Review Article

Role of neoadjuvant chemotherapy in cancer cervix: A brief review

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ABSTRACT

Neoadjuvant chemotherapy (NACT) represents a promising modality apart from or radiotherapy as initial treatment of locally advanced cervical cancer. The primary objectives of NACT in the treatment of cervical cancer include improvement in tumor characteristics, to allow avoidance of radiotherapy, to prolong disease-free and overall survival, and facilitation of fertility-sparing surgery. Though several studies have shown promising results of NACT on tumor response, downstaging, decrease in local recurrence, improved progression free survival, yet its role is controversial and plenty of study results are waiting to establish its efficacy. After reviewing the available literatures in the internet, and focusing the light of our continuous 3 years experience, we have made an effort to find out the relevance of NACT in cancer cervix. NACT is feasible and produces impressive responses in cervical carcinoma, as has been demonstrated by several phase II and phase III trials. Some meta-analysis suggested that NACT followed by surgery improves overall survival compared with nonstandard radiotherapy alone.

Key words: Chemotherapy, cervix, neoadjuvant

INTRODUCTION

Cervical cancer is still the second most common malignancy and second most common cause of cancer-related death in women worldwide.[1] Early diagnosis and screening programs are still the best strategies to diminish the disease incidence. Despite improved screening techniques for pre-invasive disease, approximately 13,000 new invasive cervical cancer cases are diagnosed, and 4,000 patients die each year.[2]

For early disease either confined to the cervix or with limited extension beyond it (International Federation of Gynecology and Obstetrics [FIGO] stage IB1-IIA), standard treatment has been traditionally radical radiotherapy or radical hysterectomy with node dissection, each giving 5-year survival rates of around 80-90%. Radical radiotherapy, comprising external beam and intracavitary irradiation, was the treatment of choice for locally advanced disease (FIGO) stage IIB, III, and IVA) and also offered an alternative to radical surgery for patients with tumors larger than 4 cms confined to the cervix (stage IB bulky). Nowadays, the standard management of cervical cancer depends on clinical stage and tumor volume. Controversies about the selection of surgical versus nonsurgical cases are still in vogue, such as the popular debate on optimal therapeutic modality for bulky cervical cancer treatment.

Many studies offer different therapeutic approaches for the early stage of the cervical cancer and the standard management of this disease is still evolving. After years of studying multimodality treatments as an alternative to radiation alone in randomized phase III trials, the standard treatment has changed to concurrent chemoradiotherapy. The addition of cisplatin-based chemotherapy concurrently to radiotherapy has improved survival in patients with bulky disease or patients with positive lymph nodes.[3-6]

In 1999, a National Cancer Institute Alert, based on the results of five randomized trials recommended that concomitant chemoradiation should be considered instead of radiotherapy alone in women with cervical cancer. A subsequent systematic review and meta-analysis

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of data presented in publications suggested a large benefit of concomitant chemoradiotherapy on survival, progression-free survival and local and distant control rates.[7] Thus, for many, concomitant chemoradiotherapy has become the new standard of care for locally advanced disease.

There are, however, still potential therapeutic advantages to giving chemotherapy along with local treatments that were standard for locally advanced disease, prior to the widespread use of concomitant chemoradiotherapy. The rationales for the use of neoadjuvant chemotherapy (NACT) are multiple. Tumor-size reduction may facilitate subsequent local therapy, whether radiotherapy or surgery. This reduction can transform inoperable tumors into radically resectable ones.[8,9] Also, NACT has been suggested to increase radiosensitivity and decrease the hypoxic cell fraction. Moreover, NACT treats the micrometastatic disease, preventing a significant proportion of relapses. Prior to surgery, the blood supply to the tumor is uncompromised, allowing improved drug delivery and distribution by NACT. Finally, response to NACT has been identified as an important prognostic factor in several studies. In addition, by giving chemotherapy prior to radiotherapy, there may be a less likelihood of increased radiotherapy toxicity, as seen with the concurrent approach.[10,11]

MATERIALS AND METHODS

We have reviewed the relevant articles from the internet in pubmed, medscape, and other sites for the topic of discussion. We have read the full texts extensively and reviewed repeatedly and made the summary of the relevant meta-analyses and trials on NACT in cervical cancer.

