Controversies in the Treatment of Women with Early-Stage Epithelial Ovarian Cancer

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Summary Points

- Surgery and chemotherapy play important roles in the treatment of women with epithelial ovarian cancer. In early disease, when there is the best chance of cure, optimizing treatment with both modalities without overtreatment can be a challenge.
- What initial surgery should be performed, both for those women who have a diagnosis of ovarian cancer prior to surgery and those whose cancer is diagnosed at or after surgery? In particular, what are the options for women who wish to preserve their childbearing potential?
- What clinical trial data can inform the need for and the choice of adjuvant chemotherapy regimen?

Introduction

Despite global efforts to optimize systemic and surgical management of epithelial ovarian cancer (EOC), it remains a disease that is primarily diagnosed at an advanced stage with extra ovarian and extra pelvic tumor involvement (FIGO III and IV) in over 70 % of the affected women [1, 2]. The prognosis of early-stage disease is significantly better than in the more common late-stage disease, with 5-year survival varying from 80 to 93 % (stage I/II) to <30 % (stage III/IV) [2–5]. Women diagnosed with stage I disease constitute a minor subgroup and are frequently identified serendipitously, being explored for a pelvic mass or for pelvic-related symptoms. These women do not generally represent a major surgical challenge in terms of multi-visceral resection techniques [6, 7]; however, accurately assessing stage is paramount to making informed decisions about appropriate adjuvant therapy. It is well described that occult disease is identified in 10–30 % of women with disease first thought to be confined to the ovary. For those who do have organ-confined disease and who are of childbearing age, consideration must be given to options of fertility-sparing surgery.

Informed choices for women with early EOC are limited by the paucity of randomized trials. Well-powered trials in this group of women are challenging due to the comparatively low incidence of early-stage disease [8] and the need for very long-term trials (>10-year follow-up) because of the relatively good prognosis, particularly when tumors are thoroughly staged.

Increasingly, these patients are excluded from participation in randomized clinical trials or relegated to a stratum where only hypothesis-generating assessments can be made. The irony in this clinical trial decision is that these patients frequently present with histologies (e.g., clear cell, endometrioid, low-grade serous) which are increasingly being identified with actionable molecular targets and, as such, may represent ideal patients to treat with novel targeted therapies [9]. When they are included in advanced disease trials, patients with early-stage disease [10–14] form small strata making evidence-based, specific recommendations for these women extremely

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difficult. To maximize information from randomized trials, extended follow-up, international collaboration, and meta-analyses are essential. The issue of when and how to treat early-stage OC is becoming increasingly important, with the identification of incident early-stage cases during prophylactic risk-reducing surgery in patients at high risk of developing OC (e.g., BRCA 1/2 carriers) and the potential for a further significant increase if cases of population screening trials (e.g., UKCTOCS [15]) are positive and demonstrate the ability to identify an increased proportion of patients with early-stage disease.

In this chapter, we address the most controversial issues regarding the treatment of early-stage EOC focusing on the therapeutic and prognostic implications of reoperation for staging after suboptimal initial surgery, the value and anatomic limits of systematic lymph node dissection at primary surgery, the role of minimally invasive surgical techniques, the type and duration of optimal adjuvant treatment, the value of targeted agents, the implementation of alternative chemotherapy regimens such as dose-dense delivery, optimal trial designs, individualized treatment approach, fertility-sparing surgical objectives, and hormone replacement and quality of life.

What Is the Role of Formal Staging Surgery for Women with Apparently Early EOC?

Since validated methods for early detection (e.g., preoperative imaging and biomarkers [CA125, HE4, OVA1]) have yet to be established, stage I disease is often identified incidentally [16]. Thus, many women initially undergo laparotomy or laparoscopy with the expectation of benign disease and may not therefore undergo adequate staging. National and international guidelines demand completion of adequate surgical staging in those cases where initial surgery was insufficient. In women for whom future fertility is important, the question of ovarian preservation complicates decisions regarding the extent of resection (cystectomy versus oophorectomy, unilateral versus bilateral resection) and the need for formal staging (risk of periovarian adhesions) [17, 18].

There are a number of arguments for the case for surgical staging:

1. Accurate surgical staging may result in unmasking of occult advanced disease (upstaging) which in turn has implications for defining optimal adjuvant treatment significantly influencing survival. Furthermore, a subgroup of patients may be identified where observation alone would suffice and the toxicity of any systemic chemotherapy avoided.

   Also, without accurate disease description, women may not be able to participate in clinical trials or benefit from future treatments with novel targeted therapeutics, tumor-specific vaccines, or immunotherapy regimens, which require accurate disease description to be available. Women with limited stage disease, arguably, may represent the ideal cohort for lasting tumor control in these programs and hence represent a cohort with the highest cure potential.
2. There is sufficient evidence that in early EOC existing conventional imaging modalities fail to accurately demonstrate peritoneal involvement, especially in the case of small volume disease. Although newer imaging modalities such as FDG-PET/CT and diffusion-weighted MRI (DW-MRI) offer an overall performance advance or an important adjuvant to conventional CT imaging, peritoneal deposits under 1 cm are frequently underappreciated by all imaging modalities [19]. Therefore, surgical assessment is still considered the most reliable method to accurately define disease distribution. The Gynecologic Oncology Group (GOG) has proscribed the surgical procedures required for complete staging in their EOC clinical trials (Table 1.1).

Table 1.1 GOG staging procedure for ovarian cancer [89]

GOG staging procedure for ovarian cancer
1. Vertical incision
2. Send peritoneal fluid. If none, send peritoneal washings
3. Inspect and palpate all peritoneal surfaces
4. Omentectomy
5. TAH-BSO
6. Resect gross disease within the abdominal cavity
7. In absence of disease beyond the pelvis, peritoneal biopsies
8. Pelvic and para-aortic nodes for:
Stage IIIB disease (microscopic disease in omentum 2 cm)
Not required for stage IIIC or IV disease, unless only disease is a palpable node

Table 1.2 Rates of upstaged women after accurate surgical staging in apparently early EOC

Structure affected by tumor in apparently early ovarian cancer after adequate staging	Rate of women [88] (%)
Cytology	20
Omentum	6
Diaphragmatic peritoneum	15
Random peritoneal biopsies	13
Para-aortic lymph nodes	14
Pelvic lymph nodes	8

Depending on the histological grade and subtype, up to 30 % of the women with apparently early EOC will be upstaged after comprehensive surgical staging [18, 20]. Table 1.2 presents the rates of upstaged women after accurate surgical staging in women with apparently early EOC.

