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Surgical treatment of “intermediate risk” lymph node negative cervical cancer patients without adjuvant radiotherapy—a retrospective cohort study and review of the literature.

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Abstract

Objectives: The role of adjuvant radiotherapy for lymph node-negative stage IB patients with tumor-related negative prognostic factors is not uniformly accepted. It is advocated based on the GOG 92 trial, which was initiated in 1989. The aim of the current study is to report the oncological outcome of “intermediate risk” patients treated by tailored surgery without adjuvant radiotherapy. Data from two institutions that refer these patients for adjuvant radiotherapy served as a control group.

Methods: Included were patients with stage IB cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy, who had negative pelvic lymph nodes but a combination of negative prognostic factors adopted from the GOG 92 trial. Data were obtained from prospectively

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Author contribution

All authors contributed to data analysis and writing of the manuscript.

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Conflict of interest

Authors do not declare any conflict of interest related to this paper.

collected databases of three institutions. Radical surgery was a single-treatment modality in one of them and in the remaining two institutes it was followed by adjuvant chemoradiation.

Results: In 127 patients who received only radical surgery, with a median follow-up of 6.1 years, the local recurrence rate was 1.6% (2 cases), and total recurrence was 6.3% (8 cases). Disease-specific survival at five years was 95.7% (91.9%; 99.4%) and 91% (83.7%; 98.3%) at 10 years. The only significant factor for disease-specific survival was tumor size ≥ 4 cm ($P=0.032$). The recurrence rate, local control or overall survival did not differ from the control group. Adjuvant radiotherapy was not a significant prognostic factor within the whole cohort.

Conclusions: An excellent oncological outcome, especially local control, can be achieved by both radical surgery or combined treatment in stage IB lymph node-negative cervical cancer patients with negative prognostic factors. The substantially better outcome than in the GOG 92 trial can be attributed to more accurate pre-operative and pathological staging and an improvement in surgical techniques.

Introduction

Adjuvant radiotherapy is advocated in early-stage cervix cancer patients following radical surgery in the “intermediate risk” group, characterized by negative pelvic lymph nodes (LN) but a combination of tumor-related high-risk features such as tumor size, LVSI, and depth of stromal invasion. The evidence for the efficacy of adjuvant radiotherapy comes from a randomized study of whole pelvic radiotherapy or no further treatment following radical hysterectomy and pelvic lymphadenectomy [1]. Adjuvant radiotherapy was associated with a 47% reduction in the risk of recurrence. Extended follow-up data published in 2006 confirmed the improvement of progression-free survival (PFS) in the adjuvant radiotherapy group [2]. Other publications reported similar improved outcomes after adjuvant radiotherapy, nevertheless suffered from limitations such as small sample size, heterogeneity of patient population, or lack of control groups. It should be noted that from today’s perspective the original GOG trial also had many limitations. The study was conducted more than two decades ago and reflects the diagnostic and treatment standards of that time. As an example, the main inclusion criterion, tumor size, was estimated by visual inspection and palpation. Most importantly, surgery, the main treatment modality, was not standardized by the protocol. The outcome of the surgery-only arm was poor by current expectations; total recurrence was 28%, mainly due to 67% of pelvic recurrences.

The aim of this study was to report data from a large single institutional cohort of “intermediate risk” (IR) patients staged by contemporary clinical and radiological staging, pathological assessment, and managed by tailored surgical treatment without adjuvant therapy. A control group was obtained from two institutions which traditionally refer IR patients for adjuvant radiotherapy. All three institutions possess prospectively collected databases of consecutively treated patients. The IR patient selection was based on negative prognostic risk factors adopted from the original GOG trial.

Methods

Selection of patients

Cases were included that had negative pelvic LN but a combination of tumor-related negative prognostic risk factors (LVSI and deep stromal invasion OR LVSI and tumor size 2 cm OR tumor size 4 cm) and which were treated between 2000 and 2015. Patients were excluded who received neoadjuvant chemotherapy; those with a rare histological type (other than squamous cancer, adenocancer or adeno-squamous cancer); those who received fertility-sparing treatment; and those in whom planned radical surgery, including radical hysterectomy followed by systematic pelvic lymphadenectomy, was abandoned.

