# Long-term Follow-up of Neoadjuvant Cisplatin and 5-Fluorouracil Chemotherapy in Bulky Squamous Cell Carcinoma of the Cervix

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Fifteen patients with bulky (designated as > 3 cm largest diameter) FIGO stage Ib or IIa squamous cervical cancer were treated with cisplatin (100 mg/m$^2$ on day 1) and 5-fluorouracil (1000 mg/m$^2$ continuously on days 1–5) administered intravenously at 21-day intervals for a total of two or three courses before planned radical hysterectomy. A complete clinical response was noted in four patients and a partial response in ten patients, which represents a 93% overall response rate. One patient had stable disease (two courses of chemotherapy), and none had progressive disease. Median tumor volume was 78.5 cm$^3$ and 2.5 cm$^3$ at diagnosis and after neoadjuvant chemotherapy, respectively ($p < 0.001$). This indicates that chemotherapy resulted in a 97% median reduction of tumor volume. Median overall and disease-free survival was not reached, and the actuarial five-year survival rate was 73% and 67%, respectively. There was no grade 4 toxicity. Myelosuppression was acceptable; however, two patients experienced significant ototoxicity, and in two patients serum creatinine increased. All patients with major toxicity received two cycles of chemotherapy only. The improved local control and survival in our series are in accordance with other results reported, but need to be confirmed in a randomized prospective trial.

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The value of radical surgery in the management of early cervical cancer is well established. However, similar efficacy of radiotherapy and surgery has recently been shown in a large randomized Italian trial (1). The major advantage of surgical therapy in malignancies of the cervix in comparison with radiation is the acceptable long-term morbidity. However, especially patients with bulky tumors, which are defined as larger than 3 or 4 cm in diameter, have poor prognoses. The survival rate of patients with stage Ib tumors decreases from 80%–90% in non-bulky tumors to 50%–60% in bulky tumors (2–5). Recurrences occur in the pelvis, but also beyond the area treated with surgery or radiotherapy. To prevent distant metastasis, efforts have been made to search for active systemic therapy. Cervical cancer has proven to be relatively chemoresistant, although a few chemotherapeutic agents have been shown to exert significant activity (for review, see (6)). Moreover, initial reports of neoadjuvant chemotherapy have demonstrated encouraging short-term results with surgical downstaging and improved resectability (7).

In an effort to improve survival among patients with stage Ib or IIa bulky squamous carcinoma of the cervix, a phase II trial in which radical surgery was modified by neoadjuvant chemotherapy including cisplatin and 5-fluorouracil was undertaken. This therapy was used as a first-line tool, i.e. administered before surgery with an awareness of its potential to improve the possibility of performing surgery with free surgical margins due to response.

## PATIENTS AND METHODS

Patients were required to have previously untreated histologically confirmed squamous cell carcinoma of the cervix FIGO stage Ib or IIa of a tumor size ≥ 3 cm. Eligibility criteria furthermore included a World Health Organization performance status of 0 to 1, age 60 years or less, no distant metastasis, normal renal, hepatic, and bone marrow function and informed consent. Patients admitted to the Department of Gynecologic Oncology at The Norwegian Radiumhospital from February 1992 until July 1993 were nominated for inclusion in the prospective non-randomized phase II trial of neoadjuvant chemotherapy (Table 1). Each patient was examined under general anaesthesia by two senior physicians. Tumor diameters were

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measured before and after chemotherapy as well as in the surgical specimen. Tumor volume was calculated from clinical measurements by assuming an ellipsoid according to Baltzer & Köpcke (8).

Neoadjuvant chemotherapy consisted of two (n = 4) or three courses (n = 11) of cisplatin 100 mg/m$^2$ administered intravenously (iv) on day 1 and 5-fluorouracil 1000 mg/m$^2$ iv continuously on days 1–5, as recently described (9). Four weeks after the last course of chemotherapy, patients underwent a type III Wertheim radical hysterectomy and bilateral pelvic lymphadenectomy (10).

Patients with positive lymph nodes received external beam irradiation 50 Gy in 2 Gy fractions, five days a week, to the small pelvis, upper border at $L_{4-5}$. All patients were followed until death or until January 1998. Follow-up information was collected from the medical case records and from the Cancer Registry of Norway. No patient was lost to follow-up.

Data were analysed by means of the data package SPSS for Windows, version 6.1 (SPSS Inc., Chicago, IL, USA) run on a personal computer. Survival was calculated from the day of diagnosis until death, regardless of the cause of death. Progression-free survival was calculated from the day of diagnosis to the time of progression or recurrence. Survival and progression-free survival curves were calculated for each selected prognostic group with Kaplan-Meier estimates and compared with the log-rank test. Comparison of tumor diameter or volume before and after neoadjuvant chemotherapy was done with the Wilcoxon matched pairs test. Factors analysed in stages Ib and IIa were compared using the Wilcoxon test. A p-value $< 0.05$ was considered significant.

