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Clinical Investigation

Outcomes for Hyperthermia Combined with Concurrent Radiochemotherapy for Patients with Cervical Cancer

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Purpose: To evaluate the effect of hyperthermia combined with concurrent radiochemotherapy (RCT) and treatment-related toxicity in patients with cervical cancer (CC) stage IB-IV.

Methods and Materials: This study was conducted between 2009 and 2013 in patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB-IV CC. The patients were randomly assigned into 2 treatment groups: RCT and RCT plus hyperthermia (RCHT). Five-year survival, treatment-related toxicity, and other prognostic factors were evaluated.

Results: Three hundred seventy-three patients completed treatment and were analyzed by per-protocol (PP) analysis. The 5-year overall survival (OS) in the RCHT group (81.9%) was better than that in RCT group (72.3%), and the log-rank test showed a statistically significant difference between the 2 groups ($P = .040$). Univariate and multivariate Cox regression analysis for 5-year OS showed a statistically significant difference ($P = .043$, $P = .045$, respectively). The 5-year local relapse-free survival in RCHT (86.8%) was also better than that in RCT (82.7%), but the difference was not significant. Acute or late toxicity was not significantly different between the 2 groups. Advanced clinical stage (FIGO) and larger tumor size showed higher risk of death and a relatively poor prognosis in univariate and multivariate analysis.

Conclusions: The study confirmed that hyperthermia combined with RCT yielded a better 5-year OS in CC. Acute and late toxicity was similar between the RCT and RCHT groups. Clinical stage (FIGO) and tumor size were independent prognostic factors in CC.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Introduction

Patients with locally advanced cervical cancer (LACC) were usually treated with radiation therapy alone before 1990s. The survival rate was relatively poor, in the 30% to 50% range.[1,2] Since 1999, 5 randomized clinical trials from the Gynecologic Oncology Group, Radiation Therapy Oncology Group, and Southwestern Oncology Group have demonstrated a 30% to 50% lower risk of recurrence or death for cervical cancer (CC) treated with concurrent chemotherapy (CT) and radiation therapy (RT), compared with RT alone.[3-7] Therefore, on the basis of these trials, the National Cancer Institute issued a clinical alert in 1999 that "women who need RT for CC should strongly consider the incorporation of concurrent RCT." Since then, concurrent RCT has become the standard treatment for the LACC in most areas of the world.

Another clinical trial conducted by the Dutch Deep Hyperthermia Group was published in *The Lancet* in 2000.[8] In this trial, the group reported that hyperthermia (HT) plus RT for LACC rendered better local control and 3-year survival compared with RT alone. Twelve-year long-term survival data subsequently confirmed the advantage of HT + RT for LACC.[9] To date, several clinical trials have contributed to an understanding of the feasibility and effect of HT in LACC[8-11] and showed that the combination of HT and RT can increase local control and survival rates.

Because concurrent RCT is the recommended treatment for LACC, and HT + RT can also improve its efficacy, would the trimodality combination approach be better? No more reliable data from a prospective, randomized trial with a large sample have supported this. A prospective, randomized trial of 101 patients showed that the triple-modality treatment increased complete response but not survival for patients with LACC.[12] Until the long-term survival data from the trimodality study become available, further study is necessary.

Based on the feasibility and safety of our previous clinical trial of HT combined with RCT for patients with CC, we conducted a randomized, controlled clinical trial to investigate the long-term survival and toxicity of 3 combination treatment modalities (RT, CT, and HT) for patients with CC.

Methods and Materials

Patients

A total of 449 patients with CC between 2009 and 2013 were recruited into this randomized clinical trial. The trial has been approved by the ethics committee, and informed consent was obtained from all patients.

The inclusion criteria included (1) age between 25 and 70 years; (2) Karnofsky performance status $\geq$70; (3) International Federation of Gynecology and Obstetrics (FIGO, 2009) stages IB-IV; (4) no prior RT, CT, or surgery; (5) histologically confirmed cervical squamous carcinoma; (6) no RT and CT contraindications and no HT contraindications (no cardiac pacemaker, no body metal); (7) normal blood routine and liver and renal function, no vital organ function failure; and (8) no double primary cancer (no malignancy except CC).

Exclusion criteria included (1) unfinished prescribed treatment of RT or CT (intolerable RT or CT), <2 HT; and (2) lost to follow-up (did not return for scheduled follow-up or could not be contacted when following up for 5 years).

Before initiation of treatment, eligible participants were randomized into 2 groups (RCT and RCT + HT) according to a computer-generated random number list.

Treatment

Radiochemotherapy

All patients received external beam RT (EBRT) using 6 or 10 MV high-energy linear accelerators. The radiation was delivered to the tumor in a fraction of 1.8 to 2.0 Gy per day, 5 days per week, with 3-dimensional conformal RT or intensity modulated RT, to a total dose of 50.4 Gy or 50 Gy. Target areas included the upper vaginal segment, cervix, uterine body, pelvic lymph node drainage area (parauterine, obturator foramen, internal iliac, external iliac, common iliac, up to the bifurcation of the aorta). After EBRT, high-dose-rate intracavitary brachytherapy was performed in patients, delivering a further dose of D_T 5 Gy/fraction, twice every week for 4 or 5 fractions, to a total dose of D_T 20 to 25 Gy to point A using the remote afterloading technique. Additionally, 1 week after the first EBRT, all patients were treated with a cisplatin and 5-fluorouracil regimen: cisplatin 30 mg/m^2, d1-3; 5-fluorouracil 350 mg/m^2, d1-5. One cycle of CT was given concurrently with the RT. There were 47 patients (12.6%) who received more than 1 cycle of adjuvant CT after the concurrent RCT.

