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STAGING AND TREATMENT OF OVARIAN CARCINOMA

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Abstract

The staging and treatment of ovarian cancer is reviewed with special attention to developments during the last decade. Pathways of spread, presurgical and surgical staging are described and discussed, as are the biologic characters of the different histologic subtypes. Principles of surgery, endoperitoneal and external radiotherapy, single-drug and multiple-drug systemic chemotherapy (therapeutic and adjuvant), intraperitoneal chemotherapy, second-line chemotherapy, hormone therapy and the use of biologic response modifiers are reported and discussed with background of recent clinical trials. It is concluded that considerable progress has been made concerning diagnosis, staging and treatment of ovarian cancer. The proportion of cases in advanced stages has thus decreased and the survival rate increased. However, it is also obvious that the long-term prognosis for patients with advanced disease has not significantly improved over the last 10 years, despite introduction of multiple-drug regimens with high initial response rates. Ovarian cancer remains the most important gynecologic cause of death in the Western countries.

Key words: Ovarian carcinoma, staging, treatment, review.

In 1972 the Division of Cancer Treatment of NCI of Bethesda published in New England Journal of Medicine a critical review with the title 'Treatment of ovarian carcinoma: possibilities of progress' (1).

The basic messages were the following. The disease is lethal in 60–70% of the cases, the extent of the disease and the results of treatment are difficult to determine and its optimal management is unknown. Identification of high risk groups, diagnosis, monitoring, staging, and controlled therapeutic studies were suggested, by many authoritative authors, as main fields for clinical investigations.

The cooperative engagement of gynecologists, medical oncologists and radiotherapists has resulted, after 10 years of investigations, in progress, disappointments, controversies and some prospects for the future.

The present situation concerning staging and treatment is surveyed in the following.

Pathways of spread

Ovarian carcinoma spreads by contiguity, by peritoneal implantation, by the retroperitoneal and the diaphragmatic lymphatic route and via the blood stream.

At autopsy the most common site of metastatic involvement is the peritoneum (about 90%). Metastases in the bones and brain occur in less than 1% of the cases, in the lungs in about 5%, and in the liver in 5–10% (2).

Peritoneal implantation. This is the main pathway for the diffusion of ovarian carcinoma. Tumor cells shed from the primary are implanted in the peritoneum, carried by the peritoneal fluid which circulates throughout the abdominal cavity.

The variations of intra-abdominal pressure caused by respiration produce a continuous circulation of the peritoneal fluid from the lower parts of the cavity (pelvis and the Douglas' cul-de-sac) to the abdominal surface of the diaphragm. Most of the ascending circulation rises along the right paracolic gutter, which is the main communication between the inframesocolic and the supramesocolic compartments of the abdominal cavity (3).

Retroperitoneal lymphatic route. Lymph drains from the ovary along 2 peduncles. The gonadic peduncle travels with the ovarian vessels to the lymph nodes at the renal hilus and para-aortic areas: on the right side it discharges into the latero-caval and intercavoaortic nodes at the L1–L2 level, on the left into the pre-aortic and latero-aortic nodes. The external iliac peduncle drains on each side into the external iliac lymph nodes (4).

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Diaphragmatic route. This is a theoretical spread rather than a common occurrence. Tumor cells on the peritoneal surface of the diaphragm may penetrate during expiration, through submicroscopic stomata between mesothelial and endothelial cells, into subperitoneal diaphragmatic lymphatic network (5) and proceed through the intradiaphragmatic plexus to the plexus on the diaphragmatic pleural surface. From here they can spread through retrosternal lymphatics to the anterior mediastinal nodes, to the right thoracic trunk and into the blood circulation via the right subclavian vein. The middle collecting diaphragmatic vessels drain to paraesophageal nodes at the hiatus. From here a drainage occurs to the thoracic duct, and then to the left subclavian vein; there is also a drainage to the nodes in the pulmonary hilus. Collecting vessels in the posterior region of the diaphragm terminate in nodes at the aortic and esophageal hiatus. These nodes communicate with those within the abdomen in the region of the coeliac axis and with the upper retroperitoneal nodes (6).

Blood stream. Spread by the blood stream is less common. Metastases in the lungs and liver parenchyma are found in less than 10% at disease presentation and metastases in bone and brain are exceptional (7). Nevertheless the latter may develop, as a late manifestation, sometimes many years after diagnosis and treatment of the primary (8).

Presurgical staging

The following examinations are useful for staging: laparoscopy with peritoneal and diaphragmatic inspection; peritoneal cytology; lymphography; colon radiography with double-contrast; chest radiography.

Laparoscopy. Laparoscopy affords direct inspection of the pelvis, peritoneum, abdominal viscera, surface of liver, omentum, and diaphragm.

In patients not subjected to abdominal surgery, laparoscopy affords excellent inspection of peritoneum, right and left diaphragm, liver surface, and pelvis. Conversely, the omentum is always hard to explore, and its posterior aspects are never visible. Thus, whereas biopsy specimens can be obtained from many suspicious areas, neoplastic implants on the omentum are very hard to see and to biopsy.

In the patients with a history of abdominal surgery, visibility of the supramesocolic compartments is usually excellent, but generally poor in the submesocolic areas and particularly in the pelvis, since it is often obstructed by adhesions. Visualization of the pelvic area is incomplete in 10 to 20% of the cases.

Morbidity from laparoscopy is low. Localized peritonitis and hematoperitoneum occur in about 3% of cases, and lesions of the visceral peritoneum in less than 2%. Nearly all these complications occur at restaging and second look (9). Metastatic spread to the subcutaneous tissues at the site of laparoscopy occurs in about 2.5% in patients with extended peritoneal spread.

Diaphragmatic inspection. Diaphragmatic metastases appear as multiple whitish nodules on the diaphragmatic peritoneum (10). Very small metastases may be found in loose adhesions between the liver capsule and diaphragmatic peritoneum. When metastatic nodules occur only in the right hemidiaphragm, the liver capsule may remain free of metastasis.

