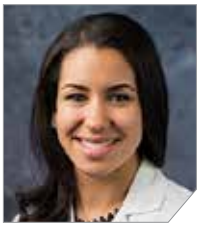

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Dr. Wright reports that he is a consultant to Clovis Oncology and Tesaro, Inc. Dr. Gamble reports no financial relationships relevant to this article.

Gynecologic malignancies continue to be among the most deadly cancers for women. In this article: HIPEC, PARP, and minimally invasive hysterectomy.

Of the major developments in 2018 that changed practice in gynecologic oncology, we highlight 3 here.

First, a trial on the use of hyperthermic intraperitoneal chemotherapy (HIPEC) for patients with ovarian cancer after neoadjuvant chemotherapy demonstrated an overall survival benefit of 12 months for patients treated with HIPEC. Second, a trial on poly-adenosine diphosphate–ribose polymerase (PARP) inhibitors as maintenance therapy after adjuvant chemotherapy showed that women with a *BRCA* mutation had a progression-free survival benefit of nearly 3 years. Third, the Laparoscopic Approach to Cervical Cancer trial revealed a significant decrease in survival in women with early-stage cervical cancer who underwent minimally invasive radical hysterectomy compared with those who had the traditional open approach. In addition, a retrospective study that analyzed information from large cancer databases showed that national survival rates decreased for patients with cervical cancer as the use of laparoscopic radical hysterectomy rose.

In this Update, we summarize the major findings of these trials, provide background on treatment strategies, and discuss how our practice as cancer specialists has changed in light of these studies' findings.

IN THIS ARTICLE

HIPEC improves overall survival in advanced ovarian cancer—by a lot

Van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378:230-240.

In the United States, women with advanced-stage ovarian cancer typically are treated with primary cytoreductive (debulking) surgery followed by platinum- and taxane-based chemotherapy. The goal of cytoreductive surgery is the resection of all grossly visible tumor. While associated with favorable oncologic outcomes, cytoreductive surgery also is accompanied by significant morbidity, and surgery is not always feasible.

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Neoadjuvant chemotherapy (NACT) has emerged as an alternative treatment strategy to primary cytoreductive surgery. Women treated with NACT typically undergo 3 to 4 cycles of platinum- and taxane-based chemotherapy, receive interval cytoreduction, and then are treated with an additional 3 to 4 cycles of chemotherapy postoperatively. Several large, randomized controlled trials have demonstrated that survival is similar for women with advanced-stage ovarian cancer treated with either primary cytoreduction or NACT.[1,2] Importantly, perioperative morbidity is substantially lower with NACT and the rate of complete tumor resection is improved. Use of NACT for ovarian cancer has increased substantially in recent years.[3]

Rationale for intraperitoneal chemotherapy

Intraperitoneal (IP) chemotherapy has long been utilized in the treatment of ovarian cancer.[4] Given that the abdomen is the most common site of metastatic spread for ovarian cancer, there is a strong rationale for direct infusion of chemotherapy into the abdominal cavity. Several early trials showed that adjuvant IP chemotherapy improves survival compared with intravenous chemotherapy alone.[5,6] Yet complete adoption of IP chemotherapy has been limited by evidence of moderately increased toxicities, such as pain, infections, and bowel obstructions, as well as IP catheter complications.[5,7]

FAST TRACK

HIPEC treatment was associated with a 3.5-month improvement in recurrence-free survival compared with surgery alone and a 12-month improvement in overall survival

Heated IP chemotherapy for recurrent ovarian cancer

More recently, interest has focused on HIPEC. In this approach, chemotherapy is heated to 42°C and administered into the abdominal cavity immediately after cytoreductive surgery; a temperature of 40°C to 41°C is maintained for total perfusion over a 90-minute period. The increased temperature induces apoptosis and protein degeneration, leading to greater penetration by the chemotherapy along peritoneal surfaces.[8]

For ovarian cancer, HIPEC has been explored in a number of small studies, predominately for women with recurrent disease.[9] These studies demonstrated that HIPEC increased toxicities with gastrointestinal and renal complications but improved overall and disease-free survival.

