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Original Paper

Long-term Survival Following Neoadjuvant Chemotherapy and Radical Surgery in Locally Advanced Cervical Cancer

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The aim of this study was to analyse the long-term survival and the relationships between prognostic factors at presentation, chemoresponsiveness and disease outcome in patients with locally advanced cervical cancer treated by neoadjuvant chemotherapy and radical surgery (RS). Two consecutive studies of neoadjuvant chemotherapy containing cisplatin, bleomycin plus/minus methotrexate followed by radical hysterectomy and systematic aortic and pelvic lymphadenectomy were carried out between January 1986 and September 1990 on 130 patients with ≥ 4 cm stage IB2–III cervical cancer. Survival analysis was performed using the Kaplan and Meier test and Cox's multivariate regression analysis. 128 (98%) of the patients enrolled were evaluable for clinical response and survival. 83% (106) of the patients responded to chemotherapy, with a 15% complete response rate. Logistic regression analysis demonstrated that International Federation of Gynecology and Obstetrics (FIGO) stage, cervical tumour size, parametrial involvement and histotype are highly predictive of response. Responding patients underwent laparotomy, but 8% were not amenable for radical surgery. The 10-year survival estimates were 91%, 80% and 34.5% for stage IB2–IIA bulky, IIB and III, respectively ($P < 0.001$). After Cox's regression analysis, the parameters significantly associated with survival were the same factors predicting response to neoadjuvant chemotherapy. No stage IB2–IIA bulky patient has so far relapsed, while 12% stage IIB and 56% stage III patients recurred. The 10-year disease-free survival estimates are 91% and 44% for stage IB2-IIB and III, respectively ($P < 0.001$). Metastatic nodes and persistent tumour in the parametria were the only two independent factors for disease-free survival after multiple regression analysis. After a long-term follow-up (median follow-up 98 months (20–129+)), our results give new evidence of the prognostic value of response to neoadjuvant chemotherapy and of a possible therapeutic benefit of the sequential treatment adopted which, however, must be verified in a randomised setting. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: neoadjuvant chemotherapy and radical surgery, locally advanced cervical cancer, long-term follow-up
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INTRODUCTION

THE PROGNOSIS of patients with locally advanced cervical cancer treated with conventional therapy is not good [1]. A new approach to treatment has been developed by combining chemotherapy and radical surgery. On the basis of published data, it seems clear that this therapeutic sequence is feasible and does not involve additional complications. In the presence of an uncompromised blood supply to the neoplasm, cervical cancer is a chemosensitive tumour [2–13], and a direct relationship between tumour size, chemoresponsiveness and prognosis has been observed in reports published so far [4–9, 13, 15]. Although these pilot studies do not address survival, the majority seem to show increased tumour-free

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survival rates. Therefore, neoadjuvant chemotherapy followed by radical surgery may be an alternative modality in the management of locally advanced disease. While mature data from current randomised trials on chemosurgical sequential treatment [16, 17] are awaited, there is a clear interest in looking at the long-term results of such an approach in a large series of patients. From 1986 to 1990 this therapeutic strategy was adopted for patients with locally advanced cervical cancer at the Department of Gynecology and Obstetrics of the Università Cattolica del Sacro Cuore in Rome. The aim of this study was to analyse the long-term survival, early and late complications and the relationships between prognostic factors at presentation, chemoresponsiveness and disease outcome in these patients.

