Preoperative chemoradiation and adjuvant surgery in locally advanced or recurrent cervical carcinoma

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SUMMARY. From February 1988 to May 1994, 31 patients (pts) with the established diagnosis of locally advanced (IB-IIA bulky,IIB,III,IVA) or recurrent cervical carcinoma were treated with simultaneous chemotherapy (CT) and external beam radiotherapy (RT) followed by radical surgery (RS) with or without intraoperative radiation therapy boost (IORT) to the high risk areas for recurrence. CT consisted of cisplatin 20 mg/m2 and 5-Flourouracil 1000 mg/m2 (maximum dose 1500 mg) in a 24-hour continuous IV infusion for 3-5 days during the first and fifth weeks of the scheduled course of RT. RT was delivered with standard fractionation up to a 40-46 Gy total dose. RS was performed 4-6 weeks later. Pathologic findings revealed complete and quasi-complete response (pCR+qpCR) in 74% of the surgical specimens and partial response (pPR) in 26%. With a median follow-up of 27+ months (3-71+), actuarial disease-free survival is 80% (91.3% for pCR+qpCR, 40% for pPR). Loco-regional control rate is 93.4%. The concurrent administration of RT and CT has moderate toxicity and can promote a high rate of pCR+qpCR as well as local control in high risk cervical carcinoma. The presence of a pCR or qpCR specimen seems to be correlated with good patient outcome.

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Key words

Preoperative chemoradiation. Pathologic response. Adjuvant surgery.

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Introduction

Full dose radiation therapy remains to be the standard treatment for primary locally advanced carcinoma of the uterine cervix. It achieves cure rates ranging from 75% to 15-25% for disease stages IIA to IVA [33]. Local control continues to be a formidable problem, with more than 60% of the recurrent patients succumbing to uncontrolled pelvic disease [1]. In general, patient outcome closely correlates with disease stage, although other clinical factors, such as tumor size [7,36] have also been reported to be significantly correlated.

The management of recurrent disease is less well established. Recurrent disease after surgery may be successfully managed with radiation therapy [33], chemoradiation [48], rescue surgery or a combination of them. Local relapses after definitive radiation therapy may only be salvaged if the recurrence is centrally located and it may be approached by way of a pelvic exenterative procedure [17].

The role of neoadjuvant chemotherapy, simultaneous chemoradiotherapy, adjuvant surgery and adjuvant chemotherapy has yet to be defined although promising results with the concomitant use of chemotherapy and full dose radiotherapy have been reported [14,37]. Only radiation therapy combined with hydroxyurea, - a cell-cycle specific chemotherapeutic agent with no apparent activity on cervical carcinoma- has proven superior over radiation therapy alone in late stage cervical cancer [14,38].

The present study reports on an ongoing trial that combines preoperative chemoradiotherapy and programmed adjuvant surgery with or without intraoperative radiotherapy. Special emphasis is given to clinical tolerance and to the pathologic findings observed in the surgical specimen. Preliminary data of patterns of failure and survival are presented.

PATIENTS AND METHODS

From February 1988 to June 1993, 31 patients with

biopsy-proven carcinoma of the cervix entered the study. Entry criteria included advanced primary tumors (IB-IIA > 4 cm diameter "bulky", IIB, IIIB, IVA disease stage) and locally recurrent disease after surgery. Patients with previous pelvic radiation therapy, distant metastases or those unable to receive chemotherapy due to inadequate bone marrow, liver or renal function were excluded. All patients gave informed consent before entering the study.

Diagnostic workup included personal history and physical and gynecological examination, complete blood count, liver chemistries, serum electrolytes, BUN, serum creatinine, chest X-rays and abdomino-pelvic CAT scan. Cystoscopy and sigmoidoscopy were performed whenever there was suspicion of organ invasion.

After the completion of the treatment program, all patients were followed up every 3 months. Patient evaluation included physical examination, blood tests, chest X-rays, intravenous pyelogram, abdomino-pelvic CAT scan and other studies when deemed necessary.

Patients age ranged from 26 to 78 years (mean 50). Twenty-five patients (80%) had primary disease while six patients (20%) presented with recurrent disease after previous types I-III radical hysterectomy. Four of these six patients were included in a previous report [25]. Tumor characteristics are shown in table I.

