available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Editorial Comment

Staging early ovarian cancer: Impact on treatment decisions

*Ralph S. Freedman**

Department of Gynecologic Oncology, The University of Texas M.D. Anderson Cancer Center, P.O. Box 301439, Houston, TX 77230-1439, United States

ARTICLE INFO

Article history:
Received 11 January 2010
Accepted 14 January 2010
Available online 16 February 2010

The search for clear evidence-based data supportive of treatment decisions in early stage ovarian cancer remains elusive. Previous trials have shown inconsistencies in surgical staging, most likely contributing to inclusion of patients with more extensive disease. In addition, tumours of low malignant potential have been included due to lack of pathology validation. Because of unanticipated delays in completing accrual, even the largest trials have had to be truncated combined or required meta-analysis to support stronger conclusions. Moreover lengthy trials could result in treatments being utilised that are different from standards of care at a trials conclusion. Nevertheless, a considerable amount of useful data have been assembled, collated and critically analysed in past reviews.[1,2] The main focus here is on the paper by Petra Timmers et al. 'Understanding the Problem of Inadequately Staging Early Ovarian Cancer,' published in this issue. The database for this paper originated from ACTION 2003,[3] and provides additional characterisation of the staging process utilised. Of the 40 participant sites, the lowest level of staging occurred at sites where fewer than 5 patients were entered. Sites entering more than 20 or even more than 10 patients had a higher frequency of optimum staging. But even at sites entering more than 20 patients complete staging was only achieved in approximately 36% of patients.

ACTION 2003[3] and ICON1[4] were two of the largest and most recent randomised trials to examine the effects of adjuvant chemotherapy in early ovarian cancer. Treatment was platinum-based but neither of these trials mandated optimum surgical staging. ACTION 2003, however, recommended and defined optimum complete staging and incorporated a planned analysis on the effects of staging completeness on overall survival (OS) and RFS outcomes. Both trials were closed by the DMC, which monitored both trials simultaneously by prearranged agreement, before the preplanned statistical end-points were reached. The length of time taken to accrue patients entered into this decision, and the results of the combined trials were published in a separate paper.[5]

Though staging could not be included in the outcomes analysis of ICON1, ICON1 has been described as the 'real world' situation, where understaging appears to be common for this group of patients. It is possible however that this situation could be changing with an increase in trained gynaecological oncologists and volume of patients being treated at specialised institutions. ICON1 also included patients where there was clinical equipoise or uncertainty about giving adjuvant chemotherapy. By contrast ACTION 2003 entered the patients deemed to be at higher risk for failure. Results from ICON1 showed that adjuvant chemotherapy had a statistically significant effect on OS. By contrast, after 5 years ACTION 2003 did not show a statistically significant benefit from adjuvant chemotherapy on OS between the two arms, although RFS was significantly different. The combined analysis of ACTION 2003 and ICON1 did show a significant treatment effect on OS.[5] ACTION 2003 also did not show a

* Tel.: +1 713 563 4545; fax: +1 713 792 7586.
E-mail address: rfreedma@mdanderson.org
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.01.017

significant interaction between completeness of staging versus treatment effects for OS. For open studies (which these were), and blinded studies, OS is a robust and definitive end-point, except possibly when extensive crossover occurs to a highly active regimen such as when platinum was first introduced, but relatively little crossover was reported in ICON1.[4] A recent review and meta-analysis from the Cochran Collaboration reported on over 1000 patients from 5 clinical trials considered to have a low risk of bias.[2] ICON1 and ACTION 2003 and an Italian trial were the main sources for OS analysis and showed that staging adequacy correlated with OS (HR 0.63; 95% CI: 0.46–0.85). Obvious limitations were that only a third of ACTION 2003 patients had complete staging whereas in ICON1, staging was not defined at all. The Italian study, however, specified retroperitoneal sampling.[6] Meta-analysis of the three trials discerned a significant improvement in overall survival of patients who received adjuvant chemotherapy (HR 0.71; 95% CI: 0.53–0.93) with no heterogeneity identified between trials.[2] As commented in the Cochran report, OS for ICON1 showed an 8% difference in the 10-year follow-up, and in the subgroup analysis, patients at high risk who received chemotherapy (Stage 1a, Grade 3, 1b or 1c, Grade 2 or 3, or clear cell) had significantly better OS (HR 0.48; 95% CI: 0.32–0.72) and better RFS (HR 0.72; 95% CI: 0.33–0.82) than no adjuvant treatment.

