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Neoadjuvant Platinum-based Chemotherapy Followed by Radical Hysterectomy for Stage Ib2-IIb Adenocarcinoma of the Uterine Cervix – An Italian Multicenter Retrospective Study

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Abstract. *Aim: To assess the patterns of recurrence and clinical outcomes of patients with cervical adenocarcinoma who underwent neoadjuvant platinum-based chemotherapy (NACT) followed by radical hysterectomy. Patients and Methods: Data were retrospectively analyzed for 82 patients with International Federation of Gynecology and Obstetrics stage Ib2-IIb cervical adenocarcinoma who underwent this chemo-surgical treatment. The median follow-up of survivors was 89 months (range=5-208 months). Results: Pathological complete response, optimal response and suboptimal response with intra-cervical residual disease were obtained in five (6%), 10 (12%) and 36 (44%) patients, respectively. Adjuvant external-beam radiotherapy with or without concurrent chemotherapy was administered to 47 patients. Nineteen (23%) out of the 82 patients experienced recurrence after a median of 12 months (range=5.3-86.8 months). Recurrent disease was pelvic in 12 (63%) patients, extra-pelvic in five (26%), and both pelvic and extra-pelvic in two (10%). According to pathological response, tumor relapsed in 10% of optimal responders, 14% of sub-optimal responders with intra-cervical residual disease, and 36% of sub-optimal responders with extra-cervical residual disease or non-responders. Five-year recurrence-free and overall survival were 77% and 84%, respectively. Patients who achieved an optimal response or sub-optimal response with intra-cervical residual disease had better 5-year recurrence-free (87% vs. 64%, p=0.017) and overall (92% vs. 74%, p=0.012) survival than those who had sub-optimal response with extra-cervical residual disease or no response. The latter had a 1.441-fold higher risk of recurrence and a 1.652-fold higher risk of death than those who obtained an optimal response or a sub-optimal response with intra-cervical residual disease. Conclusion: NACT followed by radical hysterectomy may be an option for patients with stage Ib2-IIb adenocarcinoma of the uterine cervix.*

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Concurrent cisplatin-based chemotherapy and radiotherapy (CCRT) is the standard-of-care for patients with locally advanced cervical cancer and recent meta-analyses of randomized trials have confirmed that this therapeutic approach significantly improves progression-free survival and overall survival compared to definitive radiotherapy alone (1-5). Neoadjuvant chemotherapy (NACT) followed by radical hysterectomy is an interesting alternative to CCRT for patients with locally advanced cervical cancer, especially for those with stage Ib2-IIb disease (6-16). A meta-analysis of six randomized trials, including 1078 patients with early or locally advanced disease, revealed that NACT followed by radical hysterectomy significantly reduced the risk of progression [hazard ratio (HR)=0.75, 95% confidence Interval (CI)=0.61-0.93, p=0.008] and the risk of death (HR=0.77, 95% CI=0.62-0.96 p=0.02) compared to primary radical hysterectomy (17). Moreover, a meta-analysis of five

randomized trials, including 872 patients with locally advanced cervical cancer, showed that the chemo-surgical treatment obtained better overall disease-free (HR=0.68, 95% CI=0.56-0.82), locoregional disease-free (HR=0.68, 95% CI=0.56-0.82), metastasis-free (HR=0.63, 95% CI=0.52-0.78), and overall (HR=0.65, 95% CI=0.53-0.80) survival compared with definitive radiotherapy (18). An European Organization for Research and Treatment of Cancer (EORTC) randomized trial is currently comparing NACT plus radical surgery *versus* CCRT in patients with stage Ib2, IIa or IIb cervical cancer (EORTC protocol 55994).

Adenocarcinoma of the uterine cervix represents 10-20% of all cervical cancer cases, but its relative and absolute incidence has increased over the past four decades (19, 20). Some authors have reported that cervical adenocarcinoma has a worse prognosis than cervical squamous cell carcinoma (12, 21-27).

Clinical studies regarding NACT followed by radical surgery have usually included patients with cervical squamous cell carcinoma (6-8, 11, 13, 15) or with cervical carcinoma of any histological type mainly consisting of squamous cell carcinoma (9, 12, 14, 16, 28-35), whereas very few studies have selectively investigated this therapeutic approach in patients with cervical adenocarcinoma (36-42). Some authors suggested that non-squamous carcinoma was associated with a lower response rate to NACT than squamous cell carcinoma (14, 28, 29), but others did not confirm these observations (30, 31, 33, 34).