Table I

Tumor characteristics

		n	%
FIGO STAGE	IB bulky	5	16
	IIA bulky	7	22
	IIB	6	19
	IIIB	6	19
	IVA	1	3
	Recurrent disease	6	19
	central	2	
	sidewall	4	
HISTOLOGY			
	Squamous cell cardinoma	23	74
	Adenocarcinoma	6	19
	not other specified	3	
	papillary	2	
	clear cell	1	
	Undifferentiated	1	3
	Adenosquamous	1	3
GRADE	GI	5	16
	GII	12	38
	GIII	8	25
	Not available	6	19
TUMOR SIZE (primary disease)			
	4 cm ø	15	60
	<4 cm ø	10	40

Chemotherapy consisted of two courses of cisplatin (CDDP) 20 mg/m^2 and 5-Fluorouracil 1000 mg/m^2 (maximum daily dose 1500 mg) 24-h continuous intravenous infusion for 3-5 days during the first and fifth weeks of the planned course of external beam radiation therapy. The number of days on chemotherapy was prescribed according to age, performance status and clinical tolerance to the chemoradiation regimen. Chemotherapy was administered only when the leukocyte count was greater than 3000/mm^3, the platelet count greater than 75000/mm^3 and the serum creatinine level ≤ 1.5 mg/dL. Most patients had a dosage reduction in the scheduled chemotherapy courses (table II).

External beam radiation therapy started simultaneously to chemotherapy and consisted in pelvic irradiation in all but one patient, who received pelvic plus paraortic irradiation due to enlarged pelvic nodes on CAT scan. A 2 or 4-field technique was designed to encompass the treatment volume using 15 MV photon beams. All fields were treated every day , five days a week, with a 1.8-2.0 Gy daily fractionation up to a 40-46 Gy total dose.

Surgery was programmed 4-6 weeks after the end of the chemoradiation course. Patients were evaluated for clinical response and resectability prior to surgery by gynaecologic examination and abdomino-pelvic CAT scan. Surgical procedures in primary disease included type 2-3 radical hysterectomy [39] in 22 patients, pelvic exenteration (1 anterior, 1 total) in two and trachelectomy in one patient with previous subtotal hysterectomy. Salvage surgery for recurrent disease was by parametrectomy in two patients with pelvic sidewall recurrences, anterior pelvic exenteration in one and pelvic-paraortic lymphadenectomy in two patients with nodal failures.Surgical resection was not attempted in one patient with recurrent disease due to an unresectable tumoral mass fixed to the pelvic wall at exploratory laparotomy. Pelvic lymphadenectomy was carried out in 28 patients (90%) and paraortic nodes sampling in 10 patients (32%).

Intraoperative radiotherapy was delivered to 19 patients (67%). The methodology employed and the general considerations of the IORT program have been described elsewhere [3,4]. In summary, after exploratory laparotomy and surgical resection (if possible),

Table II

Treatment characteristics. (a) IORT data refers to the total number of IORT fields treated.

			n	%
CHEMOTHERAPY				
	Number of days	10	5	16
		9	5	16
		8	14	45
		7	5	16
		6	2	6
EXTERNAL BEAM RADIATION THERAPY				
	Dose	40-44 Gy	6	19
		45-46 Gy	25	81
	Fractionation	180 cGy /day	22	71
		200 cGy / day	9	29
	Number of fields	2	17	54
		4	14	46
INTRAOPERATIVE RADIOTHERAPY[a]				
	Number of fields	1	4	21
		2	14	74
		3	1	5
	Beam energy	9 MeV	30	88
		12 MeV	4	12
	Dose	10-12 Gy	24	69
		12,5-15 Gy	11	31
	Cone diameter	6 cm	26	74
		7 cm	9	26
SURGERY				
	Type	Radical hysterectomy	22	71
		Anterior exenteration	2	6
		Posterior exenteration	1	3
		Parametrectomy	2	6
		Lymphadenectomy	2	6
		Trachelectomy	1	3
		Exploratory laparotomy	1	3

