



### Robert J. Morgan, Jr., MD

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Dr. Morgan's primary areas of investigation include clinical investigation in ovarian cancer and early drug development and innovations in curriculum design in continuing medical education. His articles have appeared in the *Journal of Clinical Oncology*, *Cancer Research*, *Clinical Cancer Research*, and others. He is a member of the American Society of Clinical Oncology and Chair of the NCCN Guidelines for Ovarian Cancer Panel and serves on the NCCN Guidelines Steering Committee and the Cervical/Uterine Guidelines Panel.

The ideas and viewpoints expressed in this editorial are those of the author and do not necessarily represent any policy, position, or program of the NCCN.

## Ovarian Cancer Guidelines: Treatment Progress and Controversies

Since the inception of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) around 15 years ago, the Ovarian Cancer Panel has seen major changes in treatment recommendations based on ever increasing knowledge of results and therapeutic developments. Nonetheless, significant controversies remain, and these controversies can cause major disagreement among experts. This issue of *JNCCN* proves this point and also illustrates the importance that we in the medical community must place on the information gathered through the clinical trials process.

Major differences of opinion on what treatment is appropriate usually only occur in cases of insufficient information to generate uniform consensus. The articles in this issue on the appropriate use of chemosensitivity (chemoresistance) assays to help determine recommended chemotherapeutic management in recurrent ovarian cancer demonstrate this controversy, which has resulted in a category 3 level of consensus (meaning major disagreement among committee members) in the current NCCN Guidelines for Ovarian Cancer. The guidelines state, "Chemosensitivity/resistance assays are being used in some NCCN centers for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available; the current level of evidence is not sufficient to supplant standard of care chemotherapy (category 3)."

This issue also illustrates how strong clinical trial and meta-analysis data over the past 15 years has resulted in significant changes in recommendations. For example, data suggesting a correlation between patient survival and extent of initial surgical debulking resulted in strengthening recommendations. "Optimal" cytoreduction is defined as less than 1 centimeter residual disease at the completion of the surgery. However, the NCCN Guidelines now state that "maximal effort should be made to remove all gross disease."

Another example is how systemic chemotherapy recommendations have evolved after studies showed that intraperitoneal chemotherapy can result in improved survival in select patients. The initial 1995 NCCN Guidelines were category 3, denoting that members of the committee strongly disagreed on whether intraperitoneal chemotherapy should be considered. New data spurred evolution to the current category 1 ranking, based on high-level evidence from randomized prospective clinical trials that intraperitoneal chemotherapy improves survival for certain subsets of patients. The treatment algorithm states that "All women undergoing surgery for ovarian cancer should be counseled about the clinical benefit associated with combined IP [intraperitoneal] and IV [intravenous] chemotherapy administration before surgery."

Furthermore, the principles of primary surgery state that "Consideration should be given to placement of an IP catheter with initial surgery in all patients who will potentially undergo an optimal debulking procedure." This example shows the panel's willingness to consider ever-increasing evidence and amend the NCCN Guidelines. The most current ongoing controversy facing the panel involves the appropriate recommendations for the addition of bevacizumab to initial treatment regimens. The committee is awaiting publication of mature data and encourages enrollment of patients to currently ongoing clinical trials.

Weak clinical data mean less robust recommendations. In surgery, advances in technique (e.g., minimally invasive surgery to treat early or advanced ovarian cancer) are reviewed by Han and Wakabayashi. Retrospective data suggest that these

approaches may result in equivalent accuracy in surgical staging; however, results from randomized prospective clinical trials confirming these findings remain elusive. The NCCN Guidelines for Ovarian Cancer continue to consider this approach as a “special situation”: “In stage 1 disease, minimally invasive techniques may be considered to achieve the surgical principles described...minimally invasive surgery performed by an experienced gynecologic oncologist may be considered in selected patients.” Han and Wakabayashi appropriately note the need for continued randomized clinical studies.

The potential benefit of secondary debulking procedures is also addressed in the 2011 NCCN Guidelines. Ongoing clinical trials are attempting to clearly define the benefit of these procedures. Retrospective data suggest that this procedure may benefit subsets of patients; however, randomized prospective data documenting effectiveness are not available, and enrollment of patients in ongoing clinical trials investigating this procedure is strongly encouraged. The guidelines further suggest that secondary debulking may be considered for platinum-sensitive patients ineligible for current clinical trials.

Similarly, results from phase II nonrandomized trials are often sufficient to result in the addition of an active single agent to the recommendations for treating recurrence. Comparison of the available agents for recurrence therapy in 1995 with those in 2010 shows that a large number of new active agents have been developed and approved, allowing for improved quality of life for many patients. These agents are often recommended as available based on the evidence of smaller nonrandomized phase II trials, but with a lower level of consensus (category 2B). This signifies a general uniformity of consensus that sufficient data are available to recommend their use as single agents but not to recommend one over another as a single agent in the recurrence setting. The panel, however, generally requires some randomized data to make a recommendation for combination chemotherapy in the recurrence setting. Current prospective randomized trials are expected to provide further guidance. The NCCN Guidelines for Ovarian Cancer will further evolve based on these and other forthcoming data.

The only conclusion available from examining the manuscripts in this issue is that the best therapeutic recommendation for all treatment or testing paradigms is enrollment and inclusion in appropriate prospective clinical trials. Only through this mechanism can we continue to improve outcomes for cancer patients.