COMPREHENSIVE DISCUSSION ON SEVERAL STUDIES WHERE NEOADJUVANT CHEMOTHERAPY WERE USED IN CA CERVIX

Since the first publication by Friedlander in 1983 on the use of primary chemotherapy in cervical carcinoma, several phase II trials and several phase III trials have been conducted using NACT in cervical cancer, some have shown favorable and some conflicting results.

In 2003, Tierney *et al.*,[12] published an individual patient data meta-analysis initiated and coordinated by the United Kingdom Medical Research Council Clinical Trials Unit and carried out by the Neoadjuvant Chemotherapy (NACT) for Cervical Cancer Meta-analysis Collaboration. Two separate treatment comparisons were included in their analysis: Comparison 1, in which NACT followed by local treatment was compared with the same local treatment (mainly radiotherapy) alone, and comparison 2, in which a combination of NACT followed by surgery (with or without radiotherapy) was compared with the (then) more standard radiotherapy alone.

First comparison was based on 2,074 patients from 18 trials, the median follow-up across all trials was 5.7 years for surviving patients. Almost 70% of patients had advanced disease (stage II or III). The study results showed that the addition of NACT to local therapy (mainly radiotherapy) did not have any impact on overall survival (hazard ratio [HR] = 1.05; 95% confidence interval [CI]: 0.94-1.19), disease-free survival (HR = 1.00; 95% CI: 0.88-1.14), or loco-regional disease-free survival (HR = 1.03; 95% CI: 0.9-1.17). However, a highly significant level of statistical heterogeneity was evident for each of the outcomes measured; viz. *P* value for survival was 0.0003. It was suggested that chemotherapy may select the radioresistant cellular clones due to cross-resistance between certain chemotherapy agents and radiotherapy.

Second comparison of the meta-analysis compared NACT followed by surgery (with or without subsequent radiotherapy) to radical radiotherapy alone. That analysis comprised 5 randomized trials with a total of 872 patients. The planned total dose of cisplatin was between 100 mg/m^2 and 300 mg/m^2 in 10-21-day cycles; external radiotherapy and intracavitary radiotherapy doses in the radiotherapy alone arm were similar across trials (45-60 Gy and 25-40 Gy, respectively). The results of the second comparison suggested a highly significant effect of NACT, with an HR of 0.65 ($P = 0.00004$), which translates into an absolute gain in 5-year overall survival of 14% (from 50% to 64%).[12]

The Gynecological Oncology Groups (GOG) has carried out three consecutive phase III trials comparing cisplatin doublets against cisplatin monotherapy for metastatic or recurrent cervical carcinoma.[13-15] In these trials, cisplatin was combined with ifosfamide (GOG-110), paclitaxel (GOG-169), and topotecan (GOG-179). All the trials showed that cisplatin doublet chemotherapy produced significantly higher rates of response and progression-free survival than did cisplatin monotherapy. Moreover, the combination of cisplatin and topotecan was associated with a statistically significant benefit in overall survival, without any impact on quality of life.[14] The summary of the results of the GOG Trials are summarized in Table 1.

Robova H and co workers,[16] reviewed their 10 years' experience with high-dose-density NACT in cervical cancer management in 141 women. Their study revealed

High-dose-density NACT and radical surgery has resulted in high clinical response rates and seemed to be feasible in the management of stage IB bulky cervical cancer. NACT-reduced tumor volume and positivity of lymph nodes and thus minimized the need for postoperative radiotherapy or chemoradiotherapy. Early and especially late toxicity of high-dose density chemotherapy was within acceptable limits. Five-year survival in patients, who underwent surgery in their study, was 80.6%.