The aim of this retrospective multicenter study was to assess the patterns of recurrence and the clinical outcomes of patients with cervical adenocarcinoma who underwent platinum-based NACT followed by radical hysterectomy.

Patients and Methods

This retrospective study was conducted on 82 patients with International Federation of Gynecology and Obstetrics (FIGO) stage Ib2-IIb cervical adenocarcinoma who underwent platinum-based NACT followed by radical hysterectomy with pelvic lymphadenectomy at the Department of Gynecology and Obstetrics of the University of Pisa and Turin between 1992 and 2014, and at the Department of Gynecology and Obstetrics of the University of Brescia and at the Department of Gynecologic Oncology of the European Institute of Milan between 1999 and 2014. Most of these patients had been included in a prior retrospective study of our cooperative group (16). Platinum-based NACT followed by surgery was the common treatment strategy for patients with stage Ib2–IIb disease, maximum age of 70 years and good performance status at our Oncologic Centers. All women of the present retrospective investigation provided written informed consent for this treatment modality. Patients who did not complete the planned cycles of NACT or who did not undergo radical surgery after NACT because of progressive disease or poor general condition were not included in the present study.

The hospital records, including surgical notes and pathological reports, of the women were collected using a common form with standardized items and a common database. Patient characteristics at initial diagnosis (date, age, FIGO stage, histological grade, tumor size), NACT regimen, type of radical hysterectomy, and pathological responses on surgical specimens were reported for each case.

Pre-treatment assessment included history, physical examination, vaginal-pelvic examination, colposcopy, biopsy, complete blood analysis, chest X-ray, and, in the last decade, pelvic magnetic resonance imaging (MRI). Cystoscopy or proctoscopy were performed if there was a clinical or CT/MRI suspicion of bladder or rectal involvement. Further investigation was performed when indicated.

Physical and vaginal-pelvic examination and abdominal-pelvic CT scan were repeated 3-4 weeks after the completion of chemotherapy. All patients underwent type II-III radical hysterectomy with pelvic lymphadenectomy within 3-6 weeks after the last cycle of chemotherapy.

Clinical response to NACT was determined using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (43).

Pathological responses were assessed as follows. Complete response was defined as the complete disappearance of the tumor in the cervix with negative nodes; optimal partial response was defined as persistent residual disease with <3 mm stromal invasion including *in situ* carcinoma on the surgical specimen and negative nodes; sub-optimal response with intra-cervical residual disease was defined as persistent residual disease with >3 mm stromal invasion within the cervix and negative nodes; sub-optimal response with extra-cervical residual disease consisted of positive nodes regardless of parametria and surgical margins, as well as positive parametria of surgical margins with negative nodes. The pathological optimal response rate was the sum of complete and optimal partial response rates.

Postoperative management was individually established on the basis of histological findings on surgical specimen, patient age and general conditions, after an exhaustive discussion with the patient by a multidisciplinary team.

The patients were periodically followed-up with clinical and radiological examinations until they died or until May 2017. The median follow-up of survivors was 89 months (range=5-208 months).

Statistical analysis. SPSS ver.13 (SPSS Inc., Chicago IL, USA) was used for computations.

The time from the first cycle of NACT to the detection of recurrence was defined as recurrence-free survival. The time from the first cycle of NACT to death or last observation was defined as overall survival.

The cumulative probabilities of recurrence-free and overall survival were estimated by the product-limit method. The log-rank test was used to compare the homogeneity of recurrence-free survival and survival functions across strata defined by categories of prognostic variables. A multiple regression analysis based on the Cox proportional hazards model was used to jointly test the relative importance of variables as predictors of recurrence-free and overall survival.

Results

Median age of patients at diagnosis was 46 years (range=23-68 years). FIGO stage was Ib2 in 53 patients (65%), IIa in 10 (12%), and IIb in 19 (23%). Tumor size was ≤5 cm in 36 patients (44%), >5 cm in 39 (48%), and not specified in seven. Histological grade was well (G1) or moderately (G2) differentiated in 34 patients (41%), poorly differentiated (G3)

