Borderline ovarian tumors show epithelial proliferation greater than that seen in their benign counterparts and variable nuclear atypia; however, in contrast to carcinomas, there is no destructive stromal invasion, and their prognosis is much better than that of carcinomas. In spite of the lack of stromal invasion, serous borderline tumors, particularly those with exophytic growth, can implant on peritoneal surfaces and, rarely (about 10% of peritoneal implants), progress to low-grade serous carcinoma (LGSC) and invade the underlying tissues [7, 8].

Although favorable in the vast majority of cases, the biologic behavior of the borderline tumors differs from that of the obviously benign tumors of the same cell type(s) and, rarely (<1%–3%), progression to invasive carcinoma occurs justifying the term ‘borderline tumor’. Alternative terms such as ‘proliferating’, ‘atypical’, and ‘atypical proliferative’ [9] are not recommended since they are nonspecific; i.e. all non-benign epithelial tumors (borderline and carcinomas) are proliferative neoplasms which exhibit nuclear atypia; also, these terms are misleading as they do not take into account the malignant potential of a small but significant number of these tumors and discourage follow-up [7, 8]. Similarly, the subdivision of the serous borderline group into benign and malignant, based on the presence of a micropapillary architecture [10], is artificial since serous borderline tumors (SBT) with or without micropapillary pattern may rarely be associated with invasive peritoneal implants and poor outcome [7, 8]. A recent study of gene expression profiling of 13 SBTs and 3 low-grade serous carcinomas showed that SBTs with (one case) and without micropapillary pattern were equally
distributed between benign-like and malignant-like subgroups [11]. Although the term ‘borderline’ may suggest uncertainty, it accurately describes the ambiguous histologic and biologic features of these neoplasms and remains the most appropriate term. Accordingly, it has been recommended by the World Health Organization (WHO) for the last four decades [2]. The majority of these tumors are associated with a favorable prognosis and the term ‘tumors of low malignant potential’ is not recommended.

With the exception of squamous cell tumors, the borderline concept applies to all types of ovarian epithelial tumors listed before; however, most data in the literature refer to the serous and mucinous gastrointestinal categories which are the two most common types and show striking clinicopathological differences. SBTs account for from 5% to 10% of ovarian serous tumors and occur at an average of 42 years. Approximately 70% are confined to one or both ovaries (stage I) at the time of diagnosis; the remaining tumors have spread within the pelvis (stage II) or upper abdomen (stage III). One-third of stage I tumors are bilateral [1–3]. Mucinous borderline tumors (MBTs) of intestinal type account for 10%–15% of ovarian mucinous tumors and are more common in the first two decades than their serous counterparts [1–3]. SBTs are confined to one or both ovaries (stage I) in almost all cases. Nearly all stage II–III MBTs are associated with pseudomyxoma peritonei and, in these patients, the ovarian tumor is virtually always secondary (metastatic) from a primary appendiceal tumor [1–3]. However, in contrast to serous tumors which are usually homogenous, primary mucinous tumors often are heterogeneous. Benign-appearing, borderline, and invasive patterns may coexist within an individual neoplasm; this continuum suggests that progression occurs from cystadenoma and borderline tumor to noninvasive, microinvasive, and invasive carcinoma [1–3, 12]. This is supported by studies of K-RAS mutations, which represent an early event in mucinous ovarian tumorigenesis. MBTs have a higher frequency of K-RAS mutations than that of mucinous cystadenomas, but lower than mucinous carcinomas [13].

