

## REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

## Mucinous Ovarian Carcinoma

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N Engl J Med 2019;380:1256-66.

DOI: 10.1056/NEJMra1813254

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NEARLY 239,000 NEW CASES OF OVARIAN CANCER (AND 152,000 ASSOCIATED deaths) are reported worldwide annually, with the highest incidence rates in North America and central and eastern Europe.<sup>1,2</sup> The most common histologic subtype is high-grade serous ovarian cancer (accounting for 65% of cases). Other histologic subtypes include low-grade serous, endometrioid, clear-cell, and mucinous ovarian cancers, as well as ovarian carcinosarcoma.<sup>3-5</sup> Mucinous ovarian cancer is a rare tumor, probably accounting for 3% of all epithelial ovarian cancers,<sup>6,7</sup> and often presents a diagnostic and therapeutic conundrum for oncologists. For decades, the management of mucinous ovarian cancer was based on guidelines developed for serous ovarian cancer. However, experience with mucinous ovarian cancer and an understanding of its biologic features have shown that it is a unique disease requiring unique management. This review highlights the distinguishing features of mucinous ovarian cancer and provides an update on its molecular landscape and surgical and medical management.

## A SEPARATE DISEASE ENTITY

The gene-expression profile of mucinous ovarian cancer is distinct from that of serous ovarian cancer.<sup>7</sup> Sixty-five to 80% of mucinous ovarian cancers are diagnosed at an early stage, according to the classification of the International Federation of Gynecology and Obstetrics (FIGO stage I, defined as a tumor confined to a single ovary) (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).<sup>8</sup> Patients with serous ovarian cancer tend to present at an advanced stage, with intraperitoneal spread in more than 80% of cases (Table 1).<sup>9,10</sup> A potential explanation for this difference is that mucinous ovarian cancers are usually very large primary tumors (typically >15 cm in diameter) that generate symptoms while the disease is still localized to the ovary. Thus, the overall prognosis is much better for women with mucinous ovarian cancer than for those with other subtypes of epithelial ovarian cancer.<sup>8</sup> Five-year overall survival among patients with localized mucinous ovarian cancer exceeds 90%; by contrast, when mucinous ovarian cancer has spread to the peritoneum in the abdominal cavity or beyond (stage III or IV), the estimated median overall survival is between 12 and 33 months.<sup>9,11-16</sup>

Mucinous tumors are characteristically diagnosed in patients who are younger than patients in whom other epithelial ovarian cancers are diagnosed.<sup>6,9</sup> In a recent analysis of data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry, 26% of mucinous ovarian cancers were diagnosed in women younger than 44 years.<sup>9</sup> Mucinous ovarian cancer is the most common histologic subtype in the subgroup of patients who are eligible for fertility-sparing surgery.<sup>17,18</sup>

**Table 1.** Epidemiologic, Clinical, and Pathological Features of Mucinous Ovarian Carcinoma as Compared with High-Grade Serous Ovarian Cancer.\*

Variable	Mucinous Ovarian Carcinoma (prevalence, 3%)	High-Grade Serous Ovarian Carcinoma (prevalence, 65%)
Age		
Median age at diagnosis (yr)	53	61
<44 yr at presentation (%)	26	7
Early stage at diagnosis (%)	65–80	5
Tumor marker	CEA or CA 19-9	CA-125
Risk factors	Smoking	Nulliparity, early menarche, late menopause, germline <i>BRCA1</i> or <i>BRCA2</i> mutations
Rate of response to platinum-based chemotherapy (%)	20–60	>70
Overall survival		
Stage 1, at 5 yr (%)	92	84
Advanced stage, median (mo)	12–33	35–60

\* Some of the data presented in the table are from Ferlay et al.,<sup>1</sup> Reid et al.,<sup>2</sup> Peres et al.,<sup>9</sup> and Torre et al.<sup>10</sup> CEA denotes carcinoembryonic antigen.

In a series of 545 patients undergoing such surgery, 51% (280 patients) had mucinous ovarian cancer.<sup>17</sup>

