International Gynecologic Cancer Society 2019 meeting summary

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ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer

Presented by: Kathleen M Schmeler

The standard of care for patients with early-stage cervical cancer is radical hysterectomy with pelvic lymphadenectomy or sentinel lymph node mapping in experienced centers. For patients interested in future fertility, the National Comprehensive Cancer Network (NCCN) Guidelines recommend radical trachelectomy with pelvic lymph node assessment as outlined above. However, both of these procedures are associated with considerable potential perioperative morbidity. Moreover, it has been shown from retrospective data that the rate of parametrial involvement in patients with low-risk disease is <1%.[1][2] Although there are no clearly defined strict criteria for the definition of low-risk cervical cancer, most would agree that this generally pertains to patients with tumor size <2 cm, squamous, adenocarcinoma, or adenosquamous carcinoma histology, and no evidence of lymphovascular invasion. A number of retrospective studies and small case series have reported on the oncologic safety of performing more conservative surgery in this group of patients, including conization for those still seeking childbearing or simple hysterectomy for those not interested in future fertility.[3] However, this conservative approach has never been proven in a prospective trial.

The ConCerv trial is one of three current prospective studies exploring the question of conservative surgery in the setting of low-risk cervical cancer. The other two trials are the SHAPE trial and GOG 278. The primary objective of the ConCerv trial was to evaluate the safety and feasibility of performing conservative surgery in women with early-stage cervical cancer. The secondary objectives were to evaluate the recurrence rate at 2 years, determine the rate of residual disease in patients undergoing hysterectomy, determine the rate of pelvic lymph node involvement, and assess quality of life factors. This was a prospective single-arm study with a total of 100 patients projected accrual, and strict central pathology review. All data monitoring was performed at MD Anderson Cancer Center.

The inclusion criteria for the study were International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA2 or IB1 cervical cancer, tumor diameter ≤2 cm, no evidence of lymphovascular invasion, squamous cell histology (any grade) or adenocarcinoma (grade 1 or 2 only), cone margins and endocervical curettage negative for malignancy (one repeat cone or endocervical curettage was allowed), cone margins and endocervical curettage negative for CINII/III or adenocarcinoma-in-situ, depth of invasion ≤10 mm, and negative preoperative CT scan, MRI, or positron emission tomography (PET)/CT imaging. There were three surgical options for patients: (a) patients desiring future fertility underwent a cone and, if eligible, underwent pelvic lymph node assessment only; (b) patients not desiring future fertility underwent cone and, if eligible, underwent simple hysterectomy and pelvic node assessment; (c) patients who had undergone an 'inadvertent' simple hysterectomy with a post-op diagnosis of cancer could also be included and, if eligible, underwent pelvic lymph node assessment. Patients were followed with pelvic exam and cytology every 3 months for 2 years. Quality of life questionnaires were completed before surgery and at four time points within 2 years after surgery. The study accrued patients from April 2010 to March 2019. There were 16 study sites in nine countries.

A total of 169 patients were enrolled in order to reach the 100 eligible patients. Of note, 47 (27.8%) patients were not eligible after central pathology review. A total of 44% underwent fertility-sparing surgery, 40% underwent cone followed by simple hysterectomy, and 16% underwent an 'inadvertent' hysterectomy. The median age of the patients was 38 years (range 23–67). Most patients had stage IB1 disease (67%) and adenocarcinoma histology (52%). The majority of patients underwent laparoscopic surgery (83%), followed by robotic (13%) and open (4%). A full lymphadenectomy was performed in 58% of patients, while sentinel lymph node biopsy plus lymphadenectomy was performed in 38% of patients, with the remaining 4% undergoing sentinel mapping alone. It was found that 5% of patients had positive lymph nodes. Residual disease was noted in one of the 40 patients (2.5%) who underwent cone with negative margins followed by hysterectomy. There have been four (4.3%) recurrences in 94 patients eligible to assess this outcome.