Metastases on the diaphragm are as a rule associated with extensive peritoneal involvement and hence characteristic of advanced malignancy (11). More than 70% of patients with peritoneal diffusion also have metastasis to the diaphragm, usually without involvement of the liver capsule. Conversely patients with parenchymal liver metastasis seldom have diaphragmatic lesions.

Peritoneal cytology. In normal subjects, the peritoneal cavity contains about 50 ml (12) of fluid originating from the blood capillaries by filtration (13). Most of this fluid simply wets the serosal surfaces and visible amounts are detected only in the most caudal part, the Douglas' cul-de-sac.

Normal peritoneal fluid contains mesothelial cells plus some histiocytes and blood cells. The fluid also collects exfoliated cells from benign, borderline, or malignant ovarian tumors. Peritoneal fluid cytology therefore becomes important for determining the extent of the disease and for treatment planning of ovarian carcinoma.

Ascites is collected with a syringe immediately after peritoneal incision. In the absence of ascites, peritoneal fluid is collected from Douglas' cul-de-sac, from the right and left paracolic gutters, and from the vesico-uterine fold. In the absence of free peritoneal fluid the peritoneal cavity can be washed with saline solution or Hanks' solution injected through the laparoscope, with shifting of the patient's position to bring lavage fluid to all parts of the peritoneal cavity.

According to published reports, 7 to 36% of patients with clinically localized ovarian malignancy yield positive cytological findings at peritoneal washing. The wide range reported reflects different peritoneal washing technique, incorrect staging, and difficulties in cytological interpretation (9, 14, 15). Benign mesothelial cells account for most errors in cytological diagnosis, especially when these cells, as is often the case, are themselves morphologically altered.

Colon radiography with double-contrast. Abnormal findings are common in patients with ovarian tumors. In most cases, however, the abnormality is limited to compression and displacement of colon segments by the tumor mass, and similar to findings seen in benign ovarian and uterine growths. Double-contrast radiography of the large bowel must be considered postitive for extrinsic pathology only if there is evidence of: adhesion (pinching of intestinal profile and reduced wall elasticity); compression and/or dislocation of extrapelvic segments of the colon; retraction of mesocolon (rigid plicae and images suggesting submucosal and mucosal productive lesions);

infiltration (retraction of colonic wall along the mesocolic insertion line with convergent plicae toward the involved segment) (16).

Double-contrast radiography should be done in staging of the disease since it affords evaluation of the size of an ovarian mass and gives preoperative information about intra-abdominal spread (16). However, small metastases in the visceral peritoneum and mesentery are difficult or impossible to visualize.

Chest radiography. Thoracic involvement as lung metastatis, hilar and/or mediastinal lymphadenopathy, or pleural effusion, occurs in not more than 5% of the cases of ovarian carcinoma. Pleural effusion makes cytological examination mandatory; when pleural effusion occurs in conjunction with ascites, it may be caused by a fibroma or struma ovarii (Meigs' syndrome).

Urography. Dislocation and compression by a space-occupying ovarian tumor are common, but do not differ from findings in benign ovarian and uterine tumors. However, i.v. urography should be done preoperatively to assess the status of the urinary apparatus, but it is not important as a staging procedure.

Computerized axial tomography (CAT) and magnetic resonance (MR). CAT scanning from diaphragm to pelvis yields useful information on the size of the primary tumor, presence of liver metastasis, ascites, and gross peritoneal spread. However, it is impossible to detect the presence of peritoneal disease $\leq$ 2cm in diameter and retroperitoneal node involvement is often overestimated. MR has probably similar utility as CAT.

Lymphography. Lymphography demonstrates lymph node metastases in 25% of cases. The frequency of retroperitoneal lymph node metastases increases with advancing disease (17) and in stage I it is only 9%.

Lymph node metastases can be detected radiologically only if they are more than 5 mm in diameter. Furthermore, lymphography is not useful for detection of metastases in nodes at the renal hilus, a site not opacified by lymphography. In experienced hands the radio-histologic correlation is correct in 100% of positive cases. Negative lymphography can of course never exclude lymph node metastases but if embolic metastases are excluded a rate of only 4% false negative results has been reported (17).

From the literature we gather a change of the stage (conversion rate) of 0 to 44% for diaphragmatic metastases, (9–11, 18–20), 9 to 25% for retroperitoneal metastases (17, 21–23), and 6 to 36% for positive peritoneal cytology (11, 14). Discrepancies between data depend on variable staging of the disease (24, 25).

Radiological, endoscopic and cytological assessment of the spread of an ovarian malignancy often gives valuable information. For several reasons, however, this information is incomplete and in order to get as good an assessment as possible of the extent of the disease, surgical staging is necessary.

Surgical staging

The best surgical approach is through a midline incision extending from xiphoid to pubis, which allows adequate inspection of the peritoneum and diaphragm. However, if the diagnosis is uncertain the incision should first extend from pubis to umbilicus.

Surgical staging includes inspection of the ovaries, tubes, uterus, and abdominal cavity (parietal peritoneum, diaphragm, liver capsule and parenchyma, spleen, colon and mesocolon, mesosigmoid, paracolic gutters, intestinum tenue, mesentery, Douglas' cul-de-sac, bladder). It also includes biopsies of suspicious lesions, selective or systematic exeresis of para-aortic, external and common iliac nodes on the basis of data derived from lymphography and/or surgical inspection and bilateral ovarosalpingectomy and hysterectomy. Total omentectomy is also recommended as metastases may be present in macroscopically normal omentum (26). Radical omentectomy is indicated in the presence of lesions in infracolic omentum. Appendicectomy is also recommended although the involvement of appendix is exceptional. In the absence of visible lesions, random biopsies (an erroneous term which means biopsies from intraabdominal sites where the disease is most frequently localized) from right diaphragm, right and left paracolic gutters, Douglas' cul-de-sac, liver capsule, mesentery, should be taken. Before inspection of the abdominal cavity, aspiration of free fluid from Douglas' cul-de-sac or washing with 500 ml of saline solution of Douglas' and paracolic gutters should be performed. Parenchymal liver biopsy with a Bio-Cut needle is indicated from ecographically suspected areas (27). Liquid content of an ovarian tumor should not be emptied at operation; the tumor must be exteriorized from the abdomen without trauma. Should this prove impossible, tumor aspiration should be done with adequate protection of the surgical field.

