Nova klasifikacija raka jajčnikov, jajcevodov in peritoneja mednarodnega združenja ginekologov in porodničarjev (FIGO)

New international federation of gynecology and obstetrics (FIGO) staging classification for cancer of the ovary, fallopian tube, and peritoneum

Avtor / Author

Ustanova / Institute

Darja Arko[1], Verena Gajser[2], Iztok Takač[1,3]

[1]Univerzitetni klinični center Maribor, Klinika za ginekologijo in perinatologijo, Maribor, Slovenija; [2]Zdravstveni dom dr. Adolfa Drolca Maribor, Maribor, Slovenija; [3]Univerza v Mariboru, Medicinska fakulteta, Katedra za ginekologijo in porodništvo, Maribor, Slovenija

[1]University Medical Centre Maribor, Division of Gynecology and Perinatology, Maribor, Slovenia; [2]Adolf Drolc Health Centre Maribor, Maribor, Slovenia; [3]University of Maribor, Faculty of Medicine, Department of Gynecology and Obstetrics, Maribor, Slovenia

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Naslov za dopisovanje / Correspondence
Doc. dr. Darja Arko, dr. med., Klinika za ginekologijo in perinatologijo, Univerzitetni klinični center Maribor, Ljubljanska 5, SI-2000 Maribor
Telefon +386 23212445
Fax +386 23212085
E–pošta: darja.arko@ukc-mb.si

Izvleček

Mednarodno združenje ginekologov in porodničarjev (FIGO) je leta 2012 sprejelo novo klasifikacijo raka jajčnikov, jajcevodov (zadnja predhodna verzija 1988) in peritoneja; slednji do sedaj ni imel svoje razdelitve v stadije. Klasifikacija je v veljavo stopila januarja 2014.

Spremembe v novi klasifikaciji so nastale kot posledica najnovejših spoznanj v razumevanju molekularne patogeneze raka jajčnikov in na podlagi novih odkritij v sklopu prognostičnih dejavnikov. Ugotovili so tudi, da so si primarni rak jajcevodov, primarni rak peritoneja in rak jajčnikov na podlagi simptomatike, zdravljenja in prognoze v mnogih pogledih zelo podobni.

Abstract

The new staging system for cancer of the ovary, fallopian tube, and peritoneum (last revision, 1988) was approved under the auspices of the International Federation of Gynaecology and Obstetrics (FIGO) in 2012. Previously, peritoneal cancer did not have a staging system. The new classification has been valid since January 2014.

New findings and a more complete understanding of the molecular pathogenesis underlying ovarian cancer, combined with scientific discoveries identifying prognostic factors have led to changes in the new FIGO classification system. Based on the same symptomatology, treatment, and prognosis, it was established that a lot of similarities are shared between ovarian cancer, primary fallopian tube cancer, and primary peritoneal cancer.

INTRODUCTION

Cancer staging is essential for patient management. Cancer staging is based on the biology of the individual tumour type, and determined by protocols that are agreed upon internationally and enable comparison and sharing of gained experience (1). The main purpose of such classification schemes is to provide a uniform terminology that allows comparison and assignment of patients and their tumours to prognostic groups requiring specific treatment. Cancer staging is a process which requires continuous development (2).

The International Federation of Gynaecology and Obstetrics (FIGO) was the first organization to develop a new staging system for classification of gynaecologic cancers (3). The beginning of cancer classification dates back to the late 1920s when the first staging system for cervical cancer was published by the League of Nations (4).

Eventually, other gynaecologic cancer staging systems joined the staging system for cervical cancer, and since 1958 FIGO has been the official patron of the classification (4).

The anatomic extension of ovarian and fallopian tube cancer staging also follows the FIGO data and suggestions. Subsequently, the staging was acquired by the International Union for Cancer Control (UICC) and the American Joint Commission on Cancer (AJCC), and adjusted to the TNM-cancer staging system. The last revision of the FIGO/TNM system was made in 1988 in Rio de Janeiro; however, the pathologic characteristics of ovarian cancer, the diagnosis, treatment, and prognosis have since changed considerably (2, 5).

