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Aspects of Surgery in Ovarian and Endometrial Carcinoma

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

SURGERY WILL continue to play an integral role in the management of malignancy. Besides the primary goal, the complete removal of the tumour, it allows accurate staging of the disease. Based on our increased knowledge of the natural history of many gynaecological cancers, such a staging procedure has found its place in both ovarian and endometrial cancer. Optimal individual treatment, based on surgical–pathological information, should avoid both under- and overtreatment. Aspects of surgery in ovarian and endometrial carcinoma will be discussed.

EARLY EPITHELIAL OVARIAN CARCINOMA

The understanding of the pattern of spread in epithelial ovarian cancer has led to the concept of careful initial surgical staging in ovarian carcinoma. A tumour confined to the ovary, may have microscopic metastases on the pelvic and abdominal peritoneal surfaces, diaphragm, omentum, ascitic fluid and both pelvic and para-aortic lymph nodes. Proper staging provides guidance on the choice of therapy. Inaccurate staging can result in an erroneous choice of therapy because metastases remained undetected.

The FIGO stage grouping for ovarian carcinoma is presented in Table 1.

The importance of careful initial surgical staging has been emphasised by the findings of several studies in which patients with apparent stage I and II disease (see Table 1 for definitions) were referred for subsequent therapy and underwent additional surgical staging. There were 20–40% "upstaged" as a result of additional surgery and about 75% of the upstaged were reclassified as having stage III disease [1–3].

In earlier series in which patients did not undergo careful surgical staging, the overall 5-year survival for patients with apparent stage I epithelial ovarian cancer was only about 60%. Since then, survival rates of 90–100% have been reported for patients properly staged and found to have stage Ia or Ib disease [4, 5].

In patients, whose preoperative evaluation suggests a probable malignancy, a midline incision to allow adequate access to the upper abdomen is recommended to start the surgical staging procedure. The ovarian tumour should be removed intact, if possible, and a frozen histological section performed to determine the diagnosis. If an ovarian malignancy appears to be confined to the ovaries or the pelvis, thorough surgical staging should be carried out, including the following steps:

— retrieving any free fluid, especially in the pelvic cul-de-sac, to be submitted for cytological examination.
— Obtaining peritoneal "washings" by instilling and recovering 50–100 ml saline from the pelvic cul-de-sac, the paracolic

Table 1. Carcinoma of ovary: FIGO staging

Stage	Criteria
Stage I	Growth limited to the ovaries
Ia	Growth limited to one ovary; no ascites No tumour on the external surfaces; capsule intact
Ib	Growth limited to both ovaries; no ascites No tumour on the external surfaces; capsules intact
Ic	Tumour either stage Ia or Ib, but with tumour on surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells; or with positive peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
IIa	Extension and/or metastases to the uterus and/or tubes
IIb	Extension to other pelvic tissues
IIc	Tumour either stage IIa or IIb, but with tumour on surface on one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells; or with positive peritoneal washings
Stage III	Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage III Tumour is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum
IIIa	Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIb	Tumour involving one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces none exceeding 2 cm in diameter. Nodes are negative
IIIc	Abdominal implants greater than 2 cm in diameter and/or positive retroperitoncal or inguinal nodes
Stage IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present there must be positive cytology to allot a case to stage IV

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gutters and beneath the hemidiaphragms for cytological analysis.
— Systemic exploration of all the intra-abdominal surfaces and viscera including the ascending, transverse and descending colon, the gutters, the recto-sigmoid, the entire length of the small intestine and its mesentery from the caecum to the ligament of Treitz, kidneys, liver and gall bladder, diaphragm and para-aortic area.
— Biopsying any suspicious area or adhesion on the peritoneal surfaces. If there is no evidence of disease, multiple intraperitoneal biopsies should be performed from the peritoneum of the cul-de-sac, the paracolic gutters, the peritoneum of the bladder and the intestinal mesenteric and the diaphragms.
— Resecting the omentum from the transverse colon (infracolic omentectomy).
— Exploring the retroperitoneal spaces to evaluate the pelvic and para-aortic lymph nodes. Nodal tissue is sampled from the external, internal and common iliac vessels, the obturator fossae and the low para-aortic area. Any enlarged lymph nodes should be resected and submitted separately for histopathological evaluation.