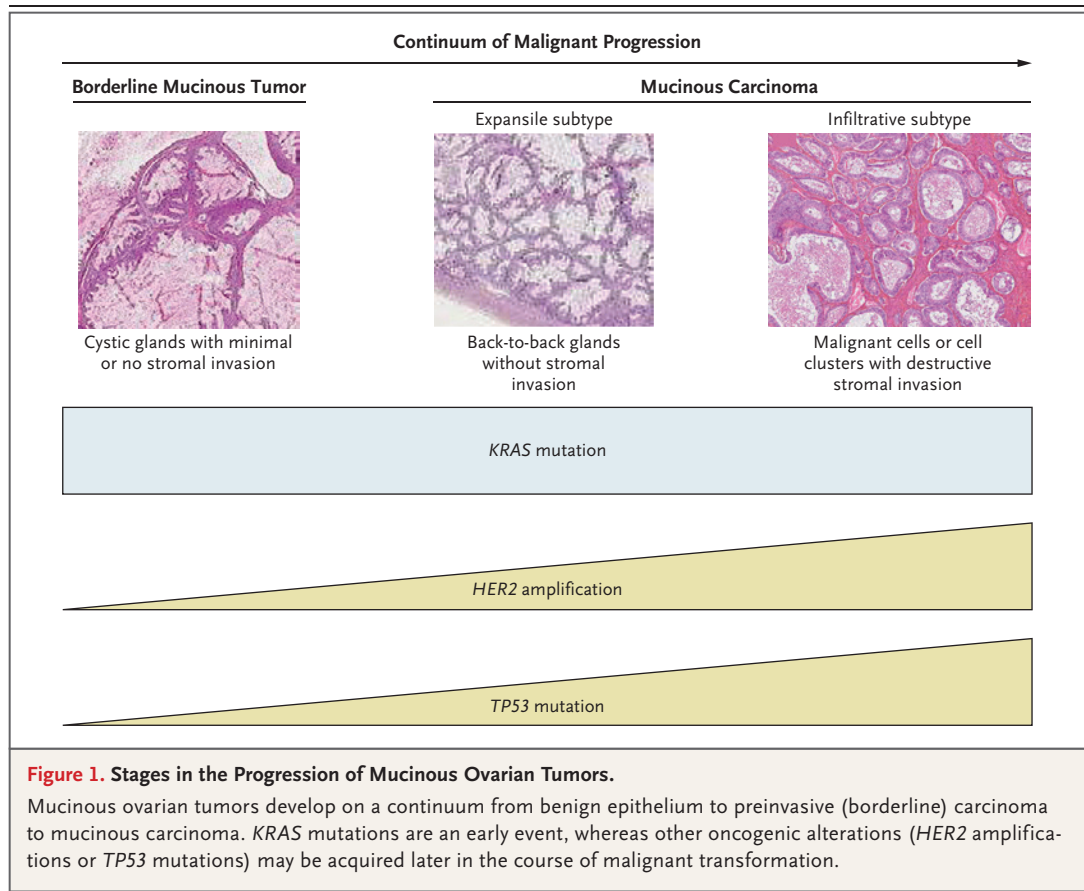
Most serous ovarian cancers originate in the fimbria of the fallopian tubes.<sup>19</sup> Mucinous ovarian cancers appear to evolve in stepwise fashion from benign epithelium to a preinvasive lesion to carcinoma (Fig. 1).<sup>3,5,20,21</sup> Mucinous ovarian cancer is frequently mixed with areas of mucinous cystadenoma or precancerous lesions (borderline mucinous tumor, borderline tumor with intraepithelial carcinoma, microinvasive carcinoma, or a combination of such lesions). This continuum of malignant progression is in stark contrast to the development of serous ovarian cancer and is similar to the development of colorectal cancer. *KRAS* mutations are observed in 40 to 65% of mucinous carcinomas. The same *KRAS* mutation has been detected in the carcinoma foci and in surrounding borderline malignant and benign areas, suggesting that the mutation is an early founder event.<sup>22–24</sup> Other genomic alterations such as *HER2* amplification or *TP53* mutation are almost exclusively observed in the carcinomatous component of mucinous tumors, supporting the view that these alterations represent later events in malignant transformation.<sup>23,24</sup> Another hypothesis regarding the histogenesis of mucinous ovarian cancers is that they may be

derived from transitional cells (Walthard cell nests are observed in 59% of mucinous neoplasms) or metaplasia at the fallopian tube–peritoneal junction.<sup>25</sup>

Risk factors for serous ovarian cancer include nulliparity, early menarche, late menopause, and germline *BRCA1* or *BRCA2* mutations, none of which are risk factors for mucinous ovarian cancer. The only clinical risk factor associated with mucinous ovarian cancer is tobacco smoking. A genomewide association study of 1644 mucinous ovarian cancers identified susceptibility alleles at 2q13, 2q31.1, and 19q13.2 (the potential candidate gene is *HOXD9* for locus 2q31.1).<sup>26</sup> The incidence of mucinous ovarian cancer decreased by 5% annually in the United States between 1995 and 2009 and has been stable since 2009.<sup>10</sup> These trends could be attributable to a decline in smoking or to improvements in the histologic diagnosis of mucinous ovarian cancer in the late 1990s and early 2000s.<sup>10,27,28</sup>