Surgery is the cornerstone of treatment of patients with SBTs and MBTs. Whereas in menopausal and postmenopausal women and in those who have completed their childbearing, the standard treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), in young women with unilateral tumors and normal-appearing contralateral ovaries who wish to preserve their reproductive capacity, unilateral oophorectomy, or even an ovarian cystectomy, is usually carried out [14, 15]. Although a staging procedure for SBTs is often thought to be too radical, comprehensive surgical staging is recommended in patients with apparent stage I SBTs to exclude the presence of invasive peritoneal implants [16]. Prolonged follow-up is mandatory to exclude development of a similar tumor in the contralateral ovary. After the patient’s family is complete, hysterectomy with residual salpingo-oophorectomy has been advocated, but its value has been questioned [17]. If a similar tumor develops in the contralateral ovary (5%–10% of the cases), the patient can be successfully treated in most cases by reoperation alone [7, 14].

The overall outcome of SBTs is very favorable. The 5-year survival rates for patients with disease that is stages I–IIIn are between 88% and >95% [18]. For patients with stage I tumors, the risk of recurrence or the development of a second SBT has been estimated to be only 5%–10% [7, 8, 14]. Other than the adverse effect of invasive implants, there is no agreement in the literature as to which prognostic factors are important [7, 8, 14, 19]. According to most investigators, SBTs with micropapillary pattern or SBTs with microinvasion have a prognosis similar to that of tumors lacking these features [7, 8, 20]. Likewise, focal lymph node involvement has not demonstrated any effect on survival. The 5-year survival rate for patients with stage I MBT nears 100%. In a recent report, 6 of 144 patients (4.2%) had tumor recurrence. Risk factors for recurrence included FIGO stage IC, microinvasive carcinoma, age <45 years, and intraepithelial carcinoma [21].

The article by Uzan et al. [22] in the current issue of Annals of Oncology focuses on risk factors for recurrence and, more specifically, for recurrence in the form of invasive carcinoma in a large series (n = 254) of macroscopic stage I borderline ovarian tumors (140 MBTs and 114 SBTs). This article stands out as it includes the largest number (n = 191) of conservatively treated patients reported to date.

Even if all cases included were macroscopic stage I tumors, and considering that the median follow-up interval was only 3.7 years, the reported 17% overall recurrence rate appears to be much higher than the corresponding figures in the literature for stage I SBT and MBT of intestinal type; i.e. 5%–10% and 4.2%, respectively [7, 8, 14]. However, the higher rate may be partly attributed to the fact that 75% of patients were treated conservatively, either by unilateral salpingo-oophorectomy (n = 121) or cystectomy (n = 70). In fact, the risk factors for overall recurrence included conservative treatment, particularly cystectomy, bilaterality (stage IB), and incomplete staging. In SBTs, the presence of tumor at the resection margin of the cystectomy specimen and multifocality with removal of more than one cyst are strong predictors of failure of cystectomy to control the disease [15]. Furthermore, the frequency of microscopic SBT in a grossly normal-appearing contralateral ovary is 5%–10% [15].

The most interesting finding of this investigation is the influence of the histological type on the nature of the recurrent tumor in young patients who underwent fertility-sparing surgery. In these patients, MBTs of intestinal type recurred less frequently than SBTs, but when they did it was more often as an invasive carcinoma. Most SBTs maintain their microscopic features and usually do not progress to frankly invasive carcinoma [7, 14]. In a recent study, progression of SBT to low-grade serous carcinoma occurred in 6%–7% of patients late in the course of the disease [8]. Almost 80% occurred in patients without prior history of invasive implants [8]. Of eight cases of SBT with malignant behavior, three exhibited focal stromal invasion greater than microinvasion, and only two were SBT with micropapillary pattern [23]. In contrast, MBTs of intestinal type represent intermediate stages of mucinous tumorigenesis and, even if a MBT per se is essentially a benign neoplasm, it may be accompanied by or may progress to intraepithelial and frankly invasive carcinoma [12].

