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Is there a benefit for adjuvant radio(chemo)therapy in early cervical cancer? Results from a population-based study

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Abstract

Purpose Due to insufficient and conflicting prospective evidence, the recommendations on when to apply adjuvant radiochemotherapy in early-stage cervical cancer vary between international guidelines. In this population-based study, we evaluated the outcome of patients with early-stage cervical cancer based on risk factors and the adjuvant therapy they received.

Methods The effect of primary therapy (surgery and radiochemotherapy RCT, surgery and radiotherapy RT, and surgery alone) on overall survival (OS) and recurrence-free survival (RFS) was evaluated in the complete cohort of 442 patients and in subgroups according to risk profile and nodal status.

Results In low-risk patients, there was no difference in OS ($p=0.276$) depending on whether patients received adjuvant therapy or not. Concerning RFS, patients with RT (including one patient with RCT) exhibited a significantly worse outcome compared to the group with surgery alone ($p=0.015$). In intermediate-risk patients, the administration of adjuvant RT significantly benefited RFS when compared to surgery only in multivariate analysis ($p=0.031$). Concerning OS, no significant influence for adjuvant treatment could be seen ($p=0.354$). Though trends towards better OS and RFS could be observed in patients of the high-risk group—both in RCT and RT groups compared to surgery alone—the effects did not prove to be significant.

Conclusion Our study reaffirms the evidence against the use of adjuvant radio(chemo)therapy in low-risk early-stage cervical cancer. In intermediate-, and less pronounced in high-risk patients, however, it seems to be beneficial. The role of adjuvant radio(chemo)therapy in early cervical cancer should be further investigated in prospective randomized trials.

Keywords Cervical cancer · Radio(chemo)therapy · Adjuvant therapy · Risk groups

Introduction

Cervical cancer is the second most common cause of cancer death in women worldwide. Even though its prevalence is considerably higher in third-world countries compared to the developed world, approximately 5000 patients in Germany are diagnosed with cervical cancer each year [1]. Thanks to screening programs in western countries, cervical cancer is increasingly diagnosed at earlier stages. The standard treatment for early-stage cervical cancer varies between countries.

While the national comprehensive cancer network (NCCN) favors radical hysterectomy over primary radio(chemo)therapy only in tumors smaller than 4 cm, the current German S3 guideline recommends radical hysterectomy for all-stage IB-IIA tumors in the absence of multiple risk factors, such as lymph node metastasis [2, 3]. Combined

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therapy, such as radical hysterectomy and lymphadenectomy plus radiochemotherapy, was shown to induce substantial morbidity. Therefore, a careful selection of patients should take place [4, 5].

International guidelines do not completely agree on the risk factors that indicate the need for adjuvant therapy. Guideline recommendations are largely based on the results of two large randomized trials conducted approximately 20 years ago [6–8]. Sedlis et al. demonstrated that adjuvant radiotherapy decreases recurrence rates in patients with certain risk factors, called the "Sedlis criteria" [7]. They consist of deep stromal invasion, capillary and lymphatic space involvement or a tumor diameter of more than 4 cm [2, 7]. In a trial by Peters et al., the combination of chemotherapy and radiotherapy proved to be superior to radiotherapy alone in patients with involved lymph nodes, residual tumor or parametric invasion [6].

Based on the available data, nodal involvement and residual tumor constitute undisputed risk factors that require adjuvant treatment. The recurrence rate in patients with lymph node metastases is increased up to 40% compared to nodal negative patients [9, 10]. Apart from that, the "Sedlis criteria" still constitute intermediate risk factors that guide adjuvant treatment decisions. A more recent analysis confirmed the role of tumor size, deep stromal invasion and lymphovascular space invasion on recurrence rates, but also established adenocarcinoma/adenosquamous histology as a risk factor [11]. While adjuvant therapy is considered necessary for parametric invasion by NCCN guidelines, this does not represent an indicator towards further treatment in the German guideline [2, 3]. This is supported by the findings of Uno et al. that demonstrated similar pelvic control rates for patients with and without parametric invasion [12]. The question whether patients with intermediate risk factors benefit from the addition of chemotherapy to adjuvant radiotherapy is currently addressed in the ongoing GOG0263 study (NCT01101451) [13]. Nevertheless, further investigation into the adjuvant treatment in early cervical cancer is desperately needed.

In this population-based study, we evaluated the outcome of patients with early-stage cervical cancer based on risk factors and the adjuvant therapy they received.

Materials and methods

Database and cohort

We retrospectively analyzed data obtained from the Clinical Cancer Registry of the Tumor Center—Institute for Quality Management and Health Services Research, University of Regensburg, Germany, which are described elsewhere [14–16].

Using the database, 1613 patients with histologically confirmed cervical cancer diagnosed between January 2003 and December 2015 were identified. We included only FIGO stages IB–IIA. We further restrained the cohort to patients that underwent radical hysterectomy. Further exclusion criteria were simultaneous or prior malignant disease of other origin, histology other than squamous carcinoma, adenocarcinoma or adenosquamous carcinoma and insufficient documentation (≤ one medical record available, Fig. 1). The remaining cohort consisted of 442 patients.

Risk groups and therapy groups

The effect of primary therapy (surgery and radiochemotherapy RCT, surgery and radiotherapy RT, and surgery alone) on overall survival OS and recurrence-free survival RFS was evaluated in the complete cohort of 442 patients and in subgroups according to risk profile and nodal status. Three risk groups were defined as follows: The low-risk group included patients without residual tumor (R0), negative nodal status (N0), and exhibiting no further histopathological risk factors (no lymph vessel invasion L0, no vein invasion V0, tumor size ≤ 4 cm, grading G1/G2). Patients in the intermediate-risk group had a diagnosis of R0 and N0 and only one or two of the four histopathological findings L1, V1, tumor size > 4 cm, G3. The high-risk group was defined as showing at least R1 or N1 or negative residual and nodal status R0/N0 combined with three or four of the histopathological findings L1, V1, tumor size > 4 cm, G3. The outcome comparisons were performed for the treatment groups surgery alone, surgery plus R(C)T (RCT or RT), RCT, and RT, respectively.