#### DIAGNOSTIC CHALLENGE

Early reports probably overestimated the prevalence of mucinous ovarian cancer, with some studies reporting that they represented 10 to 15% of epithelial ovarian cancers.<sup>9,29,30</sup> However, a central pathological review of ovarian tumors



initially classified as primary ovarian mucinous carcinomas revealed that 50 to 70% were in fact metastases from other sites. According to different reports, the true proportion of ovarian epithelial cancers that are mucinous ovarian cancers is closer to 1 to 3%.<sup>29,31</sup>

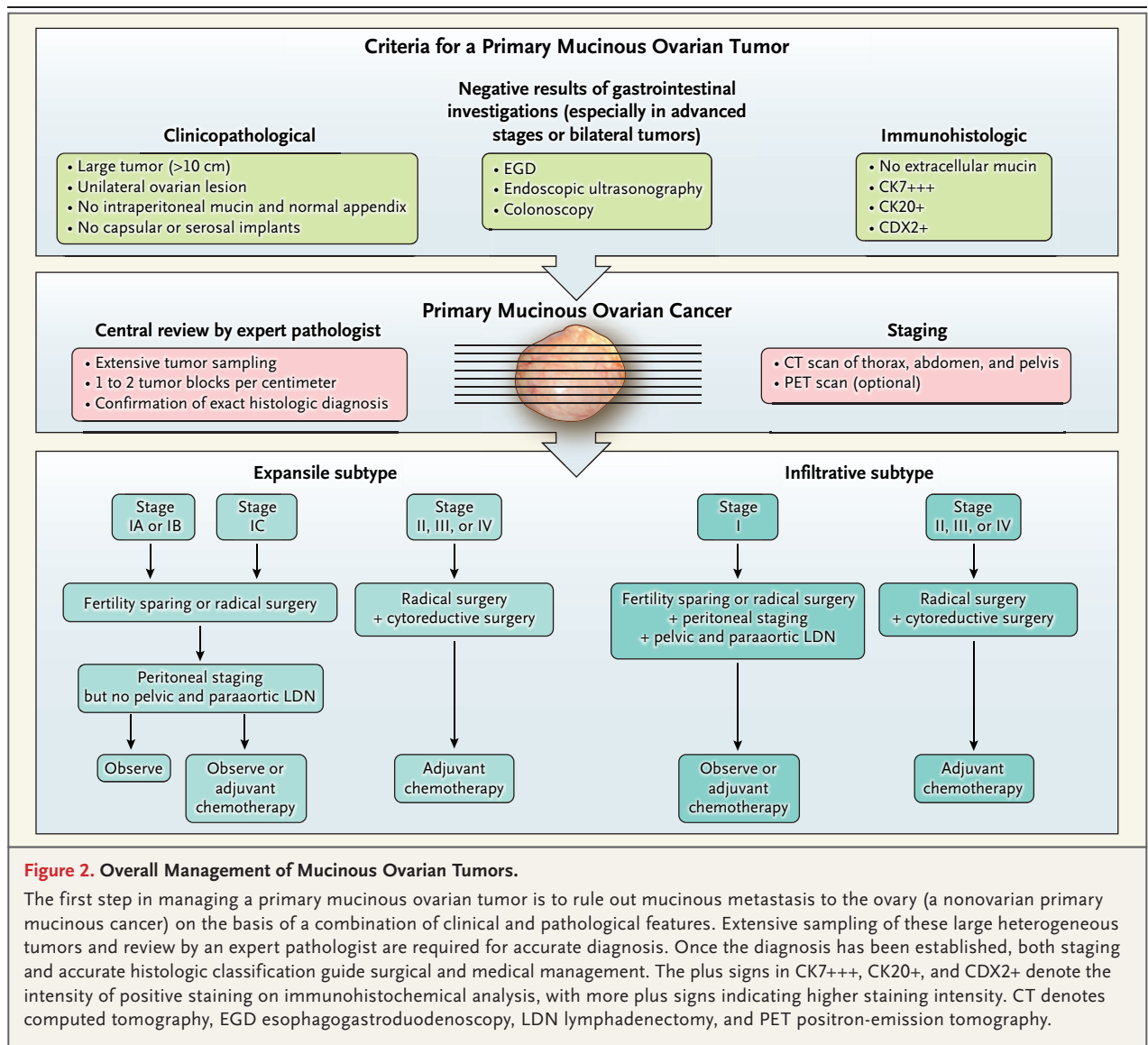
#### **RULING OUT OVARIAN METASTASES FROM NONOVARIAN OCCULT PRIMARY CANCER**

A combination of clinical, pathological, and immunohistochemical investigations is useful in distinguishing a primary mucinous ovarian tumor from metastatic disease to the ovary (Krukenberg tumor) (Fig. 2).<sup>29,32,33</sup> A comprehensive work-up is performed to rule out an occult gastrointestinal primary cancer (on the basis of colonoscopy and upper gastrointestinal endoscopy, including endoscopic ultrasonography) or a cervical, breast, or uterine cancer.<sup>29,32</sup> These investigations are recommended if clinical or radiologic findings suggest a nonovarian primary cancer on the basis of tumor size (<10 cm

in diameter), the presence of bilateral tumors, peritoneal spread or another indication of advanced stage, or a combination of these findings (Fig. 2).<sup>29</sup>