ADVANCED EPITHELIAL OVARIAN CARCINOMA

About 70% of patients with epithelial ovarian cancer have advanced disease at initial presentation. Total surgical resection of all the tumours is usually impossible. Surgical options are either biopsy only, limited surgery to include resection of the primary tumour or aggressive cytoreductive surgery.

Cytoreductive surgery

The procedure employed to minimise the tumour burden before subsequent treatment, usually chemotherapy or radiation, is instituted is called cytoreductive surgery or debulking surgery. In general, surgical removal of a tumour before treatment is unnecessary if effective chemotherapy is available. However, in epithelial ovarian cancer, chemotherapy is only moderately effective. Patients with large tumours before chemotherapy seldom attain complete remission and long-term survival. Conversely, in patients with microscopic or even small tumour nodule remnants, 40–50% will achieve a 5-year survival after platinum-based treatment [6, 7].

The rationale of cytoreductive surgery for the intermediate chemosensitive epithelial ovarian carcinomas can be summarised as follows:
— elimination of pharmacological sanctuaries by removal of poorly perfused bulky tumour masses.
— Small residual tumours are better perfused, will have a higher growth fraction and this favours the cell kill with chemotherapy.
— Smaller tumour masses require fewer cycles of chemotherapy so that there is less likelihood of induced drug resistance.
— Host immunocompetence is enhanced by the removal of large tumour masses.
— Clones of phenotypically resistant cells may possibly be removed.

The attempt to remove the tumour seems only valuable if all gross tumour is excised. In a historical retrospective study, Griffith showed that despite "debulking", there were no long-term survivors if a mass greater than 1.5 cm in diameter remained [8]. Several other studies have confirmed the relation between residual tumour mass and prognosis. In experienced hands, optimal cytoreduction is feasible in about 85% of patients, and serious morbidity is acceptably low [9]. It is not yet obvious whether the optimum margin for providing a significant survival benefit is 1, 1.5, or even 2 cm. Probably the optimum size is dependent on the chemotherapy that is used. The significance of pelvic and para-aortic lymphadenectomy as part of the cytoreductive procedure in stage III and IV patients has been subject of debate and remains unclear. At the Instituto Nazionale Tumori, Milan, the lymphonodal involvement proved to be a negative prognostic factor in 173 cases of stage III ovarian cancer [10]. According to Burghardt lymphadenectomy in these patients as part of the cytoreduction will improve survival markedly [11]. Unfortunately, his conclusions are not based on a randomised study and the results may be caused by further cytoreduction in the abdomen.

Intervention surgery

In those patients in whom debulking was not initially performed, maximum cytoreduction can be attempted as soon as chemotherapeutic reduction renders the tumour masses resectable. This is called intervention cytoreductive surgery or secondary cytoreductive surgery. The benefits of intervention surgery are not yet established. In a Dutch study, successful intervention surgery to tumour residual of less than 1 cm did not result in survival benefit [7]. Survival was even worse compared with patients who had successful cytoreduction before initiation of chemotherapy. Although these survival data may be biased, the findings suggest that if a serious attempt at cytoreduction has been made before starting chemotherapy, a second attempt by the surgeon during chemotherapy will not improve survival and may play a role only in cases in which initial debulking has not been attempted.

Second-look surgery

Second-look surgery is defined as an exploratory laparotomy to assess the cancer status of a patient who has completed a programme of chemotherapy and is clinically free of cancer with normal CA125 levels. The last part of this definition is essential. In a cumulative series of 272 patients who underwent second-look surgery, Kenemans found an enhanced CA125 in 65 (24%) of the patients. These patients are (although clinically free of disease) no longer candidates for relaparotomy because virtually all of them (62 out of 65) had tumour present at exploration. On the contrary, a normal CA125 does not exclude tumour. Among 207 patients with a CA125 of less than 35 in 99 (36%) tumour could be detected at second-look surgery [12].

