Editorial Article

Reflections on the FIGO surgical staging of invasive epithelial ovarian cancer

J. Menczer, *M.D.*

Department of Obstetrics and Gynecology, Gynecologic Oncology Unit, Edith Wolfson Medical Center, Holon
Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv (Israel)

Summary

The main aims and requirements of any staging system are: to determine the anatomical extent of disease, to allow uniform reporting of treatment results, comparison of their efficacy and pooling of data from various institutions. It should be based on the mode of spread of the neoplasm, take into consideration prognostic risk factors and be of prognostic value.

A critical review of the FIGO staging system for ovarian carcinoma indicates that these aims and requirements are not entirely fulfilled. Following are some examples. It does not include exract recommendations for comprehensive surgical staging in apparently early ovarian cancer and staging is therefore not performed uniformly. The presence of parenchymal liver and lung metastasis may be facilitated by modern imaging devices. However, according to FIGO rules only simple X-ray procedures are allowed preoperatively. The correlation between increasing stage and survival is inconsistent and sometimes contrary to that expected. Many known prognostic factors are not included in the present staging system. Although the aims of data pooling and of uniform reporting of treatment results have been achieved, the validity of some comparisons are questionable in view of the variations in staging.

The intent of this review was not to belittle the major contribution of staging to research, understanding and management of ovarian carcinoma, but to highlight its deficiencies. New data have accumulated since the FIGO staging system of ovarian carcinoma has been adopted and should prompt consideration of modifications such as incorporation of modern diagnostic procedures and of some established prognostic markers and reshuffling of certain substages.

*Key words:*Ovarian carcinoma; Surgical staging; Deficiencies of staging.

Ovarian carcinoma is the leading cause of death among gynecologic malignancies in most industrialized countries and is frequently already in an advanced stage at the time of diagnosis.

No staging system is ideal and this is also true for staging of gynecologic malignancies in general and staging of ovarian cancer in particular. Munell and Taylor [1] already proposed in 1949 one of the first stage groupings of ovarian cancer based on clinical examination and findings at exploratory laparotomy (Table 1). In Corscaden's textbook on Gynecologic Cancer (1970) edited by SB Gusberg and HC Frick (2) data are presented that indicate that it fulfilled one of the required conditions of an acceptable staging system, namely a correlation between stage and outcome. This quite simple grouping system may be regarded as the basis for the modern staging classification.

Since 1964 the International Federation of Gynecology and Obstetrics (FIGO) staging system has been universally adopted and used by gynecologic oncologists. The main principles of the FIGO staging system include, among others, the following rules:

- It should be established before any definitive treatment.
- Under no circumstances must it be changed on the basis of subsequent findings.
- Intravenous urography chest X-ray of the lung and skeleton is permitted.

Table 1. — *Munnell and Taylor classification of carcinoma of the ovary (1949).*

Stage I.	Involvment of ovary alone.
Stage II.	Both ovaries involved
Stage III.	One or both ovaries involved with extension to pelvic peritoneum or viscera (Fallopian tubes excluded).
Stage IV.	Involvement of ovaries and pelvis with spread to upper abdominal peritoneum or viscera.

The FIGO staging system of ovarian carcinoma has undergone several revisions. The current system was adopted in 1988 (Table 2). It is based on clinical findings and findings at the time of laparotomy.

The main aims of any staging system are:

1. To determine the anatomical extent of disease at the time of diagnosis
2. To allow uniform reporting of results of different treatments and comparison of the efficacy of treatments and
3. To allow pooling of data from various institutions.

A satisfactory staging system should also fulfill several requirements.

A. It should be based on the mode of spread of the neoplasm.

B. It should take into consideration prognostic risk factors.

C. It should be of prognostic value. The prognosis should correlate with the stage i.e. the higher the stage the less favorable the outcome.

The following discussion is dealing with the FIGO staging of epithelial ovarian cancer and its purpose is to examine critically whether it fulfills the aims and the requirements outlined above.

Aims

1. Determination of anatomical extent of disease

According to the FIGO staging classification (Table 2) ovarian cancer confined to the ovaries, confined to the pelvis, extrapelvic intraperitoneal spread and distant spread are defined as Stage I, II, III and IV respectively.

Allotting a patient to a certain stage is not a mathematical determination; it is rather an intelligent estimation. This is particularly relevant for early stage disease.