#### **DIAGNOSING THE SUBTYPE OF MUCINOUS TUMOR**

The diagnosis of mucinous ovarian carcinoma requires evidence of malignant proliferation covering an area of more than 10 mm<sup>2</sup> as determined on cross section. For decades, mucinous ovarian cancer was further classified as grade 1, 2, or 3 according to the presence or absence of nuclear atypia and the proportion of solid glandular component. However, in 2014, the World Health Organization (WHO) introduced a new diagnostic classification of mucinous ovarian carcinoma, with two categories according to the growth pattern: the expansile (confluent) subtype and the infiltrative subtype.<sup>5</sup> The expansile subtype is characterized by a confluent glandular growth pattern, with little intervening normal ovarian stroma (minimal or no stromal in-



**Figure 2. Overall Management of Mucinous Ovarian Tumors.**

The first step in managing a primary mucinous ovarian tumor is to rule out mucinous metastasis to the ovary (a nonovarian primary mucinous cancer) on the basis of a combination of clinical and pathological features. Extensive sampling of these large heterogeneous tumors and review by an expert pathologist are required for accurate diagnosis. Once the diagnosis has been established, both staging and accurate histologic classification guide surgical and medical management. The plus signs in CK7+++, CK20+, and CDX2+ denote the intensity of positive staining on immunohistochemical analysis, with more plus signs indicating higher staining intensity. CT denotes computed tomography, EGD esophagogastroduodenoscopy, LDN lymphadenectomy, and PET positron-emission tomography.

vasion), whereas the infiltrative subtype is characterized by obvious evidence of destructive stromal invasion by malignant glands, cell nests, or individual cells and is often associated with a desmoplastic stromal reaction (Fig. 1).<sup>5,34</sup>

#### PROGNOSTIC IMPLICATIONS OF THE WHO 2014 HISTOLOGIC CLASSIFICATION

The distinction between expansile and infiltrative subtypes is clinically important in stage I disease (Table 2), so surgical staging of these tumors is crucial.<sup>3-38</sup> The expansile growth pattern suggests a lower metastatic potential, and

several, albeit small, studies have confirmed that the risk of relapse for women with stage I expansile mucinous ovarian cancer is extremely low (3 recurrences were observed among 75 cases; 2 of the 3 were salvaged with secondary surgery).<sup>34-38</sup> Moreover, more than 95% of women with expansile mucinous ovarian cancers present with stage I disease.<sup>34-38,40</sup> Cases of the expansile subtype with peritoneal spread are very scarce (only 3 reported cases) (Table 2).<sup>35,37</sup> In contrast, infiltrative mucinous ovarian cancer is more aggressive, with at least 26% of women presenting with more advanced, nonlocalized

**Table 2.** Clinical Characteristics and Outcomes of Mucinous Ovarian Cancer According to the Subtype.

Subtype and Study	Pathological Review	Total Enrollment	Stage IA	Stage IC	Higher Stage	Recurrences and Deaths
<i>number of patients</i>						
<b>Expansile subtype</b>						
Rioper et al., <sup>35</sup> 1999	Yes	5	4*	0	1 at stage II	1 recurrence at stage II
Lee and Scully, <sup>34</sup> 2000	Yes	12 (10 in follow-up)	12	0	0	0 recurrences
Rodríguez and Prat, <sup>36</sup> 2002	Yes	15 (11 in follow-up)	10	5 (4 at stage IC1, 1 at stage IC2)	0	0 recurrences; 1 death from breast cancer
Muyldermans et al., <sup>37</sup> 2013	Yes	23	11	10	2 at stage III	2 recurrences at stage III†
Gouy et al., <sup>38</sup> 2018	Yes	29	13	16 (9 at stage IC1, 5 at stage IC2, 2 at stage IC3)	Not included	3 recurrences: 1 at stage IA, 1 at stage IC2, 1 at stage IC3; 1 death
Total		84	46	31	3	6 recurrences: 3 at stage I (3/81 [4%]), 3 at higher stage (3/3 [100%])
<b>Infiltrative subtype</b>						
Hoerl and Hart, <sup>39</sup> 1998		19	15‡	0	4 at stage III	6 recurrences: 2 at stage I, 4 at higher stages; 5 deaths
Lee and Scully, <sup>34</sup> 2000		13 (11 in follow-up)	6 (5 in follow-up)	0	3 at stage II, 3 at stage III, 1 at stage IV (5 in follow-up)	6 recurrences: 1 at stage IA, 5 at higher stages; 6 deaths
Rodríguez and Prat, <sup>36</sup> 2002		19 (15 in follow-up)	8	3	1 at stage II, 6 at stage III, 1 at stage IV (6 in follow-up)	9 recurrences: 1 at stage IC1, 2 at stage IC2, 1 at stage II, 4 at stage III, 1 at stage IV; 7 deaths§
Muyldermans et al., <sup>37</sup> 2013		21	9	3	9 at stage III	9 recurrences: 1 at stage IA, 1 at stage IC, 7 at stage III
Gouy et al., <sup>38</sup> 2018		35	20	15 (7 at stage IC1, 7 at stage IC2, 1 at stage IC3)	Not included	6 recurrences: 2 at stage IA, 1 at stage IC1, 2 at stage IC2, 1 at stage IC3; 4 deaths¶
Total		107	43	21	28	36 recurrences: 14 at stage I (14/79 [18%]) and 22 at stage III or IV (22/24 [92%])

