OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Impact of the care provided by gynecologic oncologists on outcomes of cervical cancer patients treated with radical hysterectomy

This article was published in the following Dove Press journal:
OncoTargets and Therapy
10 March 2016
Number of times this article has been viewed

Miao-fang Wu[1,*]
Jing Li[1,2,*]
Huai-wu Lu[1]
Li-juan Wang[1]
Bing-zhong Zhang[1]
Zhong-qiu Lin[1]

[1]Department of Gynecologic Oncology, Sun Yat-sen Memorial Hospital, [2]Team-based Learning Group of Clinical Study, Sun Yat-sen University, Guangzhou, People's Republic of China

*These authors contributed equally to this work

Abstract: For many malignant diseases, specialized care has been reported to be associated with better outcomes. The purpose of this study is to investigate the influence of gynecologic oncologists on treatment outcomes for cervical cancer patients treated by radical hysterectomy. Records of patients who received radical hysterectomy between January 2005 and June 2010 were reviewed. Perioperative morbidity, recurrence-free survival, and cancer-specific survival were assessed. Cox regression model was used to evaluate gynecologic oncologists as an independent predictor of survival. A total of 839 patients were included. Of these patients, 553 were treated by gynecologic oncologists, while 286 were treated by other subspecialties. With regard to operative outcomes, significant differences in favor of operation by gynecologic oncologists were found in number of patients receiving para-aortic node sampling and dissection (P=0.038), compliance with surgical guidelines (P=0.003), operative time ($P<0.0001$), estimated blood loss ($P<0.0001$), transfusion rate (P=0.046), number of removed nodes (P=0.033), and incidences of ureteric injury (P=0.027), cystotomy (P=0.038), and fistula formation (P=0.002). Patients who were operated on by gynecologic oncologists had longer recurrence-free survival (P=0.001; hazard ratio [HR] =0.64; 95% confidence interval [CI] [0.48, 0.84]) and cancer-specific survival (P=0.005; HR=0.64; 95% CI [0.47, 0.87]), and this association remained significant in patients with locally advanced disease. Care by gynecologic oncologists was an independent predictor for improved recurrence-free survival ($P<0.0001$; HR=0.57; 95% CI [0.42, 0.76]) and cancer-specific survival (P=0.001; HR=0.58; 95% CI [0.42, 0.81]), which was still significant among patients with locally advanced cancer. Given the results, we believe for cervical cancer patients receiving radical hysterectomy, operation by gynecologic oncologists results in significantly improved surgical and survival outcomes. The importance of the subspecialty of a gynecologist for cervical cancer patients should be addressed in clinical practice, especially for those in developing countries.

Keywords: gynecologic oncologist, cervical cancer, radical hysterectomy, prognosis, surgical outcome

Correspondence: Bing-zhong Zhang; Zhong-qiu Lin
Department of Gynecologic Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, 102 Western Yanjiang Road, Guangzhou 510120, People's Republic of China
Tel +86 20 34071153; +86 20 34071260
Fax +86 20 34071260; +86 20 81330211
Email mdzhangbz@163.com; zhongqiu_lin@163.com

Introduction

Cervical cancer is a leading cause of cancer death in women in developing countries;[1] in People's Republic of China, it represents a great disease burden, with a high incidence of 7.5/100,000 and mortality of 3.4/100,000.[2] For patients with Federation International of Gynecology and Obstetrics stage IB1–IIA2 cervical cancer, treatment of choice consists of radical hysterectomy (RH) with pelvic lymphadenectomy or concurrent chemoradiotherapy.[1,3] Compared with concurrent chemoradiotherapy, RH can provide more accurate staging information, remove the primary tumor, thereby obviating the

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/OTT.S99874

need for brachytherapy and reducing the risk of fibrosis of the vagina, preserve ovarian function in selected cases, dissect the bulky (2–3 cm) positive nodes that are less likely to be sterilized with primary radiation, and detect the lymph node involvement which guides decisions about subsequent radiotherapy.[4–7] For these advantages, RH is an important and viable alternative for operable patients.

Gynecologic oncology is a unique subspecialty involved in the care of women with gynecologic cancers, which combines expertise in women's health, medicine, surgery, and oncology. Compared with gynecologists in other subspecialties, such as urogynecologists, general gynecologists, and subspecialists in reproductive endocrinology and infertility, gynecologic oncologists (GOs) often spend a large proportion of time in learning specific surgical skills that are necessary to manage gynecologic malignancies, so they may offer a much more meticulous surgery, which would translate into an improved survival. However, this potential association is based on conjecture, rather than evidence. We therefore conducted a retrospective cohort study and investigated the hypothesis that for cervical cancer patients who are treated with RH, the subspecialty of the referring gynecologist would affect their surgical and survival outcomes.

Materials and methods

Patients

After obtaining approval from the Ethics Review Board of Sun Yat-sen Memorial Hospital, we reviewed the medical records of patients who received class III RH in Sun Yat-sen Memorial Hospital between January 2005 and June 2010. Inclusion criteria were: histologically confirmed invasive cervical cancer, age ≥16 years, and signed informed consent provided. Exclusion criteria were: patients with other metachronous or synchronous neoplasia, recurrent disease, metastatic disease, a history of previous radiation therapy, or a history of other types of malignancies or cervical melanoma.