Hyperthermia

After CT (namely, the third week after the first EBRT) HT was delivered to the patients enrolled in the RCHT group using the NRL-004 radiofrequency HT machine (Jilin, China). The factory-calibrated power is 1500 W, and the frequency is 30.32 MHz and 40.68 MHz. Four orthogonality thermode applicators were placed in the lower abdomen centered on the uterus and cervix, including the cervical lesions, pelvic lymphatic drainage areas, and invaded vagina. A pair of thermode applicators was situated anteroposterior and another pair bilaterally. The 4 thermode applicators worked simultaneously at 2 different frequencies. The temperature was monitored by the

thermometric detector in the vagina and rectum. The temperature was kept at an average of 40.5°C (range, 39.5°C-41.5°C) for 60 minutes, twice a week, for a total of 6 fractions. The equipment could reach the predetermined temperature after heating for more than 10 minutes. Temperature was adjusted according to the thermal sensitivity of each patient to achieve the treatment temperature, and a water sac was used to cool between the applicator and the skin to prevent burns. RT was given within 1 hour after HT. Because several patients refused to continue HT because they could not afford treatment, 17 patients (4.56%) received fewer than 6 HT fractions.

Study endpoints

The primary endpoints were 5-year overall survival (OS) and late toxicity. Secondary endpoints included locoregional relapse–free survival (LRFS) and acute toxicity. Late toxicity (effects occurring 3 months after last RT) was scored according Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria.[13] Acute toxicity was scored using the Radiation Therapy Oncology Group morbidity scale.[14]

Study design

This was an open-label, prospective, randomized clinical trial. Randomization was done by using a computer-generated random number list. A 1-sided test was used for a slightly smaller sample size requirement, and it was justified because of the hypothesized benefit of HT + RCT. With a 1-sided .05 significance level log-rank test, 430 patients were needed for a power of 0.85 if the 5-year survival rates were 66% and 76% (equivalent to a hazard ratio of 1.51) for RCT and HT + RCT, respectively. The 66% survival rate for RCT was based on our previous trial data and the prediction that the HT + RCT survival rate would increase by 10%, from 66% to 76%. The calculation

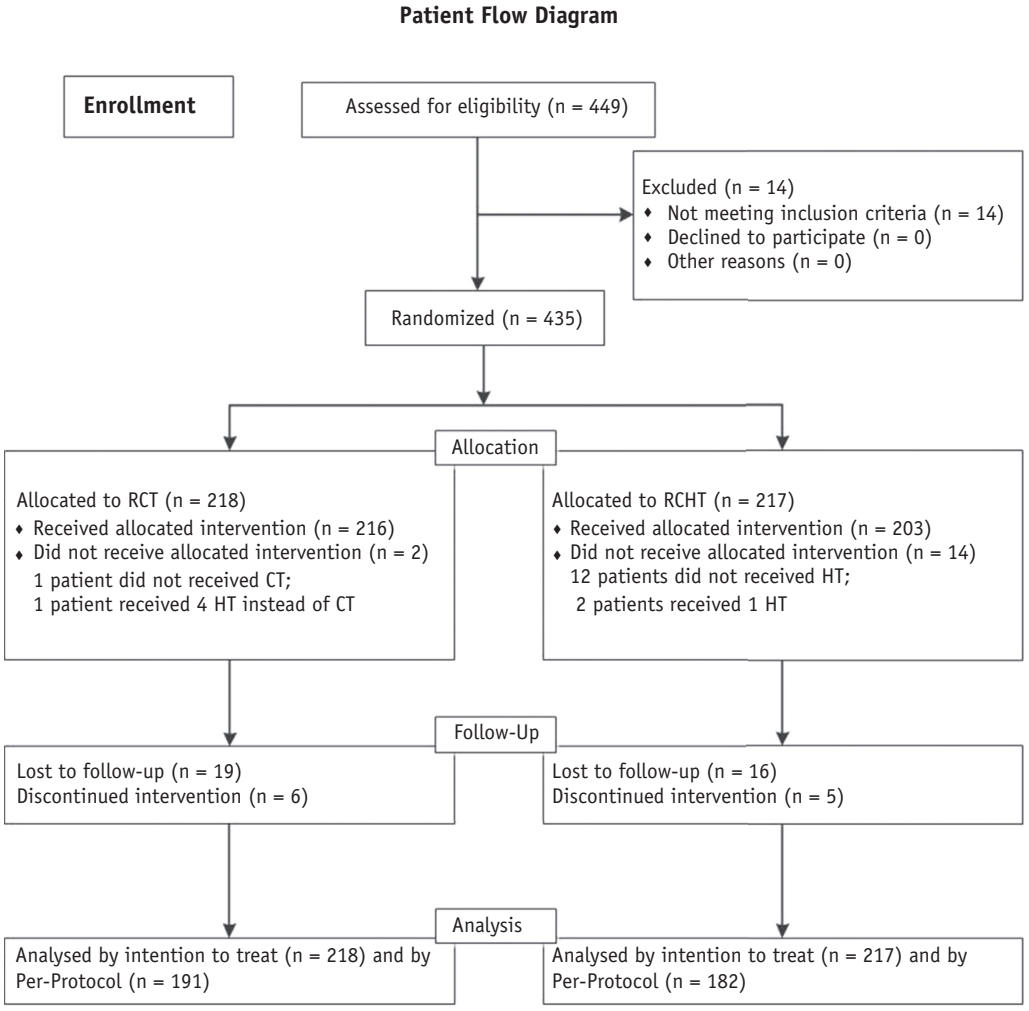

Fig. 1. Patient flow diagram.

Table 1 Patients and treatment characteristics (per protocol)