\* In this study, four patients with the expansile subtype had stage I disease that was not classified as either stage IA or stage IC.

† One additional patient with stage I disease died from acute myeloid leukemia while free of the ovarian disease.

‡ In this study, 15 patients with the infiltrative subtype had stage I disease that was not classified as either stage IA or IC.

§ One additional patient with stage I disease died from thyroid cancer while free of the ovarian disease. In the same series, two patients with recurrent infiltrative disease (one at stage III and one at stage IV) survived with persistent disease.

¶ One patient with a recurrence survived but with persistent disease.



disease at diagnosis; in 17 to 30% of patients who appear to have stage I disease, lymph-node metastases are detected (as compared with no women with expansile mucinous ovarian cancer).<sup>34-39</sup> Even if the cancer is diagnosed at an early stage, the prognosis for women with infiltrative mucinous ovarian cancer is much poorer, with fatal relapses reported for 15 to 30% of patients with stage I disease (Table 2).<sup>34-38</sup> Thus, the distinction between stage I expansile and stage I infiltrative subtypes is crucial, since it may influence indications for staging lymphadenectomy or adjuvant chemotherapy.

## SURGICAL MANAGEMENT

### MANAGEMENT OF EARLY-STAGE MUCINOUS CARCINOMA

For young patients wishing to preserve their fertility, a unilateral salpingo-oophorectomy is usually proposed, with peritoneal staging procedures (cytology, peritoneal biopsies, and omentectomy). In older patients, bilateral salpingo-oophorectomy is preferred. The priority is to choose the best surgical approach (laparotomy or a minimally invasive laparoscopic approach) for minimizing the risk of perioperative tumor rupture. Such a rupture would alter the FIGO stage and influence both surgical and medical management of histologically confirmed mucinous ovarian cancer. Unilateral salpingo-oophorectomy is a reasonable approach in women with stage I disease who wish to preserve their fertility. The risk of recurrence is lower than that reported for women with stage I serous cancers (6% vs. 20%,  $P < 0.001$ ).<sup>17,40</sup> Only one study has evaluated the results of fertility-sparing surgery in women with the expansile subtype of mucinous ovarian cancer and those with the infiltrative subtype, and the results suggest that it could be safely used for both subtypes.<sup>41</sup>

A small fraction of patients with macroscopically normal findings on surgical exploration have microscopic peritoneal spread (positive cytologic results in 5.7% of cases or microscopic involvement of the omentum or peritoneal-biopsy specimen in 1.7% of cases) or appendiceal spread (metastasis in 1.1% of cases), but peritoneal or appendiceal spread remains a rare event as compared with disease spread in other epithelial subtypes (Table S2 in the Supplementary Appendix).<sup>42,43</sup>

The rate of nodal spread is very low in cases of apparent stage I mucinous ovarian cancer (<2%).<sup>44,45</sup> However, the higher rate of nodal involvement in stage I infiltrative mucinous ovarian cancer (17 to 30%) suggests that pelvic and para-aortic lymphadenectomy should be proposed for all patients with infiltrative disease, regardless of stage, but can be safely omitted for patients with stage I expansile disease.<sup>37,42</sup>

