

**PREGNANCY-ASSOCIATED CERVICAL CANCER**

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**A dissertation submitted to the University of Cape Town  
in fulfilment of the requirements for the degree of  
Master of Medicine (Obstetrics & Gynaecology)**

**Part III**

I, JAMES NEVIN hereby declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

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**Signed** .....

J NEVIN

27 Nov 1991  
.....  
(DATE)

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CHAPTER 1
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INTRODUCTION

## A. MALIGNANCY ASSOCIATED WITH PREGNANCY

When cancer complicates pregnancy, both fetus and mother may be at increased risk<sup>1,2</sup>. Often the obstetric mandate to provide a healthy neonate is jeopardized by the oncological need to treat the tumour<sup>1,3-5</sup>.

Instead of an oncologist-patient duo, those involved include fetus, paediatrician, obstetrician and father of the child<sup>5</sup>. Does pregnancy negatively influence the survival, either through direct action or as a result of a delaying treatment in the interest of the neonate? Additional concern relates to the side-effects of treatment, which pertain not merely to the patient, but also to the baby<sup>3,5</sup>.

Recently several general statements, regarding malignancy associated with pregnancy, have been made<sup>5</sup>:

- (1) Malignancy is not affected by pregnancy per se, but may delay diagnosis and treatment.
- (2) Pregnancy is rarely affected by the cancer itself.
- (3) Irradiation and cytotoxic therapy during pregnancy carry a significant risk of teratogenesis and abortion.

Although other reports agree with these opinions there remains controversy regarding the effect of pregnancy on breast cancer<sup>1,3,6</sup>.

For the obstetrician, the problem of pregnancy-associated cancer is an unusual one<sup>3,5,7</sup>. A Finnish report found an incidence of 0.07%, excluding gestational trophoblastic disease and including cervical intraepithelial neoplasia<sup>7</sup>. In South Carolina (USA), amongst 37,101 pregnant women 144 malignancies (0.4%), including cervical intraepithelial neoplasia, were reported<sup>8</sup>. Apparently malignancy complicates less pregnancies than expected as demonstrated by a German group who found that pregnant patients had a lower incidence of cancer than the general female population (344 vs. 558.8)<sup>9</sup>.

For the oncologist however, pregnancy associated cancer is relatively more common. In the series from Carolina, Lutz et al found a 5% pregnancy rate amongst their gynaecological cancer patients<sup>8</sup>. This highlights the fact that pregnancy is a more prominent consideration to an oncologist than malignancy is to an obstetrician.

**B. INVASIVE CERVICAL CARCINOMA ASSOCIATED WITH PREGNANCY.**

Genital and breast cancer dominate published reports of malignancy complicated by pregnancy (Table I).

Table I. Pregnancy-associated tumours in order of frequency.

AUTHORS	SITE IN ORDER OF FREQUENCY %				
	1	2	3	4	5
Phelan et al (1968) (n = 52) <sup>6</sup>	Genital 51.92	Breast 21.15	Melanoma 5.77	Thyroid 5.77	Sarcoma 3.85
Niemenen & Remen (1970) (n = 85) <sup>7</sup>	Breast 28.24	Genital 23.53	Thyroid 10.59	Melanoma 5.88	
Lutz et al (1977) (n = 94) <sup>8</sup>	Genital 42.55	Breast 24.47	Sarcomas 7.45	Melanoma 5.32	GIT 3.19
Haas et al (1984) (n = 359) <sup>9</sup>	Genital 72.70	Breast 7.80	Lymphoma 5.29	Melanoma 3.34	GIT 2.51

More specifically, cervical cancer is the genital malignancy most commonly associated with pregnancy (Table II) and vulval, vaginal, endometrial and ovarian cancer are relatively rare (Table II).

TABLE II. Reported incidence of genital malignancy associated with pregnancy.

AUTHORS	PRIMARY SITE %				
	CERVIX	OVARY	CORPUS	VULV/VAG	OTHERS
Phelan et al (N=27) <sup>6</sup>	96.3	3.7	-	-	-
Niemenen & Remen (N=20) <sup>7</sup>	85	10	-	-	5
Lutz et al (N=40) <sup>8</sup>	75	10	-	15	-
Haas et al (N=261) <sup>9</sup>	88.5	7.7	1.6	1.6	2.7
Barber et al (N=62) <sup>10</sup>	75.8	16.3	3.3	4.8	-

Reported incidences of invasive cervical cancer are difficult to interpret<sup>2,3,11-14</sup>. Centres contributing to the literature are often referral centres and may receive patients from several obstetric units. Furthermore, reports may vary with regard to exact definitions e.g some include postpartum patients where the post-delivery interval can vary between 2 and 18 months. Lastly, cervical intraepithelial neoplasia i.e. preinvasive, is often reported simultaneously and figures then need adjustment for the incidence of invasive malignancy.

Probably the best clue to the incidence of pregnancy-associated cervical cancer is found in a recent review of 7 articles<sup>15</sup>. The authors reported an average of 1 pregnancy complicating every 34 cases of invasive cervical cancer (2.9%). This contrasts with their finding, from 11

reports, of 1 cervical cancer complicating every 2205 pregnancies (0.45 per 1000)<sup>15</sup>.

Cervical cancer may be amongst the most frequent tumours to be affected by pregnancy (Tables I,II), but its occurrence is still not sufficient to enable irrefutable conclusions. Enigma's in pregnancy-associated cervical malignancy include the possible influence of pregnancy on prognosis and timing of delivery<sup>2,4,10-13,15-29</sup>. In addition, and more specific to this tumour than other malignancies, are the problems of management during the second trimester and route of delivery<sup>2,11,13,15,17,18,20,26,30,31</sup>.

C. AIMS OF THIS STUDY.

Against the background of contradictions and uncertain conclusions available in the literature, a study was undertaken to describe the experience at Groote Schuur Hospital of pregnancy-associated cervical cancer. From this an attempt was made to clarify the above-mentioned dilemma's.

## CHAPTER 2

### MATERIALS AND METHODS

#### A. SOURCE OF DATA

The names of all patients in the study group were retrieved from the database of the Radiotherapy Department at Groote Schuur Hospital (GSH) in Cape Town.

Gynaecological oncology at this hospital is managed by a team of gynaecologists and radiotherapists, who review new cases of genital malignancy at a weekly Combined Assessment Clinic (CAC).

Patients are registered with the Radiotherapy Department and assigned folder numbers in numerical sequence. This register is computerised and forms the above mentioned database.

Once a patient is registered, relevant data such as patient characteristics, treatment and follow-up is recorded in a folder which is stored according to its number.

GSH is a hospital located in Cape Town with the status of a tertiary referral hospital. Most patients treated at GSH live on the Cape Peninsula. However, its associations extend eastwards along the southern Cape Province and include affiliations with hospitals in Port Elizabeth and East London. From these satellite units patients with pregnancy-associated cervical cancer are referred to GSH according to protocol. This study thus, was able to accumulate a group of patients originating from a large area, but whose management was centralized.

## B. DEFINITIONS

### 1. Carcinoma of the cervix associated with pregnancy

The exact definition of this association has not been uniform. Some studies include only patients actually pregnant at the time of diagnosis<sup>18,32,33</sup>. Most studies however include patients diagnosed within the postpartum period<sup>4,11,12,16,17,19,23,24,28,35-37,39</sup>. This inclusion is usually not motivated<sup>4,6-8,10,12-14,16,19,21-24,26-28,30,37,40</sup>. Other studies base the inclusion on the likelihood that cancer in postpartum patients must have been present at the time of delivery<sup>11,15,34,36,39-41</sup>. While it has been pointed out that most postpartum patients have symptoms of cancer going back to the time of the delivery, it has also been acknowledged that the definition is arbitrary<sup>11,17</sup>.

There is a variation in the postpartum interval and this may reach 18 months<sup>17</sup>. However, most reports refer to patients presenting within 6 to 12 months of delivery<sup>8,10,11,13-16,20,22,24,26,30,38,39</sup>.

Traditionally at Groote Schuur Hospital, the definition has been taken to include patients diagnosed as having carcinoma of the cervix within 12 months of pregnancy.

### 2. Invasive carcinoma of the cervix.

At GSH, only patients with carcinoma of the cervix greater than or equal to stage IB (FIGO) are registered with the Radiotherapy Department. Patients with stage IA or cervical intraepithelial neoplasia (CIN) are managed without referral to the CAC. As this study made use of

computerized data from the Department of Radiotherapy, it was decided not to include patients with CIN or stage IA disease.

#### C. STUDY DESIGN

Pregnancy-associated cervical cancer was studied by observation rather than experiment. The current study is primarily descriptive, but in order to analyze the influence of associated pregnancy on the survival of cervical cancer the non-concurrent cohort method was chosen.

The descriptive method was used to quantify the extent of this complication amongst GSH cervical cancer patients. The cohort method enables one to determine, on a comparative basis, the role of associated pregnancy as a risk factor in cervical cancer.

#### D. SELECTION OF PATIENTS

##### 1. Study Group

The study period was from 1970 as the radiotherapy database of GSH contains patient information from that year onwards. In order to achieve meaningful survival data, provision was made for a minimum follow-up of 5 years. Thus the study period was taken from 1970 to 1984 inclusive, allowing a 5 year follow-up until December 1989.

From the cervical cancer patients registered during the study period, the names and folder numbers were drawn of patients with associated pregnancy. These compiled the

study group. Henceforth these will be referred to as "pregnant" patients.

2. Control group

A control group was compiled of cervical cancer patients NOT associated with pregnancy i.e. non-pregnant patients. Selection of the control group was arbitrary- the patient registered immediately after a study patient was entered.

3. Exclusion criteria

Patient records were perused and the following exclusion criteria were applied:

- (1) Patients with stage IA carcinoma of the cervix, who had been erroneously registered.
- (2) Patients in the pregnant group in whom the pregnancy-diagnosis interval exceeded 12 months.
- (3) Patients from areas where adequate follow-up was not feasible.
- (4) Patients in whom cancer treatment had been initiated in other centres, prior to registration at GSH.

