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Neoadjuvant chemotherapy and radical surgery compared to radical surgery alone in bulky stage IB–IIA cervical cancer

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Abstract

Aim: The aim of this study was evaluation of the efficacy of neoadjuvant chemotherapy (NACT) and radical hysterectomy on long-term survival in stage IB–IIA locally advanced cervical cancer as compared with radical surgery alone.
Methods: We reviewed all patients with cervical cancer stage IB–IIA who were treated with two treatment modalities, i.e. NACT followed by radical hysterectomy and lymphadenectomy, and radical hysterectomy alone between March 1996 and March 2004. There were 22 patients in the NACT group (group 1) and 160 patients in the immediate radical surgery group (group 2). All patients in group 1 were followed for more than 108 months, and long-term survival and factors affecting recurrence were evaluated.
Results: Nineteen patients in the NACT arm underwent radical surgery. Pelvic lymph node metastasis was found in 8 patients in this group and in 36 in the radical surgery group. Eighteen patients in the NACT group and 96 patients in the radical surgery group were scheduled for adjuvant postoperative chemoradiation. During the 9-year follow-up, recurrence rate was 47.1% and 30.2% in NACT and control groups, respectively. In the NACT group lymph node metastasis was a significant independent risk factor for recurrence. Overall survival in the NACT arm was not statistically significantly lower than the control arm ($p = 0.06$).
Conclusion: NACT did not improve long-term overall survival of bulky early-stage cervical cancer patients compared to primary radical surgery.

Keywords: Cervical carcinoma; Neoadjuvant chemotherapy; Radical hysterectomy; Concomitant chemoradiation

Introduction

In early-stage cervical carcinoma, both the size of the lesion and the depth of stromal invasion affect survival.[1] The lesion diameter is the most important prognostic factor in early-stage cervical carcinoma.[2–4] Chemotherapy is effective in reducing tumor volume and facilitating surgical removal of bulky early-stage cervical tumors.[5,6] Earlier attempts to improve the prognosis of these patients included the use of neoadjuvant chemotherapy (NACT) followed by radiation.[7] In the mid-1980s, NACT before radical surgery was introduced for these high-risk cervical cancer patients and several clinical trials have been conducted.[7–10] Several combination regimes based on cisplatin, such as VBP (Cisplatin, Vinblastin, Bleomycin), BOMP (Bleomycin, Vincristine, Mitomycin C, Cisplatin), or BMP (Cisplatin, Bleomycin, Methotrexate) have been used before surgery or pelvic radiation.[8–10]

In recent years NACT has been proposed to improve pelvic control and to eradicate distant micrometastasis for bulky or locally advanced cervical carcinoma.[11–13] Its effectiveness awaits long-term follow-up results because overall survival and disease-free survival are the only adequate end-points for evaluating the effectiveness of any new treatment approach compared to the standard therapy. Differing results of NACT have been reported; Sardi et al. reported a statistically significantly higher overall survival

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rate in the patients who had NACT before surgery compared to the standard treatment group (80% vs. 60%).[14] According to a study by deSouza et al., 3-year survival in the NACT group was not significantly different from the control group (49.1% vs. 46%, $p = 0.94$).[15]

The goal of our study was to compare long-term follow-up of cisplatin and vincristine as NACT preceding radical hysterectomy (RH) and bilateral pelvic lymphadenectomy with radical surgery in patients with bulky stage IB or IIA cervical cancer.

Patients and methods

We reviewed the medical files of all cervical cancer patients in ValiAsr University Hospital. From March 1996 to March 2004, 235 patients with bulky cervical carcinoma stage IB–IIA were found. Twenty-two patients received NACT followed by RH, 160 patients received radical surgery with/without postoperative radiotherapy and 53 patients received radiotherapy alone. All patients had primary, previously untreated, histologically confirmed invasive cervical cancer. Bulky tumor was defined as cervical lesion either 4 cm or greater. Patients were not pregnant and had adequate bone marrow, renal, and hepatic function. All patients had lesions measured by physical examination, colposcopy, computed tomography (CT), or magnetic resonance imaging (MRI). Tumor stage was determined according to the clinical criteria established by the FIGO in 1994.[6] Although the patients' age limitation was not established, only patients with performance status 0 or 1 were enrolled in this study.

