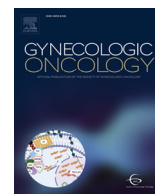




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## Role of adjuvant therapy in intermediate-risk cervical cancer patients – Subanalyses of the SCCAN study

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### HIGHLIGHTS

- We investigated the survival benefit of adjuvant therapy (AT) after radical surgery in intermediate-risk (IR) cervical cancer.
- Of 692 IR cervical cancer patients in the SCANN study, 60.4% received AT (AT+) and 39.6% did not (AT–).
- 5-year DFS (83.2% vs. 80.3%) and OS (88.7% vs. 89.0%) rates were similar in the AT– and AT+ groups.
- AT did not confer a significant survival benefit even after applying propensity score matching for confounding factors.

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### ABSTRACT

**Objective.** The “intermediate-risk” (IR) group of early-stage cervical cancer patients is characterized by negative pelvic lymph nodes and a combination of tumor-related prognostic risk factors such as tumor size  $\geq 2$  cm, lymphovascular space invasion (LVSI), and deep stromal invasion. However, the role of adjuvant treatment in these patients remains controversial. We investigated whether adjuvant (chemo)radiation is associated with a survival benefit after radical surgery in patients with IR cervical cancer.

**Methods.** We analyzed data from patients with IR cervical cancer (tumor size 2–4 cm plus LVSI OR tumor size  $>4$  cm; N0; no parametrial invasion; clear surgical margins) who underwent primary curative-intent surgery

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Intermediate risk  
GOG criteria  
Radical surgery  
Adjuvant treatment  
Radiotherapy

between 2007 and 2016 and were retrospectively registered in the international multicenter Surveillance in Cervical CANcer (SCCAN) study.

**Results.** Of 692 analyzed patients, 274 (39.6%) received no adjuvant treatment (AT−) and 418 (60.4%) received radiotherapy or chemoradiotherapy (AT+). The 5-year disease-free survival (83.2% and 80.3%;  $P_{DFS} = 0.365$ ) and overall survival (88.7% and 89.0%;  $P_{OS} = 0.281$ ) were not significantly different between the AT− and AT+ groups, respectively. Adjuvant (chemo)radiotherapy was not associated with a survival benefit after adjusting for confounding factors by case-control propensity score matching or in subgroup analyses of patients with tumor size  $\geq 4$  cm and  $< 4$  cm. In univariable analysis, adjuvant (chemo)radiotherapy was not identified as a prognostic factor in any of the subgroups (full cohort:  $P_{DFS} = 0.365$ ;  $P_{OS} = 0.282$ ).

**Conclusion.** Among patients with IR early-stage cervical cancer, radical surgery alone achieved equal disease-free and overall survival rates to those achieved by combining radical surgery with adjuvant (chemo)radiotherapy.

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## 1. Introduction

Radical hysterectomy (RH) with pelvic lymph node dissection is the standard treatment for early-stage cervical cancer, and the decision to use adjuvant therapy (AT) is determined based on histopathological risk factors [1]. Positive parametrial invasion, involvement of lymph nodes, and positive surgical margins are considered high-risk prognostic factors for tumor recurrence and the administration of adjuvant treatment is generally accepted as standard-of-care with these risk factors [2,3]. However, controversy remains regarding “intermediate risk” (IR) factors, also called “Sedlis” or “GOG criteria” [4], including tumor size  $\geq 4$  cm, or tumor size 2–3.99 cm combined with lymphovascular space invasion (LVSI) or deep stromal invasion.

Out of the entire clinical management algorithm for cervical cancer, the treatment of patients with IR tumors is the least harmonized and at least five different types of treatment are proposed: RH alone, RH followed by AT, neoadjuvant chemotherapy followed by RH with or without AT, neoadjuvant brachytherapy followed by RH with or without AT, and primary chemoradiation [5]. However, the key controversy is whether or not IR patients should be referred for AT after radical surgery.

The current international guidelines consider both types of the management, radical surgery alone or radical surgery followed by adjuvant (chemo)radiation, as the standard of care for IR cervical cancer [1,6]. However, the available literature data are inconclusive regarding the superiority of either approach [7–13]. The main argument supporting the benefit of AT comes from a single randomized study conducted  $> 20$  years ago in 1999 (GOG 92 study) [4]. In that study, adjuvant radiotherapy decreased the recurrence rate by 47%, prompting the authors to conclude that adjuvant radiotherapy significantly improves the progression-free survival after RH in patients with IR cervical cancer. However, from today’s perspective, the study suffered from significant limitations and the recurrence rate in both trial arms was much higher than would be expected today.

More recently, a number of retrospective studies have shown no benefit of AT after radical surgery in IR patients, although they were mostly single-center studies with small cohorts [7–11]. Nevertheless, the published retrospective studies have consistently reported better survival outcomes than the GOG 92 study. We can only hypothesize that the reason for the better outcomes in recent papers involves more precise detection of high-risk prognostic factors and the exclusion of such cases from the IR category.

To provide further insight into the benefit of AT in IR cervical cancer, we performed analyses of a large retrospective international SCCAN study (Surveillance in Cervical CANcer) containing data from  $> 4000$  early-stage cervical cancer patients [14]. From this cohort we selected patients who met the diagnostic criteria of IR disease to investigate whether adjuvant (chemo)radiotherapy is associated with a survival benefit after radical surgery.