### MANAGEMENT OF STAGE III OR IV MUCINOUS OVARIAN CANCER

The prognosis for women with stage III or IV mucinous ovarian cancer is poorer than the prognosis for women with other, more common subtypes (particularly serous or endometrioid ovarian cancer) and may be related to a poorer response to chemotherapy (Table S3 in the Supplementary Appendix).<sup>11,16,30,46-48</sup> Some authors have argued that this poor prognosis is due to the inherently aggressive biology of the tumor and the questionable technical feasibility of complete resection, raising doubts regarding the usefulness of an aggressive debulking surgery in women with stage III or IV mucinous ovarian cancer.<sup>13</sup> Conversely, in a series involving 50 patients with stage III or IV mucinous ovarian cancer, overall survival was increased by a factor of 3.8 among patients who underwent optimal debulking surgery.<sup>47</sup> Finally, in an analysis of three randomized trials involving 3126 patients (147 with mucinous ovarian cancer), the size of the residual disease was shown to significantly affect overall and event-free survival in a multivariate analysis of data for patients with mucinous ovarian cancer.<sup>49</sup> In conclusion, debulking surgery with the objective of a macroscopically complete resection remains a cornerstone of management for advanced mucinous ovarian cancer.

## MEDICAL MANAGEMENT

The prognosis for women with mucinous ovarian cancer depends on the stage of disease.<sup>13,49</sup> Overall survival is higher for the majority of patients presenting with stage I disease than for those with nonmucinous histologic subtypes (hazard ratio, 0.52; 95% confidence interval [CI], 0.30 to 0.92). However, the trend is the inverse for women with stage III or IV mucinous ovarian cancer, who have significantly lower overall sur-

vival than women with nonmucinous histologic subtypes (hazard ratio, 2.81; 95% CI, 2.47 to 3.21).<sup>50</sup> Retrospective series have confirmed lower response rates to first-line platinum-based chemotherapy (mainly carboplatin and paclitaxel) among women with mucinous ovarian cancer (13 to 60%) than among women with serous ovarian cancer (64 to 87%) (Table S3 in the Supplementary Appendix).<sup>11,16,30,46-48,50</sup>

Given the histologic similarities between primary mucinous ovarian cancer and gastrointestinal carcinomas and the *in vitro* synergy between oxaliplatin and fluorouracil in preclinical models of mucinous ovarian cancer, empirical use of chemotherapeutic regimens that are traditionally used for gastrointestinal cancers has been tested.<sup>51,52</sup> Gynecologic Oncology Group trial 0241 (involving European, Australian, Korean, and North American groups) was designed to study the activity of a colorectal cancer regimen in women with newly diagnosed metastatic mucinous ovarian cancer. A phase 3 trial randomly assigned women to receive treatment with either paclitaxel and carboplatin (control group) or the combination of capecitabine and oxaliplatin.<sup>31</sup> In addition, there was a secondary randomization in which women were assigned to receive bevacizumab or placebo in order to test the activity of antiangiogenesis therapy. The trial had slow accrual and was closed prematurely. Preliminary results based on the small group of patients (50) who underwent randomization showed no significant difference in progression-free survival among the treatment groups and confirmed a low objective response rate (10 of the 50 women, or 20%, had a response), regardless of the treatment regimen.<sup>31</sup>

Neoadjuvant treatment for advanced ovarian cancer has been tested in the European Organization for Research and Treatment of Cancer (EORTC) 55971 and CHORUS trials. The studies compared initial surgery with a strategy of neoadjuvant chemotherapy.<sup>53,54</sup> Patients with mucinous cancers accounted for only 1 to 3% of the patients, making it impossible to draw any conclusions.

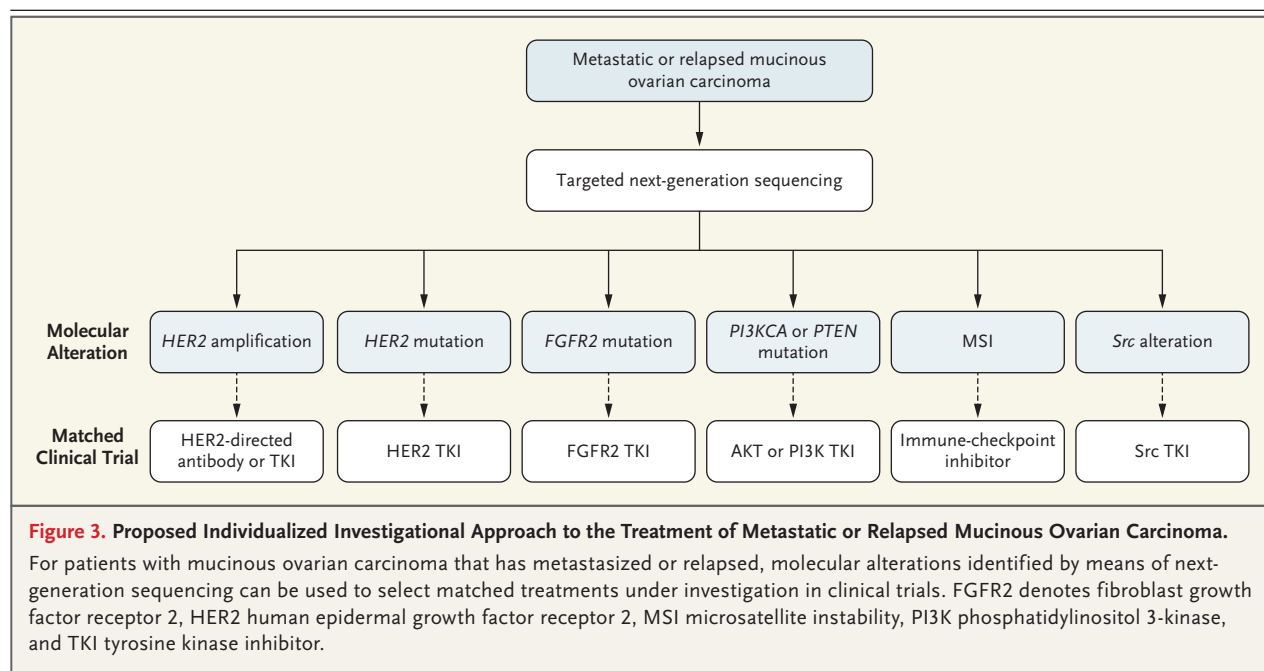
There is a dearth of data from randomized clinical trials evaluating adjuvant chemotherapy in early-stage mucinous ovarian cancer. Various national and international guidelines provide statements about indications for adjuvant chemo-