PATIENTS AND METHODS

130 patients with locally advanced cervical carcinoma were consecutively admitted to the study from January 1986 to September 1990. All patients gave informed consent on entering the study. The eligibility criteria were: International Federation of Gynecology and Obstetrics (FIGO) Stages IB2–IIA bulky, IIB and III; no previous treatment and age under 70 years. The clinical staging workup performed has been described in our previous papers [5, 6]. Two different cisplatin-based regimens were used, reflecting the changing concepts of neoadjuvant chemotherapy in cervical cancer. 77 patients (59%) underwent three courses of cisplatin (P), bleomycin (B) and methotrexate (M) (100 mg/m^2 P, day 1; 15 mg B, days 1 and 8; 300 mg/m^2 M + leucovorin rescue, day 8) every 21 days. The other 53 patients (41%) were given one or two courses of high-dose P (40 mg/m^2 days 1–5 or 1–4) and B (15 mg, days 1, 2, 8, 9 or 15 mg/m^2 days 1 and 8). Toxicity and clinical response were assessed according to the World Health Organization (WHO) criteria [18]. Patients responding to neoadjuvant chemotherapy or with cervical, vaginal or parametrial tumour judged radically resectable underwent surgery. In operable patients, surgery consisted of type III–V radical hysterectomy [19] and systematic aortic and pelvic lymphadenectomy. The non-responding patients and those still considered not amenable for radical surgery were submitted to conventional radiotherapy or salvage treatment. Postoperative treatment was given according to the criteria previously reported [7]. Tumour recurrence was defined as the presence of biopsy-proven cancer 3 months after surgery or later. The pattern of tumour relapse was defined as local (central or lateral), loco-regional lymph node, systemic, or a combination of the same. The median follow-up of the whole cohort is 98 months (range 20–129+). The cut-off date for analysis was January 1997.

Descriptive statistics are reported as frequencies or medians. Survival was calculated from the date of study entry to the date of death or date last seen. Disease-free survival was calculated from the date of surgery to the date of relapse or date last seen. The Mantel–Haenszel test was utilised to evaluate the statistical difference between the clinical and pathological parameters. All medians and life-tables were computed using the product-limit estimate by the Kaplan and Meier method [20] and the log-rank test was employed to determine the level of significance. A multiple logistic and Cox's regression model with stepwise variable selection was used to evaluate the factors related to clinical response and survival, respectively [21, 22]. The association between exposures and outcome are thus expressed in terms of odds ratio, relative risk and proportional hazards model, together with their 95% confidence intervals (95% CI). Statistical analysis was carried out using Statistical Application System (SAS) procedures.

RESULTS

Response to chemotherapy

128 (median age 54 years, range 25–70) of the 130 patients enrolled are evaluable for clinical response. 2 patients were excluded from the analysis because they refused to continue chemotherapy after the first cycle. Ninety-six per cent of the evaluable patients received 100% of the planned chemotherapy doses. 106 patients (83%) responded to neoadjuvant chemotherapy and 19 (15%) had a complete response. The results of logistic regression analysis are summarised in Table 1. There was a higher probability of no response to chemotherapy for patients with advanced stage, those with > 5 cm cervical tumour size, those with adenocarcinoma and, to a lesser extent, with a poor grade of tumour differentiation. Furthermore, the patients with bilateral parametrial involvement had a higher probability of no response than

Table 1. *Factors affecting chemotherapy response*

Variable	No. (%)	% Response	Odds ratio	95% confidence interval
FIGO stage				
IB2–IIB	73 (57)	94 (21 CR)	1	
III	55 (43)	67 (7 CR)	8.7	2.1–35.5
Histotype				
Squamous cell	95 (74)	86 (17 CR)	1	
Adenocarcinoma	33 (26)	73 (9 CR)	6.7	1.5–29.4
Grade of differentiation				
Good–mod. good	75 (59)	89 (16 CR)	1	
Poor	53 (41)	73 (13 CR)	2.22	0.87–5.66
Cervical tumour size (cm)				
4–5	68 (53)	94 (26 CR)	1	
> 5	60 (47)	70 (2 CR)	6.8	1.6–27.9
Parametrial clinical involvement				
Absent–Monolateral	92 (72)	93 (18 CR)	1	
Bilateral	36 (28)	56 (6 CR)	13.2	3.5–49.9

The following variables did not enter the logistic model: age (< 50 years, ≥ 50 years); and neoadjuvant chemotherapy regimen (PBM, PB). CR, Complete response.

patients with no parametrial involvement or unilateral parametrial involvement. Variables not significantly related to chemotherapy response included age, neoadjuvant chemotherapy regimen and number of cycles.