**Table 1**

*Patient characteristics*

| Patient characteristics | Values |
|---|---|
| n | 15 |
| Age (median and range) | 44 (32–58) |
| FIGO stage | |
| Ib | 10 |
| IIa | 5 |
| Grade | |
| 1 | 0 |
| 2 | 8 |
| 3 | 7 |
| Largest diameter in mm (median and range) | 50 (34–80) |
| Volume in cm$^3$ (median and range) | 78.5 (16.7–268) |
| No. chemotherapy cycles | |
| 2 | 4 |
| 3 | 11 |
| Surgery | |
| Yes | 13 |
| No | 2 |
| Lymph node metastasis | |
| Yes | 5 |
| No | 8 |
| No. lymph nodes removed (median and range) | 22 (12–44) |
| Median follow-up in years | 4.8 |

**Table 2**

*Toxicity of neoadjuvant chemotherapy*

| Grade | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| Nausea/emesis | 0 | 13 | 1 | 1 |
| Ototoxicity | 10 | 3 | 1 | 1 |
| Neutropenia | 10 | 2 | 2 | 1 |
| Stomatitis | 10 | 2 | 2 | 1 |
| Nephrotoxicity | 13 | 0 | 2 | 0 |

## RESULTS

In total, 15 patients were enrolled in the study and treated with two or three cycles of neoadjuvant chemotherapy. No grade 4 toxicity was observed (Table 2). Myelosuppression was acceptable, although two patients experienced significant ototoxicity and in two patients, serum creatinine increased. Serum creatinine values measured in these two patients were 280 $\mu$mol/l and 310 $\mu$mol/l, but after infusion therapy normal creatinine values were restored. These four patients received two cycles of chemotherapy only.

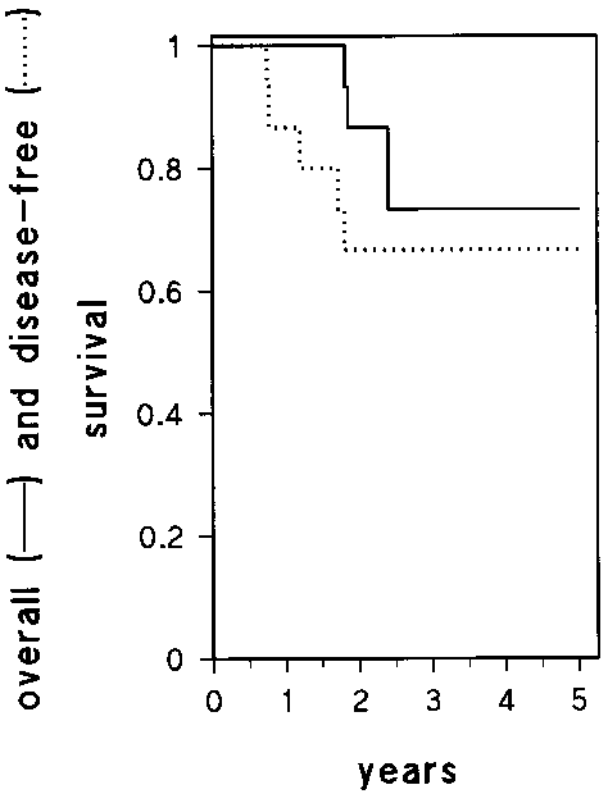


*Fig. 1.* Overall survival and time to progression of 15 patients included in the phase II trial of neoadjuvant chemotherapy in bulky cervical cancer.

**Table 3**

*Prognostic factors in bulky cervical cancer and neoadjuvant chemotherapy*

| | Overall survival | Disease-free survival |
|---|---|---|
| FIGO stage | | |
| Ib | 0.9 (1/10) | 0.8 (2/10) |
| IIa | 0.4 (3/5) | 0.4 (3/5) |
| p | 0.045 | 0.34 |
| Lymph nodes | | |
| Positive | 0.4 (3/5) | 0.4 (2/5) |
| Negative | 0.88 (1/8) | 0.75 (2/8) |
| p | 0.045 | 0.63 (NS) |
| Grade | | |
| 2 | 0.88 (1/8) | 0.75 (2/8) |
| 3 | 0.57 (3/7) | 0.69 (2/7) |
| p | 0.19 | 0.74 |
| Response | | |
| CR | 0.75 (1/4) | 1.0 (0/4) |
| PR | 0.70 (3/10) | 0.6 (4/10) |
| p | 0.85 | 0.35 |
| Volume | | |
| $<78.5$ cm$^3$ | 0.88 (1/8) | 0.75 (2/8) |
| $\geq 78.5$ cm$^3$ | 0.57 (3/7) | 0.67 (2/7) |
| p | 0.16 | 0.94 |
| Diameter | | |
| $<50$ mm | 0.75 (1/5) | 0.63 (2/5) |
| $\geq 50$ mm | 0.71 (3/10) | 0.83 (2/10) |
| p | 0.61 | 0.34 |

Results are expressed as actuarial five-year overall or disease-free survival rates and, in parentheses, number of events/number of patients.