In a more recent retrospective evaluation of 86 women with EOC grossly confined to the ovary in whom complete surgical staging was performed, 29 % were upstaged, 6 % had metastatic disease in uterus and/or fallopian tubes, 6 %

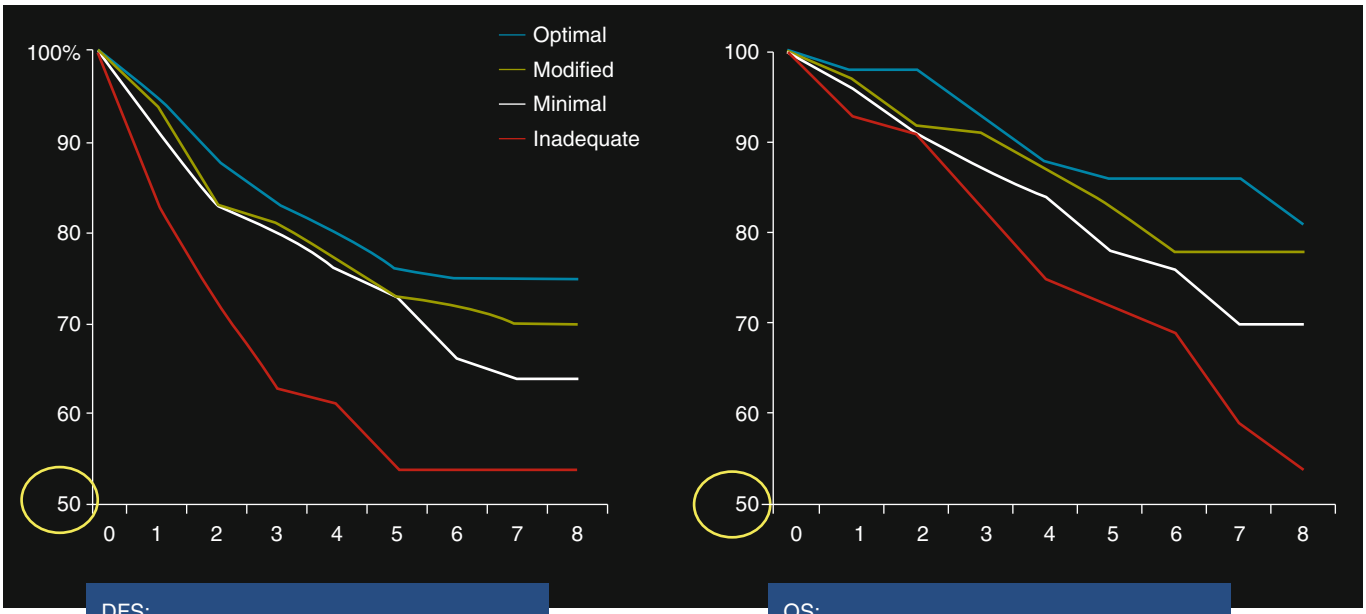

Fig. 1.1 DFS and OS according to quality of staging

in lymph nodes, and 17 % in peritoneal, omental, or adhesion biopsies [20]. In a larger analysis including 122 women of mainly stage IA (33 %) and IC (41 %) disease, a total of 19 women had positive peritoneal biopsies (16 %) at surgical staging. Even though only six (5 %) of those were from normal-appearing tissue, comprehensive staging resulted in upstaging of 4 % of all women by the random peritoneal biopsies alone. Five (4 %) women had microscopic metastases to the omentum, four (3 %) of whom were upstaged by this finding alone [21]. The authors concluded that although the rate of microscopic metastases to peritoneal tissue is low, random peritoneal biopsies might still be indicated in early-stage disease, especially considering the low morbidity of the procedure and the rapid regeneration of the peritoneum.

Unfortunately, trials conducted in early-stage disease are bereft of standardized surgical staging procedures leading to difficulty in interpretation of the value of the procedure itself. A subanalysis of EORTC Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) trial evaluated the staging characteristics of the incompletely staged cancers as well as factors leading to this outcome. Despite being an eligibility criterion, complete surgical staging was performed in only a minority of participants (34 %) [18]. The authors identified lack of surgical skills accounted for the majority of the deviations. This was followed by insufficient knowledge of the tumor behavior and routes of spread of ovarian cancer, especially in low-volume centers. Figure 1.1 presents the ACTION data regarding the significant impact of surgical quality, as measured on the completeness of staging in early EOC, on disease-free survival (DFS) and OS.

Should Patients with Inadequately Staged Early Ovarian Cancer Undergo a Second Operation?

The arguments against reoperation are:

1. Patients with organ-confined disease (i.e., IA or IB) do not need to undergo unnecessary second surgery with all associated short- and long-term morbidity if at first surgery all peritoneal surfaces appear unaffected by tumor and there are no abnormalities on postoperative imaging. Postoperative chemotherapy will be administered under these circumstances, and thus, incomplete surgical staging can be sufficiently compensated.
2. No prospectively randomized trials exist to establish the prognostic and/or therapeutic value of surgical staging in early EOC. Moreover, there is no evidence-based therapeutic

impact of removing microscopic disease in women already considered with "optimal" postoperative tumor residuum by advanced disease standards (so called R0 resection) [9, 22–25]. A retrospective analysis by Dizon et al. [17] of 88 women with stage I–II disease failed to identify any survival advantage of completion of surgical staging in women who underwent chemotherapy with 6 cycles of carboplatin and paclitaxel. With a median follow-up of 50 and 59.5 months, respectively, for staged versus nonstaged women, 5-year PFS was 85 % versus 80 % (p=0.54). Accordingly, no benefit in OS was identified with 5-year OS-rates of 85 % versus 88 %, respectively (p = 0.688). Another retrospective analysis by Le et al. [26] reviewed the impact of comprehensive surgical staging in a group of 138 women with tumor confined to the ovary. In the group of women given adjuvant platinum-based chemotherapy at a median follow-up of 58 months, 11 out of 34 (32 %) staged women relapsed compared to 8 out of 19 (42 %) unstaged women, a difference which was not statistically significant. These data raise the hypothesis that planned adjuvant chemotherapy can normalize the therapeutic difference, if it exists, between unstaged and staged women, obviating the unnecessary morbidity of a second surgery.

Some practitioners have advocated that random biopsies or omentectomy may be a surrogate for staging in cases where expert surgical help is unavailable. However, the value of random sampling of this nature is even more inconclusive. Retrospective studies suggest that random peritoneal biopsies add only little diagnostic value beyond careful inspection of the peritoneal surfaces [27]. A retrospective evaluation of 211 women with apparent early EOC revealed that only 9 women were upstaged based on pathology, hence indicating a high negative predictive value of thorough exploration and lymphadenectomy. Only one patient (1/118, 0.8 %) was upstaged from stage I disease to stage II disease based on random biopsy of pelvic peritoneum, since all other stage II women had visible disease. Interestingly, no women were upstaged from stage I disease to stage III disease due to random biopsies or microscopic omental disease. Eight women (3.8 %) were upstaged from stage II to stage III disease based on random biopsies of upper abdominal peritoneum or the omentum. Interestingly, the authors report that their treatment recommendations for adjuvant therapy were unaffected by the findings from random biopsies [27].

In summary, the available data suggest that there is merit to formal surgical staging in women where disease may be observed or in cases where such information is required for participation in a clinical trial. Women with high-risk features are prime candidates for adjuvant therapy; those without gross disease likely gain little specifically from formal staging; however, those with suspected residual disease should be explored for cytoreduction. Fertility-sparing procedures (retention of the uterus, fallopial tubes, and contralateral ovary in case of unilateral disease) appear safe, although removal of the ovaries at the completion of childbearing wish may be recommended.

Table 1.3 Rate of women with apparently early EOC with positive pelvic and/or para-aortic lymph nodes after systematic lymph node dissection

Author	Number of patients in study	%
Benedetti-Panici [28]	35	14
Petru [29]	40	23
Onda [30]	33	21
Baiocchi [31]	242	13
Suzuki [32]	47	11
Nomura [33]	79	13
Harter [43]	70	11

Should Complete Bilateral Pelvic and Para-aortic Lymph Node Dissection (LND) Be Part of Routine Staging?