For those patients in clinically complete remission and with normal CA125 levels the role of the second-look in the treatment strategy is dependent on the treatment alternatives at the time of relaparotomy. If treatment must be withheld because of toxicity and if no other effective second-line treatment is available, detailed information about whether or not residual cancer exists is unnecessary. At present, second-look will not lead to the start of treatment alternatives and will not influence patient survival. It is only investigative and in most cases nothing can be done. Those who state that second-look surgery can be accepted as part of research protocols have to consider that it is ethically questionable to perform a surgical procedure for research purposes [13, 14].

ENDOMETRIAL CANCER

Surgery, consisting of a total hysterectomy and bilateral salpingo-oophorectomy is generally accepted as the cornerstone of management of early endometrial carcinoma. When radio-

therapy proved also to be effective, combined therapy, using both irradiation and surgery, became the most commonly performed treatment for endometrial cancer. The general feeling that combined therapy is superior to surgery alone has never been proved. In his thorough review, including 6071 cases from 23 reports, Jones [15] found no difference between the 5-year survival rates for patients with stage I disease treated by surgery alone (75%) or by combined therapy (78%). However, these results may be biased by the lack of adequate information on histological grade and depth of myometrial invasion. It is likely that patients with poorly differentiated and deeply infiltrating tumours are a greater percentage of the combined treatment group.

The only prospective study to evaluate postoperative pelvic radiotherapy in clinically stage I endometrial cancer was performed at the Norwegian Radium Hospital [16]. After primary surgery 540 patients received vaginal radium delivering 6000 rad to the vaginal vault. The patients were then randomised into a group, receiving no further treatment and a group receiving additional high voltage external radiotherapy to a pelvic field with a dose of 4000 rad to the pelvic lymph nodes. During the follow-up period of 3–10 years, a significant reduction in vaginal and pelvic recurrences was found in the patients receiving additional pelvic radiation as compared with the controls (1.9 vs. 6..9%, $P < 0.01$). However, this was outweighed by the higher number of distant metastases in women who received pelvic radiation (9.9%) compared with the controls (5.4%), leading to comparable 5-year survival rates for the two groups (91% for controls and 89% for patients receiving additional pelvic radiation). A more detailed analysis of this series led to the conclusion that only patients with poorly differentiated tumours (grade 3) which infiltrate more than half the myometrial thickness, might benefit from additional external radiotherapy.

The reasons for the disappointing results of the combined treatment are obvious when data from the surgical–pathological study by the Gynecologic Oncology Group (GOG) are taken in consideration. These data indicate a substantial number of patients with extra-pelvic disease in clinical stage I [17]. Both local vaginal radiation and external irradiation are effective in reducing the incidence of vaginal vault recurrences. Lotocki *et al.* [18] reported that preoperative or postoperative vault radium decreased the incidence of vault recurrence from 14 to 1.7%. Piver *et al.* [19] compared hysterectomy only with preoperative uterine radium plus hysterectomy and with hysterectomy plus postoperative vaginal radium in a randomised trial of 189 patients with stage I disease. They found no vaginal recurrences in the postoperative vaginal radium group, compared with a 4.5% for the preoperative uterine radium patients and 7.5% for the hysterectomy-only patients.

These and other data have contributed to a trend toward postoperative rather than preoperative radiation in stage I endometrial cancer. Optimal individual treatment is best accomplished when all significant surgical–pathological information is available and both under- and overtreatment can be avoided.

For endometrial cancer a clinical staging has been used until September 1989 (Table 2). Since October 1989 a surgical–pathological classification has been introduced providing more accurate data (Table 3).

Table 2. FIGO classification of endometrial carcinoma until September 1989

Stage I	The carcinoma is confined to the corpus
Stage Ia	The length of the uterine cavity is 8 cm or less
Stage Ib	The length of the uterine cavity is more than 8 cm

Stage I cases should be subgrouped with regard to the histological type of adenocarcinoma as follows:

G1	Highly differentiated adenomatous carcinomas
G2	Differentiated adenomatous carcinomas with partly solid areas
G3	Predominantly solid or entirely undifferentiated carcinomas

Stage II	The carcinoma involves corpus and cervix
Stage III	The carcinoma extends outside the corpus but not outside the true pelvis (it may involve the vaginal wall or the parametrium but not the bladder or the rectum)
Stage IV	The carcinoma involves the bladder or rectum or extends outside the pelvis