Prior to surgery, all patients received a thorough evaluation which consisted of a complete physical and gynecologic examination, chest radiography, pelvic ultrasonography, and laboratory tests. Cystoscopy, sigmoidoscopy, and magnetic resonance imaging were performed only on clinical indication. Gynecologic examination was carried out by at least two senior gynecologists. The tumors were classified according to the Federation International of Gynecology and Obstetrics staging system.[3] All slides were examined by at least two authorized pathologists from our institution. Adjuvant radiotherapy was given to patients with positive parametrium, positive lymph nodes, or involved surgical margins, and patients with at least two of the following risk factors: greater than a third stromal invasion, lymphatic vascular space involvement, or tumor diameters ≥4 cm.[8] Postsurgical adjuvant chemotherapy was given at the discretion of the treating gynecologist.

After treatment, patients were followed up every 3 months for 2 years, every 6 months for the next 3 years, and once per year thereafter. Follow-up visits included physical examination and a Papanicolau smear of the vaginal vault.

A patient was considered as having seen a GO if her treating gynecologist was a member of the Gynecologic Oncology Society of the Chinese Medical Association. If an RH was performed as described in Rock's book, *TeLinde's Operative Gynecology*, it was defined as having adhered to surgical guidelines.[9] Follow-up information was obtained from office visits or telephone interviews. All events in our cohort were identified until death, loss to follow-up, or last follow-up. Cervical cancer-specific survival (CSS) was measured in months from the date of primary surgery until the date of death from cervical cancer or date of last follow-up. Recurrence-free survival (RFS) was defined as the length of time (in months) from the primary surgery to initial diagnosis of recurrence or date of last follow-up. Recurrence was confirmed by biopsy or imaging examinations. In the current study, more than half of the enrolled patients had locally advanced cervical cancer (LACC) (tumors of ≥4 cm in diameter). Because the optimal management of this patient subgroup is controversial, these patients were analyzed separately. Overall, the present study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[10] The study complied with the Declaration of Helsinki and was approved by the ethics review board of Sun Yat-sen Memorial Hospital (Permit Number: 201509132).

Statistical analyses

Continuous variables were tested for normality by use of the Kolmogorov–Smirnov test. Normally distributed continuous variables were compared with the use of the standard Student's *t*-test, whereas continuous data with nonnormal distribution were compared by means of the Mann–Whitney *U*-test. Frequency distributions between categorical variables were analyzed with the use of the Chi-square test (χ^2) or Fisher's exact test as appropriate. Kaplan–Meier survival curves were developed, and a log-rank test was used for the comparison of RFS and CSS. Cox proportional hazard models were used to identify the predictors for RFS and CSS. Variables that were statistically significant in the univariate

Cox regression analysis were included in a multivariate analysis. A forward stepwise progression procedure was used with a significance level of 0.10 for removing variables. All tests were two-sided and a *P*-value <0.05 was considered to be statistically significant. SPSS software (version 13.0, SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Clinical characteristics of the study population

Of the 839 patients that were included in the present study, 553 (65.91%) were treated by GOs (GO group), while 286 (34.09%) were treated by other subspecialties (non-GO group). Demographic and clinicopathologic characteristics of the patients are summarized in Table 1. There were some differences between the two groups. Specifically, patients in the GO group were older (median, 53 vs 51 years, *P*=0.045), more likely to have comorbidities (50.8% vs 27.6%, *P*<0.0001), had a lower incidence of positive surgical margin (2.2% vs 7.3%, *P*<0.0001), and less likely to be treated with neoadjuvant chemotherapy (NACT) (14.1% vs 31.1%, *P*<0.0001).

Operative characteristics and complications

Table 2 displays the operative characteristics and complications. Compared with the non-GO group, greater compliance with surgical guidelines was found in the GO group (*P*=0.003). Furthermore, more patients in the GO group received para-aortic lymph node sampling and dissection (9.8% vs 5.6%, *P*=0.038). Among patients in the GO group, we noted a shorter operative time (median, 180 vs 270 minutes, *P*<0.0001), less

Table 1 Baseline characteristics of the study population

	GO group (n=553)	Non-GO group (n=286)	*P*-value
Age (years), median (range)	53 (23–82)	51 (26–70)	0.045
BMI (kg/m^2), median (range)	23.2 (17.5–31.0)	23.1 (17.8–30.2)	0.436
Smoking, n (%)			
Never	525 (94.9)	261 (91.3)	0.093
Former	13 (2.4)	9 (3.1)	
Current	3 (0.5)	1 (0.3)	
Missing data	12 (2.2)	15 (5.2)	
Regular screening, n (%)			
No	477 (86.3)	230 (80.4)	0.080
Yes	45 (8.1)	31 (10.8)	
Missing data	31 (5.6)	25 (8.7)	
Stage, n (%)			
IB1	139 (25.1)	76 (26.6)	0.897
IB2	145 (26.2)	72 (25.2)	
IIA1	128 (23.1)	70 (24.5)	
IIA2	141 (25.5)	68 (23.8)	
Tumor histology, n (%)			
Squamous cell	464 (83.9)	244 (85.3)	0.822
Adenocarcinoma[a]	61 (11.0)	30 (10.5)	
Other[b]	28 (5.1)	12 (4.2)	
Size of tumor (cm), n (%)			
<1	22 (4.0)	19 (6.6)	0.072
1 to <2	19 (3.4)	16 (5.6)	
2 to <3	76 (13.7)	26 (9.1)	
3 to <4	150 (27.1)	83 (29.0)	
>4	286 (51.7)	142 (49.7)	
Comorbidity, n (%)			
0	272 (49.2)	207 (72.4)	<0.0001
1	133 (24.1)	40 (14.0)	
>2	148 (26.8)	39 (13.6)	
Differentiation, n (%)			
1	321 (58.0)	172 (60.1)	0.823
2	158 (28.6)	79 (27.6)	
3	74 (13.4)	35 (12.2)	