Median overall and disease-free survival was not reached, and the actuarial five-year survival rates were 73% and 67%, respectively (Fig. 1). Cervical cancer recurred in five patients exclusively in the pelvis. None has died of intercurrent disease.

The overall clinical response rate was 14 out of 15 patients (93%), with four patients achieving complete response (CR) and ten patients a partial response. One patient had stable disease (SD, two courses of chemotherapy), and none had progressive disease (PD). Only one out of the four patients with CR was also histologically without evidence of residual carcinoma cells. Response to chemotherapy (PR vs. CR), however, did not result in a different overall or disease-free survival rate (Table 3). Chemotherapy resulted in a significant reduction of tumor volume from 78.5 cm$^3$ to 2.5 cm$^3$ ($p < 0.001$, 96% reduction). No statistically significant difference was seen between FIGO stages Ib and IIa regarding age, largest diameter for both pre- and post-therapeutic measurements, or tumor volume (data not shown). Patients with stage Ib tumors, however, had significantly better overall survival, but not disease-free survival (Table 3). Tumor volume or pre-therapeutic diameter was of no prognostic importance.

Thirteen of the 15 patients underwent laparotomy with the Wertheim procedure. The other two patients were not explored surgically either due to refusal of blood transfusion or to poor clinical response, and were therefore treated with external radiotherapy and intracavitary brachytherapy. No major complications occurred during or after operation.

Positive lymph nodes were detected in five of 13 patients, whereby in three individuals only one node was involved and in the two other cases there were two and ten positive lymph nodes. In one patient a bulky lymph node, which was extensively adherent to blood vessels, was not removable. All patients with lymph node metastasis received postoperative external radiotherapy. Lymph node metastasis was also a prognostic factor regarding overall survival, but not disease-free survival.

## DISCUSSION

Combination chemotherapy based on cisplatin and 5-fluorouracil has been applied at The Norwegian Radiumhospital for the treatment of recurrent cervical carcinoma with an overall response rate of 49% (9). Based on these results this combination chemotherapy was introduced for the neoadjuvant therapy of cervix cancer. Although the number of patients included was limited, this study suggests that neoadjuvant chemotherapy might also induce a high response rate and an acceptable acute toxicity. Many other investigators have also reported significant efficacy using cisplatin-based chemotherapy in locally advanced squamous cell carcinoma of the cervix (7, 11–24). Initial reports have demonstrated encouraging short-term results with surgical downstaging and improved resectability. Moreover, our study indicates stabilization of results after a median observation period of approximately five years. Actuarial five-year survival and disease-free survival rates were 73% and 67%, respectively. Considering the predominance of poor prognostic factors in these patients treated with neoadjuvant chemotherapy, the results are encouraging.

In our study the number of patients with positive lymph nodes was relatively low for bulky tumors. However, patients with positive nodes also received postoperative radiotherapy. This reduces the value of surgery for bulky tumors, since primary radiotherapy shows a similar local control rate of the tumor, but fewer side effects than surgery combined with radiotherapy. On the other hand, reduction of lymph node metastasis by neoadjuvant chemotherapy, as also proposed by other authors (14, 18, 24) and as indicated by the reduction in distant metastasis observed by us in a study of neoadjuvant chemotherapy before radiotherapy (25), reduces the necessity of external beams for consolidation of results. The occurrence of recurrent disease exclusively in the pelvis in the present study indicates that neoadjuvant chemotherapy is able to extinguish distant metastasis. It is interesting to note that although stage was a prognostic factor, we were unable to

observe a difference in tumor diameter or volume between FIGO stages Ib and IIa.

While it is probable that neoadjuvant chemotherapy in cervical cancer may render more patients technically operable and possibly control metastasis and improve survival, a randomized phase III trial comparing cisplatin 5-fluorouracil neoadjuvant treatment with upfront surgery alone is necessary to decide the real effect of such a strategy.

It is interesting to note that in contrast to the role of neoadjuvant chemotherapy in combination with radical hysterectomy, the same chemotherapy regimen failed to improve local control and survival when teamed with radiotherapy (25). Chemotherapy and radiotherapy may act according to a common mechanism, which is also demonstrated by the cross-resistance of these two types of treatment. This may explain why the radio-chemotherapeutic regimen, but not a combination of neoadjuvant chemotherapy and surgery, failed (25).

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