high-risk areas for recurrence are exposed for IORT boost. The patient is transported under sterile conditions and careful monitoring to the IORT treatment room. A linear accelerator (Mevatron 77, Siemens) with electron beam energies ranging from 6 to 20 MeV is available for IORT. Custom-made IORT cones with diameters ranging from 5 to 15 cm and beveled ends (0º,15º,30º and 45º) allow the applicator positioning with maximum adaptation to the areas to be treated with IORT . In primary disease, one or both parametrial surgical margins are boosted with IORT, with the decision made on an individual basis. The irradiated area usually contains the surgical margin, the uterine artery stump, the internal iliac vessels, the lumbosacral plexus in depth and the upper part of the obturator fossa. Ureters are usually totally dissected and are easily mobilized out of the IORT beam. Bladder, small and large bowel are separated with retractors to allow exposure of the area to be treated with IORT. In recurrent disease, the selection of the areas to be boosted with IORT depends primarily upon operative findings and proper surgical staging.The IORT dose is prescribed to the 90% isodose curve. Once the IORT procedure is finished, the patient is transported back to the operating room where the surgical procedure is finished. IORT was not performed in 12 patients for the following reasons : surgical procedure outside our institution (2), medical contraindication for patient transport (2), abdominal carcinomatosis at exploratory laparotomy (1), surgeon preferences (7). Five patients

who did not receive IORT and who presented residual tumor in the pathologic specimen were given additional postoperative radiotherapy (external beam in two, 137Cs brachytherapy in three). The rest of data regarding treatment characteristics are shown in table II.

Three different categories of pathological response were determined; A complete pathological response (pCR) was defined as no evidence of visible tumor in the surgical specimen; A quasi-complete pathological response (qpCR) was defined if only microscopic scattered tumoral foci were observed, representing less than 5% of the surgical specimen. A partial pathological response (pPR) was defined if the amount of residual tumor was greater than in the aforementioned categories.

Survival curves were calculated according to the Kaplan-Meier actuarial method [19] from the day 1 of the first course of chemotherapy up to the date of last follow-up or death.

RESULTS

1.Histological response.-

All 31 patients were evaluable for response and toxicity. A pCR was verified in 18 out of 31 patients (58%) and a qpCR in 5 patients (16%). Eight patients (26%) displayed partial response (pPR) in the resected specimen with three of them also presenting residual tumor in the pelvic nodes. Thus, the percentage of patients with metastatic pelvic nodes after preoperative chemoradiation in the present series was 3/28 (10.2%). Pathological response according to stage is shown in table III.

Table III

Pathologic response according to stage

		n	pCR + qpCR	pPR
STAGE	IB	5	5	-
	II	13	10	3
	III	6	3	3
	IV	1	-	1
	REC	6	5	1

2.Toxicity.-

Toxicity due to the neoadjuvant protocol was mild and reversible. Three cases (9%) of WHO grade 3-4 bone marrow aplasia were noted. Two of them required hospital admission for antibiotic coverage with hematological and nutritional support and one had her radiation course suspended for two days. All patients experienced diarrhea, five of them WHO grade III.

Postoperative complications included one case of genitourinary fistula two months after surgery plus IORT. This was the only case with three IORT fields, although they were neither matched nor overlapped. No evidence of tumor recurrence was found. Unfortunately, she was lost to follow-up soon after. The rest of postoperative complications are described in table IV.

Long-term complications have been severe. Seven patients (22%) developed temporary RTOG grade 1-2 hydronephrosis (four bilateral, three unilateral) soon after surgery plus IORT which resolved spontaneously. Another additional six patients (19%) underwent RTOG grade 3-4 hydronephrosis (three bilateral, three unilateral) due to ureteral stenosis secondary to retroperitoneal fibrosis, which needed the placement of endoureteral stent(s). Renal function remained stable or improved in all but two patients due to repetitive urinary infections and/or stent displacement. These two patients underwent laparotomy for ileal diversion, which was unsuccessful due to retroperitoneal fibrosis and ischemic changes secondary to late radiation injury. They continue on endoureteral stents at 51+ and 71+ months follow-up without evidence of disease and with moderately impaired renal function.The rest of data regarding long-term toxicity are shown in table IV.

3.Patterns of failure and survival.-

All patients included in the present analysis were followed up for at least 12 months. One pPR patient was lost to follow-up and was excluded. Thus, thirty patients were evaluable. One pPR patient failed locally at 7 months. Another pPR patient developed local recurrence and distant metastases (liver) at 4 months. Three patients (2 pPR,pCR) failed at distant sites (abdominal carcinomatosis, left supraclavicular node, vulva) at 2, 7 and 11 months, respectively. The stages of the disease of the five patients who relapsed were IIA (2), IIIB, and recurrent (2). With a median follow-up of 27+ months (range: 3-71+) local and distant failure rates were 6.6% and 13.3%, respectively. Overall failure rate was 16.6%.There were no relapses within areas boosted with IORT.

