Review article

TNM classification of gynaecological malignant tumours, 8th edition: changes between the 7th and 8th editions

Hideki Tokunaga[1], M.D., Ph.D.; Muneaki Shimada, [1] M.D., Ph.D.; Mitsuya Ishikawa[2], M.D., Ph.D.; 1Nobuo Yaegashi[1], M.D., Ph.D.

[1]Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai, Japan

[2]Department of Gynecology, National Cancer Center Hospital, Tokyo, Japan

Short running title: TNM of Gynecological malignancies

Corresponding author: Hideki Tokunaga, M.D., Ph.D. 1-1 Seiryo-machi, Aoba-ku, Sendai, Japan. Tel: +81-22-717-7251, Fax: +81-22-717-7258, E-mail: tokunagahideki @med.tohoku.ac.jp

Abstract (<250)

The staging classification of gynecological malignancies has been revised by the International Federation of Gynecology and Obstetrics (FIGO) and has been subsequently reviewed by the FIGO Committee on Gynecologic Oncology, the International Union for Cancer Control TNM Committee, and the American Joint Committee on Cancer. The major change in the 8th edition of TNM classification of gynecological malignant tumors is integrated staging for ovarian, fallopian tube, and primary peritoneal carcinoma, whereas the 7th edition distinguished “ovary and primary peritoneal carcinoma” and “Fallopian tube carcinoma”. Furthermore, the new edition describes a prognostic factor grid for vulvar, cervical, endometrial and ovarian, fallopian tube, and primary peritoneal carcinoma. If these factors contribute strongly to the prognosis, they may be incorporated into future staging classifications. This paper reviews the staging system for gynecological malignancies, how it was developed, and current problems to be resolved.

Keywords: TNM, FIGO, Prognosis, female organs

Mini-abstract

Staging classification of gynecological malignancies have been revised by the International Federation of Gynecology and Obstetrics. This paper reviews the staging system, its development, and current problems to be resolved.

Introduction

Cancer staging is fundamental for assessment of cancer status and development of treatment strategies. Over the last 30 years, all changes to the International Federation of Gynecology and Obstetrics (FIGO) classification and staging system have been extensively discussed by the FIGO Committee on Gynecologic Oncology and have been issued following approval by the International Union for Cancer Control (UICC) TNM Committee, the American Joint Committee on Cancer (AJCC), and the World Health Organization (WHO). The TNM classification of malignant tumours of UICC is defined by the UICC after discussing proposals for revisions from the AJCC. For gynecological tumors, the definition in the FIGO is strongly reflected. International Classification of Diseases (ICD) is a classification published by WHO as an international statistical standard for the cause of death and disease. The code appended to each disease is defined by ICD. UICC defines TNM classification of anatomic disease stages based on WHO adoption of FIGO stages (1).

In Japan, the Japan Society of Obstetrics and Gynecology (JSOG) and the Japanese Society of Pathology have formulated general rules for clinical and pathological management for each gynecological malignant tumor, except for vulvar and vaginal tumors. Currently, the latest

published Japanese general rules for management of gynecological malignant tumors are as follows:

The General Rules for Clinical and Pathological Management of Uterine Cervical Cancer (Pathological edition (4th edition))

The General Rules for Clinical and Pathological Management of Uterine Corpus Cancer (Pathological edition (4th edition))

The General Rules for Clinical and Pathological Management of Ovarian Tumor, Fallopian Tube Cancer, and Primary Peritoneal Cancer (Clinical edition (1st edition) and Pathological edition (1st edition))

The General Rules for Clinical and Pathological Management of Trophoblastic Diseases (3rd edition).

General rules and management for vulvar and vaginal tumors have not been published yet. Staging and treatment for those tumors are described in the guideline for vulvar and vaginal cancer published by the Japan Society of Gynecologic Oncology (JSGO) in 2015.

The major change in the 8th edition is separate staging for ovarian, Fallopian (uterine) tube, and primary peritoneal carcinoma; previously, the 7th edition only delineated “ovarian and primary peritoneal carcinoma” and “Fallopian tube carcinoma”. Currently, tumor registration

of the JSOG is based on the TNM classification (UICC 8th edition). In this article, staging of all gynecological tumors are outlined.