Table 3. Surgical–pathological staging of endometrial carcinoma (adapted from FIGO cancer committee report, Rio de Janeiro, October 1989)

Stage	Ia	(G123) Tumour limited to endometrium
	Ib	(G123) Invasion to < 1/2 myometrium
	Ic	(G123) Invasion > 1/2 myometrium
	IIa	(G123) Endocervical glandular involvement only
	IIb	(G123) Cervical stromal invasion
	IIIa	(G123) Tumour invades serosa and/or adnexae and/or positive peritoneal cytology
	IIIb	(G123) Vaginal metastases
	IIIc	(G123) Metastases to pelvic and/or para-aortic lymph nodes
	IVa	(G123) Tumour invasion bladder and/or bowel mucosa
	IVb	(G123) Distant metastases including intra-abdominal and/or inguinal lymph node

TREATMENT BY CLINICAL STAGE

Stage I and stage II occult

The initial approach should be an extra fascial, total abdominal hysterectomy and bilateral salpingo-oophorectomy, preferably by a midline suprapubic incision. Suture closure of the cervix over an alcohol gauze, to prevent spillage of tumour cells during surgery, has been abandoned. No study ever demonstrated that this procedure contributed to a reduction in vaginal recurrences or in an improved survival.

A sample for peritoneal cytology should be obtained immediately upon entering the peritoneal cavity, either by aspiration of the fluid present or after irrigating the peritoneal cavity with saline solution. A careful exploration of the abdominal cavity is performed, including the liver, diaphragm, omentum, pelvic and para-aortic nodes. All suspicious lesions should be biopsied.

As soon as the uterus is removed it should be opened to visualise the tumour. Frequently the extent of the tumour, with respect to myometrial invasion and expansion to isthmus or cervix, is easy to assess with the eye. If there is doubt, the pathologist is asked to make an assessment by frozen section. Additional surgical staging, including pelvic node dissection and selective para-aortic node sampling is performed in patients with the following unfavourable prognostic characteristics:

— adenosquamous, clear cell or papillary serous carcinomas;
— tumour spread to cervix and/or adnexa;
— tumour invasion of the myometrium-inner third, grade 3; middle third, grades 2 and 3; outer third, grades 1, 2 and 3;
— an elevated pre-treatment serum CA125 level.

For the aortic node sampling it is preferable to reflect the caecum and the right colon to expose retroperitoneally the lower

aorta and vena cava. This approach minimises the likelihood of small bowel adhesions in the area of the aortic node dissection and minimises intestinal complications from additional extended-field radiotherapy.

Vaginal hysterectomy for endometrial carcinoma has been reported by several authors. This approach may be advantageous for certain patients at high risk (obesity, advanced age, poor medical condition). The vaginal procedure is often less time consuming and less traumatic compared with an abdominal operation. However, vaginal removal of the adnexa is not always easily performed and frequently not possible at all; additionally, a careful and thorough exploration of the abdomen, including the lymph nodes, is not possible.

Because of the excellent prognosis for patients with grade 1 lesions invading less than the inner third of the myometrium, adjuvant irradiation is not warranted. If, after surgical staging in the high-risk patient, both the pelvic and aortic nodes prove to be free of metastatic disease, the risk is not high enough to justify irradiation of the entire pelvis, including the pelvic wall. Irradiation by vaginal ovoids will not result in an adequate dose to the paracervical and parametrial tissues. A small-field external beam treatment would be better, because it reduces the incidence of local recurrences. In the absence of other extrapelvic intraperitoneal metastases, extended field irradiation should be reserved for patients with histologically proven aortic node metastases. Potish *et al.* reported 45% 3-year survival in aortic node-positive cases in an uncontrolled series, using modern techniques of extended field irradiation. No severe morbidity has been observed in their series [20]. In the presence of multiple or enlarged aortic node metastases, the scalene fat pad should be removed. Metastases at that level would be a contra-indication to extended field radiation therapy to the para-aortic area.