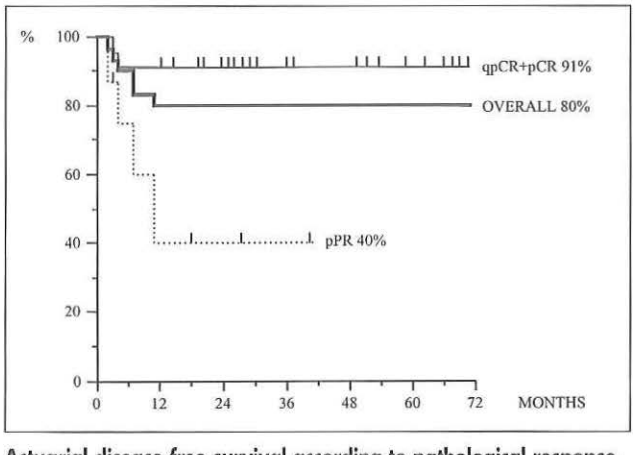
Tabla IV

Treatment toxicity. (a) RTOG toxicity grading system

		n
PREOPERATIVE		
	Bone marrow aplasia WHO grade III/IV	3
	Vaginal infection	3
	Urinary infection	2
	Acute enteritis WHO grade III	5
	Acute cistitis WHO grade III	2
POSTOPERATIVE		
	Vaginal infection	2
	Urinary infection	4
	Positive blood culture	3
	Wound infection	4
	Vesico-vaginal fistula	1
	Intrabdominal bleeding	1
	Prolongued ileus	1
LONG-TERM		
	Urinary infection	5
	Hydronephrosis (1-2) [a]	7
	Hydronephrosis (3-4)	6
	Leg edema (1-2)	5
	Pelvic pain (1-2)	1
	Lower extremity paresthesias (1-2)	1
	Chronic enteritis (1-2)	1
	Rectal ulcer (1-2)	2
	Bladder incontinence (1-2)	2
	Rectal incontinence [1-2]	1

Actuarial disease-free survival projected at a maximum follow-up of 71+ months was 80% (100% qpCR, 88.8 pCR, 40% pPR). Patient outcome is described in table V. Actuarial disease-free survival according to pathological stage is represented in figure 1.

Fig. 1



Actuarial disease-free survival according to pathological response.

Discussion

In recent years, a large number of studies on neoadjuvant chemotherapy for locally advanced or recurrent cervical cancer have been reported [2,5,6,8-10,15,18,23, 27,30,32,40,42,44,45,49,50]. Cisplatin-based regimens achieve clinical responses in 50-70% of the patients [2,5,9,23,27,30,45,49,50] with a 5-35% complete clinical response rate [2,9,27,30] before definitive treatment with full dose radiotherapy or radical surgery. These regimens have also shown activity for recurrent and metastatic cervical carcinoma, with some reported complete clinical responses [18,27]. Moreover, a pCR rate of 10-15% has been reported when cisplatin-based chemotherapy regimens are evaluated into surgical trials [8,10,30]. Thus, the activity of cisplatin against cervical carcinoma and its radiosensitizing properties makes it an ideal adjunct in chemoradiotherapy programs.

Chemoradiation programs, usually a multidrug combination containing cisplatin, mitomycin C or 5-Fluorouracil [12,15,21,22,29,43,47,48,52] which are simultaneously administered with full dose radiotherapy, render complete clinical responses in 60-85% of the cases for locally advanced disease [16,20,24,29,43,46]. Post-treatment biopsies or hysterectomy reveal a 70-90% pCR rate [31,43,52].These results, in terms of pCR rates, are similar to that obtained in the present series if patients with qpCR and pCR are considered together. Also, a lower than expected incidence of lymph node metastases (10.2%) has been found in this group of patients after treatment with preoperative chemoradiation. This has been previously reported in surgical trials comprising cisplatin-based neoadjuvant chemotherapy [10,30] or preoperative external beam radiotherapy [33].

A complete clinical and/or histological response after radiation therapy [29,33,34] or chemotherapy [6,9,23,30,45] has been reported to be a strong predictor of patient outcome. In our series only 1 out of 22 patients with pCR or qpCR failed versus 4 out of 8 patients with pPR .