So how critical is adequate surgical staging for treatment decisions of early disease? Vernooij et al. performed a retrospective analysis of 1077 stages 1–4 patients in The Netherlands of which 20–25% were suspected stage 1.[7] They showed that 24% of presumptive stages 1 and 2a patients operated on in general hospitals versus 60% of patients in semi-specialised and specialised hospitals were adequately staged ($p < 0.001$). Further, patients treated in high volume hospitals defined as greater than 12 patients per year had five times more adequately staged patients than those in low volume hospitals ($\leqslant$6 patients per year). The findings from the prospectively collected data by Timmens et al. are therefore in line with this retrospective study although the Timmens' study focused on patient volume.

Restaging of patients with ovarian cancer frequently results in upstaging at laparotomy or laparoscopy.[8,9] Others[10] have shown that in patients with tumours confined to the pelvis, 22% of patients who had systematic pelvic and aortic node dissection had histologically positive nodes versus 9% who had only sampling ($p = 0.007$). Differences reported for stage 1 were 18% versus 4% (no p value provided). However approximately one-third of all operated patients in this study were stage 2. Median operating time, blood loss, transfusion and hospital stay were increased in the systematic lymphadenectomy group. There is a likely benefit to a patient with presumed early stage but found to be more advanced upon restaging in that any question regarding adjuvant chemotherapy is clarified. In their recent review and meta-analysis, Winter-Roach et al. recognised that optimum staging had been performed at relatively few centres.[2] They reviewed studies screened for quality and concluded that a pragmatic default position would be to offer chemotherapy to a majority of patients with carefully selected low risk patients being managed expectantly with chemotherapy upon relapse. Others have suggested that observation of early stage patients versus treatment only upon relapse provided similar outcomes[11] though the effectiveness of this approach has not been tested in an adequately powered study with OS as the end-point. Contrary to the 'pragmatic position' others believe that following adequate staging, there is little to be gained by placing a majority of patients as stage 1 disease on chemotherapy.[1] This approach is based upon concerns of chemotherapy-induced toxicity and possibly also medical economics. Toxicity concerns have been linked to a recent GOG study,[12] which reported that six cycles of carboplatin-paclitaxel (considered by most a level 1 recommendation for a majority of patients with ovarian cancer) does not significantly alter recurrence rates when compared to three cycles of combination therapy and six cycles was also associated with more neurotoxicity. These conclusions have generated some controversy considering the higher dosing of platinum used.[13] Moreover the study was not powered for a determination of OS and there was no control arm.

Given that the number of adequately staged patients, even at higher volume centres, was relatively low, the default position of employing adjuvant chemotherapy in high risk patients as characterised in ICON1 and in the latest Cochran report would seem to have merit, at least until data to the contrary are provided. Treatment plans should be modified for individual patients to prevent unacceptable toxicity. The fact that some stage 1 patients eventually fail might also suggest that these patients have micrometastases that go undetected despite best efforts at staging. Clearly optimum staging or restaging is especially important when there is doubt whether adjuvant chemotherapy might be useful for an individual patient, such as in more differentiated tumours. Training and experience in laparoscopy including lymph node dissections will likely be helpful in the staging process[15] but laparoscopy for ovarian cancer staging probably requires further evaluation.