Characteristics	Patients n (%)	RCT n (%)	RCHT n (%)	*P*
Age, y				
Median	51	50	51	
Range	28-69	28-69	29-69	
<51	186 (49.87)	101 (52.88)	85 (46.70)	.233
≥51	187 (50.13)	90 (47.12)	97 (53.30)	
FIGO stage				.348
IB-IIB	237 (63.54)	117 (61.26)	120 (65.93)	
IIIA-IVB	136 (36.46)	74 (38.74)	62 (34.07)	
In detail				
IB1	5 (1.34)	4 (2.09)	1 (0.55)	
IB2	2 (0.54)	1 (0.52)	1 (0.55)	
IIA1	8 (2.14)	4 (2.09)	4 (2.20)	
IIA2	9 (2.41)	5 (2.62)	4 (2.20)	
IIB	213 (57.10)	103 (53.93)	110 (60.44)	
IIIA	9 (2.41)	5 (2.62)	4 (2.20)	
IIIB	118 (31.64)	65 (34.03)	53 (29.12)	
IVA-IVB	9 (2.41)	4 (2.09)	5 (2.75)	
Karnofsky performance status				.091
70	25 (6.70)	16 (8.38)	9 (4.95)	
80	316 (84.72)	164 (85.86)	152 (83.52)	
90	31 (8.31)	11 (5.76)	20 (10.99)	
100	1 (0.27)	0	1 (0.55)	
Pathologic grade				.943
Well	20 (5.36)	10 (5.24)	10 (5.49)	
Moderately	312 (83.65)	159 (83.24)	153 (84.07)	
Poorly	41 (10.99)	22 (11.52)	19 (10.44)	
Tumor size				.060
<4 cm	116 (31.10)	51 (25.13)	65 (35.71)	
≥4 cm	257 (68.90)	140 (74.87)	117 (64.29)	
Lymph node				.361
Positive	77 (20.64)	43 (22.51)	34 (18.68)	
Negative	296 (79.36)	148 (77.49)	148 (81.32)	
Pelvic lymph node				.230
Positive	72 (19.30)	41 (20.46)	30 (16.57)	
Negative	301 (80.70)	150 (78.53)	151 (83.43)	
Paraortic lymph node				.746
Positive	9 (2.41)	4 (2.09)	5 (2.75)	
Negative	364 (97.59)	187 (97.91)	177 (97.25)	
Mediastinum lymph node				.680
Positive	5 (1.34)	2 (1.05)	3 (1.65)	
Negative	368 (98.66)	189 (98.95)	179 (98.35)	
Supraclavicular lymph node				
Positive	0	0	0	
Negative	373 (100.00)	191 (100.00)	182 (100.00)	
Pretreatment HGB, g/L				
Mean	114.83	114.75	114.91	
External beam radiation therapy				
3DCRT				
50.4 Gy/28 f	366 (98.12)	187 (97.91)	179 (98.35)	
IMRT				
50.4 Gy/28 f	7 (1.88)	4 (2.09)	3 (1.65)	
Brachytherapy				
20 Gy/4 f	360 (96.51)	182 (95.29)	179 (98.35)	
25 Gy/5 f	12 (3.22)	9 (4.71)	3 (1.65)	

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Table 1 (*continued*)

Characteristics	Patients n (%)	RCT n (%)	RCHT n (%)	*P*
Hyperthemia times				
6	165 (44.24)	-	165 (90.66)	
4-5	10 (2.68)	-	10 (5.49)	
2-3	7 (1.88)	-	7 (3.85)	
Chemotherapy cycles				.546
1 (concurrent CT)	326 (87.40)	165 (86.39)	161 (88.46)	
2-3 (concurrent + adjuvant CT)	47 (12.60)	26 (13.61)	21 (11.54)	
Median follow-up (mo)	73	73	72	
Death				.028*
No	287 (76.94)	138 (72.25)	149 (81.87)	
Local failure				.272
No	314 (84.18)	158 (82.72)	158 (86.81)	
Total	373	191 (51.21)	182 (48.79)	

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; CT = chemotherapy; FIGO = International Federation of Gynecology and Obstetrics; HGB = hemoglobin; IMRT = intensity modulated radiation therapy; PP = per protocol; RCHT = radiochemotherapy + hyperthermotherapy; RCT = radiochemotherapy.

* $P < .05$ was considered significant.

assumes a 5-year patient enrollment period and 5 additional years of follow-up.

Follow-up and examination

After completion of therapy, patients were initially scheduled for follow-up examinations every 3 months for the first 2 years, every 6 months for the second through the fifth years, and annually thereafter. The follow-up examination included physical examination and pelvic computed tomography/magnetic resonance imaging. All patients were followed for at least 5 years.

Statistical analysis

The categorical variables were presented as counts and percentages; continuous variables were shown as median and range. The Pearson χ^2 test or Fisher's exact test was applied to assess the differences between groups in categorical variables of patient characteristics. As measures of treatment outcomes, LRFS, OS, and acute or late toxicity were considered. Univariate and multivariate analyses for LRFS and OS in patients with CC were performed using the Cox proportional hazard model. Survival curves were created according to the Kaplan−Meier method and analyzed by the log-rank test. Acute or late toxicity was summarized as the number (%) of adverse events and analyzed by the Wilcoxon rank test. Survival curves were created using Stata software (Stata/MP 15.0). Statistical analysis of all data was performed using SPSS software (PASW Statistics 18). All statistical *P* values were 2-sided, except *P* values for LRFS and OS, which were 1-sided. $P < .05$ was considered statistically significant.

Results

Patient characteristics

A patient flow diagram is presented in Figure 1. In total, 449 patients with CC were recruited into this clinical trial, and 14 patients were excluded (2 patients for histologically confirmed cervical adenocarcinoma; 1 patient for double primary cancer; 10 patients for not tolerating the treatments; and 1 patient for low white blood cell count). Four hundred thirty-five patients were assigned to 2 treatment groups according to a computer-generated random number list: 218 RCT and 217 RCT + HT. Ultimately, 373 patients completed the prescribed treatment and finished 5-year follow-up for actual survival and treatment-related toxicity, leaving 191 patients in the RCT group and 182 patients in the RCHT group for analysis.

The patient characteristics between treatment groups are listed in Tables 1 (per protocol, PP) and 2 (intention to treat [ITT]). Patient clinical characteristics with total dose of RT and CT cycles showed no significant difference between treatment groups. Median follow-up time was 73 months.

Because the cases in the IB-IIA and IIIA/IVA-IVB stages were limited, these cases were merged with the stages IIB and IIIB, respectively; thus, FIGO stage was divided into 2 parts for analysis: IB-IIB and IIIA-IVB.