Surgical treatment

All responding patients ($n = 106$) underwent laparotomy but 8 (8%) were intra-operatively judged not amenable for radical surgery. In one case this was due to unresectable primary tumour, in another to peri-lymph-node disease spread, and in the remaining 6 patients the macroscopic intraperitoneal tumour extension was the reason for abandoning radical surgery. Metastatic lesions were detected in the pelvic peritoneum (2), omentum (3), and adnexa and omentum (1). Therefore, radical hysterectomy (type III: 39; type IV: 52; type V: 7) plus systematic aortic (median number of nodes resected 19, range 15–44) and pelvic (39, range 21–85) lymphadenectomy was performed in 98 (92%) cases. Surgical resection margins were disease-free in all but one stage IIIA patient with positive vaginal margins. In keeping with clinical response, there was no detectable tumour in the surgical specimens of 18 patients (18%). In one further patient, tumour was found in both the aortic and the pelvic nodes but not in the cervical specimen. Microinvasive disease (≤ 5 mm) was detected in 21 patients (21%), and in particular to or less than 3 mm in 12 cases (12%). The remaining 58 patients (59%) showed a frank (> 5 mm) invasion of the cervical stroma. Extracervical disease was present in 45 patients (46%). The parametrium was pathologically involved in 28 patients (29%): 17% stage IB2-IIA bulky (3/18), 31% stage IIB (15/48) and 31% stage III (10/32). It is interesting to note that 6 of the 28 patients (21%) with positive parametria had microinvasive residual tumour in the cervix. Lymphatic metastases were detected in 17 (17%) cases: 15 in the pelvic (88%) and 2 in both the aortic and the pelvic nodes (12%) (median number of positive nodes: 4, range 1–12). The frequency of lymph node involvement correlated well with the clinical stage: 6% (1/18) stage IB2–IIA bulky, 12% (6/48) stage IIB and 31% (10/32) stage III ($P = 0.001$). No further relationship was found between lymph node status and the clinical and pathological characteristics. Indeed, there were lymph node metastases in 3 of the 21 (14%) and in 1 of the 19 (5%) microinvasive tumours and complete responses, respectively. Intraperitoneal disease spread was found in 6 patients (6%): microscopic metastasis in the adnexa (5%) and positive cytology in the peritoneal washings (1%). The numbers are too small to achieve statistical significance. However, it is to be noted that 2 patients had positive nodes or tumour in the parametria and 3 of the 6 patients had an adenocarcinoma.

Table 2. Surgery-related morbidity

Complications	No. of cases	(%)
Intra-operative		
Haemorrhages (≥ 1000 cc)	2	2
Injuries: Rectal	1	1
Bladder	2	2
Ureteral	2	2
Obturator nerve	2	2
Early postoperative		
Symptomatic lymphocyst	22	22
Mild thigh paresthesia	12	12
Deep venous thrombosis	12	12
Pulmonary embolism	8	8
Wound infection	6	6
Ureteral fistula	5	5
Late postoperative		
Urinary incontinence: Urge	10	10
Stress	20	20
Total	1	1
Ureteral stenosis	2	2
Laparocele	7	7
Deep venous thrombosis	2	2
Leg oedema: Mild	5	5
Moderate	2	2

Toxicity and complications

Toxic side-effects induced by chemotherapy were mild to moderate in the majority of cases. Surgery-related morbidity is summarised in Table 2. Neither intra- nor postoperative deaths were observed. Intra-operative and early (within four months from surgery) complications occurred in 9 (9%) and 46 (46%) patients, respectively.