Finally, an evaluation of residual disease in terms of numbers, diameters and sites of the lesions should be performed by the surgeon.

The final (pathological) stage is defined after completion of all histological examinations.

According to Rubin (28) clinical stage I tumor corresponds to pathological stage I in about 60% of the cases if all areas are surgically sampled. In stage II occult spread of malignancy is estimated to be much higher with retroperitoneal positive nodes in 40%; only 20% of cases remain with disease confined to the pelvis (28).

In the series of the Istituto Nazionale Tumori of Milan (29), 32 (27%) of 117 patients had histologically positive retroperitoneal nodes. The conversion rate from stage I–II to III for retroperitoneal involvement was equal to 10%. The site of metastatic involvement was para-aortic in 50%, iliac in about 19%, and para-aortic plus iliac in 31% of cases.

It is noteworthy that there exists a variation in spread

and natural history according to the histologic type of tumor.

Serous carcinoma is the most common type, accounting for about 50% of all cases. It shows a papillary structure with cells resembling those of the fallopian tube. The degree of atypia is variable and psammomatous bodies are commonly seen. The majority of patients have G2 and G3 tumors. Next to undifferentiated carcinoma, it represents the most aggressive malignancy of the ovary. It is often bilateral and tends to spread both intra- and retroperitoneally.

Undifferentiated carcinoma. This is the second most common epithelial malignancy of the ovary (about 17%). It shows the greatest aggressiveness and carries the poorest prognosis due to the frequent peritoneal, retroperitoneal and hematogeneous spread. The majority of these patients have advanced disease (stages IV and III) at presentation.

Mucinous carcinoma. This is the third type in order of frequency (about 12%). It consists of neoplastic epithelium often resembling that of the large bowel or, more rarely, the endocervical epithelium. Accordingly, secondary derivation from the colon cannot be excluded on the basis of morphology alone. It is frequently unilateral and well differentiated. The tumor tends to disseminate intraperitoneally. Carcinoembryonic antigen (CEA) is a useful tumor marker in this histologic type and is found in excess of 2.5 ng/ml in the plasma in about 65% of the patients with mucinous cystoadenocarcinoma. CEA plasma levels revert to normal between 2 and 12 weeks after radical surgery. Because of the frequency of false negative and false positive results, CEA is not suitable for screening of asymptomatic subjects, but it is useful as a supplementary diagnostic tool and, above all, for monitoring of mucinous cystoadenocarcinoma.

Endometrioid carcinoma. It accounts for about 11% and is the fourth type in order of frequency. Histologically it may show benign and malignant squamous cell differentiation. Unlike endometrial carcinoma it often shows a papillary pattern and it is mucus secreting. Endometrioid tumors may originate in foci of ovarian endometriosis. When an endometrioid carcinoma of the ovary coexists with an adenocarcinoma of the endometrium it may be impossible to identify the primary. In such instances the two malignancies must be reported separately. Endometrioid adenocarcinoma is more frequent in advanced age, it is most often G2–G3, shows local invasiveness, is usually unilateral, and has little tendency to peritoneal and retroperitoneal involvement.

Clear-cell carcinoma. This is probably a variant of the endometrioid type, accounting for about 5%; it is characterized by clear-cells containing glycogen. Histologically it should be distinguished from endodermal sinus tumor and from the rare metastases of renal cell carcinoma. The tumor is usually of grade G1–G2, unilateral and has little tendency to peritoneal, retroperitoneal and distant dissemination.

Mixed carcinoma. This definition covers tumors in which two or more cell types are represented. *Unclassified carcinoma* are tumors that show features intermediate between two or more of the preceding categories. *Malignant Brenner tumors* have a biologic behavior similar to that of the other epithelial malignancies but without a preferred characteristic.

The *surface serous papillary carcinoma* and the *borderline tumors* have different behavior.

Surface serous papillary carcinoma is a rare variant characterized by bilaterality, small size of the primaries and extensive extraovarian involvement, especially of the peritoneal lining. It is more a clinical than a pathological problem, because at abdominal inspection the ovaries may appear normal.

In all histological types of epithelial malignant ovarian tumors with exception of mucinous type, CA125 tumor marker seems useful. CA125 is a serum antigen associated (antigen levels in excess of 35 units) with most (80%) nonmucinous ovarian carcinoma. It appears more useful in diagnosis than in monitoring since a high rate of false negative results have been reported in patients with persistent microscopic disease after treatment. All the other proposed tumor markers, such as placenta-like alcaline phosphatase, ceruloplasmin, fibronectin, ovarian cystoadenocarcinoma antigen, and fibrin degradation products are today considered useless.

Borderline malignancy tumors or tumors of low malignant potential (LMP) constitute 10% of all common epithelial tumors of the ovary and are predominantly represented by the serous and the mucinous histological types. The histological criteria for the diagnosis of tumor of low malignant potential are: absence of destructive infiltrative growth; presence of cellular stratification and atypia; detachment of atypical cellular clusters and mitotic activity higher than in benign tumors. The main clinical features of tumors of low malignant potential are: indolent course, possible spontaneous regression; possible late recurrence; good prognosis. Furthermore, the tumors are bilateral in about 30% of cases, regional lymph node metastases occur but are rare, and indolent peritoneal multiple foci are found in about 50% of the cases (most frequently in the serous type).

At the end of staging, patients are classified according to the 1986 FIGO system (30) or by the very similar 1987 TNM system (31). Both classifications have the same error. The regional nodes considered also include the inguinal nodes. However, these nodes cannot be considered as regional, and the primary lymphatic drainage of the ovary occurs via the gonadic and the external iliac peduncles. Positive inguinal nodes must therefore be considered as representing stage IV.

For the postsurgical treatment it is important to determine the magnitude of residual disease. From this point of view, the patients can be subdivided into the following categories: a) no intraperitoneal residual disease, b) intra-

peritoneal minimal residual disease, c) small intraperitoneal residual disease, d) intraperitoneal gross residual disease, e) retroperitoneal disease, and f) extraperitoneal disease.