The median follow-up is currently 25 months (range 5–60). A total of 64% of patients have ≥2 years follow-up and 27% of patients have ≥5 years follow-up. There have been a total of nine (20.1%)

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pregnancies among 44 patients who underwent fertility-sparing surgery, with 75% delivering at term. In conclusion, this landmark study has shown that a conservative approach to patients with early stage cervical cancer is safe and feasible. However, one must interpret these data with great care as they pertain to oncologic outcomes for several reasons. The entire group of patients has yet to complete the 2 years of follow-up and thus we may not have seen the true recurrence rate in this group of patients. Similarly, we will need to determine what is an adequate recurrence rate that we will be willing to accept if ultimately proposing to move forward with these conservative approaches for these very low risk patients. Lastly, we need to explore what are the potential factors related to recurrence in these very low risk patients. In addition, we look forward to the results of the SHAPE and GOG 278 trials to further understand the role of conservative surgery in patients with early-stage cervical cancer.

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Open versus minimally invasive radical trachelectomy in early stage cervical cancer: International Radical Trachelectomy Assessment (IRTA) study

Presented by: Gloria Salvo

Radical trachelectomy has emerged as an alternative to radical hysterectomy in patients with early-stage disease who wish to preserve fertility. After the first publication by Daniel Dargent as a vaginal procedure, radical trachelectomy has been shown to be safe and feasible by open, robotic, or a laparoscopic approach.[1–3] Small retrospective series have compared approaches showing the benefits of the minimally invasive approach, such as less blood loss and shorter hospitalization.[4 5] In the USA there has been a significant increase in the use of minimally invasive radical trachelectomy from 29% in 2010 to 75% in 2015 (p<0.001), becoming the dominant approach by 2011 (55%).[6] Few retrospectives studies evaluated oncologic outcomes. A review by Bentivegna et al[7] showed a 5% recurrence rate for the open and 6% for the laparoscopic approach. More recently, a retrospective national database study including 246 patients undergoing open or minimally invasive radical trachelectomy was reported with the primary objective of evaluating the trends of minimally invasive radical trachelectomy.[6] However, as a subanalysis, the authors showed a 4 year overall

survival rate of 92% (95% CI 83.5% to 96.5%) for the open and 96% (95% CI 88.7% to 98.4%) for the minimally invasive approach. The authors acknowledged that although the study did not show a difference in survival between approaches, effects of the minimally invasive approach on survival remains unknown and further studies are warranted. After the concerning results of two landmark publications in the *New England Journal of Medicine* by Ramirez et al[8] and Melamed and colleagues,[9] demonstrating worse oncologic outcomes for minimally invasive radical hysterectomy, and given the rapid adoption of minimally invasive trachelectomy, the natural question was to determine whether the same findings would apply to radical trachelectomy.

Therefore, the primary objective of the IRTA study was to compare disease-free survival between patients who underwent open versus minimally invasive (laparoscopic or robotic) radical trachelectomy. As secondary objectives, the investigators evaluated overall survival, as well as the impact of risks factors, such as tumor size, conization, use of a uterine manipulator, residual disease, evidence of visible lesion, and minimally invasive approach (laparoscopy vs robotics), on oncologic outcomes.

The IRTA study is a multi-institutional, international, retrospective study including 18 sites from 12 countries. Patients were included if they had confirmed primary squamous, adenocarcinoma, or adenosquamous carcinoma, FIGO 2009 stage IA2 and IB1 (≤2 cm), underwent radical trachelectomy and pelvic lymphadenectomy (sentinel lymph node mapping optional) from January 2005 to December 2017, were 18 years or older, and each center contributed 15 cases or more (either open, minimally invasive, or both). Patients were excluded if they had prior neoadjuvant chemotherapy or radiotherapy to the pelvis, prior lymphadenectomy or pelvic retroperitoneal surgery, if they were pregnant at the time of surgery, or had aborted trachelectomy (conversion to radical hysterectomy) or vaginal approach. The study design was previously published.[10]

In total, 715 patients were entered, 17 patients were excluded, leaving 388 in the open and 310 in the minimally invasive group (180 robotic and 130 laparoscopic).