Neoadjuvant chemotherapy

NACT group patients received cisplatin, 50 mg/m^2 and vincristine 1 mg/m^2 intravenously every 10 days for three courses. Drugs were withheld if the white blood count was $<3000/mm^3$, platelet $<100{,}000/mm^3$, serum creatinine level >2.0 mg/dl, or total bilirubin >2.0 mg/dl. Patients were examined prior to each course of chemotherapy and immediately before laparatomy with cervical measurement of the tumor in two perpendicular dimensions. After completion of chemotherapy courses, the operable patients (those with resectable tumor) underwent type III radical hysterectomy (RH), upper vaginectomy plus para-aortic and pelvic lymphadenectomy. The patients in group 2 underwent type III RH, upper vaginectomy plus pelvic and para-aortic lymph node dissection. All patients had follow-up visits every 3 months until the end of the second year then every 6 months to the end of the study. The selected patients (close or involved margin, positive lymph node, deep stromal invasion) were referred to postoperative adjuvant radiotherapy. In both groups of patients survival analysis performed to determine the effects of NACT on long-term survival and outcome.

The survival rate was calculated by the Kaplan–Meier method. The log-rank test was used to test difference in survival, and level of significance was considered as $p < 0.05$.

Results

Two hundred and thirty-five patients with bulky stage IB–IIA cervical carcinoma were reviewed. Twenty-two received NACT followed by RH (group 1), and 160 underwent standard radical surgery (group 2). The patients' clinical characteristics are listed in Table 1.The two study groups were similar with respect to tumor type, FIGO stage, histological diagnosis, tumor size in two-dimensional diameter, and performance status. The median age of patients in group 1 was 48 (range 26–75) years and in group 2 was 52 (20–77) years, respectively.

In the NACT group there was no life-threatening severe (grade 2, 3) complication following chemotherapy; 20 patients had squamous cell carcinoma and 3 had adenocarcinoma. In group two 145 patients had squamous cell carcinoma and 13 had adenocarcinoma, and other pathologies (small cell carcinoma, adenosquamous) were found in 2 patients.

In the NACT group there were 9 pelvic lymph node metastases, 1 parametrial involvement, and no positive vaginal margin. In the second group there were 35 pelvic lymph node metastases, 1 parametrial involvement and 1 margin involvement. Eighty-one percent of patients in the NACT group and 60% in the control group received adjuvant postoperative radiotherapy (Fisher's Exact test = 0.047).

Twenty patients in the NACT group were eligible for surgery following completion of chemotherapy (stage IB); 2 were in stage Ib2 or II bulky and were referred to chemoradiation.

The median follow-up was 5.2 years in the NACT group and 7.8 years in the surgery group.

Table 1
Clinical characteristics of NACT and control groups

	Surgery group (range)	NACT group (range)	p Value[a]
Age (years)	52 (20–77)	48 (26–75)	NS[b]
Parity	5 (0–14)	5 (2–11)	NS
1st coitus (year)	15 (10–32)	15 (12–27)	NS
1st delivery (year)	16 (13–27)	16 (15–32)	NS
Menarche (year)	13 (9–17)	13 (12–15)	NS
Menopause (year)	49 (31–60)	49 (46–55)	NS
Symptom duration (months)	4 (1–72)	12 (1–60)	NS
Time between biopsy and treatment (months)	1 (0–28.1)	2.37 (0–115.87)	0.03
Pathology of SCC	91.2%	90.1%	NS
Pathology of adenocarcinoma	8.3%	9.9%	NS
Stage IB2	95%	93%	NS
Bulky stage IIA	5%	7%	NS

[a] Indicates the significance of the difference between two groups.
[b] NS, not significant.

Survival

The median disease-free survival (DFS) was 2.8 years (95% confidence interval [CI]: 1.1–4.6 years) for the NACT group and 6.3 years for the surgery group. Three- and 5-year DFS rates were 44% (SD: 15%) and 29% (SD: 16%) in group 1 and 63% (SE: 4%) and 57% (SE: 5%) in group 2, respectively. Ten-year DFS rates were 47% (SE: 8%) in the radical surgery group (Fig. 1).