HIPEC for primary treatment

Van Driel and colleagues explored the safety and efficacy of HIPEC for the primary treatment of ovarian cancer.[10] In their multicenter trial, the authors sought to determine if there was a survival benefit with HIPEC in patients with stage III ovarian, fallopian tube, or peritoneal cancer treated with NACT. Eligible participants initially were treated with 3 cycles of chemotherapy with carboplatin and paclitaxel. Two-hundred forty-five patients who had a response or stable disease were then randomly assigned to undergo either interval cytoreductive surgery alone or surgery with HIPEC using cisplatin. Both groups received 3 additional cycles of carboplatin and paclitaxel after surgery.

Results. Treatment with HIPEC was associated with a 3.5-month improvement in recurrence-free survival compared with surgery alone (14.2 vs 10.7 months) and a 12-month improvement in overall survival (45.7 vs 33.9 months). After a median follow-up of 4.7 years, 62% of patients in the surgery group and 50% of the patients in the HIPEC group had died.

Adverse events. Rates of grade 3 and 4 adverse events were similar for both treatment arms (25% in the surgery group vs 27% in the HIPEC plus surgery group), and there was no significant difference in hospital length of stay (8 vs 10 days, which included a mandatory 1-night stay in the intensive care unit for HIPEC-treated patients).

WHAT THIS EVIDENCE MEANS FOR PRACTICE

For carefully selected women with advanced ovarian cancer treated with neoadjuvant chemotherapy, HIPEC at the time of interval cytoreductive surgery may improve survival by a year.

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PARP inhibitors extend survival in ovarian cancer, especially for women with a *BRCA* mutation

Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379:2495-2505.

FAST TRACK

After 41 months of follow-up, the olaparib group had a disease-free survival rate of 60% versus 27% in the placebo group

Ovarian cancer is the deadliest malignancy affecting women in the United States. While patients are likely to respond to their initial chemotherapy and surgery, there is a significant risk for cancer recurrence, from which the high mortality rates arise.

Maintenance therapy has considerable potential for preventing recurrences. Based on the results of a large Gynecologic Oncology Group study,[11] in 2017 the US Food and Drug Administration (FDA) approved bevacizumab for use in combination with and following standard carboplatin and paclitaxel chemotherapy for women with advanced ovarian cancer. In the trial, maintenance therapy with 10 months of bevacizumab improved progression-free survival by 4 months; however, it did not improve overall survival, and adverse events included bowel perforations and hypertension.[11] Alternative targets for maintenance therapy to prevent or minimize the risk of recurrence in women with ovarian cancer have been actively investigated.

PARP inhibitors work by damaging cancer cell DNA

PARP is a key enzyme that repairs DNA damage within cells. Drugs that inhibit PARP trap this enzyme at the site of single-strand breaks, disrupting single-strand repair and inducing double-strand breaks. Since the homologous recombination pathway used to repair double-strand DNA breaks does not function in *BRCA*-mutated tissues, PARP inhibitors ultimately induce targeted DNA damage and apoptosis in both germline and somatic *BRCA* mutation carriers.[12]

In the United States, 3 PARP inhibitors (olaparib, niraparib, and rucaparib) are FDA approved as maintenance therapy for use in women with recurrent ovarian cancer that had responded completely or partially to platinum-based chemotherapy, regardless of *BRCA* status. PARP inhibitors also have been approved for treatment of advanced ovarian cancer in *BRCA* mutation carriers who have received 3 or more lines of platinum-based chemotherapy. Because of their efficacy in the treatment of recurrent ovarian cancer, there is great interest in using PARP inhibitors earlier in the disease course.