Rydzewska L and co workers[17] reviewed six randomized controlled trials comparing NACT with surgery vs. surgery alone in women with early or locally advanced cervical cancer who had not undergone any prior treatment likely to interfere with the treatment comparison. Progression Free Survival (PFS) was significantly better with NACT (HR = 0.76, 95% CI = 0.62 to 0.94, P = 0.01), but no Overall Survival benefit (OS) was observed (HR = 0.85, 95% CI = 0.67-1.07, P = 0.17). Furthermore, their analysis estimated both local (OR = 0.76, 95% CI = 0.49-1.17, P = 0.21) and distant (OR = 0.68, 95% CI = 0.41-1.13, P = 0.13) recurrences and rates of resection (OR = 1.55, 95% CI = 0.96-2.50, P = 0.07), either of which were in favor of NACT. There was also no difference in the effect of NACT according to total cisplatin dose, chemotherapy cycle length or by cervical cancer stage.

Hwang YY *et al.*,[18] presented a 10-year follow-up of 80 patients with locally advanced stage IB-IIB cervical cancer with tumor diameter of more than or equal to 4 cm, after NACT by cisplatin, bleomycin, vincristine, and radical hysterectomy. The study showed a reduction in tumor size after NACT in 75 cases. Overall, 5- and 10-year disease-free actual survival rates were 82% and 79.4%, respectively.

One prospective randomized study was performed in which 295 patients in stage IIB were randomly allocated to three groups: Surgery alone, radiation alone, and either of them combined with NACT. After 84-month follow-up (mean) the survival rate for surgery and NACT was 65%, and for radiation with chemotherapy was 54%, while it was 48% and 41% in the radiation alone and surgery alone arms, respectively. Hence, the best survival rate was in patients who received chemotherapy followed by surgery and radiation. Resectability was also significantly better in NACT plus surgery group (80%) compared with only-surgery group (56%) (P = 0.001).[19]

Table 1: Gynecologic oncology group randomized trials with cisplatin-based doublets in advanced cervical carcinoma

	GOG-110		GOG-169		GOG-179	
	Cisplatin	Cisplatin+ ifosfamide	Cisplatin	Cisplatin+ paclitaxel	Cisplatin	Cisplatin+ topotecan
RR (%)	19	31	19	36	13	27
PFS (mo)	3.2	4.6	2.8	4.8	2.9	4.6
OS (mo)	8	8.3	8.8	9.7	6.5	9.4

RR: Response rate, PFS: Progression free survival, OS: Overall survival, GOG: Gynecologic oncology group

In Kim's *et al.*, study cisplatin, vinblastine, and bleomycin were used before radical hysterectomy in stage I and IIA tumors larger than 4 cm; complete response rate was reported in 44% and partial response rate in 50% patients.[20] According to these results, NACT could be a good modality to decrease the size of tumors.

Napolitano U and co workers[21] carried out a prospective randomized clinical study where 192 patients of squamous cell carcinoma of the uterine cervix in Stages Ib-IIb were randomized to one of the following treatments: Three courses of NACT with cisplatin, vincristine, bleomycin (NACT arm; n = 106); conventional surgery or radiotherapy alone (RT Alone arm; n = 86). One hundred and fifty-six patients in Stage Ib-IIb (n = 86, NACT arm and n = 70, RT alone arm) and 16 patients in Stage III (NACT arm) who were sensitive to the NACT, underwent radical hysterectomy. The 5-year overall survival rates for the NACT and RT alone arm, respectively, were 78.6% and 73.2% in Stages Ib-IIa (P = NS), 68.7% and 64.3% in Stage IIb (P = NS). A 5-year disease-free survival rate for the NACT arm and RT alone arm, respectively, of 77.1% and 64.3% in Stages Ib-IIa (P < 0.05), 56.2% and 57.1% in Stage IIb (P = NS) was found. The study concluded that the responsiveness of cervical cancer to NACT allows surgical treatment in a larger number of patients and results in longer overall and disease free survival.

Chen *et al.*, attempted to evaluate whether high-dose, short-term NACT prior to[22] surgery could improve response and survival rates. In their study, patients with stage IB2 – IIB disease were randomized to undergo surgical management with or without NACT (cisplatin, mitomycin C, and 5-fluorouracil). Post-operative pelvic radiotherapy was used for patients with lymph node metastases, parametrial or vaginal involvement, lymph vascular space invasion, and/or ovarian metastases. Overall, almost 70% of patients had either a complete or partial response to chemotherapy. Pathologic findings were significantly reduced, with decreased pelvic lymph node metastases (25.0% vs. 42.9%, P = 0.02) and parametrial involvement (25.0% vs. 41.4%, P = 0.04). Those who responded to chemotherapy had fewer recurrences compared to non-responders (16.3% vs. 47.4%, P = 0.01). There was a significant difference in the 4-year overall survival between treatment arms (71.0% with NACT vs. 58.0% with control, P = 0.04).