Table I. *Recurrence rates and sites according to pathological response.*

Pathological response	Site of recurrence, n				
	Patients, n	Pelvic	Extrapelvic	Pelvic + extrapelvic	Overall, n (%)
Overall optimal	10	1	0	0	1 (10%)
Sub-optimal response with intra-cervical residual	36	4	0	1	5 (14%)
Sub-optimal response with extra-cervical residual/non-response	36	7	5	1	13 (36%)

in 35 (43%), and not specified in 13. NACT consisted of: epidoxorubicin (80 mg/m^2 day 1), paclitaxel (175 mg/m^2 day 1) and cisplatin (75 mg/m^2 day 2) (TEP regimen) every 3 weeks for three cycles in 53 patients (64.6%); ifosfamide (5 g/m^2 + mesna 5 g/m^2 24-hour continuous infusion day 1), paclitaxel (175 mg/m^2 day 2) and cisplatin (75 mg/m2 day 2) every 3 weeks for three cycles in nine (11.0%); paclitaxel (175 mg/m^2) and cisplatin (75 mg/m2) every 3 weeks for three cycles in six (7.3%); paclitaxel (80 mg/m^2) and carboplatin [area under curve (AUC)=2] every week for six cycles in six (7.3%); epidoxorubicin (80 mg/m^2) and cisplatin (75 mg/m^2) every 3 weeks for three cycles in three (3.7%); and other platinum-based chemotherapy in five (6.1%). Radical hysterectomy according to Piver and Rutledge was of type 3 and type 2 in 66 (80%) and 16 (20%) patients, respectively.

A clinical complete response and a partial response were achieved by nine and 58 patients, respectively, with a clinical overall response rate of 82%.

As far as pathological response is concerned, a complete response and an optimal partial response were obtained by five patients each, with an optimal response rate of 12%. Thirty-six patients (44%) had a sub-optimal response with intra-cervical residual disease, 24 (29%) had a sub-optimal response with extra-cervical residual disease, and 12 (15%) had a stable disease (non-responders).

Post-operative treatment was as follows. Of the 10 optimal responders, five received additional cycles of chemotherapy with the induction regimen, two received brachytherapy, and three had no further therapy. Of the 36 sub-optimal responders with intra-cervical residual disease, five received additional cycles of chemotherapy with the induction regimen, 15 (42%) underwent CCRT or external beam radiotherapy with or without brachytherapy, one received brachytherapy, and 15 had no further treatment.

Of the 36 sub-optimal responders with extra-cervical residual disease or no response, two received additional cycles of chemotherapy with the induction regimen, 32 (89%) underwent CCRT or external beam radiotherapy with or without brachytherapy (one of them with additional irradiation on the aortic area), and two had no further treatment.

At the time of the present analysis, 19 patients (23%) had experienced recurrence after a medianof 12.5 months (range=5.3 to 86.8 months). Recurrent disease was pelvic in 12 patients (63%), extra-pelvic (aortic or distant) in five (26%), and both pelvic and extra-pelvic in two (10%). Median time to recurrence was 13.7 months (range=6.7 to 86.8 months) for those with pelvic failure and 23.5 months (range=6.3 to 31.8 months) for those with extra-pelvic failure. The two patients with both pelvic and extra-pelvic failure experienced recurrence after 5.3 and 9.7 months, respectively.

According to pathological response, tumor relapsed in 10% of optimal responders, 14% of the sub-optimal responders with intra-cervical residual disease, and 36% of sub-optimal responders with extra-cervical residual disease or no response (Table I).

The optimal responder who experienced recurrence developed pelvic failure. Extra-pelvic relapse, with or without pelvic failure, was detected in one out of five (20%) sub-optimal responders with intra-cervical residual disease, and six out of 13 (46%) sub-optimal responders with extra-cervical residual disease or non-responders, who developed recurrent disease, respectively.

Table II reports the recurrence rates and sites according to postoperative treatment.

Adjuvant CCRT or external beam radiotherapy was not administered to any of the optimal responders, but was given to 42% of sub-optimal responders with intra-cervical residual disease, and 89% of sub-optimal responders with extra-cervical residual disease or non-responders.

Pelvic failure after adjuvant CCRT or external beam radiotherapy occurred in three out of 15 (20%) sub-optimal responders with intra-cervical residual disease and in seven out of 32 (22%) sub-optimal responders with extra-cervical residual disease or non-responders.