No intraperitoneal residual disease means no evidence of disease including negative peritoneal cytology and negative random biopsies. Minimal intraperitoneal residual disease means positive random biopsies and/or peritoneal cytology. Small intraperitoneal residual disease means the presence of isolated metastases, less than 10 in number, less than 2 cm in diameter, and with free space between the individual lesions. Gross intraperitoneal residual disease means the presence of peritoneal metastases, more than 10 in number, more than 2 cm in diameter, and/or without free space between the lesions. Retroperitoneal disease means the presence of histologically confirmed retroperitoneal metastases. Distant metastases means parenchymal liver metastases, extra-abdominal disease, or abdominal wall disease (32).

Surgery

Surgery constitutes the first step of almost all therapeutic programs, whether it is done for diagnostic, therapeutic, or debulking purposes.

Radical surgery (with lymphadenectomy or lymph node samplings) is possible only in stages Ia, Ib, IIa, IIb and III for omental involvement.

Debulking surgery seems useful for patients with nonresectable ovarian tumors. Its scope is to make the tumor more susceptible to further therapy. A true debulking surgery means removal of more than 90% of the tumor mass. However, it should be pointed out that such surgery is possible in only a few patients (about 40%) with stage III peritoneal disease.

Conservative surgery is rarely indicated and usually only in fertile patients under 30 years of age, with a desire for children. They should have a malignancy not beyond stage Ia (determined by accurate radiological, laparoscopic and surgical staging), histologically well-differentiated, and free of associated pathology, such as uterine fibroids, etc. Adequate follow-up should also be possible. These conditions are usually fulfilled only in mucinous carcinoma, which is a rare disease.

Restaging surgery. Patients submitted to partial surgery because of uncertain diagnosis, or incompletely operated after a correct diagnosis, should undergo laparoscopic, cytologic, and radiologic (lymphography and colon radiography) restaging (24, 33). Surgery is not necessary if nonsurgical restaging has shown the disease to be ineradicable surgically, but it becomes necessary whenever nonsurgical restaging does not reveal residual disease.

Necessity surgery. It is performed in intestinal occlusion, obstructive uropathy and for isolated distant metastases. All these conditions are unusual.

Finally a particular type of surgery consists of *second look laparotomy*.

Endoperitoneal radiotherapy

The data from the historical literature show that intraperitoneal radiotherapy with radionuclides is useless in advanced stages, whereas it appears, when used postoperatively in early stages of disease, to give a survival rate superior to that of historical controls (34). Unfortunately, the non-randomized nature of the performed studies, the small number of patients, the lack of detailed pathological information and of modern staging make definite conclusions impossible.

In the only randomized study from the past few years patients with stages Iaii, Ibi, Ibii, Ic did better after postoperative colloidal ^{198}Au (3700 MBq) plus pelvic external megavoltage radiotherapy (30 Gy) than after postoperative pelvic external megavoltage radiotherapy with 50 Gy (35).

Today, for reasons of protection and dosage accuracy, the most used radionuclide is ^{32}P in colloid form, a pure β emitter. The technique is simple: at the end of the operation, or by laparoscopy, two Tenchkoff catheters are inserted, one below the diaphragm and one along the pelvic wall. ^{32}P is injected with an activity of 550 MBq diluted in 500 ml of normal saline, after verifying patency of the peritoneal cavity with a dose of ^{99}Tc^{m} colloidal sulfur and exploration of its distribution by gamma ray scintiscanning. Good distribution of ^{32}P is promoted by spontaneous movements or by the use of a circular bed that changes the patient's position every 15 min in the first 4 h. With homogeneous distribution, an activity of 370 MBq ^{32}P will deliver about 30 Gy to the surface of the peritoneum and about 40 Gy to the surface of the omentum.

In the recent study of the Gynecologic Oncology Group (GOG) and Ovarian Cancer Study Group (OCSG) (36), patients with stage Ia–Ib–G3 and IIa–IIb with microscopic or no residual disease after careful surgical staging, were randomized to receive intraperitoneal ^{32}P or oral melphalan; with a median follow-up of 31 months, relapses were found in 14% of cases. The relapse-free survival (RFS) at 2 years was 81% and the survival at 3 years was 88%, without a significant difference between ^{32}P-treated and melphalan-treated patients.

Therefore the indications for endoperitoneal radiotherapy seem to be patients with no residual disease or minimal residual disease after surgery, and patients in which a complete remission has been obtained with chemotherapy. In these cases endoperitoneal radiotherapy may have a role as consolidation treatment but the efficacy of this treatment remains to be studied in controlled trials.

Besides abdominal pain and chemical peritonitis some severe abdominal complications may occur. Failure to obtain uniform distribution of the radionuclide due to postsurgical peritoneal pouches may result in local over-

dosage with severe damage to the gut (stenosis, fistulae), which may appear a long time after the treatment.

External radiotherapy

External megavoltage radiotherapy has been used extensively in the past for the postoperative management of stage I, II, and III either as whole abdomen irradiation or as abdominal irradiation by moving-strip technique.

Whole abdomen irradiation is given from anterior and posterior opposed fields with shielding of the kidneys and liver. The mid-point dose is about 30 Gy in 5–6 weeks. Whole abdominal irradiation is usually followed by pelvic irradiation with a 15×15 field and a dose of 20 Gy in 2 weeks (37). In the moving-strip technique the abdomen is divided into strips starting from the pelvic floor and reaching the diaphragm. Usually a tumor dose of about 26–28 Gy in 2 weeks is given. The liver is shielded both when the anterior and posterior fields are treated, the kidneys only when the posterior fields are irradiated. Usually additional 20 Gy in 2 weeks is given to the pelvis (37).

Two randomized studies have shown that radiotherapy and chemotherapy do not differ much in terms of therapeutic effectiveness or survival rates. In the study of the M. D. Anderson Hospital, patients with stage I–II and III with residual masses smaller than 2 cm, no ascitis, and no implants in areas where the radiation dosage had to be limited (such as liver, inferior surfaces of the diaphragm, and peritoneum over the kidneys) were randomized to receive either irradiation to the whole abdomen by the moving-strip technique plus pelvic boost, or melphalan (0.2 mg/kg orally for 5 days every 4 weeks) for 12 cycles (38, 39). No significant differences were seen between the 2 groups concerning RFS at 5 and 10 years. However, the group treated with irradiation showed a high incidence of intestinal complications which necessitated surgery (38–40) while 2 cases of acute non-lymphocytic leukemia were observed in the melphalan-treated patients (41).