It is generally agreed that when early ovarian carcinoma is encountered and especially when it is apparently confined to one or both ovaries, accurate surgical staging should be performed. On one hand this may result in upstaging of 20 to 30% of the patients [3, 4]. On the other hand comprehensive surgical staging of early

Table 2. — *FIGO staging classification 1988.*

Stage I.	Growth limited to the ovaries.
IA:	Growth limited to one ovary; no ascites; No tumor on the external surface: capsule intact.
IB:	Growth limited to both ovaries; no ascites; no tumor on the external surface, capsule intact.
IC:	Tumor either Stage IA or Stage IB but with tumor on the surface of one or both ovaries or with capsule ruptured, or with ascites* containing malignant cells or with positive peritoneal washings.
Stage II.	Growth involving one or both ovaries with pelvic extension.
IIA:	Extension and/or metastasis to the uterus or tubes
IIB:	Extension to other pelvic tissues.
IIC:	Tumor either Stage IIA or IIB or with tumor on the surface of one or both ovaries or with capsule(s) ruptured, or with ascites containing malignant cells or with positive peritoneal washings.
Stage III.	Tumor involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes; superficial liver metastases equals Stage III; tumor limited to the true pelvis with histologically verified malignant extension to small bowel or omentum.
IIIA:	Tumor grossly limited to the true pelvis with negative nodes but histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
IIIB:	Tumor of one or both ovaries; histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes negative
IIIC:	Abdominal implants greater than 2 cm in diameter or positive retroperitoneal or inguinal nodes
Stage IV.	Growth involving one or both ovaries with distant metastasis outside the peritoneal cavity. If pleural effusion is present there must be positive cytology to allot a case to Stage IV; parenchymal liver metastasis equals Stage IV.

*Ascites is the presence of peritoneal effusion, which in the opinion of the surgeon is pathological or/and clearly exceeds normal amounts.

To evaluate the impact on prognosis of the different criteria for allotting cases to Stage IC or IIC, it would be of value to know whether the rupture of the capsule was spontaneous or caused by the surgeon and if the source of malignant cells detected was peritoneal washings or ascites.

ovarian cancer can identify a group of patients that do not require adjuvant chemotherapy and these patients may be spared the inconvenience, complications and cost of such treatment [5, 6].

In order to allot a patient to truly Stage I or Stage II, multiple blind biopsies from macroscopically normal appearing peritoneal surfaces have to be taken. Microscopically involved tissue can therefore be missed and the patient understaged. The FIGO staging system does not indicate where from and how many biopsies should be taken. Obviously assessment of areas of predilection for metastases should be included, such as the omentum, the cul-de-sac, the para-colic gutters, and the undersurface of the diaphragm and other serosal surfaces. The undersurface of the diaphragm may be involved in up to 11% of presumed Stage I patients [7, 8]. It is not clear however whether the diaphragm should be biopsied or whether cytological smears or scrapings are adequate. In a recently published large retrospective study of Stage I patients [9], based on data from six countries (Canada and five European countries), peritoneal washings and scrapings of the diaphragm were routinely done only in one of them.

The status of pelvic and para-aortic lymph nodes has to be assessed as well. Microscopically involved lymph nodes may upstage an apparently early ovarian cancer patient to Stage IIIC. However the FIGO staging system does not advise how lymph-node involvement should be evaluated in presumed Stage I patients, nor does it indicate how many lymph nodes are considered a representative sample. Recommendations for comprehensive surgical staging are therefore not uniform. Thus, for example, three popular textbooks vary in their recommendations. In one [10] selected lymphadenectomy of pelvic and para-aortic nodes is recommended while in another lymph-node sampling is recommended [11] and a third [12] actually proposes lymphadenectomy as the best way to assess lymph nodes. Lymph-node assessment is also not uniform in various publications. The European Organization for Research and Treatment of Cancer (EORTC) and the Gynecologic Oncology Group (GOG) in the US recommend lymph-node sampling [13]. However, in one international study of 1,545 Stage I patients [9] biopsy or fine needle aspiration of suspicious retroperitoneal lesions was performed. In a second recent paper dealing with the benefits of comprehensive surgical staging in early ovarian cancer, the patients underwent bilateral pelvic and para-aortic lymph-node sampling [14]. In contrast, in a third study, bilateral pelvic and para-aortic lymphadenectomy up to the left renal vein is recommended [15]. It is noteworthy that an Italian randomized trial compared the value of lymph-node sampling to lymphadenectomy with regard to diagnostic ability, time to relapse and survival in apparently Stage I patients [16]. Interestingly, no difference in outcome between the groups was found although the rate of positive lymph nodes was higher in the lymphadenectomy group.