The standard approach to surgical removal of retroperitoneal nodes in EOC remains controversial. Even when the tumor is seemingly limited to the ovaries, spread to retroperitoneal nodes is not uncommon [28–33]. For that reason surgical staging includes the inspection and dissection of pelvic and para-aortic lymph nodes. What is not defined so far is how extensive the LND needs to be and if a sampling is sufficient compared to systematic dissection [34].

The Arguments for Systematic LND

The value of systematic LND lies in the accurate staging of the apparently early EOC by unmasking all occult IIIC stage disease; an upstaging that would have significant impact on decision-making process regarding adjuvant therapy. This is highlighted by the approval of antiangiogenesis therapy for advanced-stage (>stage IIIB) disease in many countries [35]. As is the case for formal peritoneal assessment of apparent early-stage women, systematic tissue sampling, in this case, lymph nodes, will identify occult disease in a proportion of women with nonclinical disease. The rate of pelvic and para-aortic node involvement is 8–15 % and 5–24 %, respectively (Table 1.3) [34, 36, 37]. In the prospective randomized trial by Maggioni et al. significantly more women in the systematic LND group had positive nodes at histologic examination than women in the lymphatic sampling arm (9 vs. 22 %, p=0.007). In this study, an adequate LND was defined as removal of 20 or more nodes in a bilateral pelvic retroperitoneal dissection and 15 or more nodes from the para-aortic chains. In addition, significantly more women undergoing sampling were administered postoperative systemic chemotherapy in the absence of formal surgical staging information

(66 % vs. 51 %, $p=0.03$). Further, these occult stage IIIC women would have been eligible for participation in advanced-stage clinical trials. And finally, women with stage IIIC disease determined solely on the basis of histologically positive retroperitoneal adenopathy appear to have a better prognosis over those stage IIIC women identified by gross intraperitoneal spread [38]. A criticism for formal surgical staging is the increased risk of operative and perioperative morbidity. In this trial, rates of transfusion and the hospital stay were increased in the systematic LND arm; however, neither the number of intraoperative nor perioperative/late complications were statistically different between the two groups (8 cases vs. 4 and 8 cases vs. 16 in the control and lymphadenectomy arm, respectively). Regarding late morbidity, most of the difference was due to formation of lymphocysts and lymphedema, which occurred in eight cases in the lymphadenectomy group versus none in the control arm. Adhesive small bowel obstruction occurred in one patient after lymph nodes sampling only and in two women after lymphadenectomy. There were no surgery-related deaths in either arm of the trial. The authors conclude that although their study was underpowered to detect an effect of systematic LND on PFS or OS, the trends in the point estimates for these hazard ratios favored the procedure particularly in light of the accuracy of diagnosis precluding some women from receiving unnecessary adjuvant therapy.

The Arguments Against Systematic LND

There is no evidenced-based benefit of systematic LND in apparently early EOC. The only randomized clinical trial of women with EOC macroscopically confined to the pelvis that compared systematic LND and lymph nodes sampling failed to identify any significant impact on PFS or on OS [34]. Considering the higher morbidity and effort of systematic LND compared to sampling alone, LN sampling should suffice for complete staging in early disease.

The only randomized trial assessing systematic LND in this setting aimed to evaluate surgical and clinical outcomes [34]. As presented above, the authors failed to identify any significant benefit of systematic LND regarding PFS or OS. At a median follow-up of 87.8 months, the adjusted risks for progression ([HR]=0.72, 95 % CI=0.46–1.21, $p=0.16$) and death (HR=0.85, 95 % CI=0.49–1.47, $p=0.56$) were lower, but not statistically significant, in the systematic LND. Five-year PFS rates were also equivalent between the two arms: 71.3 versus 78.3 % (difference=7.0 %, 95 % CI: –3.4 to 14.3 %) and 5-year OS was 81.3 versus 84.2 % (difference=2.9 %, 95 % CI=7.0–9.2 %), respectively, for sampling versus systematic LND. At the same time, surgical morbidity was significantly greater in the systematic LND arm, referring to significantly longer operating times by a median of 90 min ($p<0.001$), doubling of intraoperative blood loss (300 vs. 600 ml; $p<0.001$) with accordingly higher rates of transfusions needed (21.8 vs. 35.5 %; $p=0.012$) and significantly longer hospital stay times: 1 day in median longer ($p=0.003$).

Considering the described short- and long-term morbidity of systematic LND, such as potential vessel injury, thromboembolic risk, formation of lymphocysts and lymphedema, and adhesive small bowel obstruction in the absence of survival benefit, there is currently no indication for extensive systematic LND in apparent early EOC. This is consistent with the current trends throughout surgical oncology specialties, where extensive LND have been replaced with lesser morbid diagnostic evaluations, such as lymphatic sampling and sentinel lymph node identification.

In summary much of the support for systematic LN comes from retrospective and prospective nonrandomized studies of women with limited-appearing disease (no intraperitoneal disease) who had formal lymphatic dissection identifying metastatic disease in a small proportion [39]. The impact of this identification of occult disease is countered by the relationship of nodal spread and other high-risk features, such as high-grade, tumor rupture/surface involvement or positive cytology. These cases most often receive adjuvant chemotherapy, which could be anticipated to level the survival outcomes between LND and non-LND women. Under these assumptions, the therapeutic value of LND would have to be carried by the few low-risk women who did not receive adjuvant therapy and were not identified by the surgical procedure. Even the aforementioned randomized study could not completely evaluate the procedure fairly because adjuvant therapy was not prespecified and likely could be unethical given the mortality of recurrent disease. Our recommendation is to extend the surgical staging procedure to the retroperitoneum with the same intent as other potential metastatic sites. Until the value of a complete LND is shown, it should be avoided in order to spare the long-term morbidity from surgery that may be experienced in these “curable” women. A possible exception may be mucinous early EOC. Increasing evidence shows that the rate of positive LN in stage IA mucinous cancer is extremely low (near 0 %), reducing the value of any LND in this subgroup of women [40–42].

In Apparently Early Unilateral Disease, Is Unilateral Pelvic LND Sufficient for Adequate Staging?

This clinical issue is less a matter of “controversy” as it is an intraoperative consideration for women with stage IA disease or in cases where fertility preservation is being considered. Retrospective evidence reveals that 3.5–11 % of the women with unilateral disease will have contralateral pelvic lymph node metastases despite negative ipsilateral nodes

[28–45]. A recent large systematic review regarding lymph node metastases in early stage I and II EOC included 14 studies and showed that the mean incidence of lymph node metastases in clinical stages I–II EOC was 14.2 % (range 6.1–29.6 %), of which 7.1 % had isolated disease in the para-aortic region, 2.9 % isolated to the pelvic region, and 4.3 % in both lymphatic basins. According to histological subtype, the highest incidence of lymph node metastases was found in the serous subtype (23.3 %); the lowest was in the mucinous subtype (2.6 %). In unilateral tumors, pelvic lymph node metastases were found in 9.7 % on both sides, 8.3 % only at the ipsilateral side, and in 3.5 % only at the contralateral side [41]. Other analyses describe even higher rates of solely contralateral LN metastases of 11 % [42].

