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CERVICAL CANCER: NEOADJUVANT CHEMOTHERAPY

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It has been demonstrated that the use of preoperative chemotherapy can increase disease-free survival in several kinds of nongynecologic cancer, such as pediatric solid tumors, osteogenic sarcoma, head and neck cancer, and breast cancer.

The use of neoadjuvant chemotherapy (NACT) as apart of multimodality treatment offers some theoretical advantages, such as : uncompromised blood supply to the tumor : better tolerance to chemotherapy in patients, who have not undergone prior irradiation and myelosuppression ; local radiotherapy improved by size reduction and decrease in hypoxic cell fraction; an inoperable tumor is rendered resectable ; the possibility of eradication of subclinical metastases ; identification of the patient population that might benefit from similar chemotherapy administered as adjuvant treatment following surgery and/or radiotherapy.

In addition to theoretical advantages there are also possible disadvantages there are also possible disadvantages, such as : cross-resistance and sensitivity between chemotherapeutic agents and subsequent radiotherapy ; Limitations on the subsequent delivery of any definitive or adjuvant radiotherapy ; delay of potentially curable radiotherapy ; prolongation of treatment ; increased toxicity of treatment ; possibility of accelerated tumor proliferation.

The use of NACT as a part of multimodality treatment in invasive cervical cancer patients may shrink bulky tumors before surgical and radiation treatment and may also reduce the incidence of lymph node metastases.

Invasive cervical cancer

Despite recent advances in screening for cervical cancer and its precursors in developed countries, cancer of the cervix remains a major killer in terms of worldwide malignant disease.

Figure 1 shows the 5-year survival rates by stage and by period of treatment reported in the last volume of the Annual Report concerning the period 1950-54 to 1987-89.

Notwithstanding the slight improvement of the 5- year survival rate it indicates that with the presently available treatment modalities in their traditional way of use no further improvement is to be expected. New therapeutic approaches or a better integration of the existing modalities in the primary treatment of poor-risk patients are to be considered.

The poor-risk patients are defined as those with advanced stages of the disease (FIGO stages III and IV), and those with early-stage cervical cancer in whom lymph nodes proved to be involved or in whom other poor prognostic features are present, indicating that there might be a high chance of involved lymph nodes. In these groups of patients it is included the "bulky tumors": tumors in stage Ib, bigger than 3 or 4 cm in diameter. In these patients the survival rates decrease from 80-90% to 50-60%.

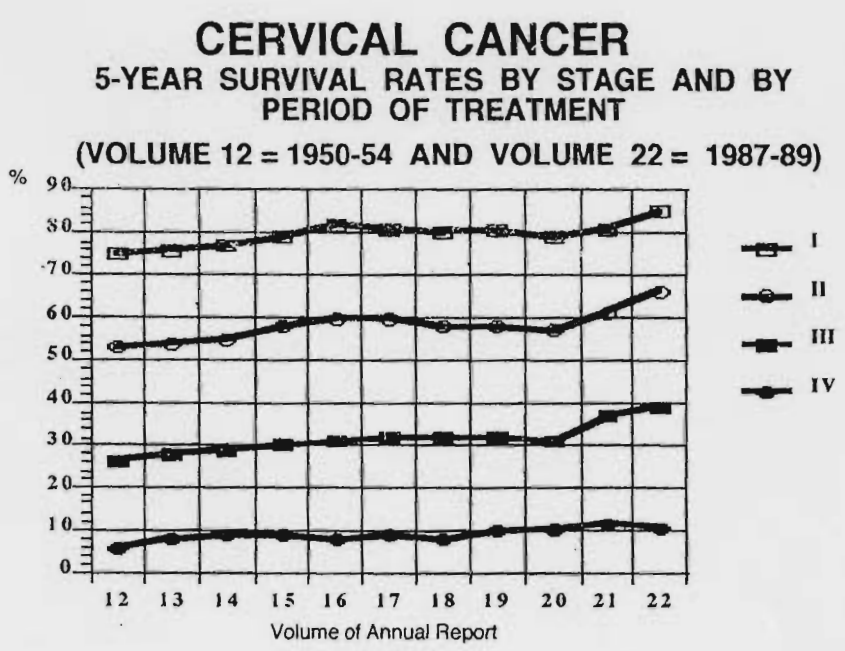
Failure to cure locally advanced squamous cervical cancer (LASCC) -stages IIb to IVa-may result from suboptimal treatment of pelvic disease or existence of infra-clinical metastatic disease outside the treatment field at diagnosis, namely in the nodes. The volume of pelvic disease is an important factor in treatment planning because the dose of radiation required, for large cervical lesions, exceeds the dose that can be delivered clinically to the pelvis in view of normal tissue tolerance.

