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Review Article

Updates on FIGO Staging Classification and the New WHO Classification for Cancer of the Ovary

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Abstract

Background: *The knowledge of different subtypes of ovarian cancer is improving with the progress in molecular pathological research. The WHO classification was revised,in parallel with the implementation of the new FIGO staging classification. The former is mainly based on the histopathological findings and defines the actual type of tumor. It has an important impact on prognosis and therapy of the patient.*

Materials and methods: *FIGO staging classification for cancer of the ovary, fallopian tube, and peritoneum published by Jaime Prat and the new WHO Classification of Ovarian Cancer published by Robert Kurman and coauthors in 2014 are summarized.*

Results: *The International Federation of Gynecology and Obstetrics recently significantly revised staging criteria for cancer of the ovary. The latest revision was based on the concept that high-grade serous tubal intraepithelial carcinoma (STIC) may be the origin of some high-grade serous carcinomas of the ovary and peritoneum. Therefore, staging criteria for the ovary, fallopian tube, and peritoneum have been unified. Understanding this background and other important revised points are essential.*

The previous focus of mesothelial origin of ovarian cancer has been eliminated in new classification. Instead, a discussion of tubal carcinogenesis of hereditary and some other high-grade serous carcinomas is featured. Regarding serous cancers, the previously assumed pathogenesis pathway may be correct for some, but not for all. The earlier transitional cell type of ovarian cancer has been removed while seromucinous tumors have been added as a new entity. The role of some borderline tumors as one possible step in the progression from benign to invasive lesions is incorporated. The article summarizes the essential updates concerning serous, mucinous, seromucinous, endometrioid, clear-cell, and Brenner tumors.

Conclusion: *The new WHO classification takes into account the recent findings on the origin, pathogenesis, and prognosis of different ovarian cancer subtypes. In both FIGO and WHO classification, the tubal origin of hereditary and some non-hereditary high-grade serous cancers is mentioned in contrast to the hitherto theory of mesothelial origin of tumors. Seromucinous tumors represent a new entity.*

Keywords: *Ovarian tumour, High-grade serous, Low-grade serous, Endometrioid, Mucinous, Clear cell, Seromucinous*

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Introduction

Ovarian cancer is the seventh most common cancer diagnosis among women worldwide, and the fifth most common cancer diagnosis among women in higher-resource regions.[1] The world rate is estimated to be 6.3 per 100 000 women, and is highest in high resource countries (9.3 per 100 000 women).[1]

The process of the proposed changes to the FIGO staging of ovarian, fallopian tube, and primary peritoneal cancer started few years ago under the leadership of the Chair of the FIGO Committee on Gynecologic Oncology, Professor Lynette Denny. The proposal was sent to all relevant gynecologic oncology organizations and societies worldwide. Input was collated, evaluated, and formulated into the staging. The new staging was reached by consensus of those participating in the FIGO meeting held in Rome, Italy, on October 7, 2012, approved by FIGO Executive Board on October 12, 2012. Subsequently, the proposal was presented to and approved by the American Joint Commission on Cancer and the International Union against Cancer (Table 1). Old stage IIC has been eliminated.[2]

A histopathological classification should be descriptive, reflect biology and behaviour and fulfil three objectives: 1) serve as a guide for clinical management, 2) provide a framework for organizing diseases that assists in furthering scientific investigation and 3) serve as an educational tool. There is an inherent tension between the first two objectives. For clinical management, a classification with a limited number of categories is more practical as clinicians have only a few therapeutic options. On the other hand, for researchers, a more complex classification is preferred because a concise classification of combined categories may obscure important differences, which may ultimately be shown to have clinical relevance. The new edition of the WHO Classification has attempted to reconcile these disparate needs.

Materials and methods

Staging classification for cancer of the ovary, fallopian tube, and peritoneum by Jaime Prat [2] and the new WHO Classification of Ovarian Cancer published by Robert Kurman[3] and coauthors in 2014 3 are described. The major changes compared to the existing classifications are presented.