The technique and extent of lymph-node excision for assessment is also not uniform. The European Guidelines for Staging of Ovarian Cancer (EGSOC) require sampling of nodes in the area between the inferior mesenteric artery and left renal vein whereas the GOG guidelines require dissecting this area only when palpable suspicious nodes are present. On the other hand the GOG guidelines require excision of the distal half of the obturator fat pad anterior to the obturator nerve while the EGSOC guidelines do not require this step [17].

In a review dealing with management of early ovarian carcinoma [18] the authors state that by thorough sampling a median of 20 pelvic and 15 para-aortic lymph nodes should be obtained. Can this goal be achieved merely by lymph-node sampling or is lymphadenectomy necessary to achieve it?

The rules for staging of more advanced disease are also not devoid of problems. Patients with parenchymal liver involvement and lung metastases are classified as Stage IV. Parenchymal liver involvement may be missed by mere manual palpation at the time of laparotomy. Similarly, parenchymal lung metastasis may be missed by simple X-ray. The presence of metastases in both these sites can be facilitated by currently available imaging procedures, such ultrasonography (US) and computed tomography CT [19]. By not using these modern techniques, patients may be unjustifiably understaged. However, according to FIGO rules only simple imaging procedures are allowed preoperatively. The reason that the use of US, CT, magnetic resonance imaging (MRI) and the more advanced positron-emission tomography (PET) are not required for staging purposes is that they are not yet universally available and because the interpretation of results are not always entirely consistent with the findings at laparotomy. Nevertheless these modern imaging procedures are often performed in many centers and used for treatment-planning, for evaluation of response to treatment and also as a basis for future follow-up and diagnosis of recurrence and recurrence-site. Modern preoperative imaging may also diagnose non-ovarian malignancies – such as carcinoma of the pancreas – that are not managed by gynecologic oncologists.

Isn't it time to reconsider the official incorporation of modern imaging procedure results into the staging system or at least as adjuncts to staging?

CT can also assist in predicting which patients may not be amenable to optimal cytoreduction and thus indentify those that are candidates for neoadjuvant chemotherapy [20, 21]. Although still regarded as experimental, many retrospective trials demonstrate that neoadjuvant chemotherapy and interval cytoreduction are feasible in the treatment of ovarian cancer patients [22-25]. Operative laparoscopy has been described as a means of surgical staging of ovarian carcinoma. This is still an unproven technique, but is gaining popularity [26-28]. Is it acceptable to allot patients to a certain stage when the anatomical extent of disease at diagnosis has been determined by CT or laparoscopy and not by laparotomy as required by the FIGO rules?

2. Uniform reporting

All modern reports of treatment results are based on the FIGO stage of ovarian carcinoma. Prospective randomized studies comparing various treatment modalities also take stage into consideration. The important GOG studies that demonstrated that comprehensive staging can identify a group of patients that can be followed without adjuvant chemotherapy [5] and the study that indicated that postoperative chemotherapy with the combination of paclitaxel and cisplatin is superior to the combination of cisplatin and cytophosphan [29] were performed on Stage I-II and Stage III-IV ovarian carcinoma patients respectively. It therefore seems that the aim of uniform reporting of treatment results allowing the comparison between different medical centers and various treatments, has been achieved. However in view of the variations in staging and substaging procedures between different institutions and different countries the validity of some comparisons are sometimes questionable.

3. Pooling of data

This aim of staging has also been achieved. Many important studies and statistically meaningful data with regard to the natural history and management of ovarian carcinoma are based on data relatively rapidly accrued by collaboration of various institutions in a specific country or international cooperation. The studies by the GOG, the European Organiztion for the Research and Treatment of Cancer (EORTC), and the International Collaborative Ovarian Neoplasm Study (ICON), are just a few excellent examples of such studies. And yet some of these studies are often criticized exactly for the reason that their results are based on data accrued in different institutions and different populations.

