxiciteit bestaat voornamelijk uit graad 3 en 4 witte bloed cel toxiciteit (55% versus 30%). Niet-hematologische toxiciteit bestaat uit graad 3 en 4 alopecia (72% en 65%) en misselijkheid en braken (36% en 12%). De combinatietherapie toont een significant hogere respons ratio dan de monotherapie ($p < 0{,}001$). Bij 39 patiënten (43%) treedt een respons op na behandeling met de combinatietherapie (13 patiënten met volledige respons, 26 met gedeeltelijke respons), tegenover 15 patiënten (17%) met respons na behandeling met monotherapie (8 patiënten met volledige respons en 7 met gedeeltelijke regressie). De mediane overleving is 9 maanden in de combinatietherapie groep, tegenover 7 maanden in de monotherapie groep (niet statistisch significant). Regressie-analyse toont dat 'performance status' statistisch significant is als prognostische factor voor overleving; na stratificatie bereikt het effect van behandeling significantie (Hazard ratio = 1,46, 95% CI 1,05-2,03, p=0,024).

In vergelijking met doxorubicine monotherapie, resulteert de combinatietherapie van doxorubicine met cisplatine in meer maar acceptabele toxiciteit. De respons ratio is significant hoger, en een bescheiden voordeel op de overleving is bewerkstelligd met de combinatietherapie, vooral bij patiënten met een goede performance status.

Hoofdstuk 5:

Behandeling van patiënten met hoogstadium of recidief endometriumcarcinomen

5.1. Behandeling van patiënten met chirurgisch stadium III en IV endometrioide endometriumcarcinomen; een overzicht

Hoofdstuk 5.1 geeft een overzicht van de literatuur betreffende de behandeling van hoogstadium endometriumcarcinomen, met de nadruk op patiënten met histo-pathologisch endometrioide type tumoren. De verschillende behandelingsmodaliteiten zijn beschreven en aanbevelingen voor behandeling worden gegeven.

Behandelingsmodaliteiten

De standaard chirurgische behandeling bestaat uit een extra-fasciale totale hysterectomie met bilaterale salpingo-oöphorectomie, afname van vocht voor peritoneale cytologie en onderzoek van de intra-abdominale inhoud. De rol van routine pelviene en para-aortale lymfklierdissectie of lymfkliersampling wordt nog steeds bediscussieerd. Hoewel het niet in een gerandomiseerde studie is bewezen, lijkt een optimale chirurgische cytoreductie in meer uitgebreide gevallen te leiden tot een verbeterde overleving. Aanvullende behandeling met radiotherapie is mogelijk geïndiceerd op basis van de histo-pathologische kenmerken om de loco-regionale controle te verbeteren. Primaire radiotherapie is geïndiceerd indien chirurgie is gecontraïndiceerd. Systemische behandeling kan bestaan uit hormonale therapie of chemotherapie. Primaire hormonale therapie kan worden overwogen voor patiënten die niet in aanmerking komen voor chirurgie en/of radiotherapie. Progestagenen zijn de hoeksteen van de hormonale therapie. Prognostische factoren voor respons op deze behandeling zijn hoge progesteron en oestrogeen receptorniveaus en histologisch tumoren met een lage graad van differentiatie. Chemotherapie kan worden toegediend als primaire, adjuvante, neo-adjuvante of inductie-therapie of als radiosensitizer. Paclitaxel is de meest actieve monotherapie en de meest actieve combinatiebehandeling is de combinatie paclitaxel, doxorubicine en cisplatine; echter vanwege de hoge toxiciteit is deze combinatiebehandeling niet de beste keus. Hoewel het niet is bewezen in een gerandomiseerde studie, is combinatiebehandeling met carboplatine en paclitaxel vanwege de effectiviteit en lage toxiciteit momenteel de voorkeursbehandeling bij patiënten met endometriumkanker.