The role of chemotherapy in squamous cervical cancer

Theoretically, chemotherapy can be used, with a palliative role, in patients with recurrent and/or metastatic cervical cancer, or as part of the primary treatment of this tumor. These strategies

include primary chemotherapy followed by surgery or radiotherapy, chemotherapy given after radical surgery, and chemotherapy given concurrently with radiotherapy.

Figure 1



Chemotherapy in recurrent and/or metastatic disease

Single-agent chemotherapy

As shown in Tables 1 and 2, adapted from Jan Vermorken, the single-agent activity of conventional agents gives a response rate ranges from 10% to 25%, with a median duration of 3 to 6 months and a survival of 5 to 9 months. On the other hand among the new agents , cisplatin is, at present, considered the single most active cytotoxic agent increasing the response rate to 20-30%, with a disappointing median response duration of 4 to 6 months and a median survival only about 7 months.

Table 1

Single-Agent Chemotherapy

Drugs	Patient Nos.	% Response
Cyclophosphamide	36/271	13
5- Fluorouracil	36/270	13
Methotrexate	12/73	16
Doxorubicin	32/172	19
Bleomycin	19/179	11
Mitomycin-c	5/23	22
Vincristine	10/58	17
Vimblastine	2/20	10

Table 2

Single-Agent Chemotherapy

Drugs	Patient Nos.	% Response
Cisplatin	238/968	25
Carboplatin	50/260	19
Ifosfamide	34/93	37
Vindesine	13/49	27
Epirubicin	23/64	36
Cpt 11	5/23	15
Paclitaxel	9/52	17

Combination chemotherapy

A great variety of regimens have been used, initially without cisplatin, but later on mainly with its addition. As shown in Tables 3 and 4, comparison of these data with those obtained with a single-agent suggests that response rates obtained with combination chemotherapy are superior to those obtained with single-agent chemotherapy. All randomized studies comparing combination chemotherapy with single-agent chemotherapy gave negative results.

Table 3

Combination Chemotherapy without Cisplatin

Regimens	Patients Nos.	% Response
Dox/Mtx	66/169	39
Dox/Blm	5/52	10
Dox/Ctx (+ 5-FU)	17/94	18
Dox / other)	48/186	26
Blm / Mtx(+VCR)	26/45	58
Blm / Mmc	83/200	41
Vcr / Blm / Mmc	80/180	43

Table 4

Combination Chemotherapy with Cisplatin

Adapted From JAB. Vermorken; Int..J.Gynecol. Oncol., 3-129 (1993)

Regimens	Patient Nos.	% Response
2- Drug Combinations	142/368	38
3- Drug Combinations	174/416	41
4- Drug Combinations	131/313	42

Neoadjuvant Chemotherapy in Cervical Cancer

There is an international agreement with respect to the efficiency of neoadjuvant chemotherapy in reducing tumor volume and tumor stage of the squamous carcinoma of the cervix.

Neoadjuvant Chemotherapy followed by surgery

Phase I Trials

The use of NACT as part of multimodality treatment offers some theoretical advantages in cervical cancer. Chemotherapy may shrink bulky tumors before radical surgery and may also reduce the incidence of lymph node metastases. After NACT radical surgery can remove residual central disease, evaluate lymph nodes, and presumably improve cure.

Table 5 shows the results of some phase II trials utilizing NACT with cisplatin and Bleomycin more or less Vimblastine followed by surgery.