The process leading to the proposed changes to the staging of ovarian, fallopian tube, and primary peritoneal cancers began 3 years ago under the auspices of FIGO. The new staging was adopted by consensus of the participants at the FIGO meeting held in Rome in 2012. The new staging was presented to the FIGO Executive Board, which granted approval 2 weeks later. In May 2013, the new staging was also presented and approved by the AJCC and UICC (2). The new FIGO staging of ovarian, fallopian tube, and peritoneal cancers was released for use in January 2014 (5).

Generally, tumours can be divided into four stages based on how the cancer spreads. Stage I includes localized tumours contained within the organ of origin, thus localized tumours are relatively small. Stage II describes disease that has spread from the tissue of origin locally into surrounding organs or structures. Stage III refers to tumours which have spread extensively. Stage IV represents metastatic disease. The basic stages can be further divided into sub-categories illustrating specific prognostic factors within a single stage (4).

Epithelial ovarian and fallopian tube cancers are also sub-classified by grading, which is important because histologic differentiation is proportional to prognosis. Epithelial ovarian and fallopian tube cancers are subdivided as follows: GX, grade cannot be assessed; G1, well-differentiated; G2, moderately-differentiated; and G3, poorly-differentiated (6, 7).

Cancers of the ovary, fallopian tube, and peritoneum

Ovarian cancer is the seventh most common cancer among women worldwide (8). Primary ovarian cancer most often affects postmenopausal women between 60 and 70 years of age (9). In 2012 there were 172 new cases of ovarian cancer diagnosed in Slovenia, with an incidence of 16.6 per 100,000 inhabitants (10). Primary peritoneal and fallopian tube cancers are rare malignancies; however, primary peritoneal and fallopian tube cancers share many similarities with ovarian cancer. Clinically, these three malignancies are treated and managed similarly (2).

Necessity for the new FIGO classification (5, 11-19)

New insights in the molecular pathogenesis underlying ovarian cancer

Approximately 90% of ovarian cancers are carcinomas (malignant epithelial tumours) and are divided into the following 5 basic sub-types: poorly differenti-

ated serous carcinoma (70%); endometrioid carcinoma (10%); clear cell carcinoma (10%); mucinous carcinoma (3%); and well-differentiated serous carcinoma (< 5%) (20). Ovarian cancers represent a very heterogeneous group of diseases (2, 21, 22). Malignant germ cell tumours (dysgerminomas, yolk sac tumours, and immature teratomas [3%]) and potentially malignant stromal tumours (sex cord tumours, mainly granulosa cell tumours [1%-2%]) are much less common. Ovarian tumours vary based on histologic type. Despite various histologic types and different patterns of disease distribution, this complex classification requiring separate staging for each type of ovarian tumour has not been chosen. Instead, a flexible classification system was chosen that considers the most essential parameters shared by all tumour types. There has been an agreement that the histologic type shall be designated at the time of staging (2).

Same symptomatology and treatment, and similar prognoses for ovarian, fallopian tube, and peritoneal cancers

Early stage ovarian cancer does not present with typical clinical symptoms. Indeed, ovarian cancer can manifest by vague pain or abdominal discomfort, menstrual symptoms, and dyspepsia (23-25). With disease progression, abdominal pain and discomfort worsen due to the presence of ascites, therefore respiratory impairment may occur (6). Urinary tract and bowel obstruction can develop, and patients lose weight (9). Fallopian tube and peritoneal cancers manifest as ovarian cancer (6).

To date, peritoneal cancer has not had a staging system

In spite of the fact that no formal staging for peritoneal cancer has been implemented, the new FIGO system is used, assuming peritoneal cancer cannot be applied to stage I (6).