In the Gynecological Oncology Center, Prague, Czech Republic (PRG), a combination of intermediate risk factors is not considered an indication for any adjuvant treatment. In patients with bulky tumors, the extent of parametrectomy is increased but only patients with LN involvement, parametrial involvement, and/or positive parametrial or vaginal margins are referred for adjuvant radiotherapy. All consecutive patients who fulfilled inclusion criteria were included in the Surgery-only group. Data were matched with the Czech National Database of Death, so mortality data and a cause of death were verified.

In Memorial Sloan Kettering Cancer Center, New York, USA (MSK) and in the Peter MacCallum Cancer Centre, Melbourne, Australia (MEL), LN-negative patients with a combination of prognostic risk factors (GOG criteria) are referred for adjuvant chemoradiation. Cases that received a combined treatment were selected from those two centers into the control group.

Surgery

The types of radical hysterectomy were classified using the Querleu-Morrow classification system [3]. Type B corresponds to a modified radical hysterectomy, type C1 to a nerve-sparing procedure, and type C2 to type III radical hysterectomy. The latter type of radical hysterectomy was performed in only one institution (PRG), in cases with tumors larger than 3 cm and/or complete infiltration of the cervical stroma.

SLN biopsy was performed in two institutions (PRG and MSK), in combination with a systematic pelvic lymphadenectomy (PRG) or using the Memorial-Sloan Kettering SLN algorithm (MSK). For the detection of SLN, a colored dye technique or a combined technique with radioactive tracer was used in both departments. In larger tumors, the tracer application technique was modified, as published recently [4].

Adjuvant radiotherapy in the control group

The technique of adjuvant radiotherapy differed between the two institutions. In the MEL, patients received central pelvic radiotherapy using a four-field technique. Forty-five to 50.4 Gray (Gy) were given in 25–28 fractions using photons (12–18 MeV). A smaller field with a 3 cm margin around the vaginal vault was further boosted to a total dose of 54 Gy in 30 fractions. The central pelvic radiation field was planned to cover the parametrial attachments, including the para vaginal space [5]. The internal iliac and obturator nodal

groups were included in the field by default; however, the anterior external iliac nodes and presacral nodes were excluded in the small field. All patients were treated prone on a belly board and given concurrent cisplatin in a single weekly dose of 40mg/m² (5–6 doses) unless contraindicated. Vaginal brachytherapy was not administered to any of the patients.

At MSK, patients were treated with postoperative pelvic IMRT. Technique was described previously [6], but in brief, the vaginal cuff and pelvic lymph nodes including presacral nodes were treated to 45–50.4 Gy at 1.8 Gy per fraction. All but 6 cases received concurrent cisplatin chemotherapy.

Follow-up

In all three institutions, follow-up visits were scheduled at similar intervals: every 3 months for the first 2 years, every 6 months for the next 3 years, and yearly thereafter. Physical examinations, including pelvic examination, were performed routinely. An assessment of symptoms or treatment complications were performed when indicated. PET/CT was used routinely in MEL, was at the surgeons' discretion in MSK, and was performed only in symptomatic patients in PRG. The length of the follow-up was determined as the interval from surgery until the last follow-up visit or patient death.

Statistical analysis

Standard descriptive statistics were applied: absolute and relative frequencies for categorical variables and mean $\pm$ standard deviation for continuous variables. The Mann-Whitney U test was used to assess the association between categorical and continuous variables, while Fisher's exact test was employed to evaluate associations between categorical variables. Estimates of overall survival, disease-specific survival, and disease-free survival were performed on the base of Kaplan-Meier. The survival curves were compared using the log-rank test. Univariate analysis of risk factors was performed using Cox proportional hazard regression models. The level $p < 0.05$ was considered statistically significant for all analyses. Statistical analyses were performed in SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

Results

In all, 231 cases were enrolled in the study; 127 from a single institution (PRG) treated with radical surgery without adjuvant treatment (surgery-only group) and 104 from two institutions (MSK = 21 cases, MEL = 83 cases), in whom radical surgery was followed by adjuvant radiotherapy (control group).

Patient characteristics are shown in Table 1. The groups were balanced in age, distribution of pathologic tumor types, depth of stromal invasion or tumor grading. The radicality of surgical treatment was more extensive in the Surgery only group, in which parametrectomy type C2 was performed in 33% of patients. The mean number of removed pelvic lymph nodes (LN) was 37 and 19 per patient in the surgery-only and control groups respectively. The duration of follow-up was longer in the control group (6.1 vs. 6.9 years; $P < 0.001$). The proportion of tumor size categories did not differ between the groups; there were, however,

more cases with stage IB2 (12% vs. 24%; $P=0.022$) and LVSI (53% vs. 75 %; $P=0.001$) in the control group. Open surgery was the prevailing surgical approach, used in 92% of patients in the surgery-only group and in 72% of control-group patients.