Dr. Timmers et al. make a useful point that future trials in early stage disease should be limited to high volume centres where the full range of expertise and knowledge about the disease is available. In this regard, the quality indicators proposed by EORTC-GCG for early disease will be important for standardising the staging and restaging process in future trials.[14] It is important that future trials should be powered for both OS and RFS. Previous experience suggests that a larger number of patients will be required than had been entered in ICON1 or ACTION 2003 to be adequately powered for OS. If the number of sites is going to be restricted by the Timmer's recommendation, this should offer an incentive for more multinational and transcontinental collaboration, with similar standards of treatment at all sites. Future trials should also include an assessment and systematic reporting of all SAEs, both for surgical staging and for chemotherapy so that a true risk benefit assessment can be made.

Conflict of interest statement

The Author has no actual or potential conflict of interest to declare.

REFERENCES

1. Tropé C, Kaern. Adjuvant chemotherapy for early-stage ovarian cancer: review of the literature. *J Cin Oncol* 2007;**25**:2909–20.
2. Winter-Roach BA, Kitchener HC, Dickinson HO. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer (review). The Cochrane Collaboration. The Cochrane Library. John Wiley & Sons Ltd; 2009.
3. Baptist Trimbos J, Vergote I, Bolis G, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European organization for research and treatment of cancer-adjuvant chemotherapy in ovarian neoplasm trial. *J Natl Cancer Inst* 2003;**95**:113–25.
4. International Collaborative Ovarian Neoplasm (ICON1) Collaborators. International collaborative ovarian neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. *J Natl Cancer Inst* 2003;**95**:125–32.
5. International Collaborative Ovarian Neoplasm (ICON1) and European Organisation for Research and Treatment of Cancer Collaborators—Adjuvant ChemoTherapy in Ovarian Neoplasm (EORTC-ACTION). International collaborative ovarian neoplasm Trial 1 and adjuvant chemotherapy in ovarian neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst* 2003; **95**:105–12.
6. Bolis G, Colombo N, Pecorelli S, et al. Adjuvant treatment for early epithelial ovarian cancer: results of two randomized clinical trials comparing cisplating to no further treatment of chromic phosphate (32P). G.I.C.O.G.: Gruppo Interregionale Collaborativo in Ginecologia Oncologica. *Ann Oncol* 1995;**6**:887–93.
7. Vernooij F, Heintz APM, Coebergh JW, et al. Specialized and high-volume care leads to better outcomes of ovarian cancer in the Netherlands. *Gynecol Oncol* 2009;**112**:455–61.
8. Bagley CM, Young RC, Schein PS, Chabner BA, DeVita VT. Ovarian carcinoma metastatic to the diaphragm—frequently undiagnosed at laparotomy. A preliminary report. *Am J Obstet Gynecol* 1973;**116**:397–400.
9. Soper JT, Johnson P, Johnson V, Berchuck A, Clarke-Pearson DL. Comprehensive restaging laparotomy in women with apparently early ovarian carcinoma. *Obstet Gynecol* 1992;**80**:949–53.
10. Maggioni A, Panici PB, Dell'Anna T, et al. Randomised study of systemic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis. *Br J Cancer* 2006;**95**:699–704.
11. Kolomainen DF, A'Hern R, Coxon FY, et al. Can patients with relapsed, previously untreated, stage I epithelial ovarian cancer be successfully treated with salvage therapy. *J Clin Oncol* 2003;**21**:3113–8.
12. Bell J, Brady MF, Young RC, et al. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: A Gynecologic Oncology Group Study. *Gynecol Oncol* 2006;**102**:432–9.
13. Markman M. To the Editor: randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: A Gynecologic Oncology Group Study. *Gynecol Oncol* 2007;**105**:279–80.
14. Verleye L, Ottevanger PB, van der Graaf W, et al. EORTC-GCG process quality indicators for ovarian cancer surgery. *Eur J Cancer* 2009;**45**:517–26.
15. Chi DS, Abu-Rustum NR, Sonoda Y, et al. The safety and efficacy of laparoscopic surgical staging of apparent stage I ovarian and fallopian tube cancers. *Am J Obstet Gynecol* 2005;**192**:1614–9.