Seven patients in the NACT group died of disease. The median overall survival (OS) in the NACT group was 3.8 years (95% CI: 1.5–6.2 years). The 3- and 5-year OS rates were 56% (SE: 15%) and 28% (SE: 16%), respectively. The 3-, 5- and 10-year overall survival rates in group 2 were 75% (SE: 4%), 68% (SE: 5%) and 58% (SE: 10%), respectively (Fig. 2). Overall survival in the NACT group was lower than in the control group, but this difference was not statistically significant ($p = 0.063$).

Ten patients in the NACT group and 48 in the control group relapsed after treatment ($p = 0.153$). Although a higher incidence of distant recurrences was noted in the NACT group, it was not statistically significant (5.9% vs. 3.8%, respectively; Fisher's Exact test = 0.11).

Discussion

Optimal management of patients with locally advanced cervical cancer is controversial. Local, regional and distant failure rate are more likely, whatever primary modality of treatment is chosen.[16] In stage IB–IIA patients with tumor diameter 3 cm or greater, 5-year survival rates after surgery or radiotherapy have been reported in the range

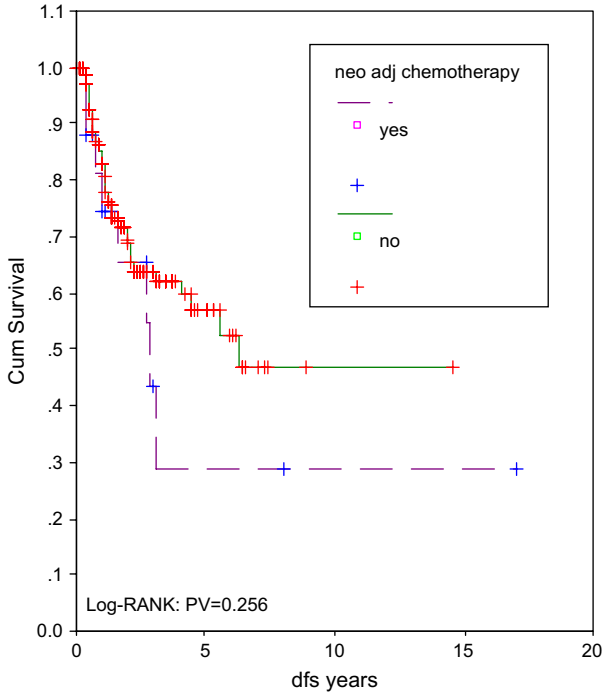

Figure 1. Disease-free survival in NACT and control groups.

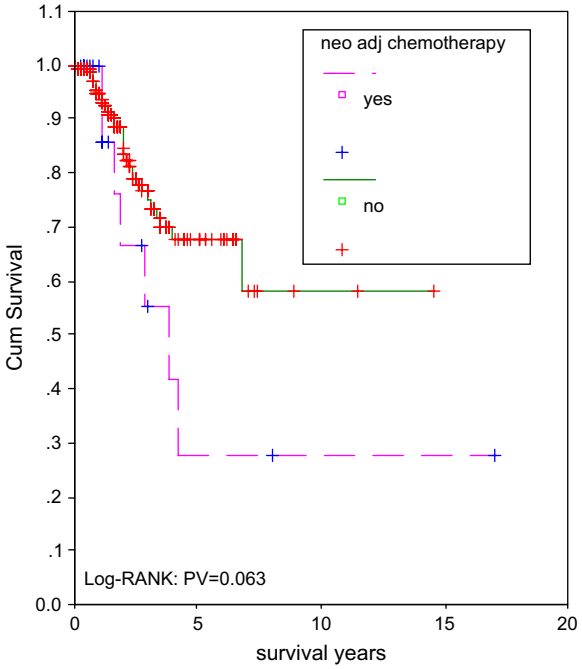

Figure 2. Overall survival in NACT and control groups.