G. Zanetta *et al.*,[23] in their study, assessed the toxic effects and antitumor activity of a multidrug neoadjuvant regimen consisting of cisplatin, ifosfamide, and paclitaxel in bulky and locally advanced cervical cancer. Thirty-eight patients with pathologically confirmed squamous-cell cervical cancer (27 IB2-IIA, two IIB, eight IIIB, and one IVA) were prospectively enrolled in their study. Treatment consisted of paclitaxel (175 mg/m^2 given over 3 hours on day 1), cisplatin 50 mg/m^2 (75 mg/m^2 in 10 patients), ifosfamide 5 g/m^2 in a 24-hour continuous infusion, and mesna. Eleven patients achieved complete clinical response, 21 had partial response, five had stable disease, and one had progression of disease. Grade 3-4 neutropenia was recorded for 71% patients, grade 3-4 thrombocytopenia for 10.5%, and grade 2 peripheral neuropathy for 2.5%. They concluded according to pathology examination, that this regimen yielded a 34% complete and optimal partial response rate with acceptable toxicity.

An Italian trial compared an ifosfamide–cisplatin doublet to an ifosfamide–cisplatin–paclitaxel (TIP) triplet in the neoadjuvant setting.[9] A total of 204 patients with disease stages IB2–IVA were randomized to receive one of the regimens for three cycles before surgery. Postoperative radiotherapy was administered for lymph node infiltration, pathologically positive margins, suboptimal response, or parametrial invasion.

The primary endpoint was response rate, defined as the sum of pathological complete remissions and excellent partial remissions (residual tumor with stromal invasion less than 3 mm). The response rate was significantly higher statistically with the TIP regimen (48% vs. 23% with the doublet), but TIP was associated with higher hematological toxicity. Unfortunately, no statistically significant differences in progression-free survival or overall survival were detected, although a trend in favor of the TIP regimen was observed. However, patients who achieved a complete response or an excellent partial response had a significantly longer duration of survival than those with a lesser response.

A review of the literature describing NACT prior to fertility-preserving surgery reveals only a few publications, all of which are case-series. The largest series, we found, was by Maneo *et al.*,[24] explored the role of NACT followed by cold knife conization and pelvic lymphadenectomy. The single-centre study enrolled 51 nulliparous patients with Stage IB1 cervical cancer.

NACT consisted of three cycles of cisplatin 75 mg/m^2, paclitaxel 175 mg/m^2, and ifosfamide 5 g/m^2 (substituted by epirubicin 80 mg/m^2 in cases of adenocarcinoma) every 3 weeks. Among 20 patients receiving the treatment protocol, all but four showed a clinical response to chemotherapy and eventually underwent a cold knife conization. After the completion of NACT, all 16 remaining patients demonstrated a complete clinical remission or minimal persistence of disease. There were no severe chemotherapy-associated toxicities. Among patients who completed the planned protocol, there were no recurrences after a median follow-up of 69 months. There were 10 pregnancies among six of nine patients attempting to conceive, resulting in one spontaneous miscarriage and nine term deliveries. The authors concluded that NACT followed by cold knife conization and pelvic lymphadenectomy should be used with caution, with careful patient selection and inclusion only of motivated women with a strong desire for future childbearing, recognizing the limitations of a small sample size in the assessment of oncologic outcomes.