Lymph nodes were regarded as positive according to the computed tomography or magnetic resonance examination

Table 2 Patients and treatment characteristics (intention to treat)

Characteristics	Patients n (%)	RCT n (%)	RCHT n (%)	*P*
Age, y				
Median	51	50	51	
Range	28-69	28-69	29-69	
<51	214 (49.20)	111 (50.92)	102 (47.00)	.415
≥51	221 (50.80)	107 (49.08)	115 (53.00)	
FIGO Stage				.873
IB-IIB	268 (61.61)	134 (61.47)	135 (62.21)	
IIIA-IVB	167 (38.39)	84 (38.53)	82 (37.79)	
In detail				.795
IB1	5 (1.15)	4 (1.83)	1 (0.46)	
IB2	4 (0.92)	1 (0.46)	3 (1.38)	
IIA1	10 (2.30)	6 (2.75)	4 (1.84)	
IIA2	9 (2.07)	5 (2.29)	4 (1.84)	
IIB	240 (55.17)	117 (53.67)	123 (56.68)	
IIIA	16 (3.68)	9 (4.13)	7 (3.23)	
IIIB	141 (32.41)	72 (33.03)	69 (31.80)	
IVA-IVB	10 (2.30)	4 (1.83)	6 (2.76)	
Karnofsky performance status				.052
70	36 (8.28)	22 (10.09)	14 (6.45)	
80	362 (83.21)	184 (84.40)	178 (82.03)	
90	35 (8.05)	12 (5.50)	23 (10.60)	
100	2 (0.45)	0	2 (0.92)	
Pathologic grade				.675
Well	22 (5.06)	11 (5.04)	11 (5.07)	
Moderately	363 (83.45)	179 (82.11)	184 (84.79)	
Poorly	50 (10.49)	28 (12.84)	22 (10.14)	
Tumor size, cm				.069
<4	129 (29.66)	56 (25.69)	73 (33.64)	
≥4	306 (70.34)	162 (74.31)	144 (66.36)	
Lymph node				.211
Positive	95 (21.84)	53 (24.31)	42 (19.35)	
Negative	340 (78.16)	165 (75.69)	175 (80.65)	
Pelvic lymph node				.199
Positive	89 (20.46)	50 (22.94)	39 (17.97)	
Negative	346 (79.54)	168 (77.06)	178 (82.02)	
Paraortic lymph node				1.000
Positive	10 (2.30)	5 (2.29)	5 (2.30)	
Negative	425 (97.70)	213 (97.71)	212 (97.70)	
Mediastinum lymph node				1.000
Positive	6 (1.38)	3 (1.38)	3 (1.38)	
Negative	429 (98.62)	215 (98.62)	214 (98.62)	
Supraclavicular lymph node				
Positive	0	0	0	
Negative	435 (100.00)	218 (100.00)	217 (100.00)	
Pretreatment HGB (g/L)				
Mean	114.12	114.02	114.22	
External beam radiation therapy				
3DCRT				
50.4 Gy/28 f	427 (98.16)	213 (97.71)	214 (98.62)	
IMRT				
50.4 Gy/28 f	8 (1.84)	5 (2.29)	3 (1.38)	
Brachytherapy				
0	1 (0.23)	1 (0.46)	0	
20 Gy/4 f	420 (96.55)	207 (94.95)	213 (98.16)	
25 Gy/5 f	14 (3.22)	10 (4.49)	4 (1.84)	

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Table 2 (*continued*)

Characteristics	Patients n (%)	RCT n (%)	RCHT n (%)	*P*
Hyperthemia times				
6	185 (42.53)	0	185 (85.25)	
4-5	12 (2.76)	1 (0.46)	11 (5.07)	
2-3	7 (1.61)	0	7 (3.23)	
1	2 (0.46)	0	2 (0.92)	
0	12 (2.76)	0	12 (5.53)	
Chemotherapy				
0	1 (0.23)	1 (0.46)	0	
1 (concurrent CT)	378 (86.90)	188 (86.24)	190 (87.56)	
2-3 (concurrent + adjuvant CT)	56 (12.87)	29 (13.30)	27 (12.44)	
Follow-up				
Median, mo	69	69	69	
Death	100 (22.99)	59 (27.94)	41 (18.88)	.043*
No	335 (77.01)	159 (72.94)	176 (81.12)	
Local failure	67 (15.40)	37 (16.97)	30 (13.82)	.363
No	368 (84.60)	181 (83.03)	187 (86.18)	
Total	435	218 (50.11)	217 (49.89)	

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; HGB = hemoglobin; RCHT = radiochemotherapy + hyperthermotherapy; RCT = radiochemotherapy.

* $P < .05$ was considered significant.

with minimum axial diameter greater than 1 cm and otherwise were regarded as negative (Tables 1 and 2).

Analyses for survival in patients with CC

Figure 2 (A and B) shows Kaplan–Meier curves for PP analysis of OS and LRFS of both groups. The 5-year OS rate of the patients in the RCT group was 72.3%, and that in the RCHT group was 81.9%; a log-rank test showed significant difference ($P = .040$). The 5-year LRFS of the patients in the RCT group (82.7%) was worse than that in RCHT group (86.8%); however, the difference was not significant ($P = .269$).

Univariate and multivariate Cox regression analysis for all variables on the OS in patients with CC is given in Table 3. On univariate analysis, FIGO stage, treatment modality, tumor size, lymph node positivity, and pretreatment hemoglobin (g/L) were the factors that affected OS in patients with CC, whereas multivariate analyses showed only FIGO stage, treatment modality, and tumor size as the factors affecting OS. Patients with advanced FIGO stage, RCT treatment modality, and larger tumor size showed significantly higher risk of death.

Figure 3 (A and B) shows Kaplan–Meier curves for ITT analysis of OS and LRFS of both groups. The 5-year OS rate of the patients in RCT group was 72.9%, and that in RCHT group was 81.1%; a log-rank test showed no significant difference ($P = .053$). The 5-year LRFS of the patients in the RCT group (83.0%) was worse than that in the RCHT group (86.2%); however, the difference was not significant ($P = .214$).

Univariate and multivariate Cox regression analysis for all variables on the OS in patients with CC are listed in Table 4 (ITT). FIGO stage and tumor size were the factors affecting OS both in univariate and multivariate analysis. Patients with advanced FIGO stage and larger tumor size showed significantly higher risk of death. On univariate analysis, the RCT treatment modality showed no significantly higher risk of death (0.056); however, multivariate analysis showed treatment modality was the factor affecting OS (0.043). Patients who received the RCT treatment modality showed significantly higher risk of death.