In the study of GOG (42), patients with stage III, stratified after reductive surgery according to residual disease, were treated with melphalan or radiotherapy to whole abdomen or radiotherapy followed by melphalan, or melphalan followed by radiotherapy. The study showed that patients with residual disease <3 cm had a significantly longer progression-free interval and survival (median 11.8 and 28.5 months) than those with residual disease >3 cm (median 7.3 and 15.7 months). However, no significant differences were observed in progression-free interval and survival between the 4 arms of treatment.

In contrast, the study of the Princess Margaret Hospital showed a superiority of pelvic plus abdomino-strip irradiation compared to pelvic irradiation plus chlorambucil in patients with stage Ib, II and asymptomatic stage III carcinoma (43).

There are some limitations for abdomino-pelvic irradiation. The first one is the size of postoperative residuum; Rizel et al. (44) found that total abdominal irradiation was not useful for patients with residual disease >5 mm. Considering that the doses needed for sterilization of peritoneal nodules 1–2 cm in diameter are >50 Gy, for nodules 0.1–1 cm in diameter about 50 Gy and for peritoneal nodules <0.1 cm in diameter about 25 Gy (45), and considering that the doses possible to obtain in abdominal irradiation without severe side effects are 30 Gy with the open fields technique and 26–28 Gy with the moving-strip technique, the remaining indication for postsurgical and postchemotherapy would be tumor residues less than 0.1 cm in diameter in the abdomen and pelvis.

The second limitation for radiotherapy is the need for shielding of kidneys and liver which gives risk for underdosage in critical sites of dissemination, for instance the diaphragm (28).

Thirdly, the side effects of radiotherapy may be severe. Whole abdomen irradiation can produce severe myelosuppression which causes delay or discontinuation of radiotherapy. The moving-strip technique without liver shielding produces radiation hepatitis in many patients. With both techniques there may be severe intestinal damage, which, in some cases, necessitates later bowel surgery (28).

Which of the 2 methods, whole abdomen irradiation and moving-strip technique, gives the best results with the least toxicity? The study of the Princess Margaret Hospital, comparing the 2 techniques (abdomino-pelvic irradiation given by either moving-strip technique or open-field technique with shielding of the kidneys, but not liver shielding, plus pelvic irradiation) yielded similar 5-year survival and RFS, but serious late complications (radiation hepatitis, intestinal damage requiring bowel surgery) were more frequent after the strip technique (43). Today abdomino-pelvic irradiation given by the open-field is usually preferred.

Combination chemotherapy

It is a common opinion that ovarian carcinoma is, besides choriocarcinoma, the gynecologic malignancy most responsive to chemotherapy.

In the past, the alkylating agents have been most extensively employed. Melphalan (PAM), cyclophosphamide (CTX), chlorambucil (CHL) and triethylene-thiophosphoramide (Thio-tepa) produce comparable responses in stage III and IV disease. The overall response rate (clinical complete regression or CR, plus partial regression or PR) was about 30%; clinical CR was obtained only in 10–20%. It is noteworthy that the activity has been slightly overestimated due to the fact that in the past no strict criteria of response have been used.

In the middle of the 1970s, doxorubicin (Adriamycin or ADM) and hexa-methylmelamine (HMM) were introduced. Both drugs induced clinical CR+PR in about 30–50% (46–49) of previously untreated patients. Clinical

CR was seen in less than 15% and its median duration was 8 months (46–48). Responding patients have about 10 months longer median survival than ADM non-responders. HMM can occasionally produce long disease-free survival (50).

The recently introduced *4'-epidoxorubicin*, has lower cardiotoxicity than ADM, while the antitumor activity is the same (51–54).

In the first years of the 1980s *cis-diaminodicloroplatinum (cis-platin or CDDP)* was introduced. CDDP is undoubtedly the most active single drug, producing CR in about 40% of cases (55, 56). An analogue, the carboplatin (JM8), has the same activity without ototoxicity and neurotoxicity (57) but with a higher myelotoxicity (58).

During the 1980s multidrug chemotherapy has been considered as the first choice of drug treatment for advanced ovarian carcinoma, while single agent chemotherapy has been restricted to patients over 70 whose age makes them ineligible for more aggressive therapy or to patients living a long way from a medical center. The most well-known combination regimens are HEXA-CAF, AC, PAC, and CHAP.

HEXA-CAF. This is the first combination chemotherapy that in a controlled study showed significant superiority to single agent chemotherapy. It contains HMM 150 mg/m^2 p.o., days 1 to 14; CTX 150 mg/m^2 p.o., days 1 to 14; methotrexate 40 mg/m^2 i.v., days 1 and 8, and 5-fluorouracil 600 mg/m^2 i.v., days 1 and 8. The cycle is repeated every 28 days. CR+PR has been reported in 75% of cases (NCI-Bethesda) and 42% (INT-Milan). The corresponding figures for CR were 32% (NCI-Bethesda) and 22% (INT-Milan) but in gross disease CR was seen in 16% (NCI-Bethesda) and 20% (INT-Milan) of the cases. Median duration of CR for all cases in these studies was >30 months and 20 months respectively (59, 60).

AC. ADM and CTX have shown synergistic effects in several experimental animal tumor models (61). Their use in combination has been suggested by several investigators. The dosage is: ADM 45 mg/m^2 i.v. and CTX 500 mg/m^2 i.v., repeated every 21 days for 10 cycles and a total ADM dosage of 450 mg/m^2. CR has been reported in about 50% (29% pathological and 20% clinical) and CR+PR in about 80% (62). Median survival of patients with clinical CR was 16 months and with pathological CR >31 months. Results reported by other groups are slightly inferior (63, 64). The INT of Milan reported pathological CR+PR in about 40% and pathological CR in only 8% (unpublished data).