(*Continued*)

Table 1 (*Continued*)

	GO group (n=553)	Non-GO group (n=286)	*P*-value
Deep stromal invasion, n (%)			
Yes	319 (57.7)	157 (54.9)	0.439
No	234 (42.3)	129 (45.1)	
LVSI, n (%)			
Yes	217 (39.2)	106 (37.1)	0.539
No	336 (60.8)	180 (62.9)	
Positive margins, n (%)			
Yes	12 (2.2)	21 (7.3)	<0.0001
No	541 (97.8)	265 (92.7)	
Positive nodes, n (%)			
Yes	186 (33.6)	79 (27.6)	0.776
No	367 (66.4)	207 (72.4)	
Positive parametrium, n (%)			
Yes	20 (3.6)	18 (6.3)	0.771
No	533 (96.4)	268 (93.7)	
NACT, n (%)			
Yes	78 (14.1)	89 (31.1)	<0.0001
No	475 (85.9)	197 (68.9)	
Adjuvant CT, n (%)			
Yes	162 (29.3)	114 (39.9)	0.002
No	391 (70.7)	172 (60.1)	
CCRT, n (%)			
Yes	312 (56.4)	161 (56.3)	0.972
No	241 (43.6)	125 (43.7)	

Note: [a]Including adenocarcinoma and adenosquamous carcinoma; [b]including clear cell carcinoma and neuroendocrine carcinoma.
Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation; CT, chemotherapy; GO, gynecologic oncologist; LVSI, lymphatic vascular space involvement; NACT, neoadjuvant chemotherapy.

Table 2 Operative characteristics and complications

	GO group (n=553)	Non-GO group (n=286)	*P*-value
Para-aortic lymph node sampling/dissection, n (%)	54 (9.8)	16 (5.6)	0.038
Surgical guidelines			
Followed	466 (84.3)	213 (74.5)	0.003
Not followed	50 (9.0)	41 (14.3)	
Unknown	37 (6.7)	32 (11.2)	
Operative time (min), median (range)	180 (120–300)	270 (180–600)	<0.0001
Estimated blood loss (mL), median (range)	350 (200–1,500)	425 (200–1,500)	<0.0001
Blood transfusion, n (%)	149 (26.9)	96 (33.6)	0.046
No of lymph nodes removed, median (range)	25 (16–33)	24 (18–33)	0.033
Hospital stay (day), median (range)	16 (10–21)	16 (10–21)	0.005
Duration until PVR <100 mL (day), median (range)	16 (12–28)	10 (7–28)	<0.0001
Intraoperative complications, n (%)			
Cystotomy	3 (0.5)	7 (2.4)	0.038
Ureteric injury	8 (1.4)	7 (3.8)	0.027
Vascular injury	6 (1.1)	3 (1.0)	1.000
Bowel injury	3 (0.5)	1 (0.3)	1.000
Postoperative complications, n (%)			
Cellulitis	13 (2.4)	2 (0.7)	0.087
Lymphocyst infection	22 (4.0)	4 (1.4)	0.041
Bowel obstruction	12 (2.2)	4 (1.4)	0.439
Fistula formation	2 (0.4)	3 (3.1)	0.002
Deep vein thrombosis	4 (0.7)	4 (1.4)	0.562
Pulmonary embolism	1 (0.2)	1 (0.3)	1.000

Abbreviations: GO, gynecologic oncologist; PVR, postvoid residual urine volume.