Prognostic parameters

In the surgery-only group, only tumor size > 4 cm was found to be significant prognostic factor for disease specific survival (DSS) by a univariate Cox proportional analysis ($P=0.032$). In the whole data set, tumor size 2–4 cm ($P=0.013$) and an adeno-squamous tumor type ($P=0.022$) were identified as significant prognostic variables (Table 4), while adjuvant radiotherapy was not significant for DSS ($P=0.745$).

Recurrence pattern

Total and pelvic recurrence rates reached 6.3% and 1.6% in the surgery-only group (Table 2). Total recurrence rates did not differ from the control group (11.5%; $P=0.168$). There were, however, fewer distant or combined recurrences (4.7% vs. 11.52%) in the surgery-only group. The death rate was not statistically different between the groups (7% vs. 14%; $P=0.084$).

Disease-specific survival and overall survival

Overall survival (OS) in the surgery-only and control groups was 95% vs. 91% over 5 years, and 89% vs. 84% over 10 years (Table 3a). DSS for 5 and 10 years reached 96% and 91% in the surgery-only group versus 95% and 90% in the control group (Table 3b). The Kaplan-Meier estimate was not significantly different between the groups for OS ($P=0.317$) (Figure 1) or for DSS ($P=0.745$) (Figure 2).

Discussion

Only two out of 127 intermediate-risk patients with a combination of tumor-related risk factors recurred in the pelvis after a tailored radical surgery without any adjuvant treatment with a median follow-up of 6 years. None of the oncologic outcome variables, such as total relapse rate, death rate, overall survival or disease-specific survival, was different from the control group of patients who had received adjuvant radiotherapy after radical surgery. The local control of the disease in both groups was much superior to the outcome of both arms of the original GOG trial (pelvic recurrence rate in surgery only arms 2% versus 19% and in combined treatment arms 0% versus 13%). The reasons for this much better outcome in the current study could be multifactorial. More precise pre-operative staging using modern imaging and improved standards of pathologic assessment of both cervix and lymph nodes could identify extrauterine disease with better precision, excluding such cases from the present study. In the surgery-only group, SLN biopsy and pathologic ultrastaging were conducted in 80% of patients. During the study period, micrometastases were detected in 33 patients by SLN ultrastaging. These patients received adjuvant radiotherapy and were excluded from the database as LN-positive cases. Consequently, the population, although defined by the same inclusion criteria, could be much better selected than 20 years ago. In addition, the technique of parametrectomy and lymph node dissection has been harmonized

internationally, which can play a significant role in the subgroup with a higher risk of parametrial and pelvic lymph node involvement.

Criteria for tumor-related negative prognostic factors were adopted from original GOG criteria but simplified. Categories of tumors ≤ 4 cm but middle 1/3 stromal invasion or even ≤ 5 cm but superficial stromal invasion, which were included in the original GOG criteria, are extremely rare if the tumor size is assessed by modern imaging or pathology. These categories appeared in the original GOG study because the tumor sizes were determined, inaccurately, by palpation. Both tumor size and stromal invasion were assessed by pathology in our trial, which reflects current clinical practice.

A study of 645 patients with squamous cervical cancer who were prospectively registered before surgery identified clinical tumor size, positive LVSI, and the depth of tumor invasion as independent prognostic factors [7]. In this study, which was conducted in the '70s, patients with at least one of the above risk factors had on average a 31% risk of recurrence. Consequently, the GOG 92 trial randomized patients with negative pelvic LNs but at least two out of three of the above risk factors, after radical hysterectomy and pelvic lymph node dissection, into two arms, with no further treatment (N=140) or adjuvant radiotherapy (N=137). Patients in the radiotherapy arm received external beam radiation (46 – 50 Gy). The trial was powered to assess recurrence-free interval but not overall survival. Recurrences were reported in 21 (15%) patients in the radiotherapy group and in 39 (28%) patients in the radical surgery-only group. The difference in risk of recurrence between the groups was highly significant (47%; $P=0.008$). Applying current standards, the multiple limitations of the GOG trial should be considered. Although patients were randomized to two adjuvant treatment strategies, the prevalence of risk factors was not balanced in the two arms, with a higher prevalence of LVSI (35% vs. 24%) and more patients with tumors > 4 cm in the RS group. Assessment of inclusion criteria, including risk factors, reflected the clinical practice of the era of more than 20 years ago. Tumor diameter was assessed by palpation, while stromal invasion was measured by pathology. The protocol of the study ignored the quality of the main treatment modality, which was the surgery. There were no specific requirements for the quality of the surgery and the paper did not report any surgical data such as the type and extent of radical hysterectomy, number of lymph nodes or duration of surgery.