PAC. This combination has the following recommended dosage: CTX 750 mg/m^2 i.v.; ADM 50 mg/m^2 i.v., and CDDP 50 mg/m^2 i.v. every 21 days (65).

The data from various sources indicate clinical CR in 30–50% and CR+PR in 65–80% (64–67). Pathological CR was obtained in 18% of cases. In randomized studies PAC has been superior to AC (64) and HEXA-CAF (67) regimens.

CHAP. CHAP consists of CTX 600 mg/m^2 i.v. on day 1; HMM 100–150 mg/m^2 p.o. on days 8 to 21; ADM 25 mg/m^2 i.v. on day 1; and CDDP 50–75 mg/m^2 i.v. on day 1. The cycle is repeated every 30 days (68). Clinical CR+PR has been obtained in 50 to 70% (68, 69) with pathological CR in about 30% (69). The CHAP regimen is more active than HEXA-CAF (70). The CHAP with introduction of a CDDP analogue, JM8 (350 mg/m^2) and dose modifications of the other drugs seems to have the same therapeutic efficiency with a lower toxicity (71).

There is unquestionable evidence that combination chemotherapy regimens, including active drugs as CTX, HMM, ADM and CDDP, give a clinical CR rate of 50–80% and pathological CR rate not exceeding 30%. It is also evident from the 4 most well-known studies (HEXA-CAF, AC, PAC, CHAP) that the pathological CR rate is high when the residual disease is <3 cm, whereas it is very low (5–15%) in bulky disease (72).

Recently several studies have shown that a combination of CTX and CDDP is equally effective with respect to rates of pathological CR, progression-free survival and survival as combination of 3 (CTX+CDDP+ADM) (58, 73) or 4 (CTX+CDDP+ADM+HMM) (74, 75) drugs. Furthermore, in the study of GICOG (73), the rate of pathologic CR, RFS and survival were not different in the 3 treatment (PAC vs. CP vs. CDDP alone) arms.

These trials also showed that the probability of achieving CR diminished with increasing tumor volume at the time for initiation of the chemotherapy.

Adjuvant chemotherapy

It is possible that adjuvant chemotherapy may give a higher cure rate in early ovarian carcinoma.

In the GOG study, patients in stages Ia and Ib after BSO+TAH were randomly assigned to one of three regimens: no further treatment; pelvic irradiation (50 Gy in 5–6 weeks); and PAM 0.2 mg/kg daily p.o. for 5 days every 4 weeks for a total of 18 months (76). While the rates of pelvic recurrence were similar in the 3 groups, distant or pelvic plus distant recurrences were less frequent in the PAM group. Thus radiotherapy did not prevent pelvic recurrences while PAM adjuvant therapy was beneficial in the prevention of distant recurrences. However, in this study staging was not precise since exploration of diaphragm and lymph nodes, peritoneal cytology and omentectomy were not performed; the significance of these parameters was not recognized when the study was started.

In the GOG and OCSG studies (36), patients with stage Ia–Ib–G1–G2 were randomized to receive no further treatment or PAM; after a median follow-up of 26 months there were no differences in RFS and survival.

In the non-randomized INT study on patients without residual disease following surgery performed in other hos-

pitals and complete non-surgical restaging, treated with adjuvant PAM (10 mg daily p.o., for a total of 12 cycles of 5 consecutive days each), the RFS from the onset of adjuvant PAM at 96 months was 77% for stage I patients and 73% for all patients. The survival was 87% for stage I patients and 81% for all patients (77).

The possible value of adjuvant chemotherapy can be evaluated when long-term results of ongoing studies become available. As a possible negative effect one must bear in mind the increased risk of acute non-lymphocytic leukemia (ANLL) in long-term survivors after therapy with alkylating agents (78). However, no case of ANLL has been observed with a cumulative dose of PAM below 700 mg (79)

Intraperitoneal chemotherapy

The peritoneal space is a separate body compartment with its own kinetic characteristics. When chemotherapy is administered by systemic route, the intraperitoneal drug levels are rather low. Therefore, intraperitoneal (i.p.) administration of chemotherapeutic agents may be advantageous for tumors, such as ovarian carcinoma, confined to the peritoneal cavity throughout most of its natural history (80).

In recent years, pharmacokinetic studies have demonstrated that i.p. administration of MTX, 5-FU, ADM, ARAC, PAM and CDDP gives prolonged exposure of the peritoneal surface to the drug, a higher drug concentration in target tissues than achieved by i.v. bolus injection, a plasma concentration of the drug, at 24 h of delivery, close to those obtained after the same interval when the same dose is infused by i.v. bolus injection, a toxicity similar, if not inferior, to that obtained by systemic route and a high local toxicity (abdominal pain) for MTX, 5-FU, and ADM but not for PAM and CCDP (81–84).

Clinical feasibility studies of i.p. therapy with CDDP, the drug of choice, have demonstrated the safety of the treatment (4).

The i.p. administration of CDDP is at INT of Milan performed by a Tenchkoff catheter positioned in the abdomen during surgery or some days after surgery. CDDP is administered every 21 days at the dose of 90 mg/m^2 in 2 l of normal saline plus 15 mEq/l KCl plus 1 000 U/l heparin. The infusion is given during 15 min with the same systemic precautions as for i.v. infusion. After 6 h the residual dialysate is drained from the abdomen. Complications (bowel perforation, leakage of fluid around the catheter) can follow i.p. CDDP administration, but are uncommon.

The theroretical indications of i.p. CDDP may be the following: a) as an alternative to i.p. radionuclides in early stages; b) for remission consolidation after pathologic CR obtained by systemic chemotherapy; c) as treatment after surgical CR; and d) as a means of treating non-bulky and bulky disease in combination with systemic chemotherapy.

Studies are in progress to assess the therapeutic efficacy of i.p. CDDP in patients with no residual or minimal residual disease following surgery.