Vulvar carcinoma (ICD-O-3 C51)

There is no change in TNM classification of vulvar carcinoma between the 7th and 8th editions. The classification reflects surgical staging adopted by FIGO in 2008 (Table 1a, b). FIGO adopted surgical staging classification instead of the conventional clinical staging classification in 1988. For vulvar cancer, surgical therapy was usually performed, thereby allowing pathological disease evaluation. It was speculated that pathologically evaluating regional lymph node metastasis, an important prognostic factor, enabling surgical staging classification to more accurately reflect prognosis. Additionally, even if the tumor was localized only to the vulva, a tumor with a maximum diameter exceeding 2 cm was considered to be stage II. In 1994, stage I was subdivided into Ia (T1a: depth of stromal invasion of 1 mm or less) and Ib (T1b: depth of stromal invasion exceeds 1 mm), but it was suggested that the prognosis was not yet accurately reflected. In 2008, tumors exceeding a maximum diameter of 2 cm without lymph node metastasis were included in stage IB. The reason was based on data from the Surveillance, Epidemiology and End Results Program

(SEER), which showed that prognosis was favorable in cases with negative lymph node metastasis, even with a bulky tumor (2). Vulvar cancer staging in the 7th edition of TNM staging classification was updated from the 6th edition in 2009 based on this FIGO 2008 staging, and it has not been changed in the 8th edition.

The N classification is subdivided according to the size of lymph node metastatic lesion and the number of metastatic lymph nodes. For pN, histologic examination of regional lymphadenectomy specimens will ordinarily include six or more lymph nodes. For TNM staging, cases with fewer than six resected nodes should be classified using the TNM pathologic classification according to the status of those nodes (e.g., pN0; pN1) as per the general rules of TNM. In contrast, FIGO classifies cases with less than six nodes resected as pNX. Factors that reflect prognosis are shown in Table 1c; in addition to anatomical evaluation, biological characteristics may be reflected in future progressive stage classification.

Vaginal cancer (ICD-O-3 C52)

A tumor that spreads between the vagina and the uterine cervix is classified as cervical cancer. When a tumor spreads to the vulva, it is classified as vulvar cancer. Therefore, few cases are

diagnosed as vaginal cancer. FIGO adopted clinical staging classification in 1971 and has not been revised thereafter. Seventy-five percent of vaginal cancer is diagnosed as stage II to IV. However, pathological assessment is difficult, and surgical staging classification has not been adopted. Accordingly, radiotherapy is often chosen as the main treatment. The TNM classification follows the FIGO staging classification and has not been revised for a long time (Table 2a, 2b). The rule for pN of vaginal carcinoma follows that of cervical carcinoma.

Cancer of the cervix uteri (ICD-O C53)

Cervical cancer staging is the oldest staging in the literature. According to the FIGO staging system, cervical cancer is primarily a local disease in the pelvis. Finally, surgical staging cannot be employed worldwide, especially in low‐resource countries where late stages are common and surgical facilities are scarce. In the 8th edition, the definitions of staging for cervical cancer have not been revised. The TNM category is shown in Table 3a, and correspondence between TNM and FIGO staging is listed in Table 3b.

Stage IA cannot be assessed macroscopically. There are data indicating that subdividing by size (with a 4 cm cut‐off for maximum diameter) is appropriate for Stage IIA, while there are no available data for Stage IIB in the literature supporting a subdivision regarding tumor

size. The decision not to subdivide Stage IIB and IIIB according to uni - or bilateral parametrial extension is also because the treatment is identical in both situations and that subdivision would not affect management. Furthermore, lympho-vascular space invasion and lymph node metastasis affect prognosis and decision-making regarding treatment after hysterectomy. These factors have been taken into consideration when staging cervical cancer. Nevertheless, these important risk factors were not included in the staging nomenclature because of their subjective definition, as this influences the assessment of its extension and thus its significance. Despite improvements in imaging techniques, the FIGO Committee on Gynecologic Oncology has not performed lymph nodal assessment *per se* regarding its importance for staging. However, the FIGO Committee encourages the use of imaging techniques for the evaluation of the extension and size of the lesion(s).

The TNM classification also recommends various imaging modalities such as magnetic resonance imaging and computed tomography, although they are not mandatory. Pelvic examination under anesthesia, cystoscopy, sigmoid-colonoscopy, and Drip Infusion Pyelography are optional rather than essential. The number of lymph nodes necessary to establish pN classification is six, which is the same as that for the vulva. FIGO classifies cases with less than six nodes resected as pNX.