There was no difference in age (p=0.09), the body mass index was higher in the minimally invasive group (p<0.01), with no difference in stage (p=0.40). More patients had visible lesions and larger tumors (p<0.001), as well as more adenosquamous carcinomas in the open approach (p=0.02). The median follow-up time was 50.9 months (range <1–179) for the open and 32.2 months (range <1–125) for the minimally invasive group with shorter surgical time (180 min (range 45–425) and 262 min (range 120–485), p<0.001) and higher EBL (200 mL (range 50–4500) and 50 mL (range 0–3000), p<0.001) in the open approach. More patients in the minimally invasive group underwent sentinel lymph node mapping (139 (45%) vs 101 (26%), p<0.001). As it pertains to radicality, there were more patients who underwent type 3 or C1/C2 radical trachelectomies in the open group (208 (54%) vs 74 (24%), p<0.001). There was no difference in intraoperative complications (p=0.23) with longer hospitalization in the open approach (p<0.001). There was no difference in postoperative complications (89 (23%) in the open and 77 (25%) in the minimally invasive group, p=0.56; however, the rate of re-admission (7 (2%) vs 33 (11%), p<0.001) and re-operation (6 (2%) vs 15 (5%), p=0.01) was higher in the minimally invasive group. The rate of trachelectomy-related complications was similar between groups (56 (14%) in the open and 38 (12%) in the minimally invasive

group, p=0.44), with cervical stenosis the most frequent for both approaches, followed by cerclage erosion, uterine necrosis, anastomosis separation, and amenorrhea. The open group was more likely to have residual disease (p<0.001), larger tumors (p<0.001), and grade III (p=0.002) with no difference in parametrial or vaginal involvement, margin positivity, lymphovascular invasion, or nodal compromise. More patients required adjuvant treatment in the open approach (49 (13%) vs 18 (6%), p=0.002). Overall, there was no difference in disease-free survival between approaches with a 5.4% recurrence rate in the open versus 6.4% in the minimally invasive group (p=0.37). The 4.5 year disease-free survival (open vs minimally invasive) was 93.6% (95% CI 92.2% to 95.0%) versus 91.1% (95% CI 89.1% to 93.2%), respectively. Overall survival was similar between groups (p=0.91). The investigators evaluated recurrence rate based on tumor size, and found that patients who underwent minimally invasive surgery and had tumors 1–2 cm before surgery were more likely to have a recurrence compared with those who underwent open surgery (12.1% vs 8.3%, p=0.010). There was also an analysis of the impact of preoperative conization on oncologic outcomes, and it was demonstrated that patients who underwent minimally invasive surgery and did not have a cone before surgery were more likely to have a recurrence than those who underwent open surgery (19.7% vs 8.8%, p<0.001). Not all surgeries in the study were concurrent, therefore, a timeframe sub-analysis was performed including only concurrent cases and there was no difference in disease-free survival (p=0.58) or overall survival (p=0.93) between the surgical approaches. Regarding risk factors for recurrence, the investigators found that patients with a visible lesion before surgery were more likely to have a recurrence (9.0% vs 3.8%), regardless of the type of surgery. However, there was no difference when comparing open versus minimally invasive surgery (8.2% vs 10.7%, p=0.83). There was no difference in recurrence rate if a uterine manipulator was used versus no uterine manipulator (p=0.37). There was no difference in the rate of recurrence between the patients who underwent robotic versus laparoscopic surgery (6% vs 8% respectively, p=0.62).

Among the strengths of this study are the fact that it is the largest series comparing oncologic outcomes between open and minimally invasive radical trachelectomy, the confirmation of surgeon proficiency as 15 cases or more were required to participate in the study, and all participating sites were high-volume centers. In addition, a data dictionary was available and a strict data audit requesting 10% of source documents per site was performed. There are several weaknesses of this study: it was a retrospective analysis prone to bias and the known risk of missing values, not all cases were concurrent, and the groups were unbalanced for several variables.

