

# Cancer of the Ovary: There Is Reason for Optimism!

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Epithelial ovarian cancer continues to be the leading cause of death from a gynaecologic malignancy in Canada and the developed world. In 2008, an estimated 2500 Canadian women were diagnosed with ovarian cancer, and approximately 1700 died from their disease, still a very sobering and unfortunate reality for the disease that often only “whispers.”<sup>1</sup> While survival in early stage and particularly in low grade tumours approaches 90%, the majority of women will present with advanced FIGO stage 3 or 4 disease, will have manifested only vague abdominal symptoms, and can only expect a survival rate of approximately 15% to 40%.<sup>2</sup>

Conventional screening modalities such as the ovarian cancer tumour marker serum CA-125 and trans-vaginal pelvic ultrasound have been disappointing, with studies demonstrating a less than optimal positive predictive value and specificity for malignant tumours. This is in part because ovarian cancer is relatively uncommon but also because of the enigmatic lack of a defined pre-malignant precursor lesion, despite an ever increasing understanding of ovarian cancer biology.<sup>3</sup> Nevertheless, there have been the remarkable treatment breakthroughs of platinum-based and paclitaxel chemotherapy. Paclitaxel, in particular, is a fascinating story of drug development in the treatment of ovarian cancer; it is a story that included commercial and environmental lobbying and conflicts and the overcoming of serious drug toxicity, while at the same time addressing an increasing patient and public demand for better cancer treatment.<sup>4</sup> This demand, at the time, in many ways gave profile to a disease that had previously received only modest attention, particularly in the public domain. For many, ovarian cancer was merely that rare and perhaps “inherited”

gynaecologic malignancy that claimed the life of the dynamic actress Gilda Radner. There was a lack of awareness of ovarian cancer, its early symptoms, and diagnosis and treatment. Moreover, this gap in awareness, understandably present in the public arena, was also an issue with women’s health care providers. The past 10 to 15 years, however, have seen the profile of ovarian cancer increase dramatically, particularly for women and their primary caregivers. In large measure, this has been due to the efforts of the gynaecologic oncology community, patients and their families, ovarian cancer support groups, and formal advocacy organizations. One such group founded 10 years ago, Ovarian Cancer Canada, is dedicated to “overcoming ovarian cancer” and is a Canadian success story in disease awareness and education. Early efforts at advocacy have matured into educational programs, scientific conferences, and numerous fundraising events.<sup>5</sup> Prominent in these efforts, particularly for patients and their families, but also for the communities of care providers, has been the desire for a breakthrough in the early detection of ovarian cancer. A major focus of advocacy and awareness is now to educate women about the early symptoms of ovarian cancer, screening, and early diagnosis. Recent literature has given support to the concept that indeed there may be some vague symptoms that should be paid attention to, that may be predictive, and these are being collated into a “symptom index.”<sup>6</sup>

Nevertheless, the availability of an acceptable, predictable test capable of identifying a malignant tumour at an early stage is one of the primary criteria of a screening method, and is something desired by the primary care and gynaecologic community. Unfortunately, despite significant advances in the understanding of the biology of ovarian cancer, conventional screening modalities have had minimal impact on mortality. Necessity has bred discovery, however, and advancements in proteomic technology over the past decade have resulted in the development and testing of novel biomarkers. Proteomics has facilitated the

characterization and validation of dysfunctional or altered proteins secreted by early ovarian tumours and present in small amounts in the serum.<sup>7</sup> One such biomarker, HE4, has in combination with CA-125 improved sensitivity and specificity for ovarian cancer, potentially assisting the primary care and gynaecology communities in determining when to refer a patient with a pelvic mass to a gynaecologic oncologist.<sup>8</sup> Other biomarkers and “panels” of markers have been and are being investigated, and there appears to be increasing potential and growing anticipation that proteomic technology may soon enhance traditional screening tools to levels that are acceptable, practical, and affordable for a screening test.<sup>9</sup>

The value of ovarian cancer screening using serial CA-125 assays and pelvic ultrasound is also being investigated in large clinical trials. These include the United Kingdom Collaborative Trial of Ovarian Cancer Screening, a randomized trial involving 200 000 postmenopausal women with an endpoint of ovarian cancer mortality, and the NIH Prostate, Lung, Colorectal and Ovarian cancer screening trial. Large scale studies such as these will surely add to our knowledge of early ovarian cancer and our capacity to screen for it.

Much innovative investigation has also been undertaken in pelvic and ovarian imaging, both as screening modalities complemented by tumour markers and as predictors of malignancy in the presence of an ovarian mass.<sup>10</sup> Two-dimensional transvaginal ultrasound, the “gold standard” of ovarian imaging, is now sharing the spotlight with modalities such as MRI, which is potentially valuable in a patient with an indeterminate adnexal mass. Three-dimensional ultrasound is on the cusp of providing additional and useful information in ovarian imaging. Moreover, the development of the “Risk of Malignancy Index” (RMI), a scoring scheme that includes a combination of menopausal status, 2-D ultrasound features and CA-125 has now been well studied and validated.<sup>11</sup> As well, the quality of image reporting, primarily through efforts to identify gaps and variations and ultimately through standardization, will continue to improve and will result in enhanced predictive values for malignancy in patients with an ovarian mass.<sup>12</sup>

Although efforts are concentrated on identifying patients with early cancer of the ovary, and recognizing that advanced disease is a persistent challenge for patients and their health care professionals, recent progress has also been made in managing stage 3 and 4 disease. Intraperitoneal chemotherapy, a previously investigated but essentially abandoned treatment modality, has made a return to the treatment scene, with results that are superior to standard chemotherapy administration in patients with minimal residual disease following tumour debulking.<sup>13</sup>

With the knowledge that current best practice for staging and cytoreduction of advanced ovarian cancer includes surgery performed by a gynaecologic oncologist, and with the goal of surgery being minimal residual disease, renewed efforts are being explored by oncologists in the domain of cytoreductive surgery. Investigators are currently reporting on innovative techniques for “maximal,” particularly upper abdominal, tumour resection to achieve minimal residual disease and potentially a survival advantage.<sup>14,15</sup> Platinum-based chemotherapy, whether administered following cytoreduction, or in a “neo-adjuvant” setting prior to surgical debulking has been a cornerstone of advanced ovarian cancer therapy. A recent trial has not only supported the safety of neoadjuvant therapy but also has confirmed the importance to patient survival of optimal tumour cytoreduction.<sup>16</sup> New, different, and potentially better cytotoxics continue to be investigated, and novel biologic targeted therapy has an emerging role in the continued battle against this challenging disease.

Have we succeeded in defining the optimal therapy for advanced ovarian cancer? No, we have not. Have we validated a practical and effective diagnostic modality for early ovarian cancer? Again, no. But surely we should feel confident as a women’s health care community about the progress that has been made in understanding ovarian cancer biology, in awareness, and in early diagnosis and treatment of this disease, and optimistic about the answers to our questions that are yet to come.

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