E. COMPOSITION OF DATA

Once study and control groups had been compiled, patient records were examined by two observers and the following aspects given attention:

### 1. Age

This was calculated as the number of calendar years completed at diagnosis.

### 2. Parity

Where study patients were pregnant at diagnosis, parity equalled the number of previous pregnancies producing a viable infant. For postpartum patients, the pregnancy associated with the carcinoma was included in the parity.

### 3. Stage

The criteria for staging of cervical cancer has been set by the Oncology Committee of the Federation International Gynaecologie et Obstetrie (FIGO)<sup>42-44</sup>.

### 4. Histology

Records listed histology number, tumour type and differentiation.

Using the histology number, an attempt was made to recover as many histology specimens as possible. Where original histological analysis was not performed in Cape Town, an attempt was made to obtain original histology specimens from other laboratories (i.e. East London and Port Elizabeth). The specimens thus retrieved were reviewed by a single pathologist (Professor A. Tiltman). Although aware of the diagnosis i.e. carcinoma of the cervix, he was unacquainted with all other patient details.

### 5. Time of diagnosis in relation to pregnancy

At diagnosis study patients were either:

- a) antenatal or
- b) postpartum.

Note: (Control patients were "non-pregnant").

The method of diagnosis is important in making this distinction as it was often necessary to make a clinical diagnosis in order to manage the patient appropriately. Consider the patient who has never had antenatal care and who presents in labour. If her attendant practitioner suspects cervical cancer, he may be influenced to perform a Caesarean section. This in fact happened in areas where frozen section was unavailable. Thus some patients have been labelled antenatal even though the diagnosis was only confirmed histologically postpartum.

a) Antenatal patients. With regard to antenatal patients, the gestational age at diagnosis was calculated. On occasions, this figure was difficult to assess accurately as, for most of the study period, ultrasonography was not available at Groote Schuur. It was necessary thus to use a combination of menstrual dates and clinical assessment to arrive at an estimation of gestational age.

b) Postpartum patients. The interval between delivery and assessment at CAC was recorded. It was assumed that the date of assessment at the CAC represented the onset of active treatment of the patient. In some cases, the exact date of delivery was not mentioned in patient records and thus the time interval was recorded only as a certain number of months. An estimation was made in weeks by assuming 30 days to each month.

#### 6. Delivery of study patients

Details concerning delivery were obtained from all study patients, whether postpartum or antenatal.

#### 7. Treatment

Records for each patient were reviewed to see if surgery, radiotherapy, a combination thereof or no treatment had been used. Details of treatment were recorded.

#### 8. Survival

For each patient, the interval between registration with the CAC and exit from the study was determined. Exit from the study was the date of last recorded entry into a patient's folder.

In order to construct survival curves, it was necessary to determine each patient's status at exit from the study. Thus patients could be:

- a) alive with no evidence of disease;
- b) alive with disease;
- c) dead from cervical cancer;
- d) dead from unrelated causes;
- e) lost to follow-up.

### F. ANALYSIS OF DATA

1. Study and control patients were compared for:
  - a) Age;
  - b) Parity;
  - c) Stage distribution
  - d) Histological characteristics;
  - e) Treatment;
  - f) Survival.

2. Study patients were analyzed for the effect on survival of:

- a) Stage distribution;
- b) Mode of delivery;
- c) Relationship to pregnancy;
- d) Treatment modality.

#### G. STATISTICAL CONSIDERATIONS

The Institute of Biostatistics at the Medical Research Council (MRC) was consulted about data analysis.

Study and control groups were compared for age, parity, stage distribution and histology, using the chi-square test.

Survival data was analysed by constructing survival curves and the logrank test was used to assess for significant differences.

Where survival was thought to be influenced by co-variables, Cox's Proportional Hazards Regression methods were used to achieve multivariate analysis.

CHAPTER 3
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RESULTS

A. PROPORTIONAL OCCURRENCE

In the period 1970 to 1984, 62 patients were treated at Groote Schuur Hospital for cervical cancer associated with pregnancy. In the same period, 1303 patients were treated for cervical cancer at this institution. Thus the proportion of cervical cancer patients with associated pregnancy was 4.76%. A negative trend was found during the study period (Table III).

TABLE III. Proportion of cervical cancer patients with associated pregnancy.

	1970-74	1975-79	1980-84	TOTAL
Ca.Cx. associated with pregnancy	25	20	17	62
Total Ca.Cx. population treated at GSH	349	388	566	1303
Proportion of pregnancy associated Ca.Cx.	7.16%	5.15%	3.60%	4.76%

Proportion 1970-74 vs 1975-79  $P < .4$  (ch.sq)  
 1975-79 vs 1980-84  $P < .2$  (ch.sq)  
 1970-74 vs 1980-84  $P < .006$  (ch.sq)

The proportion of pregnant patients with cervical cancer during these years was not calculated because GSH radiotherapy and obstetric services cater for different populations.

## B. AGE

The mean age of the patients in the study group was 32.5 years (range 19-43 years). Patients in the control group averaged 49.6 years (range 27-91 years) and were significantly older than study patients (Wilcoxon 2-sample test  $P < 0.001$ )

## C. PARITY

Mean parity was almost identical in study and control patients (4.97 and 4.98 respectively) with ranges which were also similar (2 - 12 and 0 - 15 respectively).

## D. STAGE DISTRIBUTION

Analysis of stage distribution revealed that there were significantly more pregnant patients with stage IB disease. Alternately more patients in the control group presented with stage IIIB carcinoma of the cervix (Table IV).

TABLE IV. Stage distribution.

STAGE	STUDY n=62	CONTROL n=62	SIGNIFICANCE P-value
IB	19	8	<.03
IIA	9	6	.58
IIB	17	11	.28
IIIA	--	1	--
IIIB	15	29	<.009
IV	2	7	--
TOTAL	62	62	

These results were rationalized further into early stage disease (ESD) i.e. stage IB and IIA, and late stage

disease (LSD) i.e. stage IIB to IV. A significant difference could again be demonstrated using this rationalization (Table V).

TABLE V. Rationalized stage distribution.

STAGE	STUDY n=62	CONTROL n=62	SIGNIFICANCE P-value
ESD	28	14	<.02
LSD	34	48	
TOTAL	62	62	

ESD = Early Stage Disease  
LSD = Late Stage Disease

#### E. HISTOLOGY

Slides were recovered for 30 study patients and 26 controls (Table VI). Analysis of this data revealed no significant differences.

TABLE VI. Distribution of histological types.

HISTOLOGY	STUDY n=30 (%)	CONTROL n=26 (%)
Squamous ca.	23 (76.7)	16 (61.5)
Adenoca.	1 (3.3)	4 (15.4)
Adenosquamous ca.	4 (13.3)	4 (15.4)
Glassy cell ca.	2 (6.7)	0 (0)
Undifferentiated ca.	0 (0)	2 (7.3)
Total recovered	30 (100)	26 (100)

#### F. TIME OF DIAGNOSIS IN RELATION TO PREGNANCY

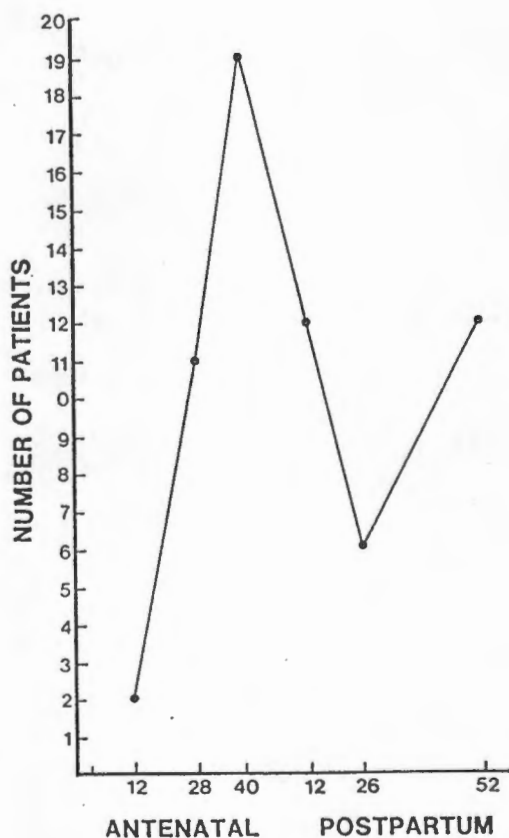
Thirty two patients (51.6%) in the study group were pregnant at presentation while the remaining 30 (48.4%) were postpartum when diagnosed as having pregnancy-

associated cervical cancer. Of the former, 3 patients (9.3%) were treated during the first trimester, 11 (34.4%) in the second and 18 (56.3%) in the third trimester.

Amongst the postpartum patients, 18 patients (60%) were treated in the 6 months following delivery and 12 (40%) thereafter.

Analysis of the time of diagnosis in relation to delivery, when defined as either an abortion (early or late) or third-trimester delivery, was carried out. This revealed that 31 patients (50%) were diagnosed either in the last 12 of pregnancy or in 12 weeks following delivery (Figure 1).

FIGURE 1. Time of diagnosis in relation to delivery.



G. EFFECT OF TIME OF DIAGNOSIS IN RELATION TO PREGNANCY, ON  
STAGE DISTRIBUTION

Gestational age and postpartum interval at diagnosis appeared to influence stage distribution insofar as more advanced disease was found later in pregnancy and as the postpartum interval increased (Table VII). However, the small number involved negated meaningful statistical analysis.

TABLE VII. Stage distribution vs relationship  
to pregnancy

	ESD n=28	LSD n=34
1st & 2nd	12	2
3rd	8	10
6 mths postpartum	8	10
6-12 mths postpartum	0	12
TOTAL	28	34

Patients diagnosed postpartum had significantly (ch.sq.  $P < 0.01$ ) more advanced disease than those in the antenatal group (Table VIII).