Summary

The low rate of contralateral metastases in the setting of negative ipsilateral nodes in women with stage IA disease lowers one's enthusiasm for "routinely" performing the procedure. However, accurate information at the time of surgery is largely unknown, and with bilateral rates being as high as 8 % in women with stage IA disease, exploration is indicated. Women with fertility preservation goals should be counseled to the risk-benefit trade-off of not performing a pelvic node dissection in the hopes of reducing postoperative tubal/ovarian adhesions. There may be an opportunity to assess lymphatic mapping in these cases as newer intraoperative imaging techniques, such as near-infrared fluorescence lymphatic tracers become available [46].

Is Fertility-Sparing Surgery a Viable Option for Women with Early-Stage Epithelial Ovarian Cancer?

Organ and fertility-preserving surgery in a highly aggressive disease such as EOC constitutes a therapeutic dilemma for treating physicians and affected patients. The desire for the best clinical outcome with respect to cancer cure may be counterbalanced by a desire for organ sparing to maximize the chance of future childbearing. Furthermore, the hormonal milieu of pregnancy and puerperium may increase risk of EOC recurrence.

Review of the available clinical data suggests that fertility-sparing surgery (FSS) in early-stage EOC is a reasonable option for women younger than 40 years who wish to preserve their childbearing potential. However, careful consideration of histologic subtypes is warranted. The optimal indication appears to be stage IA G1/G2 disease. Less clear is stage IC disease. In IC disease the value of histological subtype has to be additionally considered: e.g., non-clear cell, and the way IC was determined (ovarian surface involvement vs. iatrogenic rupture vs. spontaneous rupture). Iatrogenic rupture has been associated with less favorable outcomes after FSS in terms of reduced conception potential and less favorable overall prognosis [47].

Satoh et al. systematically studied selection criteria for FSS in 211 stage I EOC (stage IA, $n=126$, stage IC, $n=85$) women based on clinical outcomes [48]. The majority of the women underwent unilateral salpingo-oophorectomy ($N=205$), with 142 (69 %) having additional "staging" procedures (e.g., omentectomy, lymph nodes, and biopsy of the contralateral ovary); 6 women had cystectomy. At a median follow-up of 78 months, 18 (8.5 %) of women recurred with 5 (28 %) recurring in the retained ovary; all 5 of these women were salvaged with surgery. Of those recurring outside the ovary, 3 were without evidence of disease, 5 were alive with disease, and 5 had died of disease. Recurrence was linked to stage IC disease, grade 3 histology, and unfavorable cell types (in this study, clear cell).

In the analysis of recurrent disease, nonlocal recurrence was associated with a significantly higher mortality rate compared to recurrence in a retained ovary exclusively. Thus, based on these observations and patterns of recurrence, the authors recommended that FSS is safe in women with stage IA, grade 1 or 2, and favorable histology, with or without adjuvant chemotherapy. In addition, women with stage IA clear cell or stage IC with unilateral ovarian involvement and favorable histology would be amenable to FSS as long as they underwent complete surgical staging and adjuvant platinum-based chemotherapy. FSS was not recommended in stage IA, G3 disease or stage IC, and clear cell or G3 histology as these women represented the highest risk for recurrence and nonlocalized recurrence [48]. The fertility rate in those attempting conception after treatment was 53 %.

While this trial represents the largest patient cohort examined, the results are consistent with others in the literature [49–55]. In these studies, the mean relapse rates are approximately 10 %, although many also include women with stage IC disease. Nevertheless, when accurately examining the characteristics of the women who suffered from relapse, they belonged mainly to the subgroup with IC and/or G3 tumors. Interestingly, many studies failed to demonstrate differential outcomes based on the way stage IC was allocated. That is similar outcomes were seen among those with iatrogenic rupture, those with positive cytology, and those with ovarian surface involvement. Kajiyama et al. [54] assessed survival after FSS in women with either iatrogenic rupture versus surface involvement/positive cytology. They concluded that while PFS and OS were significantly worse for women with stage IC (surface involvement/positive cytology) compared to those with stage IA after FSS, there was no difference in survival in women with stage IA disease compared with those with stage IC disease based on iatrogenic rupture. In the study of Zanetta et al. none of the women undergoing bilateral oophorectomy had microscopic foci of cancer in the normal-looking contralateral ovary suggesting contralateral biopsy to be of little value in these circumstances [49]. In two

recent studies, the feasibility of fertility-sparing surgery was assessed in women with clear cell or mucinous carcinoma of the ovary, two histological types which have been associated in various reports with a rather less favorable prognosis [48, 54]. In both analyses, the authors concluded that FSS in presence of these two histological subtypes was not necessarily associated with a poorer prognosis compared to radical surgery and hence is feasible. The incongruence may be attributed to the negative impact of unfavorable histology on survival in advanced-stage (stage III/IV) disease [9, 56].

These data highlight the difficulty in profiling women at greatest risk for relapse following FSS, even women with stage IA disease as many of the existing studies include women with varying degrees of accurate surgical staging [48, 57]. Overall, reported disease-specific death rates are ranging between 2 and 15 %.

Fertility Success: Results

Successful fecundity rates after FSS in all women who present with early EOC is about 30 %; however, this rate rises to more than 66 % in various series if the denominator includes only those who actively tried to conceive. These are close to fecundity rates for noncancer women. Also, where reported, only a minority of women ultimately conceiving after FSS required assisted reproductive techniques [47]. The incidence of spontaneous abortions ranges between 11 and 33 % and is also consistent with the general age-matched population. These data might be expected as the rates of normal menstrual function following FSS is close to 97 % [48]. In this series, 6 (5.0 %) of the 121 women who received platinum-based chemotherapy presented with persistent secondary amenorrhea up to 224 months after completion of 4–6 cycles of adjuvant treatment. Five (9.1 %) of the 55 women who successfully conceived did so with assisted fertility treatments. Interestingly, only a minority of these women (9.4 %) underwent completion surgery after childbearing, consisting of hysterectomy and contralateral salpingo-oophorectomy. Where reported, none of the women who successfully conceived and gave birth presented any relevant, cancer-related clinical problems during the perinatal period. Also no higher rates of congenital malformations or abnormal fetal outcomes have been reported in the current literature [47, 48, 58].

Women considering FSS in EOC should be thoroughly counseled to the risks and benefits to a conservative approach. Since new options (e.g., ovarian cortex cryopreservation, autologous transplantation) are becoming available to women considering future fertility preservation, we recommend counseling by fertility experts of the affected women with careful balancing of the risks and benefits. The treating gynecologic oncologist should be fully aware of the need to provide care for young women with malignant disease as well as taking account of her need to retain fertility by considering fertility-sparing alternatives when allowed so by tumor stage and histologic differentiation.

Future Directions: Fertility-Sparing Surgery

All women after FSS in early EOC should be systematically and prospectively collected in a central database with assessment of all factors regarding both oncologic and reproductive outcomes including hormonal stimulation treatments assisted reproductive technologies and years of attempting to conceive.

What Is the Optimal Adjuvant Treatment of Early EOC?