## 2. Methods

### 2.1. Study design and patients

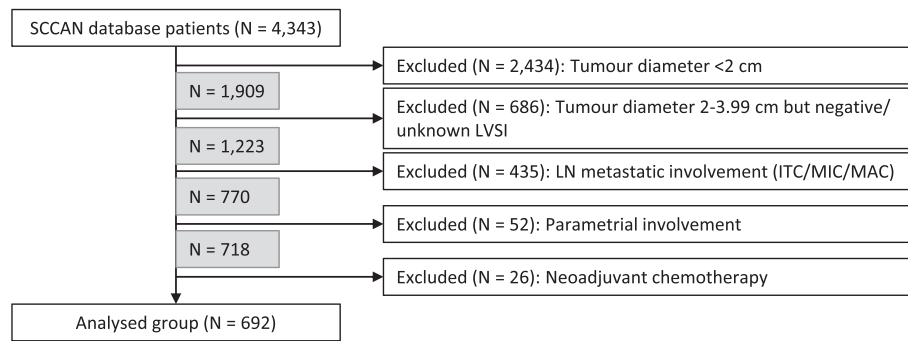
The SCCAN study is an international, multicenter, retrospective cohort study that evaluated the recurrence patterns of cervical cancer survivors. The SCCAN study consortium consisted of 20 tertiary centers located in Europe, Asia, North America, and Latin America (Supplementary Table 1). Patients were retrospectively included if they met the following inclusion criteria: (i) pathologically confirmed cervical cancer treated between 2007 and 2016; (ii) Pathological FIGO 2018 stage 1A to 2B [15]; and (iii) primary surgical management, including fertility-sparing procedures. Patients were eligible irrespective of the pre-operative staging procedures or imaging tests, type of AT, neoadjuvant chemotherapy, tumor type, lymph node (LN) status, or LN staging. Patients were ineligible if they had precancer disease, they underwent definitive radiotherapy/chemoradiotherapy, or if primary surgical treatment was abandoned intra-operatively. Complete resection with negative surgical margins was a prerequisite for database inclusion. The following data regarding primary treatment were collected: type of uterine procedure, type of parametrectomy, surgical approach, LN staging and extent, and AT. The type of parametrectomy was classified using the Querleu–Morrow modified classification system [16]. Disease characteristics included information about the type and largest size of the tumor (pathologically confirmed), pathologic stage, number and size of removed/positive LNs, parametrial involvement, LVSI, and grade. The tumors were classified histologically according to the World Health Organization classification. Information regarding disease recurrence included the diagnosis, precise location of the recurrence, presence of symptoms, and treatment modality. The database comprised data from 4343 patients with early-stage cervical cancer. The design of the SCCAN study was published in more detail in a previous report [14].

For the present subanalyses of SCCAN, we only included patients with the following pathologic risk factors for IR cervical cancer: (i) tumor size  $\geq 4$  cm or 2–3.99 cm + LVSI; (ii) LN negative for any type of metastasis (macrometastases, micrometastases, or isolated tumor cells); and (iii) no parametrial involvement. Also, patients who received neoadjuvant chemotherapy were excluded (Fig. 1).

The protocol was first approved by the institutional review board at the lead institution (General University Hospital in Prague, Czech Republic; approval number: 2183/18S-IV) in 2019, and subsequently by the institutional review boards at each participating site. Due to the retrospective nature of the study, the institutional review boards waived the need for informed consent. The study was performed in accordance with the Declaration of Helsinki.

### 2.2. Data analyses

Standard descriptive statistics were used to summarize the data. Categorical variables were described using the absolute and relative



**Fig. 1.** Patient flowchart.

Abbreviations: ITC, isolated tumor cells; LN, lymph node; MAC, macrometastasis; MIC, micrometastasis; SCCAN, Surveillance in Cervical CANcer study.

frequencies, and continuous variables were described as the mean with standard deviation or median with interquartile range. Differences between the AT– and AT+ groups were assessed using Fisher's exact test or the Mann–Whitney *U* test as appropriate.

Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan–Meier method and the log rank test was used to compare the survival curves between the two groups. The associations between patient characteristics with DFS and OS were evaluated by univariable Cox proportional hazard models and reported as hazard ratios (HR) with 95% confidence intervals (CI) and the corresponding *P*-values.

In order to ensure comparability between AT– and AT+ groups (in total and in subgroups stratified by tumor size), we used the case-control propensity score matching procedure. Patients were matched based on tumor size (2–3.99 cm vs  $\geq 4$  cm), LVSI, tumor histotype, age (tolerance  $\pm 5$  years), and surgical approach.

All tests were two-tailed with a significance level of 0.05. The statistical analyses were performed using SPSS software version 28 (IBM, Armonk, NY, USA).

### 3. Results

#### 3.1. Patient characteristics

Of 4343 patients included in the SCCAN database, 692 patients with pathologically confirmed cervical cancer met the criteria for IR disease and were eligible for this study (Fig. 1). The majority of patients had squamous cell carcinoma (71.2%) or adenocarcinoma (20.4%). Overall, 397 (57.4%) had a combination of a tumor size 2–3.99 cm and positive LVSI and 295 (42.6%) had a tumor size  $\geq 4$  cm. The predominant surgical procedure was RH (95.5%) with laparotomy being the preferred approach, performed in 74% of patients. Pelvic and paraaortic lymphadenectomy was completed in 97.8% and 29.5% of patients. Sentinel lymph node (SLN) biopsy, including ultrastaging, was performed in 21.1% of patients.

In the overall cohort, 274 (39.6%) patients underwent radical surgery alone (AT– group) and 418 (60.4%) underwent radical surgery followed by AT (AT+ group). AT included concomitant chemoradiotherapy (34%), external beam pelvic radiotherapy (65.1%), and adjuvant chemotherapy (1%). The AT– and AT+ groups were well balanced in terms of tumor characteristics; however, the AT– group had lower stage disease ( $P < 0.001$ ) and more frequently underwent SLN biopsy ( $P = 0.008$ ). By comparison, paraaortic lymphadenectomy was more frequently performed in the AT+ group ( $P < 0.001$ ). The patient characteristics stratified by AT administration are summarized in Table 1.