In conclusion, minimally invasive radical trachelectomy was found to have worse oncologic outcomes in tumors 1–2 cm. However, no difference was noted in patients with smaller tumors. In addition, patients undergoing minimally invasive surgery had higher re-admission and re-operation rates than those undergoing the open approach, with no difference in trachelectomy-related complications.

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Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiation for stage IB2-IIb cervical cancer (EORTC 55994)

Presented by: Fabio Landoni

The EORTC (European Organisation for Research and Treatment of Cancer) study was a randomized prospective multicentric (25 institutions from 10 European countries) trial that enrolled 626 patients with cervical carcinoma with squamous or adeno (squamous) cell type FIGO 2009 stage IB2, IIA >4 cm, or IIB, between May 2002 and January 2014 (140 months). Patients were randomized in two arms: Arm 1 (314 patients) underwent neoadjuvant cisplatin-based chemotherapy (≥225 mg/m²) followed by radical hysterectomy within 6 weeks after last chemotherapy administration. Post-surgical chemoradiotherapy was recommended in cases of positive lymph nodes, tumor invasion into the parametria, or <5 mm distance from the resection borders (27% patients). Patients randomized to Arm 2 (312 patients) received standard chemotherapy and radiation. External radiotherapy at 45–50 Gy was given to the pelvis combined with external boost or brachytherapy. Minimal total dose is 75 Gy EQD2 to point A or 80 Gy to high-risk planned targeted volume all completed within 50 days. Concomitant chemotherapy with an initial dose ≥40 mg/m² cisplatin was administered weekly during radiotherapy. The planned total cisplatin dose was 200–240 mg/m². Adjuvant hysterectomy was allowed in the case of histologically proven residual tumor (8% patients). The primary endpoint was overall survival at 5 years. Secondary endpoints were: progression-free survival, toxicity, and quality of life.

The sample determination was based on an overall survival assumed at 5 years in the chemotherapy and radiation arm of 67%.

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To detect a 10% difference with a two-sided α of 5% and power of 80%, a total sample size of 625 patients with 5 years of follow-up was required. A quality assurance project was implemented to check the accuracy of data collection and investigate protocol adherence in the different treatment modalities.

The median age in the group of neoadjuvant chemotherapy and surgery was 46 years, and ECOG 1 was assigned to 88% of patients. Of the 314 patients, 26% were classified as FIGO stage IB2, 15% as stage IIA (>4 cm), and 57% as stage IIB. The hystological type of cervical carcinoma were squamous cell (85%), adenocarcinoma (10%), or adenosquamous (5%).

In the chemoradiotherapy group, the median age was 47 years and an ECOG 1 was assigned to 88% of patients. Regarding FIGO 2009 stage, of the 312 patients, 28% had stage IB2, 15% had stage IIA (>4 cm), and 57% had stage IIB. The hystological types were squamous cell (85%), adenocarcinoma (11%) and adenosquamous (4%). Of the 314 patients in the neoadjuvant chemotherapy and surgery group, 15 patients did not start treatment (5%) due to following reasons: six patient refused, six were ineligible, and three patients for other reasons; thus 299 patients were in the final analysis.

Regarding treatment compliance, of 314 patients, 74 (24%) received no surgery. The main reasons were: chemotherapy toxicity in 25 (34%) patients, progression in 18 (24%) patients, insufficient response in 12 (16%) patients, refusal in 10 (14%) patients, protocol violations in six (8%) patients, or other causes in three (4%) patients. Of the 314 patients, 240 (76%) underwent surgery. The type of surgery was: Piver-Rutledge III, IV, V or other in 86%, 4%, 6%, and 5%, respectively. Regarding chemotherapy agents, cisplatin alone was administered to 46% of patients, whereas cisplatin and paclitaxel or cisplatin, paclitaxel, and ifosfamide or cisplatin plus other were given to 20%, 19%, and 15% of patients, respectively.