At the time of the present analysis, 56 patients (68%) were alive with no evidence of tumor, three (4%) were alive with tumor, 16 (19%) had died of tumor, and seven (8%) died of concurrent disease with no evidence of tumor. Of these latter seven patients, three were sub-optimal responders with intra-cervical residual disease, two were sub-optimal responders

Table II. *Recurrence rates and sites according to postoperative treatment.*

Postoperative treatment	Patients, n	Site of recurrence, n			
		Pelvic	Extrapelvic	Pelvic + extrapelvic	Overall, n
Optimal responders (n=10)					
Chemotherapy	5	0	0	0	0
BCT	2	1	0	0	1
No further treatment	3	0	0	0	0
Suboptimal responders with intracervical disease (n=36)					
Chemotherapy	5	1	0	0	1
CCRT or EBRT±BCT	15	2	0	1	3
BCT	1	0	0	0	0
No further treatment	15	1	0	0	1
Suboptimal responders with extracervical disease or non-responders (n=36)					
Chemotherapy	2	0	0	0	0
CCRT or EBRT±BCT	32	7	5	0	12
No further treatment	2	0	0	1	1

BCT, Brachytherapy; CCRT, concurrent chemotherapy and radiotherapy; EBRT, external beam radiotherapy.

Table III. *Variables predictive of 5-year recurrence-free survival (RFS) and overall survival (OS) by univariate analysis.*

Variable	Patients, n	RFS rate	*p*-Value	OS rate	*p*-Value
Age					
≤46 Years	42	76%	0.902	84%	0.697
>46 Years	33	76%		83%	
FIGO stage					
Ib2-IIa2	59	76%	0.477	83%	0.195
IIb	16	78%		86%	
Tumor diameter*					
≤5 cm	36	77%	0.190	85%	0.537
>5 cm	32	84%		84%	
Histological grade**					
G1-G2	32	76%	0.179	97%	0.051
G3	32	69%		70%	
Chemotherapy regimen					
TEP	51	73%	0.455	82%	0.391
Other	24	86%		90%	
Pathological response					
Optimal+suboptimal intra-cervical residual	43	87%	0.017	92%	0.012
Suboptimal extra-cervical residual/no response	32	64%		74%	
Radical hysterectomy					
Type 3	60	79%	0.212	89%	0.082
Type 2	15	67%		66%	

G1, Well-differentiated; G2, moderately differentiated; G3, poorly differentiated; TEP, paclitaxel+epidoxorubicin+cisplatin. *Data available on 68 patients; **data available on 64 patients.

with extra-cervical residual disease, and two were non-responders.

For the entire series of 82 patients, 5-year recurrence-free and overall survival were 72% and 77%, respectively.

The seven patients who died of concurrent disease with no evidence of tumor were not included in the subsequent survival analyses. Among the remaining 75 patients, 5-year recurrence-free and overall survival were 77% and 84%, respectively.

Recurrence-free and overall survival by univariate analysis are shown in Table III.

The patients who achieved an optimal response or sub-optimal response with intra-cervical residual disease had

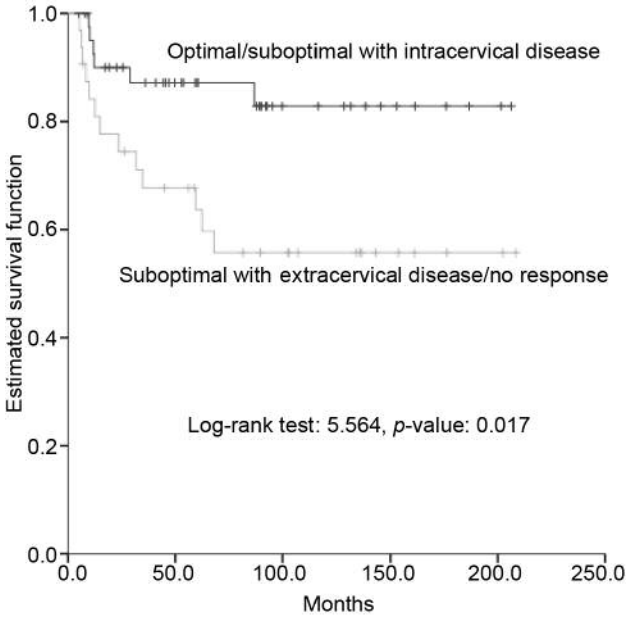

Figure 1. Recurrence-*free survival by pathological response*.