Statistical analyses

Continuous data are presented as mean, median, minimum, maximum values and standard deviation. Categorical data are described using absolute frequencies and relative percentages. Statistical comparisons were made using *t* test for continuous data in case of normal distribution; otherwise, Mann–Whitney *U* test was performed. Pearson's Chi-square test was used for testing independence of categorical variables; in case of small numbers, Fisher's exact test was applied.

Data on life and recurrence status were obtained from medical records, death certificates, and registration offices. Overall survival (OS) and recurrence-free survival (RFS) were estimated by means of Kaplan–Meier method and Cox regression model from the date of cancer diagnosis until the date of death of any cause, until the date of first recurrence report, or last date recorded alive, respectively. A cut-off date was set at 12/31/2019. In multivariate regression analyses, adjustments were made for potential confounding parameters: age at diagnosis, Charlson Comorbidity Index

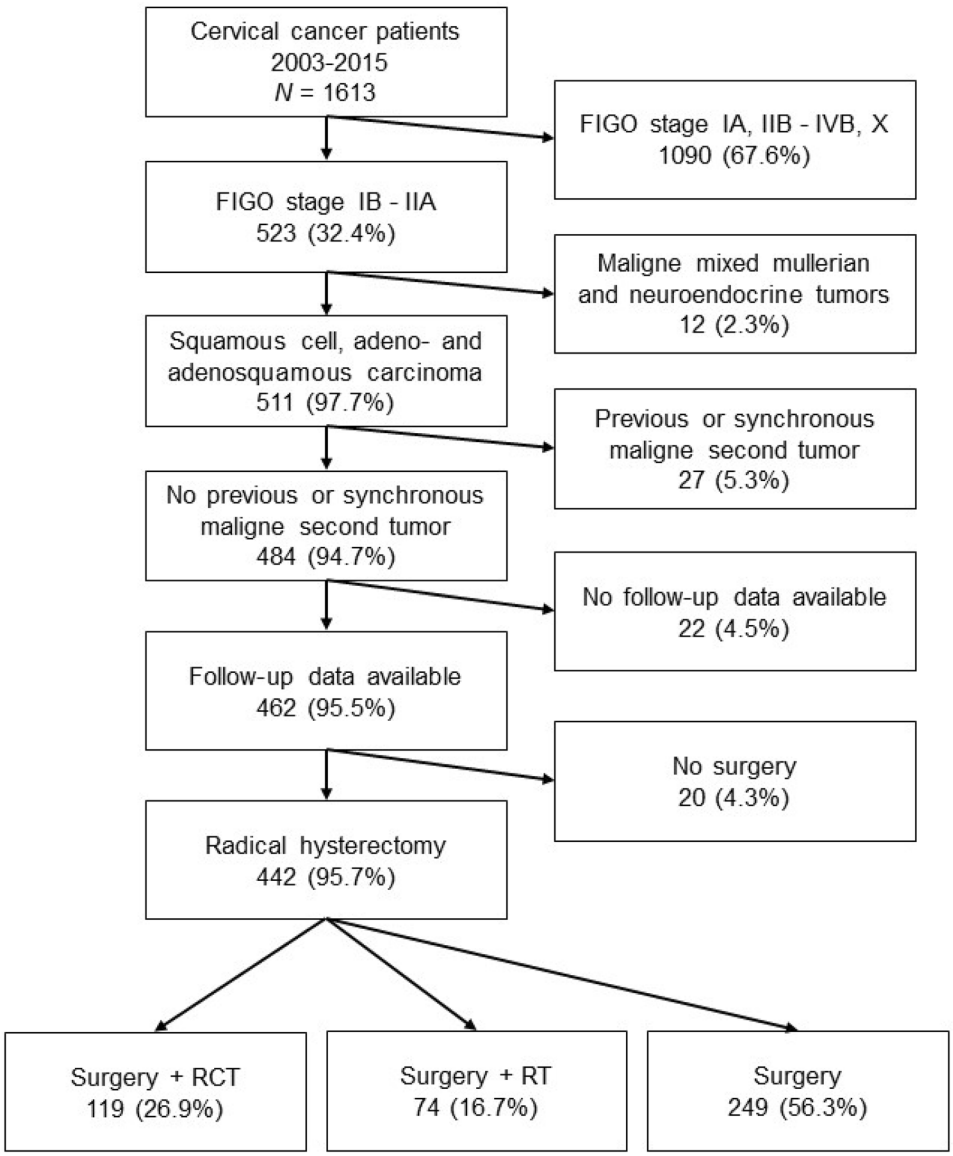


Fig. 1 Flow chart showing inclusion and exclusion criteria

[17], histology, grading, FIGO stage, tumor size, nodal status, lymph vessel invasion, blood vessel invasion, and residual tumor status. Hazard ratios (HR) were considered significant if the corresponding 95% confidence interval (95% CI) excluded 1. All *t* tests were calculated two-sided. *p* values < 0.05 were considered statistically significant. All calculations were performed using IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Description of patient cohort

398 patients (90.0%) with stage IB and 44 patients (10.0%) with stage IIA cervical cancer were included in the study (Table 1). Median follow-up was 7.8 years (95% CI 7.0–8.6), mean follow-up 8.7 years (95% CI 8.3–9.1). Median age at diagnosis was 48.0 years (mean 50.1 SD 13.1 years). In most patients (86.0%), Charlson comorbidity score did not surpass 2, meaning that they suffered from no other disease than cervical cancer. Squamous cell cancer (72.4%) was the prevailing histology, followed by adenocarcinoma (21.9%) and adenosquamous carcinoma (5.7%). Grading was predominantly G2 (45.1%) or G3 (49.3%), whereas G1 and GX were present in only 5.4% and 0.2% of cases, respectively. Lymphatic and vascular invasion was present in 41.0% and 9.3%, respectively. Surgical lymph node staging was performed in 96.2% of patients, 79.9% of whom were N0, 16.7% N1 and 3.5% not documented. 31.4% of patients had less, and 61.5% had more than 25 lymph nodes removed with a median of 30

Table 1 Distribution of demographic and clinicopathological patient characteristics according to primary therapy group