In the chemoradiotherapy group, there were 312 patients. A total of 292 started the treatment as planned; 20 patients did not start treatment (6.8%). Reasons were: 11 patients refused, five patients were ineligible, and four patients for other reasons. Of the 312 patients, 292 (94%) patients received chemotherapy and radiation, with a median dose of 46 Gy (pelvic). An external boost was administered to 123 (42%) patients, with a median dose of 10 Gy. Brachytherapy was administered to 280 (96 %) patients. Chemotherapy with cisplatin as single agent was given to 87% of the patients and cisplatin and paclitaxel to 13% of patients. In Arm 1, of 220 patients that completed the protocol treatment, 60 patients received some form of adjuvant treatment, whereas 160 patients did not. The indications for adjuvant treatment were: positive lymph nodes, parametrial infiltration, and/or positive surgical margins. Results of pathological evaluation were available for 240 patients who underwent protocol surgery. In the neoadjuvant chemotherapy and surgery group, there was a complete response, defined as no microscopic residual disease, in 54 patients (23%), an optimal response (carcinoma in situ or stromal invasion <3 mm) in 35 patients (15%), a suboptimal response (neither complete nor optimal) in 124 patients (52%), and other or missing response (not assessable, missing, unknown) in 27 patients (11%). Surgical margins were positive in 32 patients (13%), and pelvic lymph nodes were positive in 66 patients (27%). Of the most common regimens used, cisplatin alone had the lowest response rate with 32%

(38/119) reporting either complete or optimal response; however, this difference was not statistically significant.

The progression-free survival at 5 years in the intent to treat population was 56.9% (51.1–62.3%) for the neoadjuvant chemotherapy and surgery group, and 65.6% (59.9–70.7%) for the chemotherapy and radiation arm, with a difference at year 5 of 9% (2–18%) (p=0.021). Similar results were seen in eligible and per protocol populations. The sub-groups with the most benefit from chemotherapy and radiation were patients >50 years old and those with low BMI. There were no statistical differences in overall survival (73% in the neoadjuvant chemotherapy and surgery group and 76% in the chemotherapy and radiation group); there was a trend for improved results in the neoadjuvant chemotherapy and surgery group for stage Ib2. Also, there was a trend for improved outcomes for the chemotherapy and radiation group for stage IIb and for patients >50 years. The short-term grade 3 and 4 toxicity was higher in the neoadjvant chemotherapy and surgery group (41% vs 3%), as well as long-term toxicity (20% vs 15%).

According to the authors, progression-free survival was lower in the group that underwent neoadjuvant chemotherapy and surgery, compared with the group that received chemo-radiotherapy. There was no difference in overall survival, but the group receiving neoadjuvant chemotherapy and surgery had more grade 3 and 4 toxicity.

Surgical staging versus clinical staging in locally advanced cervical cancer: results of an international randomized trial (Uterus 11)

Presented by: Simone Marnitz ●

Locally advanced cervical cancer is associated with a high risk of para-aortic nodal involvement. Current imaging modalities such as CT, MRI, and PET/CT have considerable limitations and are associated with a risk of under- or overstaging.[1] [2] A previous randomized trial, evaluating the impact of surgically staged locally advanced cervical cancer patients, failed to show a benefit of this approach and was terminated prematurely after 65 patients accrued.[3]

There are a number of different recommendations in the international guidelines[4] [5] regarding surgical staging of locally advanced cervical cancer. Current evidence shows that surgical staging leads to upstaging in a significant number of patients with locally advanced cervical cancer, but oncologic benefit has been controversial.[6–9]

Uterus 11 is the only randomized, prospective, multicentric trial (Charité Berlin, Barretos Cancer Center Brazil, and eight German study centers) that has completed accrual. It aimed to evaluate the oncological benefit of surgical staging in locally advanced cervical cancer patients. The primary endpoint was to evaluate progression-free survival between surgically versus clinically staged patients. The secondary endpoints were: overall survival, local disease control, acute and late toxicity, and quality of life and sexuality assessment. Patients with histologically confirmed cervical cancer

FIGO 2009 stages IIB-IVA were randomized to undergo either surgical staging (n=125) or clinical staging with CT scan imaging (n=125). Those with histologically positive para-aortic nodes received primary pelvic chemo-radiation including extended field, and those with negative lymph nodes underwent primary pelvic chemo-radiation. Patients were followed for 5 years.