#### 3.2. Univariable analysis of prognostic factors for DFS and OS

The results of the univariable analysis of prognostic factors for DFS and OS are summarized in Table 2. Out of the tested variables, only

laparoscopic surgical approach ( $P_{DFS} = 0.029$ ;  $P_{OS} = 0.027$ ) and rare tumor histotype ( $P_{DFS} = 0.004$ ;  $P_{OS} = 0.007$ ) were associated with worse DFS and OS. Type A parametrectomy was associated with worse OS. The analyses did not reveal a survival benefit of AT on either DFS ( $P_{DFS} = 0.365$ ) or OS ( $P_{OS} = 0.282$ ) (Table 2).

In the subgroup analysis of prognostic factors in patients with tumor size 2–3.99 cm and positive LVSI, laparoscopic surgery was negatively associated with both DFS ( $P_{DFS} = 0.007$ ) and OS ( $P_{OS} = 0.002$ ), and parametrial resection type A was associated with worse OS ( $P_{OS} = 0.009$ ). In the subgroup analysis of patients with tumor size  $\geq 4$  cm, only adenosquamous histology was associated with worse DFS ( $P_{DFS} = 0.022$ ) (Supplementary Tables 2 and 3).

#### 3.3. Oncological outcomes and pattern of recurrence according to the use of AT

Due to the negative prognostic significance of the rare tumor histological types, we excluded those patients ( $N = 14$ ) from further survival analyses; three patients were excluded from the AT– group (of which 2 relapsed) and 11 were excluded from the AT+ cohort (of which 9 relapsed).

The median follow-up period of the further analyzed cohort ( $N = 678$ ) was 4.6 years (25th–75th percentile: 2.7–6.3 years) and was not significantly different between the AT– and AT+ groups (4.3 vs 4.7 years). DFS was not significantly different between the two groups ( $P_{DFS} = 0.372$ ), with 5-year DFS rates of 83.7% (95% CI: 78.9%–88.5%) and 81.2% (95% CI: 77.8%–85.1%) in the AT– and AT+ groups, respectively (Fig. 2A). Furthermore, there was no benefit of AT on OS ( $P_{OS} = 0.234$ ), with 5-year OS rates of 89.6% (95% CI: 85.3%–94.0%) and 89.6% (95% CI: 86.4%–92.8%) in the AT– and AT+ groups, respectively (Fig. 2B).

The location of recurrence differed significantly between AT– and AT+ groups ( $P = 0.03$ ). Of 44 AT– patients with recurrence, 67.4% had pelvic recurrence and 14.0% had distant recurrence. Of 84 AT+ patients with recurrence, 44% had pelvic recurrence and 32.1% had distant recurrence. The treatment modalities for recurrence in the AT– and AT+ groups are summarized in Table 1.

##### 3.3.1. Subgroup analysis of patients with tumor size 2–3.99 cm and positive LVSI

Of 397 patients with a tumor size 2–3.99 cm and positive LVSI, 241 (60.7%) received AT (AT+) and 156 (39.3%) did not receive AT (AT–). Both groups were balanced in terms of major surgical characteristics, including the surgical approach, uterine procedure, and parametrial resection. However, the AT– group had a lower pathological stage ( $P = 0.001$ ) and slightly smaller tumor size ( $P < 0.001$ ), with a median of 2.6 cm vs 2.8 cm in the AT+ group. SLN biopsy with ultrastaging was more frequently performed in the AT– group ( $P = 0.045$ ) (Supplementary Table 4).

