

# NEOADJUVANT PREOPERATIVE CHEMOTHERAPY IN PATIENTS TREATED FOR STAGE IB2 CERVICAL CANCER

*L.Ševčík, J.Klát, P.Gráf, Z.Jalůvková, A.Mladěnka*

*Dept. of Ob./Gyn., University Hospital, Ostrava, Czech Republic*

**Introduction:** Cervical cancer (CC) first extends to paracervical tissues, spreads to regional lymph nodes (LN) and only later metastasizes to distant anatomical structures. Women with bulky tumors stage IB2 have a higher local failure and worse survival rates compared to patients with small tumors. The optimal strategy is controversial and includes primary chemo radiation or neoadjuvant chemotherapy (NAC) followed by radical surgery with benefit of information about lymphatic spreading. NAC reduces tumor volume and renders radical surgery feasible. The most beneficial is a dose-density strategy of cisplatin based NAC which avoids delays of other primary treatments for nonresponders. Benefits of this management include micrometastases clearing, elimination of pathological risk factors and improvement of prognosis in responding patients.

**Objective:** The aim of the study was to analyze the clinical efficacy of NAC followed by radical surgery in patients treated for stage IB2 cervical cancer.

**Table 1. RESPONSE RATE OF NEOADJUVANT CHEMOTHERAPY**

AUTHOR	N	NAC REGIME	OS	CR	PR	SD	PD
Matsumura	46	DDP+irinotecan	80.40%	-	-	-	-
Poujade	54	-	-	33.50%	67.00%	-	-
Mon	30	CBDCA+TAX	87.00%	7.60%	87.80%	15.20%	0%
Park	43	DDP+TAX	90.70%	39.50%	51.20%	9.30%	0%
Ki	51	PVB	72.50%	13.70%	58.80%	25.50%	2%
Termrugru-angiert	28	DDP+Gemcitabin	88.90%	33.30%	55.50%	11.10%	0%
Duenas - Gonzalez	41	DDP+Gemcitabin	87.00%	-	-	-	-
Watari	46	DDP+I/M/CA/TAX	76.10%	-	-	23.90%	-
Ševčík	32	DDP+IF (ADRIA)	93.70%	15.60%	78.60%	6.25%	0%

**Table 2. HEMATOLOGIC TOXICITY**

GRADE III-IV		
Anemia	6 patients	18.70%
Neutropenia	17 patients	53.10%
Trombocytopenia	12 patients	37.50%

**Table 3. SURVIVAL RATE**

AUTHOR	N	2-YEAR	3-YEAR	5-YEAR	OVERALL
Matsumura	46	91.20%	86.10%		
Rocconi				69.00%	
Mon	30			78.60%	81.80%
Park	43	94.50%		89.20%	
Ki	51	74.90%		61.30%	
Termrugru-angiert	28		88.90%		
Benedetti - Panici	210			58.90%	
Watari	46	72.00%	70.00%	64.00%	
Ševčík	32		72.00%	60.00%	78.00%

**Patients and methods:** From May 2003 to April 2009, 32 patients with locally advanced cervical cancer were included into the study. Median age was 42 years (range 27-74). Squamous carcinoma was diagnosed in 27 patients, adenocarcinoma in 5 patients. All patients underwent MRI or ultrasonographic evaluation before and after three cycles of high dose density regime of NAC (ifosfamide 1,75mg/m2 and cisplatin 75 mg/m2 in squamous carcinoma or adriamycin 30mg/m2 and cisplatin 75 mg/m2 in adenocarcinoma) every ten days. Tumor response was evaluated according to the RECIST criteria (response evaluation criteria in solid tumors) as follows: complete response (CR) was defined as the complete disappearance of all measurable lesions, partial response (PR) was defined as a more than 30% reduction in measurable lesions, stable disease (SD) was defined as any situation that did not qualify as a response or progression, and progressive disease (PD) was defined as a more than 20% increase in measurable disease or appearance of any new lesions. All patients received radical hysterectomy C 2 secundum Querleu-Morrow and systematic regional lymphadenectomy level 2-3 according evaluating sentinel LN during surgery. Median number of resected LN was 34 (range 12-65). All patients underwent a physical examination and ultrasonographic evaluation every 3 months during the first 2 years. During the next years examinations and measurement of serum tumor markers were carried out every 6 months. Local and distant metastases were evaluated by using CT or PET/CT according the levels of tumor markers. After radical surgery patients received adjuvant therapy according pathological prognostic factors. Median follow-up period was 48 months (range 19-90 months).