There were a total of 130 surgically staged patients (group A) and 125 clinically staged patients (group B); from those, 121 and 119 patients, respectively, were eligible for final analysis. The mean age was 47.2 years for group A and 49.6 years for group B. The percentage of patients diagnosed with FIGO 2009 for group A were stages IIB (70%), IIA (3.5%), IIB (24%), and IV (2.5%); and for group B were stages IIB (67%), IIA (5%), IIB (20%), and IV (8%). The median number of pelvic and para-aortic lymph nodes removed were 19 and 21, respectively (groups A and B). The mean number of pelvic and para-aortic lymph nodes involved were 2.4 and 1.3, respectively. The surgery was done by a laparoscopic approach in 96.7% of patients, and just one patient needed conversion due to obesity and severe adhesions. The authors reported that two patients had bleeding >500 mL, and another two patients delayed start of treatment (4 and 5 days). There was no intraoperative mortality. The rate of pathological upstaging in group A was 33% versus 6% in group B (CT guided para-aortic biopsy). The time to start chemo-radiotherapy after surgery ranged between 7 and 21 days. Regarding radiotherapy techniques, 64% of patients received intensity-modulated radiotherapy and 36% were treated with 3D-radiotherapy. No grade 5 toxicity was observed during chemo-radiotherapy treatment. After a median follow-up of 90 months in both groups, the authors found no difference in either progression-free survival (p=0.08) or overall survival (p=0.068), but reported a statistically significant difference in specific cancer survival (p=0.028).

The strengths of the study include: it is the only completed prospective randomized trial on surgical staging of patients with locally-advanced cervical cancer; nearly all surgical staging procedures were done by a minimally invasive approach; and only modern radiation techniques were used. In addition, patients had a long follow-up (90 months), with high data completion and only six patients (2.5%) lost to follow-up.

Among the weaknesses of the study, the authors acknowledged that PET/CT was not included in the initial work-up because of lack of reimbursement by insurance companies in the participating countries.

The authors concluded that laparoscopic surgical staging is a safe procedure with an upstaging rate >30%. In addition, surgical staging neither delayed primary chemoradiation nor increased complication rates. Regarding oncological outcome, they demonstrated a cancer-specific survival benefit in favor of (laparoscopic) staging compared with clinical staging.

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Oral apixaban compared to subcutaneous enoxaparin for thromboprophylaxis in women undergoing surgery for suspected gynecologic cancer: final results of a multi-institutional randomized, controlled trial

Presented by: Saketh R Guntupalli ⓘ

Nearly 100 000 women will undergo surgery for known or suspected gynecologic malignancy in the USA this year. Many of these cases will be open debulking procedures as surgical cytoreduction of ovarian and uterine cancers has been shown to improve survival.[1] As complexity of surgical debulking increases, so does the risk of intraoperative bleeding, nosocomial infection, and venous thromboembolic events.

In fact, one of the most common causes of mortality after debulking surgery remains the sequelae of postoperative venous thromboembolism. Without postoperative prophylaxis, rates of deep venous thrombus after surgery for gynecologic cancers can be as high as 26%, with 9% of patients experiencing a pulmonary embolus.[2] For that reason, the American College of Chest Physicians strongly recommends deep vein thrombosis (DVT) prophylaxis for women undergoing surgery for gynecologic malignancies with the use of preoperative heparin, sequential compression devices, and postoperative anticoagulation therapies.[3] For the latter, most surgeons use subcutaneous enoxaparin. However, administration of this form of prophylaxis can cause pain and bruising at the injection site which can cause not only discomfort but also non-compliance.

For those reasons, investigators have sought to use alternative oral formulations for postoperative DVT prophylaxis. Apixaban, an

oral factor Xa inhibitor, is one such anticoagulant that has been shown to be a safe alternative to subcutaneous enoxaparin for DVT prophylaxis in patients undergoing hip and knee surgeries.[4 5] The objective of this study was to determine if oral apixaban is a safe modality for the prevention of venous thromboembolism for women following surgery for gynecologic malignancies.