	Primary therapy								
	Surgery + RCT		Surgery + RT		Surgery		Total		Chi-square
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*p*
Age at diagnosis									
< 40	30	25.2%	8	10.8%	66	26.5%	104	23.5%	< 0.001
40–49	52	43.7%	20	27.0%	74	29.7%	146	33.0%	
50–59	26	21.8%	16	21.6%	54	21.7%	96	21.7%	
60–69	8	6.7%	16	21.6%	27	10.8%	51	11.5%	
70+	3	2.5%	14	18.9%	28	11.2%	45	10.2%	
Charlson-Comorbidity-Index									
2	108	90.8%	57	77.0%	215	86.3%	380	86.0%	0.027
> 2	11	9.2%	17	23.0%	34	13.7%	62	14.0%	
Histology									
Squamouscell cancer	92	77.3%	51	68.9%	177	71.1%	320	72.4%	0.143
Adenocarcinoma	18	15.1%	17	23.0%	62	24.9%	97	21.9%	
Adenosquamous cancer	9	7.6%	6	8.1%	10	4.0%	25	5.7%	
Grading									
G1/2	43	36.1%	34	45.9%	146	58.6%	223	50.5%	0.001
G3/4	76	63.9%	40	54.1%	102	41.0%	218	49.3%	
GX	0	0.0%	0	0.0%	1	0.4%	1	0.2%	
FIGO stage									
IB	99	83.2%	63	85.1%	236	94.8%	398	90.0%	0.001
IIA	20	16.8%	11	14.9%	13	5.2%	44	10.0%	
Tumor size									
≤ 40	63	52.9%	50	67.6%	205	82.3%	318	71.9%	< 0.001
> 40	50	42.0%	15	20.3%	26	10.4%	91	20.6%	
Unknown	6	5.0%	9	12.2%	18	7.2%	33	7.5%	
Tumor size									
< = 20	20	16.8%	12	16.2%	70	28.1%	102	23.1%	0.010
> 20	61	51.3%	30	40.5%	87	34.9%	178	40.3%	
Unknown	38	31.9%	32	43.2%	92	36.9%	162	36.7%	
Nodal status									
N0	62	52.1%	61	82.4%	233	93.6%	356	80.5%	< 0.001
N1	55	46.2%	12	16.2%	6	2.4%	73	16.5%	
Unknown	2	1.7%	1	1.4%	10	4.0%	13	2.9%	
Lymph vessel invasion									
L0	22	18.5%	23	31.1%	121	48.6%	166	37.6%	< 0.001
L1	86	72.3%	32	43.2%	63	25.3%	181	41.0%	
LX	11	9.2%	19	25.7%	65	26.1%	95	21.5%	
Vene invasion									
V0	56	47.1%	36	48.6%	156	62.7%	248	56.1%	< 0.001
V1	24	20.2%	8	10.8%	9	3.6%	41	9.3%	
VX	39	32.8%	30	40.5%	84	33.7%	153	34.6%	
Risk group									
Low risk	1	0.8%	30	40.5%	170	68.3%	201	45.5%	< 0.001
Intermediate risk	43	36.1%	22	29.7%	59	23.7%	124	28.1%	
High risk	75	63.0%	22	29.7%	20	8.0%	117	26.5%	
Lymphadenectomy									
Yes	116	97.5%	71	95.9%	238	95.6%	425	96.2%	0.672
No	3	2.5%	3	4.1%	11	4.4%	17	3.8%	

Table 1 (continued)

	Primary therapy								
	Surgery + RCT		Surgery + RT		Surgery		Total		Chi-square
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*p*
Number of lymph nodes resected									
< 25	27	22.7%	28	37.8%	84	33.7%	139	31.4%	0.196
25+	86	72.3%	40	54.1%	146	58.6%	272	61.5%	
N unknown	3	2.5%	3	4.1%	8	3.2%	14	3.2%	
No resection	3	2.5%	3	4.1%	11	4.4%	17	3.8%	
Residual tumor									
R0	107	89.9%	68	91.9%	243	97.6%	418	94.6%	0.002
R1/2	5	4.2%	5	6.8%	5	2.0%	15	3.4%	
RX	7	5.9%	1	1.4%	1	0.4%	9	2.0%	
Total	119	100.0%	74	100.0%	249	100.0%	442	100.0%	

(range 3–117). In 3.2% of patients, the number of nodes removed is unknown.

Tumor size was smaller than 4 cm in 71.9% and larger than 4 cm in 20.6% of cases. For the remaining 7.5% of cases, information was irretrievable. The actual tumor size in mm was only recorded for 63.4% of the patients. Considering a cut-off 2 cm, 23.1% of the patients showed a tumor size smaller, and 40.3% a tumor size larger than 2 cm. In most patients, resection status was R0 (94.6%). Residual tumor (R1 or R2) was present in 3.4%. Resection status was unclear in 2.0% of patients. 201 (45.5%), 124 (28.1%) and 117 (26.5%) patients were classified as low, intermediate and high risk, respectively. 249 patients received surgery alone (56.3%), 74 received adjuvant radiotherapy (RT, 16.7%) and 119 received radiochemotherapy (RCT, 26.9%). The patients with either RCT or RT added up to 193 [R(C)T, 43.7%]. The patients' characteristics in the differentiated groups surgery plus RCT, surgery plus RT, and surgery only are depicted in Table 1. Distribution of patients' characteristics according to treatment groups surgery and R(C)T vs surgery only is shown in Table 1.

Recommended and performed adjuvant treatment according to risk group

In the low-risk group, adjuvant therapy was recommended according to information from discharge letters in only 41 of 201 patients (20.4%), of whom 31 (75.6%) actually received R(C)T (30 patients with RT only and one patient with RCT). Six patients refused therapy, no reason for deviation from the treatment recommendation was found for the remaining four patients.

From 81 (65.3%) recommended adjuvant treatments in the 124 patients of the intermediate-risk group, 65 (80.2%) were actually performed (43 RCT, 22 RT), 11 were rejected by the patients, no information was available for five cases.

As expected, the highest rate of recommendations for adjuvant treatment (93.1%, $N = 109$) was observed in the 117 high-risk patients, which is in accordance to the German S3 guideline. The contraindications named in the discharge letters of eight patients without recommendation were uniformly advanced age and comorbidities, either alone or combined. From the 109 planned treatments, 97 (89.0%) were implemented as RCT (in 75 cases) and RT (in 22 cases), 7 were rejected by the patient, and in 5 cases, no reason for deviation was given.