Survival

At the time of the present evaluation, 78 patients (61%) are alive and 50 (39%) have died (45 of tumour and 5 of intercurrent disease). The overall 10-year survival estimate is 60.2% (stage IB2–IIA bulky 91%, IIB 80%, III 34.5%). 19 of the 22 (86%) clinically non-responding patients have died. The remaining 3 are still alive, one being free of disease. The median survival for non-responding patients is 18 months (range 4–70+ months). All the 8 inoperable patients at laparotomy died in spite of salvage treatment. The patient with positive surgical resection (vaginal) margins is alive with no evidence of disease 8 years after colpectomy and intracavity radiotherapy. Figure 1 shows the 10-year survival curves of two FIGO stage subgroups. 10-year survival of the stage IB2–IIB patients (81%) was significantly longer than that of stage III patients (34.5%) ($P < 0.001$). The median survival of the second group was 3.16 years (range 1–9.41). After Cox's regression analysis the parameters significantly associated with survival were the same factors predicting response to neoadjuvant chemotherapy (Table 3). 24 (24%) of the 98 radically operated patients recurred with a median time to relapse of 17.5 months (range 3–42), 9 of whom relapsed 24 months after surgery. No stage IB2-IIA bulky patients have so far relapsed, while 6 out of 48 (12%) stage IIB and 18 out of 32 (56%) stage III patients have recurred. 14 (58%) patients recurred in the vaginal cuff, 4 (17%) in the loco-

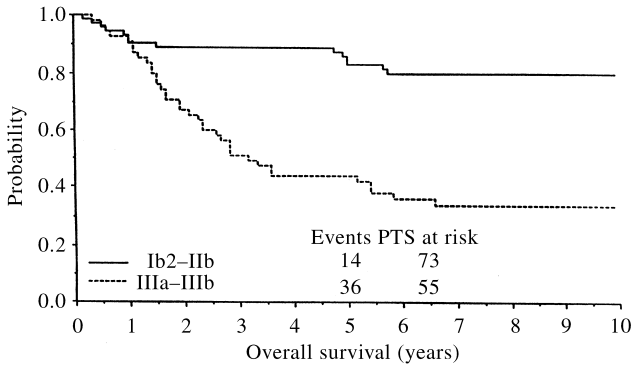

Figure 1. Ten-year overall survival estimated in FIGO stage IB2–IIB and III ($P < 0.001$). PTS: patients.

Table 3. Factors affecting survival

Variable	Relative risk	95% confidence interval
FIGO stage		
IB2–IIB	1	
III	3.57	1.87–6.80
Histotype		
Squamous cell	1	
Adenocarcinoma	2.06	1.07–3.96
Grade of differentiation		
Good–mod. good	1	
Poor	2.46	1.33–4.53
Cervical tumour size (cm)		
4–5	1	
>5	2.16	1.16–3.99
Parametrial clinical involvement		
Absent–monolateral	1	
Bilateral	2.31	1.29–4.11

The following variables did not enter the Cox model: age (< 50 years*, ≥ 50 years); and neoadjuvant chemotherapy regimen (PBM*, PB). *Reference category.

regional lymph nodes, 2 (8%) in the lung, and 4 (17%) both in the pelvis and in distant organs. 4 of the 14 cases (28%) with a central recurrence were treated with surgery and radiotherapy and are presently alive, all but one with evidence of disease. The overall 10-year DFS estimate rate is 75%. The analysis of DFS by FIGO stage revealed a rate of 91% and 44% for stage IB2–IIB and III, respectively, showing a statistically significant difference between the two groups ($P < 0.001$; Figure 2). A summary of prognostic factors for DFS is shown in Table 4. The categories of parametrial infiltration and lymph node metastasis are each independently significant for poorer DFS. For patients without lymph node metastasis, the following subsets showed significantly poorer DFS: parametrial infiltration ($P = 0.01$) and intraperitoneal microscopic disease ($P = 0.001$), resulting in a relative risk of recurrence of 3.77 (95% CI: 1.20–14.23) and 2.46 (95% CI: 1.18–4.96), respectively.