Requirements

A. Mode of spread

There are three main modes of spread of ovarian cancer. One is local, i.e., in continuity to pelvic organs. The second is by intraperitoneal dissemination of free tumor cells shed from the ovary and their distribution by normally circulating peritoneal fluid. The third important mode of spread is by lymphatic pathways to lymph nodes. Hematologic spread is rare.

The FIGO stage classification is indeed based on these modes of spread. However it seems to imply that there is a gradual progression from involvement of one ovary to involvement of both ovaries, than involvement of pelvic organs and finally further spread to other intraperitoneal organs and formation of distant metastases. The anatomical extent of the tumor is of great prognostic value. But, to the best of my knowledge, a gradual, stepwise expansion of ovarian carcinoma has not been proven. Once it was assumed that epithelial ovarian cancer arises synchronically in many foci in the peritoneal cavity and that this was the reason that the majority of these malignancies are diagnosed when the disease is already present far beyond the ovaries. Presently it has been shown that ovarian carcinoma is a monoclonal disease [30, 31]. However the actual natural history of the anatomical progression of ovarian carcinoma after oncogenesis is not known.

B. Prognostic value

In the 1998-FIGO annual report on the results of treatment in gynecological cancer [32], of almost 3,000 ovarian carcinoma patients diagnosed between 1990 to 1992, there is a consistent gradual decrease in the sur-

vival rate with advancing stage (Table 3). This correlation is however less consistent when substages are looked at. The survival in Stage IC is better than in Stages IB and IIA and the survival in Stage IIC is better than in Stage IIB. The differences may not be significant, but these results are strange and contrary to what should be expected. Similarly in a large study of Stage I patients [9] a significantly better survival of Stage IA than Stage IB patients was found. But in that study there seems to be no difference in survival between Stage IB and Stage IC patients, according to the presented survival curves.

In carefully staged patients, from nine Dutch oncology centers, with Stage IA to Stage IIA well differentiated tumors, a 100% 5-year disease-free survival was reported for all the substages [33] and a watch and wait policy was advocated in these substages with the possible exception of Stage IC.

In 1994 the SGO issued a handbook on staging of gynecologic malignancies. In the discussion of ovarian carcinoma staging it is noted that the survival of patients with Stage I grade 3 tumors, Stage IC tumors due to the presence of malignant cells in ascites or peritoneal washings, Stage II and Stage IIIA tumors, is remarkably similar.

Intra-abdominal spread allots the patient to Stage III. In one study the substaging of Stage III tumors was found to be valid and of prognostic significance [34]. Indeed the distinction by FIGO according to size of the macroscopic tumor at the time of diagnosis of Stage III disease is rightfully made (< 2 cm = Stage IIIB; > 2 cm = Stage IIIC). Patients with Stage III large volume disease who are successfully cytoreduced to residual tumor of less than 1 cm do not have as favorable a prognosis as those presenting with small volume extrapelvic disease [35]. This indicates that large tumor size at the time of diagnosis indicates a biologically more aggressive tumor type with a more unfavorable prognosis. The size of extrapelvic tumor at the time of diagnosis of Stage III tumors, is thus of prognostic importance. However, Stage IIIC comprises patients with disease outside the pelvis larger than 2 cm and also patients that have only retroperitoneal lymph-node involvement regardless of the intraperitoneal findings. Should these patients be grouped under one substage? Do the situations resulting from diverse modes of spread indicate different biologic behavior or are these patient groups identical? Is their treatment outcome identical? It has been shown that patients with presumed Stage I/II ovarian carcinoma upstaged to Stage III after systematic lympadenectomy have similar survival to Stage I/II patients and a superior survival to other Stage III patients [36]. Retrospective studies indicate that the 5-year survival of patients with Stage IIIC disease with only retroperitoneal spread exceeds 60% and is higher than of Stage IIIC patients with intraperitoneal spread [37]. In this context it is noteworthy that in the 1998 FIGO annual report the survival of patients with Stage IIIC is very similar to that in patients with Stage IIIB, possibly due to the inclusion of patients with only lymph node involvement in the IIIC group.

With regard to stage-subdivision of ovarian carcinoma, the current system does not fulfill the condition of an inverse correlation between advancing stage, especially between some substages, and survival rate. It seems that the division into substages is more intuitive than based on solid data.