In April 2018, the FIGO Gynecologic Oncology Committee proposed modifications of the current Cervical Cancer Staging System. Although this is not a decision item, because of the poor disease prognosis associated with lymph node metastasis(3), the inclusion of lymph node metastasis is likely to be revised in the staging classification in the near future . Other risk factors for cervical cancer are shown in Table 3c.

Endometrial cancer (ICD-O-3 C54.1, C55)

In 1988, the FIGO Committee decided to divide the myometrium so that Stage IA was limited to the endometrium, Stage IB to the inner one‐half, and Stage IC to the outer one‐half of the myometrium. The current TNM categories and FIGO staging are shown in Table 4a and 4b. Prognostic factors not related to staging are listed in Table 4c.

Staging has changed considerably, and data collection now allows identification and analysis of specific prognostic factors in surgical‐pathological staging. In volume 26 of the FIGO Annual Report, surgical Stage IA G1, IB G1, IA G2, and IB G2 had 5-year survival rates of 93.4%, 91.6%, 91.3%, and 93.4%, respectively, with no difference among the stages (4). This resulted in revisions to the staging system for endometrial cancer adopted in 2008. In addition, stage IA and IB, adopted in 1988, have been combined so that now Stage IA involves the

endometrium and/or myometrial invasion of less than one-half, and IB applies to tumors that extend to or beyond the outer one half of the myometrium.

In addition, Stage II no longer has a subset A and B. Involvement of the endocervical glandular portion of the cervix is now considered Stage I. The other area of note is that pelvic and para‐aortic node involvement have been separated rather than combining them in a single substage. This seems to be reasonable, since data suggests that the prognosis is worse if the para‐aortic nodes are involved. As a result, Stage IIIC is now categorized as IIIC1 (indicating N1: positive pelvic nodes) and IIIC2 (indicating N2: positive para‐aortic nodes with or without positive pelvic nodes) (5, 6).

Histologic grade is also an important prognostic factor: three grades (G1, G2 and G3) are defined according to the degree of differentiation of the adenocarcinoma. Special types such like serous, clear cell and mixed mesodermal tumors are high risk and considered G3 (4).

Furthermore, positive cytological findings may adversely impact prognosis, but this remains controversial and requires further study. Regardless, although cytology results are no longer included in staging classification, they should be recorded.

Uterine sarcomas (leiomyosarcoma, endometrial stromal sarcoma, adenosarcoma)

(ICD-O-3 53, 54)

The staging described in this part is adopted to uterine sarcomas, except for carcinosarcoma (Table 4d-f). Sarcoma in the corpus uteri is distinguishable owing to its biological behavior. Moreover, tumor size impacts prognosis of leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS), hence T1 is divided into two categories: T1a (tumor diameter 5 cm or less) and T1b (more than 5 cm) (7). In adenosarcoma, tumor size correlates with deep myometrial invasion (MI), which is an independent prognostic factor (8). T1 is divided into three categories: T1a (no MI), T1b (MI less than 1/2), and T1c (MI more than 1/2). In addition, incidence of lymph node metastasis is low. Moreover, many cases of uterine sarcoma that are thought to be benign are diagnosed after hysterectomy. The exact effect regarding the prognosis of lymph node metastasis were previously unknown.

The prognosis of patients with uterine sarcomas has not changed in recent decades: the overall 5‐year survival has been between 17.5% and 54.7% in various studies (9). In a recently reported series of 100 cases, the 2‐, 5‐, and 10‐year overall survival rates were 62%, 51%, and 38%, respectively. Additionally, in multivariate analysis, stage, age, tumor size, and parity have independently influenced overall survival (9-11). Recently, the impact of lymph node metastasis on survival of uterine sarcomas was reported by analyzing data from the SEER

study. The incidence of lymph node metastasis in uterine sarcomas is low, especially in adenosarcoma compared to leiomyosarcoma and endometrial stromal sarcoma; however lymph node metastasis is associated with a worse prognosis (8). Finally, ESS has two subtypes: high-grade and low-grade; lymph node metastasis is frequent in high-grade ESS compared to that of low-grade ESS and is a risk factor of cause-specific survival (12).