Outcome

Complete cohort

In the complete cohort of 442 patients, the 5-year rates were 86.6% for OS, and 77.1% for RFS (Table 2). Patients with adjuvant R(C)T yielded a 5-year OS of 83.8% compared to 88.8% in patients with surgery only (log rank $p = 0.121$). The difference was smaller and not significant when comparing RFS, showing 5-year rates of 75.8% and 77.9%, respectively ($p = 0.366$). After adjusting for age at diagnosis, Charlson Comorbidity Index, histology, grading, FIGO stage, tumor size, nodal status, lymph vessel invasion, blood vessel invasion, and residual tumor status in multivariate analyses, adjuvant therapy did not prove to be advantageous for OS (HR 0.774, 95% CI 0.453–1.322, $p = 0.348$, Table S2, Table 2) and RFS (HR 0.882, 95% CI 0.562–1.383, $p = 0.584$, Table S3, Table 3). Comparing patients with surgery plus RCT and surgery plus RT separately to patients with surgery only, likewise no significant benefit was detected. The HR for OS in surgery group vs RCT group was 0.875 (95%-CI 0.438–1.746, $p = 0.705$), compared to the RT group, the HR for OS was 0.722 ((95% CI 0.396–1.313, $p = 0.285$). Concerning RFS, the HR for RCT compared to surgery only was 0.766 (95% CI 0.426–1.375, $p = 0.372$), for RT compared

Table 2 Kaplan–Meier estimates comparing overall survival and recurrence-free survival of surgery + (R(C)T) treated vs non-treated patients in total cohort and subgroups according to risk

Cohort	Therapy group	Patients, *N*	Events, *N*	5-year rate (%)	10-year rate (%)	*p* value logrank
Overall survival						
Total	All therapy groups	442	91	86.6	77.1	
Total	Surgery + R(C)T	193	48	83.8	74.9	0.121
	Surgery only	249	43	88.8	78.9	
Low risk	Surgery + R(C)T	31	6	89.4	89.4	0.611
	Surgery only	170	24	91.4	81.1	
Intermediate risk	Surgery + R(C)T	65	13	90.4	79.9	0.367
	Surgery only	59	13	86.2	77.9	
High risk	Surgery + R(C)T	97	29	77.7	67.0	0.737
	Surgery only	20	6	75.0	66.7	
Recurrence-free survival						
Total	All therapy groups	442	124	77.1	70.2	
Total	Surgery + R(C)T	193	60	75.8	68.4	0.366
	Surgery only	249	64	77.9	71.6	
Low risk	Surgery + R(C)T	31	13	66.2	60.7	0.025
	Surgery only	170	38	80.3	74.0	
Intermediate risk	Surgery + R(C)T	65	14	88.8	79.1	0.074
	Surgery only	59	18	77.6	69.0	
High risk	Surgery + R(C)T	97	33	70.3	63.5	0.418
	Surgery only	20	8	59.2	59.2	

Summary of numbers of patients and events, 5-year and 10-year rates, and *p* values derived from log-rank test

to surgery, it was 0.958 (95% CI 0.586–1.566, $p = 0.864$, Table 4).

In multivariate Cox regression analyses, the following patient characteristics proved to be significant risk factors for OS: age at diagnosis ($p < 0.001$), comorbidity defined by Charlson comorbidity score ($p = 0.049$), FIGO stage ($p = 0.027$), nodal status ($p = 0.015$), and residual status ($p < 0.001$). Lymph and blood vessel invasions, on the other hand, were not significantly associated with OS ($p = 0.277$ and $p = 0.192$, respectively) (Table S2).

RFS was significantly associated with age at diagnosis ($p < 0.001$), tumor size ($p = 0.021$) and residual tumor ($p = 0.028$) in multivariate analysis. There was a trend towards significance for FIGO Stage ($p = 0.051$) and nodal status ($p = 0.083$) (Table S3).

Risk groups

In the low-risk group, the 5-year OS rate was 91.1%, in the intermediate group 88.3%, and in the high-risk group 77.2%, exhibiting a significant difference of OS between low- and high-risk groups with $p = 0.001$. The corresponding 5-year rates for RFS were 78.2%, 83.5%, and 68.1%, showing no difference between low and intermediate risks ($p = 0.963$), and a small but non-significant difference between low and high risks ($p = 0.076$).

Table 2 and Fig. 2 show the results from Kaplan–Meier survival analyses in dependence of adjuvant R(C)T in the named subgroups. The corresponding results from univariate and multivariate regression analyses are listed in Table 3. Table 4 shows the results for the more detailed subgroups, the adjuvant therapy group divided into RCT and RT.

Low risk

In the low-risk group, the majority of patients was treated by surgery only ($N = 170$; 84.6%). Only 1 (< 1%) and 30 patients (14.9%) received RCT and RT, respectively. There was no difference in OS from Kaplan–Meier ($p = 0.611$ and multivariate regression analysis ($p = 0.276$) depending on whether patients received adjuvant therapy or not. Concerning RFS, patients with RT (including one person with RCT) exhibited a significantly worse outcome compared to the group with surgery only both in univariate and multivariate analysis: 5-year RFS rates were 66.2% vs 80.3% ($p = 0.025$), HR was 2.348 (95% CI 1.183–4.660, $p = 0.015$).