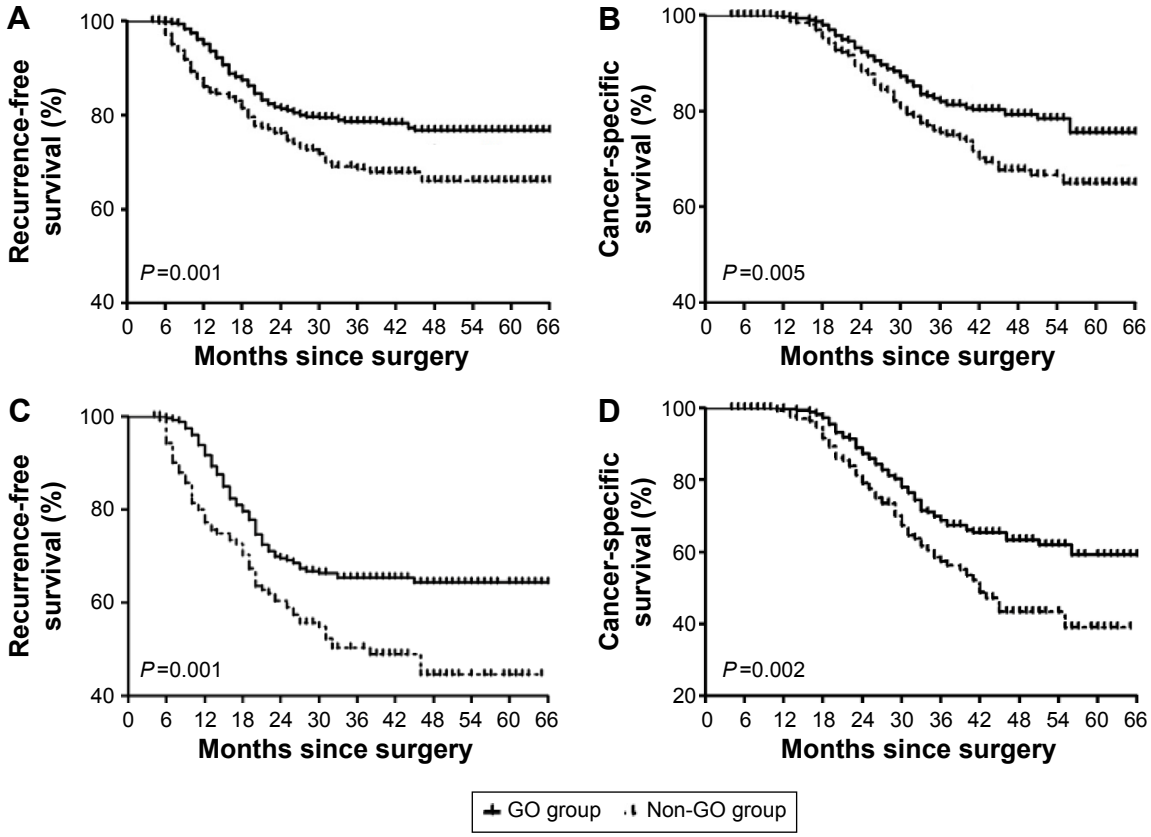

Figure 1 Survival of patients with cervical cancer treated with radical hysterectomy.

Notes: (**A**) Kaplan–Meier estimates of recurrence-free survival. The two groups are cervical cancer patients operated on by gynecologic oncologists and cervical cancer patients operated on by others. (**B**) Kaplan–Meier estimates of cancer-specific survival. The two groups are cervical cancer patients operated on by gynecologic oncologists and cervical cancer patients operated on by others. (**C**) Kaplan–Meier estimates of recurrence-free survival. The two groups are cervical cancer patients with locally advanced disease who are operated on by gynecologic oncologists and cervical cancer patients who are operated on by others. (**D**) Kaplan–Meier estimates of cancer-specific survival. The two groups are cervical cancer patients with locally advanced disease who are operated on by gynecologic oncologists and cervical cancer patients who are operated on by others.

estimated blood loss (median, 350 vs 425 mL, $P<0.0001$), lower transfusion rate (26.9% vs 33.6%, $P=0.046$), more removed nodes (median, 25 vs 24, $P=0.033$), longer length of hospital stay (median, 16 vs 16 days, $P=0.005$), and longer duration until postvoid residual urine volume <100 mL per day (16 vs 10 days, $P<0.0001$). In terms of the intraoperative complications, patients in the non-GO group experienced more ureteric injury (1.4% vs 3.8%, $P=0.027$) and cystotomy (0.5% vs 2.4%, $P=0.038$). Regarding the risk of postoperative complications, more patients in the GO group experienced lymphocyst infection (4.0% vs 1.4%, $P=0.041$), whereas the incidence of fistula formation was lower in the GO group (0.4% vs 3.1%, $P=0.002$).

Survival

Survival outcomes

With a median follow-up of 36 months, 116 patients in the GO group (21.0%) and 86 patients in the non-GO group (30.1%) experienced recurrence, and the median overall recurrence was not reached in either group. The cumulative 5-year RFS rates were 79.0% and 69.9% in the GO and non-GO groups, respectively. A comparison of Kaplan–Meier curves for RFS showed a significant difference between the two groups ($P=0.001$; hazard ratio [HR] =0.64; 95% confidence interval [CI] [0.48, 0.84]) (Figure 1A). There were 95 (17.2%) cervical cancer-related deaths in the GO group, compared to 73 (25.5%) in the non-GO group. The cumulative 5-year CSS of patients in the GO group was 82.8% compared with 74.5% for those in the non-GO group. A comparison of Kaplan–Meier curves for CSS demonstrated that the difference between the two groups was statistically significant ($P=0.005$; HR=0.64; 95% CI [0.47, 0.87]) (Figure 1B).

Univariate and multivariate analysis for survival

Table 3 summarizes the univariate and multivariate analyses results for RFS. Univariate analysis showed care from

Table 3 Cox proportional hazard model of potential factors associated with recurrence-free survival in patients with cervical cancer

	Recurrence-free survival					
	Univariate analysis			Multivariate analysis		
	P-value	HR	95% CI	*P*-value	HR	95% CI
Care from a GO (yes vs no)	0.002	0.64	(0.48, 0.84)	<0.0001	0.57	(0.42, 0.76)
Age	0.507	1.01	(0.99, 1.02)	–	–	–
BMI (kg/m^2)	0.518	0.98	(0.93, 1.04)	–	–	–
Tumor histology (nonsquamous vs squamous)	<0.0001	2.44	(1.80, 3.32)	<0.0001	1.96	(1.43, 2.70)
Tumor stage	<0.0001	1.37	(1.21, 1.55)	–	–	–
Tumor differentiation (G1–2 vs G3)	0.050	1.44	(1.00, 2.07)	–	–	–
LACC (yes vs no)	<0.0001	5.09	(3.56, 7.28)	0.028	0.51	(0.28, 0.93)
Deep stromal invasion (yes vs no)	<0.0001	5.81	(3.87, 8.71)	–	–	–
LVSI (yes vs no)	<0.0001	2.86	(2.15, 3.80)	–	–	–
Positive margins (yes vs no)	0.001	4.76	(3.08, 7.36)	0.001	2.15	(1.36, 3.40)
Positive nodes (yes vs no)	<0.0001	5.28	(3.94, 7.07)	<0.0001	2.70	(1.93, 3.78)
Positive parametrium (yes vs no)	<0.0001	4.84	(3.22, 7.27)	0.024	1.64	(1.07, 2.53)
Presence of a combination of high-risk factors[a] (yes vs no)	<0.0001	7.66	(5.14, 11.44)	<0.0001	7.85	(3.98, 15.46)
NACT (yes vs no)	<0.0001	2.59	(1.94, 3.45)	–	–	–