Aanbevelingen voor behandeling

Stadium IIIA op basis van alleen positieve peritoneale cytologie: op basis van de aanwezigheid van ongunstige prognostische factoren (i.e. tumor graad, myometriuminvasie,

leeftijd en lymfangioinvasie) worden patiënten behandeld met adjuvante bekken radiotherapie of verder gestadieerd met pelviene lymfklierdissectie. Omdat de waarde van adjuvante chemotherapie in aanvulling op bekken radiotherapie bij patiënten met een hoog risico op metastasen op afstand niet bekend is bij patiënten met hoogstadiumziekte, moeten deze patiënten bij voorkeur worden behandeld in internationale studies die chemotherapie bevatten.

Stadium IIIA op basis van betrokkenheid serosa of adnex(a): bekken radiotherapie met of zonder brachytherapie verbetert de locale controle maar niet de overleving. Chemotherapie met of zonder radiotherapie lijkt voor deze patiënten geschikte postoperatieve behandeling. Of chemoradiatie en adjuvante systemische therapie de klinische uitkomst verbetert en het aantal recidieven op afstand vermindert, moet worden onderzocht in studies zoals PORTEC-3.

Stadium IIIB: primaire pelviene radiotherapie gevolgd door exploratieve laparotomie wordt aanbevolen voor deze patiënten. De meeste patiënten worden echter tijdens of na chirurgie gediagnosticeerd met stadium IIIB ziekte, dan is postoperatieve pelviene radiotherapie met of zonder chemotherapie geïndiceerd.

Stadium IIIC: behandeling moet starten met chirurgie inclusief verwijdering van de (aangetaste) klieren. Neo-adjuvante of inductiechemotherapie moet worden overwogen voor patiënten met primaire inoperabele ziekte in de klieren. Postoperatieve behandeling kan bestaan uit uitwendige bekken radiotherapie of chemotherapie. Radiotherapie met uitgebreid veld naar de para-aortale regio is alleen geïndiceerd voor patiënten met histologisch bewezen metastasen in de iliacale (niveau van a. iliaca communis) of para-aortale lymfklieren. Sequentiële radiotherapie en chemotherapie zijn uitvoerbaar en mogelijk geïndiceerd bij patiënten met een hoog risico op afstandsmetastasen, dit is echter nog niet bewezen in deze populatie.

Stadium IVA: indien ingroei in blaas of darm wordt ontdekt tijdens chirurgie, en als de operatie niet wordt gestaakt, moet chirurgie gericht zijn op cytoreductie; of dit ook een exenteratie inhoudt staat ter discussie. Postoperatieve radiotherapie is gebruikelijk, echter voor een macroscopisch residu is mogelijk chemotherapie gevolgd door radiotherapie geïndiceerd. Indien ingroei in blaas of rectum preoperatief is vastgesteld, kan de behandeling begonnen worden met neo-adjuvante of inductiechemotherapie, gevolgd door cytoreductieve chirurgie (en/of radiotherapie). Voor een goedgeïnformeerde patiënte, kan een primaire exenteratie de voorkeur van behandeling zijn. De precieze waarde van postoperatieve chemotherapie of radiotherapie en de plaats van neo-adjuvante of inductiechemotherapie in deze patiëntenpopulatie is nog niet goed gedefinieerd.

Stadium IVB: voor patiënten met stadium IVB ziekte op basis van intra-abdominale uitbreiding van tumor, is cytoreductieve chirurgie geïndiceerd, met (inductie of postoperatieve) chemotherapie en/of radiotherapie op individuele basis. Voor patiënten met stadium IVB ziekte op basis van afstandsmetastasen, is behandeling afhankelijk van de aanwezigheid van

klachten, lokalisatie van de ziekte op afstand en of de tumor hormoon receptor positief of negatief is. In het algemeen is in patiënten met ziekte op afstand systemische therapie gerechtvaardigd: hormonale therapie voor patiënten met hormoonreceptor positieve tumoren, en chemotherapie voor patiënten met klachten die onmiddellijke behandeling behoeven (onafhankelijk van hormoonreceptor status) en voor alle patiënten met hormoonreceptor negatieve tumoren. Het primaire doel van de behandeling is om de patiënt te genezen. Indien genezing niet haalbaar is gezien tumorkarakteristieken of co-morbiditeit van de patiënt, dient behandeling gericht te zijn op palliatie.

