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Does the robotic platform reduce morbidity associated with combined radical surgery and adjuvant radiation for early cervical cancers?

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Abstract

Objective—Open radical hysterectomy followed by adjuvant radiation for cervical cancer has been associated with significant rates of morbidity. Radical hysterectomy is now often performed robotically. We sought to examine if the robotic platform decreased the morbidity associated with radical hysterectomy followed by adjuvant radiation.

Methods/Materials—A retrospective cohort of cervical cancer patients undergoing radical hysterectomy from 1995-2013 was evaluated. Complications were assessed using electronic record review and graded. Chi square tests and Student t-tests were used for analysis.

Results—Overall, 243 patients underwent radical hysterectomy for cervical cancer. Surgical approach was 43% open and 57% robotic. Eighty-three patients (34.2%) required adjuvant radiation. Overall, radical hysterectomy plus adjuvant radiation was associated with increased risk of complication (29%) compared to radical hysterectomy alone (7%) ($p < 0.001$). Complications included lymphedema ($n=18$), bowel-associated complications ($n=10$), and urinary complications ($n=7$). There was no difference in time to initiation of radiation between open and robotic surgery (43 v 47 days, $p=0.33$). There was no difference in grade 2/3 complications in patients receiving adjuvant radiation between open and robotic surgery (27.5% v 27.9%, $p=0.97$). Patients undergoing open surgery followed by radiation experienced a trend towards increased adhesion-related complications, such as bowel obstruction and ureteral stricture (10 v 2.3%, $p=0.19$). While patients undergoing robotic surgery followed by radiation experienced a trend toward increased lymphedema (19 v 8%, $p=0.20$).

Conclusions—We found no difference in long-term complications between patients who underwent robotic as compared to open radical hysterectomy with adjuvant radiation. There may be fewer adhesion-related complications with robotic surgery. However, as many radiation related complications occur at later time points, continued follow-up to evaluate for potential differences between the two groups is necessary.

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Keywords

cervical cancer; morbidity; radical hysterectomy; radiation; robotic

Introduction

In 2016 there are estimated to be 12,990 new cases of invasive cervical cancer in the United States and 4,120 deaths (1). Over the last 30 years, there has been a significant reduction in the number of deaths from cervical cancer, largely due to widespread use of the Pap test. Additionally, widespread use of screening allows a large proportion of cervical cancers to be diagnosed at an early stage (1).

Determining optimal treatment for stage IB-IIA cervical cancers can be complex. In a landmark randomized trial by Landoni *et al*, the rate of morbidity associated with open radical hysterectomy (RH) followed by adjuvant radiation was 28% compared to 12% morbidity in women who received primary chemoradiation (2). There was no difference in recurrence rate or 5-year overall survival between the two arms. This data has since been confirmed in a small cohort with a 24% rate of serious adverse events with RH followed by radiation (3). Given the concerns regarding the morbidity of dual modality therapy, primary chemoradiation is often preferred in patients whose preoperative evaluation suggests a high likelihood of meeting pathologic criteria for postoperative adjuvant radiation, as defined by Sedlis *et al* (4). However, more recently multiple authors have found a survival benefit to RH over primary chemoradiation, even in tumors measuring up to 6 cm, further complicating the decision for primary treatment (5-7). Furthermore, despite an effort to avoid using both radical surgery and adjuvant radiation, some women undergoing RH will ultimately meet pathologic criteria for adjuvant radiation on final evaluation.

Recently, the widespread introduction of minimally invasive surgery, specifically robotic surgery, has offered an alternative to open RH (8). The use of the robotic platform has offered reduction in operative blood loss and increased lymph node counts in type III radical hysterectomy for cervical cancer compared to an open approach (9, 10). Additional benefits include shorter hospitalization and reduced postoperative complications (9, 11). A key advantage of utilizing the robot for RH is to gain the benefits of a minimally invasive approach without the steep learning curve and traditionally long operative times seen with traditional laparoscopic radical hysterectomy or laparoscopic assisted radical vaginal hysterectomy (12).