The investigators designed a prospective, randomized open-blinded endpoint (PROBE) study for efficacy, with the primary endpoint of incidence of major bleeding and clinically relevant non-major bleeding (CRNM bleeding), and secondary endpoints that included venous thromboembolism (efficacy). Major bleeding was defined as a decrease in hemoglobin ≥2 g/dL, or transfusion of ≥2 units of blood after initiation of therapy, or bleeding resulting in death. CRNM bleeding was defined as events that required medical intervention, unscheduled contact with a physician, temporary cessation of drug therapy, or impairment of activities of daily life. Additionally, patients completed self-assessed quality of life, satisfaction, and compliance surveys.

Women were included if they were aged 18–89 and were undergoing surgical evaluation (open or minimally invasive) for suspected or confirmed gynecologic malignancy. Patients were excluded if they had a non-gynecologic cancer, a known history of venous thromboembolism, were taking anticoagulation/antiplatelet therapy, had an active bleeding condition, or had significant renal or liver disease. Participants were randomized to 28 days postoperatively of oral apixaban 2.5 mg orally twice a day or subcutaneous enoxaparin 40 mg daily. All patients were followed for 90 days after surgery.

Five hundred patients were screened and eventually 400 patients were consented and randomized (apixaban n=204, enoxaparin n=196). In the apixaban cohort, major bleeding occurred in 0.5% of patients, CRNM bleeding was seen in 5.4%, venous thromboembolism in 1.0%, and adherence was 84.8%. In the enoxaparin group, major bleeding occurred in 0.5% of patients, CRNM bleeding was seen in 9.7%, venous thromboembolism in 1.5%, and adherence was 83.7%. There were no differences between the two groups for any of these outcomes. As would be expected, patients who were randomized to the apixaban group had significantly less pain compared with enoxaparin (2.1% vs 49.2%, p<0.001) as well as having less difficulty taking medications (98.9% vs 58.8%, p<0.001).

In conclusion, the investigators found that postoperative venous thromboembolism prophylaxis with oral apixaban is potentially as safe as standard therapy with subcutaneous enoxaparin. Venous thromboembolism rates between the two groups were similar, suggesting efficacy. Finally, patient satisfaction was greater with apixaban compared with enoxaparin.

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Olaparib monotherapy versus chemotherapy for germline *BRCA*-mutated platinum-sensitive relapsed ovarian cancer patients: phase III SOLO3 trial

Presented by: Richard T Penson

Ovarian cancer is traditionally treated with cytoreductive surgery and platinum-based chemotherapy. The majority of women with advanced stage disease will relapse, and receive further lines of chemotherapy. Non-chemotherapy treatments, such as PARP (poly ADP ribose polymerase) inhibitors, have demonstrated a significant response in ovarian cancer, increasing the time to subsequent relapse—in other words, a longer chemotherapy-free interval for this group of patients. Based on the results from the SOLO1 trial,[1] the PARP inhibitor olaparib has been approved as maintenance therapy for women with *BRCA*-mutated advanced epithelial ovarian cancer in complete or partial response to first-line platinum-based chemotherapy in the USA. It is also approved as maintenance therapy for women with platinum-sensitive, recurrent epithelial ovarian cancer who are in complete or partial response to platinum-based chemotherapy, irrespective of BRCA mutation status, based on the results of the SOLO2 trial.[2]

The SOLO3 trial was a confirmatory phase III trial looking at response to olaparib therapy. In this trial 266 women with platinum-sensitive, relapsed, high-grade serous or endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer germline BRCA mutation, who had received ≥2 previous lines of platinum-based chemotherapy, were randomized to receive either olaparib 300 mg twice daily or a physician's choice of non-platinum chemotherapy in a 2:1 randomization. The primary endpoint was overall response rate; secondary endpoints included progression-free survival, safety, and quality of life.