Table 5

Cervical Cancer
Neoadjuvant Chemotherapy Before Surgery
Regimen : Cisplatin + Bleomycin ±Vinblastine

Ref.	STAGE	#PTS	%RR	%PCR	FUP (m)
DS KIM (1989)	IB-IIB	54	94	13	36
P BENEDETTI (1991)	IB-III	26	88	19	18
R FONTANELLI	IB-IIB	27	78	7	16.5

Table 6 and 7 show other phase II results, with NACT, including different combinations, followed by surgery.

Table 6

Cervical Cancer
Neoadjuvant Chemotherapy Before Surgery
Regimen : Vincristine + Cisplatin + Bleomycin ± Mitomycin C

REF.	STAGE	#PTS	%RR	%PCR	FUP(M)
A Giaroli (1990)	IB-III	169	79	NS	24
G Zanetta (1993)	IB-IIIB	24	76	0	36
Pr Dottino (1991)	IB-IVA	28	100	14	24

Table 7

Cervical Cancer
Neoadjuvant Chemotherapy Before Surgery

REF.	STAGE	#PTS	%RR	%PCR	FUP(M)
P. Benedetti (1991)(1)	IB-III	75	83	13	30
G. Deppe (1991)(2)	IB-IIIB	17	76	20	14.5
P. Benedetti(1996)(3)	IB-IIB	42	79		54

(1) Cisplatin+Bleomycin+Methotrexate (2) Cisplatin+Mitomycin C
(3) Cisplatin+Bleomycin+Methotraxate / Hd Cisplatin+Bleomycin / Cisplatin+Doxorubicin

The most interesting observation made in studies on NACT followed by surgery is the reduced incidence of positive lymph nodes. Table 8 confirms this data.

Table 8

Neoadjuvant Chemotherapy Before Surgery
Incidence Of Positive Lymph Nodes

REF.	STAGE	PTS	%LNN
DS KIM (1989)	IB-IIB	54	20
A GIAROLLI (1990)	IB-III	169	23
P BENEDETTI (1991)	IB-III	75	24
PR DOTTINO (1991)	IB-IVA	28	32
R FONTANELLI (1992)	IB-IIB	27	15
G. DEPPE (1991)	IB-IIIB	10	40
G. ZANETTA (1993)	IB-IIIB	19	65
WITHOUT NACT	IB-IIA		40-80

n and

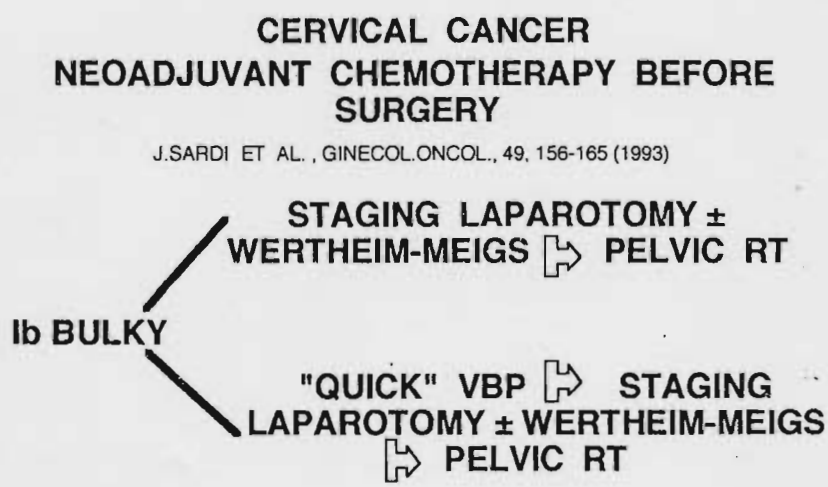
The Buenos Aires Trial, reported by Giaroli, shows a significant correlation between the incidence of lymph node metastases and the clinical stage, as well as the tumor grade, the tumor volume, the residual tumor and the response to NACT. A significant decrease in the incidence of lymph node involvement was observed in good responders. Survival rates, after 2 years of follow-up, improved in those cases with small residual tumor, negative parametria and negative nodes.