Huidig onderzoek richt zich op het ontwikkelen van nieuwe medicijnen, optimale chemotherapeutische schema's en multimodaliteitsstrategieën.

5.2. Behandeling van patiënten met een recidief endometrioid endometriumcarcinoom

In hoofdstuk 5.2 wordt een overzicht over de behandeling van recidief endometriumkanker gepresenteerd aan de hand van de beschikbare literatuur, waarbij de nadruk ligt op patiënten met histopathologische endometrioide type tumoren. De gebruikte behandelingsmodaliteiten worden beschreven en aanbevelingen voor behandeling worden gegeven.

Behandelingsmodaliteiten

Indicaties voor chirurgische behandelingen zijn afhankelijk af van de resectabiliteit, lokalisatie en grootte van de tumor en performance status van de patiënt. Indicaties voor radiotherapie hangen af van de lokalisatie van het recidief en ook van de toegepaste behandeling voor de primaire tumor. Indien systemische therapie wordt overwogen is het belangrijk om de lichamelijke conditie van de patiënt in ogenschouw te nemen en de toegepaste behandeling voor de primaire tumor. De keuze voor systemische behandeling hangt af van het type tumor. De behandeling voor patiënten met een recidief endometriumcarcinoom met hormoongevoelige tumoren (positieve receptoren, laag-gradige tumoren en lange ziekte-vrije intervallen) zijn progestagenen als eerstelijns behandeling en tamoxifen als tweedelijns behandeling (indien eerder respons heeft opgetreden op progestagen). Patiënten met hoog-gradige tumoren, negatieve hormoonreceptoren en een korte ziekte-vrije intervallen kunnen het beste met chemotherapie worden behandeld. De combinatietherapie van carboplatine met paclitaxel is momenteel, onofficieel, de standaard behandeling.

Aanbevelingen voor behandeling

Lokaal recidief: patiënten met een lokaal recidief in een eerder bestraald gebied hebben het meest baat bij chirurgie, waarbij alle tumor met voldoende marge wordt verwijderd, wat mogelijk een exenteratie inhoudt. Indien de snijranden microscopische tumor bevatten, kan intra-operatieve radiotherapie worden overwogen. Patiënten met een lokaal recidief die niet eerder met radiotherapie zijn behandeld, hebben een goede prognose na behandeling met uitwendige radiotherapie en brachytherapie. Een andere aanpak bestaat uit chirurgie, met als

doel alle tumor met voldoende marge te verwijderen of neo-adjuvante chemotherapie gevolgd door chirurgie en/of radiotherapie; deze aanpak heeft mogelijk de voorkeur bij patiënten met grote tumoren.

Regionaal recidief: radiotherapienaïeve patiënten met een regionaal recidief in de pelviene lymfklieren kunnen het beste worden behandeld met uitwendige bekken radiotherapie, met of zonder chirurgie gericht op optimale cytoreductie. Voor recidieven in de bovenbuik of peritoneale recidieven wordt systemische behandeling, met of zonder radiotherapie, aanbevolen. Alternatieven zijn gecombineerde operatieve en radiotherapeutische behandeling (CORT), radicale resectie in combinatie met intra-operatieve radiotherapie (IORT) of hyperthermische intraperitoneale chemotherapie (HIPEC).

Recidief op afstand: patiënten met een recidief op afstand worden behandeld met systemische therapie. Hoewel de literatuur over metastasectomie beperkt is, kan dit individueel worden overwogen. Radiotherapie is geïndiceerd voor palliatie.