It is yet to be determined if the use of a minimally invasive approach results in less tissue damage and therefore reduced complications when combined with postoperative adjuvant radiation. We hypothesized that the combination of RH and adjuvant radiation would be less morbid than the combination of open RH and radiation.

Materials and Methods

Study Design and Setting

Following internal review board approval, a retrospective cohort study of cervical cancer patients diagnosed from January 1995 until December 2013 at a single, academic hospital was performed. During the study period, 13 different attending surgeons performed open RH and 5 different attending surgeons performed robotic RH. All patients underwent RH with evaluation of the pelvic lymph nodes in 93% of cases (n=236 had nodal dissection, nodal dissection not performed in 3 in the open RH group and 4 in the robot RH group). Inclusion criteria were: (1) patients undergoing type III RH for primary treatment of cervical cancer and (2) receipt of postoperative adjuvant radiation therapy.

During the study timeframe, standard administration of adjuvant radiation was administered to patients who met Sedlis criteria for adjuvant radiation; thus, tumors less than 2cm must have had deep third stromal invasion and show lymphovascular space invasion (LVSI). Tumors between 2-4cm would need to have middle third stromal invasion and LVSI to qualify for adjuvant radiation. Tumors over 4cm with deep or middle third invasion without LVSI and tumors over 5cm with superficial third invasion and LVSI would also undergo adjuvant radiation(4). Following the publication of GOG 109 in 2000, high-risk patients (positive lymph nodes, positive margins, and microscopic parametrial involvement) received radio-sensitizing Cisplatin in addition to adjuvant radiation (13). Additionally, GOG 263 was open at our institution and some patients with intermediate risk pathology were randomized to chemoradiation for adjuvant therapy. Finally, during the study timeframe our standard administration of adjuvant radiation for patient's meeting criteria was 3-dimensional whole pelvic radiation using standard 4 field box technique with shielding of normal tissues based on anatomy given at a dose of 180cGy daily for a 4500-5040 cGy.

Outcomes and Variables of Interest

Our primary outcome was postoperative complication. The exposure of interest was mode of surgery (open compared to robotic). Data was abstracted from the electronic medical record. Complications were defined as urinary complications, bowel complications, and lymphedema presenting greater than 30 days after completion of therapy. Complications were then graded using the same grading described by Landoni *et al* with grade 1 representing mild symptoms not affecting the patient's health and easily cured, grade 2 representing symptoms that could be resolved with long term medical therapy, and grade 3 representing major symptoms requiring surgery or invasive procedures (2). Mode of surgery was obtained from the operative report.

Secondary outcomes of interest included time to initiation of postoperative radiation treatment in each group, rate of adhesion-related complications (defined as bowel obstruction or ureteral stricture), rates of lymphedema, and rates of complication in large tumors (defined as >4cm).

Statistical Methods

This study represents a convenience sample and a de novo power calculation was not performed. Students' t-test was used for continuous variables. Chi square test and Fischer's exact test were used for categorical variables as appropriate. SPSS version 20.0 (IBM Corp: Armonk, NY) was used for all analysis.

Results

We identified 243 patients who underwent RH performed by thirteen surgeons. There were 104 (43%) open RH and 139 (57%) robotic RH during our study period. Median follow up was 30 months (interquartile range 10.5-61.1 months). Demographics and operative characteristics of the robotic and open arms are summarized in Table 1. There was no difference in age, BMI, or operative time between open and robotic cases. Key differences in surgical characteristics between the open and robotic arm were higher estimated blood loss (462 mL open versus 94mL robotic, $p < 0.001$) and transfusion rate (8% versus 2%, $p = 0.04$) in the open arm. Patients in the robotic arm had higher lymph node counts (25 nodes open versus 30 nodes robotic, $p = 0.005$). The 30-day surgical complication rate for grade 2 and 3 complications was significantly increased in the open arm (30% versus 14%, $p = 0.003$).