Intermediate risk

In the intermediate-risk group, treatment approaches were distributed more evenly. Fifty-nine patients (47.6%) received surgery only, 22 patients (17.7%) were treated by

Table 3 Hazard ratios (HR) for overall and recurrence-free survival in patients with surgery + R(C)T vs surgery only derived from univariable and multi-variable Cox–Regression analyses for total cohort and subgroups according to risk and nodal status

Cohort	Therapy group	Univariable Cox-regression				Multivariable[a] Cox-regression			
		p	HR	Lower 95% CI	Upper 95% CI	*p*	HR	Lower 95% CI	Upper 95% CI
Overall survival									
Total	Surgery		1.000				1.000		
	Surgery + R(C)T	0.122	1.384	0.917	2.089	0.348	0.774	0.453	1.322
Low risk	Surgery		1.000				1.000		
	Surgery + R(C)T	0.612	1.262	0.513	3.103	0.297	1.675	0.636	4.412
Intermediate risk	Surgery		1.000				1.000		
	Surgery + R(C)T	0.370	0.697	0.316	1.535	0.354	0.617	0.222	1.713
High risk	Surgery		1.000				1.000		
	Surgery + R(C)T	0.737	0.860	0.357	2.074	0.268	0.553	0.194	1.576
Tumor size ≤ 40	Surgery		1.000				1.000		
	Surgery + R(C)T	0.123	1.563	0.887	2.755	0.822	0.917	0.431	1.952
Tumor size > 40	Surgery		1.000				1.000		
	Surgery + R(C)T	0.095	0.539	0.261	1.114	0.274	0.585	0.223	1.531
Tumor size ≤ 20	Surgery		1.000				1.000		
	Surgery + R(C)T	0.168	2.771	0.651	11.805	0.360	6.335	0.121	330.818
Tumor size > 20	Surgery		1.000				1.000		
	Surgery + R(C)T	0.574	1.189	0.651	2.172	0.188	0.581	0.258	1.305
Nodal status N0	Surgery		1.000				1.000		
	Surgery + R(C)T	0.568	1.159	0.699	1.921	0.548	0.830	0.451	1.526
Nodal status N1	Surgery		1.000				1.000		
	Surgery + R(C)T	0.416	0.606	0.181	2.028	0.431	0.536	0.114	2.530
Recurrence free survival									
Total	Surgery		1.000				1.000		
	Surgery + R(C)T	0.366	1.176	0.827	1.673	0.584	0.882	0.562	1.383
Low risk	Surgery		1.000				1.000		
	Surgery + R(C)T	**0.028**	**2.024**	**1.077**	**3.802**	**0.015**	**2.348**	**1.183**	**4.660**
Intermediate risk	Surgery		1.000				1.000		
	Surgery + R(C)T	0.079	0.525	0.256	1.078	0.087	0.455	0.185	1.120
High risk	Surgery		1.000				1.000		
	Surgery + R(C)T	0.420	0.727	0.335	1.578	0.282	0.607	0.244	1.508
Tumor size ≤ 40	Surgery		1.000				1.000		
	Surgery + R(C)T	0.573	1.147	0.711	1.851	0.809	0.925	0.491	1.742
Tumor size > 40	Surgery		1.000				1.000		
	Surgery + R(C)T	0.099	0.570	0.292	1.112	0.590	0.791	0.337	1.856
Tumor size ≤ 20	Surgery		1.000				1.000		
	Surgery + R(C)T	0.168	2.771	0.651	11.805	0.360	6.335	0.121	330.818
Tumor size > 20	Surgery		1.000				1.000		
	Surgery + R(C)T	0.518	0.841	0.497	1.422	0.096	0.569	0.292	1.105
Nodal status N0	Surgery		1.000				1.000		
	Surgery + R(C)T	0.564	1.133	0.742	1.728	0.870	1.043	0.632	1.720
Nodal status N1	Surgery		1.000				1.000		
	Surgery + R(C)T	0.142	0.451	0.156	1.306	0.290	0.468	0.114	1.911

HR hazard ratio, *95% CI* 95% confidence interval

Significant results are displayed in bold

[a]Multi-variable Cox-regression adjusted for age at diagnosis, Charlson Comorbidity Index, histology, grading, FIGO stage, tumor size, nodal status, lymph vessel invasion, vene invasion, residual tumor status

Significant results are displayed in bold

Table 4 Hazard ratios (HR) for overall and recurrence-free survival in patients with surgery + RCT and surgery + RT vs surgery only derived from univariable and multivariable Cox-Regression analyses for total cohort and subgroups according to risk and nodal status

Cohort	Therapy group	Univariable Cox-regression				Multivariable[a] Cox-regression			
		p	HR	Lower 95% CI	Upper 95% CI	*p*	HR	Lower 95% CI	Upper 95% CI
Overall survival									
Total	Surgery		1.000				1.000		
	Surgery + RCT	0.257	1.317	0.818	2.120	0.705	0.875	0.438	1.746
	Surgery + RT	0.141	1.490	0.876	2.536	0.285	0.722	0.396	1.313
Low risk	Surgery		1.000				1.000		
	Surgery + RCT	–[b]	–	–	–	–	–	–	–
	Surgery + RT	0.567	1.301	0.529	3.200	0.276	1.715	0.649	4.528
Intermediate risk	Surgery		1.000				1.000		
	Surgery + RCT	0.306	0.625	0.255	1.536	0.741	1.225	0.367	4.086
	Surgery + RT	0.767	0.853	0.299	2.434	0.094	0.321	0.085	1.213
High risk	Surgery		1.000				1.000		
	Surgery + RCT	0.544	0.754	0.302	1.879	0.253	0.535	0.183	1.563
	Surgery + RT	0.668	1.254	0.446	3.528	0.512	0.630	0.159	2.506
Tumor size < = 40	Surgery		1.000				1.000		
	Surgery + RCT	0.407	1.350	0.664	2.746	0.694	0.815	0.295	2.250
	Surgery + RT	0.087	1.827	0.917	3.641	0.948	0.973	0.428	2.211
Tumor size > 40	Surgery		1.000				1.000		
	Surgery + RCT	0.061	0.471	0.214	1.035	0.241	0.516	0.171	1.560
	Surgery + RT	0.632	0.786	0.294	2.103	0.531	0.686	0.210	2.235
Tumor size < = 20	Surgery		1.000				1.000		
	Surgery + RCT	0.219	2.745	0.549	13.723	0.281	12.616	0.126	1266.316
	Surgery + RT	0.276	2.816	0.438	18.106	0.447	4.812	0.084	275.196
Tumor size > 20	Surgery		1.000				1.000		
	Surgery + RCT	0.755	1.114	0.565	2.194	0.181	0.520	0.200	1.356
	Surgery + RT	0.471	1.340	0.605	2.966	0.396	0.656	0.248	1.736
Nodal status N0	Surgery		1.000				1.000		
	Surgery + RCT	0.807	0.917	0.457	1.840	0.769	1.139	0.478	2.712
	Surgery + RT	0.263	1.408	0.773	2.565	0.354	0.720	0.360	1.441
Nodal status N1	Surgery		1.000				1.000		
	Surgery + RCT	0.381	0.577	0.169	1.974	0.389	0.503	0.106	2.397
	Surgery + RT	0.664	0.728	0.174	3.053	0.652	0.660	0.108	4.016
Recurrence free survival									
Total	Surgery		1.000				1.000		
	Surgery + RCT	0.950	0.987	0.645	1.508	0.372	0.766	0.426	1.375
	Surgery + RT	0.070	1.508	0.967	2.353	0.864	0.958	0.586	1.566
Low risk	Surgery		1.000				1.000		
	Surgery + RCT	–[b]	–	–	–	–	–	–	–
	Surgery + RT	**0.021**	**2.106**	**1.121**	**3.957**	**0.007**	**2.586**	**1.298**	**5.150**
Intermediate risk	Surgery		1.000				1.000		
	Surgery + RCT	0.089	0.492	0.217	1.114	0.619	0.765	0.266	2.200
	Surgery + RT	0.319	0.599	0.219	1.639	**0.031**	**0.258**	**0.075**	**0.885**
High risk	Surgery		1.000				1.000		
	Surgery + RCT	0.276	0.639	0.285	1.431	0.306	0.610	0.237	1.570
	Surgery + RT	0.889	1.069	0.421	2.717	0.411	0.596	0.173	2.047
Tumor size ≤ 40	Surgery		1.000				1.000		
	Surgery + RCT	0.622	0.851	0.448	1.617	0.286	0.614	0.250	1.505
	Surgery + RT	0.134	1.553	0.873	2.763	0.753	1.113	0.572	2.166