31–66%.[2,4,17] Based on the results of previous phase II studies, induction chemotherapy involving two to three courses of cisplatin/vincristine/bleomycin is effective in reducing tumor volume and facilitating surgical removal of bulky early-stage cervical tumors.[5,6]

This study was performed to compare the efficacy of NACT followed by RH with that of surgery in patients with locally advanced stage cervical carcinoma. NACT has become the standard of care or a promising modality in several solid tumors, but in cervical carcinoma it still remains an experimental therapy.[18] Despite the lack of randomized trials comparing radiation with radical surgery after induction chemotherapy, emerging data from a growing number of neoadjuvant trials suggest that surgical resection could be better as it bypasses the cross-resistance between chemotherapy and radiation.[19,20] The benefit on survival of NACT in solid tumors is mostly limited to patients with complete clinical or pathological response; therefore, the employment of an effective induction scheme of chemotherapy seems necessary in order to obtain better survival figures.[21]

The theoretical benefits of NACT were as follows: reduction of bulky tumor mass and/or stage with increased operability, reduction of pelvic lymph node metastasis, possible improvement of long-term survival. In two studies, 73–100% cumulative operability rates were obtained for stage IB–IIA bulky patients after NACT.[23,24] Similarly, in our study operability rate in the NACT group was 90%.

Lymph node metastasis

Several studies have reported a pelvic lymph node metastasis rate of 22–25% after NACT for the locally

advanced stage IB–IIA patients;[25,26] however, in our study lymph node metastasis rate in the NACT group was higher (42.1%). In other studies, in early-stage cervical cancer with standard treatment (radiotherapy or radical surgery), lymph node metastasis has been reported in the range 19–32%.[27–29] Likewise, in our study lymph node metastasis in the control group was 22.2%. In the present study lymph node positivity was considerably higher in the NACT group, but this difference was not statistically significant (Fisher's Exact test = 0.08).

Adjuvant radiation

The role of adjuvant or postoperative radiation or chemoradiation is well determined in early-stage patients treated by RH. In the Gynecology Oncology Group study, high-risk patients (node-positive, parametrial infiltration, and positive surgical margins) who received adjuvant concurrent chemoradiation had prolonged survival compared to radiation alone.[22]

In the study by Duenas-Gonzalez et al., 63% of patients who received NACT were scheduled for adjuvant chemoradiation.[30] In one randomized study, 28% of the patients in the NACT group received adjuvant radiotherapy (XRT). In our study, 81% of patients received postoperative XRT.

Chang et al.[31] reported that 21% of the patients in the NACT arm and 12% in the XRT arm had local relapse. In another study, during a 10-year follow-up period 20% of the patients with NACT treatment had recurrence and all of these patients died of recurrence.[23] In our study, 47.1% of patients in the NACT group and 30.2% in the control group relapsed, and a higher incidence of distant recurrence was noted in the NACT group.

Pathologic findings such as initial tumor size, depth of invasion, parametrial invasion, and pelvic lymph node metastases have been cited as prognostic factors for recurrence after conventional therapy. In the study by Hwang et al.[23] positive lymph node was a significant factor for recurrence ($p = 0.0016$) but initial tumor size, clinical response, and residual tumor size were not risk factors for recurrence after NACT. The prognostic significance of pelvic lymph node metastasis for recurrence has been confirmed again in this study. In our study, other prognostic factors were not significant risk factors for recurrence.

Sardi et al.[14] compared the efficacy of NACT plus RH plus adjuvant radiotherapy with that of RH plus adjuvant radiotherapy in the treatment of stage IB cervical cancer. A subgroup analysis specific to the patients with bulky tumors showed a statistically significantly higher overall survival rate (80% vs. 60%) in the group who had NACT before surgery compared to the group not treated with NACT.

Survival

According to deSouza et al.,[15] the 3-year survival in the chemotherapy group was not significantly different from the control group (49.1% vs. 46%, $p = 0.94$). In the present study 3-year overall survival of the NACT arm was 56% compared with 75% in the control group.

In this study, in spite of significant partial response of primary tumor size in cervical cancer after NACT (25%), there was nearly double the rate of lymph node metastasis in the NACT group (42.2% vs. 22.2%). Several studies have demonstrated the significant inverse effect of lymph node metastasis on survival in early-stage cervical cancer.[16,17,22,28]

Those patients who have been treated with NACT and radical surgery followed by adjuvant radiotherapy may be at increased risk of complications compared to those who are treated with either modality alone.[32]

Conclusion

In this study, in bulky early stage of cervical cancer, NACT did not improve long-term overall survival. Future prospective randomized studies can lead to better clinical treatment planning for this category of patients.

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