Analyses for survival in patients with CC in different stratifications

Figure 2 (C and D) shows Kaplan–Meier curves for PP analysis of OS in the 2 treatment groups in patients with FIGO stage IIIA-IVB and tumor size ≥4 cm, respectively. In patients with FIGO stage IIIA-IVB, the 5-year OS rates were 72.6% and 59.5% in the RCHT and RCT groups, respectively; however, the log-rank test showed no significant difference ($P = .121$). For tumor size stratification, 5-year survival in the RCHT group was better than that in the RCT group (76.9% vs 70.0%, respectively), however, and there was no significant difference ($P = .261$).

Figure 3 (C and D) shows Kaplan–Meier curves for ITT analysis of OS of the 2 treatment groups in patients with FIGO stage IIIA-IVB and tumor size ≥4 cm, respectively. The results were similar to PP analysis, with no significant difference.

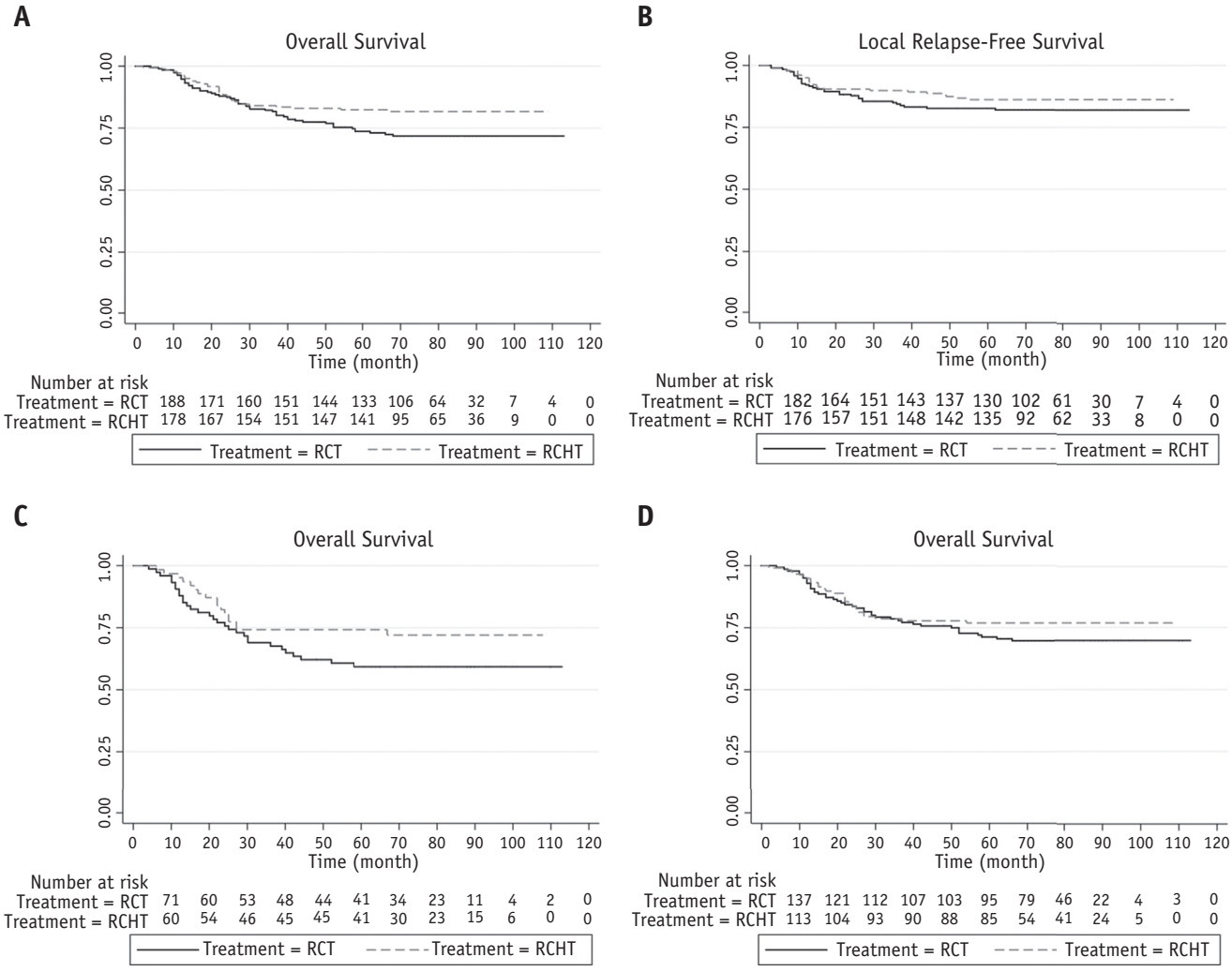

Fig. 2. Per-protocol analysis. (A) The 5-year overall survival for patients ($P = .040$). (B) The 5-year local relapse−free survival for patients ($P = .269$). (C) The 5-year overall survival for patients with International Federation of Gynecology and Obstetrics stage IIIA-IVB disease ($P = .121$). (D) The 5-year overall survival for patients with tumor size ≥4 cm ($P = .261$).

Acute and late toxicity

Acute and late toxicity after treatment is summarized in Tables 5 and 6. The toxicity showed no significant difference between the 2 treatment groups.

In PP data, gastrointestinal and genitourinary toxicity were mainly grade 1 or 2. Only 3 patients experienced grade 3 nausea in the RCHT group, and 1 patient in the RCT group experienced grade 3 vomiting. Fewer patients in each group had grade 4 blood toxicity. No patients in the RCHT group showed any blistering reaction or fat sclerosis related to HT. Late adverse reactions and degree were also similar between the 2 groups. Twenty patients (12%) and 22 patients (12.1%) had grade 1 rectal bleeding in the RCT and RCHT groups, respectively. Three patients (1.6%) in the RCT group and no patients in RCHT group had grade 2 rectal bleeding. Nineteen patients (11%) and 18 patients (9.9%) had grade 1 hematuria in the RCT and RCHT groups, and 2 patients (1%) and 1 patient (0.5%) had grade 2 hematuria in the RCT and RCHT groups, respectively. There were no grade 3 and 4 hematuria and rectal bleeding in the RCT or RCHT group.