Of the 243 RH reviewed, 34.2% ($n = 83$) of cases received postoperative adjuvant radiation and thus comprised our primary population of interest. There was no difference in need for postoperative radiation between the open ($n = 40$, 38.5%) and robot arms ($n = 43$, 31.4%) ($p = 0.25$). The median follow up for the robotic arm was shorter at 23 months (range 1-95 months) compared to 45 months (2-174 months) in the open arm. There was also no difference in receipt of chemoradiation (85% versus 77%, $p = 0.76$). Comparison of these two populations is summarized in Table 2. There was no difference in the mean time to initiation of radiation between open and robot groups (43.2 ± 15.6 days versus 47.3 ± 19.6 days, $p = 0.33$). Overall, receipt of postoperative radiation was associated with an increased risk of complications (28.9% versus 7.0%, $p < 0.001$). Observed complications included lymphedema ($n = 18$), bowel-associated complications (enteritis/proctitis $n = 8$, obstruction $n = 2$), and urinary complications (hemorrhagic cystitis $n = 1$, neurogenic bladder $n = 2$, fistula $n = 1$, and ureteral stricture $n = 3$).

There was no difference in grade 2/3 complications in patients receiving postoperative radiation between the open RH plus radiation and robot RH plus radiation groups (27.5% versus 27.9%, $p = 0.97$). There was a trend towards more grade 2/3 lymphedema in the robot RH plus radiation group (19%) compared to the open RH plus radiation (9%), $p = 0.20$. Patients undergoing open RH experienced a trend towards increased adhesion-related complications, such as bowel obstruction and ureteral stricture (10% versus 2.3% $p = 0.19$).

Looking specifically at large tumors (defined as > 4 cm), there were an equal number of large tumors in each group, 28% ($n = 11$) of open RH plus radiation and 28% ($n = 12$) of robot RH plus radiation. For large tumors, there was a trend toward fewer grade 2/3 complications in the robotic RH plus radiation arm compared to the open RH plus radiation arm (8% versus 18%, $p = 0.40$).

Discussion

Nearly 20 years following the publication of the 28% morbidity rate of receiving radical surgery followed by adjuvant pelvic radiation, our study confirms this complication rate in a similar cohort of patients. We found no difference in complication rate when comparing patients undergoing robotic and open radical hysterectomy followed by adjuvant pelvic radiation (27.9% versus 27.5%, $p=0.97$). While we did not find an improvement in the complication rate with use of robotic surgery over open surgery, we did note a low complication rate in patients receiving surgery alone (7%) compared to patients receiving both surgery and radiation (29%). This finding suggests that the morbidity of combination treatment in this cohort is largely due to the radiation exposure, rather than the mode of surgery. Thus, it is not surprising that no discernable effect of the robotic platform could be appreciated.

In evaluating the differences between open and robotic RH, we attempted to focus on areas where the robotic platform may offer the greatest benefit. Previous authors have shown that postoperative adhesions, and subsequent complications due to adhesions, are significantly reduced in patients undergoing minimally invasive simple hysterectomy compared to laparotomy. Rates of bowel obstruction following open abdominal hysterectomy have been reported at 13.6 per 1,000 hysterectomies with no bowel obstructions following minimally invasive hysterectomies (14). We hypothesized there would be a reduction in postoperative adhesion-related complications in the robotic group compared to laparotomy. We found that 10% of open radical hysterectomies had an adhesion related complication compared to 2% of robotic cases, but statistical significance was not reached likely due to small sample size ($p=0.19$).

Further, we noted a trend toward increased lymphedema in the robotic RH group (19% versus 9%), which is consistent with increased nodal counts in this group. Eight of 12 grade 2/3 complications in the robotic surgery arm were due to lymphedema. During the study time period, all patients at our institution who underwent sentinel lymph node biopsy also had completion lymphadenectomy. The use of sentinel nodes in cervical cancer staging could reduce this morbidity and ultimately reduce the morbidity seen when combining robotic RH and adjuvant radiation.

