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Ovarian Cancer: Diagnostic Second Laparotomy and Salvage Intra-peritoneal Chemotherapy Fail Again

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THE PAPER by de Jong and associates in this issue (pages 709–713) is yet another report of intra-peritoneal (i.p.) chemotherapy used in an effort to salvage incomplete response to initial chemotherapy for metastatic ovarian cancer.

Two findings are especially notable. Firstly, the "third" laparotomy, used as an endpoint in 9 patients, proved to be a false negative in 6/7 women, with the median time to disease progression being 12 months, even when laparotomy with multiple biopsies could find no evidence of tumour. Secondly, even in selected patients with only microscopic residual tumour, i.p. chemotherapy produced only a 14-month median time to relapse and a projected 85% relapse rate at 30 months—poor results indeed. For gross disease that was still < 2 cm in diameter (half of which was < 0.5 cm in diameter), the median time to relapse was only 8 months—even worse.

In general, it can now be concluded that a negative laparotomy after therapy for ovarian cancer offers little reassurance that the patient will do well for more than a short period of time. Those of us old enough to recall the 'second laparotomy' experience of the 1960s and 1970s may well wonder why negative results that were once associated with an excellent prognosis are no longer reliable. Four reasons are apparent.

Firstly, laparotomies are being performed after shorter periods of therapy, allowing more patients who would once have relapsed while still receiving 12 or 18 months of melphalan chemotherapy, to relapse after having a negative laparotomy after 6 months of combination chemotherapy based on cisplatinum [1].

Secondly, the increased palliative power of cisplatin-based chemotherapy recruits more patients with a poor prognosis into very good remission, but does not cure them. Thus, a report from the Memorial Hospital in the mid-1980s showed an 80% relapse rate 4 years after cisplatin-based chemotherapy and negative second laparotomy for tumours staged III and IV at diagnosis [1].

Thirdly, as more homogeneously poor populations of patients are explored, one could expect that the results, even among those with negative repeat laparotomies after further therapy, would become worse. Early series of second laparotomy included patients with stage I and II disease. With or without second laparotomy, the cure rates among such patients are substantial. As shown in a recent report from the Memorial Hospital, among stage III and IV cisplatin patients treated in the 1980s with a negative laparotomy, the relapse rate was 55% compared to 21.4% for stages I and II [2].

In the paper by de Jong and associates (pages 709–713), all the patients had achieved only partial remissions to induction systemic chemotherapy, and so would be expected to do worse on cisplatin given by any route than those in whom cisplatin has produced a long and asymptomatic remission. Several experiences have shown that those women relapsing after such remissions often respond again with excellent and prolonged remissions to cisplatin given either systemically or i.p. [3–7]. The absence of such women from the de Jong trial would make the remissions shorter and the reliability of negative second laparotomy seem less than that seen in salvage i.p. experiences studies in which they were included.

Fourth, and paradoxically, a repeat laparotomy is more likely to miss persisting disease after treatment of microscopic residual disease than after gross disease is treated—no one would expect to miss persistent tumour if multiple 1 gram lesions are reduced to 100 mg lesions still 1 mm in diameter, but reducing 3 mg lesions (0.03 cm in diameter) to 0.3 gram would still not produce a cure, but could easily lead to a false-negative repeat laparotomy by random failure to find the positive sites on biopsy.

In the de Jong series then, the median time to progression after negative second laparotomy was 12 months, while it was 23 months for those never subjected to second laparotomy who were doing well on clinical evaluation at the same timepoint. Little should be made of the difference because of the small numbers involved, but certainly there was no obvious advantage to those who had the laparotomy with negative findings compared to those who had not.

If one had good therapy to give after initial chemotherapy for ovarian cancer to women with a high risk of relapse, a good case could be made for giving it to all such women, regardless of laparotomy findings, since negative laparotomy does not overcome poor prognostic factors. Several predictive indices have been developed to indicate those with a poor prognosis, and thus a need for better (more?) therapy, without resorting to second laparotomy [8, 9]. Alternatively, if the prognostic factors are favourable, such as in stage I disease with negative tumour markers, then the likelihood of positive findings at second laparotomy are small, and most patients will be subjected to a needless surgical procedure. In neither circumstance does performing laparotomy make sense. Therefore, it should not be performed, even as a trial endpoint!