**Table 1**  
Characteristics of patients stratified by the absence or presence of adjuvant treatment.

Characteristic		AT– (N = 274)	AT+ (N = 418)	P	
Age at surgery	(years)	45 (38–56)	50 (41–59)	<b>&lt;0.001</b>	
Type of uterine/cervical procedure	Radical hysterectomy	259 (94.5%)	400 (96.2%)	0.073	
	Simple hysterectomy	5 (1.8%)	10 (2.4%)		
	Radical trachelectomy	9 (3.3%)	4 (1.0%)		
	Other	1 (0.4%)	2 (0.5%)		
	Not available	0 (0.0%)	2 (0.5%)		
Type of parametrial resection	A	4 (1.5%)	12 (3.0%)	0.097	
	B	29 (10.9%)	62 (15.3%)		
	C1	124 (46.6%)	196 (48.4%)		
	C2	109 (41.0%)	135 (33.3%)		
	Not available	8 (2.9%)	13 (3.1%)		
Surgical approach	Open	217 (79.2%)	300 (71.8%)	0.171	
	Laparoscopic	33 (12.0%)	74 (17.7%)		
	Robotic/vaginal	24 (8.8%)	44 (10.5%)		
SLN performed	Yes	72 (26.3%)	74 (17.7%)	<b>0.008</b>	
Pelvic lymphadenectomy	Yes	270 (98.5%)	407 (97.4%)	0.425	
No. of pelvic LN retrieved	(if >0)	26 (20–36)	25 (18–34)	0.141	
Para-aortic lymphadenectomy	Yes	55 (20.1%)	149 (35.6%)	<b>&lt;0.001</b>	
No. of para-aortic LN retrieved	(if >0)	11 (6–14)	11 (6–16)	0.580	
Pathologic stage (FIGO 2018)*	1b2	150 (54.7%)	206 (49.3%)	<b>&lt;0.001</b>	
	1b3	114 (41.6%)	52 (36.4%)		
	2a1	6 (2.2%)	35 (8.4%)		
	2a2	4 (1.5%)	25 (6.0%)		
	Not available	8 (2.9%)	13 (3.1%)		
Tumor diameter	(cm)	3.5 (2.5–4.2)	3.5 (2.7–4.5)	0.053	
	2–3.99 cm	156 (56.9%)	241 (57.7%)		0.875
	≥4 cm	118 (43.1%)	177 (42.3%)		
Tumor histotype	Squamous cell	192 (70.3%)	299 (71.7%)	0.438	
	Adenocarcinoma	63 (23.1%)	78 (18.7%)		
	Adenosquamous	16 (5.9%)	30 (7.2%)		
	Other	3 (1.3%)	11 (2.6%)		
Grade	1	18 (9.9%)	22 (6.8%)	0.456	
	2	94 (51.6%)	176 (54.2%)		
	3	70 (38.5%)	127 (39.1%)		
	Not available	92 (33.6%)	93 (22.2%)		
LVSI	No	57 (22.7%)	77 (18.8%)	0.233	
	Yes	194 (77.3%)	332 (81.2%)		
	Not available	23 (8.4%)	9 (2.2%)		
Cervical cancer recurrence	Yes	44 (16.1%)	84 (20.1%)	0.194	
Recurrence type (if recurrence = yes)	Isolated	32 (74.4%)	54 (64.3%)	0.317	
	Multiple	11 (25.6%)	30 (35.7%)		
	Not available	1 (2.3%)	0 (0.0%)		
Location of recurrence (if recurrence = yes)	Pelvic	29 (67.4%)	37 (44.0%)	<b>0.030</b>	
	Distant	6 (14.0%)	27 (32.1%)		
	Combined	8 (18.6%)	20 (23.8%)		
	Not available	1 (2.3%)	0 (0.0%)		
Treatment modality for recurrence (if recurrence = yes)	CRT	14 (32.6%)	3 (4.2%)	<b>&lt;0.001</b>	
	Chemotherapy	13 (30.2%)	35 (48.6%)		
	Radiotherapy	9 (20.9%)	0 (0.0%)		
	Surgery	1 (2.3%)	7 (9.7%)		
	Surgery + CRT	4 (9.3%)	27 (37.5%)		
	No treatment	2 (4.7%)	4 (5.6%)		
	Not available	1 (2.3%)	8 (9.5%)		
	Not available	1 (2.3%)	8 (9.5%)		
Disease status at last follow-up visit	Alive with disease	9 (3.3%)	23 (5.5%)	0.178	
	Died of other cause	2 (0.7%)	9 (2.2%)		
	Died of disease	21 (7.7%)	40 (9.6%)		
	No evidence of disease	242 (88.3%)	346 (82.8%)		

Categorical variables are described as absolute and relative frequencies and calculated from available data. Continuous variables are described as the median (25th–75th percentile). P-values were determined by Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables.

Abbreviations: AT, adjuvant therapy; CRT, chemoradiotherapy; LN, lymph node; LVSI, lymphovascular space invasion; SLN, sentinel lymph node.

\* International Federation of Gynecology and Obstetrics staging system 2018 [15].

There were no differences between the groups in terms of DFS ( $P_{DFS} = 0.129$ ) and OS ( $P_{OS} = 0.575$ ) (Fig. 2C,D). There was, however, a significant difference in the location of recurrence between the groups ( $P = 0.04$ ); pelvic recurrence was more frequent in the AT– group (73.7% vs 42.7%) and distant recurrence was more frequent in the AT+ patients (5.3% vs 30.6%).

### 3.3.2. Subgroup analysis of patients with tumor size ≥4 cm

Of 295 IR patients with a tumor size ≥4 cm, 177 (60.0%) received AT (AT+) and 118 (40.0%) did not (AT–). Regarding the surgical

characteristics, only para-aortic lymphadenectomy was significantly more frequently performed in the AT+ group. Regarding disease characteristics, the AT– group tended to have a lower stage disease ( $P = 0.009$ ) whereas LVSI was more frequent in the AT+ ( $P = 0.03$ ) (Supplementary Table 5).

There were no differences in DFS ( $P_{DFS} = 0.129$ ) or OS ( $P_{OS} = 0.575$ ) between the AT– and AT+ groups (Fig. 2E,F). Furthermore, there were no significant differences in the type ( $P = 0.771$ ) and location ( $P = 0.463$ ) of recurrence.