The follow-up of the original GOG 92 paper was published in 2006 [2]. Interestingly, only 7 additional recurrences were reported. The improvement in overall survival did not reach significance ($HR=0.70$; $P=0.074$). Importantly, only 7 patients were lost to follow-up in the first two years, but it was not reported how many more were lost during the extensive follow-up period.

The Cochrane meta-analysis published in 2012 concluded that, based on moderate quality evidence, adjuvant radiotherapy decreases the risk of disease progression without improving overall survival [8]. The authors advocated for a new randomized trial powered to detect the benefit of adjuvant radiotherapy in different prognostic subgroups; however, that trial has never been conducted. Meta-analysis was based on only two randomized control trials. In addition to GOG 92, a second trial had already been published in 1982, originating in the German Democratic Republic. It randomized 120 patients after radical surgery for no further

treatment of adjuvant radiotherapy with 52 Gy by external radiation with a Co60 unit [9]. The oncological outcome was identical in both arms, although there were three local recurrences in the surgery-only arm, while all recurrences in the radiotherapy arm were outside the pelvis. One patient died due to the radiotherapy complication. The paper did not report any data on prognostic parameters.

Although there were many more papers published on the same topic later, none of them contributed substantially to the quality of evidence brought by the GOG trial. All of them were retrospective, cohorts were small, and they were unable to avoid a selection bias. Two retrospective cohorts of 116 patients treated by radical surgery and 55 patients by radical surgery followed by adjuvant radiotherapy were analyzed from the Harvard Medical School [10]. Patients with LVSI were less likely to develop recurrence after combined treatment. The two groups were not balanced by the prevalence of risk factors, however. In another paper, a group of authors from two institutions from Belgium and Australia concluded that even small field pelvic radiation appears to significantly improve disease-free survival in intermediate risk LN-negative patients [5]. The conclusion was, however, based on 25 cases that were compared with the outcome of the non-irradiated arm of the GOG trial. Another paper compared two adjuvant radiotherapy strategies in the same population [11]. Based on similar disease-specific survival, they concluded that lower pelvic radiotherapy is equally effective as whole pelvic radiation. The conclusion is rather surprising, considering that there were 5 patients with upper-pelvic relapse in the low pelvic radiotherapy group while no such recurrence site was reported in the control group. Another retrospective study compared 3 cohorts of patients without adjuvant treatment (N=34), with adjuvant RT (N=49), and with adjuvant chemoradiation (N=89) and concluded that adjuvant RT can improve the outcome. [12]. Differences in 3-year DFS were significant (68% vs. 91% vs. 98%). Selection bias was very likely in place in this study, considering major differences in the outcome between the groups. The benefit of adjuvant radiotherapy was also reported by a Dutch group, based on significantly better 5-year disease-free survival (57% vs. 43%) [13]. The outcome of only 34 cases was compared to a small historical cohort of 17 patients. Other trials were either very small [14,15] or they included other risk factors such as positive surgical margins or positive LN [16,17].

The role of adjuvant radiotherapy in the management of early-stage cervical cancer patients is becoming increasingly important for the future of radical surgery in the management of cervical cancer. According to the new ESGO-ESTRO-ESP guidelines for the management of cervical cancer, radical surgery should not be performed if an indication for adjuvant radiotherapy is known before the surgery [18]. A patient should be referred for primary chemoradiation instead, and a combined treatment by two modalities avoided. Currently, the SHAPE study (NCT01658930) is evaluating the safety of parametrectomy avoidance in tumors below 2 cm. If, in the future, the SHAPE trial was positive and all IR patients were referred for primary chemoradiation, only a small group of patients would remain candidates for radical surgery (tumors 2 – 4 cm, LVSI negative). This makes the topic challenged in this article, if all IR patients must be radiated after radical surgery, so actual.