Since Landoni *et al* first reported on the significant morbidity seen with combination radical hysterectomy and adjuvant radiation(2), minimally invasive surgery has become widely adopted due to reductions in blood loss, length of stay, and febrile morbidity (11). Additionally, laparoscopic and robotic radical hysterectomies have been shown to have equivalent cancer outcomes to when compared to open approaches(15). A concern surrounding use of robotic surgery has been related to cost, however, a study in 2012 by Wright *et al* utilizing a large national billing database found a similar cost when comparing abdominal radical hysterectomy (\$9,618) to laparoscopic radical hysterectomy (\$11,774) and robotic radical hysterectomy (\$10,176)(16). These similar costs in the setting of improved surgical morbidity highly favor the use of a minimally invasive approach, including robotic surgery, for treatment of early cervical cancers. Furthermore, a cost-analysis has also shown radical hysterectomy with tailored postoperative radiation to be

superior to primary chemoradiation (17). Triaging strategies are needed to further identify women preoperatively to allow as many women as possible the potential survival and cost benefits of surgical management of their cervical cancer, while avoiding the high morbidity of dual therapy.

As with all single-institution, retrospective studies, our study has limitations, which should be taken into account when interpreting these findings. We are unable to account for bias related to the choice in mode of surgery. Further, our relatively small sample size likely limits our ability to detect a statistically significant difference in complication rates between the robotic and open groups. Our relatively long follow up period of 30 months does vary between arms (23 versus 45 months) and may account for variations in practice as well as introduce bias in finding long term complications. Further long-term effects of radiation treatment continue to accumulate over time and thus may differ between groups. The inclusion of 13 different surgeons helps to improve the variety of surgical care delivered. Finally, since the late 1990s there have been significant changes in radiation delivery including the use of intensity-modulated radiation therapy (IMRT). IMRT has been associated with a reduction in both acute and chronic gastrointestinal, genitourinary, and hematologic side effects due to radiation without compromising oncologic outcomes (18). Given that IMRT was not used at our institution during the study timeframe, further evaluation of the effect of IMRT on complication rates following RH is warranted.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016; 66(1):7–30. [PubMed: 26742998]
2. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet.* 1997; 350(9077):535–40. [PubMed: 9284774]
3. Zivanovic O, Alektiar KM, Sonoda Y, Zhou Q, Iasonos A, Tew WP, et al. Treatment patterns of FIGO Stage IB2 cervical cancer: a single-institution experience of radical hysterectomy with individualized postoperative therapy and definitive radiation therapy. *Gynecol Oncol.* 2008; 111(2): 265–70. [PubMed: 18774596]
4. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecol Oncol.* 1999; 73(2):177–83. [PubMed: 10329031]
5. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Kim YS, et al. Comparison of outcomes between radical hysterectomy followed by tailored adjuvant therapy versus primary chemoradiation therapy in IB2 and IIA2 cervical cancer. *J Gynecol Oncol.* 2012; 23(4):226–34. [PubMed: 23094125]
6. Bansal N, Herzog TJ, Shaw RE, Burke WM, Deutsch I, Wright JD. Primary therapy for early-stage cervical cancer: radical hysterectomy vs radiation. *Am J Obstet Gynecol.* 2009; 201(5):485, e1–9. [PubMed: 19879394]
7. Rungruang B, Courtney-Brooks M, Beriwal S, Zorn KK, Richard SD, Olawaiye AB, et al. Surgery versus radiation therapy for stage IB2 cervical carcinoma: a population-based analysis. *Int J Gynecol Cancer.* 2012; 22(3):484–9. [PubMed: 22249576]