Results

FIGO Staging classification for cancer of the ovary.

The International Federation of Gynecology and Obstetrics recently revised staging criteria for cancer of the ovary.[2] The latest revision was based on the concept that high-grade serous tubal intraepithelial carcinoma (STIC) may be the origin of some high-grade serous carcinomas of the ovary and peritoneum. Therefore, staging criteria for the ovary, fallopian tube, and peritoneum have been unified.[2]

The main purpose of staging systems is two: it provides standard terminology that allows comparison of patients between centers; and assigns patients and their tumors to prognostic groups requiring specific treatments. Ovarian cancer is staged surgically and pathologically. Cancer staging evolves continuously as scientific developments occur, diagnostic methods improve, and more accurate prognostic information becomes available.[2] Over the past two decades, several scientific developments have challenged traditional concepts in ovarian cancer. Initially, it was recognized that ovarian cancer is not a homogeneous disease, but rather a group of diseases— each with different morphology and biological behavior. Approximately 90% of ovarian cancers are carcinomas (malignant epithelial tumors) and, based on histopathology, immunohistochemistry, and molecular genetic analysis, at least 5 main types are currently distinguished: high-grade serous carcinoma (HGSC [70%]); endometrioid carcinoma (EC [10%]); clear-cell carcinoma (CCC [10%]); mucinous carcinoma (MC [3%]); and low-grade serous carcinoma (LGSC [<5%]).[4] These tumor types (which account for 98% of ovarian carcinomas) can be diagnosed by light microscopy and are inherently different diseases, as indicated by differences in epidemiologic and genetic risk factors; precursor lesions; patterns of spread; and molecular events during oncogenesis, response to chemotherapy, and prognosis.[5,6] Much less common are malignant germ cell tumors (dysgerminomas, yolk sac tumors, and immature teratomas [3% of ovarian cancers]) and potentially malignant sex cord-stromal tumors (1%–2%, mainly granulosa cell tumors). The biomarker expression profile within a given histotype is consistent across stages. Ovarian cancers differ primarily based on histologic type.[2]

Another discovery that influenced the new FIGO staging occurred in 2001, when patients with BRCA mutation (breast–ovarian cancer syndrome) undergoing risk-reducing salpingo-oophorectomy were found to have high-grade serous tubal intraepithelial carcinoma (STIC) not in the ovary but in the fallopian tube and, particularly, in the fimbria.[7] Although STIC is capable of metastasizing and, therefore, cannot be considered carcinoma in situ, compelling evidence for a tubal origin of BRCA-positive HGSC (approximately 60% of BRCA cases) has accumulated over the past decade.[8,9] The relative proportion of HGSCs of ovarian and tubal derivation is unknown, mainly because tumor growth in advanced stage

cancers conceals the primary site. Even in cases involving BRCA mutation, evidence of a tubal origin of HGSCs is incomplete and a multicentric origin of these tumors (i.e. arising from ovarian surface mesothelial invaginations or inclusion cysts with subsequent müllerianneometaplasia, from implantation of tubal-type epithelium into the ovary [endosalpingiosis], or from the pelvic peritoneum [the so-called secondary müllerian system]) cannot be excluded.[2]

Stage I: Tumor confined to ovaries or fallopian tube(s)

Stage I ovarian or fallopian tube cancer is confined to the ovaries or the fallopian tubes and peritoneal fluid/washings. Tumor rupture or surface involvement by tumor cells warrants a stage of IC. It is not possible to have stage I peritoneal cancer.

Recommendations

- Histologic type, which in most cases includes grade, should be recorded.
- All individual subsets of stage IC disease should be recorded.
- Dense adhesions with histologically proven tumor cells justify upgrading to stage II.
- If rupture is noted, peritoneal washing and cytology study are indicated.