DISCUSSION

As expected, this study confirms that neoadjuvant chemotherapy followed by radical surgery is a feasible combination, as has been widely reported in the literature [2–11, 13–15]. In accordance with our previous results [5–7], as well as those of other investigators [23, 24], the toxicity induced by front-line

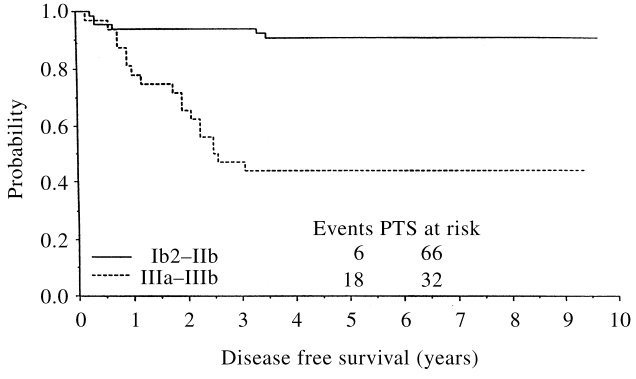

Figure 2. Ten-year disease-free survival estimated in FIGO stage IB2–IIB and III ($P < 0.001$). PTS: patients.

Table 4. Factors affecting disease-free survival in radically operated patients

Variable	Relative risk	95% confidence interval
Pathological parametrial involvement		
Absent	1	
Present	2.91	1.26–6.66
Lymph node status		
Negative	1	
Positive	3.07	1.32–7.12

The following variables did not enter the Cox model: histotype (squamous cell*, adenocarcinoma); grade of differentiation (good–mod. good*, poor); Cervical infiltration (absent or ≥ 5 mm*, ≥ 5 mm). *Reference category.

chemotherapy was generally mild to moderate with rare severe toxic effects and no cases of delayed surgery. Moreover, surgery-related complications that occurred were most likely due to the type of surgery (type IV–V: 45%) rather than prior chemotherapy. This is supported by the same rate and pattern of complications seen in the absence of any prior treatment and for the same surgical approach [25–27].

If there are no doubts as to the chemosensivity of cervical cancer, the question of whether a response is followed by an actual increase in survival must be answered. This is the first long-term survival analysis reported in the literature for patients undergoing neoadjuvant chemotherapy and radical surgery, and seems to corroborate the results previously published [5–10, 13]. The estimated 10-year survival was 91, 80 and 34.5% for stage IB2–IIA bulky, IIB and III, respectively. It seems quite reasonable to think that the survival observed for stage IB2–IIB is somewhat better than would otherwise be expected in this group of patients following conventional treatments. Five-year survival rates ranging from 60–70% and from 35–65% have been reported in bulky stage IB2–IIA and IIB, respectively, following radiotherapy either with or without surgery [1, 16, 28–32]. In contrast, the survival observed in stage III patients does not seem to be markedly improved when compared with that generally reported [1, 33–36]. However, it is to be considered that the data available mostly concern 5-year survival analyses and that, on the basis of our own results, a clear 10% decrease is to be expected in a further 5 years of follow-up. An increase in the cure rate, even if limited, seems to be also suggested by the less than 30% 10-year survival recently reported by a French cooperative group in a series of stage IIB–III patients treated with radiotherapy in a randomised setting [29]. In accordance with our previous results [6], response to chemotherapy has been confirmed as a potent predictor of survival. Only 1 (4.5%) of the 22 non-responders is presently free of tumour and the vast majority (86%) of them have died of disease. The correlation above is particularly supported by the fact that, after Cox's regression analysis, the parameters significantly associated with survival were the same factors as those predicting response to chemotherapy. Moreover, the presence of macroscopic intraperitoneal tumour at laparotomy was highly predictive of a negative outcome. The frequency of relapse was clearly stage-dependent, being 9 and 56%, for stage IB2–IIB and III, respectively. The marked difference in the recurrence rate between the two groups is most likely due to the significantly higher incidence of both

metastatic nodes and persistent tumour in the parametria in the latter group. These parameters were the only two independent factors for disease-free survival after multiple regression analysis. It is to be stressed that, in the node-negative patients, the presence of intraperitoneal microscopic tumour is the only independent factor for disease-free survival other than parametrial disease. This finding confirms the negative association of intraperitoneal spread with survival, as already shown for macroscopic diffusion.