DISCUSSION

NACT represents a promising alternative to surgery or radiotherapy as initial treatment of locally advanced cervical cancer. The primary objectives of NACT in the treatment of cervical cancer include improvement in tumor characteristics to allow avoidance of radiotherapy, prolonged disease-free and overall survival, and facilitation of fertility-sparing surgery. The impact on survival of this relatively new approach is still a matter of discussion, and different treatment strategies may be considered. Some authors have observed that NACT followed by radiation has yielded neither higher response rates nor longer survival,[25] possibly due to the development of selective resistance to radiation after chemotherapy. Some authors have reported that NACT followed by surgery may improve survival in locally advanced cervical cancer as compared to radical surgery.[26,27] According to some authors, only patients in complete or optimal partial response (minimal foci of microscopic tumor in the removed uterus) can benefit significantly in terms of disease-free survival.[20,28] An ongoing trial by the European Organization for Research and Treatment for Cancer (EORTC) Gynecologic Group has been designed to compare NACT followed by surgery to standard chemoradiotherapy, and the final results are eagerly awaited.

Some studies have shown that the response to NACT may serve as an important prognostic factor, guiding the direction of subsequent therapy.[29] Whether the response to NACT simply identifies a subset of patients who are destined to fare better than non-responders has been questioned. However, as a group, those receiving NACT have in some studies demonstrated improved progression-free and overall survival.

Finally, NACT may optimize a patient's pathologic risk factors, introducing the option of fertility-sparing treatment to a patient who would otherwise not be a candidate. In this setting, NACT offers benefits other than an equivalent oncologic outcome. Upon review of the available evidence, there has been no consistently proven benefit in overall survival to NACT prior to surgery (versus surgery alone) or radiotherapy (versus radiotherapy alone). Most randomized studies include inadequate patient numbers to support conclusions. So the overall survival benefit (OS) of NACT is yet to be established. Fertility preservation with successful obstetrical outcomes following neoadjuvant chemotherapy and fertility-sparing surgery has been possible.

CONCLUSION

NACT is feasible and produces impressive responses in cervical carcinoma, as has been demonstrated by several phase II and phase III trials. Some meta-analysis suggested that NACT followed by surgery improves overall survival compared with nonstandard radiotherapy alone.