Voor de behandeling van patiënten met een recidief endometriumcarcinoom, moet rekening worden gehouden met lokalisatie en uitbreiding van de tumor en de toegepaste behandeling voor de primaire tumor.

Hoofdstuk 6:

Algemene discussie

Dit proefschrift geeft inzicht in de huidige aanpak van behandeling van patiënten met een hoogstadium en recidief endometriumcarcinoom. Tot op heden wordt de behandeling van deze patiënten vaak geïndividualiseerd. In dit hoofdstuk worden opvallende klinische kenmerken van patiënten met hoogstadium en recidief endometriumkanker besproken, wordt aandacht besteed aan klinische studies, worden aanbevelingen voor behandeling besproken en worden voorstellen voor toekomstig onderzoek gedaan.

Bibliography

S Bramer, FH van Wijk, BWJ Mol, AH Adriaanse. Risk indicators for neonatal early-onset GBS-related disease, a case-control study. Journal of Perinatal Medicine 1997; 25: 469-475.

K Kluivers, FH van Wijk, JThM van der Schoot. Primaire infectie met HIV-type 1. SOA-bulletin 1999; 3: 4-6.

FH van Wijk, H Wolf, JMJ Piek, H Buller. Wound haematoma and timing of low molecular weight heparin thromboprophylaxis at caesarean section. BJOG: An International Journal of Obstetrics and Gynaecology 2002; 109(8): 955-957.

FH van Wijk, C Lhommé, G Bolis, V Scotto di Palumbo, S Tumolo, M Nooij, CF de Oliveira, JB Vermorken. Phase II study of carboplatin in patients with advanced or recurrent endometrial carcinoma: A trial of the EORTC Gynaecological Cancer Group. European Journal of Cancer 2003; 39(1): 78-85.

FH van Wijk, MS Aapro, G Bolis, B Chevallier, MEL van der Burg, A Poveda, CF de Oliveira, S Tumolo, V Scotto di Palumbo, M Piccart, M Franchi, F Zanaboni, AJ Lacave, R Fontanelli, G Favalli, P Zola, JP Guastalla, R Rosso, C Marth, M Nooij, M Presti, C Scarabelli, TAW Splinter, E Ploch, LVA Beex, W ten Bokkel Huinink, M Forni, M Melpignano, P Blake, P Kerbrat, C Mendiola, A Cervantes, A Goupil, PG Harper, C Madronal, M Namer, G Scarfone, JEGM Stoot, I Teodorovic, C Coens, I Vergote, JB Vermorken. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. Annals of Oncology 2003; 14: 441-448 & 811.

MS Aapro, FH van Wijk, MEL van der Burg, JB Vermorken, W ten Bokkel Huinink, JP Guastalla, R Rosso, A Kobierska, LVA Beex, M Namer, TEW Splinter, I Vergote. Phase II study of fotemustine in patients with advanced ovarian carcinoma; A trial of the EORTC Gynaecological Cancer Group. European Journal of Cancer 2003; 39(8): 1141-3.

LJ Blok, EE Hanekamp, PE de Ruiter, LCM Kuhne, B Boers, P Hanifi-Moghaddam, FH van Wijk, A Klaassens, SCJP Gielen, CW Burger. Is de progesteronreceptorstatus van belang voor het zich ontwikkelende endometriumcarcinoom?. Nederlands Tijdschrift voor Obstetrie en Gynaecologie 2004; 117(6): 156-8.

P Hanifi Moghaddam, SCJP Gielen, HJ Kloosterboer, ME de Gooyer, AM Sijbers, AJ van Gool, M Smid, M Moorhouse, FH van Wijk, CW Burger, LJ Blok. Molecular portrait of the progestagenic and estrogenic actions of tibolone: Behavior of cellular networks in response to tibolone. Journal Clinical Endocrinology and Metabolism 2005; 90(2): 973-83.

