Surgical Debulking Before or After Chemotherapy: Stemming the Tide on Ovarian Cancer Recurrence

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Joe V. Meigs, a surgeon at Massachusetts General Hospital, initially described the technique of ovarian tumor debulking in 1934 [1]. The concept did not really catch on until the mid-1970s when C. Thomas Griffiths published a paper suggesting a survival benefit [2]. Numerous case series and other retrospective reports rapidly followed and further supported the efficacy of this aggressive surgical approach [3–5]. One of the theoretical arguments that is often made in favor of debulking is that removal of chemo-resistant clones – or ovarian cancer stem cells (CSC) – is advantageous [6].

In this issue of ONKOLOGIE, Lim et al. [7] postulate that residual cancer stem cells reside within regressed tumors after partial treatment with neoadjuvant chemotherapy (NACT). They advocate radical procedures during interval debulking surgery to remove these clones and conclude that this strategy results in a clinical benefit (median survival 55 months) when compared to historical controls. The manuscript has all of the limitations of a retrospective review, in addition to the bias of patient selection. Unfortunately, there is no mention of morbidity, time of discharge or other complications that may have either directly or indirectly resulted from aggressive surgery to remove subclinical disease.

As the authors mention, cytoreductive status is the most important prognostic factor in patients with advanced ovarian cancer undergoing surgery. In primary debulking surgery, survival rates have been shown to improve accordingly when the paradigm is revised to a more aggressive philosophy incorporating ultra-radical techniques such as splenectomy, diaphragmatic stripping and liver resection [8]. NACT followed by interval debulking often results in fewer radical procedures, higher rates of optimal debulking, less morbidity and in some series comparable survival compared to primary debulking surgery [9, 10]. However, other reports have sug-

gested NACT in lieu of primary debulking is associated with an inferior overall survival [11]. Thus, there is still no compelling evidence that NACT prior to debulking surgery is a superior strategy at the present time [12].

Among their 60 patients treated by NACT and interval debulking, Lim et al. [7] reported 100% success in achieving less than 1 cm of residual disease and 35% of these patients had complete cytoreduction to no visible tumor. In the unpublished phase III European trial of primary debulking versus NACT plus interval debulking that is referenced in abstract form [13], optimal debulking was identified as the strongest independent prognostic factor, but the timing of surgery did not seem to matter. It would seem that additional radical procedures might be indicated in the population of Lim et al. to increase the percentage of complete resection, but it is difficult to understand how removal of regressed tumors is helpful when miliary or small volume disease is left behind in other areas. The manuscript does not provide details about which patients had what procedure performed.

The authors' hypothesis is provocative, but their data do not substantiate the claim that clinically important non-palpable regressed tumor warrants radical dissection at the time of interval debulking. It is interesting to speculate that CSC may reside in these tissues and removal would facilitate eradication of the residual, more chemoresistant tumor cells. Based on their reported observations, this possibility remains just that – speculation. Nevertheless, many of the characteristics of ovarian cancer indirectly argue in favor of either this disease being a product of CSC or CSC potentially contributing to the pathogenesis and/or recurrence of the disease. Moreover, subsets of ovarian tumor cells have been identified, functionally characterized, and shown to have tumor initiating capacity and share many of the characteristics normally attrib-

uted to benign stem cells [14–17]. The authors appreciate the idea that CSC are more likely to be chemoresistant and this is believed to be due in part to an increase in multidrug transporter activity and their relative quiescence which renders them less susceptible to current chemotherapy protocols which target replicating cells.

It is generally believed that the number of tumor cells that have the capacity to initiate new tumor is relatively small. Whether these CSC are distributed throughout the tumor or limited to focal areas in the primary or metastatic lesion(s) is yet to be determined. The idea that more aggressive surgical procedures immediately prior to chemotherapy or following NACT will serve to eliminate CSC and/or progenitor cells is an interesting argument. However, given that optimal debulking is defined as leaving no residual tumor greater than 1 cm in mass would suggest that unless chemotherapy is more effective in less bulky disease the chances that one procedure would be more effective over the other in eliminating the presumed CSC population is not readily obvious. Residual stem cells have been shown in other tumor types following chemotherapy or radiation [18–21]. More interesting, however, it has been reported that CSC remain or in some instances increase

in number after chemotherapy or radiation [18–21]. Whether there is truly an overall increase or just a change in the ratio of stem-progenitor to more differentiated cells is not always clear. The stability of the stem cell niche must also be considered. If chemotherapy is targeting the more rapidly proliferating tumor cells and/or the vascular component thereby disrupting the bulk of the tumor microenvironment, the surviving cancer stem-progenitor cells would need to not only survive the toxicity but also ‘re-awaken’ and undergo some form of asymmetric or symmetric replication process to secure and recruit a viable blood supply along with supportive somatic cells.

While there are limitations to this study the authors’ hypothesis is intriguing and potentially testable. We agree there is a need for more extensive and well designed prospective studies investigating the role of CSC in recurrent disease and how they may influence surgical management of ovarian cancer.

Conflict of Interest

The authors have no conflict of interests to declare.

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