The authors are aware of the limitations of this study, mainly its retrospective nature. Having a control group from two different institutions cannot substitute a prospective design. The

prevalence of risk factors in the two groups in our study was not equally balanced. LVSI was more frequent in the control group, which can be an explanation for the higher incidence of distant metastases [19]. Also, surgery may have been more extensive in the surgery-only group, as demonstrated by the higher lymph node count and the higher proportion of the more radical type of parametrectomy. In spite of these limitations, the value of this trial is in reporting an excellent local control in a large cohort of IR patients treated by tailored radical surgery without any adjuvant therapy. We should keep in mind that no major improvement of distant control can be expected from loco-regional treatment modality, including both surgery and radiotherapy. Therefore, the pelvic recurrence rate should be the main end-point of a trial comparing these two modalities or their combination. In our surgical cohort, 127 patients would have to receive adjuvant radiotherapy to prevent only two local recurrences, which still can be potentially salvaged.

Another limitation of our study is the lack of morbidity assessment in both groups. The retrospective evaluation and comparison of morbidity is always challenging and can be inaccurate due to the differences in follow-up strategies, the lack of a universally accepted classification system for the assessment of treatment complications and, also, the difficulties in comparing the severity of different types of complications and their impact on quality of life, which may occur at different intervals after surgery or radiotherapy.

Conclusion

An excellent local control can be achieved by radical surgery as a single modality, in IR cervical cancer patients without LN involvement. This study should stimulate the design of a prospective study about the role of adjuvant radiotherapy and the identification of a subgroup of patients who may benefit from a combined treatment in this era of modern imaging, precise pathology assessment, and improved surgical standards.

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Highlights

Intermediate risk patients with IB N0 cervical cancer have excellent oncological outcome after radical surgery only.

Recurrence rate in this group was 6% and local recurrence rate 2%, without adjuvant treatment.

No significant differences in oncological outcome were found between the groups with or without adjuvant radiotherapy

Substantially better outcome was reported in our groups in comparison to the original GOG 92 trial.

Number of patients at risk:

Surgery-only group:

127	126	114	103	86	69	60	44	33	27	21
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Control group:

104	102	94	89	83	77	65	55	49	44	38
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Figure 1.

Kaplan-Meier estimate of overall survival in patients who received a combined treatment (control group) or radical surgery only (surgery-only group).

Number of patients at risk:

Surgery-only group:

127	126	114	103	86	69	60	44	33	27	21
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Control group:

104	102	94	89	83	77	65	55	49	44	38
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Figure 2.

Kaplan-Meier estimate of disease-specific survival in patients who received a combined treatment (control group) or radical surgery only (surgery-only group).

Table 1:

Characteristics of the whole group

Parameter		Total (N = 231)	Surgery only group (N = 127)	Control group (N = 104)	P ^I
Age		47.1 ± 13.1	47.0 ± 13.5	47.3 ± 12.5	0.565
Type of radical hyst	B	22 (9.9%)	22 (18.5%)	0 (0.0%)	<0.001
	C1	162 (72.6%)	58 (48.7%)	104 (100.0%)	
	C2	39 (17.4%)	39 (32.8%)	0 (0.0%)	
Largest tumor size	(mm)	29.7 ± 12.4	27.6 ± 11.5	32.2 ± 13.2	0.003
	20 mm	55 (23.9%)	34 (26.8%)	21 (20.4%)	0.160
	21–40 mm	139 (60.4%)	78 (61.4%)	61 (59.2%)	
	> 40 mm	36 (15.7%)	15 (11.8%)	21 (20.4%)	
Depth of stromal invasion	(mm)	13.9 ± 5.7	13.0 ± 6.3	13.4 ± 6.0	0.261
Histologic type	Adeno	56 (24.2%)	27 (21.3%)	29 (27.9%)	0.124
	Adenosquam	12 (5.2%)	4 (3.1%)	8 (7.7%)	
	Squamous	163 (70.6%)	96 (75.6%)	67 (64.4%)	
pT	IB1	191 (82.7%)	112 (88.2%)	79 (76.0%)	0.022
	IB2	40 (17.3%)	15 (11.8%)	25 (24.0%)	
Grade	1	23 (10.1%)	10 (8.1%)	13 (12.6%)	0.368
	2	100 (44.1%)	59 (47.6%)	41 (39.8%)	
	3	104 (45.8%)	55 (44.4%)	49 (47.6%)	
SLN biopsy		108 (46.8%)	100 (78.7%)	8 (7.7%)	<0.001
No. of removed pelvic LNs		28.9 ± 15.6	37.4 ± 14.0	18.6 ± 10.4	<0.001
LVSI		145 (62.8%)	67 (52.8%)	78 (75.0%)	0.001
Duration of follow-up	(years)	6.9 ± 3.7	6.1 ± 3.3	7.9 ± 4.0	<0.001