Ovarian, Fallopian tube, and primary peritoneal carcinoma (ICD-O-3 C56; ICD-O-3 C57)

TNM categories and FIGO stages are shown in Table 5a. Ovarian cancer is thought to arise from the surface epithelium of the ovary. However, the relationship between high-grade serous carcinoma (HGSCs) in the tubal epithelium and the decreased incidence of ovarian cancer after prophylactic salpingectomy indicate that a significant number of HGSCs arise from the Fallopian tube. Moreover, endometrioid carcinoma and clear cell carcinoma are strongly related to endometriosis on the ovary or peritoneum (13). Therefore, the committee decided to integrate the staging systems of the “ovary and peritoneum” with that of the Fallopian tube in the 8th edition. Ovarian, fallopian tube, and peritoneal cancers have a similar clinical presentation and are treated similarly, and current evidence supports staging

all three cancers in a single system. The primary site (i.e., ovary, Fallopian tube, or peritoneum) should be designated where possible, and the histologic type should be recorded. In the 7th edition, T2a comprises tumors arising from the unilateral ovary (or tube) and extending to the tube(s) (or ovaries); in the 8th edition, T2a is defined as tumor involving one or both ovaries or Fallopian tubes with pelvic extension (below the pelvic brim) or primary peritoneal cancer. When a tumor involves the bilateral ovaries (or tubes), it is difficult to determine whether the cancer is T1b or T2a. The presence of a transitional lesion of the malignant tumor from a benign tumor in each ovary (or tube) with an intact capsule may suggest T1b. Occasionally, a large-stage IB ovarian tumor is associated with a contralateral normal-size ovary exhibiting small and superficial foci of the tumor; this suggests that superficial foci are metastatic. Pathologically proofed stage II cancer exhibits a worse prognosis than does surgical stage II, demonstrating adherence between the tumor and pelvic organs without pathological tumor infiltration (14). Intraoperative rupture ("surgical spill") comprises T1c1, capsule rupture before surgery or a tumor on the ovarian or Fallopian tube surface comprises T1c2, and positive peritoneal cytology with or without rupture comprises T1c3. However, it is controversial whether surgical spill affects prognosis. Nevertheless, preoperative capsule rapture and positive washings are independent predictors of worse

disease-free survival (15). Stage II cancer comprises a small and heterogenous group. During revision, the committee described that there was a lack of biological evidence to support subdividing this small category into IIB1and IIB2. Moreover, for FIGO stage II, the IIc sub-stage has been eliminated, as the cytology results do not influence outcome. The new staging includes a revision of stage III patients; assignment to stage IIIA1 is based on spread to the retroperitoneal lymph nodes without intraperitoneal dissemination. In addition, N1 was divided into N1a and N1b according to size of the metastatic tumor nest in the lymph node. pN should be diagnosed pathologically by retrieving at least one node from both the pelvic and para-aortic lymph nodes or more than one node from each lesion. There is, however, a significant difference in overall survival between Stage IIIA/B and IIIC. Nonetheless, there are no data supporting quantification of the size of metastasis in IIIA1 (16, 17). Stage IIIC (T3c-N0 or 1-M0) indicates spread to the surface of peritoneal cavity organs beyond the pelvis. In stage III, the 2 cm cut-off between IIIB and IIIC remains a controversial issue, as it is unclear which is worse: a few metastatic sites over 2 cm or numerous sites under 2 cm. M1b indicates isolated parenchymal metastases and should be distinguished from T3 as a tumor on the surface without infiltration or metastases in the stroma of peritoneal cavity organs. Finally, positive cytology in pleural effusion is categorized as M1a and Stage IVA and

does not necessarily suggest parenchymal metastasis of the lung (16, 18).

It has also been suggested that serous tubal intraepithelial carcinoma and BRCA gene status (somatic and germline) should be included in the staging system (19). The Committee will not be issuing a statement at this time, but will do so when the next cycle of revision takes place (20). Additional risk factors are shown in Table 5b.

Gestational trophoblastic tumors (ICD-O-3 C58)

The classification for gestational trophoblastic tumours is based on that of FIGO and were adopted in 1992 and updated in 2002. The definitions of T and M categories correspond to the FIGO stages (Table 6a). There is no regional designation in the staging of these tumors. Node metastases are classified as metastatic (M1) disease. A prognostic scoring index (Table 6b), based on factors other than the anatomic extent of the disease, is used to assign cases to high- and low-risk categories, and these categories are used in stage grouping.