Despite exact histology, the origin of cancer in advanced-stage disease cannot be clearly located (ovary, fallopian tube, and peritoneum)

A problem arises in determining the origin of the tumour in patients with a poorly-differentiated ovarian cancer, which is the most common ovarian carcinoma and accounts for 80% of advanced-stage disease (2). Novel histologic, molecular, and genetic findings have shown that several tumours, defined as poorly-differentiated ovarian or peritoneal tumours, originate in the fimbrial end of the fallopian tube. Consequently, the incidence of fallopian tube cancer might have been underestimated (6). The opinion that the apparently multi-centric origin of a poorly-differentiated ovarian cancer along Müllerian-derived tissues and the high frequency of ovarian, fallopian tube, and peritoneal cancers should be considered as a common entity is supported by recent data. Moreover, designating malignomas of unclear origin as ovarian cancer should also be omitted (2, 6). The primary site (ovaries, fallopian tubes, and peritoneum) shall be designated whenever possible (2). The C-classification shall be used to distinguish between tumour origins, as follows: C56, ovary; C57, fallopian tube; and C48, peritoneum (5). If it is not possible to delineate the origin of a cancer, it should be marked as "undesignated" (2). In practice, the descriptor "tubo-ovarian poorly-differentiated carcinoma" can also be used for those cases of advanced stage cancer when the primary origin of the tumour cannot be defined (1).

New discoveries in the field of prognostic factors

The new staging system also includes data on the size of metastases in the retroperitoneal lymph nodes and reasons for ruptured capsules in stage Ic/T1c (5).

The new FIGO classification

The intra-abdominal spread of disease can be outlined with the use of CT scanning; however ovarian, fallopian tube, and peritoneal cancer staging should be surgical. A precise histologic diagnosis and staging is based on operative findings (6); treatment and prognosis depend on surgical staging (9).

In practice, it is recommended to stage ovarian, fallopian tube, and peritoneal tumours according to the new FIGO staging (Table 1) and TNM classification system (Table 2) (5).

Table 1. *New staging classification for cancers of the ovary, fallopian tube, and peritoneum (2)*

Stage I	Tumour confined to the ovary(ies) or fallopian tube(s)
IA	Tumour limited to one ovary (capsule intact) or fallopian tube; no tumour on the ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IB	Tumour limited to both ovaries (capsule intact) or fallopian tubes; no tumour on the ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IC IC1 IC2 IC3	Tumour limited to one or both ovaries or fallopian tubes, with any of the following: Surgical spill Capsule ruptured before surgery or tumour on the ovarian or fallopian tube surface Malignant cells in the ascites or peritoneal washings
Stage II	Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below the pelvic brim) or primary peritoneal cancer
IIA IIB	Extension and/or implants on the uterus and/or ovaries Extension to other intraperitoneal pelvic tissues
Stage III	Tumour involves one or both ovaries of fallopian tubes, or primary peritoneal cancer, with cytologically- or histologically-confirmed spread to the peritoneum outside the pelvis and/or metastases to the retroperitoneal lymph nodes
IIIA1 IIIA2	Positive retroperitoneal lymph nodes only (cytologically- or histologically-proven) (i) Metastases ≤ 10 mm in greatest dimension (ii) Metastases > 10 mm in greatest dimension Microscopic extra-pelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB	Macroscopic peritoneal metastases beyond the pelvis ≤ 2 cm in greatest dimension, with or without metastases to the retroperitoneal lymph nodes
IIIC	Macroscopic peritoneal metastases beyond the pelvis ≥ 2 cm in greatest dimension, with or without metastases to the retroperitoneal lymph nodes (includes extension of the tumour to the capsule of the liver and spleen without parenchymal involvement of either organ)
Stage IV	Distant metastases, excluding peritoneal metastases
IVA	Pleural effusion with positive cytology
IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Stage I. The cancer is limited to the ovary or fallopian tube and the peritoneal fluid/washings (2). In comparison to the old staging system, stages IA and IB did not change. The delineation of stage IC underwent the most changes. According to the new FIGO staging system, the detection of malignant cells in ascites or peritoneal washings is staged as IC3. According to the staging system introduced in 1988, this criteria was used to distinguish between stage IIB (extension to other pelvic tissues, and no malignant cells in ascites/washings) and IIC (extension to the pelvis [IIA or IIB], and ascites present containing malignant cells in ascites/washings) and to define the old IC category (3, 5). According to the new classification, stage IC was further sub-divided into IC1, IC2, and IC3 based on various prognoses associated with the aetiology of tumour rupture (26); however, it remains controversial whether or not intra-operative capsule ruptures result in higher risk of disease recurrence (2). A multivariable analysis has shown that capsule rupture and positive cytologic washings remain independent predictors of worse survival in patients (12).