Which women to treat, the choice of the optimal adjuvant chemotherapy regimen and the duration of treatment in early-stage OC are subjects of continuing debate with no clear international consensus on two main issues. Firstly, is adjuvant therapy necessary in all patients with early EOC and secondly if adjuvant therapy is needed, what regimen and how much therapy is recommended? These questions are critical in this group of women that includes those with highest chance of being cured of their disease but also of being affected by longer-term side effects of surgical and chemotherapy treatments. Table 1.4 presents a summary of adjuvant trials in early-stage ovarian cancer, with observation as a control arm. There are a

Table 1.4 Early-stage ovarian cancer trials of platinum-based adjuvant therapy versus observation

Trial	*N*	Adjuvant treatment arm	Median follow-up (months)	Endpoint	HR adjuvant chemotherapy versus observation (95 % CI)	*p* value
Bolis et al. [81]	83	Cisplatin	71	RFS	0.48 (0.24–1.14)	0.095
				OS	1.15 (0.44–2.98)	0.773
Trope et al. [66]	162	Carboplatin	46	RFS	0.98 (0.52–1.83)	0.90
				OS	0.94 (0.37–2.36)	0.90
ACTION [22]	448	Platinum	59	RFS	0.63 (0.43–0.92)	0.02
				OS	0.69 (0.44–1.08)	0.104
ICON1 [59]	477	Platinum	51	RFS	0.65 (0.46–0.91)	0.01
				OS	0.66 (0.45–0.97)	0.03

number of challenges in interpreting the results of these trials. Firstly, the majority of the trials were too small to provide meaningful conclusions. Secondly, in order to recruit sufficient patients, the entry criteria were a broad range of early-stage (I and II) patients, for example, the ACTION and ICON1 trials included women with stage IA/IB, grade 2/3, stage IC/IIA, all grades, and clear cell histology. By modern standards, it is not helpful to have such a wide range of early-stage patients included.

The Case for Adjuvant Treatment

The two largest trials (ICON1 and ACTION) were set up in the 1990s to address the uncertain benefit of immediate adjuvant chemotherapy in early-stage disease, in terms of recurrence-free survival (RFS) and overall survival (OS) [22, 59]. The primary analysis of ICON1 on its own, with a median follow-up of 4 years, demonstrated a significant improvement in both RFS (hazard ratio (HR) = 0.65, 95 % CI = 0.46–0.91, $p = 0.01$) and OS (HR = 0.66, 95 % CI = 0.45–0.97, $p = 0.03$) in favor of immediate adjuvant chemotherapy [59]. Very similar findings were reported in the ACTION trial [22]. A preplanned combined analysis which included 925 women (477 from ICON1 and 448 from ACTION) randomized to platinum-based chemotherapy or observation was pooled for analysis [60]. At a median follow-up of 5 years, an 8 % OS benefit (82 vs. 74 %, hazard ratio = 0.67, 95 % CI 0.50–0.90, $p = 0.008$) and an 11 % recurrence-free survival benefit (76 vs. 65 %, hazard ratio = 0.64, 95 % CI 0.50–0.72, $p = 0.001$) were observed, favoring adjuvant chemotherapy. The magnitude of chemotherapy benefit was maintained in the performed subgroup analysis, even among women with stage IA disease. The sizes of these two trials were a major factor in a meta-analysis on the topic coming to the same conclusion [61].

Ten-year follow-up results of ICON1 and updated results from the ACTION trial are now available and provide further evidence to inform the debate. The updated median follow-up in ICON1 is 10 years with a further 32 women who relapsed (7 after 5 years), giving a total of 165 (35 %) women who have developed disease recurrence or died (71 immediate adjuvant chemotherapy, 94 no immediate adjuvant chemotherapy) [62]. Comparison of Kaplan-Meier curves for recurrence-free survival gives an estimated hazard ratio (HR) of 0.69 (95 % CI = 0.51–0.94, $p = 0.02$) (Fig. 1.2a). This translates into a 10 % RFS improvement from immediate adjuvant chemotherapy at 10 years, from 60 to 70 %. The absolute difference of RFS and 95 % confidence interval (CI) of the difference between immediate adjuvant therapy and no immediate adjuvant therapy over time is displayed in Fig. 1.2c.

A further 48 women died, giving 151 (32 %) deaths in total (66 immediate adjuvant chemotherapy, 85 no immediate adjuvant chemotherapy), of which 72 % were attributable to OC. Comparison of Kaplan-Meier curves (Fig. 1.2b) gave an estimated HR = 0.71 (95 % CI = 0.52–0.98, $p = 0.04$) in favor of immediate adjuvant chemotherapy, translating into a 9 % OS improvement at 10 years, from 64 to 73 %. The absolute difference of OS from immediate adjuvant therapy over no immediate adjuvant therapy over time is displayed in Fig. 1.2d.

The effect of immediate adjuvant chemotherapy in stage I patients ($n = 428$) by recurrence risk was explored using previously published risk stratifications [10] (Table 1.5, Fig. 1.2e for RFS and Fig. 1.2f for OS). The benefit of immediate adjuvant chemotherapy appears greatest in women with high-risk stage I disease. For RFS the HR = 0.48 (95 % CI = 0.31–0.73, $p < 0.001$) equates to an improvement at 10 years of 23 % (95 % CI = 11–33 %) from 45 to 68 %. For OS in these women, the HR = 0.52 (95 % CI = 0.33–0.81, $p = 0{\cdot}004$) translates into an 18 % (95 % CI = 7–27 %) improvement at 10 years, from 56 to 74 %. In the low-/intermediate-risk groups, for RFS, the HR = 0.92 (95 % CI = 0.52–1.64, $p = 0.78$) equates with a 2 % (95 % CI = −13 to 12 %) improvement at 10 years from 73 to 75 %; for OS the HR = 0.91 (95 % CI = 0.49–1.69, $p = 0.77$) gives an improvement at 10 years of 2 % (95 % CI = −12 to 11 %) from 78 to 80 %. The tests for interaction for RFS ($p = 0.075$) and OS ($p = 0.15$) are suggestive of a different size of effect between the high-risk and low-/intermediate-risk groups, but these tests have low power and the trial was not powered for testing interaction.

Long-term follow-up data from ICON1 therefore confirmed the long-term PFS and OS benefit from adjuvant platinum-based chemotherapy in women with early-stage OC. Results were consistent with previous trials and meta-analyses [22, 59–61]. The magnitude of benefit appeared greatest in women with high-risk early-stage disease, which indicates that chemotherapy should be standard of care in these patients. A small benefit in women with lower-risk early-stage disease could not be excluded, and the recommendation was that chemotherapy should be discussed, considering individual patient and disease characteristics including cyst rupture, age, and histological subtype [63–65]. Additional prognostic biomarkers have been reported which might enable selection of high-risk patients, including DNA ploidy [66–68], CA125 [25, 69], and HE4 [70], but data are conflicting and currently none are routinely used clinically to tailor treatments.

