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Correspondence

Neo-adjuvant chemotherapy in stage IIIC potentially resectable epithelial ovarian cancer

I would like to comment on the recently (October 2016 issue of Gynecologic Oncology) published guideline for neoadjuvant chemotherapy (NACT) in newly diagnosed ovarian cancer and specifically with regards to potentially resectable disease (Recommendation 3.1) (Wright et al., 2016). The decision to proceed with NACT or primary surgery (PCS) in newly diagnosed stage IIIC disease should not be confused with the decision of whether surgery is at all appropriate in a given patient because of her general condition or comorbidities. This should be clarified first and be distinct from the decision of timing of cytoreductive surgery. The appropriateness of surgery may of course be modified if there is a progression during NACT (as Recommendation 7 of the guideline advocates) or conversely if an unexpected improvement of the clinical condition of the patient is obtained during palliative chemotherapy. Availability of the NACT option should not be an "excuse" for not operating on a potentially resectable patient because of other comorbidities that would increase her surgical complication risk or because of concerns of inexperienced surgeons that a primary debulking surgery would be more difficult. Instead the general status of the patient should weight in the decision of proceeding with NACT only if it is believed to be related to the burden of the cancer and patients that are expected to be technically more difficult should be referred to more experienced centers.

In the case of surgery deemed appropriate the main factor that should be considered in the decision for the timing of surgery and tip the balance towards or away from PCS is the stage and bulk of the disease. Patients who could be considered for NACT are those that meet the criteria used in the EORTC/NCIC trial (FIGO IIIC and IV) (Vergote et al., 2010) except for patients in the lower range of FIGO IIIC staging (major tumor masses of 2–5 cm) as these patients appear to have better outcomes with PCS (van Meurs et al., 2013). It is noteworthy that in both trials of PCS versus NACT, that have survival data available at present, the complete response rate is more than double in the NACT arm, nevertheless survival outcomes are similar (Vergote et al., 2010; Kehoe et al., 2015). On the other hand the bulk of residual disease after primary surgery is known to be the best predictor of survival outcomes (Bristow et al., 2002). This may imply that microscopic residual disease post-NACT is more extensive and difficult to visually identify than microscopic disease at presentation (Hynninen et al., 2013). A possible cause of this could be that chemotherapy is able to kill the bulk of cells in the diffuse peritoneal nodules but stem or tumor initiating cells resistant to treatment remain and repopulate the tumors (Chang, 2016). In other tumor types such as triple negative breast cancers where neoadjuvant chemotherapy is used and tumors respond well, radiopaque coils are placed pre-NACT to guide excision of the residual if macroscopically invisible (Pinder et al., 2015). This is obviously impractical in ovarian cancers but in fact is a strong theoretical disadvantage of NACT in these tumors. Thus, both available data and theoretical considerations support primary radical surgery over NACT in patients with potentially resectable stage IIIC and certainly those stage IIIC patients with smaller tumor masses of less than 5 cm in major diameter. NACT should remain a second best option in these patients and should be reserved as first option for patients with stage IV disease, patients with a high risk for perioperative complications clearly due to tumor-related factors (where reducing tumor load may improve surgical risks), or for patients that are unlikely to receive optimal cytoreduction even with a meticulous surgical effort. Both PCS and especially NACT will benefit from better methods for identification of microscopic disease in the future (Cocco et al., 2015).

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Ioannis A. Voutsadakis
Division of Medical Oncology, Department of Internal Medicine, Sault Area Hospital, Sault Ste. Marie, ON, Canada
Division of Clinical Sciences, Northern Ontario School of Medicine, Sudbury, ON, Canada
Corresponding author at: Division of Medical Oncology, Department of Internal Medicine, Sault Area Hospital, 750 Great Northern Road, Sault Ste. Marie, ON P6B 0A8, Canada.
E-mail addresses: ivoutsadakis@yahoo.com, ivoutsadakis@nosm.ca.

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