C. Prognostic risk factors

In addition to stage, many prognostic factors of ovarian carcinoma have been hitherto identified. These include age and performance status [34, 38, 39] and the presence of large volume ascites [40]. Histological grade is also a very important prognostic indicator (9). The histological clear cell carcinoma subtype has been shown to have a worse prognosis than other histological subtypes [41, 42]. Shouldn't at least some of these factors be accounted for in the staging system? Bilaterality, tumor excrescences and pre- or intraoperative tumor rupture are included in the substages of Stage I. However in some studies [40, 43] these factors had no influence on prognosis.

Table 3. — *Survival of ovarian carcinoma patients (1990-1992) by stage and substage according to the 1998 FIGO annual report.*

	Stage									
	I			II			III			IV
	IA	IB	IC	IIA	IIB	IIC	IIIA	IIIB	IIIC	
Survival (%)	86.9	71.3	79.2	66.6	55.1	57.0	41.1	24.9	23.4	
Total		82.1			58.5			25.1		11.1

The currently standard concept of the surgical approach to ovarian cancer is the necessity for optimal cytoreduction. Optimal cytoreduction is not well defined and is variously considered when the diameter of the largest residual postoperative tumor nodule is smaller than 2, 1.5, 1, 0.5 cm or when there is no macroscopic residual disease. It should however be pointed out that to date no prospective randomized study of cytoreductive surgery has been performed. It is therefore not known whether the surgical intervention actually produces improved survival or whether there is some inherent biologic behavior of a given ovarian cancer that allows optimal cytoreduction, thus conferring a more favorable prognosis. In other words it is not known whether optimal cytoreduction is more a marker for, rather than the cause of improved survival. Aggressive cytoreductive surgery is strongly supported by some authors [44-46] and seriously questioned by others [47-50]. Nevertheless, it has been shown in innumerable retrospective studies that the smaller the size of the residual disease the better the outcome. This seemingly important prognostic factor is also not included in the staging procedure.

New techniques of ovarian tumor assessment are also currently available, such as flow cytometry, quantitative tissue analysis, molecular biological assessment techniques for cell proliferation markers, oncogenes and tumor suppressor genes [51-53]. While the prognostic value of these techniques has as yet not been definitively established, future staging classifications may also have to take some of them into account.

With regard to the relation between stage and therapy, two diverse concepts seem to exist. One concept maintains that staging should also be used as a guideline to therapy, and the other regards staging only as a means of describing the anatomical extent of disease. These two distinct concepts are very prominent in staging of cervical cancer and are expressed by the different definitions of early invasive cervical carcinoma [54, 55]. The Society of Gynecologic Oncologists (SGO) in the US defines microinvasive cervical carcinoma as a lesion in which the neoplastic epithelium invades the stroma in one or more places to a depth of 3 mm or less below the basement membrane and in which lymphatic or vascular space (LVS) involvement is not present. The FIGO definition of Stage IA1 disease is identical with regard to depth of invasion (with the additional condition that horizontal extension should be no more than 7 mm) but LVS involvement is not taken into account. Microinvasion according to the SGO definition can be treated conservatively and is thus a guideline for therapy while the FIGO definition of Stage IA1 cannot serve this purpose. In contrast, an admirable attempt to combine these two concepts has been made by the new proposed FIGO classification of trophoblastic disease. It combines the previous FIGO classification based on anatomic extension with a risk factor scoring system. This staging/scoring system allows not only uniform reporting and valid comparison between different treatments, but also serves as a guideline for therapy. Patients with a low score are treated by single-agent and patients with a high score with combination chemotherapy [56].

These diverging concepts with regard to staging and therapy may not be relevant to ovarian carcinoma. Only a small subgroup of carefully staged stage I patients are treated by surgery alone. All patients with Stage IC or higher, receive the same type of postoperative adjuvant chemotherapy. The substaging of Stages II-IV is therefore of no therapeutic importance. Therefore many studies are lumping these stages when treatment results are reported [29, 57, 58].

Staging is a very important tool in gynecologic oncology. The intent of this discussion was not to belittle its major contribution to the research, understanding and management of ovarian carcinoma. Its main purpose is to highlight and increase the awareness of its deficiencies. The current FIGO staging of ovarian carcinoma has prevailed for the last 15 years. Meanwhile, new data have been accumulated and should prompt some modifications of this staging system. The task of the FIGO staging committee is going to be very difficult. It should consider the use of some modern diagnostic procedures, reshuffling of some of the substages and incorporation of some of the clinical, and histological prognostic factors, as well as biological prognostic markers into the staging system.