ICON1 was a pragmatic trial aligned with routine clinical practice at the time, designed to include patients in whom the indication for chemotherapy was uncertain, and without mandating specific disease staging. Despite this ICON1 remains the largest trial ever performed in early OC, and it is unlikely that trials in this setting without a major change in treatment modality (such as immunotherapy) and of this size will be repeated. The long-term follow-up of ICON 1 provides important confirmatory results that aid decision-making by clinicians treating women with early-stage OC. The updated results of the EORTC ACTION trial concentrate on a retrospective subgroup analysis investigating the effect of immediate

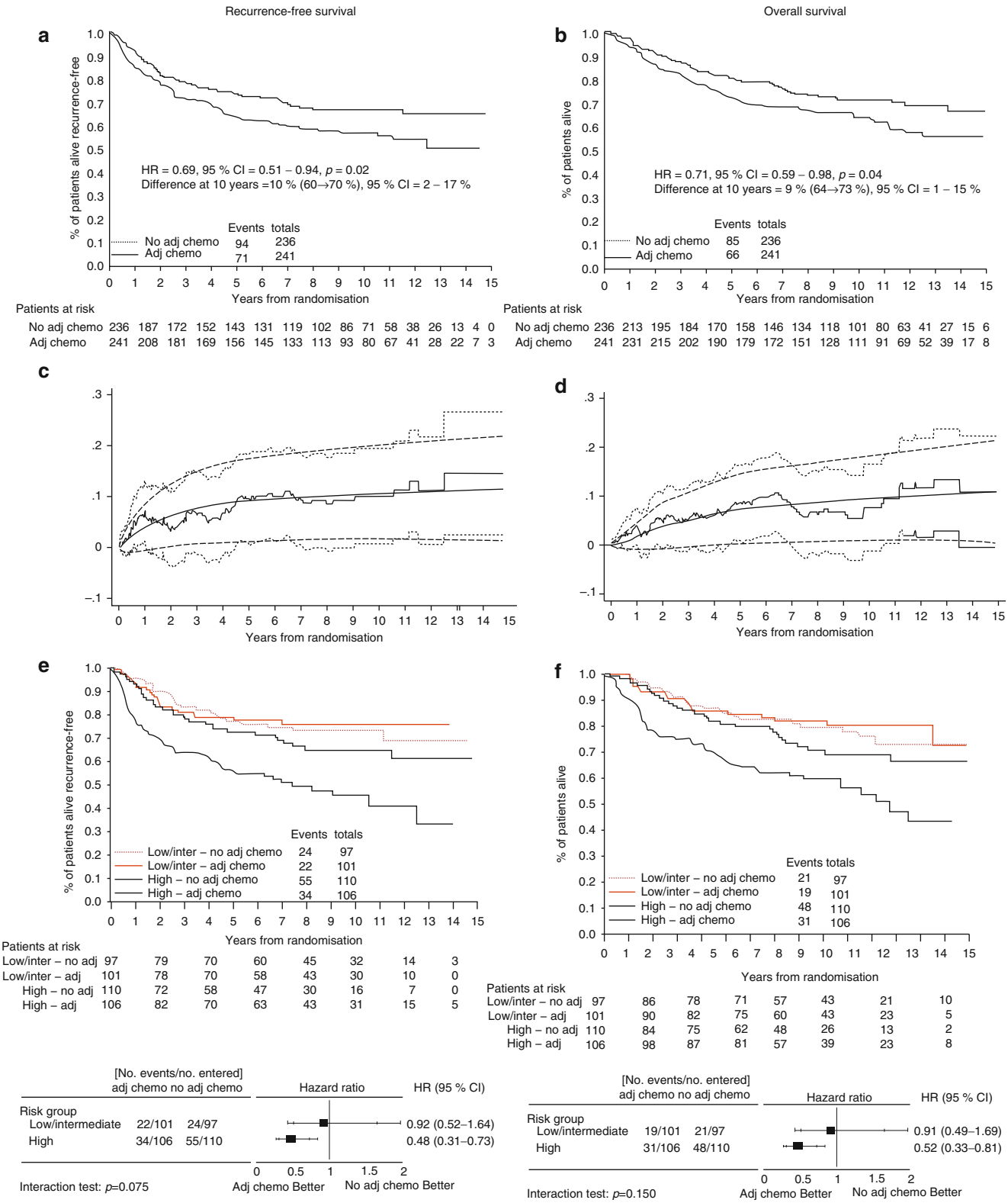

Fig. 1.2 Updated ICON1 results with median follow-up 10 years [62]. (**a**) Recurrence-free survival by treatment arms, (**b**) overall survival by treatment arms, (**c**) difference of recurrence-free survival (95 % CI) of immediate adjuvant therapy over no immediate adjuvant therapy over time, (**d**) difference of overall survival (95 % CI) of immediate adjuvant therapy over on immediate adjuvant therapy over time, (**e**) recurrence-free survival by treatment arms and risk groups, and (**f**) overall survival by treatment arms and risk groups

Table 1.5 Classification of stage I patients by risk of recurrence [10]

	Grade 1	Grade 2	Grade 3
Stage IA	13 %	20 %	10 %
Stage IB	3 %	4 %	4 %
Stage IC	15 %	17 %	12 %
Figures represent the proportion of patients in ICON1 (2 % unknown)			
Low risk (13 %)			
Intermediate risk (38 %)			
High risk (47 %)			

adjuvant chemotherapy in patients optimally surgically staged and those non-optimally surgically staged. Benefit of immediate chemotherapy was only demonstrated in non-optimally surgically staged patients; however, the subgroup of optimally surgically staged patients was small ($n=151$) [71]. Exploratory analyses by high- and low-risk patients were not possible in the ACTION trial as patients with lower-risk disease (grade 1 stage IA/IB) were excluded. One body of opinion is that, given the initial and long-term follow-up results of ICON1, the EORTC ACTION subgroup analyses do not provide sufficient evidence to exclude the benefit of adjuvant chemotherapy in the optimally staged cohort and that, if optimal staging can only be delivered in one-third of women even in a clinical trial setting, there is a strong argument to support treatment for a wide range of women with early ovarian cancer. However, even those who support the use of adjuvant treatment in selected low-risk patients recognize the caveat that this may result in overtreatment in unselected cases. Continued work evaluating key prognostic factors governing recurrence is necessary to better individualize treatment recommendations.

In conclusion, supporters of adjuvant treatment argue that the benefit of adjuvant postoperative chemotherapy for early-stage OC is confirmed with long-term follow-up of ICON1 and that the magnitude of benefit is greatest in patients with features that place them at a higher risk of recurrence.

The Case Against Adjuvant Treatment

While most clinicians and published guidelines recommend against routine adjuvant therapy in women with optimally staged IA grade 1 disease, all other scenarios raise questions that are difficult to answer from the available literature. A major criticism in the evidence to date is due to lack of quality control for surgical staging and the impact on generalizability of trial results which include a high proportion of patients for whom formal staging is unknown and who therefore might have had unrecognized advanced disease. As discussed earlier, only about one-third of the ACTION/ICON-1 cohort was optimally surgically staged. In a subgroup analysis of this cohort, the impact of adjuvant therapy was lost. Indeed, a meta-analysis of adequately staged, stage I women demonstrated no benefit from receiving additional chemotherapy (HR: 0.91, 95 % CI: 0.51–1.61) [64]. It is not known whether new biomarkers such as DNA ploidy or genomic biomarkers may help to bring better precision to the question of adjuvant treatment. Nevertheless, stage I women with high risk for recurrence (stage IC, clear cell, and grade 3 histology) are frequently recommended adjuvant therapy.

Summary

Adjuvant treatment for low-risk women remains controversial. Some may conclude that adjuvant chemotherapy is best reserved for women where accurate staging information is not available or in whom high-risk factors for recurrence are present, such as grade 3, clear cell histology, stage IC, and stage II disease. Women with grade 2 disease are more challenging as they have been both included and excluded from adjuvant trials.