Second-line chemotherapy

Patients unresponsive to first-line chemotherapy generally show low response rate to second-line chemotherapy. In patients extensively treated with combination chemotherapy the response rate is about zero, whereas in series treated with a single agent the response rate may be relatively high (10%–30%) (47, 50, 85). CDDP seems to be the most effective single drug for second-line chemotherapy. Doses of 30–50 mg/m^2 have produced PR in about 30% (56, 86) in patients with failure after alkylating agent therapy. High doses (120 mg/m^2) may be more effective than smaller doses. In patients who fail to respond to treatment with alkylating agents, high doses of CDDP have produced CR+PR in 50% (87).

Mount Sinai investigators, who have systematically evaluated combination chemotherapy with CDDP in previously treated ovarian carcinoma patients, reported that the CHAP regimen produced clinical CR+PR in more than 40% in patients with good performance status who did not respond to therapy with PAM, CTX + 5-FU, or thiotepa + MTX. The rate of CR was 14% (88).

The activity of CDDP has been confirmed by numerous studies. In a SWOG study CDDP administered for 12 cycles in combination with 5-FU and HMM to patients resistant to ADM+CTX, and in combination with HMM+ADM+5-FU to patients resistant to alkylating agents produced 31% and 25% pathological PR respectively. In view of the low response rate afforded by ADM, HMM, and 5-FU, this relatively high rate seems attributable to CDDP (89). In the Milan INT experience, CDDP used as rescue chemotherapy in patients with gross disease and extensive prior treatment, produced PR in 37% with a median duration of 6 months (unpublished data).

In a recent study (90) high-dose carboplatin (400 mg/m^2 by continuous infusion for 24 h for 2 consecutive days, cycle repeated every 35 days) induced clinical CR+PR in 27% of patients not responding to prior chemotherapy. In this study there was a marked cross-resistance between cisplatin and carboplatin; in fact no responses were observed in patients who had progressive disease during a prior cis-platinum regimen.

Hormone therapy

In the past some good results have been reported with progestogen therapy. If these old studies are reviewed according to the WHO criteria (91) PR occurred in about 10% (92–95).

In the recent years, a renewed interest in hormone therapy has been stimulated by the studies on estrogen and progesterone receptors.

The presence of cytoplasmic estrogen receptors (ER) and progesterone receptors (PgR) in the common epithelial cancer of the ovary was ascertained in the beginning of the 1980s (96–109).

ER and PgR are simultaneously present (ER+/PgR+) in 55% of cases, ER+/PgR− in 20%, ER−/PgR+ in 5%, whereas 20% of cases are receptor negative (ER−/PgR−). ER and PgR are present also in the normal ovary, in benign and in borderline tumors. The ER content of normal ovarian tissue is less than 3 fmol/mg protein (102, 103, 106, 107), while in about half of the primary ovarian carcinomas the estrogen binding levels 30 fmol/mg cytosol protein (108). The PgR content has been reported to be 8–80 fmol/mg protein.

The presence of ER and PgR seems dependant on the histological type, histological grade, and menopausal status. About 80% of endometrioid carcinomas had positive ER and PgR; conversely, no mucinous tumor and only 50% of serous tumors contained ER or PgR receptors. As in endometrial carcinomas, the ER content decreases with decreasing tumor differentiation.

As in breast cancer, premenopausal patients have a low incidence of ER positive tumor, probably because their high blood hormone levels block estrogen binding sites in the tissues (94). This finding has been reported by some authors (100, 110) but not by other (96, 98, 99, 106, 108, 111). Also, concerning the correlation between histological type and presence of ER there is no general agreement. ER was absent in mucinous carcinomas in the series of Ford et al. (98), while other authors have reported detectable although low levels of ER in this type of tumors (107, 108). Furthermore, some authors (97) have not observed any correlation between histological tumor grade and ER content.

Since tumor responses to hormone therapy are mediated through the steroid receptors there is the theoretical possibility that ovarian carcinoma also responds to progestin therapy. On this basis medroxyprogesterone acetate (MPA) has been used, although without direct determination of receptor status, in patients with advanced disease irresponsive to chemotherapy. In these newer studies MPA has been used at the following doses: i.m. injection of 500 mg daily for 3–4 weeks and then 500 mg weekly ×8 weeks or 500 mg twice weekly for 4 weeks. Another regimen has been i.m. 1 000 mg weekly × 8 weeks (112–115).

In one study a PR of 15% was reported in patients with advanced chemotherapy-resistant ovarian carcinoma (113), but in all other studies the PR has not exceeded 4% with a maximum duration of 5 months (112, 114, 115). Stable disease accounted for 13%. No responses were obtained with oral high doses (112, 113).

Even if the response rate is low there is no doubt that MPA produces beneficial subjective effects in terms of improved cenesthesia and improved performance status.

Antiestrogens, such as tamoxifen, appear to have in vitro a direct antiproliferative action on ovarian carcinoma cells with high levels (>30 fmol/mg cytosolic protein) of ER and PgR (116). In a recent study of GOG (117), tamoxifen at the dose of 20 mg twice daily administered to 80 patients after failure of combination chemotherapy, gave CR in 11% with a median duration of 8 months; PR accounted for 10% and SD for 35% of cases.

There is no doubt that ovarian carcinoma cells contain ER and PgR but at present its prognostic and therapeutic implications are only beginning to be assessed. More studies need to be done to determine if the presence of steroid receptors can predict the response to hormone therapy (118); if hormone receptor levels can give prognostic information, as reported by several investigators in small number of cases (97, 104, 105, 110); if sequential use of chemotherapy and hormone therapy can offer improvement of the results (118), and if high levels of ER can provide an opportunity for the development of new therapeutical means (radiopharmaceutical agents attached to high-affinity ER ligands) as suggested by several authors (102, 119, 120).

Biological response modifiers (BRM)

Interferon (alpha, beta, lymphoblastoid) has been used in small series and given i.m. (121–123), i.v. (123) and i.p. (124). In the study of GOG, lymphoblastoid interferon was administered, at the dose of 5×10^6 IU/m^2 i.m. × 5 days/week × 6 weeks, in patients with ovarian carcinoma unresponsive to chemotherapy. Clinical CR+PR was obtained in 19% of cases (121). In experimental models the i.p. administration of interferon gamma and tumor necrosis factor has increased the survival of tumor-bearing animals (125).