Stage II

When endometrial carcinoma extends into the cervix it becomes accessible to the lower uterine vasculature and may metastasise by the cervical lymphatics. The incidence of pelvic node metastases is higher in stage II (35%) compared with stage I (11%) [21]. The chances of parametrial and upper vaginal tumour extension and pelvic node metastasis make the stage II patient a more likely candidate for radical hysterectomy and pelvic lymphadenectomy. However, modern megavoltage irradiation has proved to be effective in destroying metastatic sites of adenocarcinoma in the parametrium, upper vagina and pelvic nodes. Therefore, many gynaecologists prefer to perform a conventional extrafascial hysterectomy in combination with radiotherapy in older patients who are frequently of poor risk medically.

In his review on this subject, Rutledge [22] concluded that a more extended treatment is mandatory for most patients with stage II disease. However, no superior treatment regimen could be selected from the available literature.

From the Oslo stage II study [23], it was found that microscopic or grossly visible tumour involvement of the cervix was of prognostic significance. The latter group had a higher death and recurrence rate (40%) compared with patients with microscopic tumour involvement of the cervix (17.5%; $0.05 < P < 0.10$). The survival and recurrence rate for patients with microscopic cervical involvement was comparable with that reported for patients with stage I disease. Microscopic and macroscopic (grossly visible) tumour extension into the cervix are, therefore, managed differently.

The treatment of patients with microscopic tumour spread into the cervix is identical to that for patients with high-risk stage I disease: primary hysterectomy and surgical staging.

The treatment of patients with macroscopic (grossly visible) tumour spread into the cervix justifies a different approach. Most commonly a combination of radiation, i.e. preoperative external pelvic irradiation and/or intracavitary radium or caesium. 4–6 weeks later a total abdominal hysterectomy and bilateral salpingo-oophorectomy are performed. Preoperative radiation allows for optimal geometry of the intracavitary insertion and reduces the risk of bowel fixation in the pelvis. Since there is no convincing evidence of the value of preoperative radiation therapy, a more rational approach for stage II disease is to perform primary surgery including a radical hysterectomy, surgical staging and individualised postoperative radiation.

Stage III

In the presence of an adnexal mass, surgery usually should be performed initially in order to determine the nature of the mass. The main sites of extra-uterine tumour extension in patients wth stage III disease are the parametrium and the vagina. Therefore, many of these patients are not candidates for curative surgery. However, the results from a study at the Norwegian Radium Hospital [24] illustrated the importance of surgery. If surgical eradication of all macroscopic tumour was part of the treatment, the 5-year actuarial survival rate was 41%. Without (complete) surgery only 11% survived for 5 years. Even in cases of limited parametrial or vaginal involvement, surgery should seriously be considered as it improves the patients' chances of being cured by subsequent radiotherapy.

Radiotherapy is the only treatment modality for patients with non-resectable stage III disease. The basic treatment is whole pelvis megavoltage irradiation to an adequate dose. After 2–4 weeks the patient is re-examined. Depending on the reaction of the tumour and the extent of residual disease, the treatment is either continued by intracavitary irradiation or by external irradiation to a reduced field. A subsequent hysterectomy and bilateral salpingo-oophorectomy should be considered if the initial irradiation (40 Gy) has reduced the extra-uterine tumour extension to such a degree that surgery seems justifiable. The majority of treatment failures in stage III disease are detected outside the pelvis and so that need for adjuvant systemic therapy is obvious.

Stage IV

The variety of extrapelvic tumour sites in patients with stage IV disease necessitates individualised treatment. Most extrapelvic tumour sites are only suitable for therapy with hormones or chemotherapy. Additional treatment of pelvic disease seems rational for two reasons: firstly, to improve the chances of being cured by subsequent therapy and secondly, to relieve local symptoms and improve the quality of life. In a series of 72 patients with stage IV disease, reported from the Norwegian Radium Hospital, control of pelvic disease was achieved in 20 patients (28%) using radiation alone or in combination with surgery and/or progestogens [25].

Some extrapelvic tumour sites are suitable for radiotherapy. In the case of bone metastases relief of pain and dysfunction and the prevention of spontaneous fractures may result from radiotherapy. Other suitable sites are supraclavicular and axillary lymph node metastases. Irradiation of thoracic structures may be indicated when there is obstruction of vital structures requiring immediate relief.

CONCLUSION

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

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Systemic Treatment in Disseminated Endometrial Cancer

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

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