What Is the Optimal Chemotherapy Regimen and Duration of Therapy?

When immediate adjuvant chemotherapy is used in early-stage OC, the choice of optimal chemotherapeutic regimen and duration of treatment also remains unclear. Some of the discrepancy is related to the adjuvant trials where physician discretion was allowed for type of chemotherapy and a range of 4–6 cycles. Single-agent carboplatin was the chemotherapy most frequently used in ICON1 and ACTION (87 % of patients in ICON1 and 57 % of patients in the combined ICON1/ACTION analysis) [60]. There were no treatment-related deaths in ICON1, but cytotoxic chemotherapy can have potentially serious and/or long-term complications [72], which are increased when taxanes are added to platinum-based therapy. In clinical practice, both carboplatin and carboplatin/paclitaxel are utilized in this setting, although there is no clear evidence base to support the use of combination therapy.

There are no prospective randomized clinical trials directly comparing the use of carboplatin and carboplatin/paclitaxel in this setting; however, data were available from stage I patients enrolled into the ICON3 trial, which compared the addition of paclitaxel to platinum-based adjuvant chemotherapy in patients with OC [73]. In ICON3, there were 120 (6 % of total) stage I patients randomized with a ratio of 1:2 to either carboplatin/paclitaxel ($n=44$) or single-agent carboplatin ($n=76$). After 51 months of median follow-up, 44 women have relapsed (13 carboplatin/paclitaxel, 31 carboplatin), and comparison of Kaplan-Meier curves shows a trend towards improved progression-free survival in favor of carboplatin/paclitaxel (HR = 0.71, 95 % CI = 0.39–1.32, $p=0.28$)

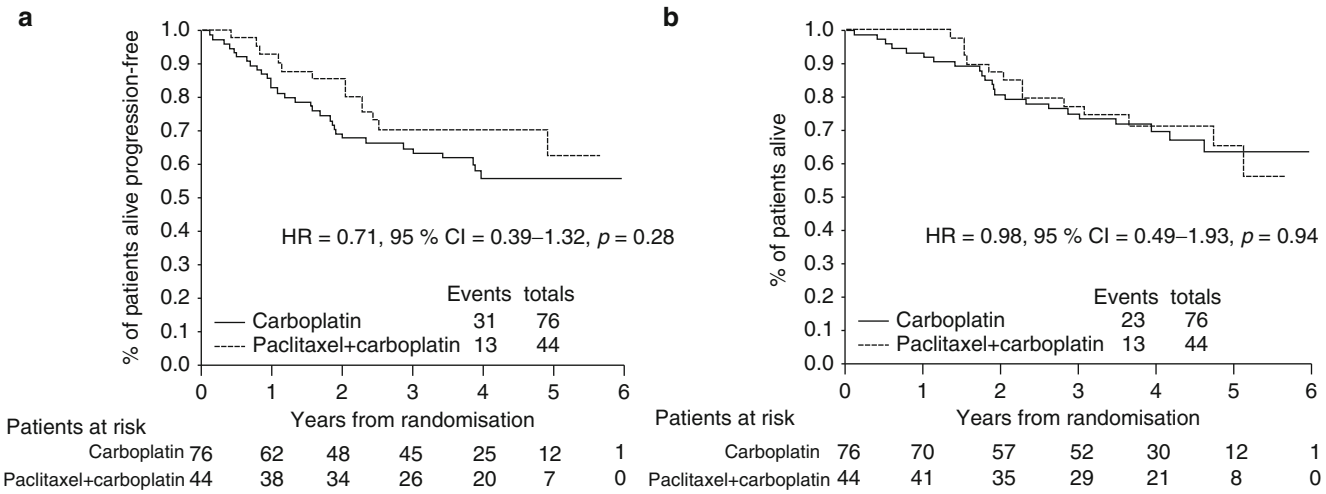

Fig. 1.3 Stage I patients randomized to carboplatin versus paclitaxel + carboplatin in ICON3 trial [73]. (**a**) Recurrence-free survival by treatment arms. (**b**) Overall survival by treatment arms

(Fig. 1.3a). Thirty-six patients have died (13 carboplatin/paclitaxel [30 %], 23 carboplatin [30 %]), and comparison of Kaplan-Meier curves shows no evidence of a difference in OS between the arms (HR = 0.98, 95 % CI = 0.49–1.93, $p = 0.94$) (Fig. 1.3b). The small number of patients leads to wide confidence intervals in the estimates of treatment difference. Some argue that the HR of 0.71 for PFS, despite the wide confidence intervals, supports the use of carboplatin/paclitaxel, whereas others argue that the HR of 0.98 for OS and increased toxicities with doublet therapies supports the use of single-agent carboplatin. In the absence of any prospective comparative randomized trials in this setting, a body of clinicians support the use of less toxic single-agent carboplatin. Further evidence for carboplatin alone comes from a small retrospective study which demonstrated no evidence of a difference in OS between carboplatin and carboplatin/paclitaxel [74]. Two randomized phase III trials have addressed the duration of chemotherapy. GOG 157 randomized 427, surgically staged, stage IA/B, grade 3, stage II, and clear cell women to 3 versus 6 cycles of adjuvant paclitaxel (175 mg/m^2) and carboplatin (AUC 7.5) [75–77]. The primary endpoint was PFS and the median follow-up was 6.8 years. Overall, 71 % of the population had adequate surgical staging and 69 % were stage I. The recurrence risk was 24 % lower in the 6 cycles arm, however, not significantly (HR: 0.76, 95 % CI: 0.51–1.13); similarly, estimated probabilities of recurrence at 5 years and OS were similar between the arms (3 vs. 6 cycles 20 % vs. 25 % and HR 1.02, 95 % CI 0.66–1.57, respectively). Toxicity, as expected, was significantly higher in the longer-duration-treated women. Of interest, in a post hoc analysis of this study by histology, duration of chemotherapy appeared to impact overall survival. When limited to serous histology (23 % of the sample), there was a significant reduction in recurrence with 6 cycles of therapy (HR = 0.33, 95 % CI: 0.14–0.77) in contrast to those with non-serous histology [78]. In the second GOG trial, GOG 175, 571 women with a similar eligibility and staging request were randomized to 3 cycles of paclitaxel and carboplatin or the same regimen with maintenance weekly paclitaxel for 24-week maintenance [79]. The cumulative probability of recurring within 5 years was similar between the arms (23 % observation vs. 20 % maintenance paclitaxel, HR: 0.81, 95 % CI: 0.57–1.15). Similarly, no difference in OS was observed. The maintenance arm was more toxic and led to an approximate 1 % discontinuation per week over the course of therapy. Unfortunately, definitive conclusions cannot be made from GOG 157 due to the ambitious 50 % reduction in recurrence targeted and the relatively small sample size, although due to the limited data in this area this study has impacted on standard practice in North America. Since 3 cycles of therapy appear to be well tolerated and feasible, this may be an appropriate compromise.

Other options for therapy, including adding a third drug (OVAR-9, gemcitabine) or radiation (IP phosphorous-32, whole abdominal radiation), have been investigated in stage I women without demonstrable benefit [80–82].