In ITT data, the results were similar to PP data; the toxicity showed no significant difference between the 2 treatment groups.

Discussion

For patients with LACC, RT alone was the main treatment about 2 decades ago.[1] Since 1999, 5 randomized clinical studies have compared the effect of RT alone and that with concurrent RCT and reported a better treatment outcome and decreased risk of death in patients with CC treated with concurrent RCT.[3-7] Cisplatin-based concurrent RCT has become the standard treatment in LACC. Subsequently, 2

Table 3 Univariate and multivariate analyses for overall survival in patients with cervical carcinoma (per protocol)

Variable	Overall survival			
	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
Age, y				
<51	1			
≥51	0.807 (0.528-1.233)	.322		
FIGO Stage				
IB-IIB	1		1	
IIIA-IIIB	2.449 (1.601-3.746)	.000*	2.148 (1.384-3.334)	.001*
Pathologic grade				
Well	1			
Moderately	1.478 (0.465-4.700)	.508		
Poorly	2.964 (0.863-10.174)	.084		
Tumor size	1.206 (1.087-1.339)	.000*	1.145 (1.018-1.289)	.024*
Lymph node				
Negative	1		1	
Positive	1.654 (1.032-2.650)	.036*	1.282(0.786-2.092)	.320
Pretreatment HGB (g/L)	0.990 (0.981-1.000)	.053	0.998(0.988-1.009)	.708
Treatment type				
RCHT	1		1	
RCT	1.566 (1.014-2.418)	.043*	1.569 (1.010-2.435)	.045*

Abbreviations: CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; HGB = hemoglobin; HR = hazard ratio; PP = per protocol; RCHT = radiochemotherapy + hyperthermotherapy; RCT = radiochemotherapy.
* $P < .05$ was considered significant.

meta-analyses confirmed the effect of RCT on CC; however, they also suggested a decreasing relative effect of RCT on survival with increasing tumor stage and cautioned against extrapolation of the results to more advanced stages.[15,16] In the 5 randomized studies, most patients were in a relatively early stage (FIGO stage ≤II), and furthermore, patients were excluded for suspected or confirmed paraortic lymph node metastasis.

In 2000, the Dutch Deep Hyperthermia Group trial compared RT alone with combined RT and HT for the treatment of LACC.[8] They demonstrated that adding HT to RT led to better survival in LACC with FIGO stage IIB lateral or high, with approximate doubling of the 3-year OS from 27% to 51% and 3-year local control from 41% to 61%. Long-term survival was also included in the subsequent publications, and the results showed that local control remained better in the RT + HT group (37% vs 56%; $P = .01$) and survival was persistently better after 12 years: 20% (RT) and 37% (RT + HT; $P = .03$). Since then, combined RT and HT for LACC has begun to become the standard treatment approach for the LACC in several Dutch RT institutes, although concurrent RCT has been most widely accepted for LACC.[10] Subsequently, several studies have been devoted to the effects of adding HT for LACC[10,11,17,18] and most of them suggested results similar to the Dutch Deep Hyperthermia Group trial—that compared with concurrent RCT, combined HT and RT were better for treating LACC with FIGO stage ≥IIB. The proportions of patients with FIGO stage ≥IIB were larger (70%,[8] 90%,[10] or 100%[17]) in RT + HT clinical trials than those in RT + CT clinical trials (0.0%,[7] 47.7%,[5] 30.4%,[4] and 38.0%[6]). Only 1 trial showed no beneficial effect of adding HT to standard RT,[18] but this trial has been criticized by experts because the HT technique used and the thermometry data obtained were considerably short.[10,19,20] Moreover, EBRT and brachytherapy radiation techniques were not standardized in multinational centers. Those factors may have led to the negative results.

Because HT combined with RT exhibited preferable therapeutic efficacy for more advanced CC, could the combination of trimodality induce even better therapeutic efficacy for advanced CC? Some studies have contributed to an understanding of the feasibility and effectiveness of a triple treatment modality on patients with CC.[12,21-28] However, large-sample, randomized, controlled trials were lacking. Thus, we conducted the current randomized clinical study to assess the efficacy and safety of this tri-combination therapy compared with RCT alone based on 373 patients with CC.

In this trial, the 5-year OS rates of 373 patients were 72.3% and 81.9% with RCT and RCHT, respectively. The survival rate was higher in the RCHT group, and the log-rank test showed a statistically significant difference ($P = .040$). Univariate and multivariate analysis for OS also showed a significant difference ($P = .043$, $P = .045$, respectively). The 5-year LRFS (86.8%) with RCHT was also better than that with RCT (82.7%); however, the difference was not significant. Our results suggest that adding HT to standard RCT yields a better OS in patients with CC based on PP analysis. The advantage of HT plus concurrent RCT treatment was also indicated in several previous clinical studies. In 2005, Westermann et al reported on

