Cancer Chemother Pharmacol (1990) 26 (Suppl): S 17–S 21

Cancer Chemotherapy and Pharmacology

The potential for adjuvant therapy in early-stage cervical cancer*

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Summary. Adjuvant therapy may potentially improve prognosis in women with early-stage cervical cancer who are at high risk of relapse after primary therapy. Patients with lymph node involvement at surgery are at high risk of recurrence and may benefit from adjuvant therapy, but many patients are treated with radical radiotherapy. At present there is no method of accurately identifying patients at high risk of recurrence in the latter group. A retrospective analysis of 141 surgically managed cases with stage I/IIa cervical cancer is presented. The study aims were to characterize patients at high risk of relapse, identify independent prognostic variables predicting for relapse and, using these variables, develop a model, that would accurately predict high-risk patients. Univariate analysis identified depth of invasion, substage, lymph node involvement, lymphatic and blood vessel invasion and tumour differentiation as significant prognostic variables. After stratification for depth of invasion, which did not conform to the proportional hazards assumption implicit in the Cox model, Cox regression analysis showed substage, lymphatic and vascular invasion and histological tumour type to be independent prognostic variables. Using these variables, classification models were constructed that would be applicable to patients treated with either surgery or radiotherapy. Applying the models to 110 cases with >18 months follow-up, 11/18 (61%) and 11/19 cases (58%) predicted as being at high risk of relapse have developed recurrence. Highly active chemotherapy is now available for this disease. We have demonstrated that combined bleomycin, ifosfamide and cisplatin (BIP) is one of the most active regimens in this disease. BIP produces cytoreduction in around 70% of patients with recurrent and primary advanced disease. Responses are achieved rapidly and acute radiotherapy toxicity is not enhanced by giving chemotherapy prior to radical local radiotherapy. A multicentre, prospective randomized trial testing the role of BIP as adjuvant therapy in patients with positive nodes at radical hysterectomy is now in progress. A complementary study testing the role of adjuvant chemotherapy in high-risk patients treated with radical radiotherapy is in preparation.

Introduction

Carcinoma of the uterine cervix is a curable disease if it is detected and treated at an early stage. Although survival in treated women with early-stage (I/IIa) disease is high, the results of treatment have remained disappointingly unaltered over the last 20 years. Despite the apparently favourable prognosis in what is increasingly a young patient population [10], around 20%–25% of women presenting with early-stage disease relapse within 5 years of primary treatment. The prognosis for women with recurrent disease is poor, with <15% being alive 1 year after diagnosis [4]. Thus, surgery and radiotherapy, the traditional cornerstones of management in early-stage disease, cannot be considered to constitute the optimal therapeutic approach. Since the only realistic chance of achieving a cure is with primary treatment, there is a need to explore new therapeutic avenues in this disease.

Conventional therapy fails either because the disease extends beyond the treatment field by direct extension of the primary tumour and metastatic spread to regional and distant lymph nodes or because the disease is not sensitive to the treatment; radiobiological differences between tumours are unpredictable. These limitations suggest a potential role for highly active, systemic adjuvant therapy. Although cisplatin-containing regimens that are highly active in the disease have been developed [1, 6], this approach can only be justified if a population of patients at high risk of relapse can be identified prospectively and if a

* Presented at the Satellite Symposium "Ifosfamide in Gynecological Tumors" of the 5th European Conference on Clinical Oncology and Cancer Nursing, London, September 3–7, 1989

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Table 1. Patient characteristics ($n = 141$)

Median age (range)		35 (22–67) years
Median parity (range)		2 (0–12)
Median follow-up[a] (range)		37 (11–103) months
Premenopausal		124
Relapsed		25
Stage	Ia	10
	Ib occult	66
	Ib	59
	IIa	6
Cervical invasion	< half	95
	> half	26
	Full thickness	11
	Parametrial	9
Histology	Squamous	112
	Adenosquamous	16
	Adenocarcinoma	13
Differentiation	Good	18
	Moderate	37
	Poor	42
	Unknown	44
Presentation	Abnormal cytology	90
	Symptoms	51
Vascular invasion		38
Pelvic nodes involved		25

[a] Calculated from the date of surgery

significant advantage in such patients is demonstrated by prospective randomized studies.