Nevertheless, the diehard proponents of second laparotomy assert that the procedure allows the physician to select optimal patients for i.p. therapy and to place the catheters necessary for its administration. However, disappointing experience with i.p.

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therapy has been the norm, making this argument for second laparotomy unconvincing. In de Jong's current report, for instance, 6 of 7 women with negative repeat laparotomies after i.p. therapy relapsed at a median of 12 months. Overall, median time to disease progression was 11 months, with only 22% free of progression after 2 years.

Enthusiasm for i.p. therapy was initially based on a small series of patients without repeat laparotomy reported by Howell from San Diego, with 74% survival after 4 years for those with small volume residual disease at entry [10]. However, a similar 60% survival 4 years after second laparotomy has been reported after a variety of therapies for similar patients with microscopic residual tumour at second laparotomy treated in the Netherlands in the mid-1980s [11]. It remains plausible that the long-term survival rate reported by Howell would have been achieved by following the patients to relapse and retreatment with cisplatin chemotherapy at that time. It is notable that Howell's original paper included only survival data, and no information on relapse.

Howell's 1987 paper noted that women with bulky disease did poorly with i.p. chemotherapy, with a median survival of only 8 months [10]. Since that time, numerous studies have uncovered large groups of women who seem to do poorly with i.p. chemotherapy: those with large masses (> 1 cm, only 2/13 responses confirmed at later laparotomy [12]), those with tumour whose resistance to systemic cisplatin is established (overall response rate of 11% and surgical complete response rate of 3% [13]), those with diffuse carcinomatosis in the peritoneal cavity (only two partial responses and no complete responses at laparotomy among 11 patients [14]), and, of course, those with poor distribution of fluid instilled into the peritoneum and with retroperitoneal or extraperitoneal disease.

These predictors of poor outcome for i.p. salvage therapy were used to explain the very disappointing results of a Gynaecologic Oncology Group pilot study of i.p. cisplatin together with interferon [15]. In this trial, 33% of patients were taken off treatment for toxicity, and there was only one responder among the 18 women of 48 entered who could be evaluated for response. As Ozols asked in the title of an accompanying editorial, "Who is left to treat?" [16].

A subsequent study by the same group using i.p. cisplatin and etoposide again confirmed the difficulty of carrying though the complex treatment plan. Again, a minority of entered patients (41/92) were evaluable for response. Only six complete and four partial responses were observed at later laparotomy among 25 "favourable" patients, and only one of each among 16 with "unfavourable" characteristics [17].

The hope most of us shared 15 years ago, when i.p. therapy for ovarian cancer came under study, was that the almost unique preferred peritoneal mode of spread of this disease would also allow its eradication. We hoped that the very high concentrations of drug we could achieve in the peritoneal cavity would overcome the resistance that allowed the disease to decrease remarkably in size, but did not kill the last tumour cell.

While Howell and others [10] have noted that i.p. therapy can relieve ascites and improve performance, the real thrust of the research effort has been to increase the cure rate in this disease in which cure has been reported even with single alkylating agents. Thus, the emphasis in most papers has been on the reporting of complete remissions confirmed by multiple peritoneal biopsies. These were felt to be the prerequisite for cure, and it was hoped that a major portion of those with negative repeat laparotomy would not relapse.

Alas, as in de Jong's series, negative repeat laparotomy has been a false endpoint after salvage i.p. therapy. Markman recently reported from the Memorial Hospital in New York that 12/19 laparotomy-proved complete remitters with small tumours at the start of i.p. therapy had relapsed [18], including 7 of 9 with tumours visible but ≤ 0.5 cm in diameter. Thus, durable complete remission is very rare with any gross disease.