TABLE VIII. Stage distribution vs , time of  
diagnosis

	ESD n=28	LSD n=34
Pregnant	20	12
Postpartum	8	22
TOTAL	28	34

ch.sq  $P < 0.01$

#### H. METHOD OF DELIVERY

In the study group, 23 (37.1%) of 62 patients delivered vaginally. This included 3 patients who aborted and 1 patient who was given radiotherapy prior to evacuation of her uterus. This last patient has been excluded from further analysis of the influence of mode of delivery on survival.

Thirty nine patients (62.9%) were delivered abdominally. This included 27 patients who had Caesarean section, 9 who had a hysterotomy and 1 patient who had a radical hysterectomy with fetus-in-situ. Two patients in this abdominal group were excluded from further analysis of survival. One patient defaulted before initiation of therapy after abdominal delivery (Caesarean section). The second patient underwent a hysterotomy within 4 days of the first radium application. At laparotomy a uterine perforation was diagnosed which presumably had occurred during the radium application. This patient died immediately afterwards of fulminating sepsis.

Therefore 59 patients were suitable for analysis of stage distribution and survival.

Evaluation of stage distribution vs mode of delivery showed that patients who delivered vaginally had a trend towards late stage disease but did not show a significant difference (ch.sq.  $P=0.08$ ) (Table IX).

TABLE IX. Extent of disease vs mode of delivery

STAGE	VAGINAL (n = 22)	ABDOMINAL (n =37)
IB	3	15
IIA	3	5
IIB	9	7
III	6	9
IV	1	1
ESD	6	20
LSD	16	17

ch.sq. P=0.08

#### I. THERAPY

Analysis of the treatment amongst the 124 patients showed that primary radiotherapy was the commonest form of treatment. For both groups there was no significant difference in the frequency of its application. For the other modalities small numbers precluded meaningful statistical analysis (Tables X & XI).

TABLE X: Summary of therapy

	Pregnant n=62	Non-pregnant n=62
Primary XRT	42	53
Primary surgery	9	3*
Primary surgery + 2° XRT	8	3
Primary XRT and 2° surgery	2	0
No treatment	1	3

\*1 patient received chemotherapy post-operatively

TABLE XI: Therapy according to stage of disease

	ESD		LSD	
	PREGNANT	NON-PREGNANT	PREGNANT	NON-PREGNANT
1° surgery alone	9	3*	0	0
1° XRT alone	11	8	32	44
1° surgery+2° XRT	6	3	0	0
1° XRT+2° surgery	1	0	2	1
No treatment	1	0	0	3
Total	28	14	34	48

\* 1 patient received chemotherapy post-operatively

### 1. Surgery

Primary surgery i.e. radical hysterectomy and pelvic lymphadenectomy, was always an attempt at definitive, curative therapy. In 11 patients this was deemed to be adequate. Of these, 9 patients were pregnant, while 2 patient belonged in the control group (Table XI).

In six study patients, surgery was performed but adjuvant treatment was required. In 1 patient surgery was abandoned after frozen section of an enlarged common iliac node showed metastatic disease. In 4 patients adjuvant radiotherapy was thought necessary because of risk factors (incomplete resection in 3 patients and pelvic nodal disease in the surgical specimen of 1 patient). Thus 40% of patients in whom radical surgery was attempted required adjunctive therapy. The last patient had radiotherapy after surgery because histology of a simple hysterectomy specimen, performed for suspected stage IA disease, revealed frank invasion.

In the control group, 3 patients required postoperative radiotherapy. Two of these patients had nodal metastases at staging laparotomy. The third had

unsuspected invasive cervical cancer found after a simple hysterectomy.

Two pregnant patients received radiotherapy followed by surgery. One patient had stage IIIB disease. Radiotherapy was given and this was followed by a salvage hysterectomy because of excellent tumour regression. The second patient presented in labour and was diagnosed as having cervical cancer. Post-delivery she was staged as IIB and given irradiation in the form of three radium applications. However she defaulted from external radiotherapy and only reappeared after four months. Considerable regression of tumour warranted a radical hysterectomy and pelvic lymphadenectomy. No residual disease was found.

Summarizing these results it appears that in 15 pregnant patients and in 6 non-pregnant patients radical surgery was attempted. The results of this therapeutic approach were thought to be sufficient in 9 pregnant patients ( $9/15=60\%$ ) and in 2 non-pregnant patients ( $2/6=33\%$ ). A comparison is not possible because of the small numbers involved.

## 2. Radiotherapy

Conventional brachytherapy and/or teletherapy was employed where suitable. The former was by way of radium insertions and the latter using a cobalt source. Amongst the group associated with pregnancy there were 34 cases who had late stage disease. Of these, 32 patients (94.1%) received radiotherapy only, while the remaining 2 patients (5.9%) had radiotherapy followed by surgery. These 2

patients were described earlier. Forty-eight control patients had late stage disease. Forty four of these patients (91.7%) had primary radiotherapy. In 3 patients (6.3%) the disease was considered too advanced to warrant any form of treatment. The last patient was administered adjuvant radiotherapy after histology of a hysterectomy specimen confirmed a previously unsuspected cervical carcinoma.

Of 28 study patients with early stage disease 11 (39.3%) were treated with primary radiotherapy. Amongst controls, eight (57.1%) with early stage disease (n=14) were similarly treated. Statistical analysis revealed no significant difference (P=0.9) in the overall use of primary radiotherapy for early stage disease.

The use of primary radiotherapy in early stage disease was investigated further and it was found that before 1978, all these patients (study and control included; n=20) were treated with primary radiotherapy. Thereafter, with the exception of two patients (1 in each group) an attempt was always made to treat patients with early stage disease (n=22) with radical surgery.

## J. SURVIVAL

### 1. Overall survival

The overall survival for 124 patients analysed is depicted numerically in Table XII.

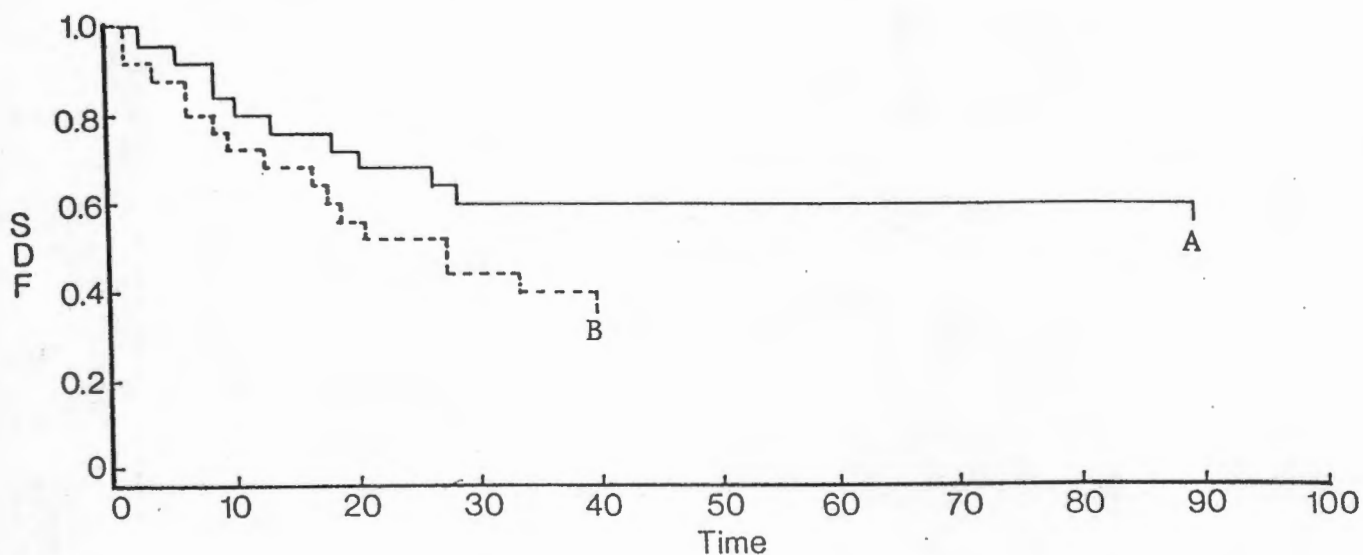
TABLE XII. Overall survival

Survival	Pregnant n=62(%)	Non- pregnant n=62(%)	P value ch.sq.
Survival at 5 yrs	23(37.1)	18(29)	.2
Lost to follow-up within 5 yrs.	15(24.2)	6(9.7)	.06
Died due to disease within 5 yrs	20(32.3)	36(58.1)	.007
- from 0-2 yrs	15(24.2)	29(46.8)	.01
- from 2-5 yrs	5(8.1)	7(11.3)	.7
Died due to treatment	2(3.2)	1(1.6)	NA
Died from unrelated causes	2(3.2)	1(1.6)	NA

NA: Not applicable because of small numbers

Table XII depicts survival in two ways: 5 years survival and death rate. The apparent contradiction between these two measurements of survival can be explained by the difference in loss to follow up which existed between study and control groups (P=0.06). A third method of assessing survival i.e. the survival curve, was employed (Figure 2). The logrank test comparing the two groups showed a significant difference with a better survival for the pregnant patients (P=0.03).

FIGURE 2. Overall survival: study vs control.