In patients treated by radical surgery, the presence of metastases in the pelvic and para-aortic lymph nodes represents a well-recognized adverse prognostic factor. However, around 50%–60% of patients with positive pelvic lymph nodes are alive 5 years after conventional treatment, and 10%–15% of patients with apparently negative nodes relapse. Furthermore, this approach is not applicable to the many patients who are treated primarily with radical radiotherapy. Identification of patients at high risk of recurrence after radical radiotherapy may be possible using a combination of prognostic factors that do not require recourse to laparotomy. Clearly, more precise identification of a high-risk group would be a significant advance in the evaluation of adjuvant chemotherapy.

Identification of a high-risk group

Tumour volume, stage, depth of invasion, lymphatic and blood vessel invasion, tumour type and differentiation and patient age have all been implicated as significant prognostic factors in cervical cancer [10, 12, 16]. We carried out a retrospective analysis of surgically treated cases in our centres. The aims were to characterize patients at low and high risk of recurrence, identify independent prognostic variables to predict recurrence and, using these variables, develop a model for the identification of a more appropriate group of high-risk patients to test the role of adjuvant systemic therapy after primary radical therapy.

Patients and methods

Patients. Between 1980 and 1986, 141 patients with stage I/IIa cervical cancer were treated surgically at the Birmingham and Midland Hospital for Women, Dudley Road Hospital, Birmingham, and The Northern General Hospital, Sheffield. Data from the case records of these patients form the basis of this report. All patients underwent radical hysterectomy carried out with curative intent. The operation comprised extended hysterectomy with wide excision of the parametrium and paracolpos and a vaginal cuff and bilateral pelvic lymphadenectomy with removal of parametrial, obturator, external and internal iliac lymph nodes. Bilateral salpingo-oophorectomy was undertaken if ovarian conservation was not required. Para-aortic lymph nodes were not routinely sampled unless there was clinical evidence of involvement. A total of 13 cases at the beginning of the study period had preoperative intracavitary radium as described by Stallworthy and Wiernik [15], but this practice was subsequently discontinued. In all, 23 patients received postoperative external-beam radiotherapy because of identification of poor prognostic factors on subsequent examination of the surgical specimen. All case records were reviewed, with particular attention to presenting symptoms, and demographic data were extracted. The patients' characteristics are shown in Table 1.

Stage was recorded according to the recommendations of the International Federation of Obstetrics and Gynaecology (FIGO) [9]. Where a case had not been allocated a substage by the operating surgeon, this was assessed retrospectively according to the documented results of clinical examination with the patient under anaesthesia and of intravenous urography and cystoscopy. It was not possible on the basis of this retrospective analysis to ascertain tumour volume; however, substage within stage I may reflect tumour volume. Cases were allocated to stages Ia and Ib occult on the basis of the original pathology reports and a statement in the case records that no clinically detectable disease was present at diagnosis.

All histology reports were reviewed with particular attention to depth of cervical invasion by the tumour, lymphatic and blood vessel invasion, tumour type and differentiation and the presence of lymph node involvement. Because of the difficulty of obtaining absolute measurements with regard to the depth of cervical invasion, this was expressed as a proportion of the cervix invaded, i.e. < half, > half, full thickness invasion and extension beyond the cervix into the parametrium.

Details of post-operative follow-up were also obtained. If the patient had moved from the area and follow-up was being carried out at another centre, the appropriate clinician was contacted and confirmation of follow-up and relapse status was obtained. If the patient was lost to follow-up, the general practitioner was contacted for the appropriate information.

Data collection and analysis. Data were collected on pro forma sheets and stored on a VAX 730 minicomputer at the West Midlands Cancer Research Campaign Clinical Trials Unit. All statistical analyses were carried out using the BMDP statistical software package [5]. Time to relapse, defined as the time from Wertheims-Meigs hysterectomy until the date of diagnosis of recurrent cervical cancer, was measured in months. Patients were censored from the analysis at the time at which they were last seen if they were disease-free. Differences in relapse-free interval between groups were analysed with the log-rank test [11]. The independent prognostic effect of variables was assessed by Cox regression analysis [3].