Note: [a]High-risk factors include LACC, LVSI and greater than one-third stromal invasion.
Abbreviations: BMI, body mass index; GO, gynecologic oncologist; LACC, locally advanced cervical cancer; LVSI, lymphatic vascular space involvement; NACT, neoadjuvant chemotherapy; HR, hazard ratio; CI, confidence interval.

a GO was found to be associated with RFS (Table 3). On multivariate analysis, care from a GO was identified as an independent factor of an improved RFS. Table 4 summarizes the univariate and multivariate analysis results for CSS. After adjustment for other prognostic factors, multivariate analysis demonstrated that the treatment provided by a GO was an independent predictor of an improved CSS.

Subgroup analysis for patients with LACC

Of the 839 patients, 428 (51.0%) had LACC (286 in the GO group and 142 in the non-GO group). The cumulative 5-year RFS and CSS for LACC patients in the GO group was 66.4% and 69.9% compared with 51.4% and 57.0% for LACC patients in the GG group. The Kaplan–Meier curves and log-rank tests are displayed in Figure 1C and D, with significant differences in RFS (*P*=0.001; HR=0.55; 95% CI [0.39, 0.77]) and CSS (*P*=0.002; HR=0.57, 95% CI [0.40, 0.82]). Univariate and multivariate Cox proportional hazard analysis showed that care by GOs was associated with a significant improvement in RFS and CSS (Table 5).

Of the 428 patients with LACC, NACT was given to 162 (37.9%). The cumulative 5-year RFS and CSS for patients who underwent NACT was 56.2% and 60.5% compared with 64.7% and 68.8% for patients who did not receive NACT. No significant differences were found in RFS (*P*=0.105; HR=1.29; 95% CI [0.95, 1.76]) or CSS (*P*=0.096; HR=1.32; 95% CI [0.95, 1.83]) between the two groups categorized by NACT.

In univariate analysis, the use of NACT was not a significant predictive factor of RFS or CSS for patients with LACC. To explore the factors that were associated with the use of NACT, we conducted a multivariable stepwise linear-regression analysis. After adjusting for other confounders that included patient age, body mass index, tumor histology (nonsquamous vs squamous), and tumor Federation International of Gynecology and Obstetrics stage (IIA2 vs IB2), we found patients who did not undergo surgery by a GO (*P*<0.0001; OR=0.25; 95% CI [0.16, 0.39]) and those with poorly differentiated tumors (G3) (*P*=0.013; OR=0.45; 95% CI [0.24, 0.84]) were more likely to receive NACT.

Table 4 Cox proportional hazard model of potential factors associated with cancer-specific survival in patients with cervical cancer

	Cancer-specific overall survival					
	Univariate analysis			Multivariate analysis		
	P-value	HR	95% CI	*P*-value	HR	95% CI
Care from a GO (yes vs no)	0.005	0.64	(0.47, 0.87)	0.001	0.58	(0.42, 0.81)
Age	0.844	1.00	(0.99, 1.02)	–	–	–
BMI (kg/m^2)	0.947	1.00	(0.94, 1.06)	–	–	–
Tumor histology (NSQ vs SQ)	<0.0001	2.76	(1.99, 3.83)	<0.0001	2.18	(1.55, 3.06)
Tumor stage	<0.0001	1.50	(1.30, 1.72)	–	–	–
Tumor differentiation (G1–2 vs G3)	0.009	1.67	(1.14, 2.46)	–	–	–
LACC (yes vs no)	<0.0001	8.20	(5.19, 12.96)	–	–	–
Deep stromal invasion (yes vs no)	<0.0001	10.10	(5.84, 17.46)	–	–	–
LVSI (yes vs no)	<0.0001	3.53	(2.56, 4.87)	–	–	–
Positive margins (yes vs no)	<0.0001	5.36	(3.41, 8.41)	0.001	2.32	(1.44, 3.72)
Positive nodes (yes vs no)	<0.0001	6.81	(4.86, 9.54)	<0.0001	2.85	(1.97, 4.14)
Positive parametrium (yes vs no)	<0.0001	5.58	(3.64, 8.56)	0.022	1.69	(1.08, 2.66)
Presence of a combination of high-risk factors[a] (yes vs no)	0.001	13.79	(7.98, 23.85)	<0.0001	7.36	(4.10, 13.21)
NACT (yes vs no)	<0.0001	2.91	(2.13, 3.97)	–	–	–

Note: [a]High-risk factors include LACC, LVSI, and greater than one-third stromal invasion.
Abbreviations: BMI, body mass index; GO, gynecologic oncologist; LACC, locally advanced cervical cancer; LVSI, lymphatic vascular space involvement; NACT, neoadjuvant chemotherapy; NSQ, nonsquamous; SQ, squamous; HR, hazard ratio; CI, confidence interval.