A - Pregnant

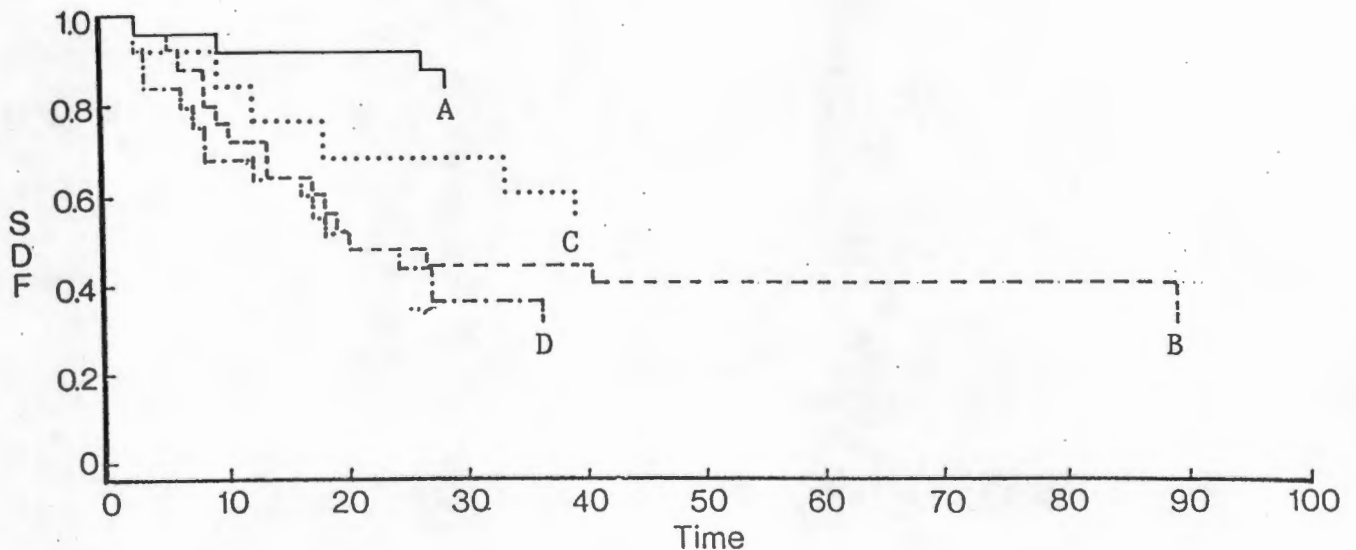
B - Non-pregnant

SDF - Survival distribution function

## 2. Survival vs stage

As there was a significant difference in stage distribution between the two groups, stage was investigated for its effect on survival and was shown to affect survival (Wilcoxon P-value = 0.004). In the light of this result survival was stratified for stage (ESD, LSD). Life tables were thus constructed to analyse the performance of pregnant and non-pregnant patients (Figure 3).

FIGURE 3. Survival stratified for stage: study vs control.



A - Pregnant ESD  
 B - Pregnant LSD  
 C - Non-pregnant ESD  
 D - Non pregnant LSD  
 SDF - Survival distribution function

The logrank test was applied to this data and showed no difference in survival between the pregnant and non-pregnant patients when stratified for stage. For patients with ESD, the logrank P-value was 0.07, while for patients with LSD, the logrank P-value equalled 0.61.

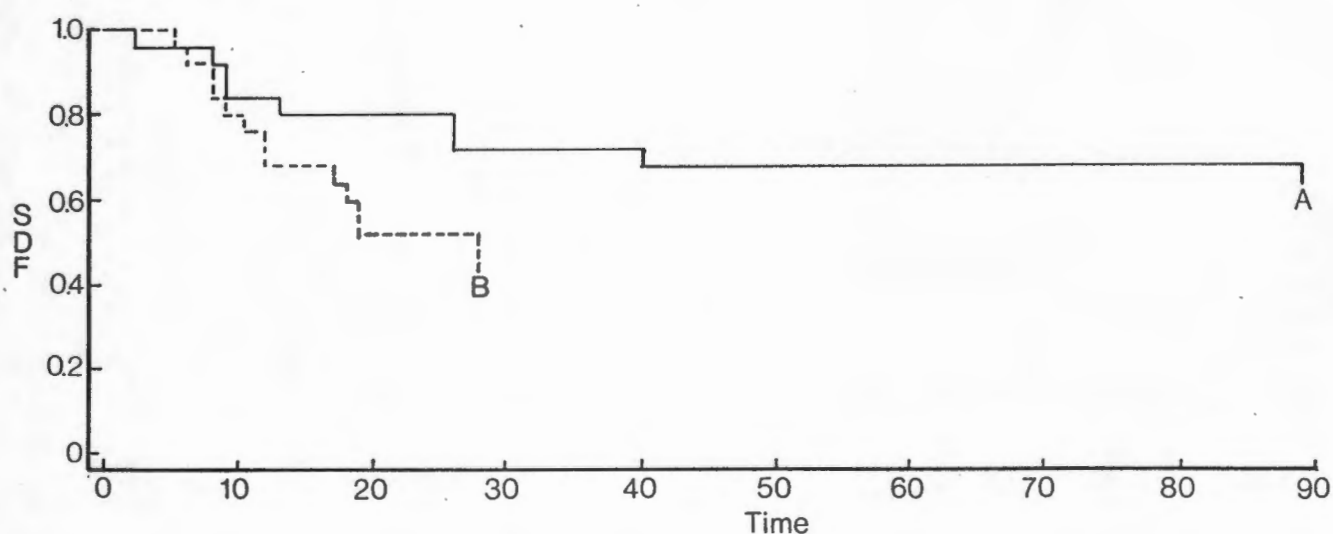
### 3. Survival vs therapy

Survival was assessed for any difference according to treatment modality. This comparison was irrelevant in LSD as radiotherapy was uniformly applied to this stage grouping. The survival of ESD for the study and control groups showed no difference (Willcoxon:P=.19) when stratified for therapy i.e. radiotherapy or surgery.

#### 4. Survival vs mode of delivery

Patients with associated pregnancy were analysed for the influence of mode of delivery on survival. Of patients suitable for this analysis 22 patients delivered vaginally and 37 delivered abdominally (See section H of this chapter). Overall survival for these two groups showed no significant difference (logrank;  $P=0,1$ ) and is represented in Figure 4.

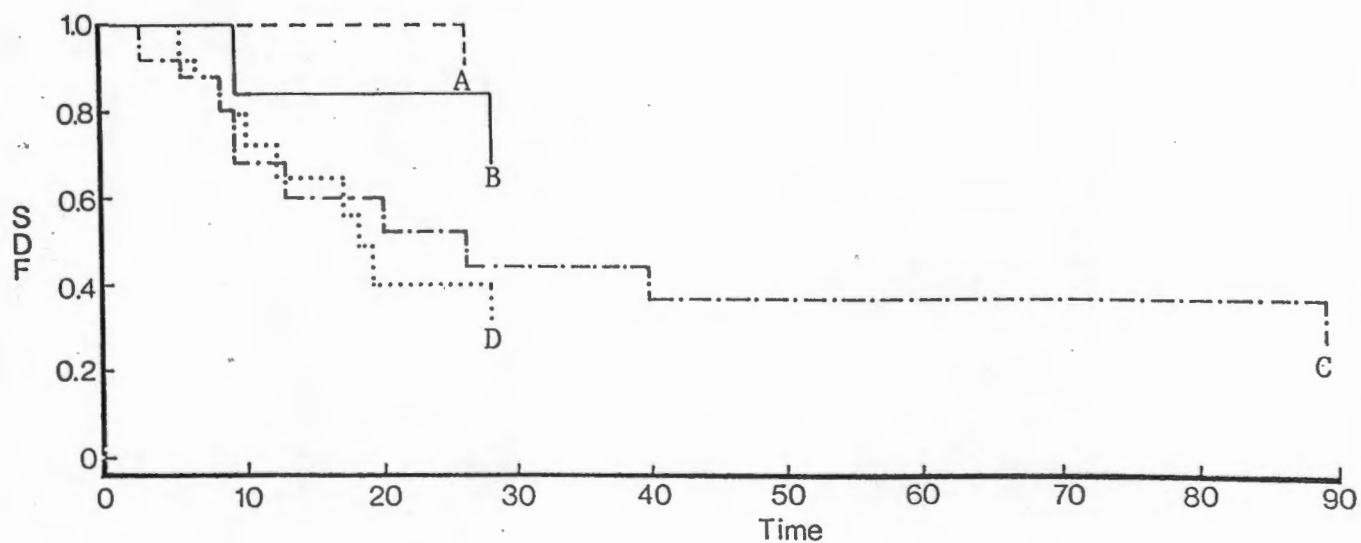
FIGURE 4. Survival according to mode of delivery



A - Abdominal delivery  
 B - Vaginal delivery  
 SDF - Survival distribution function

After stratifying for stage the method of delivery was again found to have no significant effect (Wilcoxon;  $P = 0,46$ ) on survival (Fig. 5).

**FIGURE 5. Survival according to mode of delivery stratified for stage**

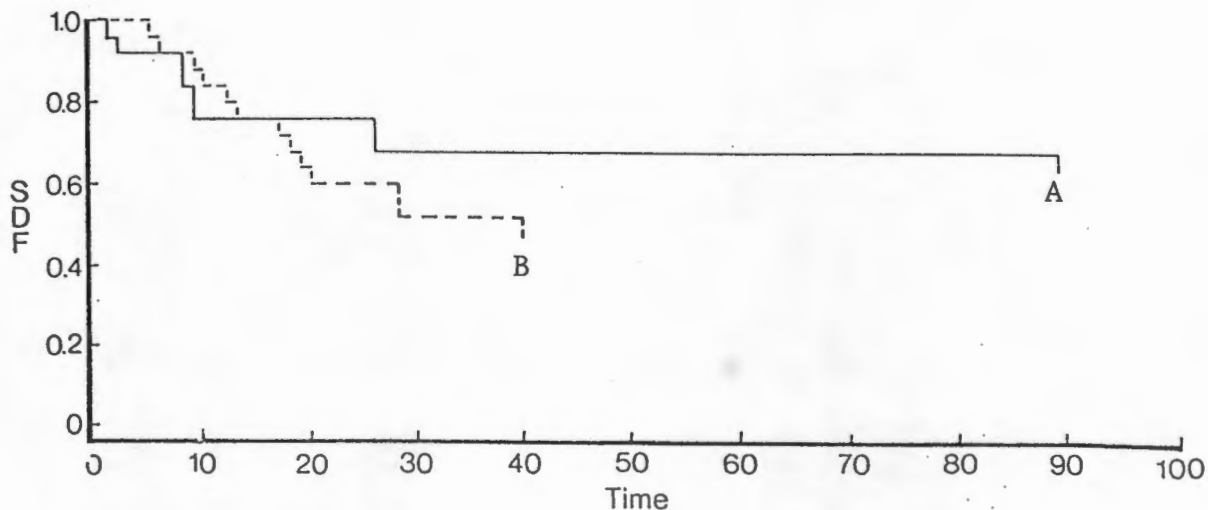


A - ESD + abdominal delivery  
 B - ESD + vaginal delivery  
 C - LSD + abdominal delivery  
 D - LSD + vaginal delivery  
 SDF - Survival distribution function

##### 5. Survival vs relationship to pregnancy

The survival for patients diagnosed antenatally and postnatally was evaluated and demonstrated no significant difference (logrank;  $P=0,4$ ) for these two groups of patients (Fig. 6).