REFERENCES

1. WHO. World Health Organization Report: Comprehensive Cervical Cancer Control: A Guide to Essential Practice. World Health Organization Web site; 2006. Available from: http://www.who.int/reproductive-health/publications/cervical_ cancer_gep/index.htm [Last accessed on 2008 Feb].
2. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics. CA Cancer J Clin 2002;52:23-47.
3. Jurado M, Martinez-Monge R, Garcia-Foncillas J, Azinovic I, Aristu J, Lopez-Garcia G, *et al*. Pilot study of concurrent cisplatin, 5-fluorouracil, and external beam radiotherapy prior to radical surgery +/- intraoperative electron beam radiotherapy in locally advanced cervical cancer. Gynecol Oncol 1999;74:30-7.
4. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, *et al*. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154-61.
5. Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, *et al*. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606-13.
6. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, *et al*. Concurrent cisplatinbased chemoradiation in locally advanced cervical cancer. N Engl J Med 1999;340:1144-53.
7. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, *et al*. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: A systematic review and meta-analysis. Lancet 2001;358:781-6.
8. Benedetti-Panici P, Greggi S, Scambia G, Amoroso M, Salerno MG, Maneschi F, *et al*. Long term survival following neoadjuvant chemotherapy and radical surgery in locally advanced cervical cancer. Eur J Cancer 1998;34:341-6.
9. Buda A, Fossati R, Colombo N, Fei F, Floriani I, Alletti DG, *et al*. Randomized trial of neoadjuvant chemotherapy comparing paclitaxel, ifosfamide, and cisplatin with ifosfamide and cisplatin followed by radical surgery in patients with locally advanced squamous cell cervical carcinoma: The SNAP01 (Studio Neo-Adiuvante Portio) Italian Collaborative Study. J Clin Oncol 2005;23:4137-45.
10. Sardi J, Sananes C, Giaroli A, Bayo J, Rueda NG, Vighi S, *et al*. Results of a prospective randomized trial with neoadjuvant chemotherapy in stage IB, bulky, squamous carcinoma of the cervix. Gynecol Oncol 1993;49:156-65.
11. Stewart LA, Tiernay JF. Neoadjuvant chemotherapy and surgery versus standard radiotherapy for locally advanced cervical cancer: A meta-analysis using individual patient data from randomised controlled trials. Proc ASCO 2002;21:207a.
12. Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Metaanalysis Collaboration. Neoadjuvant chemotherapy for locally advanced cervical cancer: A systematic review and meta-analysis of individual patient data from 21 randomised trials. Eur J Cancer 2003;39:2470-86.
13. Omura GA, Blessing JA, Vacarello L, Berman ML, Clarke-Pearson DL, Mutch DG, *et al*. Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol 1997;15:165-71.
14. Moore DH, Blessing JA, McQuellon MP, Thaler HT, Cella D, Benda J, *et al*. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: A gynecologic oncology group study. J Clin Oncol 2004;22:3113-9.
15. Long HJ 3rd, Bundy BN, Grendys EC Jr, Benda JA, McMeekin DS, Sorosky J, *et al*. Gynecologic Oncology Group Study. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A Gynecologic Oncology Group study. J Clin Oncol 2005;23:4626-33.
16. Robova H, Halaska M, Pluta M, Skapa P, Strnad P, Lisy J, *et al*. The role of neoadjuvant chemotherapy and surgery in cervical cancer. Int J Gynecol Cancer 2010;20 (11 Suppl 2):S42-6.
17. Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. Cochrane Database Syst Rev 2010:CD007406.
18. Hwang YY, Moon H, Cho SH, Kim KT, Moon YJ, Kim SR, *et al*. Ten-year survival of patients with locally advanced, stage Ib-IIb cervical cancer after neoadjuvant chemotherapy and radical hysterectomy. Gynecol Oncol 2001;82:88-93.
19. Disaia PJ, Creasman WT. Invasive cervical cancer. In: Disaia PJ, Creasman WT, editors. Clinical Gynecology Oncology. St. Louis: Mosby; 2002. p. 53-80.
20. Kim DS, Moon H, Kim KT, Hwang YY, Cho SH, Kim SR. Two-year survival: preoperative adjuvant chemotherapy in the treatment of cervical cancer stages Ib and II with bulky tumor. Gynecol Oncol 1989;33:225-30.
21. Napolitano U, Imperato F, Mossa B, Framarino ML, Marziani R, Marzetti L. The role of neoadjuvant chemotherapy for squamous cell cervical cancer (Ib-IIIb): A long-term randomized trial. Eur J Gynaecol Oncol 2003;24:51-9.
22. Chen H, Liang C, Zhang L, Huang S, Wu X. Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: Randomized study. Gynecol Oncol 2008;110:308-15.
23. Zanetta G, Lissoni A, Pellegrino A, Sessa C, Colombo N, Gueli-Alletti D, *et al*. Neoadjuvant chemotherapy with cisplatin, ifosfamide and paclitaxel for locally advanced squamous-cell cervical cancer. Ann Oncol 1998;9:977-80.
24. Maneo A, Chiari S, Bonazzi C, Mangioni C. Neoadjuvant chemotherapy and conservative surgery for stage Ib1 cervical cancer. Gynecol Oncol 2008;111:438-43.
25. Tattersall MH, Ramirez C, Coppleson M. A randomized

trial comparing platinum-based chemotherapy followed by radiotherapy versus radiotherapy alone in patients with locally advanced cervical cancer. Int J Gynecol Cancer 1992;2:244-51.
26. Serur E, Mathews RP, Gates J, Levine P, Maiman M, Remy JC. Neoadjuvant chemotherapy in stage IB2 squamous-cell carcinoma of the cervix. Gynecol Oncol 1997;65:348-56.
27. Sardi JE, Giaroli A, Sananes C, Ferreira M, Soderini A, Bermudez A, *et al*. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: The final results. Gynecol Oncol 1997;67:61-9.
28. Giaroli A, Sananes C, Srdi JE, Maya AG, Bastardas ML, Snaidas L, *et al*. Lymph node metastases in carcinoma of the cervix uteri: Response to neoadjuvant chemotherapy and its impact on survival. Gynecol Oncol 1990;39:34-9.
29. Zanetta G, Lissoni A, Pellegrino A, Sessa C, N Colombo, Gueli-Alletti D, *et al*. Neoadjuvant chemotherapy in locally advanced uterine cervical cancer: Correlation between pathological response and survival. Proc Am Soc Clin Oncol 1998;17:352-5.

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