8. Mendivil A, Holloway RW, Boggess JF. Emergence of robotic assisted surgery in gynecologic oncology: American perspective. *Gynecol Oncol.* 2009; 114(2 Suppl):S24–31. [PubMed: 19573702]
9. Boggess JF, Gehrig PA, Cantrell L, Shafer A, Ridgway M, Skinner EN, et al. A case-control study of robot-assisted type III radical hysterectomy with pelvic lymph node dissection compared with open radical hysterectomy. *Am J Obstet Gynecol.* 2008; 199(4):357, e1–7. [PubMed: 18928973]
10. Maggioni A, Minig L, Zanagnolo V, Peiretti M, Sanguineti F, Bocciolone L, et al. Robotic approach for cervical cancer: comparison with laparotomy: a case control study. *Gynecol Oncol.* 2009; 115(1):60–4. [PubMed: 19638333]
11. Shazly SA, Murad MH, Dowdy SC, Gostout BS, Famuyide AO. Robotic radical hysterectomy in early stage cervical cancer: A systematic review and meta-analysis. *Gynecol Oncol.* 2015; 138(2): 457–71. [PubMed: 26056752]
12. Magrina JF, Zanagnolo VL. Robotic surgery for cervical cancer. *Yonsei Med J.* 2008; 49(6):879–85. [PubMed: 19108008]
13. Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol.* 2000; 18(8):1606–13. [PubMed: 10764420]
14. Al-Sunaidi M, Tulandi T. Adhesion-related bowel obstruction after hysterectomy for benign conditions. *Obstet Gynecol.* 2006; 108(5):1162–6. [PubMed: 17077238]
15. Mendivil AA, Rettenmaier MA, Abaid LN, Brown JV 3rd, Micha JP, Lopez KL, 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.* 2015
16. Wright JD, Herzog TJ, Neugut AI, Burke WM, Lu YS, Lewin SN, et al. Comparative effectiveness of minimally invasive and abdominal radical hysterectomy for cervical cancer. *Gynecol Oncol.* 2012; 127(1):11–7. [PubMed: 22735788]
17. Jewell EL, Kulasingam S, Myers ER, Alvarez Secord A, Havrilesky LJ. Primary surgery versus chemoradiation in the treatment of IB2 cervical carcinoma: a cost effectiveness analysis. *Gynecol Oncol.* 2007; 107(3):532–40. [PubMed: 17900674]
18. Folkert MR, Shih KK, Abu-Rustum NR, Jewell E, Kollmeier MA, Makker V, et al. Postoperative pelvic intensity-modulated radiotherapy and concurrent chemotherapy in intermediate- and high-risk cervical cancer. *Gynecol Oncol.* 2013; 128(2):288–93. [PubMed: 23159818]

Table 1

Demographic and clinical characteristics of open and robotic radical hysterectomy

	Open radical hysterectomy, n=104	Robotic radical hysterectomy, n=139	p-value
Age (years)	43.2 (\pm 11.6)	45.5 (\pm 11.3)	0.10
BMI (kg/m²)	30.4 (\pm 6.6)	28.5 (\pm 7.3)	0.50
Operative time (min)	221.4 (\pm 47.5)	213.5 (\pm 51.9)	0.45
Uterine weight (gm)	150 (\pm 134)	133 (\pm 92)	0.32
Estimated blood loss (mL)	462 (\pm 323.5)	94 (\pm 77.4)	<0.001
Blood transfusion	8 (8)	3 (2)	0.04
Lymph node count	25 (\pm 13.6)	30 (\pm 13.6)	0.005
30-day complication	31 (30)	20 (14)	0.003

Continuous variables are reported as mean (\pm standard deviation); Categorical variables are reported as n (%).

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Table 2

Comparing patients undergoing open radical hysterectomy with radiation to robotic radical hysterectomy with radiation

	Open radical hysterectomy with radiation, n=40	Robotic radical hysterectomy with radiation, n=43	p-value
Tumor Stage			0.59
IB1	27 (68)	33 (77)	
IB2	11 (28)	9 (21)	
IIA	2 (5)	1 (2)	
Days to initiation of radiation	43.2 (\pm 15.6)	47.3 (\pm 19.6)	0.33
Grade 2/3 complications	11 (27.5)	12 (27.9)	0.97
Grade 2/3 lymphedema	3 (8)	8 (19)	0.20
Adhesion-related complications	4(10)	1 (2)	0.19
Grade 2/3 complication with tumor >4cm *	2 (18)	1 (8)	0.40

Continuous variables are reported as mean (\pm standard deviation); Categorical variables are reported as n (%).

* 11 open patients had tumor >4cm and 12 robotic patients had tumor >4cm.