**Table 2**  
Univariable regression models for DFS and OS in all IR patients (N = 692).

Predictor	Category	DFS		OS	
		HR (95% CI)	P	HR (95% CI)	P
AT	No	Reference		Reference	
	Yes	1.18 (0.82–1.71)	0.365	1.31 (0.80–2.16)	0.282
Age at surgery (years)	Per 1-year increase	0.99 (0.98–1.01)	0.269	1.01 (0.99–1.03)	0.582
	< 40	Reference		Reference	
	40–49	0.80 (0.51–1.26)	0.330	0.86 (0.45–1.62)	0.631
	50–59	0.65 (0.39–1.07)	0.090	0.88 (0.46–1.70)	0.712
	≥ 60	0.95 (0.59–1.54)	0.842	1.16 (0.60–2.23)	0.657
Surgical approach	Open	Reference		Reference	
	Laparoscopic	1.62 (1.05–2.50)	<b>0.029</b>	1.90 (1.08–3.36)	<b>0.027</b>
	Robotic/vaginal	0.94 (0.49–1.81)	0.854	1.13 (0.48–2.65)	0.776
Grade	1	0.45 (0.14–1.44)	0.179	0.83 (0.25–2.77)	0.767
	2*	Reference		Reference	
	3	1.44 (0.94–2.20)	0.092	1.51 (0.86–2.66)	0.155
Tumor histotype	Squamous cell	Reference		Reference	
	Adenocarcinoma	0.85 (0.53–1.36)	0.499	0.61 (0.31–1.21)	0.157
	Adenosquamous	1.68 (0.94–3.01)	0.082	0.57 (0.18–1.83)	0.347
	Other	4.30 (1.58–11.75)	<b>0.004</b>	4.96 (1.54–15.95)	<b>0.007</b>
Tumor diameter	2–3.99 cm	Reference		Reference	
	≥ 4 cm	1.18 (0.83–1.67)	0.351	1.06 (0.67–1.69)	0.794
Type of parametrial resection	A	1.67 (0.67–4.15)	0.269	3.02 (1.06–8.58)	<b>0.038</b>
	B	0.89 (0.52–1.52)	0.675	1.23 (0.62–2.46)	0.557
	C1	Reference		Reference	
	C2	0.84 (0.57–1.25)	0.399	1.15 (0.68–1.95)	0.601
No. of pelvic + paraaortic LN retrieved	Per 1-LN increase	0.99 (0.98–1.00)	0.294	0.99 (0.98–1.01)	0.358
	< 10	1.06 (0.47–2.39)	0.880	1.49 (0.56–3.98)	0.425
	10–19	0.98 (0.59–1.62)	0.943	1.32 (0.70–2.50)	0.392
	20–29	Reference		Reference	
	30–39	1.11 (0.70–1.78)	0.654	0.74 (0.36–1.50)	0.400
	40–49	0.89 (0.49–1.63)	0.716	1.09 (0.51–2.33)	0.824
	≥ 50	0.68 (0.34–1.37)	0.277	0.86 (0.36–2.04)	0.731
LVSI	No/unknown	Reference		Reference	
	Yes	0.94 (0.63–1.40)	0.753	1.20 (0.68–2.11)	0.536
Pathologic T stage (pT)	1b2	Reference		Reference	
	1b3	1.17 (0.78–1.77)	0.455	1.04 (0.61–1.76)	0.895
	2a1	1.39 (0.63–3.06)	0.416	1.27 (0.47–3.44)	0.635
	2a2	1.88 (0.80–4.44)	0.151	1.19 (0.69–5.32)	0.216

Abbreviations: AT, adjuvant therapy; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IR, intermediate risk; LN, lymph node; LVSI, lymphovascular space invasion; OS, overall survival.

\* Grade 2 chosen as a reference due to limited number of cases with grade 1.

### 3.3.3. Case-control propensity score matching of patients with and without AT

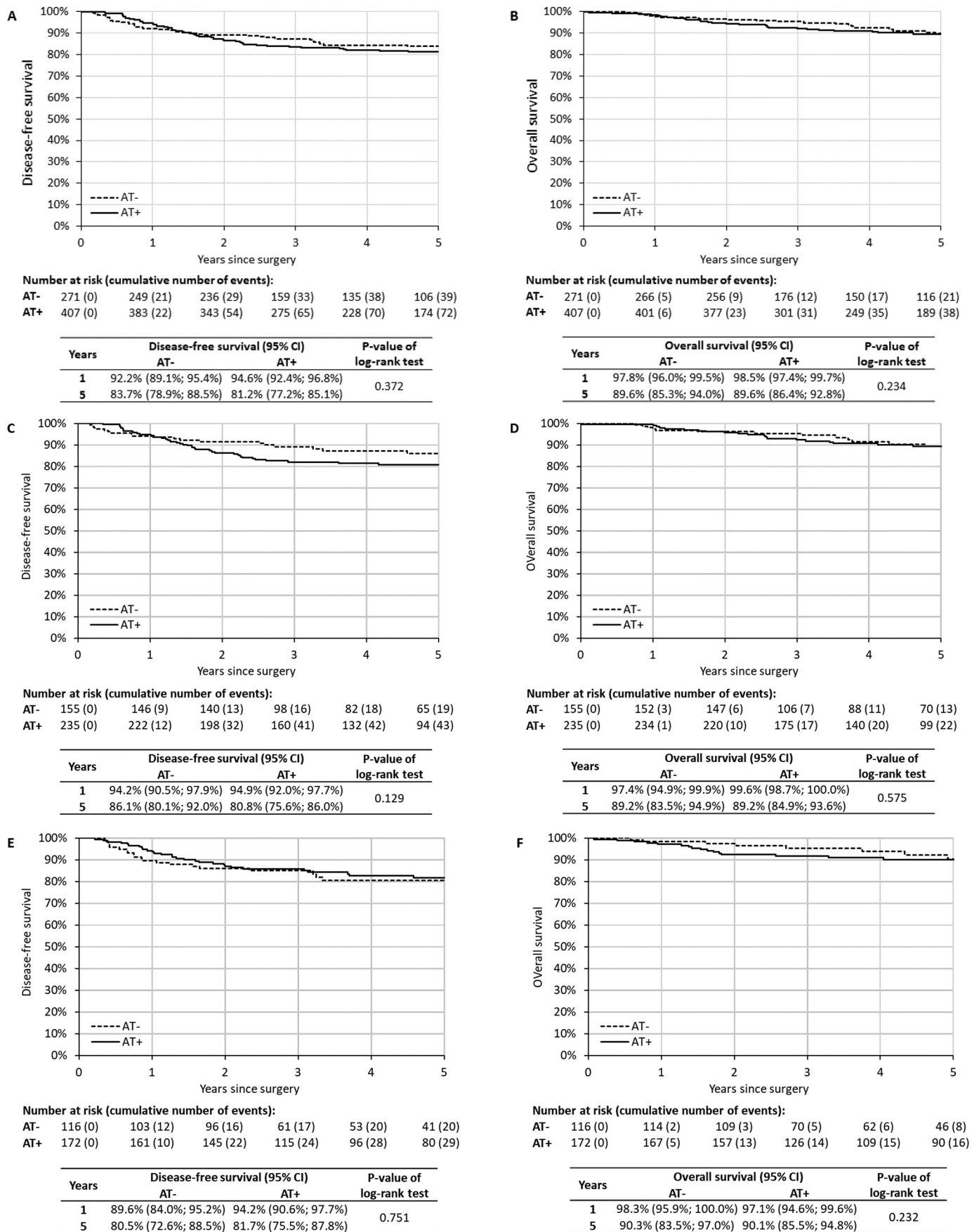
To reduce potential bias caused by imbalanced distribution of certain prognostic factors, we also matched patients in the AT– and AT+ groups 1:1 using the case-control propensity score matching procedure. DFS and OS were not influenced by the administration of AT after matching for potentially relevant covariates, including tumor size, LVSI, histotype, age, and the surgical approach ( $P_{DFS} = 0.915$ ;  $P_{OS} = 0.634$ ). In addition, when we applied propensity score matching for the subgroups of patients stratified by tumor size (2–3.99 cm and ≥4 cm) separately, we found no significant differences in DFS and OS between the AT– and AT+ groups (Supplementary Fig. S1).