Olaparib is effective in women with *BRCA* mutations

In an international, randomized, double-blind, phase 3 trial, Moore and colleagues sought to determine the efficacy of the PARP inhibitor olaparib administered as maintenance therapy in women with germline or somatic *BRCA* mutations.[13] Women were eligible if they had *BRCA1* or *BRCA2* mutations with newly diagnosed advanced (stage III or IV) ovarian, fallopian tube, or peritoneal cancer and a complete or partial response to platinum-based chemotherapy after cytoreduction.

Women were randomly assigned in a 2:1 ratio, with 260 participants receiving twice daily olaparib and 131 receiving placebo.

Results. After 41 months of follow-up, the disease-free survival rate was 60% in the olaparib group, compared with 27% in the placebo arm. Progression-free survival was 36 months longer in the olaparib maintenance group than in the placebo group.

Adverse events. While 21% of women

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treated with olaparib experienced serious adverse events (compared with 12% in the placebo group), most were related to anemia. Acute myeloid leukemia occurred in 3 (1%) of the 260 patients receiving olaparib.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

For women with deleterious *BRCA1* and/or *BRCA2* mutations, administering PARP inhibitors as a maintenance therapy following primary treatment with the standard platinum-based chemotherapy improves progression-free survival by at least 3 years.

Is MIS radical hysterectomy (vs open) for cervical cancer safe?

Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med. 2018;379:1895-1904.

Melamed A, Margul DJ, Chen L, et al. Survival after minimally invasive radical hysterectomy for early-stage cervical cancer. N Engl J Med. 2018;379:1905-1914.

For various procedures, minimally invasive surgery (MIS) is associated with decreased blood loss, shorter postoperative stay, and decreased postoperative complications and readmission rates. In oncology, MIS has demonstrated equivalent outcomes compared with open procedures for colorectal and endometrial cancers.[14,15]

Increasing use of MIS in cervical cancer

For patients with cervical cancer, minimally invasive radical hysterectomy has more favorable perioperative outcomes, less morbidity, and decreased costs than open radical hysterectomy.[16-20] However, many of the studies used to justify these benefits were small, lacked adequate follow-up, and were not adequately powered to detect a true survival difference. Some trials compared contemporary MIS enrollees to historical open surgery controls, who may have had more advanced-stage disease and may have been treated with different adjuvant chemoradiation.

Despite these major limitations, minimally invasive radical hysterectomy became an acceptable—and often preferable—alternative to open radical hysterectomy for early-stage cervical cancer. This acceptance was written into National Comprehensive Cancer Network guidelines,[21] and minimally invasive radical hysterectomy rapidly gained popularity, increasing from 1.8% in 2006 to 31% in 2010.[22]

Randomized trial revealed surprising findings

Ramirez and colleagues recently published the results of the Laparoscopic Approach to Cervical Cancer (LACC) trial, a randomized controlled trial that compared open with minimally invasive radical hysterectomy in women with stage IA1–IB1 cervical cancer.[23] The study was designed as a noninferiority trial in which researchers set a threshold of -7.2% for how much worse the survival of MIS patients could be compared with open surgery before MIS could be declared an inferior treatment. A total of 631 patients were enrolled at 33 centers worldwide. After an interim analysis demonstrated a safety signal in the MIS radical hysterectomy cohort, the study was closed before completion of enrollment.

Overall, 91% of patients randomly assigned to treatment had stage IB1 tumors.