When comparing all patients, the overall response rate for the olaparib group was 72% vs 51% for the chemotherapy group. Progression-free survival by blinded independent central review for the olaparib group was 13.4 months versus 9.2 months for the chemotherapy group. Although the decrement in health-related quality of life with olaparib was half that with chemotherapy, the difference was not statistically significantly different in between groups. In regards to safety, the most common serious side effect in the olaparib group was anemia, with grade 3 in 21% of patients, and the common side effects of fatigue and nausea. Serious adverse events were reported by 24% of patients in the olaparib group versus 18% in the chemotherapy group. Adverse events that led to treatment discontinuation occurred in 7% in

the olaparib group versus 20% of women in the chemotherapy group.

In conclusion, a statistically significant and clinically meaningful improvement in overall response rate and progression-free survival was seen in the olaparib group compared with the chemotherapy group, with tolerability profiles consistent with previously published data. In addition, women in the chemotherapy group were more than twice as likely to discontinue study treatment due to an adverse event. This is the first trial to compare a PARP inhibitor to chemotherapy in a heavily pre-treated group of patients. Olaparib appears to be be a reasonable alternative to chemotherapy, and better tolerated in women with recurrent, platinum-sensitive *BRCA* mutated ovarian cancer, as a chemotherapy-free option.

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Impact of ERAS program implementation in gynecologic surgery on healthcare costs

Presented by: Larissa Meyer

The implementation of the enhanced recovery after surgery (ERAS) program has led to decreased length of hospital stay and improved patient outcomes.[1][2] Defining value as the intersection of healthcare outcomes and the cost to achieve these outcomes, it is important to understand the different ways to estimate healthcare costs. For example, cost effectiveness models that examine cost and outcomes from a societal perspective often employ national reimbursement rates to populate the model as opposed to 'true costs' or charges. Another technique sometimes employed to evaluate cost is time driven, activity based costing (TDABC). This approach may be more reflective of what it truly costs to deliver care at an institution and more frequently represents value from the individual or hospital level. This method, however, can be very work intensive and may not be generalizable to other patients or hospital systems. One additional approach to estimate healthcare costs involves cost or charge differences for an individual or hospital. In this study, the investigators use this latter approach to evaluate differences in hospital charges for women who undergo surgery for a suspected gynecologic cancer on an ERAS program as compared with conventional perioperative care. To do so, they compared historical controls from a cohort of patients who had conventional postoperative care to a cohort of patients who had postoperative care under an ERAS program. All itemized cost and charge data, both technical and professional, from day of surgery to 30 days postoperatively were reviewed. These included surgical, inpatient, and emergency services. Charges and costs for adjuvant therapy (chemotherapy and/or radiation therapy) were excluded.

Two hundred and seventy-one patients were included in this study. The historical (pre-ERAS) cohort (n=58) underwent surgery from May 2014 to October 2014, while the ERAS cohort (n=213) went from November 2014 to November 2015. Over 70 000 technical charges and 6775 professional charges were reviewed for this study.

There was no difference between the two groups in regards to age, length of surgery, re-operation or re-admission rates, or surgical complexity. In addition, there was no difference in race, ethnicity, body mass index, ASA status, Charlson comorbidity score, tumor type, tumor site, or 30 day complication rates. The ERAS cohort did have a shorter postoperative length of stay compared with the historic group (3 days vs 4 days, p=0.001).

There was no difference between the two groups in charges related to perioperative services, diagnostic procedures, emergency room charges, transfusion related services, interventional radiology procedures, and physical or occupational therapy. The ERAS cohort saw a 20% reduction in laboratory charges, a 64% reduction in material goods charges, a 30% reduction in pharmacy charges, and a 25% reduction in room and board charges (which makes sense as length of stay dropped by 25% from 4 days to 3 days in the ERAS group). Due to proprietary restrictions, only the differences in charges could be discussed.

This study demonstrates significantly lower perioperative resource utilization in the ERAS cohort. As value is patient outcomes divided by cost, implementation of an ERAS program is bound to increase value as it increases patient outcomes while decreasing patient costs. Successful adoption of ERAS principles can enhance healthcare value for patients undergoing gynecologic surgery.

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