FIGURE 6. Survival: antenatal vs postnatal.



A - Antenatal  
 B - Postnatal  
 SDF - Survival distribution function

Because of the small numbers involved it was not feasible to stratify for stage.

#### 6. Multivariate analysis of survival

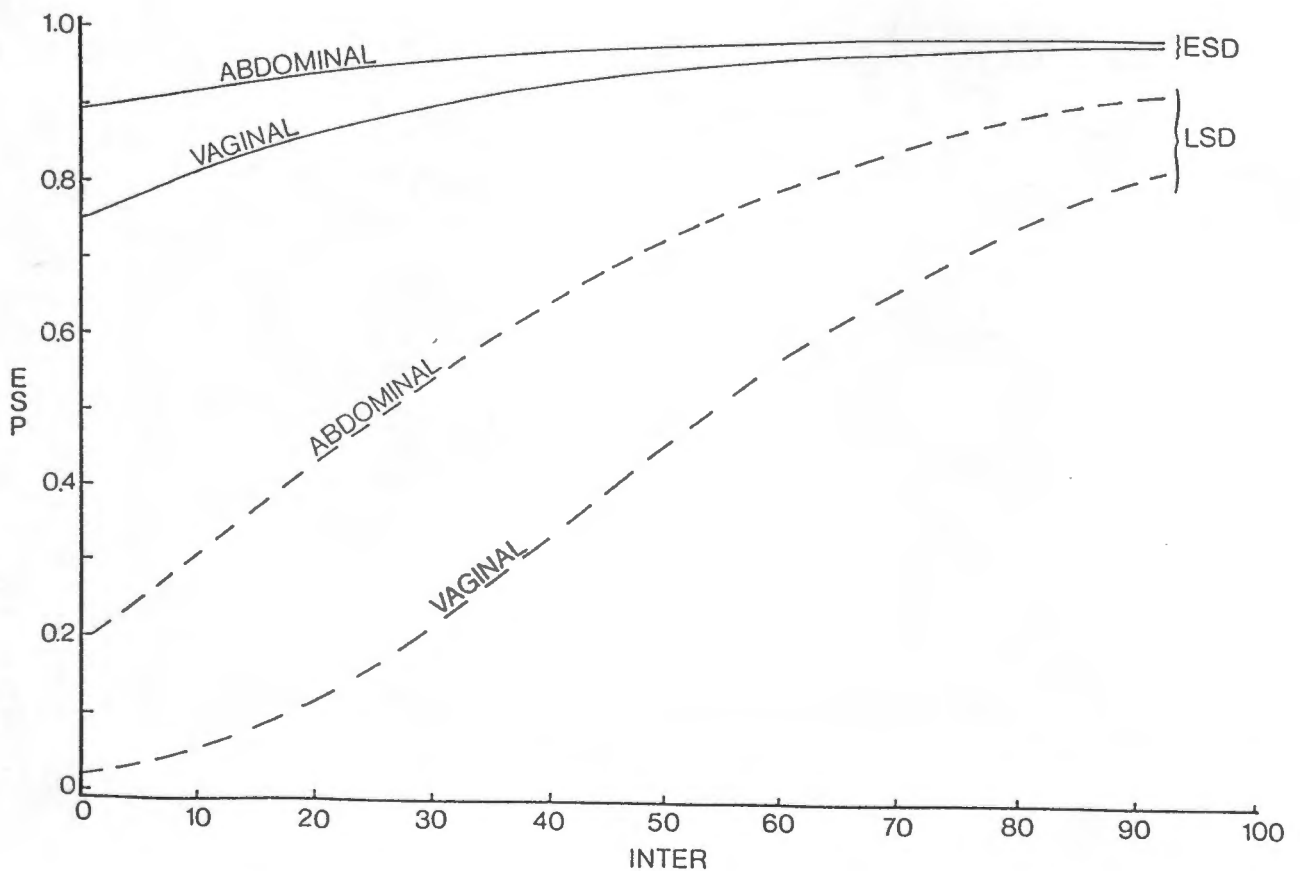
A forward step-wise sequence analysis of chi-squares for Wilcoxon showed that stage, mode of delivery and time of diagnosis in relation to pregnancy had the greatest influence on survival. A Proportional Hazards General Linear Model was then used to determine the direction of this influence and the following result were found:

- (1) Stage had a significant influence on survival ( $P < 0.0001$ ).
- (2) The interval between conception and diagnosis significantly ( $P < 0.03$ ) affected survival; in other words the further (in time) from conception a patient was diagnosed, the better the survival.

(3) The mode of delivery influenced survival to a certain degree ( $P=0.08$ ) i.e. in this study the prognosis of patients who delivered vaginally seemed to be worse than those who were delivered abdominally.

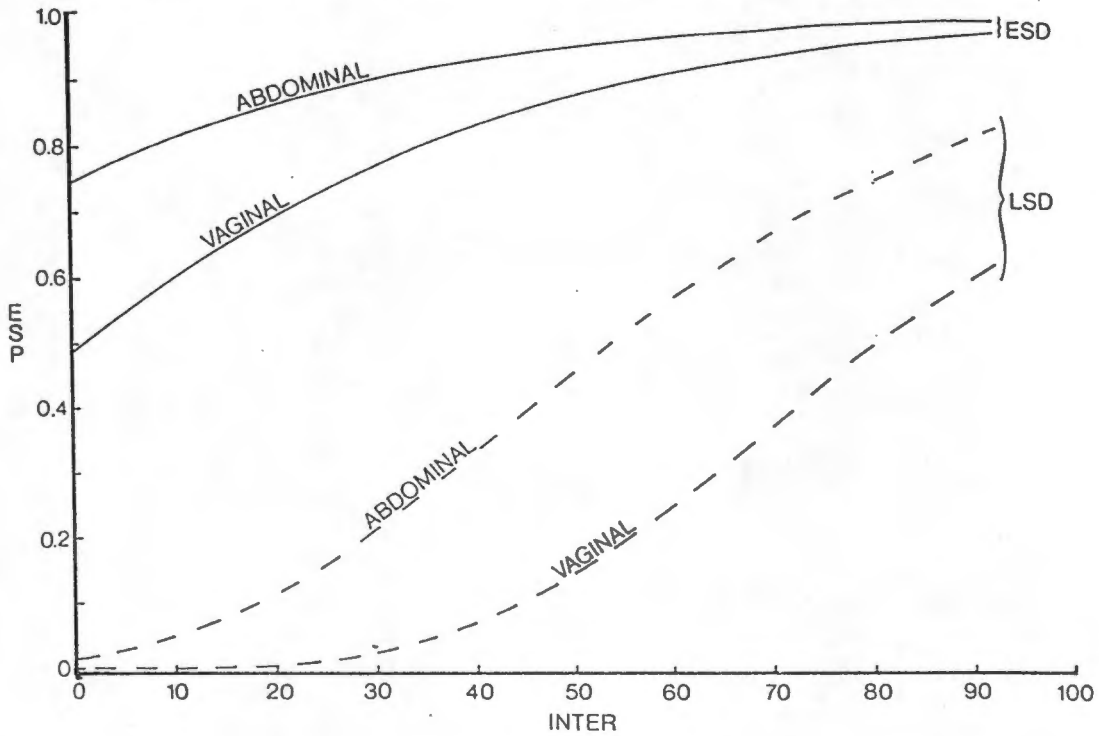
Based on the results of the multivariate analysis, 1, 3 and 5-year survival probability curves were constructed (Figure 7a,b,c).

FIGURE 7a. Survival probabilities at 1 year.



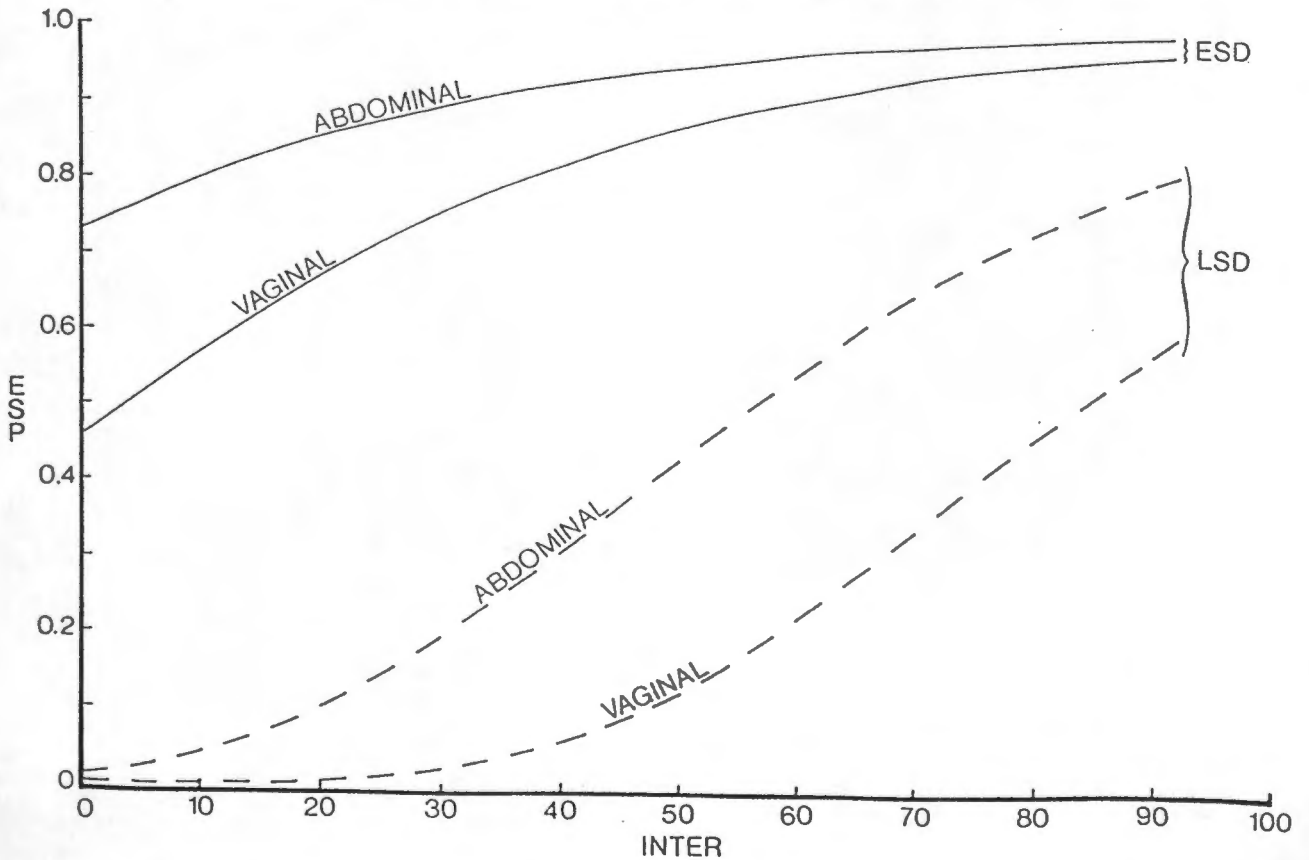
ESP - Estimated survival potential  
 Inter - Interval (weeks) between conception and treatment