Interestingly, in spite of prior chemotherapy, there was a distant component in 25% of recurrences. This seems to be less than the 50% generally reported for the same stage and size following conventional treatments [37–39] and belies the supposedly high rate of micro/occult metastases at initial diagnosis in locally advanced disease. However, after neoadjuvant chemotherapy and radical surgery, local recurrence is the main problem in over half the relapsing cases, thus suggesting the need for new integrated treatments in selected patients.

There was no correlation as regards the pattern of recurrence in patients with or without lymph node involvement. This is in contrast with other findings [8], but the low number of events must be taken into account.

Eighty-three per cent of our patients responded to chemotherapy, with a 15% complete response. Clinical response rates as high as 100% have been reported [9], but most observations range between 70 and 90% [2–4, 8, 10] which is in keeping with our results. Logistic regression analysis demonstrates that the degree of tumour extent, however expressed (i.e. FIGO stage, cervical tumour size, parametrial involvement), is highly predictive of response. It is easy to interpret these data as the logical consequence of the correlations between the disease volume and the tumour cell kinetics. The greater the volume, the larger the hypoxic and resting-phase cell population with reduced or no chemosensitivity and the probability of developing resistant clones. However, complete responses were obtained, although in less than 5% of cases, even in stage IIIB and in patients with bilateral tumours involvement of the parametria. Moreover, adenocarcinomas and, to a lesser magnitude, poorly differentiated tumours showed a higher probability of non-response, thus supporting the hypothesis that intrinsic tumour characteristics can also determine chemoresponsiveness. Squamous cell carcinoma (SCC) antigen pretreatment levels proved to be an independent indicator of chemoresistance (data not shown). On the basis of SCC values and clinical variables, a mathematical formula expressing the probability of non-response to chemotherapy has been elaborated and recently published by our group [40]. Further studies are now needed to clarify the biological aspects that link SCC expression to clinical chemoresistance and aggressiveness of cervical cancer.

Even though it does not automatically follow that increased operability improves prognosis, it is a fact that neoadjuvant treatment makes most inoperable tumours operable, and theoretically allows a greater possibility of cure in these patients. Overall, radical surgery was, therefore, possible in 76% of cases. While non-response of pelvic disease was the main cause (18%) of persistent inoperability, the intra-operative detection of macroscopic intraperitonal extension or peri-lymph-node spread, justified abandoning radical surgery in a further 6% of cases. The presence of intraperitoneal tumour, even in a limited fraction of patients and despite neoadjuvant chemotherapy, is further evidence of the advanced stage at diagnosis.

The finding of microinvasive disease in the cervical specimen in 21% of cases further confirms the chemoresponsiveness of cervical cancer. However, neoplastic foci were detected in the parametria of approximately 30% of these patients which suggests that, in spite of a striking response, either islands of tumours can be left or the degree of response may not be the same in all sites involved by tumour. In our opinion, these data justify the extensive surgery performed even in the presence of a massive clinical response.

According to neoadjuvant literature, lymph node metastases are detected in 17% of cases [8, 11, 13, 16, 41]. This is much less than expected for the same stage and tumour size, when compared with the incidence in patients not submitted to neoadjuvant chemotherapy [8, 35, 42]. Moreover, from our own and other studies, there is evidence of a very low (2%) incidence of aortic metastases in every stage, and of a low number of metastatic nodes [8, 11]. It is interesting to note that lymphatic metastases were found in only 5% of the cases with no detectable tumour and in 22% of those with invasive residual disease in the cervical specimen.

Our results on the relatively large number of patients give new evidence of the prognostic value of response to neoadjuvant chemotherapy and of a possible therapeutic benefit of the sequential treatment adopted. Moreover, long-term follow-up showed a very low incidence of late side-effects, the vast majority of patients being currently free of complications. On the basis of our experience, an Italian cooperative randomised trial was launched in 1990 comparing a policy of neoadjuvant chemotherapy followed by radical surgery with standard treatment using radiotherapy alone [17]. The accrual phase of the study has been recently closed and survival data will be available very soon.

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