GYNECOLOGY

Surgical outcomes among elderly women with endometrial cancer treated by laparoscopic hysterectomy: a NRG/Gynecologic Oncology Group study

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OBJECTIVE: Tolerance of and complications caused by minimally invasive hysterectomy and staging in the older endometrial cancer population is largely unknown despite the fact that this is the most rapidly growing age group in the United States. The objective of this retrospective review was to compare operative morbidity by age in patients on the Gynecologic Oncology Group Laparoscopic Surgery or Standard Surgery in Treating Patients With Endometrial Cancer or Cancer of the Uterus (LAP2) trial.

STUDY DESIGN: This is a retrospective analysis of patients from Gynecologic Oncology Group LAP2, a trial that included clinically early-stage uterine cancer patients randomized to laparotomy vs laparoscopy for surgical staging. Differences in the rates and types of intraoperative and perioperative complications were compared by age. Specifically complications between patients <60 vs ≥60 years old were compared caused by toxicity analysis showing a sharp increase in toxicity starting at age 60 years in the laparotomy group.

RESULTS: LAP2 included 1477 patients ≥60 years old. As expected, with increasing age there was worsening performance status and disease characteristics including higher rates of serous histology, high-stage disease, and lymphovascular space invasion. There was no significant difference in lymph node dissection rate by age for the entire population or within the laparotomy or laparoscopy groups. Toxicity analysis showed a sharp increase in toxicity seen in patients ≥60 years old in the laparotomy group. Further analysis showed that when comparing laparotomy with laparoscopy in patients <60 years old vs ≥60 years old and controlling for race, body mass index, stage, grade, and performance status, patients <60 years old undergoing laparotomy had more hospital stays >2 days (odds ratio, 17.48; 95% confidence interval, 11.71–27.00, $P < .001$) compared with patients <60 years old undergoing laparoscopy. However, when comparing laparotomy with laparoscopy in patients ≥60 years old, in addition to hospital stay >2 days (odds ratio, 12.77; 95% confidence interval, 8.74–19.32, $P < .001$), there were higher rates of the following postoperative complications: antibiotic administration (odds ratio, 1.63; 95% confidence interval, 1.24–2.14, $P < .001$), ileus (odds ratio, 2.16; 95% confidence interval, 1.42–3.31, $P < 0.001$), pneumonias (odds ratio, 2.36; 95% confidence interval, 1.01–5.66, $P = .048$), deep vein thromboses (odds ratio, 2.87; 95% confidence interval, 1.08–8.03, $P = .035$), and arrhythmias (odds ratio, 3.21; 95% confidence interval, 1.60–6.65, $P = .001$) in the laparotomy group.

CONCLUSION: Laparoscopic staging for uterine cancer is associated with decreased morbidity in the immediate postoperative period in patients ≥60 years old. These results allow for more accurate preoperative counseling. A minimally invasive approach to uterine cancer staging may decrease morbidity that could affect long-term survival.

Key words: endometrial, LAP2, older

Endometrial cancer, which is predominantly a disease of postmenopausal women, is expected to increase in prevalence with an increasingly aged and obese population. In 2017, there will be an estimated 61,380 cases of endometrial cancer diagnosed in the United States and 10,920 deaths.[1] Despite the increased rates of endometrial cancer mortality seen in older patients, studies show these patients receive less surgical and adjuvant therapy than their younger counterparts, which is, in part, due to the fact that treating physicians believe older patients cannot tolerate such therapy. This view is supported by literature showing that advanced age is an independent risk factor for perioperative morbidity, even when controlling for medical comorbidities.[2]

Minimally invasive surgical (MIS) management is used for many types of cancers. There is a significant amount of data showing similar oncological outcomes and decreased morbidity with minimally invasive techniques vs laparotomy (LAP).[3,4]

Most recently, the Laparoscopic Approach to Cancer of the Endometrium trial was reported. This randomized phase 3 trial compared exploratory laparotomy with total laparoscopic hysterectomy (TLH) with or without lymph node dissection in clinical stage I endometrioid endometrial cancer. They demonstrated no difference in disease-free survival. While age ≥65 years was a prognostic factor for disease recurrence (hazard ratio, 3.14 [1.57-6.26]), no separate analysis of complications among study participants, including the 44% who were ≥65 years old was presented in this paper.[5]

Based on this and other work, we know that oncological outcomes appear

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equivalent, regardless of surgical approach (LAP, TLH, laparoscopic assisted vaginal hysterectomy [LAVH] or robotic assisted total laparoscopic hysterectomy [RaTLH]).