FIGURE 7b. Survival probabilities at 3 years.



ESP - Estimated survival potential  
 Inter - Interval (weeks) between conception and treatment

FIGURE 7c. Survival probabilities at 5 years



ESP - Estimated survival potential  
 Inter - Interval (weeks) between conception and treatment

These curves confirm that the probability of survival increases in early stage disease, with progressive interval between conception and diagnosis, and in patients delivered abdominally. This probability also plateaus after 36 months.

CHAPTER 4
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DISCUSSION

This study on pregnancy-associated cervical carcinoma was undertaken to determine the extent of this problem at Groote Schuur Hospital (GSH) and an attempt was made to clarify the uncertainties regarding management and survival. In order to do this a number of parameters required investigation.

A. STUDY SIZE AND PROPORTIONAL OCCURRENCE.

This study compiled a report of 62 patients with cervical carcinoma, in whom pregnancy was associated. This represents the GSH experience between 1970 and 1984.

In a review on this subject, Shingleton and Orr listed 24 reports in which patient numbers range from 12 to 327 (median 41; mean 61)<sup>2</sup>. Thus the current study, in terms of patient numbers, is comparable to existing studies.

In the current study the proportional occurrence of pregnancy associated cervical carcinoma was 4,76%. Comparing this figure with existing literature requires caution as cervical dysplasia is frequently reported with invasive carcinoma and the postpartum period allowed also varies<sup>8-21,23,24,26,27,32,34-36,38-41</sup>. These factors will have an incremental influence on proportional occurrence. Only seven studies refer exclusively to invasive cervical carcinoma and a postpartum interval of 12 months<sup>11,13,16,22,24,30,39</sup>. In five of these studies the average number of patients with pregnancy associated

invasive carcinoma was 170 (range 30 to 327) and the average occurrence 3.18% (range 1,9 to 3,9%). The two remaining studies did not allow these calculations<sup>11,16</sup>. As the number of patients in the current study is well within the range of these comparable studies it is justified to conclude that the proportional occurrence of pregnancy associated cervical carcinoma at GSH is higher than elsewhere.

#### B. AGE

The average age of the patients with pregnancy associated cervical carcinoma in the current study was 32.48 (range 19 - 43). This is similar to previously reported studies in which mean age ranged from 31 to 36.5 years<sup>8,11-14,17,18,22,24,26,30,34,35,37,38</sup>.

In previous reports the difference in mean age between pregnant and non-pregnant patients varied between 15 and 18 years<sup>11,24,30,34,35</sup>. The pregnant patients in the current study were 17,15 years younger than non-pregnant patients, which confirms a similarity to those elsewhere in the world in respect of age.

Although the prognostic influence of age on the survival of cervical carcinoma is controversial<sup>45,46</sup>, at GSH it has been shown not to influence outcome<sup>47</sup>. Thus despite a mean age difference of 17.15 years between study and control groups, an analysis of the influence of pregnancy, as a single prognosticator, was justified.

#### C. PARITY

The parity of the pregnant patients in this study averaged 4,97 and was comparable to that of the non-pregnant

patients (average 4,98). Thus an association of multiparity and cervical carcinoma was demonstrated. In a review by Hacker et al, the average parity of pregnant cervical carcinoma patients was 4.5<sup>15</sup>. This emphasizes that the parity of the pregnant patients in the present study was similar to that reported elsewhere.

#### D. STAGE DISTRIBUTION

The entire subject of pregnancy associated cervical carcinoma is handicapped by small numbers which hinder statistical analysis<sup>2,12,15-21</sup>. This becomes evident if stage distribution in the current study is analyzed (Table IV). Therefore 28 patients were categorized as having early stage disease (ESD) including stages IB and IIA, and 34 patients as late stage disease (LSD) which comprised stages IIB, III and IV. This sub-classification of disease progression has been utilized elsewhere to make analysis more meaningful<sup>48,49</sup>. Such a sub-classification has practical implications in that ESD patients are candidates for radical surgery whereas LSD patients are traditionally treated with radiotherapy<sup>10,24,28,36,50</sup>. This approach to treatment is also applied at GSH.

Between 1970 and 1984 nearly half (45%) of the patients with pregnancy associated cervical carcinoma at GSH had ESD. Comparing this figure with that in other studies proves to be difficult for a number of reasons.

- (1) Only 7 studies define the staging classification utilized<sup>8,12,13,18,26,27,41</sup>.

- (2) Three of these referred to the League of Nations' staging<sup>13,27,41</sup>, while the remainder used the FIGO staging<sup>8,12,18,26</sup>.
- (3) FIGO staging criteria were compiled in 1950, modified in 1961,1970, 1976 and most recently in 1988<sup>42-44,51,52</sup>. These modifications are particularly relevant with regard to the distinction between microinvasive and frankly invasive disease.
- (4) Only 8 studies on this subject allow distinction between stages IA and IB<sup>7,8,18,19,28,33,36,37</sup>. The current study specifically excluded patients with IA disease.
- (5) Lastly, in only 6 studies were patients with stage II disease divided into "A" and "B"<sup>7,8,18,19,33,36</sup>. This meant that the ESD/LSD system could not be universally applied for reasons of comparison. Although the staging system in 4 of these reports was not specifically mentioned it can reasonably be assumed that the FIGO classification was operative.

In order to overcome these variations in reporting and to achieve a comparison regarding stage distribution in the GSH study, the 6 studies mentioned under (5) were reviewed<sup>7,8,18,19,33,36</sup> (Table XIII). In these 6 reports microinvasive disease was distinguished from IB disease, although admittedly, definitions of microinvasion varied.

TABLE XIII: Comparative stage distribution in carcinoma of the cervix associated with pregnancy.

	ESD	LSD	%ESD
Niemenin <sup>7</sup>	11	2	84.6
Lutz <sup>8</sup>	10	4	71,4
O'Leary <sup>18</sup>	9	1	90
Sall <sup>36</sup>	29	5	85,3
Thompson <sup>19</sup>	18	3	85,7
Dudan <sup>33</sup>	15	2	88,2
TOTAL	92	17	84,4
GSH	28	34	45,2

ESD: Early Stage Disease

LSD: Late Stage Disease

Table XIII suggests, that at GSH, ESD was considerably less common than elsewhere. Further analysis of the 6 reports however showed that 3 of these reports included no postpartum patients<sup>7,18,33</sup>; the fourth included patients within two months of delivery<sup>36</sup>, the fifth within three months of delivery<sup>19</sup> and the last report included a postpartum period of 6 months<sup>8</sup>. These observations are to a certain degree relevant as postpartum interval has been reported to influence stage distribution<sup>15</sup>. Considering only patients in the current study who were pregnant or within three months of delivery, 60% had ESD (27/45). This ESD rate is still lower than reported elsewhere (Table XIII).

In the review by Hacker et al, the accumulated frequency of pregnant patients with stage IB disease, which included varied postpartum interval, was 42%

(637/1517)<sup>15</sup>, whilst amongst the GSH patients the equivalent figure was only 30,6% (19/62).

These comparisons point to the occurrence amongst GSH patients, of more advanced disease than elsewhere.

In the current study the occurrence of ESD in pregnant (45,1% ESD) and non-pregnant patients (22,6% ESD) was significantly different (ch.sq.  $P < 0.02$ ). This difference may result from the greater exposure of pregnant patients to health care e.g. antenatal visits, vaginal examination and cervical cytology<sup>14,34,38,40,53</sup>. Additionally, more advanced disease might prevent conception<sup>39</sup>. Lastly, this difference may merely be a manifestation of the age difference between study and control groups. Jennings in his recent analysis of age related cervical carcinoma at GSH found almost identical difference in stage distribution between a younger (mean age 29.9 years) and an older group (mean age 53.4 years)<sup>47</sup> (Table XIV).

TABLE XIV. Stage distribution GSH pregnant vs. GSH young patients

	ESD(%)	LSD(%)
GSH pregnant	45.2	54.8
GSH young <sup>47</sup>	48.1	51.9

The increased proportion of ESD in the pregnant group signals a positive influence on the survival of these patients. Unfortunately, the ESD/LSD system cannot be used to compare the occurrence of ESD in the current study with that reported elsewhere. Control patients in other reports are not described in sufficient detail-not even the

reports in Table XIII help in this comparison. Hacker et al studied the occurrence of stage IB disease in pregnant patients and compared this to the occurrence of IB disease reported by FIGO<sup>15,43</sup>. Table XV illustrates these figures alongside those from the GSH study and it seems as though our patients, whether pregnant or not, presented with more advanced disease than elsewhere. However, the difference between our pregnant and non-pregnant patients (30,6% vs. 12.9%) seems to be comparable to elsewhere (42% vs. 26,8%) (Table XV).