The findings of Uzan et al. [22] clearly confirm the different nature of SBTs and MBTs of intestinal type. The so-called malignant recurrences, which occurred in the contralateral ovary in five of eight patients with MBTs initially treated by unilateral salpingo-oophorectomy, most likely represent independent primary mucinous tumors, typically heterogeneous, containing...
benign-appearing, borderline, and carcinomatous elements. Noteworthy, three of the five MBTs initially resected already had intraepithelial carcinoma. In contrast, the recurrences of the three SBTs that progressed to carcinoma typically occurred in the peritoneum as invasive implants; i.e. low-grade serous carcinoma. The only patient from this subgroup who underwent conservative treatment (bilateral cystectomy) had a SBT with micropapillary pattern which was incompletely staged. Her tumor first recurred as SBT 6 months postoperatively and as invasive carcinoma 4 years later. As recognized by the authors, the prognostic value of the micropapillary pattern in this single case is limited. The term ‘micropapillary’ is flawed as all SBTs have micropapillae descriptively, and their extension may range from a few papillae to a huge number of them. Bilaterality, ovarian surface growth, and advanced stage (mainly noninvasive peritoneal implants) are more common features of extensively micropapillary SBTs than of typical SBTs, but a strong association of the former tumors with invasive implants and poor outcome has been inconsistent [7, 8, 19, 20].

Uzan et al. [22] demonstrate that the results of fertility-sparing surgery in patients with borderline ovarian tumors depend not only on the possibility of residual tumor and/or multicentric tumorigenesis, but also on the tumor’s histological type. Whereas SBTs usually recur as such and rarely progress to low-grade serous carcinomas (i.e. invasive peritoneal implants), MBTs of intestinal type are more frequently associated with carcinoma either in retained tumor or within independent primary MBTs developing in the contralateral ovary. In other words, SBTs and MBTs of intestinal type are different diseases with different biologic behavior.

Also in this issue, the study by Trillsch et al. [24] investigates the safety of fertility-sparing surgery in a large number of patients selected from a cohort of 950 women with borderline ovarian tumors collected over 11-year period from 24 German institutions. Patients younger and older than 40 years (n = 280 and 670, respectively) were analyzed separately and subsequently compared regarding clinicopathological variables, site of recurrence, and malignant transformation. Fertility-sparing surgery was carried out in 149 of 280 (53.2%) patients <40 years with preservation of some ovarian tissue from the ovary involved by tumor in 32 (21.5%) cases. Recurrence was more frequent in patients <40 years (18% versus 4%). However, it occurred mainly in the retained ovarian tissue, and there were no cases of cancer recurrence in this site. Therefore, it appears that the higher recurrence rate may be partly explained by the fact that younger patients are more likely to have ovarian tissue left. The older patients had a higher number of extravarian recurrences and, significantly, more cancer recurrences (15/21 versus 6/18). Similar to the findings of Uzan et al., MBTs of intestinal type recurred as invasive carcinoma more frequently than SBTs (60% versus 22.4%).

The recurrence rates after fertility-sparing surgery in the two series of borderline ovarian tumors reported by Uzan et al. [22] and Trillsch et al. [24] are similar (17% and 18%, respectively) and higher than those in the literature; however, most ‘recurrent’ tumors, particularly in young patients, were SBTs that regrew as such in retained ovarian tissue and were safely controlled by additional surgery. A word of caution: in both studies, a significant number of recurrent MBTs of intestinal type were associated with invasive carcinoma reflecting the characteristic heterogeneity of ovarian mucinous tumors. This finding raises the issue of completing surgery after childbirth in patients with MBTs of intestinal type.

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references
Netupitant and palonosetron (NEPA): a winning team in the race for the optimal treatment of chemotherapy-induced nausea and vomiting?