Results

The log-rank univariate analysis identified substage, depth of cervical invasion, lymph node involvement, lymphatic and blood vessel invasion, tumour differentiation and the presence or absence of symptoms at presentation as being significant prognostic factors for relapse. Tumour type,

Table 2. Univariate analysis

Variable	Grouping	Relapsed	χ^2	Degrees of freedom	*P* value
Cervical invasion	< half	7/95	27.4	2	0.00001
	> half	8/26			
	Full thickness/parametrial	10/20			
Stage	I a	0/10	17.1	3	0.0007
	I b occult	5/66			
	I b	18/59			
	II a	2/6			
Symptoms	Absent	8/90	13.2	1	0.0003
	Present	16/51			
Node involvement	Absent	16/116	7.6	1	0.0058
	Present	9/25			
Vascular invasion	Absent	14/103	6.7	1	0.0096
	Present	11/38			
Differentiation	Good	0/18	7.2	2	0.0275
	Moderate	8/37			
	Poor	14/42			
Histology	Squamous	18/112	1.593	2	0.4509
	Adenosquamous	3/16			
	Adenocarcinoma	3/12			
Age	<40 years	16/96	0.058	1	0.8909
	>40 years	9/45			
Parity	Nulliparous	8/36	2.04	3	0.5642
	≤ 2	10/48			
	$>2-\leq 4$	5/42			
	>4	2/15			
Menopausal status	Premenopausal	23/124	0.332	1	0.5643
	Postmenopausal	2/17			

Table 3. Hazard functions

Including depth of invasion:

$H1 = H1_0 e^{1.3V+1.0S-0.9H}$

$H2 = H2_0 e^{1.3V+1.0S-0.9H}$

Excluding depth of invasion:

$H3 = H3_0 e^{1.5V+1.4S-1.0H}$

H1, H2 = Hazard functions stratified by depth of invasion
H3 = Hazard function without depth of invasion
$H1_0$, $H2_0$ = Baseline hazard functions stratified by depth of invasion
$H3_0$ = Baseline hazard function without depth of invasion

Variable:	Categories:	Value:
S= Substage	I a	1
	I b occult	2
	I b	3
	II a	4
V= Vascular invasion	Absent	1
	Present	2
H= Histology	Squamous	1
	Other	2

patient age, parity and menopausal status did not appear to be significant factors predicting recurrence (Table 2).

The significant variables in the univariate analysis were not independent. For example, women with deep cervical invasion were more likely to have been classified as having a more advanced substage and were also more likely to have pelvic lymph node involvement. To determine the independent prognostic effect of each of the factors and to exclude the possibility that the most highly significant variables might be masking the effect of other potentially significant factors, Cox regression analysis was performed. Because of the large number of cases with incomplete information as to tumour differentiation, this variable was not included in the analysis. The assumptions implicit in the Cox model were only satisfied after stratification for the depth of cervical invasion which did not conform to the requirement for proportionality; after stratification for this variable, stepwise analyses were carried out. After stratifying for depth of invasion, the presence of involved nodes ceased to be of significance in predicting relapse. In successive steps, vascular invasion and substage were entered into the model. After controlling for these variables, histological tumour type became a significant covariable but all other variables considered remained non-significant.

The constants derived from the analysis for the significant variables were used to derive a series of hazard functions (Table 3). With this model, estimated relapse functions were computed and predicted relapse curves were drawn for all combinations of the covariables; from these curves, patients were classified as being at either high or low risk of relapse. This model was tested by applying it to

Table 4. Classifications of patients

Variable	Grouping	Relapsed
Classification model (with invasion)	High risk	11/18 (61%)
	Low risk	14/92 (15%)
Classification model (without invasion)	High risk	11/19 (58%)
	Low risk	14/91 (15%)
Cervical invasion	> half	18/39 (46%)
	< half	7/71 (10%)
Stage	Ib/IIa	20/50 (40%)
	Ia/Ib occult	5/60 (8%)
Symptoms	Present	17/43 (40%)
	Absent	8/67 (12%)
Node involvement	Present	9/20 (45%)
	Absent	16/90 (18%)
Vascular invasion	Present	11/28 (39%)
	Absent	14/82 (17%)
Histology	Adenosquamous/ adenocarcinoma	4/12 (33%)
	Squamous	21/98 (21%)