## 4. Discussion

In our study of 692 IR SCCAN study [14] patients, the 5-year DFS and OS rates did not differ between the two groups of patients stratified by the use of AT ( $P_{DFS} = 0.372$ ;  $P_{OS} = 0.234$ ) with a median follow-up of 4.8 years. Furthermore, we found no survival benefit of AT in subgroup analyses of patients with tumor size 2–3.99 cm and positive LVSI ( $P_{DFS} = 0.129$ ;  $P_{OS} = 0.575$ ) or in patients with tumor size ≥4 cm ( $P_{DFS} = 0.751$ ;  $P_{OS} = 0.232$ ). These results are also supported by the results of the case-control propensity score matching analysis in which patients were matched for several prognostic factors.

The current international guidelines consider both types of management, namely radical surgery alone or radical surgery followed by

adjuvant (chemo)radiation, the standard of care for IR cervical cancer [1,6]. A Cochrane meta-analysis published in 2012 concluded that, based on moderate-quality evidence, adjuvant radiotherapy decreases the risk of disease progression without improving OS in this cohort of patients [13]. However, due to the quality of the evidence and because the meta-analysis was based on two rather outdated randomized controlled trials, the authors advocated for further randomized controlled trials in this setting. The first of the trials included in the meta-analysis was published in 1982 and 120 patients who underwent radical surgery were randomized to either adjuvant radiotherapy or no further treatment [17]. Although the oncological outcome was identical in both arms, one patient died due to a complication of radiotherapy. The second trial was the prospective GOG 92 study [4] in which patients with negative pelvic LNs and at least two IR factors after RH and pelvic lymphadenectomy were randomized to either adjuvant external beam radiotherapy ( $N = 137$ ) or no further treatment ( $N = 140$ ). Comparing to the present study, the GOG 92 included even a small proportion of patients (14%) with tumors ≤2 cm in size. Recurrences were reported in 21 (15%) patients of the radiotherapy group and in 39 (28%) patients of the radical surgery-only group, a difference that was highly significant (47%;  $P = 0.008$ ). However, it must be mentioned that the parameters of the trial reflected clinical practice of the era, >20 years ago. Tumor diameter was assessed by palpation. Furthermore, surgery, the main treatment modality, was not included in the protocol and the manuscript did not report any surgical data. Moreover, the prevalence of risk factors was not balanced between the two arms. A follow-up to the original GOG 92 paper was published in 2006 but did not



**Fig. 2.** Survival outcomes of patients stratified by the use of adjuvant treatment. Disease-free survival and overall survival in the entire cohort (A, B), in patients with tumor size 2–3.99 cm (C, D) and patients with tumor size  $\geq 4$  cm (E, F). Time 0 represents the date of surgery. Only patients with squamous cell, adenocarcinoma, or adenosquamous carcinoma were included in the survival analyses. AT–: no adjuvant treatment; AT+: adjuvant (chemo)radiotherapy or chemotherapy; CI: confidence interval.

substantially contribute to previously published evidence [18]. In that survival analysis, only seven additional recurrences were reported and the improvement in OS in the radiotherapy arm did not reach significance (HR 0.70, 90% CI 0.45–1.05;  $P = 0.074$ ). Importantly, only seven patients were lost to follow-up in the first year, but it was not reported how many more were lost during the longer follow-up period, raising questions about the reliability of the follow-up data [18].

Other papers showing a similar benefit of AT in IR patients were published later, though all of them were retrospective, the cohorts were small, and they were unable to avoid selection bias. A comprehensive overview of the literature supporting better survival after AT was published recently [19].

In 2018, a retrospective study compared the outcomes of IR patients after two treatment strategies in three institutions with different treatment strategies. The first institution did not administer AT to any of the IR patients (=AT– group), irrespective of tumor size, whereas the other two sites followed the “GOG criteria” and referred all IR patients for AT (=AT+ group). Only two out of 127 patients experienced pelvic recurrence after tailored radical surgery in the AT– group over a median follow-up of 6 years. None of the oncological outcomes, including the total relapse rate, OS, and disease-specific survival (DSS), in the AT– group differed from those of the control AT+ group. Local disease control in both groups was superior to the outcome of the original GOG trial [11].