Moreover, a specific definition of whether or not the tumour is present on the ovarian or fallopian tube surface is required. Surface involvement is established when tumour cells are exposed to the peritoneal surface (2).

Additionally, many multivariable analyses have shown the differentiation degree/grade to be the most significant prognostic survival indicator in patients (Figure 1) (27-29).

Table 2. *FIGO and the adapted TNM classification for cancers of the ovary, fallopian tube, and peritoneum (5) (T – tumour, N – lymph nodes, M – metastasis)*

Stage	IA	T1a	N0	M0
Stage	IB	T1b	N0	M0
Stage	IC1	T1c1	N0	M0
Stage	IC2	T1c2	N0	M0
Stage	IC3	T1c3	N0	M0
Stage	IIA	T2a	N0	M0
Stage	IIB	T2b	N0	M0
Stage	IIC	T2c	N0	M0
Stage	IIIA1	T1/T2	N1	M0
Stage	IIIA2	T3a	N0/N1	M0
Stage	IIIB	T3b	N0/N1	M0
Stage	IIIC	T3c	N0/N1	M0
Stage	IV	every T	every N	M1

Stage II. Stage II is defined as the extension of the tumour or metastases to extra-ovarian or extra-tubal pelvic organs. Stage II includes treatable tumours that have spread to neighbouring organs without metastases and metastasized tumours of the peritoneum with a poor prognosis. This stage is still considered challenging. All stage II tumours are treated with adjuvant chemotherapy, therefore sub-divisions IIB into IIB1 and IIB2 (i.e., microscopic and macroscopic pelvic peritoneal metastases) are considered redundant. Stage IIC (extension to pelvis [IIA or IIB] and malignant cells present in ascites/peritoneal washings) originating from the old classification was considered unnecessary, and was therefore omitted in the new classification (2).

Figure 1 (See text for details)

Rectosigmoid infiltration has been categorized as stage IIB (5). Dense adhesions with histologically proven tumour cells should be categorized as stage II (Figure 2) (2).

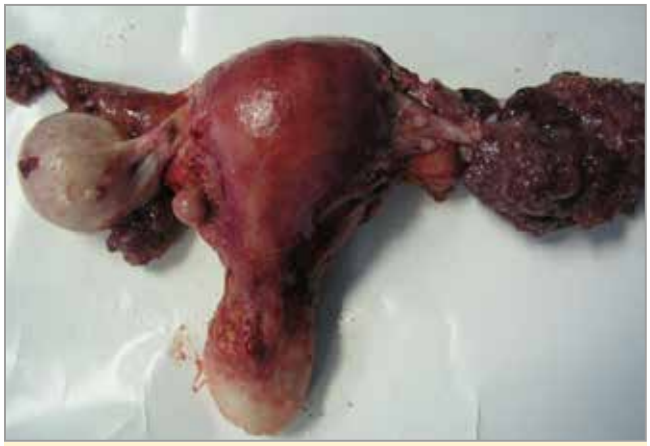

Figure 2 (See text for details)

Stage III. A large proportion of tumours are represented as poorly-differentiated serous carcinomas detected in stage III, mostly in stage IIIC (84%). Stage III tumours spread along peritoneal surfaces comprising peritoneal and abdominal peritoneum (including the omentum), the surface of the small and large intestines, the paracolic gutters, the diaphragm, and the peritoneal surfaces of the liver and spleen. Lymph node metastases are present in most patients who undergo a lymph node biopsy or dissection and in 78%

of patients with advanced-stage disease. Approximately 9% of patients, who would otherwise be diagnosed with stage I, have lymph node metastases (2).

The old staging system considered local lymph node metastases as stage IIIC; however, the new staging system classifies lymph node metastases as stage IIIA1 (5).

Less than 10% of ovarian cancers have spread outside the pelvis with the involvement of the retroperitoneal lymph nodes without intraperitoneal dissemination. According to the literature, such patients do have a better prognosis. Stage IIIA is further subdivided into IIIA(i) and IIIA(ii), although there is no information supporting the quantification of the metastasis size in stage IIIA. The involvement of the retroperitoneal lymph nodes must be established cytologically or histologically (2).