Anatomical spread of gestational trophoblastic disease does not always reflect prognosis. Lung is the first metastatic site in the earlier stage, so lung disease should be handled separately from that of other organs. In Japan, a diagnostic scoring index for clinical choriocarcinoma has been used, and the Japanese registration project for gestational

trophoblastic disease has continued to be based on it. Moreover, although FIGO scoring system and the Japanese diagnostic scoring system have high commonality, the FIGO score does not indicate a pathological diagnosis.

Conclusion

The TNM classification is originally based on anatomic spread of malignant disease; this basic concept has been successfully adopted for almost all malignancies of various organs. With the development of new drugs, the development of medical technology and equipment, the staging classification has changed. Biological features are different among primary organs, histological types, and genetic backgrounds. New prognostic factors may be included into categories defining stages. A good staging system must be valid, reliable, and practical. Special equipment and expensive inspections are not preferable for the staging system to be accepted globally. Stages of disease reflect prognosis of malignancies and are the most important guidelines to determine treatment strategy. Accordingly, clinicians must precisely record the stage of malignant tumors as well as the clinical information to assist in the development of better prognostic indicators.

Funding

None.

Conflict of interest statement

The authors declare that they have no conflict of interest.

References

1. Odicino F, Pecorelli S, Zigliani L, Creasman WT. History of the FIGO cancer staging system. Int J Gynaecol Obstet 2008;101:205–10.

2. Hacker NF. Revised FIGO staging for carcinoma of the vulva. Int J Gynaecol Obstet 2009;105:105–6.

3. Kidd EA, Siegel BA, Dehdashti F et al. Lymph node staging by positron emission tomography in cervical cancer: relationship to prognosis. J Clin Oncol 2010;28:2108–13.

4. Creasman WT, Odicino F, Maisonneuve P et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 2006;95 Suppl 1:S105–43.

5. Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J

Gynaecol Obstet. 2009;105(2):109.

6. Lewin SN, Wright JD. Comparative Performance of the 2009 International Federation of Gynecology and Obstetrics' Staging System for Uterine Corpus Cancer. Obstet Gynecol 2011;117:1226.

7. Giuntoli RL, 2nd, Lessard-Anderson CR, Gerardi MA et al. Comparison of current staging systems and a novel staging system for uterine leiomyosarcoma. Int J Gynaecol Cancer 2013;23:869–76.

8. Machida H, Nathenson MJ, Takiuchi T, Adams CL, Garcia-Sayre J, Matsuo K. Significance of lymph node metastasis on survival of women with uterine adenosarcoma. Gynecol Oncol 2017;144:524–30.

9. Koivisto-Korander R, Butzow R, Koivisto AM, Leminen A. Clinical outcome and prognostic factors in 100 cases of uterine sarcoma: experience in Helsinki University Central Hospital 1990-2001. Gynecol Oncol 2008;111:74–81.

10. Giuntoli RL, 2nd, Metzinger DS, DiMarco CS et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. Gynecol Oncol 2003;89:460–9.

11. Prat J. FIGO staging for uterine sarcomas. Int J Gynaecol Obstet 2009;104:177–8.

12. Seagle BL, Shilpi A, Buchanan S, Goodman C, Shahabi S. Low-grade and high-grade endometrial stromal sarcoma: A National Cancer Database study. Gynecol Oncol 2017;146:254–62.

13. Kurman RJ, Shih Ie M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 2010;34:433–43.

14. Seidman JD, Cosin JA, Wang BG et al. Upstaging pathologic stage I ovarian carcinoma based on dense adhesions is not warranted: a clinicopathologic study of 84 patients originally classified as FIGO stage II. Gynecol Oncol 2010;119:250–4.

15. Bakkum-Gamez JN, Richardson DL, Seamon LG et al. Influence of intraoperative capsule rupture on outcomes in stage I epithelial ovarian cancer. Obstet Gynecol 2009;113:11–7.

16. Prat J, Oncology FCoG. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 2014;124:1–5.

17. Pereira A, Perez-Medina T, Magrina JF et al. International Federation of gynecology and obstetrics staging classification for cancer of the ovary, fallopian tube, and peritoneum: estimation of survival in patients with node-positive epithelial ovarian cancer. Int J Gynecol Cancer 2015;25:49–54.

18. Prat J. Abridged republication of FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum. Cancer 2015;121:3452–4.

19. Tjalma WA. Staging classification for cancer of the ovary and fallopian tube should include in situ carcinoma. Cancer 2016;122:651.

20. Denny L. Reply to staging classification for cancer of the ovary and fallopian tube should include in situ carcinoma. Cancer 2016;122:652.