AH Klaassens, FH van Wijk, P Hanifi-Moghaddam, B Sijmons, PC Ewing, MJ ten Kate-Booij, GS Kooi, HJ Kloosterboer, LJ Blok, CW Burger. Histological and immunohistochemical evaluation of postmenopausal endometrium after 3 weeks of treatment with tibolone, estrogen-only, or estrogen plus progestagen. Fertility and Sterility 2006; 86(2): 352-61.

FH van Wijk, FJ Huikeshoven, L Abdulkadir, PC Ewing, CW Burger. Stage III and IV endometrial cancer; a 20 year review of patients. International Journal of Gynecological Cancer 2006; 16(4): 1648-55.

FH van Wijk, FJ Huikeshoven, L Abdulkadir, PC Ewing, CW Burger. Recurrent endometrial cancer; a retrospective study. European Journal of Obstetrics & Gynecology and Reproductive Biology 2007; 130(1):114-20.

P Hanifi-Moghaddam, B Boers-Sijmons, AHA Klaassens, FH van Wijk, MA den Bakker, MC Ott, GL Shipley, HAM Verheul, HJ Kloosterboer, CW Burger, LJ Blok. Molecular analysis of human endometrium: Short-term tibolone signaling differs significantly from estrogen and estrogen+progestagen signaling. Journal of Molecular Medicine 2007; 85(5): 471-80.

P Hanifi-Moghaddam, B Boers-Sijmons, AHA Klaassens, FH van Wijk, WFJ van IJcken, P. van der Spek, HAM Verheul, HJ Kloosterboer, CW Burger, LJ Blok. Difference in signalling between various hormone therapies in endometrium, myometrium and upper part of the vagina. Human Reproduction 2008; 23(2):298-305.

List of co-authors

Leyla Abdulkadir, MD	Department of Obstetrics and Gynecology, University Hospital, Leuven, Belgium.
Maria E.L. van der Burg, MD PhD	Department of Medical Oncology, Erasmus MC, Rotterdam, The Netherlands
Curt W. Burger, MD PhD	Department of Gynecological Oncology, Erasmus MC, Rotterdam, The Netherlands
Helena C. van Doorn, MD PhD	Department of Gynecological Oncology, Erasmus MC, Rotterdam, The Netherlands
Patricia C. Ewing, MD PhD	Department of Pathology, Erasmus MC, Rotterdam, The Netherlands
Frans J. Huikeshoven, MD PhD	Department of Obstetrics and Gynecology, Ruwaard van Putten Hospital, Spijkenisse, The Netherlands
Ignace Vergote, MD PhD	Division of Gynaecological Oncology, Department of Obstetrics and Gynaecology, University Hospital, Leuven, Belgium

On behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Gynecological Cancer Group:

M.S. Aapro (Switzerland), L.V.A. Beex (The Netherlands), P. Blake (United Kingdom), W. ten Bokkel Huinink (The Netherlands), G. Bolis (Italy), M.E.L. van der Burg (The Netherlands), A. Cervantes (Spain), B. Chevallier (France), C. Coens (Belgium), G. Favalli (Italy), R. Fontanelli (Italy), M. Forni (Switzerland), M. Franchi (Italy), A. Goupil (France), J.P. Guastalla (France), P.G. Harper (United Kingdom), P. Kerbrat (France), A.J. Lacave (Spain), C. Lhommé (France), C. Madronal (Spain), C. Marth (Austria), M. Melpignano (Italy), C. Mendiola (Spain), M. Namer (France), M. Nooij (The Netherlands), M. Piccart (Belgium), E. Ploch (Poland), A. Poveda (Spain), M. Presti (Italy), R. Rosso (Italy), C. Scarabelli (Italy), G. Scarfone (Italy), V. Scotto di Palumbo (Italy), T.A.W. Splinter (The Netherlands), J.E.G.M. Stoot (The Netherlands), I. Teodorovic (Belgium), S. Tumolo (Italy), C.F. de Oliveira (Portugal), I. Vergote (Belgium), J.B. Vermorken (Belgium), F. Zanaboni (Italy), P. Zola (Italy).