The new classification does not comprise the extracapsular extension of lymph node metastases. Notwithstanding, it is recommended that the extracapsular extension is documented in the medical record (Figure 3) (5).

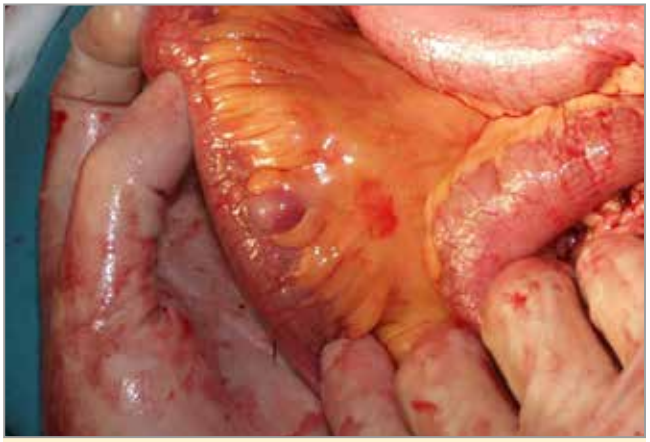

Figure 3 (See text for details)

Stage IV. Of patients diagnosed with stage IV (12%-21%), which is defined as detection of distant metastases and includes patients with parenchymal metastases in the liver and/or spleen and outside the abdominal cavity. It is essential to distinguish the extension of the tumour from the omentum to the liver or spleen (stage IIIC) from isolated parenchymal metastases (stage IVB). Transmural intestinal infiltration and umbilical deposits, as well as metastases throughout the body (lungs and bones), should be classified as stage IVB (Figure 4 and 5) (2).

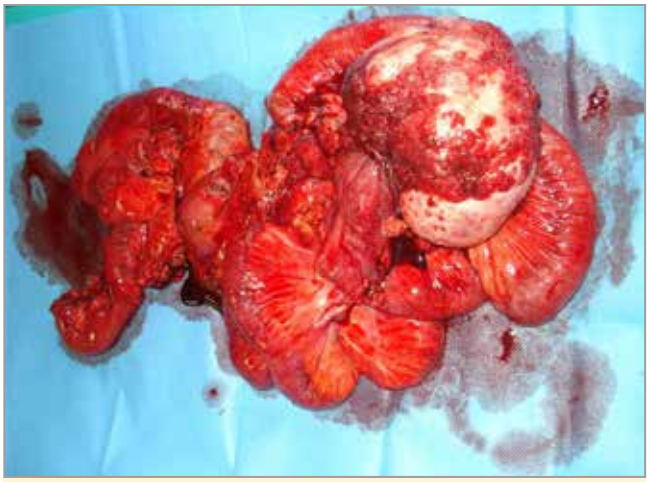

Figure 4 (See text for details)

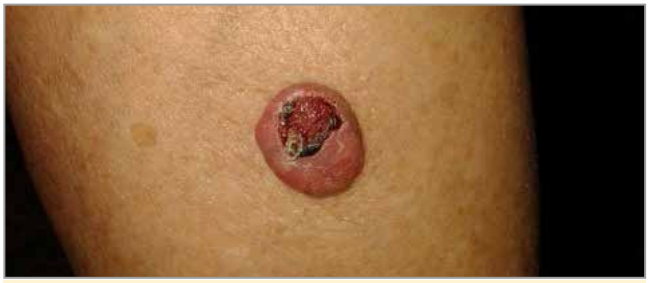

Figure 5 (See text for details)

CONCLUSION

Cancer staging systems must be user-friendly and supported by evidence. Cancer staging systems must be made on the basis of recent scientific findings and up-to-date knowledge. During the past 70 years, the gynaecological cancer staging system has undergone a gradual transformation to follow the explosive growth of new medical research and general clinical practice (3). The new FIGO classification for ovarian, fallopian tube, and peritoneal cancers has been changed based on the new scientific findings, thus providing a unified cancer staging system since January 2014.

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