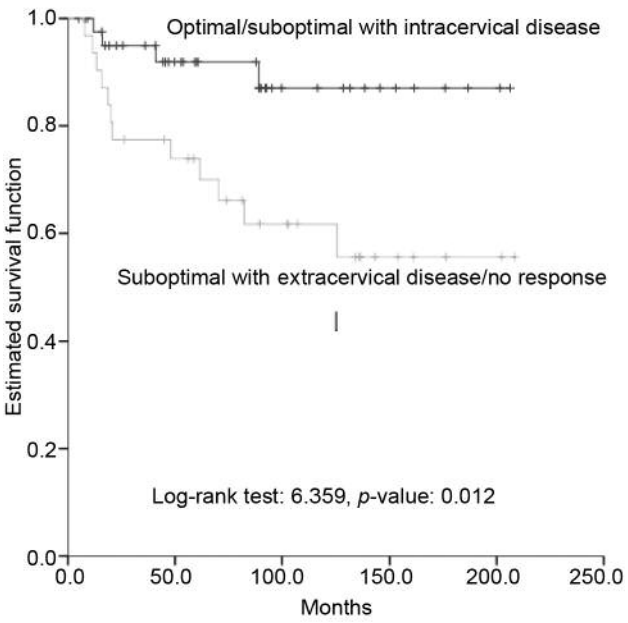

Figure 2. *Overall survival by pathological response*.

better 5-year recurrence-free (87% *versus* 64%, p=0.017; Figure 1) and overall (92% *versus* 74%, p=0.012; Figure 2) survival than those who had sub-optimal response with extracervical residual disease or no response. The TEP regimen gave no benefit compared with two-drug regimens.

On multivariate analysis, pathological response to NACT was an independent prognostic variable for both recurrence-free survival (Wald χ^2=7.336, HR=1.441, 95% CI=1.106-1.877, p=0.007) and overall survival (Wald χ^2=9.965, HR=1.652, 95% CI=1.210-2.256, p<0.002).

Discussion

Platinum-based NACT followed by radical hysterectomy has obtained good results in stage Ib2-IIb squamous cell carcinoma of the uterine cervix (6-8,11,13-15), whereas few data are currently available about the efficacy of this chemo-surgical treatment in cervical adenocarcinoma, with clinical overall response rates ranging from 50% to 93% (34, 36-42) (Table IV). Pooled data from three consecutive trials using different regimens showed a 5-year overall survival rate of 84% in the 33 responding patients, whereas all 9 non-responders died after a median of 10 months (p<0.0001) (36). The clinical response to NACT was the only independent prognostic variable for survival. Radical hysterectomy was feasible in 29 of the responding patients, and a complete response was detected in 10% of them. Zanetta *et al*. reported a clinical overall response rate of 67% among 21 patients who received at least four cycles of NACT. Eighteen of them underwent surgery and hysterectomy specimen showed the persistence of microscopic disease in four (19%) and macroscopic disease in 14 (37).

In the study of Iwasaka *et al*., 12 patients with stage Ib-II disease underwent radical hysterectomy after NACT and the mean survival was 47.5 months for responders and 28.3 months for non-responders. Conversely, all four patients with more advanced disease, who were treated with radiotherapy or second-line chemotherapy, died of disease after a median of 10 months (38).

The pathological examination of surgical specimens of 14 patients treated with NACT and radical hysterectomy by Tabata *et al*. revealed no residual disease in six patients and microscopic residual disease <5 mm in two, with a pathological optimal response rate of 57% Optimal responders experienced a longer overall survival compared to patients with macroscopic residual disease (p=0.012) (39).

In a phase II Japanese study, 50 (96%) out of 52 patients underwent radical hysterectomy after NACT. The 2-year overall survival was 82% for stage Ib2, 86% for stage IIa2, and 93% for stage IIb (42).

Shoji *et al*. achieved a clinical overall response in 78% of 23 patients scheduled for radical hysterectomy. Surgery was completed in 18 patients whose median progression-free and overall survival were 26 months and 35 months, respectively. Conversely, all five patients in whom surgery was not complete died of tumor within 35 months (41).

Table IV. *Clinical response rate to platinum-based neoadjuvant chemotherapy (NACT) in patients with adenocarcinoma of the uterine cervix.*