In another report, concerning the results of NACT in squamous carcinoma of the cervix, the Buenos Aires Group make the following conclusions : squamous carcinoma of the cervix is a neoadjuvant chemosensitive tumor; there are groups of different prognosis, according to tumor response; tumor response is related to initial volume; surgery is very effective second -line treatment, irrespective of tumor postchemotherapy volume.

Randomized Trials

A prospective randomized trial was carried out by the Buenos Aires Group, in patients with squamous carcinoma of the cervix uteri, stage Ib bulky (Fig.2.) The protocol considers two arms : the control group (75 patients) and the neoadjuvant one (76 patients). In the control group, a staging laparatomy was performed, during which the surgeon decided if the tumor could be resected or not, with free surgical margins. Such cases were subjected to a Wertheim-Meigs operation, with para-aortic lymphadenectomy, followed by adjuvant whole- pelvis irradiation. In the neoadjuvant group the same procedures were carried out but three courses of "quick" VBP scheme (10-day interval) were given before the treatment.

Figure 2



The new therapeutic strategy proved to be very useful in bulky tumors in which the clinical examination showed a cervix increased in size (>4cm). In those cases statistically significant differences were found between both groups, when free disease interval and survival were considered. These were due to the operability improvement and the parametrial extension decrease as well as to other risk factors such as vascular embolism, lymph node involvement, tumor-cervix quotient, and tumor volume. The use of this new strategy is not justified in small tumors (<3-4cm) because survival is not improved with neoadjuvant therapy, in those cases.

Neoadjuvant chemotherapy before radiotherapy

Phase II Trials

The goals of neoadjuvant chemotherapy are the reduction of primary tumor size before initiating radiation therapy and eradication of micrometastases.

As shown in Table 9 a variety of multiagent regimens, administered before radiotherapy, has been examined in phase II studies. However these trials were non- informative with respect to any influence on survival by NACT. In these trials it was not evident that NACT enhanced the acute toxic effects of pelvic radiotherapy.

Table 9

Neoadjuvant Chemotherapy Before Radiation Therapy-Phase II Trials

REF.	STAGE	PTS	REGIMEN	%RR(CT)	%CR(CT+T)
SYMONDS(1987)	III-IVA	30	CDDP+VCR +BLM	59	25
KIRSTEN(1987)	III-IVA	27	CDDP+VLB +BLM	52	NR
LARA(1990)	IIIB	24	CDDP+IFM	62	54
RABINOVICH(1991	IIB-IVA	33	CDDP+VCR+BLM (q)	23	26
BUXTON(1992)	IIB-IVA	19	BLM+IFM +CDDP	68	NR

Randomized Trials

Tables 10 and 11 show the results of randomized trials of NACT followed by radiotherapy "versus" radiotherapy alone. Unfortunately, these trials proved to be disappointing, both in terms of complete response percentages that can be reached with NACT and its impact on survival.

Table 10

Advanced Cervical Cancer
Neoadjuvant Chemotherapy Before
Radiation Therapy-Randomized Trials

REF.	TREAT	%PTS	%LOCAL COMPL CONTROL	SURVIVAL
L.SOUHAMI 1991	RT VBMP+RT	52 39	32.5 47	(5Y)39 (5Y)23
E.J..BUXTON 1992	RT BIP+RT	34 32	56 75	NO DIF.

Table 11

Advanced Cervical Cancer
Neoadjuvant Chemotherapy Before
Radiation Therapy-Randomized Trials

REF.	TREAT	#PTS	%LOCAL COMPL CONTROL	SURVIVAL
TATTERSALL 1995	RT EP+RT	131 129	65 43	(3Y)70 (3Y)50 (P=0.02)
K.SUNDER 1996	RT P5FU+RT	47 47	57 53	NO DIF.