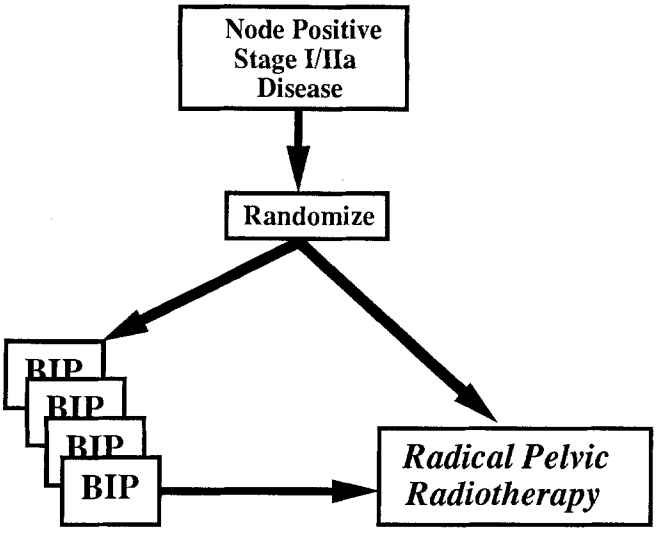

Fig. 1. Adjuvant study in node-positive patients

cases with a follow-up of >18 months. In all, 11 of 18 cases (61%) classified as high-risk relapsed, whereas only 14 of 92 classified as low-risk (15%) did so with 81% of cases being correctly classified overall. The classification of this group using the classification model and the individual covariables is shown in Table 4.

To determine whether a model for predicting relapse could be developed that would be applicable in patients treated with radical radiotherapy, a further Cox regression analysis was carried out, omitting all factors that could only be determined as the result of a laparotomy. From this analysis, a further classification function was derived based on substage, vascular invasion and histological type (Table 3). Applying this model to cases with >18 months' follow-up, 11/19 classified (58%) as high-risk relapsed by 18 months (Table 4).

Adjuvant chemotherapy in early-stage cervical carcinoma

The selection of patients who may benefit from further adjuvant treatment has traditionally rested on the results of pelvic lymphadenectomy at the time of radical surgery. Patients with metastatic spread to pelvic and para-aortic nodes are at high risk of recurrence and are often treated with postoperative external-beam pelvic radiotherapy, although the value of this approach in terms of improved survival has not been ascertained. Such patients may be regarded as having systemic disease and thus may benefit from adjuvant therapy with systemic chemotherapy.

Chemotherapy that is highly active in this disease is now available. In a series of multicentre studies, we have demonstrated that the combination of bleomycin, ifosfamide and cisplatin, one of the most active regimens reported in this disease, produces a response in around 70% of patients with recurrent or advanced, previously untreated disease [1]. Responses are achieved rapidly, within four cycles, with acceptable toxicity. Furthermore, giving chemotherapy prior to radical pelvic radiotherapy does not appear to enhance either acute or long-term radiotherapy toxicity [2]. We recently initiated a prospective randomized trial testing the role of adjuvant BIP in patients found to have involved nodes at radical hysterectomy; patients are randomized to receive either four cycles of BIP followed by conventional external-beam radiotherapy or radiotherapy alone (Fig. 1). To date, 15 patients have been entered on study. A complementary study in high-risk patients treated with radical radiotherapy is planned.

Discussion

A number of phase II studies have recently been reported in the literature, exploring the feasibility of giving adjuvant chemotherapy in patients who are found to have pelvic node involvement after radical surgery for early-stage cervical cancer [7, 14]. Although this is a logical progression from the development of highly active, cisplatin-containing systemic chemotherapeutic regimens in recurrent disease and early studies of neoadjuvant chemotherapy in advanced disease, enthusiasm for this approach must be tempered with the knowledge that not all patients found to have positive nodes relapse after conventional treatment. Furthermore, a major proportion of patients with early-stage disease are treated with radical radiotherapy alone. In these cases, accurate documentation of nodal disease would require surgical staging. The role of adjuvant chemotherapy in node-positive patients is now being tested in randomized trials, but it would clearly be a significant advance if a more precise method of predicting high-risk patients could be devised, particularly if it could be applied to patients for whom information regarding node in involvement is lacking.

Univariate analysis of the cases in this study confirmed the previously well-recognized association between stage, depth of invasion, lymph node involvement, tumour differentiation and lymphatic and blood vessel invasion and the risk of disease recurrence. It also revealed that symptomatic presentation was an adverse prognostic factor. This analysis did not confirm a previously reported association between relapse and histological type of tumour and patient age [8, 13]. Tumour volume is one of the most important prognostic factors in many malignancies, including cervical cancer [12]. This variable is difficult to assess in cervical cancer and requires detailed histopathological examination beyond the means of most clinical pathology departments. It was not possible retrospectively in this study to assess tumour volume reliably. However, it was possible to assess substage and the depth of cervical invasion from the case records, and these variables are likely to reflect tumour volume; it is therefore not surprising that these were identified as the two most important prognostic variables in the univariate analysis.