These results were later supported by a group from Amsterdam [7] who reported the outcomes of 161 patients with IR cervical cancer who underwent radical surgery without AT. Only four patients (2.5%) died due to local treatment failure (pelvic recurrence). In a larger retrospective study of 861 IR patients, there were no significant differences in the 5-year DFS ( $P = 0.27$ ) and DSS ( $P = 0.20$ ) between the AT+ group (radiotherapy,  $N = 283$ ; chemoradiotherapy,  $N = 493$ ) and the AT– group ( $N = 85$ ) [8]. Similar observations were reported in cohorts from Turkey and Japan [9,20]. Finally, the most recent retrospective study of 765 IR patients who underwent RH and pelvic lymphadenectomy did not reveal any OS benefit of adjuvant radiotherapy ( $\pm$  chemotherapy) ( $P = 0.44$ ), not even in subgroup analyses according to tumor histotype and surgical approach [10]. However, it is important to mention that this study was based on The National Cancer Database, which does not collect data on tumor recurrence, location of relapse, or surgery radicality. It is therefore impossible to draw any conclusions on DFS or DSS based on the reported data.

The reasons for the better outcomes reported in the more recent studies than in the GOG 92 trial or older retrospective cohorts are likely multifactorial. Preoperative staging using modern imaging, allowing for more precise tumor, LN, adjacent structures, and even distant spread assessment, and improved standards for pathologic assessment of the cervix and LN could identify extrauterine disease with better precision, upgrading such cases to the high-risk category. As an example, in the surgery-only arm in one of the retrospective studies [11], SLN biopsy and pathologic ultrastaging were available in 80% of patients. In the group of 160 patients, micrometastases, which would be missed by standard pathological assessment, were detected in 33 (20.6%) patients by SLN ultrastaging. These patients were excluded from the IR group as high-risk cases and received adjuvant radiotherapy. Therefore, the IR population, although defined by the same inclusion criteria, could be more precisely selected than was possible 20 years ago when the GOG 92 trial was conducted. In addition, the techniques of parametrectomy and LN dissection have become more standardized, and better-quality surgery can contribute to improved outcomes in certain patient subgroups with a higher risk of parametrial and pelvic LN involvement.

The major limitation of this study is its retrospective design, which may introduce some bias, especially related to cohort selection. Because the measurement of the depth of stromal invasion is not well standardized, it was not recorded in the SCCAN database, even though it is a traditional GOG criterion. Instead, we used the pathologically confirmed

size of the tumor as the key prognostic parameter. It should also be noted that patients who received neoadjuvant chemotherapy were excluded. Preoperative chemotherapy makes the assessment of risk factors difficult and different from standard management due to the potential of tumor downsizing as well as lowering the rate of lymph node involvement. Inevitably, some risk factors are assessed at the time of diagnosis and others at the time of surgery.

Despite the retrospective design, the AT+ and AT– were balanced regarding key disease characteristics. The significant difference in disease stage is mainly due to the greater frequency of the 2a1 stage in the AT+ group, but not in the tumor size groups of  $<4$  and  $\geq 4$  cm. Moreover, we sought to attenuate the limitations of the retrospective design by employing case-control propensity score matching analyses to account for potential differences in key prognostic factors. The main difference between the groups was the higher frequency of distant recurrences in the AT+ group. However, this difference should not be significantly influenced by use of AT.

To our knowledge, our study represents one of the largest retrospective cohorts to show a lack of a survival benefit of AT after radical surgery. Due to the evidence from a prospective randomized trial, even though it was performed  $>20$  years ago, a definitive change to clinical practice will require a new prospective study. In fact, an international prospective randomized trial CERVANTES was recently launched and is expected to provide new evidence on the management of IR cervical cancer, reflecting 21st century standards in diagnostics, surgery, and radiotherapy [21].

In conclusion, our study of patients with IR cervical cancer has shown that radical surgery alone can achieve equal survival to that of radical surgery combined with adjuvant (chemo)radiation. We found no benefit of AT on either DFS or OS, and none of the subgroups of patients analyzed in this study showed a benefit of AT.

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## CRediT authorship contribution statement

**David Cibula:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – original draft. **Huseyin Akilli:** Investigation. **Jiri Jarkovsky:** Data curation, Formal analysis, Visualization. **Luc van Lonkhuijzen:** Investigation. **Giovanni Scambia:** Investigation. **Mehmet Mutlu Meydanli:** Investigation. **David Isla Ortiz:** Investigation. **Henrik Falconer:** Investigation. **Nadeem R. Abu-Rustum:** Investigation. **Diego Odetto:** Investigation. **Jaroslav Klát:** Investigation. **Ricardo dos Reis:** Investigation. **Ignacio Zapardiel:** Investigation. **Giampaolo Di Martino:** Investigation. **Jiri Presl:** Investigation. **Rene Laky:** Investigation. **Aldo López:** Investigation. **Vit Weinberger:** Investigation. **Andreas Obermair:** Investigation. **Rene Pareja:** Investigation. **Renata Poncová:** Investigation. **Constantijne Mom:** Investigation. **Nicolò Bizzarri:** Investigation. **Martina Borčinová:** Data curation, Formal analysis, Methodology, Writing – original draft. **Koray Aslan:** Investigation. **Rosa Angélica Salcedo Hernandez:** Investigation. **Guus Fons:** Investigation. **Klára Benešová:** Data curation, Formal analysis, Visualization. **Lukáš Dostálek:** Data curation, Investigation. **Ali Ayhan:** Investigation.

## Declaration of Competing Interest

The authors declared no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jgyno.2023.01.014>.