Explanations for these observations cannot be given with certainty, but some events have been suggested : delay in commencement of pelvic radiotherapy may contribute to the increase of local recurrence rate; chemotherapy may itself change tumor-cell kinetics in the surviving population, rendering it less sensible to a subsequent radiotherapy; the development of cross-resistance to certain chemotherapeutic agents and radiotherapy.

More recently the Sardi group, from Buenos Aires, presented the results of randomized trial comparing radiotherapy, neo-adjuvant chemotherapy before radiotherapy and neo-adjuvant chemotherapy before surgery. The best results were achieved in the group of neo-adjuvant chemotherapy before surgery (Table 12).

Table 12

Cervical Cancer Neoadjuvant Chemotherapy Before Surgery Or Radiotherapy

J. Sadri et al., Int J. Gynecol Cancer, 6, 85-93 (1996)

TREAT	#PTS	%LOCAL COMPL CONTROL	SURVIVAL
RT	53	50	(4Y)37
VBP+RT	52	78(p=0.0003)	(4Y)53 (p=0.2)
VBP+SUR+RT	50	NA	(4Y)53 (p=0.005)

The BIP-Regimen

Several studies had confirmed the activity of Ifosfamide in cervical cancer, as well as they had established cisplatin as one of the most active single agents and also demonstrated Bleomycin as single-agent actives in cervical cancer.

The BIP-regimen concerns Bleomycin, cisplatin and ifosfamide. Mesna was administered concurrently with ifosfamide and for 12 hours additional. Table 13 shows the results of BIP "versus" other regimens in recurrent or metastatic cervical cancer.

Table 13

Cervical Cancer
Chemotherapy With BIP-Regimen "Versus" Other Regimens In Recurrent Or Advanced Metastatic Cancer

Adapted from E.J. Buxton (Semin. Oncol., 19, 9, 1992)

	IFOSFAMIDE	IFOSFAMIDE + CISPLATIN	BIP	IFOSFAMIDE + BLEOMYCIN
#PTS	71	44	49	8
% RR	31	36	69	12
% CR	10	5	20	0

Table 14 shows the results of a phase II trial of NACT with BIP before radiotherapy and the results of a randomized trial, comparing NACT with BIP before radiotherapy "versus" radiotherapy alone.

Table 14

Cervical Cancer
Neoadjuvant Chemotherapy Before Radiation Therapy
BIP-Regimen : Phases II and III

PHASE	STAGE	TREAT	#PTS	%RR (CT)	%LOCAL COMPL. CONTROL (CT+RT)
II	IIA-IV	BIP + RT	19	68	NR
III	IIA-IV	RT BIP + RT	34 32	65	56 75

In short the activity of BIP in previously untreated disease has been shown to be similar to that seen in patients with recurrent disease, and acute and late radiotherapy morbidity and mortality do not appear enhanced by this approach.

Resolution of pelvic disease appears to be improved by neoadjuvant BIP. The survival advantage remains to be demonstrated.

In January 1991 the Portuguese Group of Gynecological Oncology started a randomized trial of neoadjuvant BIP in locally advanced squamous cervical cancer. Data of 37 stage III patients entered are presented in this analysis. The response rate, the recurrence rate, the local of recurrences are similar in both groups. There is a significant difference concerning the overall survival: 42% in the control group and 59% in the study group (Tables 15 and 16 and Figures 3 and 4). We did not registered severe toxicity in any case.

Table 15

Cervical Cancer - Stage III B
Neoadjuvant BIP Before Radiation Therapy
Portuguese Trial

	RT	BIP + RT
Nb. PTS	20	17
Median Age	54.4	50.5
Local Complete Control	55%	68%
Recurrence Rate	21%	26%
Local Rec.	7%	13%
Distant Rec.	14%	13%

Table 16

Cervical Cancer - Stage III B
Neoadjuvant BIP Before Radiation Therapy
Portuguese Trial

	RT	BIP + RT
Median Time to Progression	16 m	NR (48)
Median Survival	22 m	NR (48 m)
Overall Survival	(4Y) 42%	(4Y) 59% (p=0.02)