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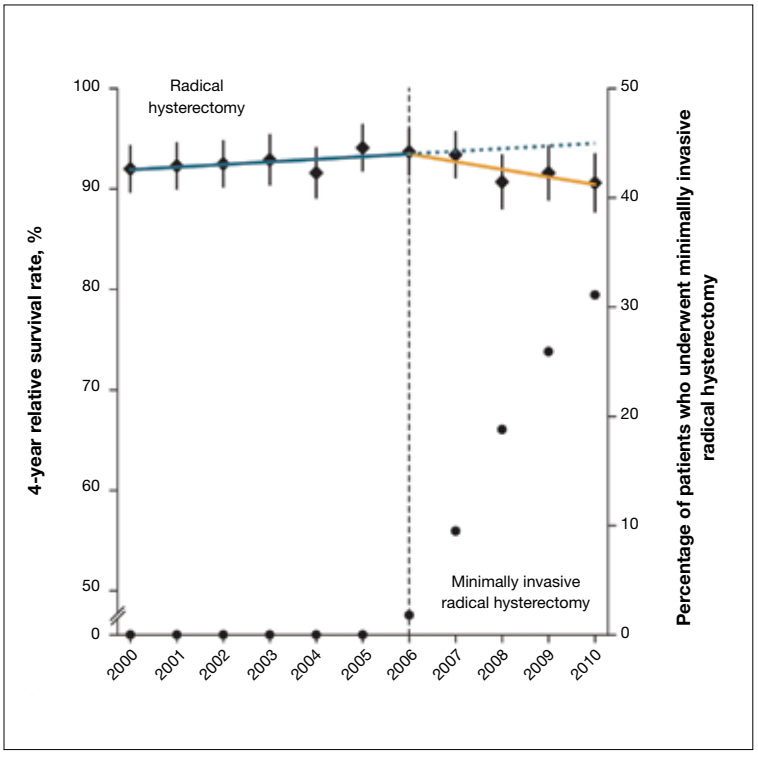
FIGURE Interrupted time-series evaluation of radical hysterectomy[22]



Shown are the 4-year relative survival rates among women who underwent radical hysterectomy for cervical cancer by any surgical approach (diamonds) with 95% confidence interval (CI) (error bars) and the percentages of radical hysterectomies that were undertaken with the use of a minimally invasive approach (circles). The adoption of minimally invasive radical hysterectomy in 2006 was associated with a significant change of temporal trend (as indicated by the dotted blue line) (P = .01) and a declining 4-year relative survival rate after 2006 (yellow line) (annual percentage change, 0.8%; 95% CI, 0.3–1.4). Used with permission.

At the time of analysis, nearly 60% of enrollees had survival data at 4.5 years to provide adequate power for full analysis.

Results. Disease-free survival (the time from randomization to recurrence or death from cervical cancer) was 86.0% in the MIS group and 96.5% in the open hysterectomy group. At 4.5 years, 27 MIS patients had recurrent disease, compared with 7 patients who underwent abdominal radical hysterectomy. There were 14 cancer-related deaths in the MIS group, compared with 2 in the open group.

Three-year disease-free survival was 91.2% in the MIS group versus 97.1% in the abdominal radical hysterectomy group (hazard ratio, 3.74; 95% confidence interval, 1.63–8.58) The overall 3-year survival was 93.8% in the MIS group, compared with 99.0% in the open group.[23]

Retrospective cohort study had similar results

Concurrent with publication of the LACC trial results, Melamed and colleagues published an observational study on the safety of MIS radical hysterectomy for early-stage cervical cancer.[22] They used data from the National Cancer Database to examine 2,461 women with stage IA2–IB1 cervical cancer who underwent radical hysterectomy from 2010 to 2013. Approximately half of the women (49.8%) underwent minimally invasive radical hysterectomy.

Results. After a median follow-up of 45 months, the 4-year mortality rate was 9.1% among women who underwent MIS radical hysterectomy, compared with 5.3% for those who had an abdominal radical hysterectomy.

Using the complimentary Surveillance, Epidemiology, and End Results (SEER) registry dataset, the authors examined population-level trends in use of MIS radical hysterectomy and survival. From 2000 to 2006, when MIS radical hysterectomy was rarely utilized, 4-year survival for cervical cancer was relatively stable. After adoption of MIS radical hysterectomy in 2006, 4-year relative survival declined by 0.8% annually for cervical cancer (**FIGURE**).[22]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Both a randomized controlled trial and a large observational study demonstrated decreased survival for women with early-stage cervical cancer who underwent minimally invasive radical hysterectomy. Use of minimally invasive radical hysterectomy should be used with caution in women with early-stage cervical cancer.