## References

- [1] D. Cibula, R. Potter, F. Planchamp, E. Avall-Lundqvist, D. Fischerova, C. Haie Meder, et al., The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer, *Radiother. Oncol.* 127 (2018) 404–416.
- [2] L. Dostalek, E. Avall-Lundqvist, C.L. Creutzberg, D. Kurdiani, J. Ponce, I. Dostalkova, et al., ESGO survey on current practice in the Management of Cervical Cancer, *Int. J. Gynecol. Cancer* 28 (2018) 1226–1231.
- [3] NCCN Guidelines Version 2.20202020.
- [4] A. Sedlis, B.N. Bundy, M.Z. Rotman, S.S. Lentz, L.I. Muderspach, R.J. Zaino, 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.* 73 (1999) 177–183.
- [5] D. Cibula, Early-stage intermediate-risk—the group with the most heterogenous management among patients with cervical cancer, *Int. J. Gynecol. Cancer* 32 (2022) 1227.
- [6] A. de Juan, A. Redondo, M.J. Rubio, Y. Garcia, J. Cueva, L. Gaba, et al., SEOM clinical guidelines for cervical cancer (2019), *Clin. Transl. Oncol.* 22 (2020) 270–278.
- [7] J. van der Velden, C.H. Mom, L. van Lonkhuijzen, M.Y. Tjong, H. Westerveld, G. Fons, Analysis of isolated loco-regional recurrence rate in intermediate risk early cervical cancer after a type C2 radical hysterectomy without adjuvant radiotherapy, *Int. J. Gynecol. Cancer* 29 (2019) 874–878.
- [8] L. Cao, H. Wen, Z. Feng, X. Han, J. Zhu, X. Wu, Role of adjuvant therapy after radical hysterectomy in intermediate-risk, early-stage cervical cancer, *Int. J. Gynecol. Cancer* 31 (2021) 52–58.
- [9] H. Akilli, Y.A. Tohma, A.N. Bulut, L.A. Karakas, A.N. Haberal, U.E. Kuscu, et al., Comparison of no adjuvant treatment and radiotherapy in early-stage cervical carcinoma with intermediate risk factors, *Int. J. Gynaecol. Obstet.* 149 (2020) 298–302.
- [10] D. Nasioudis, N.A. Latif, R.L. Giuntoli li, A.F. Haggerty, L. Cory, S.H. Kim, et al., Role of adjuvant radiation therapy after radical hysterectomy in patients with stage IB cervical carcinoma and intermediate risk factors, *Int. J. Gynecol. Cancer* 31 (2021) 829.
- [11] D. Cibula, N.R. Abu-Rustum, D. Fischerova, S. Pather, K. Lavigne, J. Slama, et al., Surgical treatment of “intermediate risk” lymph node negative cervical cancer patients without adjuvant radiotherapy—a retrospective cohort study and review of the literature, *Gynecol. Oncol.* 151 (2018) 438–443.
- [12] Q.D. Pieterse, J.B.M.Z. Trimbos, A. Dijkman, C.L. Creutzberg, K.N. Gaarenstroom, A.A.W. Peters, et al., Postoperative radiation therapy improves prognosis in patients with adverse risk factors in localized, early-stage cervical cancer: a retrospective comparative study, *Int. J. Gynecol. Cancer* 16 (2006) 1112–1118.
- [13] L. Rogers, S.S. Siu, D. Luesley, A. Bryant, H.O. Dickinson, Radiotherapy and chemoradiation after surgery for early cervical cancer, *Cochrane Database Syst. Rev.* 5 (2012) Cd007583.
- [14] D. Cibula, L. Dostalek, J. Jarkovsky, C.H. Mom, A. Lopez, H. Falconer, et al., The annual recurrence risk model for tailored surveillance strategy in patients with cervical cancer, *Eur. J. Cancer* 158 (2021) 111–122.
- [15] N. Bhatla, J.S. Berek, M. Cuello Fredes, L.A. Denny, S. Grenman, K. Karunaratne, et al., Revised FIGO staging for carcinoma of the cervix uteri, *Int. J. Gynaecol. Obstet.* 145 (2019) 129–135.
- [16] D. Querleu, D. Cibula, N.R. Abu-Rustum, 2017 update on the Querleu-Morrow classification of radical hysterectomy, *Ann. Surg. Oncol.* 24 (2017) 3406–3412.
- [17] K. Bilek, K. Ebeling, H. Leitsmann, G. Seidel, Radical pelvic surgery versus radical surgery plus radiotherapy for stage Ib carcinoma of the cervix uteri. Preliminary results of a prospective randomized clinical study, *Archiv. Geschwulstforschung* 52 (1982) 223–229.
- [18] M. Rotman, A. Sedlis, M.R. Piedmonte, B. Bundy, S.S. Lentz, L.I. Muderspach, et al., A phase III randomized trial of postoperative pelvic irradiation in stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study, *Int. J. Radiat. Oncol. Biol. Phys.* 65 (2006) 169–176.
- [19] J. Rodriguez, D. Viveros-Carreño, R. Pareja, Adjuvant treatment after radical surgery for cervical cancer with intermediate risk factors: is it time for an update? *Int. J. Gynecol. Cancer* 32 (2022) 1219.
- [20] H. Yahata, K. Sonoda, S. Inoue, N. Yasutake, K. Kodama, H. Yagi, et al., Is adjuvant therapy necessary for patients with intermediate-risk cervical cancer after open radical hysterectomy? *Oncology* 1–6 (2020).
- [21] D. Cibula, M. Borčinová, R. Kocian, D. Felzl, S. Argalacsova, P. Dvorak, et al., CERVANTES: an international randomized trial of radical surgery followed by adjuvant (chemo) radiation versus no further treatment in patients with early-stage, intermediate-risk cervical cancer (CEEGOG-CX-05; ENGOT-CX16), *Int. J. Gynecol. Cancer* 32 (2022) 1327.