The role of adjuvant surgery after preoperative irradiation for bulky cervical cancer remains controversial. Although classic articles [11,28] support the use of adjuvant surgery showing excellent local control rates, the supremacy of such approach has been put in question in recent reviews [26,36]. A randomized trial of preoperative irradiation plus surgery vs irradiation alone in non-bulky stages IB and IIA by Perez et al [34] did

Table V

Patient outcome		
	n	%
ALIVE NED[a]	24	80.0
DEAD WITH DISEASE	5	16.6
DEAD FREE OF DISEASE	1	3.3

(a) 1 patient lost to follow-up not included

not show differences in treatment results or toxicity. Other authors, however, have reported statistically significant increased toxicity with the combined approach [26]. In our series, complete resection was successful in 25 out of 31 patients. It must be emphasized that most patients did not initially meet the criteria for radical surgery with curative intent (see table I). Willemse [52] treated 35 patients with stages IB to IVA with concomitant chemotherapy and radical radiotherapy with planned delayed surgery, achieving resectability in 22 out of 35. In our opinion, radical surgery after chemoradiation provides local control rates comparable to those of full dose irradiation, allows a thorough examination of the abdominopelvic contents and reliable pathologic verification of the response to neoadjuvant treatment. In high-risk patients, it also makes possible to deliver intraoperative radiotherapy to suspicious or pathologically-verified tumor residual areas.

Ureteral toxicity has become a matter of concern in this trial. RTOG grade 3-4 hydronephrosis developed in 6 patients (19%) due to ureteral stricture. At the present time, this is a very rare complication following high dose radiotherapy or radical surgery [13,33,35] . A higher complication rate is expected for larger tumors due to higher irradiation doses or more extensive surgery [33]. Perez et al [34] in a randomized study of preoperative irradiation plus surgery vs irradiation alone indicated 3/62 ureteral strictures in the preoperative group vs 1/56 in the radiation alone group, although the overall incidence of severe complications did not differ among those groups. Mendenhall et al [26] reported 2/75 ureteral strictures with the combined approach versus none in the irradiation alone group. An interim analysis of the present series disclosed a significant higher incidence of ureteral stenosis in those patients operated in the former years of the trial. This may be explained by a change in the surgical policy to perform less radical surgery due to the observed toxicity, greater confidence in the cytoreductive properties of the chemoradiation regimen and excellent outcome of the patient population.

The role of IORT in locally advanced or recurrent cervical carcinoma cannot be determined from this study. IORT was integrated in this multidisciplinar protocol to prevent pelvic sidewall recurrence after obtaining a good chance for pelvic central control with adjuvant surgery. With a median follow-up of 27+ months, no patient has developed recurrence within areas boosted with IORT. Although no definitive conclusions about the therapeutic contribution of IORT may be obtained from these results, it should be noted that 16 out of 31 patients in our series presented with lateral disease (6 IIB,6 IIIB, 4 pelvic sidewall recurrences).

The analysis of patterns of relapse and patient outcome is hampered by the fact that chemoradiation series do not integrate adjuvant surgery as definitive treatment, using brachytherapy or external beam radiotherapy boost after the neoadjuvant chemoradiation course. Willemse [52] reported a 2-year local control rate of 84%, similar to ours. Chemoradiation series report long-term local control rates in excess of 80% for stages IB-II [21,47] , 40-60% for stages III-IV [12,21,47] and over 50% for recurrent disease after surgery [48]. Our series includes the previously shown disease stages with an overall local control rate of 93.4% at a maximum follow-up of 64+ months.

In the present series, with a median follow-up of 27+ months, actuarial disease-free survival rate is 80% at 71+ months. Willemse [52] reported a 65% 2-year survival rate for stages IB to IVA. Other chemoradiation series report outstanding long-term (>3 year) survival rates of 70% for stages I-II [47] and 40-45% for stages III-IV [12,38,47].

Simultaneous cisplatin/5 Fluorouracil chemoradiation is highly active in locally advanced and recurrent carcinoma of the uterine cervix and provides an outstanding rate of pCR + qpCR (74%). Acute toxicity is mild and tolerable. Chronic toxicity, specially, ureteral stricture, will probably benefit in the future from less radical surgery without compromising patient outcome. After a median follow-up of 27+ months, local control and overall survival rates appear encouraging and support the exploration of this approach for high-risk patients, specially those with a poor chance for tumor control with either surgery or definitive radiotherapy alone.

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