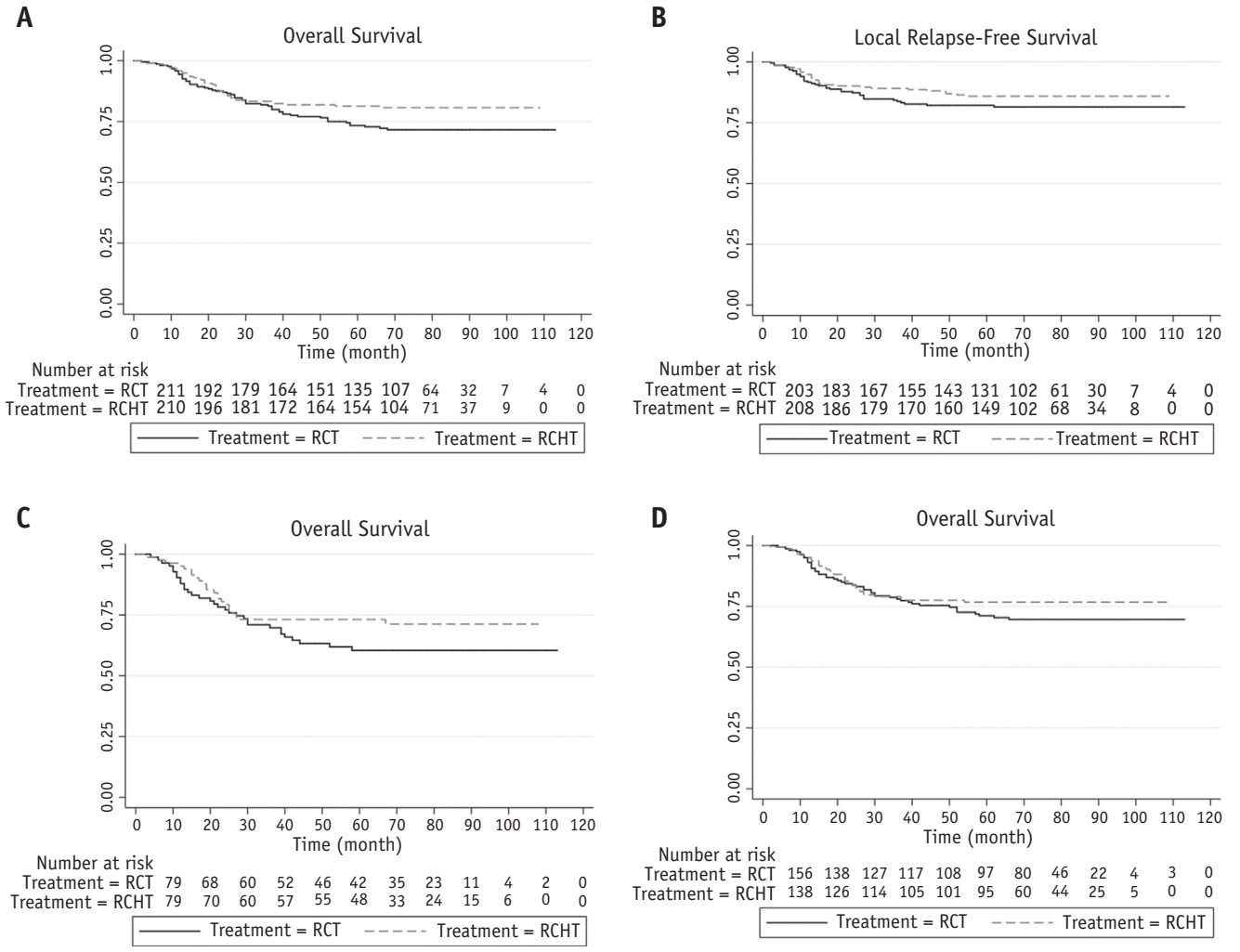

Fig. 3. Intention-to-treat analysis. (A) The 5-year overall survival for patients ($P = .053$). (B) The 5-year local relapse–free survival for patients ($P = .214$). (C) The 5-year overall survival for patients with International Federation of Gynecology and Obstetrics stage IIIA-IVB disease ($P = .172$). (D) The 5-year overall survival for patients with tumor size $\geq$4 cm ($P = .252$).

triple-modality treatment HT combined with RT and CT for patients with stage IIB-IVA CC,[24] and the long-term survival was subsequently published in 2012.[26] Although this study showed an improvement in OS in the RCHT group compared with the previously standard RCT, it had only 1 arm and lacked randomization, thus greatly reducing the study's efficacy and credibility.

In 2016, Harima et al investigated the clinical response and survival of 101 patients treated with cisplatin-based RCT or RCT with HT.[12] They found that the 5-year OS, disease-free survival, and LRFS in the RCT + HT group (77.8%, 70.8%, and 80.1%, respectively) were better than those in the RCT group (64.8%, 60.6%, and 71.0%, respectively) but showed no statistically significant difference ($P = .077$, $P = .073$, $P = .087$, respectively). Harima et al indicated that the reason for no statistically significant difference may be the small sample size. Our study enrolled 373 patients, a larger number of patients than Harima's study, and demonstrated a significantly better OS in our RCHT group.

In 2018, Ohguri et al continued to explore the effect of HT on standard RCT based on the same group of 101 patients with CC used in Harima's study.[28] They found that the most important factor affecting HT with RCT was the thermal dose. Disease-free survival, LRFS, and complete response rate for patients with higher CEM43T90 ($\geq$1 minute) in RCHT were significantly better than those with RCT alone ($P = .036$, $P = .036$, and $P = .048$, respectively). It seemed that HT with high thermal dose had the better survival.[28,29] However, the temperature was kept at 40.5°C $\pm$ 1°C in the RCHT group and still acquired the advantage of HT in our study. Thus, whether the thermal dose made a difference for the effect of HT in patients with CC should be further studied.

Table 4 Univariate and multivariate analyses for overall survival in patients with cervical carcinoma (intention to treat)

Variable	Overall survival			
	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
Age, y				
<51	1			
≥51	0.817 (0.551-1.210)	.313		
FIGO stage				
IB-IIB	1		1	
IIIA-IIIB	2.284 (1.539-3.388)	.000*	2.019 (1.342-3.038)	.001*
Pathologic grade				
Well	1			
Moderately	1.658 (0.523-5.248)	.391		
Poorly	2.964 (0.979-11.182)	.054		
Tumor size	1.210 (1.095-1.337)	.000*	1.149 (1.027-1.285)	.015*
Lymph node				
Negative	1		1	
Positive	1.488 (0.957-2.316)	.078	1.150 (0.729-1.816)	.547
Pretreatment HGB (g/L)	0.990 (0.981-0.999)	.024*	0.996 (0.986-1.006)	.432
Treatment type				
RCHT	1		1	
RCT	1.475 (0.990-2.197)	.056	1.512 (1.012-2.259)	.043*

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; RCHT = radiochemotherapy + hyperthermotherapy; RCT = radiochemotherapy.

* $P < .05$ was considered significant.