Author (Ref)	Patients, n	Stage	NACT regimen	CR, n	PR, n	OR,%
Benedetti *et al.* (36)	42	Ib2-IIIB	Different regimens	3	30	79%
Zanetta *et al.* (37)	21	Ib2-IIb	50 mg/m^2 CDDP weekly 70 mg/m2 EPIDX weeks 1, 4, 7	4	10	67%
Iwasaka *et al.* (38)	16	Ib-IV	50 mg/m^2 CDDP d1 + 10 mg/m^2 MIT-C d1 + 100 mg/m^2 VP-16 d1, 3, 5 every 4 weeks	3	5	50%
Tabata *et al.* (39)	14	Ib1-IIb	15 mg/m^2 CDDP d 1-5 + 15 mg/m^2 MIT-C d1 + 70 mg/m^2 VP-16 d 1-3, + 30 mg/m^2 EPIDX d1 every 4 weeks	7	6	93%
Shimada *et al.* (42)	52	Ib2-IIb	DOC 60 mg/m^2 + CBDCA AUC5 every 3 weeks	5	31	69%
Shoi *et al.* (41)	23	Ib2-IIb	175 mg/m^2 PTX or 70 mg/m^2 DOC + CBDCA AUC6 every 3 weeks	5	13	78%
Hu *et al.* (34)	67	Ib1-IIb	Different cisplatin-based regimen	10	43	79%
Present series	82	Ib2-IIb	Different platinum-based regimen	9	58	82%

CR, Complete response; PR, partial response; OR, overall response; CDDP, cisplatin; EPIDX, epidoxorubicin; MIT-C, mitomycin-D; VP-16, etoposide; DOX, docetaxel; CBDCA, carboplatin; AUC: area under receiver operating characteristics curve; PTX, paclitaxel.

In the retrospective study of Hu *et al.*, the pathological examination of surgical specimens showed complete disappearance of tumor or residual tumor with less than 3 mm stromal invasion in 15% of 62 patients with cervical adenocarcinoma who underwent surgery following NACT (34).

The results of the present retrospective investigation, including 82 patients treated in four Italian gynecological oncological centers, compared favorably with literature data in terms of clinical response rate, recurrence-free survival and overall survival. The pathological optimal response rate was similar to that of Hu *et al.* (34), Benedetti Panici *et al.* (36), and Zanetta *et al.* (37) and was lower than that reported by Tabata *et al.* (39). However, the latter Japanese study analyzed only 14 patients and included patients with microscopic residual disease <5 mm among optimal responders, whereas in our investigation, optimal partial response was defined as persistent residual disease with <3 mm stromal invasion including *in situ* carcinoma. In the present study, disease recurred in 23% of the patients after a median of 12.5 months, and the pelvis was the most frequent site of failure. Extra-pelvic relapse, with or without pelvic failure, was detected in 0%, 20%, and 46% of optimal responders, sub-optimal responders with intra-cervical residual disease, sub-optimal responders with extra-cervical residual disease or non-responders, who developed recurrent disease, respectively.

He *et al.* reassessed two randomized trials and nine observational studies, including a total of 1,559 patients, to determine whether the efficacy of NACT was different between those with squamous cell carcinoma and those with adenocarcinoma/adenoquamous carcinoma of the uterine cervix (44). No difference in terms of either overall response rate or complete response rate was found between those with squamous and non-squamous carcinomas, whereas the long-term outcome in terms of overall survival and progression-free survival was better for those with squamous cell carcinomas. However, we must take into consideration that adenocarcinoma of the uterine cervix has a wide histopathological spectrum and that it can be classified into seven subtypes (45, 46). No meaningful clinical data are currently available on the sensitivity to chemotherapy of each single subtype.

Some authors reported that clinical response (36, 38) or pathological response (39) to NACT had a relevant impact on survival. In the present investigation, the patients who achieved a pathological optimal response or sub-optimal response with intra-cervical residual disease had a significantly better 5-year recurrence-free (87% *vs.* 64%, p=0.017) and overall (92% *vs.* 74%, p=0.012) survival than those who had a sub-optimal response with extra-cervical residual disease or no response. These latter had a 1.441-fold higher risk of recurrence and a 1.652–fold higher risk of death for tumor than those who obtained an optimal response or sub-optimal response with intra-cervical residual disease.

The number of patients analyzed in retrospective studies on chemo-surgical treatment in cervical adenocarcinoma ranges from 14 to 62. The strengths of the present investigation are represented by the fairly large number of patients of an uncommon clinical scenario, the long-term follow-up, and the accurate reporting of the pattern of recurrence. Similarly to a prior study of our cooperative group on 333 patients with squamous or non-squamous cervical carcinoma treated with NACT and radical surgery (16), the weaknesses of this investigation are mainly represented by its retrospective design, the lack of control group, the variety of adjuvant treatment, changing use of chemotherapy, the 20-year study period, and the lack of data on patients who dropped out.

In conclusion, our data showed that platinum-based NACT followed by radical hysterectomy may be an option for patients with stage Ib2-IIb adenocarcinoma of the uterine cervix.

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