Discussion

There is growing evidence that physicians with different subspecialty backgrounds affect treatment outcomes of patients with malignant disease.[11–13] However, for cervical cancer patients, this possible association has received little attention. We explored this hypothesis in the current study and did find significant differences in surgical and survival outcomes between patients who underwent RH by a GO and those who underwent RH by a non-GO. Our data suggest GOs confer significant benefit in terms of a shorter operative time, less estimated blood loss, lower transfusion rate, more removed nodes, and lower risks of cystotomy, ureteric injury, and postsurgical fistula formation. Furthermore, surgery performed by a GO has positive influence on survival rates, which could reduce the risk of disease recurrence and death from cancer by more than 35%, and this survival benefit even remains significant among patients with LACC.

More than 80% of our cohort did not receive regular cervical cancer screening. An important reason for the result is that an up to date, well-organized, nationwide cervical cancer screening system has not been established in People's Republic of China.[14,15] In fact, among women who live in remote areas with limited access to health services, the basic awareness of the benefit of screening for cervical cancer is lacking.[14] Because tumors cannot be detected at an early stage or in a precancerous lesion, a proportion of patients have advanced disease at the time of diagnosis. This could also provide an explanation for our finding that more than 50% of the study population were diagnosed with LACC. Additionally, we found patients treated by GOs tended to be older, have a higher incidence of comorbidity, and have larger tumors. Considering the fact that there is no comprehensive referral system for women with gynecologic cancers in People's Republic of China and whether a patient is treated by a GO or a non-GO largely depends on patients' choice, we believe patients with multiple comorbidities and those with larger tumor would tend to select GOs and receive specialized diagnostic workup, treatment, and care.

Our multivariate analysis showed that care from a GO was an independent predictor of improved RFS and CSS; even in

Table 5 Cox proportional hazard model of potential factors associated with disease-free survival and cancer-specific survival in patients with locally advanced cervical cancer

	Disease-free survival						Cancer-specific overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	P-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI
Care from a GO (yes vs no)	0.001	0.59	(0.43, 0.80)	0.001	0.59	(0.42, 0.81)	0.003	0.60	(0.44, 0.84)	0.007	0.62	(0.44, 0.88)
Age	0.436	1.01	(0.99, 1.02)	–	–	–	0.429	1.01	(0.99, 1.03)	–	–	–
BMI (kg/m^2)	0.925	1.00	(0.94, 1.06)	–	–	–	0.874	1.00	(0.94, 1.06)	–	–	–
Tumor histology (NSQ vs SQ)	<0.0001	1.92	(1.35, 2.73)	0.007	1.65	(1.14, 2.38)	<0.0001	2.22	(1.55, 3.18)	0.001	1.89	(1.30, 2.75)
Tumor stage (IIA2 vs IB2)	0.700	0.94	(0.70, 1.27)	–	–	–	0.844	0.97	(0.70, 1.33)	–	–	–
Tumor differentiation (G3 vs G1–2)	0.181	1.31	(0.88, 1.93)	–	–	–	0.049	1.50	(1.00, 2.24)	0.036	1.54	(1.03, 2.31)
Deep stromal invasion (yes vs no)	0.005	2.77	(1.36, 5.65)	–	–	–	0.003	3.45	(1.52, 7.82)	–	–	–
LVSI (yes vs no)	0.097	1.32	(0.95, 1.82)	–	–	–	0.039	1.44	(1.02, 2.05)	–	–	–
Positive margins (yes vs no)	<0.0001	3.82	(2.41, 6.06)	0.001	2.31	(1.42, 3.75)	<0.0001	4.00	(2.51, 6.37)	<0.0001	2.63	(1.62, 4.28)
Positive nodes (yes vs no)	<0.0001	3.34	(2.31, 4.82)	0.000	3.13	(2.15, 4.56)	<0.0001	3.57	(2.40, 5.32)	<0.0001	3.21	(2.13, 4.84)
Positive parametrium (yes vs no)	<0.0001	2.96	(1.94, 4.51)	0.017	1.71	(1.10, 2.65)	<0.0001	3.14	(2.02, 4.88)	0.010	1.84	(1.16, 2.92)
NACT (yes vs no)	0.105	1.29	(0.95, 1.76)	–	–	–	0.096	1.32	(0.95, 1.83)	–	–	–

Abbreviations: BMI, body mass index; GO, gynecologic oncologist; LVSI, lymphatic vascular space involvement; NACT, neoadjuvant chemotherapy; NSQ, nonsquamous; SQ, squamous; HR, hazard ratio; CI, confidence interval.

the subgroup of patients with LACC, its positive influence remains significant. Differences in the radicality and extent of lymphadenectomy might explain some differences in patient outcomes by the subspecialty of a gynecologist. Published evidence has shown that a larger number of lymph nodes removed are related to a better survival for patients with cervical cancer.[16,17] In the present study, more lymph node yield was noted in the GO group, which suggests that GOs can allow a more thorough lymphadenectomy (Table 2). As lymph node micrometastases are independently associated with poor survival,[18] and those with greater numbers of lymph nodes analyzed are more likely to have lymph node micrometastases detected,[19] patients who receive care from GOs would benefit more from pelvic lymphadenectomy. In addition, compared with patients in the non-GO group, more patients in the GO group received para-aortic lymph node sampling and dissection. Therefore, patients with occult para-aortic nodal metastasis are more possible to be identified by GOs, and thus have a much better chance to receive timely extended-field radiation and an improved survival.[20,21] We believe the differences in the number of removed lymph nodes may be related to the surgical dexterity. GOs usually own more proficient surgical skills compared with non-GOs and thus they have the capacity to deliver a much more radical lymphadenectomy. For the same reason, when para-aortic nodal enlargement is suspicious, they are more likely to perform para-aortic lymphadenectomy, which is associated with an increased risk of unmanageable bleeding of retroperitoneal blood vessels.