During the lifetime of many healthcare professionals reading this article, the way in which chemotherapy induced nausea and vomiting (CINV) is approached and treated has transformed. The three papers reporting phase 2 and 3 dose–response studies of NEPA on day 1 with dexamethasone (DEX) on days 1–3 [1–3, Table 2; (i) dose-finding [1], efficacy and safety [1–3] studies of an oral fixed-dose combination (netupitant and palonosetron, NEPA) of a tachykinin NK1 receptor [substance P (SP)] antagonist (NK1 RA, netupitant, 300 mg) and a 5-hydroxytryptamine 3 receptor antagonist [5-HT3 RA, palonosetron (PALO), 0.5 mg] are the latest clinical developments in the search for optimal anti-emetic therapy. This shift in approach to CINV is multifactorial: (i) a change in the attitude of healthcare professionals to nausea and vomiting, now viewed as something to be treated rather than tolerated by the patient; (ii) identification of risk factors initially: age, sex, alcohol consumption and emetic history, but screening for polymorphisms that may influence efficacy of 5-HT3 RA (e.g. ABCB1, [4]) could be included; (iii) anti-emetic guidelines [5]; (iv) the introduction of the highly emetic cisplatin in the 1980s stimulated research into anti-emetics [6, 7]; (v) the recognition of anticipatory, acute and delayed phases of CINV [8] and insights into their differing mechanisms and pharmacology [9–11]; (vi) a shift in the way that identification of novel anti-emetics was approached by using models such as the ferret in which emesis was induced by cisplatin and which led to identification of the involvement of 5-HT3 and NK1 receptors [12]. Research into the involvement of 5-HT3 and NK1 receptors continues [13, 14].

Clinical significance

The papers make three advances of note: (i) a single oral dose of NEPA on day 1 with dexamethasone (DEX) on days 1–4 in patients receiving the first cycle of highly emetic chemotherapy (HEC)-based regimes blocked emesis in 98.5% of patients in the acute and 91.9% in the delayed phases with similar ‘no significant nausea’ values (98.5% and 90.4%, respectively) [1, Table 2]. Although NEPA is only given on day 1, the efficacy extends over the 120 h of study. In comparison with PALO (0.5 mg) alone, NEPA increased the acute and delayed no emesis rates by ∼10% and the ‘no significant nausea’ rate by ∼5% in the acute and ∼10% in the delayed and overall phases [1, Table 2]. (ii) In moderately emetic chemotherapy (MEC), a single oral dose of NEPA and DEX on day 1 produced acute and delayed no emesis rates of 90.9% and 81.8% and no significant nausea of 87.3% and 76.9% [2, Table 2]. NEPA + DEX was superior to PALO + DEX with regard to acute and delayed emesis (including no rescue medication, [2, Figure 2]), but interestingly for ‘no significant nausea’ NEPA + DEX was only superior in the delayed phase [2, Table 2]. (iii) Maintenance of anti-emetic efficacy over repeated chemotherapy cycles is a challenge and the present study [3] investigated NEPA given on day 1 of each cycle with DEX on days 1–4 in HEC and only on day 1 in MEC. The complete response (no emesis and no rescue) rate for the overall responses (81%, 0–120 h) was maintained over six cycles; of the 309 patients evaluated in cycle 1, 75% completed four cycles and 40% six cycles [3, Figure 2]. The ‘no significant nausea’ rates ranged from 84% to 92%.

Scientific rationale

The inclusion of PALO as the 5-HT3 receptor antagonist in NEPA is of particular interest. PALO differs from the earlier ‘setrons’ in having a longer plasma half-life (>40 h), inhibition of receptor function and higher binding affinity [14]; although these go some way to explaining the enhanced clinical efficacy, there is evidence that PALO has additional properties. Of particular relevance is 5-HT3 R internalisation triggered by PALO binding, allosteric binding to the 5-HT3 R and probably of most potential significance inhibition of intracellular ‘crosstalk’ between 5-HT3 and NK1 receptors [14–17]. The functional consequence of the latter is proposed to be that PALO and netupitant have a synergistic action to reduce the SP-mediated response [14]. Note that PALO is not an NK1 RA. The contribution of the ‘crosstalk’ mechanism to the clinical efficacy of NEPA requires investigation. It may be possible to test the...