TABLE XV. Occurrence of stage IB disease in pregnant and non-pregnant patients.

	Occurrence of Stage IB Disease	
	Pregnant	Non-pregnant
GSH	30,6%	12.9%
Hacker et al <sup>15</sup> .	42%	26.8%

In summary, GSH patients with cervical carcinoma, whether or not associated with pregnancy, present with later disease. This may be a reflection of a "Third World" situation

#### E. HISTOLOGY

Tumour type is thought to be important as a prognosticator for cervical carcinoma<sup>54</sup>. Adenocarcinoma and adeno-squamous carcinoma have been reported to carry a greater risk<sup>54</sup>. The low yield of specimens in the current study negated any meaningful statistical analysis.

The most common tumour type occurring in pregnancy-associated cervical carcinoma is squamous carcinoma<sup>15</sup>.

Glassy cell carcinoma of the cervix has been reported to occur more frequently in association with pregnancy<sup>53,55</sup>. This tumour type is the least differentiated form of adeno-squamous carcinoma of the cervix and carries a poor prognosis.

F. TIME OF DIAGNOSIS IN RELATION TO PREGNANCY.

Various reports have demonstrated the relevance of the time of diagnosis in relation to pregnancy. In most studies it appears that patients who are diagnosed antenatally have a better survival than their postpartum counterparts<sup>13,15-17,22,30,39,40,56</sup>. Moreover, the earlier during pregnancy that a diagnosis is made, the better the prognosis<sup>8,13,15,16,22,27,34,38,41</sup>. Contradictory reports to the latter statement do however exist<sup>17,18</sup>.

In the current study as many patients were diagnosed antenatally (32/62; 51.6%) as postpartum (30/62; 48.4%) whereas in comparable studies (i.e. where a postpartum interval of 12 months was taken into consideration) it was shown that more patients were diagnosed postpartum<sup>10,11,13,22,24,30,39</sup>. In other series, no more than 50% of the patients were diagnosed during the antenatal period (Table XVI).

TABLE XVI. Distribution of patients in relation to time of diagnosis.

	Time of diagnosis	
	Antenatal(%)	Postnatal(%)
Barber et al <sup>10</sup>	10/32(31.3)	22/32 (68.8)
Waldrop et al <sup>11</sup>	50/182 (27.5)	132/182 (72.5)
Sablinska et al <sup>22</sup>	63/327 (19,3%)	264/327 (80.7)
Gustafsson et al <sup>13</sup>	82/239 (34,3%)	157/239 (65.7)
Mikuta <sup>24</sup>	14/30 (46,7%)	16/30 (53.3)
van Praagh et al <sup>30</sup>	41/84 (48,8%)	43/84 (51.2)
Bosch et al <sup>39</sup>	26/66 (39.4)	40/66 (60.6)
GSH	32/62 (51,6%)	30/62 (48.4)

Not many factors have been identified which contribute to a more frequent postpartum diagnosis. There is however some concern about delayed diagnosis which results from the reluctance of practitioners to adequately examine the cervix of pregnant patients with suspicious symptoms such as vaginal bleeding or discharge 10,13,22,30,38. Routine vaginal examination and cervical cytology, as part of antenatal care, will reduce the occurrence of postpartum diagnosis<sup>11,16,18,20,22,39,57,</sup>

It is surprising that in the current study, time of diagnosis was equally distributed between antenatal and postpartum patients. In a so-called "Third World" environment, with its supposed sub-optimal antenatal care and poor patient compliance, one would expect a greater proportion of patients diagnosed postnatally. An easy explanation for this finding could not be found.

G. THE EFFECT OF THE TIME OF DIAGNOSIS, IN RELATION TO PREGNANCY, ON STAGE DISTRIBUTION.

Survival in patients with pregnancy-associated cervical carcinoma may be affected by the time of diagnosis as a result of tumour stage<sup>8,14-16,27,34,36,38,39</sup>. In previous studies more advanced disease has been found in later pregnancy and in the postpartum period<sup>2,11,13,14,22,30,38,39,58</sup>. In the current study 62.5% of the antenatal patients presented with ESD, while only 39.2% (ch.sq.  $P < 0.01$ ) of the postnatal patients were found to present with ESD.

Comparing the findings of this study with those of Sablinska et al<sup>22</sup>, it appeared that, at GSH, fewer antenatal and postnatal patients presented with IB disease, but that the differences between these groups of patients was similar in both studies (39.4 vs 33.6%)(Table XVII).

TABLE XVII. Stage IB disease in relation to time of diagnosis

	Stage IB disease	
	Antenatal(%) Frequency	Postnatal(%) Frequency
Sablinska et al <sup>22</sup>	43/63(68.3)	71/264(28.9)
GSH	15/32(46.9)	4/30 (13.3)

Several factors, alone or in combination, have been suggested to explain the propensity for more advanced disease if a diagnosis is made later in pregnancy or postpartum. Firstly, the already mentioned reluctance to examine pregnant patients with relevant symptoms might

explain this phenomenon<sup>10,13,22,30,38</sup>. Secondly, postpartum bleeding due to tumour may be misinterpreted as physiological<sup>39</sup>. Thirdly, postpartum disease might have been present for longer and thus be more advanced<sup>30,38</sup>. Fourthly, advanced carcinoma may prevent conception, thus reducing the likelihood of advanced carcinoma in early pregnancy<sup>39</sup>. Fifthly, laxity of pelvic ligaments due to pregnancy may induce understaging of the tumour<sup>28,34,37,65</sup>. Finally, advanced disease in the postpartum period may be a reflection of poor patient compliance<sup>22</sup>.

#### H. METHOD OF DELIVERY

The relevance of method of delivery has been discussed in previous studies because of its possible impact on long-term prognosis<sup>2,4,11,13,15-18,20,23,26,30,34,38,59-61</sup>. Moreover, fears have been expressed at the possibility of dystocia, sepsis, haemorrhage and dissemination of tumour cells caused by dilatation of an untreated malignant cervix<sup>4,10,12,15,16,23,34,38,39,59</sup>. Concern has not been voiced, particularly regarding the first and second trimesters, if radiotherapy is given prior to delivery<sup>3-5,11-13,15,16,30,37-39,41</sup>.

A 37.3% vaginal delivery rate in this series is much lower than reported elsewhere. Shingleton and Orr in a review list 12 reports and found that 77.6% (436/562) of the patients had delivered vaginally (range:44.4 to 93.3%)<sup>2</sup>. However, accurate comparison is problematic, as the figures do not include all stages of disease or

deliveries earlier than the 3rd trimester, and the postpartum interval in their review was not uniform.

Three previous reports were found, which referred to a postpartum interval of 12 months, and included all stages and gestational ages (Table XVIII).

TABLE XVIII. Proportion of patients delivered vaginally

	Vaginal deliveries	
	Rate	%
Barber et al <sup>10</sup>	28/32	87.5
Mikuta <sup>24</sup>	16/28	57.1
Bosch et al <sup>39</sup>	34/66	51.5
GSH	22/59	37.3

An explanation for the relatively low vaginal delivery rate at GSH might be that the majority of the patients in the current study presented with late, and therefore obvious, disease. Obvious disease would have favoured an abdominal delivery. Another explanation can be sought in the fact that in the current study, with the exception of one patient, all patients who delivered vaginally, were not pretreated with radiotherapy, while in previous studies a larger, but unknown number of patients, who delivered vaginally were pretreated and had a deliberate vaginal delivery.

#### I. STAGE DISTRIBUTION VS METHOD OF DELIVERY.

In the current study only 27.3% (6/22) of patients who delivered vaginally had ESD. On the other hand, the proportion of ESD amongst patients delivered abdominally

was 54.1% (20/37). This tendency has been found in one previous study<sup>60</sup> and obviously has an impact on survival for these 2 groups.

Other studies stratify for stage according to method of delivery, but provide insufficient detail concerning each stage to allow a meaningful comparison<sup>2,11,14,20,26,39</sup>.

Further analysis of the 22 patients who delivered vaginally, revealed, that with the exception of one patient, diagnosis was always postpartum (95.5%). Conversely, only 9 patients out of 37 (24.3%) who delivered abdominally, were diagnosed in the postpartum period. It has already been mentioned that the ESD rate in the "vaginal" group was only 27.3%. It is only appropriate to analyze the ESD rate in the postpartum "abdominal group" and amongst these 9 patients the ESD rate was similarly poor (22.2%; 2/9). Therefore it is justifiable to speculate that it is more likely to be the postpartum diagnosis which influences stage distribution, than the method of delivery.

#### J. THERAPY.

The treatment of carcinoma of the cervix in a pregnant patient has been discussed at length in the literature. It would seem that such a treatment should be individualized rather than part of a rigid protocol<sup>18,38</sup>.

Surgery and radiotherapy were used at Groote Schuur Hospital during the study period.

Radiotherapy was nearly always (94.1%; 32/34) used in "pregnant" patients who presented with LSD, whilst surgery

was reserved for palliation or salvage hysterectomy (5.9%; 2/34). This approach did not differ from that in the non-pregnant group with LSD, where radiotherapy was used in 91.7% of the patients (44/48) and in 4 patients (8.3%) palliative surgery was performed.

Amongst "pregnant" ESD patients, radiotherapy alone was used in 39.3% of the patients (11/28) and surgery alone in 32.1% (9/28). Surgery and radiotherapy in combination were used in 25% of the patients (7/28), while the remaining patient with ESD defaulted and did not undergo any form of treatment. In comparison, 14.3% (2/14) of the patients in the non-pregnant group with ESD had surgery alone, 57.2% (8/14) received radiotherapy and 28.6% (4/14) had combination treatment.