Table 4 (continued)

Cohort	Therapy group		Univariable Cox-regression				Multivariable[a] Cox-regression			
			p	HR	Lower 95% CI	Upper 95% CI	*p*	HR	Lower 95% CI	Upper 95% CI
Tumor size > 40	Surgery			1.000				1.000		
	Surgery + RCT	0.063		0.504	0.245	1.037	0.624	0.778	0.286	2.119
	Surgery + RT	0.654		0.812	0.327	2.019	0.677	0.805	0.290	2.235
Tumor size ≤ 20	Surgery			1.000				1.000		
	Surgery + RCT	0.174		2.499	0.668	9.350	0.872	1.257	0.077	20.438
	Surgery + RT	0.501		1.788	0.329	9.700	0.631	0.517	0.035	7.627
Tumor size > 20	Surgery			1.000				1.000		
	Surgery + RCT	0.426		0.784	0.430	1.428	0.126	0.541	0.246	1.187
	Surgery + RT	0.911		0.960	0.467	1.973	0.225	0.603	0.266	1.366
Nodal status N0	Surgery			1.000				1.000		
	Surgery + RCT	0.313		0.725	0.389	1.354	0.739	0.878	0.409	1.887
	Surgery + RT	0.057		1.602	0.985	2.604	0.693	1.115	0.651	1.908
Nodal status N1	Surgery			1.000				1.000		
	Surgery + RCT	0.134		0.437	0.148	1.289	0.270	0.452	0.110	1.853
	Surgery + RT	0.326		0.516	0.138	1.931	0.503	0.556	0.100	3.100

HR hazard ratio, *95% CI* 95% confidence interval

Significant results are displayed in bold

[a]Multi-variable Cox-regression adjusted for age at diagnosis, Charlson Comorbidity Index, histology, grading, FIGO stage, tumor size, nodal status, lymph vessel invasion, vene invasion, residual tumor status

[b]Model did not converge, number of cases too small

Significant results are displayed in bold

adjuvant RT and 43 (34.7%) by adjuvant RCT. Neither in univariate nor multivariate analysis, OS correlated with whether patients received adjuvant treatment ($p = 0.370$ and $p = 0.354$, respectively). Furthermore, it was not significantly correlated with the type of adjuvant treatment ($p = 0.741$ for RCT vs surgery, $p = 0.094$ for RT vs surgery). A benefit for RFS, however, was significantly associated with the administration of adjuvant RT when compared to surgery only in multivariate analysis (HR 0.258, 95% CI 0.075–0.885, $p = 0.031$). This was not the case in the RCT group.

High risk

In the high-risk group, only 20 patients (17.1%) did not receive adjuvant treatment. 22 (18.8%) and 75 patients (67.0%) were treated by adjuvant RT and RCT, respectively. There was no significant difference in OS comparing patients that received adjuvant therapy and those who did not in univariate ($p = 0.737$) or multivariate analysis ($p = 0.268$). Type of adjuvant treatment RCT or RT was not associated with an increased OS (Table 4). No therapy group, be it combined or differentiated, yielded a better RFS than the surgery only group (Tables 3, 4). Though trends towards better OS and RFS could be seen in patients of the high-risk group—both in RCT and RT groups compared to surgery alone—the effects did not prove to be significant.

Tumor size

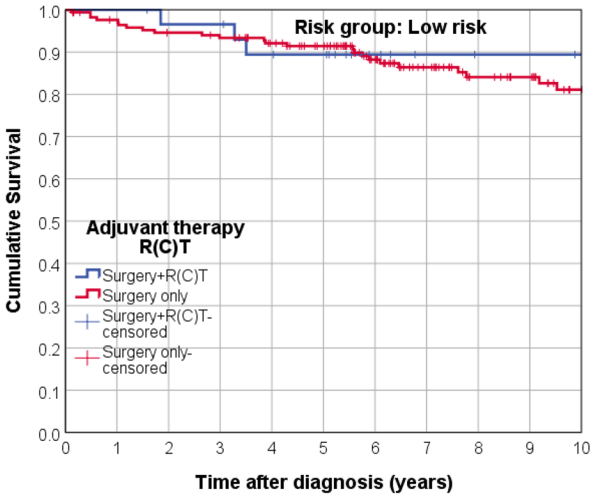
The intenseness of therapy increased with tumor size: among 91 patients with a tumor size larger than 4 cm, 65 (71.4%) received R(C)T. In patients with tumors smaller than 4 cm, the portion was only 35.5% (113 from 318). Patients with tumors larger than 2 cm received R(C)T in 51.1% (91 of 178 cases), as opposed to patients with tumors smaller than 2 cm (31.4%, 32 of 102 cases).