Stage II: Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer

Stage II ovarian cancer is still difficult to define. It comprises a small and heterogeneous group making up less than 10% of ovarian cancers. It is defined as extension or metastasis to extraovarian/extratubal pelvic organs and may include curable tumors that have directly extended to adjacent organs but have not yet metastasized, as well as tumors that have seeded the pelvic peritoneum by metastasis and, therefore, have a poor prognosis. Of note, the sigmoid colon is within the pelvis, and therefore sigmoid involvement only is considered stage II. The Committee felt that subdividing this small category further into IIB1 and IIB2 (i.e. microscopic and macroscopic pelvic peritoneal metastases) was not based on evidence/biology. All stage II disease is treated with adjuvant chemotherapy, so subclassification is not essential. Also, the old substage IIC (i.e. IIA or IIB but with tumor on surface, capsule ruptured, or ascites or positive peritoneal washing) was considered redundant and eliminated.

Recommendations

- To separate direct extension from metastases.
- To compare outcome of stage II and early stage III cases.

Stage III: Tumor involves 1 or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

Most ovarian cancers are HGSCs that usually present in stage III, with the vast majority (84%) stage IIIC.[10] These tumors characteristically spread along peritoneal surfaces involving both pelvic and abdominal peritoneum including the omentum, surfaces of the small and large bowel, mesentery, paracolic gutters, diaphragm, and peritoneal surfaces of the liver and spleen. A finding of ascites occurs in two-thirds of cases. Lymph node metastases are found in the majority of patients who undergo node sampling or dissection and in up to 78% of advanced stage patients.[11] Approximately 9% of patients with tumors that otherwise appear to be stage I, have lymph node metastases; the corresponding figures for stages II, III, and IV are 36%, 55%, and 88%, respectively.[12] Rarely, inguinal or supraclavicular (stage IV)node metastases will be the presenting manifestation of ovariancarcinoma.[13] Less than 10% of ovarian carcinomas extend beyond the pelvis with exclusively retroperitoneal lymph node involvement. Evidence in the literature indicates that these cases have a better prognosis than that of tumors with abdominal peritoneal involvement.[14-16]. The new staging includes a revision of stage III patients and assignment to stage IIIA1 based on spread to the retroperitoneal lymph nodes without intraperitoneal dissemination. Stage IIIA1 is further subdivided into IIIA1(i) (metastasis ≤10mm in greatest dimension) and IIIA1(ii) (metastasis N10 mm in greatest dimension), even if there are no retrospective data supporting quantification of the size of metastasis in IIIA1. Involvement of retroperitoneal lymph nodes must be proven cytologically or histologically.

Recommendations

- To classify IIIA1 cases histologically.
- To compare outcome of stage IIIA1(i) and IIIA1(ii) cases.
- To compare outcome of stage IIIA1 and IIIA2 cases.

Stage IV: Distant metastasis excluding peritoneal metastases

Stage IV is defined as distant metastasis and includes patients with parenchymal liver/splenic metastases and extra-abdominal metastases; 12%–21% of patients present with stage IV disease.[10] Extension of tumor from omentum to spleen or liver (stage IIIC) should be differentiated from isolated parenchymal metastases (stage IVB).

Recommendation for future consideration

- Splenectomy seems to take care of isolated metastases in a better way than partial hepatectomy. In future, isolated splenic metastasis may be considered stage IIIC rather than stage IV, whereas parenchymal liver metastasis would remain stage IVB.[2]

Table-I

FIGO Ovarian Cancer Staging Effective Jan. 1, 2014 (Changes are in italics)