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References

1. Vergote I, Trope CG, Amant F, et al; European Organization for Research and Treatment of Cancer–Gynaecological Cancer Group; NCIC Clinical Trials Group. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med.* 2010;363:943-953.
2. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet.* 2015;386:249-257.
3. Melamed A, Hinchcliff EM, Clemmer JT, et al. Trends in the use of neoadjuvant chemotherapy for advanced ovarian cancer in the United States. *Gynecol Oncol.* 2016;143:236-240.
4. Markman M. Intraperitoneal antineoplastic drug delivery: rationale and results. *Lancet Oncol.* 2003;4:277-283.
5. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol.* 2001;19:1001-1007.
6. Armstrong DK, Bundy B, Wenzel L, et al; Gynecologic Oncology Group. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med.* 2006;354:34-43.
7. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med.* 1996;335:1950-1955.
8. van de Vaart PJ, van der Vange N, Zoetmulder FA, et al. Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin-DNA adduct formation in patients and ovarian cancer cell lines. *Eur J Cancer.* 1998;34:148-154.
9. Bakrin N, Cotte E, Golfier F, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advanced ovarian carcinoma: a multicenter, prospective study of 246 patients. *Ann Surg Oncol.* 2012;19:4052-4058.
10. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. *N Engl J Med.* 2018;378:230-240.
11. Burger RA, Brady MF, Bookman MA, et al; Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365:2473-2483.
12. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature.* 2005;434:917-921.
13. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med.* 2018;379:2495-2505.
14. Walker JL, Piedmonte MR, Spirtos NM, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. *J Clin Oncol.* 2012;30:695-700.
15. Clinical Outcomes of Surgical Therapy Study Group, Nelson H, Sargent DJ, et al. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med.* 2004;350:2050-2059.
16. Lee EJ, Kang H, Kim DH. A comparative study of laparoscopic radical hysterectomy with radical abdominal hysterectomy for early-stage cervical cancer: a long-term follow-up study. *Eur J Obstet Gynecol Reprod Biol.* 2011;156:83-86.
17. Malzoni M, Tinelli R, Cosentino F, et al. Total laparoscopic radical hysterectomy versus abdominal radical hysterectomy with lymphadenectomy in patients with early cervical cancer: our experience. *Ann Surg Oncol.* 2009;16:1316-1323.
18. Nam JH, Park JY, Kim DY, et al. Laparoscopic versus open radical hysterectomy in early-stage cervical cancer: long-term survival outcomes in a matched cohort study. *Ann Oncol.* 2012;23:903-911.
19. Obermair A, Gebski V, Frumovitz M, et al. A phase III randomized clinical trial comparing laparoscopic or robotic radical hysterectomy with abdominal radical hysterectomy in patients with early stage cervical cancer. *J Minim Invasive Gynecol.* 2008;15:584-588.
20. Mendivil AA, Rettenmaier MA, Abaid LN, et al. Survival rate comparisons amongst cervical cancer patients treated with an open, robotic-assisted or laparoscopic radical hysterectomy: a five year experience. *Surg Oncol.* 2016;25:66-71.
21. National Comprehensive Care Network. NCCN clinical practice guidelines in oncology: cervical cancer, version 1.2018. http://oncolife.com.ua/doc/nccn/Cervical_Cancer.pdf. Accessed February 11, 2019.
22. Melamed A, Margul DJ, Chen L, et al. Survival after minimally invasive radical hysterectomy for early-stage cervical cancer. *N Engl J Med.* 2018;379:1905-1914.
23. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. *N Engl J Med.* 2018;379:1895-1904.