The addition of bacille Calmette Guerin (BCG) to multidrug chemotherapy regimens seems to have increased response rates and survival. In the SWOG series (126), BCG was administered by skin scarifications in the amount of 6×10^6 viable organisms on days 8 and 15 of treatment cycles including ADM (40 mg/m^2 i.v. on day 1) and CTX (200 mg/m^2 i.v. on days 3 and 6) repeated every 3–4 weeks. Pathological CR plus PR was obtained in 53% of cases with AC+BCG as opposed to 36% with AC alone ($p=0.05$). The median survival of the AC+BCG patients was statistically longer (23.5 months) than that of patients who received AC only (13 months) ($p<0.004$). These results were confirmed by the study of Wilbur et al. (127) in which patients at stage III–IV treated with CTX (1 000 mg/m^2 i.v. every 3 weeks) or CTX (750 mg/m^2 i.v.) plus CDDP (40 mg/m^2 i.v.) every 4 weeks, were randomly assigned within each arm to receive BCG by the tine technique 1–2 weeks after each chemotherapy dose. The survival and the median time to progress in the groups

receiving BCG was significantly longer than in the other group.

Corynebacterium parvum administered i.p. seems to inhibit the growth of ovarian carcinoma. In the study of the Sidney Faber Institute patients with minimal residual disease (<5 mm in diameter) after chemotherapy obtained pathological CR in about 20% of cases by the i.p. administration of Corynebacterium parvum at the dose of 250 $\mu g/m^2$ 4000 $\mu g/m^2 \times 3$–8 cycles every 2 weeks (128).

The BRM seem to have a certain activity in ovarian carcinoma. Nevertheless their clincal use has not yet confirmed the validity hypothesized on experimental models.

Surgical second look

To evaluate status after chemotherapy, laparoscopy and/or CT may be used. Unfortunately, the absence of disease by laparoscopy or CT scan is not confirmed by second look laparotomy (129). In fact, comparison between findings at laparoscopy or CT and at laparotomy has shown a large proportion of false negative cases, which for CT scan amounts to about 32% for visible tumor (<1 or >=1 cm, in size) (130).

Therefore, laparoscopy and CT scan can only exclude the presence of gross disease in critical sites, while surgical second look is the only valid method for detection of minor tumor foci.

Surgical second look may be indicated in patients with CR after chemotherapy for control of the therapeutic results and in patients with >50% reduction in tumor mass after chemotherapy in order to perform reductive or radical surgery. However, it can be questioned whether surgical second look can be curative or influence the prognosis and survival, and the procedure is therefore not uncontroversial (131). Surgical second look continues to be performed in the absence of a suitable alternative, but it is true that in cases with no residual or minimal residual disease, surgical second look is certainly useless. In such patients only a laparoscopic-radiologic restaging should be done at 12–18 months after beginning of therapy.

Prognostic factors

Several factors influence the prognosis of ovarian carcinoma as clinical stage, histological type, histological grade, age, extent of residual disease after surgery, and most likely type of treatment. Histological grade, and the extent of residual disease after surgery are the most important factors.

Stage. Before the introduction of modern staging, the 5-year survival of patients with ovarian carcinoma, regardless of treatment, was reported as follows: stage Ia: 62%; stage Ib: 59%; stage Ic: 53%; stage IIa: 62%; stage IIb: 39%; stage III: 7%; stage IV: 0% (1). In 'stage I', about 20% of the patients are really in stage III due to diaphragmatic or retroperitoneal metastases, and about 10% in stage Ic due to positive peritoneal cytology. The survival of true stage I patients is therefore much better than currently reported for stage I.

Histological type. The prognosis is worse for the serous, and undifferentiated types. These data, however, are also influenced by clinical stage and histological grade. As regards the clinical stage, about 90% of serous and undifferentiated carcinomas are diagnosed at an advanced stage. As regards the histological grade, serous carcinomas usually belong to G3 (132).

Histological grade. The prognosis of ovarian carcinoma varies inversely with the degree of differentiation (133). Well differentiated (G1) tumors have a better prognosis than moderately differentiated (G2) and, especially, poorly differentiated (G3) tumors. The differences in survival curves between grades 1–2–3 are in all reported series highly significant. Undifferentiated tumors carry a high risk of recurrence. Within each stage, an increase in degree entails a poorer prognosis (134).

Age. The 5-year survival is lower in patients aged >40 than in those <40 years. However, the influence of age on prognosis is only indirect, since the younger patients on average have lower clinical stage and histological grade. This is clearly evident from the data of M. D. Anderson Hospital and of INT (135, 136), whose patients in stages I and II were significantly younger (median 43.3 years) than those in stages III and IV (median 51.5 years).

Residual disease. The most important prognostic factor is the presence and the magnitude of residual disease after surgery.

Patients with negative peritoneal cytology have far better survival than patients with positive cytology. Thus, stages Ia ii and Ib ii have the same prognostic significance as stage Ic and in the recent FIGO classification these stages have been combined (30).

Stage III patients free of postoperative masses have a better prognosis than those in stage III peritoneal with residual disease after surgery. The 5-year survival appears related to the size of residual tumor. Stage III peritoneal and stage III peritoneal plus retroperitoneal patients have similar survival (29). The rare cases with stage III due to retroperitoneal involvement alone have a good prognosis (29).

Patients in stage IV with extra-abdominal disease (pleura alone; distant nodes alone) have survival comparable to (137) or longer than stage III patients with gross peritoneal disease. However, stage IV patients with distant metastasis alone are rare (29).

Conclusions

In conclusion, there is no doubt that progress has been made concerning diagnosis, staging and treatment of ovarian carcinoma. The proportion of cases in advanced stages has decreased and the survival rate within the initial stage has improved. But it is also true that despite

the introduction of combination chemotherapy the long-term prognosis for patients with advanced disease has not significantly changed over the last 10 years (138).

Although the understanding of biological characteristics and natural history of the disease and the more adequate use of the therapeutic armamentarium give some premises for an improved prognosis, ovarian carcinoma remains the most important gynecologic cause of death (139) and the major problem for gynecologists in years to come.

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