References

[1] Munell E. W., Taylor H. C.: "Ovarian carcinoma; A review of 200 primary and 51 secondary cases". *Am. J. Obstet. Gynecol.*, 1949, *58*, 943.

[2] "Cancer of the ovary". In: "Corscaden's Gynecological Cancer". Gusberg SB, Frick HC (eds.), Baltimore, MD. Williams and Wilkins Co. (fourth edition), 1970, 555.

[3] Young R. C., Decker D. G., Wharton J. T., Piver M. S., Sindler W. F., Edwards B. K *et al.*: "Staging laparotomy in early ovarian cancer". *JAMA*, 1983, *250*, 3072.

[4] Wu P. C., Qu J. Y., Lang J. H., Huang R. L., Tang M. Y., Lian L. J.: "Lymph node metastasis of ovarian cancer: a preliminary survey of 74 cases of lymphadenectomy". *Am. J. Obstet. Gynecol.*, 1986, *5*, 1103.
[5] Young R. C., Walton L. A., Ellenberg S. S., Homeseley H. D., Wilbanks G. D., Decker D. G.: "Adjuvant therapy in stage I and stage II epithelial ovarian cancer". *New Engl. J. Med.*, 1990, *322*, 1021.
[6] Monga M., Carmichael J. A., Sheley W. E., Kirk M. E., Krepart G. V., Jeffrey J. F. *et al.*: "Surgery without adjuvant chemotherapy for early ovarian epithelial carcinoma after comprehensive surgical staging". *Gynecol. Oncol.*, 1991, *41*, 195.
[7] Piver M. S., Barlow J. J., Lele S. B.: "Incidence of subclinical metastasis in stage I and II ovarian carcinoma". *Obstet. Gynecol.*, 1978, *52*, 100.
[8] Soper J. T., Johnson V., Berchuk A., Clarke-Pearson D. L.: "Comprehensive restaging laparotomy in women with apparent early stage ovarian carcinoma". *Obstet. Gynecol.*, 1992, *80*, 949.
[9] Vergote I., Barbanter J. D., Fyles A., Bertelsen K., Einhorn N., Sevelda P. *et al.*: "Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma". *Lancet*, 2001, *357*, 176.
[10] "Epithelial ovarian cancer". In: "Clinical Gynecologic Oncology". (sixth edition). DiSaia P. J., Creasman W.T. (eds.), St. Luis, Toronto, London, Mosby Inc. 2000, 1.
[11] "Principles and Practice of Gynecologic Oncology". Hoskins W. J., Perez C. A., Young R. C. (eds.), Philadelphia, JB Lipincott Co. 1992, 746.
[12] Surgical Gynecologic Oncology. Burghardt E. (ed.), New York, Thieme, 1993, 457.
[13] Trimbos J. B.: "Staging of early ovarian cancer and the impact of lymph node sampling". *Int. J. Gynecol .Cancer*, 2000, *10 (suppl. 1)*, 8.
[14] Le T., Adolph A., Krepart G. V., Lotocki R., Heywood M. S.: "The benefits of comprehensive surgical staging in the management of early-stage epithelial ovarian carcinoma". *Gynecol. Oncol.*, 2002, *85*, 351.
[15] Leblanc E., Querleu D., Narduci F., Chauvet M. P., Chevalier A., Lesoin A. *et al.*: "Surgical staging of early invasive epithelial ovarian tumors". *Semin. Surg. Oncol.*, 2000, *19*, 36.
[16] Favalli G., Odicino F., Torri V., Pecorelli S.: "Early stage ovarian cancer: the Italian contribution to clinical research. An update". *Int. J. Gynecol. Cancer*, 2001, *11 (suppl. 1)*, 12.
[17] Trimbos J. B., Bolis G.: "Guidelines for staging of ovarian cancer". *Obstet. Gynecol. Survey*, 1994, *49*, 814.
[18] Young R. C., Pecorelli S.: "Management of early ovarian cancer". *Sem. Oncol.*, 1998, *25*, 335.
[19] Coakley F. V.: "Staging ovarian cancer: role of imaging". *Radiol. Clin. N. Am.*, 2002, *40*, 609.
[20] Nelson B. E., Rosenfeld A. T., Schwartz P. E.: "Preoperative abdominopelvic computed tomographic prediction of optimal cytoreduction in epithelial ovarian carcinoma". *J. Clin. Oncol.*, 1993, *11*, 166.
[21] Byrom J., Widjaja E., Redman C. W., Jones P. W., Tebb S.: "Can preoperative computed tomography predict resectability of ovarian carcinoma at primary laparotomy?". *Br. J. Obstet. Gynecol.*, 2002, *109*, 369.
[22] Schwartz P. E., Chaers J. T., Makuch R.: "Neoadjuvant chemotherapy for advanced ovarian cancer". *Gynecol. Oncol.*, 1994, *53*, 33.