Figure 3

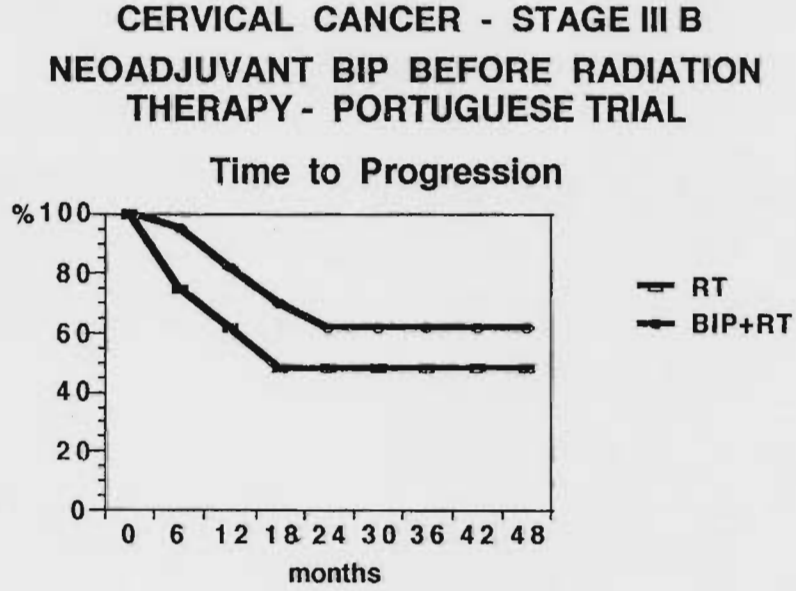
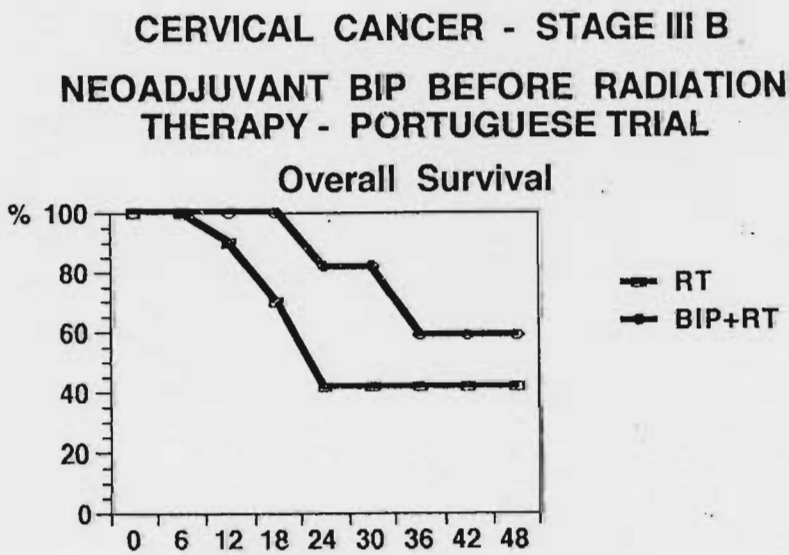


Figure 4



Final Conclusions

1 - NACT, given before radiotherapy, in patients with locally advanced cervical cancer, causes tumor shrinkage in a significant proportion of patients.

2 - NACT given before radiotherapy seems to be a predictor of response to radiotherapy.

3 - NACT and subsequent radiotherapy does not improve local control of survival.

5 - Data on NACT before surgery seem more promising.

6 - NACT before surgery is useful in bulky tumors (>4cm):

- improves operability;
- reduces the incidence of positive lymph nodes;
- improves tumor volume and other prognostic factors;
- seems to improve disease free interval and survival;

7 - NACT before surgery is not justified in small tumors (<3-4 cm)

8 - There is enough indication to start randomized trials using NACT before surgery in bulky cervical tumors.

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საშვილოსნოს ყელის კიბო: ნეოადიუვანტური ქიმიოთერაპია

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РАК ШЕЙКИ МАТКИ: НЕОАДЮВАНТНАЯ ХИМИОТЕРАПИЯ

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