In this series, median time to relapse from repeat laparotomy was 15 months for those with visible disease ≤ 0.5 cm, and 32 months for the 10 patients with only microscopic residual disease at start of i.p. therapy [18]. The 7 "surgical" complete remitters followed between 24 and 48 months at the time of the report are the "tail" on the curve of 132 patients begun on three successive trials over 5 years, including 58 with < 0.5 cm residual masses. The 132 were selected for favourable characteristics (fluid distribution, bulk, disease extent, performance status, etc). Clearly then, very few women with ovarian cancer will benefit in a major way from salvage i.p. therapy, at least in the way it has been given over the past decade.

Why hasn't salvage i.p. therapy worked? Only a portion of the relapses have been extraperitoneal, so that it is not only an anatomical failure because of disease distribution outside the treated field. Some treated patients undoubtedly had pockets of inadequately bathed peritoneum because of adhesions or loculations. Many patients probably had tumour cells too far from the peritoneal cavity to be killed by i.p. drug. Some probably have some tumour cells resistant even to the very high concentrations achieved. Some might have done better with more treatment—four to six cycles in the current trial, six in most others. In retrospect, with all these factors going against it, i.p. salvage therapy was a long shot; a therapy unlikely to succeed from the start.

In rejecting diagnostic second laparotomy and salvage i.p. chemotherapy, one need not also reject their cousins, interval cytoreductive surgery [19] and initial i.p. chemotherapy where drug resistance has not yet been established. Hopefully, the recent report from Europe of survival benefit for interval cytoreductive surgery after 9 weeks of systemic chemotherapy will be confirmed. As of this writing, the results have not been published and the characteristics of the women who had technically successful cytoreduction (from residual bulky tumour to one < 1 cm in diameter) have not been defined. Since only 27% of patients subjected to laparotomy achieved such cytoreduction, one would expect the benefits to be confined to this group, and one would hope to avoid interventional surgery in those unlikely to benefit [19]. Previous efforts at tumour resection after induction chemotherapy have not been particularly successful.

A national effort in the U.S.A. in the 1980s looked at the value of i.p. versus intravenous cisplatin together with intravenous cyclophosphamide for "optimal" stage III ovarian cancer. The early results of this trial indicate a prolongation of median survival from 41 to 49 months by switching cisplatin administration from intravenous to intraperitoneal [20]. Data on comparative time to first relapse (a more sensitive measure of treatment efficacy than survival, which encompasses increasingly effective salvage therapy now that paclitaxel is available), longer follow-up, details of patient characteristics at entry, and extent of protocol compliance with dose intensity, route and duration of therapy, will be critical to interpretation of the initial favourable report. It remains conceivable that while salvage i.p. therapy cures almost nobody, initial i.p. therapy could nudge the cure rate up significantly.

Finally, a point needs to be made regarding palliation of those not cured of their disease. The argument has been made that

surgically defined response, even if transient, is an indicator of effective palliative therapy, since tumour is being controlled, at least transiently. This ignores the substantial toxicity of aggressive therapy and the not negligible toxicity of i.p. drug administration and multiple laparotomies. If a woman with symptomatic metastatic ovarian cancer has been rendered free of symptoms and fully functional, administration of toxic therapy and major surgical interventions at the point of an excellent response will produce immediate symptoms, and thus greatly impair the quality of her life. This is done in the undocumented hope of some future gain. Current data indicate that it is precisely those few patients who do well after i.p. therapy who are also most likely to respond to retreatment at relapse with systemic chemotherapy based on cisplatin [3–6].

It is thus inappropriate to term salvage i.p. therapy "effective palliation" when asymptomatic patients are treated and there is no definitive study showing enhanced quality or duration of life compared to policies of watchful waiting for relapse or alternative systemic therapy employed when markers are available to follow the patient for response.

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Childhood Cancer: Trends in Incidence, Survival and Mortality

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IN THE past 30 years there have been dramatic improvements in survival rates for childhood cancers—at least in developed countries. This is due to the introduction of new treatments and to the extent to which children with cancer are now treated, or have their treatment planned, at specialist centres. There is now a widespread use of improved methods of treatment and the results are clear both from analyses of population-based survival