Variation in patient outcomes by subspecialty would also be related to the radicality of RH. Patients in the GO group were observed to experience a much longer duration until postvoid residual urine volume <100 mL per day (Table 2). Bladder dysfunction after RH results from the injury to the pelvic autonomic nerves that supply to the muscle of the bladder,[22] and the more radical the surgery, the more severe the postoperative bladder dysfunction.[23] Considering this fact and our finding that GOs have greater compliance with surgical guidelines than other subspecialists, including urogynecologists, general gynecologists, and subspecialists in reproductive endocrinology and infertility (Table 2), we believe GOs have greater capacities to offer adequate surgical extent. In addition, consistent with published evidence, our analysis identified positive surgical margin as an independent factor of poor survival (Tables 3 and 4).[1] Because positive surgical margins were more frequently detected in patients of

the non-GO group, from an oncological perspective, GOs will be more likely to ensure the radicality of RH and therefore better disease control.

NACT combined with RH has been used for several years in People's Republic of China.[7] In our study, NACT was prescribed to ~38% of patients with LACC (Table 1). NACT helps decrease tumor volume thereby making patients with clinically inoperable disease surgically amenable, increase the possibility of obtaining a wider negative surgical margin, and decrease the risk of lymph node metastasis.[24–27] Because of these advantages, in many parts of the world, such as Asia, Italy, and South America, NACT is used in up to 25% of patients.[28] Nevertheless, these benefits should be weighed against the potential risks. First, NACT can result in a longer duration of treatment, accelerate the repopulation of resistant cancer cells, and induce tumor cells to produce cross-resistance with radiotherapy.[29–31] Second, for patients with persistent lymph nodes metastasis, NACT has proven to be detrimental to survival.[32] Third, after NACT and RH, if radiotherapy is delivered, substantial morbidity will result from a combination of these three treatment modalities.[27] Finally, it should be noted that data in support of NACT are from only a small number of trials, and most of these trials are retrospective.[27] Since there is no definitive evidence that the use of NACT can translate into improvements in survival, we concur with the National Comprehensive Cancer Network guideline and consider NACT as not a necessary treatment for patients with LACC.[1] In the current study, more patients in the non-GO group received NACT; moreover, our multivariate analysis identified physicians who were not specialized in GO were independently associated with the utility of this treatment strategy. Considering the potential detrimental effects associated with NACT, we argue that GOs are more able to treat patients without unnecessary treatment or undue morbidity. A possible reason for the discrepancy between GOs' attitude and non-GOs' attitude to the utility of NACT could be that non-GOs may consider the tumor-size reduction after NACT helps the surgery achieve much wider resection margins. On the other hand, GOs follow current guidelines more strictly and tend to treat patients without unnecessary treatment or undue morbidity. Moreover, their surgical skills ensure an adequate tumor-free surgical margin without other adjuvant treatment, including NACT.

Our study had some limitations. First, it is a retrospective study; because of a lack of randomization and blinding, there is unbalanced and unrecognized bias. Second, the objectivity of the current study is dependent on accurate charting and documentation, which at times could be incomplete or inaccurate. Third, our data only reflect a single-institution experience. As the study population was from a specific geographical area, further investigation at multiple centers is needed. Fourth, some patients received adjuvant chemotherapy after surgery and radiotherapy. It was given at the discretion of the treating physician, and different chemotherapeutic regimens were used, so its exact impact on patient outcomes could not be clarified. Fifth, patient follow-up was performed by several physicians in our hospital, and hence the observational bias of recurrence events. Finally, not all patients received radiotherapy in the same institution, so the effect of variation in irradiation technique cannot be eliminated. The strengths of our study include the large sample size, relatively long duration of follow-up, and performance of the pathologic review by a single team of pathologists in our institution, which is particularly important if data on pathologic variables are analyzed. Moreover, to the best of our knowledge, this is the first study explicitly exploring the effects of physician subspecialty on outcomes of cervical cancer patients.

In conclusion, the present study identified the importance of the subspecialty of a gynecologist for cervical cancer patients. Because an RH that is performed by GOs affords an improvement in surgical and survival outcomes, and even among patients with LACC, this positive influence is still significant, we believe cervical cancer patients deserve to be referred to a center with GOs. Because of the limitations, we think further studies are warranted to confirm our conclusion.

Author contributions

All authors read and met the ICMJE criteria. BZZ and ZQL are coguarantors. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Koh WJ, Greer BE, Abu-Rustum NR, et al. Cervical cancer, Version 2. 2015. *J Natl Compr Canc Netw*. 2015;13:395–404.
2. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer*. 2013;132: 1133–1145.
3. Wiebe E, Denny L, Thomas G. Cancer of the cervix uteri. *Int J Gynaecol Obstet*. 2012;119(Suppl 2):S100–S109.
4. Boronow RC. The bulky 6-cm barrel-shaped lesion of the cervix: primary surgery and postoperative chemoradiation. *Gynecol Oncol*. 2000; 78:313–317.
5. Hacker NF, Wain GV, Nicklin JL. Resection of bulky positive lymph nodes in patients with cervical carcinoma. *Int J Gynecol Cancer*. 1995; 5:250–256.