How well older patients tolerate each of these surgical options remains unknown. Several retrospective studies show decreased morbidity in older patients managed with minimally invasive techniques; however, there are no prospective data comparing outcomes in older patients.[6-9]

In 1996, the Gynecologic Oncology Group (GOG) opened a randomized, prospective clinical trial (GOG-2222 or Laparoscopic Surgery or Standard Surgery in Treating Patients With Endometrial Cancer or Cancer of the Uterus [LAP2]) to compare comprehensive surgical staging by LAP vs LAVH for the treatment of women with stage I to stage IIA uterine cancer (n = 2616).

In 2009 and 2012, the GOG published the results of LAP2 regarding the completeness of surgical staging, recurrence-free survival, complications, and quality of life of LAVH vs LAP. Results showed improved quality of life and decreased complication in the LAVH group with no decrement in survival in patients managed with laparoscopy compared with laparotomy. LAP2 is the largest prospective trial to date looking at minimally invasive surgical approaches in clinically early-stage endometrial cancer. Our current study includes all patients from LAP2 with 1477 patients ≥60 years old. This allows for the assessment of a large subset of older patients with clinically early-stage endometrial cancer.[10,11]

The goal of this ancillary review was to compare intraoperative, perioperative, and postoperative surgical morbidity outcomes in LAVH vs LAP by age in patients who participated in the GOG LAP2 trial. The GOG LAP2 trial included patients with primarily early-stage disease and good performance status and required complete surgical staging, making this a highly selected patient population. The results from this study will allow clinicians to more accurately evaluate the benefits of surgery and its potential complications in older endometrial cancer patients.

Materials and Methods

This was an analysis of patients who were enrolled in LAP-2, a GOG clinical trial. The details of inclusion and exclusion criteria were reported in the original manuscript.[10] Briefly, the study was designed to compare LAVH with LAP for the purpose of complete comprehensive surgical staging of uterine cancer.

The primary outcome of the study was recurrence-free survival. Other endpoints included perioperative adverse events, LAVH conversion to LAP, length of hospital stay after surgery, operative time, quality of life, sites of recurrence, and survival. Eligibility requirements were clinical stage I to IIA uterine cancer, adequate bone marrow, renal and hepatic function, and GOG performance status of less than 4. All patients gave written informed consent prior to study entry in compliance with local institutional review board and federal guidelines.

In our current study, surgical outcomes were compared between patients by age. While it is generally agreed upon in the literature that elderly is defined as >65 or 70 years old, our initial toxicity data showed increased toxicity starting at age 60 years; therefore, our results show surgical outcomes compared between patients <60 years old vs ≥60 years old.

The same analysis was performed using an age cutoff of 70 years old and similar results were found. An intention-to-treat analysis was used for the assessment of surgical complications. The perioperative time period included the first 30 days after surgery and the postoperative time period included up to 6 weeks after the surgery. These parameters were set by the LAP2 protocol.

For statistical analysis, categorical variables were compared between the patient subgroups by the Pearson χ^2 test[12] and continuous variables by the Wilcoxon-Mann-Whitney test[13] or the Kruskal-Wallis test.[14] A logistic regression model was used to evaluate specific operative morbidities and to estimate their covariate-adjusted odds of following LAVH or LAP.

A linear regression model was used to estimate the covariate-adjusted relationships of patients' independent baseline factors to severe toxicity. The nonlinearity of the effect of continuous variables was assessed using restricted cubic splines.[15] All statistical tests were 2 tailed with the significance level set at alpha = 0.05. Statistical analyses were performed using the R programming language and environment.[16]

Institutional Review Board and Institutional Biosafety Committee approvals were obtained at each institution, and all eligible patients signed an informed consent before study entry in compliance with institutional, state, and federal regulations. Permission to perform this retrospective analysis was obtained from the GOG.

Results

LAP2 population demographics, pathology, and outcomes

From the total LAP2 population, 762 patients are 60-69 years old, and 715 patients are ≥70 years old. Demographic data, including BMI, performance status, disease characteristics, postoperative therapy, recurrence, and survival by decade of age, are shown in Table 1. As [T1] age increases, BMI decreases ($P < .001$) and performance status worsens ($P < .001$), and when looking at disease characteristics, there are increasing rates of serous histology ($P < .001$), higher-stage disease ($P < .001$), and more lymphovascular space invasion ($P < .001$).

The majority of patients on LAP2 had endometrioid or serous histology, so only these histologies are shown in Table 1 but all histological subtypes were included in the analysis. When looking at survival by age, older patients have significantly higher rates of recurrence ($P < .001$) and higher rates of death because of disease ($P < .001$). With increasing age, there is also a higher rate of conversion to LAP (<50 years old, 23.8% vs ≥80 years old, 36.8%; $P = .003$ for all ages).

Although full surgical staging was required in GOG LAP2, not all patients underwent complete lymph node dissection. While a small percentage of patients had only pelvic or only

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