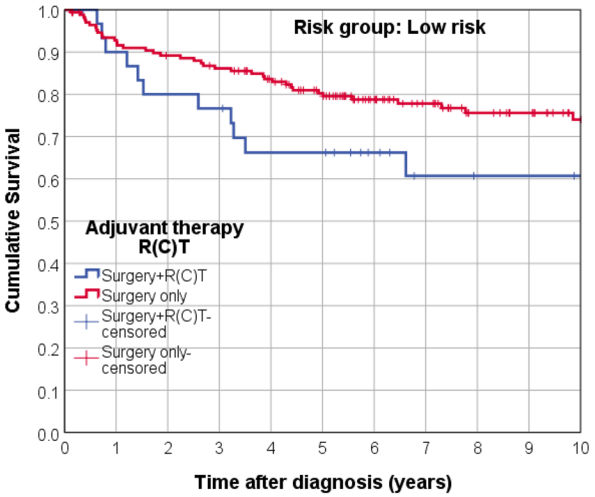
Considering OS and RFS, no significant benefit was observed from R(C)T in patients with small and large tumors, be it the threshold of 4 cm or 2 cm. However, a tendency towards a positive effect on OS and RFS was seen in patients with larger tumors—greater than 2 cm—with a HR for R(C)T vs surgery only of 0.581 (95% CI 0. 258–1.305, $p = 0.188$) and 0.569 (95% CI 0.292–1.105, $p = 0.096$), respectively. This tendency was less obvious when considering the tumor size limit of 4 cm.

Overall survival

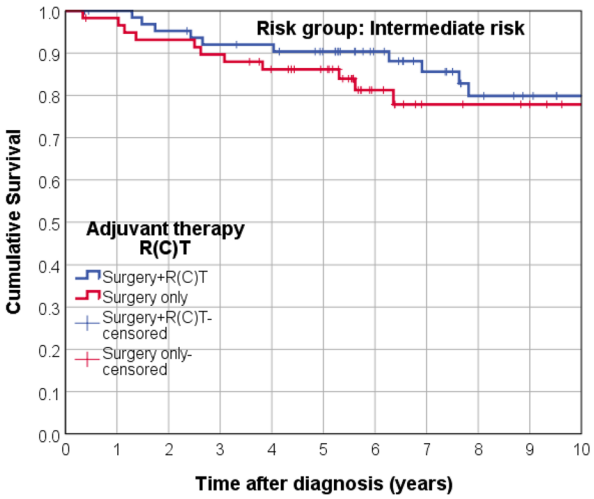
Recurrence-free survival

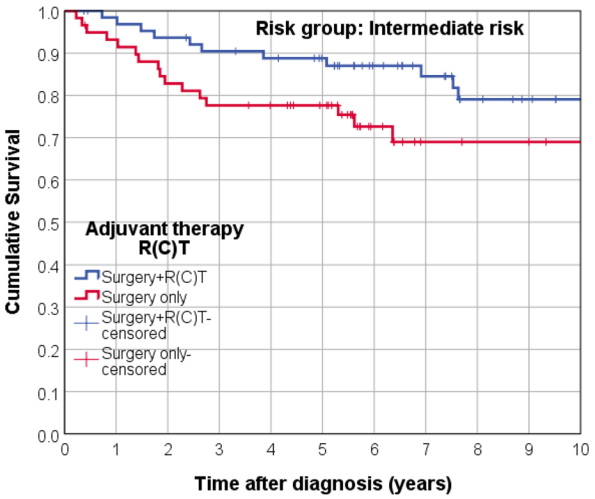
A Low risk



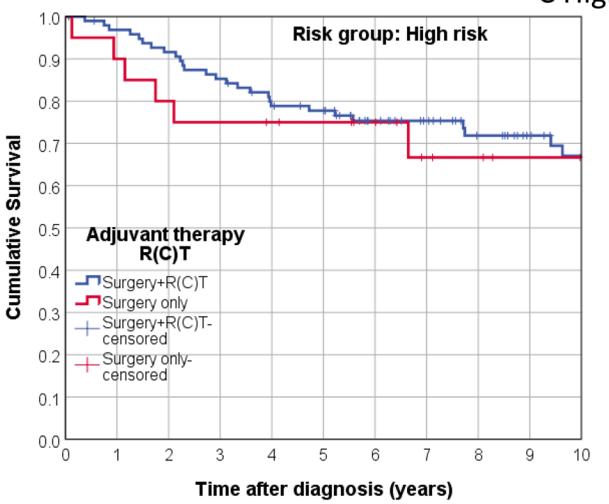


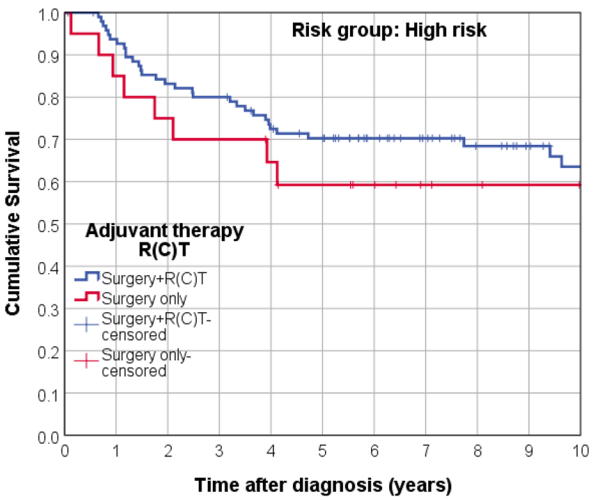
B Intermediate risk





C High risk





◂**Fig. 2** Kaplan–Meier curves comparing overall survival (left) and recurrence-free survival (right) of adjuvant (R(C)T) treated (blue) vs non-treated patients (red) in patients of low- (A), intermediate- (B) and high-risk group (C)

Nodal status

Node negative patients (N0) were preferably treated by surgery only ($N=233$ of 356, 65.4%), RCT and RT being less common ($N=62$, 17.4%, $N=61$, 17.1%, respectively). In 73 patients with positive regional lymph nodes (N1), surgery plus RCT was the most dominant treatment ($N=55$, 75.3%), followed by surgery plus RT ($N=12$, 16.4%) and surgery only ($N=6$, 8.2%).