6. Kupets R, Thomas GM, Covens A. Is there a role for pelvic lymph node debulking in advanced cervical cancer? *Gynecol Oncol.* 2002;87: 163–170.
7. Hu T, Li S, Chen Y, et al. Matched-case comparison of neoadjuvant chemotherapy in patients with FIGO stage IB1-IIB cervical cancer to establish selection criteria. *Eur J Cancer.* 2012;48:2353–2360.
8. 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;73:177–183.
9. Chi DS, Abu-Rustum NR, Plante M, Roy M. Cancer of the cervix. In: Rock JA, Jones HW, editors. *TeLinde's Operative Gynecology*, 10th ed. Philadelphia: Lippincott Williams and Wilkins; 2008: 1227.
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP; STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453–1457.
11. Chan JK, Kapp DS, Shin JY, et al. Influence of the gynecologic oncologist on the survival of ovarian cancer patients. *Obstet Gynecol*. 2007; 109:1342–1350.
12. Read TE, Myerson RJ, Fleshman JW, et al. Surgeon specialty is associated with outcome in rectal cancer treatment. *Dis Colon Rectum*. 2002;45:904–914.
13. Farjah F, Flum DR, Varghese TK Jr, Symons RG, Wood DE. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. *Ann Thorac Surg*. 2009;87:995–1004; discussion 1005–1006.
14. Goss PE, Strasser-Weippl K, Lee-Bychkovsky BL, et al. Challenges to effective cancer control in China, India, and Russia. *Lancet Oncol*. 2014;15:489–538.
15. Kang LN, Castle PE, Zhao FH, et al. A prospective study of age trends of high-risk human papillomavirus infection in rural China. *BMC Infect Dis*. 2014;14:96.
16. Ditto A, Martinelli F, Lo Vullo S, et al. The role of lymphadenectomy in cervical cancer patients: the significance of the number and the status of lymph nodes removed in 526 cases treated in a single institution. *Ann Surg Oncol*. 2013;20:3948–3954.
17. Pieterse QD, Kenter GG, Gaarenstroom KN, et al. The number of pelvic lymph nodes in the quality control and prognosis of radical hysterectomy for the treatment of cervical cancer. *Eur J Surg Oncol*. 2007;33:216–221.
18. Horn LC, Hentschel B, Fischer U, Peter D, Bilek K. Detection of micrometastases in pelvic lymph nodes in patients with carcinoma of the cervix uteri using step sectioning: Frequency, topographic distribution and prognostic impact. *Gynecol Oncol*. 2008;111:276–281.
19. Lentz SE, Muderspach LI, Felix JC, Ye W, Groshen S, Amezcua CA. Identification of micrometastases in histologically negative lymph nodes of early-stage cervical cancer patients. *Obstet Gynecol*. 2004; 103:1204–1210.
20. Kim HJ, Ha SW, Wu HG. Treatment outcomes and prognostic factors in uterine cervical cancer patients treated with postoperative extended field radiation therapy. *J Gynecol Oncol*. 2009;20:227–231.
21. Stehman FB, Bundy BN, DiSaia PJ, Keys HM, Larson JE, Fowler WC. Carcinoma of the cervix treated with radiation therapy. I. A multi-variate analysis of prognostic variables in the Gynecologic Oncology Group. *Cancer*. 1991;67:2776–2785.
22. Zullo MA, Manci N, Angioli R, Muzii L, Panici PB. Vesical dysfunctions after radical hysterectomy for cervical cancer: a critical review. *Crit Rev Oncol Hematol*. 2003;48:287–293.
23. Marin F, Plesca M, Bordea CI, et al. Postoperative surgical complications of lymphadenohysterocolpectomy. *J Med Life*. 2014;7:60–66.
24. Sardi JE, Giaroli A, Sananes C, et al. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: the final results. *Gynecol Oncol*. 1997; 67:61–69.
25. Hwang YY, Moon H, Cho SH, et al. Ten-year survival of patients with locally advanced, stage ib-iib cervical cancer after neoadjuvant chemotherapy and radical hysterectomy. *Gynecol Oncol*. 2001;82:88–93.
26. Robova H, Halaska M, Pluta M, et al. The role of neoadjuvant chemotherapy and surgery in cervical cancer. *Int J Gynecol Cancer*. 2010; 20:S42–S46.
27. Colombo N, Peiretti M. Critical review of neoadjuvant chemotherapy followed by surgery for locally advanced cervical cancer. *Int J Gynecol Cancer*. 2010;20:S47–S48.
28. Ryu HS, Kang SB, Kim KT, Chang KH, Kim JW, Kim JH. Efficacy of different types of treatment in FIGO stage IB2 cervical cancer in Korea: results of a multicenter retrospective Korean study (KGOG-1005). *Int J Gynecol Cancer*. 2007;17:132–136.
29. Kim HS, Sardi JE, Katsumata N, et al. Efficacy of neoadjuvant chemotherapy in patients with FIGO stage IB1 to IIA cervical cancer: an international collaborative meta-analysis. *Eur J Surg Oncol*. 2013;39: 115–124.
30. Loizzi V, Cormio G, Vicino M, Selvaggi L. Neoadjuvant chemotherapy: an alternative option of treatment for locally advanced cervical cancer. *Gynecol Obstet Invest.* 2008;65:96–103.
31. Gonzalez-Martin A, Gonzalez-Cortijo L, Carballo N, et al. The current role of neoadjuvant chemotherapy in the management of cervical carcinoma. *Gynecol Oncol*. 2008;110:S36–S40.
32. Zanetta G, Colombo A, Milani R, Placa F, Mangioni C. Long-term results of sequential postoperative treatment with vincristine, bleomycin, mitomycin c, cis-platin and radiotherapy after surgery for high-risk patients with cervical carcinoma stage IB-IIA. *Int J Gynecol Cancer*. 1995;5:40–44.