STAGE I: Tumor confined to ovaries				
OLD			NEW	
IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings/ascites		IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings/ascites
IB	Tumor involves both ovaries otherwise like IA.		IB	Tumor involves both ovaries otherwise like IA.
IC	Tumor involves 1 or both ovaries with any of the following: capsule rupture, tumor on surface, positive washings/ascites.		IC	Tumor limited to 1 or both ovaries
			IC1	Surgical spill
			IC2	Capsule rupture before surgery or tumor on ovarian surgery or tumor on ovarian surface
			IC3	Malignant cells in the ascites or peritoneal washings
STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer				
OLD			NEW	
IIA	Extension and/or implant on uterus and/or Fallopian tubes		IIA	Extension and/or implant on uterus and/or Fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues		IIB	Extension to other pelvic intraperitoneal tissues
IIC	IIA or IIB with positive washings/ascites.			
Old stage IIC has been eliminated				
STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes				
OLD			NEW	
IIIA	Microscopic metastasis beyond the pelvis.		*IIIA (Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis)*	
			IIIA1	*Positive retroperitoneal lymph nodes only*
				IIIA1(i) — *Metastasis > 10 mm*
				IIIA1(ii) — *Metastasis > 10 mm*
			IIIA2	*Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes*
IIIB	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm in greatest dimension.		IIIB	*Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.*
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm in greatest dimension and/or regional lymph node metastasis.		IIIC	*Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.*
STAGE IV: Distant metastasis excluding peritoneal metastasis				
OLD				NEW
IV	Distant metastasis excluding peritoneal metastasis. Includes hepatic parenchymal metastasis.		IVA	*Pleural effusion with positive cytology*
			IVB	Hepatic and/or *splenic parenchymal* metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)
Other major recommendations are as follows: ● Histologic type including grading should be designated at staging ● Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible ● Tumors that may otherwise qualify for stage I but involved with dense adhesions justify ● Upgrading to stage II if tumor cells are histologically proven to be present in the adhesions				

The new WHO classification for cancer of the ovary

In parallel with the FIGO classification for the staging of ovarian cancer[2] the WHO classification was revised[3,17]and is valid since 2014. Most of the current clinical guidelines of ovarian cancer refer to the previous FIGO and WHO classification systems.Both of which are revised in 2014. This review will clarify the clinical implications of the news definitions.[18,19] Both qualities - the tumor stage (according to FIGO classification) and the type of tumor (according to WHO classification)—are essential criteria for the treatment decision-making process of a differentiated therapy.

The following sections provide an overview of changes to the WHO classification which was published in 2014 and has current validity.[3] The chapter on ovarian cancer in the old classification focused on the mesothelial surface of the ovary as the point of origin of epithelial ovarian tumors. The new classification eliminates this focus. Instead, it features a discussion of tubal carcinogenesis of high-grade serous carcinomas. This is in spite of the fact that, in up to 30 % of these tumors, no tubal precancerous lesions can be found. The previously assumed pathogenesis pathway is therefore certainly correct for some but not for all serous cancers. It remains to be emphasized that it will frequently not be possible to judge the point of origin of advanced serous cancers with certainty. The new classification (see Table 1) has become more consistent. The earlier transitional cell type of ovarian cancer class has been removed, while seromucinous tumors have been added as a new entity. The role of some borderline tumors as a step in the progression from benign to invasive lesions is incorporated.[3]

Serous tumors

The dividing line between adenomas and borderline tumors (SBOTs) has been sharpened in the new WHO classification. Cystic serous tumors with >10 % BOT architecture are now classified as SBOTs. If the lesion shows a BOT fraction smaller than 10%, the term ''serous cystadenoma with focal epithelial proliferation'' applies. The diagnostic criteria of SBOTs have remained essentially the same.[3]

The ''KommissionOvar of AGO'' claims the pathology report should mention also the previous classification, since current recommendations for clinical management are still based on it.[18-20] Microinvasion of an SBOT is still limited metrically (at a 5 mm breadth for individual foci). Analogously to the FIGO classification, the continuous grading of serous cancer in G1–G3 has been eliminated and replaced by a sub-classification into low-grade and highgrade carcinomas. Tumors, formerly classified as grade 2 serous carcinoma are candidates for p53 immunohistochemistry. If p53 immonostaining is negative, the tumor is classified low grade. If p53 immunostaining is positive, the tumor is classified high grade. Transitional cell cancer of the ovary which may be associated with BRCA1 inhibition no longer stands as a separate entity. But the corresponding histological growth pattern is to be described as a variant of serous or (less frequently) endometrioid cancer (high-grade or G3).[3]