therapy to help guide physicians, but these statements are not based on clear evidence of a benefit. The National Comprehensive Cancer Network (NCCN) guidelines recommend surgery alone for stage IA or IB mucinous ovarian cancer and adjuvant platinum-based chemotherapy (carboplatin and paclitaxel, or oxaliplatin with fluorouracil or capecitabine) for stage II or more advanced disease. In the case of stage IC mucinous ovarian cancer, the NCCN guidelines recommend either observation or adjuvant chemotherapy ([www.nccn.org/patients/guidelines/ovarian/index.html#69/z](http://www.nccn.org/patients/guidelines/ovarian/index.html#69/z)).

Given the previously mentioned retrospective studies supporting the prognostic information provided by the growth pattern, other European guidelines have further refined treatment recommendations for stage I mucinous ovarian cancer according to the expansile versus infiltrative subtype (Fig. 2). For stage IA or IB expansile mucinous ovarian cancer, which is considered to be low risk, observation alone is recommended, whereas adjuvant chemotherapy is discussed for stage IC expansile mucinous ovarian cancer and is proposed for most cases of stage I infiltrative mucinous ovarian cancer, thus further underscoring the essential role of high-quality pathological review in the management of these rare tumors ([www.ovaire-rare.org/TMRG/medecin/adenocarcinome\\_mucineux.aspx](http://www.ovaire-rare.org/TMRG/medecin/adenocarcinome_mucineux.aspx)) (Fig. 2C).<sup>55</sup>

#### MOLECULAR LANDSCAPE OF MUCINOUS OVARIAN CANCER AND THERAPEUTIC OPPORTUNITIES

Serous ovarian cancers lack genomic alterations in typically actionable driver oncogenes such as *HER2*, *EGFR*, *ALK*, and *BRAF* but are characterized by defects in homologous recombination DNA-repair genes, such as *BRCA1* or *BRCA2*. This deficiency in homologous recombination has been successfully exploited with the use of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors. This drug class represents the first targeted therapy with a demonstrated clinical benefit for women who have relapsed high-grade ovarian cancer. Mucinous ovarian cancers are not associated with *BRCA* mutations or defects in homologous recombination, making them unlikely to benefit from PARP inhibitors. However, they frequently display mutations or amplifications that might be targetable. The most frequent alterations are *KRAS* mutations (in 40 to



65% of cases), *c-MYC* amplifications (in 65%), *HER2* amplifications (in 20 to 38%), and *TP53* mutations (in 50 to 75%). In addition, other alterations have been identified at lower frequencies, such as homozygous deletions in *CDKN2A/B* (in 25% of cases), mutations in *PI3KCA* (in 13%), and mutations in *PTEN*, *BRAF*, *FGFR*, *KIT*, or *STK11* (in 2 to 5%).<sup>23,24,56-60</sup>

These genomic profiling studies allow mucinous ovarian cancers to be grouped into therapeutically relevant subsets (Fig. 3). For example, *KRAS* mutations and *HER2* amplifications tend to be mutually exclusive.<sup>23,60</sup> The subset of *HER2* (human epidermal growth factor receptor 2)-positive tumors with wild-type *KRAS* may be particularly suited to *HER2*-directed therapies such as trastuzumab. Anecdotal objective responses have been described in case reports of patients with metastatic, *HER2*-amplified, mucinous ovarian cancer treated with either trastuzumab alone or trastuzumab combined with the oral tyrosine kinase inhibitor lapatinib.<sup>61,62</sup> The identification of *HER2* or *HER3* mutations in an additional 2 to 12% of patients could justify the inclusion of such patients in basket trials of *HER* inhibitors.<sup>23,58</sup>