**Table 4. PROGRESSION AND DEATH N 7 (21%)**

N/AGE	TYPE	GRADE	NAC REDUCTION	LN	ADJUVANT TREATMENT	DFI	RECUR META	SURVIVAL (months)
1/43	spino	1	81%	28/4 bilat	RT	8M	FLUIDO	10M
2/41	adeno	3	78%	59/4 bilat	RT	4M	HEP	4M
3/61	spino	2	99%	15/1	RT	30M		33M
4/46	spino	3	0%	36/3 bilat	RT	12M	OS	14M
5/35	adeno	3	95%	46/0	CT	46M	LOCAL	56M
6/40	spino	3	52%	29/3 bilat	RT	12M		12M
7/44	spino	3	22%	33/2	RT	18M		18M

**Results:** In the group of 32 patients the overall clinical response rate was 93.7% (CR 15.6%, PR 78.2%, SD 6.2% and PD 0%). Both adjuvant radiotherapy and chemotherapy were indicated in 14 patients (43.7%), 4 patients (12.6%) were without adjuvant therapy. Hematological toxicity of NAC are listed in table 1. The frequency of hematological toxicity was high, 17 patients required growth factors. No patient died from treatment-related complications. Lymph node metastases was found in 17 patients (53.1%) and parametrical involvement in 2 patients (6.2%). Recurrence of disease and death was observed in 7 patients (21%). Six of these patients received adjuvant radiotherapy, only one patient received adjuvant chemotherapy. Five of the patients with adjuvant radiotherapy had distant metastases, only one patient had progression in regional LN after 23 months. One patient with adjuvant chemotherapy had regional progression after 48 months after therapy. The estimated 3-year, 5-year and overall survival were 72%, 60% and 78% respectively. The most significant prognostic factor was multiple and bilateral positivity of LN and grade 3 of the tumor.

**Discussion:** Several studies have shown the sensitivity to chemotherapy of CC. The overall response to NAC in our study was 93.7% which is comparable to that reported by other authors. The evaluation of the tumor regression after NAC allowed us to choose the treatment strategy. Postoperative chemo radiotherapy is accompanied by morbidities such as leg edema, bowel or ureteral obstruction, urinary fistulas and other significant late toxicities. It remains controversial whether NAC confers any clinical benefits in the treatment of CC. In the study comparing NAC followed by radical surgery with primary radiotherapy Panici et al reported a survival benefit in NAC and surgery arm but Chang et al. reported no differences in disease free survival and overall survival. NAC followed by surgery plus postoperative chemotherapy but no radiotherapy is a viable option in the treatment of stage IB2 CC. This treatment may allow avoidance of the long-term morbidities that arise from radiotherapy. Depending on the prognostic histopathological factors of the tumor, initial treatment exclusive of radiotherapy may be the option, which can be reserved for possible pelvic recurrence.

**Conclusions:** NAC enables radical surgery by reducing tumor size and avoiding radiotherapy by improving pathological prognostic factors and increasing quality of life. Cervical cancer stage IB2 is prognostic unfavorable disease with high risk of recurrence in which combination of the treatment methods is necessary. NAC followed by radical surgery and postoperative chemotherapy in patients without negative prognostic factors or adjuvant radiotherapy in patients with positive prognostic factors is feasible and does not constitute over-treatment.