Mucinous tumors

The subcategorization of mucinous borderline tumors (MBOTs) into an intestinal and an endocervical type has been dispensed with. Formerendocervical MBOTs are now found in the newly-created seromucinous tumor group; MBOT therefore now applies to the former intestinal variety. The new WHO classification emphasizes the consideration of metastasis of an extragenital malignancy even in cases of MBOT. Bilaterality, small tumors and a peritoneal involvement are particularly suspicious with respect to metastasis. Diagnostic categories in between MBOT and mucinous invasive carcinoma are MBOT with intraepithelial cancer, microinvasive MBOT, and microinvasive mucinous cancer, respectively. Even so, the new classification puts forth no satisfactory solution to the problem of defining invasion in cases of mucinous cancer. The sub-classification of mucinous cancer into an expansive and a destructive-invasive type has been kept.[3]

Endometrioid tumors

Atypical endometrioses may also be associated with developing endometrioid (and clear-cell) ovarian cancer.[21,22] The new WHO classification, therefore, places endometrioid cysts in the same neoplastic context as endometrioidcystadenomas. Two different subtypes of endometrioid borderline tumors (intracystic and adenofibromatous) have been defined more exactly, the former evolving from an endometrioidadenofibroma, the latter from an endometrioidcystadenoma or endometrioid cyst. The diagnostic term ''with intraepithelial carcinoma'' is recommended for EBOTs with high-grade nuclear atypia, analogously as with the MBOTs. Again, the problem of differential diagnosis between EBOT and invasive endometrioid carcinoma has not be solved satisfactory, an analogous situation to the mucinous tumors. Endometrioid invasive carcinoma is morphological heterogeneous with areas of squamous differentiation, secretory modifications, mucinous differentiation, oxyphile variants, or sex cord stromal pattern. Endometrioid ovarian tumors are also suspicious to be metastases instead of primary tumors.[3]

Clear cell tumors

The new WHO classification has not brought any essential changes pertaining to the clear cell tumors. Clear cell BOTs are very similar to clear cell adenomas, and both components are regularly found within one tumor. By contrast clear cell carcinomas have a different architecture, characterized by papillary structures, and solid components with desmoplastic and hyalinizedstroma and high-grade nuclear atypia.[3] Clear cell carcinoma may be

Table-II

Previous and New WHO classification of Ovarian Cancer (4)

Previous	New (2014)
Serous tumors	
Benign	
Cystadenoma	Cystadenoma
Papillary cystadenoma	Adenofibroma
Surface papilloma	Surface papilloma
Adenofibroma and cystadenofibroma	x
Borderline (SBOT)	
Papillary cystic BOT	Serous BOT/atypical proliferating tumor
Papillary surface BOT	SBOT, micropapillary type/non-invasive, serous low-grade carcinoma
Adenofibromatous and cystadenofibromatous BOT	x
Malignant	
Adenocarcinoma	Serous low grade carcinoma
Papillary surface carcinoma	Serous high grade carcinoma
Adenocarcinofibroma	x
Mucinous tumors	
Benign	
Cystadenoma	Cystadenoma
Adenofibroma and cystadenofibroma	x
Mucinous cystic tumor with mural modules	x
Mucinous cystic tumor with pseudomysomaperitonei	x
Borderline (MBOT)	
Intestinal type	**Mucious BOT**/atypical proliferating mucinous tumor
Endocervical type	
Malignant	
Adenocarcinoma	Mucinous carcinoma
Adenocarcinofibroma (malignant adenofibroma)	x
Endometrioid tumors	
Benign	
	Endometriosis cyst
	Endometrioidcystadenoma
Cystadenoma	Endometrioidcystadenofibroma
Adenofibroma and cystadenofibroma	
Borderline (EBOT)	
Cystic tumor	Endometrioid BOT/atypical proliferating endometrioid tumor
Adenofibroma and cystadenofibroma	
Malignant	
Adenocarecinoma NOS	Endometrioid carcinoma
Adenocarcinofibroma (malignant adenofibroma)	
Malignant Mullerian mixed tumor (carcinosarcoma)	
Adenosarcoma	
Endometrioid stromal sarcoma (low grade)	
Undifferentiated ovarian sarcoma	
Clear cell tumors	
Benign	
Cystadenoma	**Cystadenoma**
Adenofibroma and cystadenofibroma	**Adenofibroma**
Borderline (CBOT)	
Cystic tumor	**CCBOT/atypical proliferating clear cell tumor**
Adenofibroma and cystadenofibroma	
Malignant	
Adenocarcinoma	Clear cell carcinoma
Adenocarcinofibroma (malignant adenofibroma)	x