*EGFR* amplification or mutations in *BRAF*, *FGFR*, or *STK11* have been detected in *HER2*-negative tumors with wild-type *KRAS*, suggesting that

these tumors may be responsive to inhibitors of *EGFR* (epidermal growth factor receptor), *BRAF*, *FGFR2* (fibroblast growth factor receptor), or *mTOR* (mammalian target of rapamycin), respectively. The absence of a *KRAS* mutation identifies a subset of patients with colorectal cancer who are more likely to benefit from the *EGFR*-inhibiting antibody, cetuximab. Preclinical studies have shown that cetuximab inhibits proliferation in mucinous ovarian cancer cell lines with wild-type *KRAS* and in a single in vivo model, whereas it has no antitumor effect in a model of *KRAS*-mutated mucinous ovarian cancer.<sup>63</sup>

Most mutations in the *PI3K* (phosphatidylinositol 3-kinase) pathway occur with a *KRAS* mutation, and preclinical studies have shown synergy between *MEK* (mitogen-activated protein kinase) and *PI3K* inhibition in mucinous ovarian cancer cell lines with *KRAS* mutations.<sup>64</sup> Although the number of patients was small, a phase 1 trial of molecularly guided therapies for rare subtypes of ovarian cancer showed encouraging objective responses to combined *MEK* and *PI3K* inhibition in patients with *KRAS*-mutated ovarian cancer.<sup>65</sup>

*TP53* mutations are detected at a remarkably high frequency in mucinous ovarian cancer (in 50 to 75% of cases).<sup>23,66</sup> *APR-246* is a small molecule designed to restore wild-type *p53* function, whereas the *WEE1* inhibitor, *AZD1775*, abrogates



the G2-M cell-cycle checkpoint, selectively sensitizing p53-deficient cells to DNA-damaging agents.<sup>67</sup> Both agents are being investigated in clinical trials of TP53-mutated tumors.

Finally, defects in the mismatch-repair pathway of DNA repair that result in a tumor with microsatellite instability have been detected in 15 to 20% of patients with mucinous ovarian cancer.<sup>68-70</sup> Given that tumors with microsatellite instability have high mutation burdens and dense immune infiltrates that are characteristic of other tumor types that respond to immune-checkpoint inhibition, enthusiasm is high for testing inhibitors of PD-1 (programmed death 1) or PD-L1 (programmed death ligand 1) in the subset of mucinous ovarian cancers with microsatellite instability.<sup>71</sup>

#### FUTURE DIRECTIONS

Important questions remain regarding the management of high-risk, localized mucinous ovarian cancer (stage I infiltrative subtype or stage IC expansile subtype). What are the criteria for selecting patients with high-risk stage I disease for adjuvant treatment? What is an ideal cytotoxic regimen? Will therapy that has some activity against gastrointestinal tumors have meaningful activity against mucinous ovarian cancer? In the future, targeted therapy may be worth testing in patients who have mucinous ovarian cancer with selected genetic alterations such as *HER2* muta-

tions or microsatellite instability (Fig. 3).<sup>72,73</sup> The rarity of the tumor mandates international collaboration to evaluate new therapies in a timely fashion.

In line with these questions, the Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup identified four key areas for further research in mucinous ovarian cancer: improvement in the histologic criteria for diagnosis, definition of the optimal surgical and medical approaches to the management of high-risk localized disease, identification of an active cytotoxic regimen, and enrollment of patients in clinical trials of new therapeutics.<sup>74</sup>

Dr. Morice reports receiving advisory board fees from Roche, lecture fees from Johnson & Johnson, and fees for participating on a board from Clovis; Dr. Gouy, receiving consulting fees from Roche; and Dr. Leary, receiving fees for serving as chief investigator or principal investigator on clinical trials, travel support paid to her institution, and advisory board fees from AstraZeneca; fees for serving as principal investigator on clinical trials, travel support paid to her institution, and advisory board fees from Clovis; travel support and advisory board fees from Tesaro; advisory board fees from Gridstone, Seattle Genetics, and Biocad; grant support paid to her institution from Merus and Inivata; fees for serving as chief investigator or principal investigator on a clinical trial paid to her institution from Roche, Pfizer, MSD, BMS, and Pharmamar; and grant support paid to her institution, fees for serving as chief investigator on a clinical trial, and advisory board fees from GamaMabs. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Catherine Genestie, Patricia Pautier, and Jean Charles Soria for their comments and suggestions regarding an earlier draft of the manuscript.

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