The issue of additional and maintenance therapy is more controversial and, unfortunately, not completely addressed in the current literature. However, if toxicity precludes additional therapy, the data would support the efficacy of less than 6 cycles. This recommendation is bolstered by the post hoc analysis of the 74 women who recurred after completing therapy in GOG 157 [83]. In this analysis, the median time to recurrence was 21 months. The overall survival after recurrence was only 24 months and was dependent on time to recurrence (10 months for those less than 24 months vs. 35 months for those recurring after 24 months). These data are similar to those with advanced-stage disease and highlight the difficulty of controlling metastatic disease.

Should Intensified Chemotherapy Regimens Including Dose Dense and Intraperitoneal Therapies and Targeted Therapies Be Considered for the Adjuvant Treatment of Early EOC?

Adequately staged and hence true early EOC is associated with higher survival rates compared to more advanced disease. However, even in these early cases, systemic chemotherapy has been shown to improve survival. Thus, it is reasonable to consider whether recent alternatives to standard chemotherapy, such as intraperitoneal (IP) and dose-dense therapy, as well as the impact biological could positively impact outcomes in this cohort of women.

The Case Supporting Alternative (Dose-Dense/IP/Targeted Therapy) Strategies: Evidence

A highly significant improvement of both PFS and OS by merely changing the dose schedule of conventional chemotherapy, without addition of any novel agents, was accomplished by the Japanese GOG group by randomly assigning women with stage II to IV EOC who were randomized to weekly paclitaxel (80 mg/m^2 on day 1, 8, 15) in combination with 3 weekly carboplatin (carboplatin AUC 6 on day 1) [84, 85]. At 6.4 years of median follow-up of 631 eligible women, a highly statistically significant improvement in median PFS in favor of the dose-dense group was achieved compared with to the conventional group (28.1 vs. 17.5 months, [HR] 0.75, 95 % CI, 0.62–0.91; $p=0.0037$). Furthermore OS at 5 years was also higher in the dose-dense group than the conventional group (58.6 % vs. 51.0 %, HR 0.79, 95 % CI: 0.63–0.99, $p=0.0448$) [49, 50]. Even though no stage I women were included, these results could theoretically be extrapolated also to those early EOC women.

Impressive improvements in both PFS and OS have been shown in [86] in 429 women with optimally debulked stage III EOC randomly assigned to intravenous paclitaxel plus cisplatin versus a combination of intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel. The experimental intraperitoneal arm was associated with significantly improved PFS (23.8 vs. 18.3 months, HR=0.80, 95 % CI 0.64–1.00, $p=0.05$) and OS (65.6 vs. 49.7 months, HR=0.75, 95 % CI 0.58–0.97, $p=0.03$) [28] at a median follow-up of 48 months. Remarkably, the OS gain of 15.9 months, at the median, in favor of the intraperitoneal arm was higher than the gain reached when paclitaxel was added to the first-line treatment [75]. Here also, there is a clear hypothesis that the benefit of IP chemotherapy might be projected into earlier stage disease because they are by definition without extra-ovarian disease or, at least, minimal unrecognized extra-ovarian disease. However, the increased toxicity of the schedule should be taken into account and results of confirmatory studies with less toxic schedules awaited.

Biological agents are also attractive in this setting, although the only agent thus far evaluated in early-stage disease has been bevacizumab (ICON7) [14]. However, the hypothesis of the value of maintenance therapy may be linked to small volume/microscopic disease after completing chemotherapy. This has spawned several trials of biological agents in the maintenance setting, such as pazopanib, sorafenib, nintedanib, and erlotinib, as well as several immunotherapy strategies. In ICON7, the addition of bevacizumab to conventional chemotherapy (paclitaxel/carboplatin) resulted in significantly higher PFS and also overall response rates, albeit no improvement of OS. The rate of complete or partial remission was 48 % in the standard-therapy group and 67 % in the bevacizumab group—a highly significant difference of 19 % (95 % CI: 11–28, $p<0.001$) [52]. As opposed to the GOG 218 [87], ICON7 allowed the enrollment of high-risk early-stage disease (9 % of all women). Although a post hoc subgroup analysis was unable to differentiate a benefit in outcome in this cohort, it remains a topic of investigation. The AGO BOOST trial (Ovar 17) is comparing 15- versus 30-month bevacizumab in the maintenance setting, and women with stage IC disease are eligible to participate (NCT01462890).

The Case Against Alternative (Dose-Dense/IP/Targeted Therapy) Strategies: Evidence

While the advances in ovarian cancer adjuvant therapy are impressive, it is tempered by the fact that they rarely included women with early-stage disease and their findings apply in nearly every case to women with advanced measurable residual disease. Since all women with stage I disease are essentially undergoing complete resection (R0), it is a legitimate concern to extrapolate the data to this cohort of women. Even the JGOG dose-dense regimen failed to demonstrate any significant impact on survival in completely resected (R0) cancers [84, 85]. While the ICON7 trial did enroll a small cohort of high-risk stage I women, the benefit of bevacizumab was not evident among this cohort or in those with small volume tumor residuum, but it must be acknowledged that the subgroup was small (capped at 10 % of 1,528 patients). Considering the significantly higher toxicity of bevacizumab, such as hypertension (up to 19 %) and intestinal perforation (3 %), the EMA, which approved this agent in 2012, only licensed its use for stage IIIB and higher. In addition, poor tolerability and high dropout rates prior to completion of therapy in women receiving IP or dose-dense paclitaxel therapy also limit enthusiasm in women with early-stage disease. Furthermore, as stated above, even though in clinical practice both carboplatin and carboplatin/paclitaxel are usually

applied, no clear evidence exists to support the use of combination therapy in stage I disease.

Future Directions: Intensive Dose-Dense/IP/Targeted Therapy

Research efforts try currently to provide answers to a number of important questions relating to treatment duration, the incorporation of new drugs into treatment regimens, and maintenance therapy in advanced disease. The subanalysis of the BOOST (AGO-OVAR 17) trial will enlighten the value of antiangiogenic treatment in stage IC disease. If positive results emerge, then further randomized trials are warranted to prospectively evaluate their role in high-risk early disease.

Future Directions of 1st-Line Chemotherapy in Early EOC

Future clinical trials designed specifically for women with early-stage ovarian cancer are unlikely to be conducted using the current methodology applied to advanced-stage disease due to the small sample size and low risk for recurrence. Patient with high-risk features are increasingly allowed into advanced-stage trials where the strata are evaluated. If development of effective prevention strategies were identified, such as vaccination or novel biological response agents that can reasonably be administered over an extended duration of time, reevaluation would be attractive. However, accurate surgical staging and better interrogation of driving genomic biology will offer new clues into better identifying the risk factors that may help better allocate treatment.

Concluding Comments

- Apparent early-stage epithelial ovarian cancer can present a therapeutic enigma due to a variety of controversial issues including considerations of potential fertility preservation, optimal adjuvant treatment, the value of targeted agents (increasingly utilized in advanced-stage disease), and the appropriate degree of surgical radicality.
- Since most apparent early-stage ovarian cancer patients will have limited disease after formal surgical staging assessment, it is clear that not all patients require surgical castration and, as such, some patients may be amenable to fertility-sparing procedures.
- Equally concerning is under-assessment and under-treatment, which could prove fatal with the development of metastatic recurrence—a clinical scenario that is not easily screened.

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