These results demonstrate that patients with cervical carcinoma, whether associated with or not associated with pregnancy, were treated similarly and could therefore be compared for survival.

Previous reports shared a similar experience and advocated a stage-related approach to cervical carcinoma, irrespective of whether or not associated pregnancy was present<sup>8,11,16,34,38,40</sup>.

Many authors note that tissue planes during surgery in a pregnant patient, are more pronounced because of oedema<sup>10,12,18,27,34,36,39,40,62,64</sup>. Nevertheless, there are maternal complications specifically related to the treatment of pregnancy-associated cervical carcinoma, such as increased intraoperative bleeding, prolonged operating time and an increased risk for radiotherapy/surgery induced fistulae<sup>2,15,16,18-20,33</sup>.

There are also fetal risk factors, such as teratogenesis after radiotherapy<sup>4,10,38</sup> and the sequelae of prematurity which is surgically induced<sup>12</sup>. Although controversial, there may be a case for delaying treatment in an attempt to achieve viability of the fetus<sup>3-5,8,10,12,14-17,19,25,26,34-36,39-41,57</sup>. It is generally accepted that immediate treatment should be instituted in the first half of pregnancy<sup>4,17</sup>. Thereafter a maximum delay of four to six weeks has been suggested<sup>2,15</sup>. However, in exceptional circumstances this delay can be extended<sup>17,25,26</sup>.

In the first trimester radiotherapy usually results in a timeous abortion<sup>3,4,12,15,17,34,40,41</sup>. This effect is less predictable in the second trimester and the resultant delay has led to reports of the delivery of viable, but badly damaged fetuses<sup>3,12,17,27,31,34,40</sup>. A hysterotomy in this trimester can obviate this problem<sup>8,11,12,14,15,26,31,34,39,40</sup>.

The route of delivery as part of the treatment in the third trimester, is of particular relevance. Although the so-called "vaginal route" is associated with more advanced disease, in this study it has been attributed to postpartum diagnosis rather than the dissemination of tumour cells during cervical dilation. Nevertheless enough theoretical objections exist to justify avoiding a vaginal delivery if possible<sup>4,6,8,10,14-16,18,23,34,38-41</sup>.

Primary radiotherapy was used very frequently (45.2%) for treating ESD in the GSH patients. Analysis shows that radiotherapy was uniformly applied to both ESD and LSD before 1978. After 1978 all except one patient in each of

the pregnant and non-pregnant groups, were treated for ESD with primary surgery. This distinct shift from radiotherapy to surgery can be attributed to the appointment in 1978 of a suitably competent gynaecological oncologist.

#### K. SURVIVAL

The ultimate aim of this study was to investigate the effect of associated pregnancy on the survival of patients with cervical carcinoma. Although there is some controversy, most authors found little influence of the pregnancy on survival and outcome<sup>11-14,16-18,21,26,27,30,34-36,39-41</sup>.

In order to draw conclusions of this nature, previous authors have used for comparison, data drawn from either their cervical cancer population in toto, or their entire non-pregnant cervical cancer population or a population of non-pregnant cervical cancer patients of a similar age<sup>13,14,16,17,19,21,26,28,32-34,38,60</sup>. In the current study, for reasons of practicality and validity, a randomly selected sample of non-pregnant patients with cervical carcinoma was used. This approach has been utilized before to assess the influence of age on survival, in patients with cervical carcinoma<sup>45,47</sup>.

Incomplete follow-up, inherent to a qualitative assessment of survival in the "Third World" situation, necessitated the construction of survival curves in this study. This method to assess survival has previously been well described<sup>63</sup>.

A comparison of survival data with previous reports, is fraught with difficulties for a number of reasons:

- (1) Survival data in the literature is, with very few exceptions, expressed as 5-year survival rates and therefore cannot be compared to the findings in the current study.
- (2) Because survival was analyzed according to the ESD/LSD system, comparison could only be contemplated with 6 reports (Table XIII). Inadequate follow-up i.e. less than 5 years, in these reports unfortunately negated any meaningful comparison.
- (3) Furthermore, none of the 6 reports mentioned in Table XIII contain any data on a control group.

#### 1. Overall survival

The overall survival in the study group at 5 years was 60%, whilst that of the control group was 35% (Figure 2). The difference between these survival curves was significant (logrank; P 0.03) and may have resulted from the disparity in the stage distribution of these 2 groups (Table V).

Figure 7 shows that after 36 months, there is a tendency for survival to plateau. This phenomenon has often been mentioned and seems to occur irrespective of associated pregnancy<sup>14,28,47</sup>.

## 2. Survival according to stage.

In this study, stage as a single variable, was the most powerful factor to influence survival when determined by both univariate (Wilcoxon;  $P=0.004$ ) and multivariate analysis (Proportional Hazards General Linear Model  $P=0.0001$ ). Because of this finding any comparison of survival must be stratified for stage.

The survival, at 5 years, of study and control groups presenting with LSD, was similar (40% vs 35%). For ESD, it was surprising to find that, although not significant (logrank;  $p=0.07$ ), patients in the pregnant group tended to have a better survival at 5 years (85%) than those in the non-pregnant group (56%). An easy explanation for this finding cannot be given, but one could speculate on the possible protective influence of associated pregnancy on the survival of patients presenting with early stage cervical carcinoma.

Most authors found that it was stage which influenced survival of patients with cervical cancer rather than associated pregnancy<sup>13,14,16,27,30,34,36,39</sup>. In their large review, Hacker et al found that compared to a control group, pregnant patients with early carcinoma of the cervix (Stages IB and II) had a similar 5-year survival (75%), whereas in late disease (stages III and IV), the pregnant patients had a lesser survival (16% for pregnant patients vs 28% for controls)<sup>15</sup>. On the other hand Nisker and Shubat found that in 49 pregnant patients with stage IB disease the 5-year survival was 70% whilst in their control group it was 87%, suggesting that survival is adversely affected by coexisting pregnancy<sup>20</sup>.

Thus the evidence for an effect of pregnancy on survival is conflicting.

### 3. Survival according to time of diagnosis.

In many studies, patients diagnosed postpartum have a worse survival than those diagnosed antenatally<sup>13,15-17,22,30,39,40,56</sup>. Furthermore, some are able to show a worse prognosis for patients diagnosed later in pregnancy when compared to those diagnosed in the first trimester<sup>8,13,15,16,27</sup>. However, these findings are likely to be a function of stage distribution as there is often an equivalent stage-for-stage survival according to time of diagnosis<sup>8,13-15,17,39</sup>. Only one study has been able to demonstrate an improved survival for antenatal patients after stratifying for stage<sup>22</sup>.

The current study confirms that despite a higher proportion of advanced disease in the postpartum patients, the survival in this group was similar to that of the patients in the antepartum group (Figure 6). Moreover, multivariate analysis confirms that if stratified for stage and method of delivery, patients in the postpartum group had a better survival than patients in the antenatal group ( $P < 0.03$ ). This finding is graphically illustrated in Figure 7.

One can only speculate upon the explanations for this finding. Firstly, this might just be a chance finding. However, it may relate to problems, during pregnancy itself, with radiation dosimetry, and the need to interrupt radiotherapy more frequently because of genital tract sepsis<sup>15</sup>. Understaging during pregnancy (due to

laxity of pelvic ligaments) may possibly give rise to an apparent worsening of stage-for-stage survival.

#### 4. Survival according to method of delivery.

Vaginal delivery in this study did not adversely affect overall or stage-for-stage survival. Other reports have reached the same conclusions by comparing survival after abdominal with that after vaginal delivery<sup>2,11,14,20,26,39</sup>. Two studies have even managed to show improved survival after vaginal delivery<sup>11,39</sup>. Where objections have been raised to delivery through a malignant cervix, they are often unsubstantiated, based on anecdotal and non-comparative evidence, and refer to possible sepsis, dystocia, haemorrhage and dissemination of tumour cells during vaginal delivery<sup>4,10,16,23,24,34,38,40,41,59,60</sup>.

Shingleton and Orr in their review observed that the risk of widespread dissemination of carcinoma during vaginal delivery may be based more on theoretical consideration than on factual findings<sup>2</sup>. The difficulty in compiling concise guidelines regarding route of delivery is exemplified in the review by Hacker et al. These authors found an improved survival of the "vaginal" patients but refrained from any further analysis as their review was retrospective and involved a number of different studies<sup>15</sup>.

Against this background of uncertainty the results of multivariate analysis in the current study are noteworthy. Although the influence of vaginal delivery on survival does not reach levels of significance, it does show a

possible trend ( $P=0.08$ ). The small numbers involved may obscure a more meaningful result.

Based on both previous reports and findings in the current study it is prudent to electively deliver pregnant patients with cervical carcinoma, via the abdominal route. However, inadvertent vaginal delivery through an untreated malignant cervix does not signify decreased survival and thus deviation from an existing treatment protocol is not indicated.

CHAPTER 5
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CONCLUSIONS

1) The proportional occurrence of pregnancy-associated cervical carcinoma is higher at Groote Schuur Hospital than elsewhere, but is decreasing with time.

2) Patients with pregnancy-associated cervical carcinoma present with earlier disease and therefore have an overall better prognosis than cervical carcinoma patients in general. However, survival analysis after stratifying for stage, shows that the associated pregnancy per se has no influence.

3) Associated pregnancy does not warrant a deviation from an existing treatment protocol for cervical carcinoma.

4) However, in the late second and early third trimester intervention may be delayed in the interest of fetal maturity without compromising maternal prognosis.

5) Vaginal delivery in patients with pregnancy-associated cervical carcinoma, should be avoided.

6) At GSH, it appears that a postpartum diagnosis has a positive effect on prognosis. This does not concur with other published studies.

7) Pregnancy-associated cervical carcinoma at GSH seems similar to that described elsewhere, with the exception of a worse stage distribution. This difference in stage distribution might be a manifestation of "Third world" conditions.

8) The infrequent association of pregnancy with cervical carcinoma, precludes unequivocal conclusions.

Furthermore, accurate metanalysis is hindered by variable reporting.

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