[23] Vergote I., de Werer I., Tjalma W., van Gramberen M., Decloedt J., van Dam P.: "Interval surgery: an alternative for primary surgical debulking?". *Semin. Surg. Oncol.*, 2000, *19*, 49.
[24] Kuhn W, Rutke S., Spathe K., Schmalfeldt B., Florak G., von Hundelshausen B. *et al.*: "Neoadjuvant chemotherapy followed by tumor debulking prolongs survival for patients with poor prognosis in International Federation of Obstetrics and Gynecology stage IIC ovarian cancer". *Cancer*, 2001, *92*, 2585.
[25] Huober J., Meyer U., Wallwiener D.: "The role of neoadjuvant chemotherapy and interval laparotomy in advanced ovarian cancer". *J. Cancer Res. Clin. Oncol.*, 2002, *128*, 153.
[26] Childers J. M., Lang J., Surwit E. A., Hatch K. D.: "Laparoscopic surgical staging of ovarian cancer". *Gynecol. Oncol.*, 1995, *59*, 25.
[27] Chi D. S., Curtin J. P.: "Gynecologic cancer and laparoscopy". *Obstet. Gynecol. North Am.*, 1999, *26*, 201.
[28] Ben David Y., Bustan M., Shalev E.: "Laparoscopy as part of the evaluation and management of ovarian and cervix neoplasms". *Harefuah*, 2001, *140*, 464.
[29] McGuire W. P., Hoskins W. J., Brady M. F., Krucera P. R., Partridge E. E., Look K.Y. *et al.*: "Cyclophosphamide and cysplatin compared with paclitaxel and cisplatin in patients with stage III and IV ovarian cancer". *N. Engl. J. Med.*, 1996, *334*, 1.
[30] Mok C. H., Tsao S. W., Knapp R. C., Fishbaugh P. M., Lau C. C.: "Unifocal origin of advanced human epithelial ovarian cancers". *Cancer Res.*, 1992, *52*, 19.
[31] Gallion H. H., Guarino A., DePriest P. D., van Nagel J. R. Jr, Vaccarello L., Berek J. S. *et al.*: "Evidence for unifocal origin in familial ovarian cancer". *Am. J. Obstet. Gynecol.*, 1996, *174*, 1102.
[32] FIGO Annual report on the results of treatment in gynecological cancer. *J. Epidem. Biostat.*, 1998, *3*, 76.
[33] Trimbos J. B., Schueler J. A., van der Burg M., Hermans J., van Lent M., Heinz A. P. *et al.*: "Watch and wait after careful surgical treatment and staging in well differentiate early ovarian cancer". *Cancer*, 1991, *67*, 597.
[34] Partridge E. E., Gunter B., Gelder M. S., Alvarez R. D., Soong S. J., Austin J. M. *et al.*: "The validity and significance of substages in advanced ovarian carcinoma". *Gynecol. Oncol.*, 1993, *48*, 236.
[35] Hoskins W. J., Bundy B. N., Thigpen J. T., Omura G. A.: "The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage II epithelial ovarian cancer: a Gynecologic Oncology Group study". *Gynecol. Oncol.*, 1992, *47*, 159.
[36] Onda T., Yoshikawa H., Yasugi T., Mishima M., Nagokawa S., Yamada M. *et al.*: "Patients with ovarian carcinoma upstaged to stage III after systematic lympadenectomy have similar survival to stage I/II patients and superior survival to stage III patients". *Cancer*, 1998, *83*, 1555.
[37] Di Re F., Baiochi G.: "Value of lymph node assessment in ovarian cancer: Status of the art at the end of the second millennium". *Int. J. Gynecol. Cancer*, 2000, *10*, 435.
[38] Thigpen T., Brady B. S., Omura G. A., Creasman W. T., McGuire W. P., Hoskins W. J. *et al.*: "Age as a prognostic factor in ovarian carcinoma". *Cancer*, 1993, *7*, 606.
[39] Cervantes A.: "Prognostic factors in advanced ovarian carcinoma". *Int. J. Gynecol. Cancer*, 1997, *7 (suppl. 1)*, 4.
[40] Dembo A. J., Stenwig A. E., Berle E. J., Bush R. S., Kjorstad K.: "Prognostic factors in patients with stage I epithelial ovarian cancer". *Obstet. Gynecol.*, 1990, *75*, 263.
[41] Goff B. A., de la Cuesta S., Muntz H. G., Fleischhacker D., Ek M., Rice L. W. *et al.*: "Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease". *Gynecol. Oncol.*, 1996, *60*, 412.