Dankwoord

Het verrichten van promotieonderzoek leek aanvankelijk een eenzaam bestaan. Zonder hulp was dit boek er echter nooit gekomen. Ik wil dan ook alle collega AIOS en ANIOS niet alleen bedanken voor de gezelligheid en samenwerking in de kliniek en voor de vriendschappen daarbuiten, maar ook voor de ruimte die ik kreeg om dit proefschrift tijdens mijn opleiding af te ronden. Alle collega onderzoekers wil ik bedanken voor de nuttige tips en adviezen. Alle opleiders en gynaecologen wil ik bedanken voor alle begrip, betrokkenheid en vertrouwen. Alle patiënten uit binnen- en buitenland ben ik dankbaar voor deelname aan de EORTC studies. En natuurlijk gaat ook veel dank uit naar mijn familie, schoonfamilie, vrienden, vriendinnen en Demeterianen. Veel dank voor de mogelijkheid dat ik ook dit voor elkaar heb gekregen; en dank voor de afleiding, gezelligheid, oppasuurtjes en -dagen op mijn meiden en nog veel meer.

'The Story'

Het begon met het duwtje in de rug van Anca Ansink, 'durf te leven', en daar ging ik dan op weg naar Brussel. Een jaartje onderzoek doen bij de EORTC voor de Gynecological Cancer Group was iets volstrekt anders dan werken in de kliniek, maar beviel me prima. Samen met de andere Medical Research Fellows was het goed toeven op kantoor en in het Brusselse nachtleven. Catherine Lhommé was zo vriendelijk om samen in haar kliniek in Villejuif (Parijs) een aantal dagen aan het carboplatin artikel te werken; dat was een bijzondere samenwerking waarbij de een communiceerde in het Frans en de ander antwoordde in het Engels. Tijdens dat jaar bij de EORTC ontstond het idee om te promoveren bij Ignace Vergote, ik had mij dan ook geen betere chairman van de EORTC GCG kunnen wensen. Terug in Nederland, alhoewel mijn vrienden uit Amsterdam Breda niet allemaal Nederland zullen noemen, begon ik met veel plezier in de kliniek in Breda te werken. Ik heb nog vaak teruggedacht aan de goede raad van Marianne ten Kate-Booij. 'Opleiding, promotie en moederschap, het zal lukken, maar let op je timemanagement, het hoeft niet allemaal tegelijk, verdeel de energie'. Ook ik moest toegeven dat ik de hele wereld niet tegelijk aankon. Daarna kwam het contact met Curt Burger, die de mogelijkheid bood om bij hem in Rotterdam te promoveren. Vanaf het begin werd ik gewaarschuwd voor 'toppen en dalen', en ja, die ben ik uiteindelijk allebei tegengekomen. Het was heerlijk dat Curt Burger en Theo Helmerhorst mij de mogelijkheid hebben gegeven om dit proefschrift uiteindelijk in alle rust af te ronden. In het begin van mijn onderzoeksperiode op het Erasmus MC maakte ik deel uit van de Endometriumgroep van Leen Blok. Dankzij de vrijheid die ik kreeg om het Tibolon-project op te zetten, resteerde er tijd voor andere nuttige zaken, zie hier het resultaat. Frans Huikeshoven had goede ideeën om mijn eerste artikelen aan te vullen en zo mijn proefschrift verdere inhoud te geven. Ook de site-seeing in Los Angeles was een prima idee. Het was een eer dat Lena van Doorn het laatste jaar de taak als copromotor op zich wilde nemen. Ik heb genoten van haar enthousiasme en gastvrijheid en kon zo een heerlijke doorstart maken. De grote inzet van Maria van