As far as treatment modalities are concerned, no significant differences in OS and RFS could be derived in both the N0 and N1 groups from univariate and multivariate survival analyses (Tables 3 and 4). However, the HR for R(C)T compared to surgery only in N1 patients was 0.468 (95% CI 0.114–1.911, $p=0.290$) and 1.043 (95% CI 0.632–1.720, $p=0.870$) in N0 patients, respectively.

Discussion

Cervical cancer is a significant cause of morbidity and mortality. Despite its high prevalence, data on optimal treatment approaches are scarce. Previously, we demonstrated an improvement in OS through the addition of adjuvant RCT to surgery in FIGO stage IIB disease regardless of lymph node status [16]. In this study, we evaluated the effect of adjuvant treatment in early-stage cancer depending on the presence of risk factors. Only two randomized prospective studies exist on the subject. Sedlis et al. randomized FIGO IB patients without residual tumor or involved lymph nodes but with two or more intermediate risk factors later named the "Sedlis criteria" to receive observation or RT following radical surgery. Adjuvant radiotherapy led to a reduction of recurrence rates at the cost of an approximately 4% higher rate of grade 3/4 adverse events. There was no increase in OS but an improvement of long-term PFS [7, 8, 18]. Another randomized controlled trial by Peters et al. compared adjuvant radiotherapy to adjuvant radiochemotherapy. Patients with clinical-stage IA(2), IB and IIA carcinoma with parametric invasion, residual tumor and/or lymph node involvement were included in the study. PFS as well as OS was significantly improved by the addition of chemotherapy [6]. A retrospective analysis of the clinical and histopathological data of the study discovered that the absolute benefit of the addition of chemotherapy was less evident among patients with only one involved lymph node and smaller primary tumors (< 2 cm) [18]. Hence, some questions concerning adjuvant treatment in early-stage cancer remain. It is unclear whether patients with only one intermediate risk factor benefit from RT and whether additional chemotherapy is beneficial in patients apart from those with nodal involvement, residual tumor or parametric invasion. Furthermore, risk factors may not be limited to the ones mentioned above. Due to these uncertainties, international guidelines on the topic are inconsistent. The risk group stratification in this study was based on the recommendations of the German S3 guideline. A tumor size of 4 cm or more, deep stromal invasion and lymphatic as well as vascular space invasion indicate intermediate risk when at least two of them are present. Residual tumor and lymph node metastases are regarded as high-risk factors. Our investigation demonstrates a gradual decrease of OS rates from low to high risk, the effect being less pronounced for RFS. Particularly, tumor size, residual tumor and nodal status had a significant impact on OS and apart from nodal status also on RFS. The effect of blood and lymph vessel invasion on OS and RFS, on the other hand, could not be confirmed in this cohort.

Our retrospective analyses did not show a benefit of adjuvant therapy in patients without risk factors. This is in line with international guideline recommendations [2, 3]. This question was addressed in only one other retrospective study reaching a comparable conclusion [19]. We even perceived a significantly inferior RFS in low-risk patients treated with adjuvant radio(chemo-)therapy. The reason for this effect remains unclear. A potential explanation is the presence of other risk factors than the ones evaluated. These might have prompted physicians to propose adjuvant treatment to the patients and could lead to a negative selection bias for R(C)T. Taking into account the substantial morbidity induced by the combination of surgery and adjuvant R(C)T patients without risk factors should be spared from this treatment [4, 7].

The administration of adjuvant therapy in intermediate-risk patients did not lead to an improvement in OS, but improved RFS. This was restricted to radiotherapy and did not apply to treatment with adjuvant radiochemotherapy. Similar results were obtained in the high-risk group with three or more intermediate risk factors or lymph node involvement or residual tumor. Though the Hazard ratios suggest an improvement in OS and RFS in patients of the high-risk group—both in RCT and RT groups compared to surgery alone—the effects did not prove to be significant. In our patient cohort, the additional beneficial effect of chemotherapy to radiotherapy in high-risk patients proposed by the Intergroup 0107/GOG 109 trial could not be reproduced. This observation may result from a number of factors [6]. First, patient numbers are not powered to detect minor differences in survival, especially in the light of an uneven patient distribution across treatment groups. Second, the administered chemotherapy regimen will probably vary from the one used in the Intergroup 0107/GOG 109 trial in some

patients without well-founded evidence for its equivalence. Moreover, a survival advantage is only expected for patients with residual tumor and lymph node involvement, not for the other patients classified as high risk due to 3 or more risk factors. Recent findings suggest that lymph node involvement is the most relevant factor predicting the survival benefit of RCT, while patients with positive margins and/or parametric invasion alone might not benefit from RCT [20]. In addition, the benefit for patients with only one involved lymph node seems to be lower than initially expected [18]. In our cohort, the effect of adjuvant treatment on OS and RFS in lymph node positive patients was not significant. However, a closer look on the hazard ratios proposes that the death rate and the rate of patients experiencing recurrence or death are approximately halved in patients receiving adjuvant radio(chemo)therapy.

Stratified for tumor size, we did not perceive a significant benefit for adjuvant therapy in patients with primary tumors smaller or larger than 2 cm. However, a tendency towards a positive effect on OS and RFS was seen in patients with tumors > 2 cm.

As mentioned above for the cohort of high-risk patients in general, the effect of adjuvant therapy in node positive patients may be masked by the low number of patients in this group. Since this study included only tumor stages IB–IIA, the influence of parametric invasion was not assessed. Previously, we demonstrated that FIGO IIB cervical cancer patients benefit from a combination of surgery and radiochemotherapy, whereas no benefit was seen for surgery and adjuvant radiotherapy without chemotherapy [16]. In combination, the results from both studies suggest parametric invasion being the most relevant risk factor for the effect of RCT.

Conclusion

In summary, our data reaffirm the evidence from previous studies against the use of adjuvant therapy in low-risk early-stage cervical cancer [7, 8, 18]. In intermediate- and less pronounced in high-risk patients, however, it seems to provide an advantage over treatment by surgery alone. The relevance of different risk factors should be further investigated in prospective randomized trials.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. This article does not contain any studies with human participants or animals performed by any of the authors.

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