[42] Sugiyama T., Kamura T., Kigawa J., Terakawa N., Kikuchi Y., Suzuki M. *et al.*: "Clinical characteristics of clear cell carcinoma of the ovaries: a distinct histologic type with poor prognosis and resistance to platinum based chemotherapy". *Cancer*, 2000, *88*, 2584.
[43] Sevelda P., Vavra N., Schemper M., Salzer H.: "Prognostic factors for survival in stage I epithelial ovarian carcinoma". *Cancer*, 1990, *65*, 2349.
[44] Eisenkop S. M., Friedman R. L., Wang H. J.: "Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study". *Gynecol. Oncol.*, 1998, *69*, 103.
[45] Bristow R. E., Montz F. J., Lagasse L. D., Leuchter R. S., Karlan B. Y.: "Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer". *Gynecol. Oncol.*, 1999, *72*, 278.
[46] Bordman C. H., Webb M. J.: "Surgery in ovarian cancer". *Eur. J. Gynecol. Oncol.*, 2001, *22*, 89.
[47] Heinz A. P.: "Surgery in advanced ovarian carcinoma. Is there proof to show the benefit?". *Eur. J. Surg. Oncol.*, 1988, *14*, 91.
[48] Menczer J.: "Cytoreductive surgery in the treatment of advanced ovarian carcinoma. Some controversial aspects". *Eur. J. Gynecol. Oncol.*, 1992, *13*, 246.
[49] Covens A. L.: "A critique of surgical cytoreduction in advanced ovarian cancer". *Gynecol. Oncol.*, 2000, *78*, 269.
[50] Hunter R. W., Alexander N. D., Sutter W. P.: "Meta-analysis of surgery in advanced ovarian carcinoma: is maximum cytoreductive surgery an independent determinant of prognosis". *Am. J. Obstet. Gynecol.*, 1992, *166*, 504.
[51] Fox H.: "Clinical value of new techniques of gynecologic tumor assessment". *Int. J. Gynecol. Cancer*, 1997, *7*, 337.
[52] Tay Y. T., Lee S., Weisman C., Strabel T., Canistra S. A.: "BAX protein expression and clinical outcome in epithelial ovarian cancer". *J. Clin. Oncol.*, 1998, *16*, 2583.
[53] Cooper B. C., Sood A. K., Davis C. S., Ritchie J. M., Soroski J. I., Anderson B. *et al.*: "Preoperative CA125 levels: an independent prognostic factor for epithelial ovarian cancer". *Obstet. Gynecol.*, 2002, *100*, 59.
[54] Creasman W. T.: "New gynecologic cancer staging". *Gynecol. Oncol.*, 1995, *58*, 157.
[55] Creasman W. T.: "Stage IA of the cervix: Finally some resolution of definition and treatment?". *Gynecol. Oncol.*, 1999, *74*, 163.
[56] Kohorn E.: "The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: descriptive and critical assessment". *Int. J. Gynecol. Oncol.*, 2001, *11*, 73.
[57] ICON2: randomized trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin and cisplatin) in women with ovarian cancer. *Lancet*, 1998, *352*, 1571.
[58] ICON3 Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cysplatin in women with ovarian cancer: the ICON3 randomized trial. *Lancet*, 2002, *360*, 505.

Address reprint requests to:
J. MENCZER, M.D.
Gynecologic Oncology Unit
Dept. of Obstetrics and Gynecology
E. Wolfson Medical Center
Holon (Israel)