Table-II
Previous and New WHO classification of Ovarian Cancer (Continued)

Previous	
Transitional cell tumors	**Brenner tumors**
Benign	
Brenner tumor	Brenner tumor
Metaplastic type	x
Borderline	
Borderline Brenner tumor	Borderline Brenner-tumor/atypical proliferating Brenner tumor
Proliferating type	
Malignant	
Transitional cell carcinoma	x
Malignant Brenner Tumor	Malignant Brenner tumor
x	**Seromucinous tumors**
	Benign
x	Seromucinouscystadenoma
x	Seromucinousadenofibroma
	Borderline tumor
x	Seromucinous borderline tumor/atypical proliferating seromucinous tumor
x	Seromucinous carcinoma
Squamous epithelial tumors	x
Mixed epithelial tumors	x
Undifferentiated and unclassifiable tumors	**Undifferentiated carcinoma**

associated with Lynch syndrome or endometriosis and is the most common ovarian cancer with paraneoplastic symptoms (thrombembolies or hypercalcemia).[21,22]

Brenner tumors

The previously named ‘‘transitional cell tumors’’ is now entitled ‘‘Brenner Tumors.’’ Brenner tumors, associated with other epithelial tumors in up to 25 % of cases, are composed of cell nests whose sizes vary and are characterized by transitional cell differentiation. Brenner BOTs have in contrast to Brenner tumors a much more extensive epithelial proliferation. Therefore, they are signiûcantly larger (mean 18 cm) and (b) having a much higher epithelial volumes than benign Brenner tumors. This BOT category now also contains an ‘‘intraepithelial carcinoma’’. Invasive malignant Brenner tumors are characterized by a destructive stroma invasion, but the morphology is not further specified. As in the previous classification, these tumors display at least focal highgrade nuclear atypia.[3]

Seromucinous tumors

Within the new WHO classification,this group of tumors is a new entity among ovarian cancer. Essentially, it comprises the former endocervical-type mucinous BOT, although the WHO now requires at least two types of Muellerian differentiation for the diagnosis. The architecture of the seromucinous BOTs resembles that of the SBOTs; but one-third of them are associated with endometriosis, and by virtue of the ARID1A-mutations they are closer on the molecular level to endometrioid tumors than to the serous tumors. In this category, too, there are both microinvasive and micropapillary SMBOTs; in contrast to SBOTs, which never contain areas of intraepithelial carcinoma, seromucinous BOTs may present with intraepithelial cancer. Because no one has amassed extensive experience with this group of tumors, it remains to be seen what its clinical significance will be.[3]

Any classification of ovarian cancers and its precursor lesions remains imperfect and has to be renewed as scientific knowledge progresses.[1]Thus, further molecular, histopathological, and clinical investigations will enlighten the character of the different ovarian cancer subtypes and will necessitate the actualization of the current WHO classification. The latter will contribute to an even better prognosis of serous ovarian borderline tumors, since the cases with invasive implants are no longer considered borderline tumors but low-grade serous cancers.

Since the histopathological assessment of borderline tumors is difficult and contains incorrect diagnoses up to 15% and more, the German Ovary Board (AGO) recommends to involve an assessment by a reference pathologist.[20,23]

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