der Burg leerde ik al waarderen bij de EORTC, en later ook in het Erasmus MC. Door Maria kreeg ik meer inzicht in de ziekte en hoe deze te behandelen. Dit leidde tot kritische noten op mijn laatste hoofdstukken; het eindresultaat mag er gelukkig zijn. Patricia Ewing was zo vriendelijk om daar waar nodig de pathologie en Engelse taal te reviseren van beide Erasmus MC studies. Voor het verzamelen van de patiëntengegevens van deze studies kon ik rekenen op de hulp van Leyla Abdulkadir, die daar als co-assistent veel vrije uren in heeft gestoken. Bij Anita de Voogt kon ik niet alleen altijd terecht voor allerlei hand- en spandiensten, maar ook voor het vinden van een gaatje in Curts volle agenda. Dankbaar maakte ik ook gebruik van het aanbod van Yvonne von Berg, om mijn overige Engelse teksten taalkundig te corrigeren. Dat bewuste feestje in Amsterdam was mij veel waard. Wat een luxe dat Kevin Termohlen, Judith Klijn en Marly Mulders van mijn manuscript een professioneel boek hebben gemaakt. Ik wil iedereen hartelijk danken voor alles!

De leden van de beoordelingscommissie, Prof.dr. Th.J.M. Helmerhorst, Prof.dr. G.G. Kenter en Prof.dr. J. Verweij, en ook de overige leden van de commissie dank ik hartelijk voor hun kritische blik op mijn proefschrift. Het is een eer dat Anca, Maria en Leen plaats kunnen nemen in de commissie.

Het is buitengewoon plezierig als goede vrienden ook je paranimf willen zijn. Daarom is het heerlijk dat Juanne Rours naast me staat; door jouw geweldige organisatietalent kan er vandaag niets meer mis gaan. En het is voor mij bijzonder dat Griet Boon hier ook staat, samen weer even terug naar daar waar het begon, bij de EORTC in Brussel. Ik kan het niet laten om hier Anne Marieke de Jonghe en Barthold Kuiken niet te noemen. Anne Marieke, dat jouw welverdiende wereldreis en mijn langverwachte promotie nu net samenvallen is toeval, laten we ervan genieten! Jammer dat jij, Barthold, als chirurg in spe, met zo je eigen kijk op gynaecologen, er vandaag ook niet bij kunt zijn. We evalueren alles nog wel eens.

Martijn, mijn allerliefste Martijn, jij bleef er in geloven dat ik het zou afmaken. ‘Schrijf jij de inhoud maar, dan zorg ik voor de rest’. En dit boek mag er zijn! Lieve Sigrid en lieve Lucie, huup-huup Barbatruuk, het boek van mama is klaar.

Curriculum vitae

Flora Hermina (Heidy) van Wijk was born on the 11th of September 1973 in Rijswijk (Gelderland), The Netherlands. After graduating from the Koningin Wilhemina College (Gymnasium) in Culemborg in 1991, she studied Medical Biology at the University of Amsterdam for one year and passed her propedeutic exam. She attended Medical School at the University of Amsterdam from 1992 – 1998 where she graduated cum laude. After Medical School she worked as a resident in the Obstetrics and Gynecology department of the Sint Lucas Andreas Hospital and Academic Medical Center in Amsterdam and the Amphia Hospital in Breda. From September 2000 – September 2001 she worked as a Medical Research Fellow for the Gynecological Cancer Group (chairman: Prof.dr. I. Vergote) at the European Organisation for Research and Treatment of Cancer (EORTC) in Brussels, Belgium. The foundation of her thesis was based on studies performed at the EORTC. From July 2002 she worked at the Erasmus MC, Rotterdam and participated in the Tibolone project within the Endometrial Cancer Group (head: Dr.ir. L.J Blok). In November 2003 she started her Obstetrics and Gynecology training at the Ikazia Hospital (head: Dr. J.W. de Leeuw) and Erasmus MC, Rotterdam (head: Prof.dr. C.W. Burger).