It was apparent from the initial analysis that a number of the variables were interrelated. To determine the independent prognostic importance of each variable, exclude masking of significant variables and determine which combination of covariables provided the optimal model for identifying high- and low-risk patients, it was necessary to carry out Cox regression analysis. Depth of invasion was so highly associated with risk of relapse that it did not conform to the requirement for proportionality implicit in the Cox model; it was therefore necessary to stratify for this variable in the subsequent analysis. Even after stratification, lymphatic and blood vessel invasion and substage remained highly significant. Histological tumour type became significant after controlling for the other variables. From the analysis and using the covariables, it was possible to construct a model that provided a more accurate classification of the study group than could have been achieved using any single variable. Additionally, further analysis demonstrated that it may be possible to identify a high-risk group of patients without the need for information as to node status and depth of cervical invasion.

Although this was a small study that required replication on a further data set, it clearly shows the possibility of providing a more accurate means of identifying high-risk patients who may benefit from further adjuvant therapy after surgery. This would avoid overtreatment of a significant number of patients who are at low risk of developing recurrence and also identify a more appropriate population for testing the role of adjuvant therapy. The latter has important implications for the design of randomized studies, since it may increase recruitment and thus improve the ability of such studies to discern small but significant improvements in the results of treatment.

References

1. Buxton E, Meanwell C, Hilton C, Mould J, Spooner D, Chetiyawardana A, Lateif T, Paterson M, Redman C, Luesley D, Blackledge G (1989) Combination bleomycin, ifosfamide and cisplatin chemotherapy in cervix cancer. J Natl Cancer Inst 81: 359–361
2. Buxton E, Meanwell C, Mould J, Latief T, Chetiyawardana A, Spooner D, Tobias J, Sokal M, Alcock C, Hilton C, Paterson M, Luesley D, Lawton F, Redman C, Blackledge G (1989) Phase II studies of bleomycin, ifosfamide and cisplatinum in cervix cancer. Acta Oncol 27: 545–549
3. Cox D (1972) Regression models and life tables. J R Stat Soc 34: 187–220
4. Di Saia P, Rich W (1975) Advanced and recurrent carcinoma of cervix. In: Gynecologic oncology. Churchill Livingstone, New York, pp 517–527
5. Dixon W, Brown M, Engelman L, Frane J, Hill M, Jennrich R, Toporek J (1985) BMDP statistical software manual, 5th edn. University of California Press, Berkeley
6. Friedlander M, Kaye S, Sullivan A, Green D, Houghton R, Solomon H, Russell P, Tattersall M (1983) Cervical carcinoma: a drug-responsive tumour – experience with combined cisplatin, vinblastine and bleomycin therapy. Gynecol Oncol 16: 275–281
7. Hakes T, Wertheim W, Daghestani A, Nori D, Clark D, Lewis J (1984) Adjuvant chemotherapy for poor risk stage Ib/IIa cervix carcinoma patients – a pilot study with cisplatin/bleomycin. Proc Am Soc Clin Oncol 3: 171
8. Ireland D, Cole S, Kelly P, Monaghan J (1987) Mucin production in cervical intraepithelial neoplasia and in stage 1b carcinoma of the cervix with pelvic lymph node metastases. Br J Obstet Gynaecol 94: 467–472
9. Kottmeir M, Kolstad P (1976) Annual report on the results of treatment in carcinoma of the uterus, vagina and ovary. FIGO report 16
10. Meanwell C, Kelly K, Wilson S, Roginski C, Woodman C, Griffiths R, Blackledge G (1988) Young age as a prognostic factor in cervical cancer: analysis of population based data from 10022 cases. Br Med J 296: 386–391
11. Peto R, Pike M, Armitage P, Breslow N, Cox D, Howard S, Mantel N, McPherson K, Peto J, Smith P (1977) Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. Br J Cancer 35: 1–39
12. Piver M, Chung W (1975) Prognostic significance of cervical lesion size and pelvic node metastases in cervical carcinoma. Obstet Gynecol 46: 507–510
13. Shepherd J (1985) Surgical management of early invasive cervical cancer. Clin Obstet Gynecol 12: 183–202
14. Shiromizu K, Matsuzawa M, Takahashi M, Ishihara O (1988) Is postoperative radiotherapy and maintenance chemotherapy necessary for carcinoma of the uterine cervix? Br J Obstet Gynaecol 95: 503–506
15. Stallworthy J, Wiernik G (1976) Management of cervical malignant disease – combined radiotherapy and surgical techniques. In: The cervix. WB Saunders, London, pp 474–493
16. Zander J, Baltzer J, Lohe K, Ober K, Kaufman C (1981) Carcinoma of the cervix: an attempt to individualize treatment. Results of a 20-year cooperative study. Am J Obstet Gynecol 139: 752–759