Data are described by absolute (relative) frequencies or mean ± SD.

^IP-value of Fisher's exact test for categorical variables and P-value of Mann-Whitney U test for continuous variables.

LN, lymph node; LVSI, lymphovascular space invasion; SLN, sentinel lymph node.

Relapse rate, site of relapse, and death rate in patients who received a combined treatment (Control group) or radical surgery only (Surgery only group).

Table 2:

Parameter	Surgery only group (N = 127)	Control group (N = 104)	<i>p</i> ^{<i>f</i>}
Relapse	8 (6.3%)	12 (11.5%)	0.168
Site of relapse	Combine d or distant	12 (11.5%)	0.147
(if relapse = yes)	Pelvic	0 (0.0%)	
Death	9 (7.1%)	15 (14.4%)	0.084

Data are described by absolute (relative) frequencies.

^{*f*}*p*-value of Fisher's exact test.

ITC, isolated tumor cells; MIC, micrometastasis.

Table 3a:

Kaplan-Meier estimate of **overall survival** in patients who received a combined treatment (Control group) or radical surgery only (Surgery only group).

Overall survival	Surgery only group (N = 127)	Control group (N = 104)	P [/]
1-year	99.2% (97.7%; 100.0%)	98.1% (95.4%; 100.0%)	
5-year	94.5% (90.2%; 98.9%)	90.6% (84.7%; 96.5%)	0.317
10-year	88.5% (80.6%; 96.4%)	84.4% (76.3%; 92.6%)	

[/] P-value of log-rank test.

Kaplan-Meier estimate of **disease-specific survival** in patients who received a combined treatment (Control group) or radical surgery only (Surgery only group).

Table 3b:

Disease-specific survival	Surgery only group (N = 127)	Control group (N = 104)	p ¹
1-year	99.2% (97.7%; 100.0%)	99.0% (97.1%; 100.0%)	
5-year	95.7% (91.9%; 99.4%)	94.6% (90.0%; 99.2%)	0.745
10-year	91.0% (83.7%; 98.3%)	90.4% (83.9%; 96.9%)	

¹P-value of log-rank test.

Table 4:

Risk factors for **disease-specific survival** (univariate Cox proportional hazard regression models) in the whole cohort

Predictors (N = 231)		No. (%) of events	HR (95% CI)	P
Age	10-year increment	15 (6.5 %)	1.07 (0.72; 1.59)	0.741
Largest tumor size	20 mm	0 (0.0 %)	Ref.	
	21–40 mm	13 (9.4 %)	-	0.013 [/]
	> 40 mm	2 (5.6 %)	-	0.078 [/]
Histologic type	Adenocancer	3 (5.4 %)	Ref.	Ref.
	Adeno-squamous	3 (25.0 %)	6.51 (1.31; 32.46)	0.022
	Squamous	9 (5.5 %)	1.00 (0.27; 3.70)	0.997
Grade	1	1 (4.3 %)	Ref.	
	2	3 (3.0 %)	0.75 (0.08; 7.20)	0.803
	3	11 (10.6 %)	2.56 (0.33; 19.81)	0.369
No. of removed LNs	Increment of 10	15 (6.5 %)	1.00 (0.72; 1.39)	0.994
LVSI	No	2 (2.3 %)	Ref.	
	Yes	13 (9.0 %)	3.37 (0.76; 14.99)	0.110
Adjuvant radiotherapy	No	7 (5.5 %)	Ref.	
	Yes	8 (7.7 %)	1.18 (0.43; 3.28)	0.745

[/]HR could not be computed; P-value of log-rank test is reported.

LN, lymph node; LVSI, lymphovascular invasion.

Ref.: reference category within given variable categories.