Table 5 Acute toxicity and late toxicity (per protocol)

Toxicity	n (%) of patients								
	RCT (n = 191)				RCHT (n = 182)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	*P*
Acute toxicity									
Gastrointestinal									
Nausea	52 (27.2)	19 (9.9)	0	0	47 (25.8)	26 (14.3)	3 (1.6)	0	.211
Vomiting	33 (17.3)	12 (6.3)	1 (0.5)	0	20 (11.0)	27 (14.8)	0	0	.443
Diarrhea	32 (16.8)	8 (4.2)	0	0	26 (14.3)	13 (7.1)	0	0	.799
Genitourinary									
Urinary tract pain, frequency, urgency	19 (9.9)	0	0	0	22 (12.1)	0	0	0	.509
Blood									
WBC	17 (8.9)	87 (45.5)	77 (40.3)	3 (1.6)	23 (12.6)	86 (47.3)	65 (35.7)	1 (0.5)	.200
PLAT	41 (21.5)	13 (6.8)	2 (1.0)	0	32 (17.6)	21 (11.5)	1 (0.5)	0	.871
HGB	50 (26.2)	68 (35.6)	15 (7.9)	5 (2.6)	51 (28.0)	65 (35.7)	19 (10.4)	5 (2.7)	.341
Weight less	6 (3.1)	5 (2.6)	0	0	3 (1.6)	7 (3.8)	1 (0.5)	0	.872
Fatigue	11 (5.8)	0	0	0	15 (8.2)	0	0	0	.347
Blistering	-	-	-	-	0	0	0	0	
Fat sclerosis	-	-	-	-	0	0	0	0	
Mean HGB (g/L)									
Before treatment	114.75			114.91					
After treatment	110.41			108.47					
Late toxicity									
Rectal bleeding	20 (12.0)	3 (1.6)	0	0	22 (12.1)	0	0	0	.966
Hematuria	19 (11.0)	2 (1.0)	0	0	18 (9.9)	1 (0.5)	0	0	.851

Abbreviations: HGB = hemoglobin; PLAT = platelet; RTOG = Radiation Therapy Oncology Group morbidity scale; RCHT = radiochemotherapy + hyperthermia; RCT = radiochemotherapy; WBC = white blood cell.

$P < .05$ was considered significant.

Table 6 Acute toxicity and late toxicity (intention to treat)

Toxicity	No. (%) of patients								
	RCT, N = 218				RCHT, N = 217				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	P^*
Acute toxicity									
Gastrointestinal									
Nausea	59 (27.1)	23 (10.6)	2 (0.9)	0	66 (30.4)	27 (12.4)	3 (1.4)	0	.809
Vomiting	38 (17.4)	16 (7.3)	3 (1.4)	0	26 (12.0)	28 (12.9)	0	0	.097
Diarrhea	33 (15.1)	8 (3.7)	0	0	32 (14.7)	13 (6.0)	0	0	.315
Genitourinary									
Urinary tract pain / frequency / urgency	20 (9.2)	0	0	0	28 (12.9)	0	0	0	1.000
Blood									
WBC	20 (9.2)	97 (44.5)	90 (41.3)	4 (1.8)	26 (12.0)	102 (47.0)	78 (35.9)	3 (1.4)	.174
PLAT	47 (21.6)	14 (6.4)	5 (2.3)	1 (0.5)	36 (16.6)	23 (10.6)	2 (0.9)	0	.329
HGB	51 (23.4)	76 (34.9)	24 (11.0)	6 (2.8)	57 (26.2)	82 (37.8)	22 (10.1)	6 (2.8)	.627
Weight less	8 (3.7)	7 (3.2)	0	0	5 (2.3)	7 (3.2)	1 (0.5)	0	.347
Fatigue	13 (6.0)	1 (0.5)	1 (0.5)	0	19 (8.8)	0	0	0	.106
Blistering	-	-	-	-	0	0	0	0	
Fat sclerosis	-	-	-	-	0	0	0	0	
Mean HGB (g/L)									
Before treatment	114.02				114.22				
After treatment	108.76				108.62				
Late toxicity									
Rectal bleeding	20 (9.2)	3 (1.4)	0	0	23 (10.6)	0	0	0	.135
Hematuria	20 (9.2)	2 (0.9)	0	0	20 (9.2)	1 (0.5)	0	0	.582

Abbreviations: HGB = hemoglobin; ITT = intention to treat; PLAT = platelet; RCHT = radiochemotherapy + hyperthermia; RCT = radiochemotherapy; RTOG = Radiation Therapy Oncology Group morbidity scale; WBC = white blood cell.

* $P < .05$ was considered significant.

One study found that patients with advanced-stage tumors or large tumor size may have more benefit from the combination of HT and RT than from RCT.[10] However, OS showed no statistical differences between the 2 treatment groups in subgroup of patients with more advanced FIGO stage (FIGO stage IIIA-IVB, $P = .121$) or large tumor size (tumor size $\geq$4 cm, $P = .261$) in our study.

In addition, there have been several reports regarding the toxicity of HT, but no significant difference was observed in acute or late toxicity between HT and non-HT groups.[8,27] The same results were also found in our trial—the toxicity between the 2 groups was similar, with no significant difference. Most patients experienced mild toxicity, and severe complications were rarely observed.

Our study also investigated other prognostic factors affecting OS in CC. Previous studies have reported several prognostic factors.[30,31] Clinical stage, histologic type, hemoglobin levels, and lymph node invasion were confirmed in predicting prognosis of CC.[30-32] Based on our trial data, FIGO stage and tumor size were correlated with the OS of patients with CC in univariate and multivariate analysis ($P < .001$, $P = .001$; $P < .001$, $P = .024$, respectively). However, other prognostic factors, such as lymph node positivity and hemoglobin levels, were not significantly correlated with prognosis.

Conclusions

Adding HT to standard RCT yielded a better survival in patients with CC based on PP analysis instead of ITT analysis. Although ITT analysis (survival analysis) was not significantly different ($P = .053$), there was a tendency toward improved survival (multivariate Cox regression analysis showed a significant difference: $P = .043$). Acute and late toxicity were similar between the 2 groups. Advanced clinical stage and larger tumor size were independent prognostic factors that predicted relatively worse survival. Therefore, HT will be one of the most effective additional treatments.[33]

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