INVASIVE CARCINOMA OF THE CERVIX IN YOUNG WOMEN: A CONTROLLED STUDY (1974-1983) INCLUDING RE-EXAMINATION OF THE HISTOLOGY AND CYTOLOGY FOR EVIDENCE OF HUMAN PAPILLOMAVIRUS INFECTION

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CONTENTS

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Part III

I, O G JENNINGS 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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O G N JENNINGS

14 February 1990

(DATE)

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SUMMARY

Invasive carcinoma of the cervix was compared in women under and over 35 years of age in a 10-year cohort study for the period 1974 - 1983. The aim was to determine if there were any significant differences in disease characteristics and survival. A non-concurrent prospective study design was employed with a follow-up period of at least 5 years. All eligible young patients (n = 82) were studied out of a total patient population of 1522 and compared with a 13% random sample (n = 82) of equally eligible older patients. There were three study losses in each group (3,7%), giving a final comparison number of 79.

Patient data included disease stage, treatment type and complications, recurrence time and site and survival time. Tumour pathological characteristics were reviewed and evidence of Human Papillomavirus (HPV) was sought on histology and cytology specimens. Life table analyses were performed on the survival data and compared by the logrank test. The covariates of disease stage, treatment type and tumour type were included in the analysis of the effect of age group on survival. Multivariate analysis with a proportional hazards general linear model was performed for simultaneous control of confounding factors. Other disease characteristics were compared using the Chi-square test.

The overall proportion of young women was 11,6%. (This did not change for the period 1984 - 1988.) Five-year

survival was 57% for the young and 46% for the older group (not statistically significant: p = 0,198). There was no statistically significant difference in a number of characteristics, including tumour size, endocervical site, grade or type. There were 8 non-squamous tumours in the young (10%). Residual disease, time to recurrence, rate and site of distant metastasis, and treatment of recurrent tumour did not differ significantly; nor did rate of spread to lymph nodes, adequacy of follow-up or treatment complications. Evidence of HPV was found in 35% of evaluable histology and 21% of malignant cytology. There was no significant excess of HPV in the young group. The same applied to the length of the preinvasive phase and the false negative cytology rate - no significant differences were found.

There were significantly more Stage 1B tumours in the young group (p = 0,01), surgery was used more often for treatment in young patients (p = 0,027) and the difference in survival between the disease stages was highly significant (p = 0,0001). Multivariate analysis showed that the effect of age on survival was non-significant (p = 0,850).

The conclusion of the study is that cervical carcinoma in young women is not a different disease with a worse prognosis than in older women. Furthermore, it is not becoming more common in the young locally. Young women tend more often to have early stage disease.

1. INTRODUCTION

1.1 CARCINOMA OF THE CERVIX

Invasive carcinoma of the uterine cervix is, overall, the most common cancer in females in the world[1]. In the developed world it may comprise as little as 5% of all female cancers and be far exceeded in incidence by other cancers, e.g. carcinoma of the breast or of the uterine corpus, but in parts of the developing world it may comprise up to 35% of all cancer in females[1]. The percentage lifetime risk from birth to age 74 for invasive carcinoma of the cervix approaches 7% in Columbia; in the United Kingdom it is 1.25%.[2] For the entire United States of America the average annual age adjusted incidence of squamous cell carcinoma of the cervix for 1976 was 13,7 per 100 000 white women.[2] For Black women in South Africa it was 60 per 100 000 in 1986.[8] The incidence rate is as high as 85 per 100 000 women in certain areas of Panama.

A number of risk factors for developing invasive cervical carcinoma have been identified, which may partly explain the differing incidences noted above. In 1842 Rigoni-Stern commented on the vastly different

incidence of cervical cancer in prostitutes when compared to nuns, and this led to a large number of epidemiological studies which have confirmed the importance of a sexually transmitted agent in the aetiology of cervical cancer.[3] Age of first intercourse below 17 years is the most powerful sexual discriminating variable. There are however a number of very important covariables associated with the putative sexually transmitted agent; these are socio-economic class, tobacco smoking and the use of oral contraceptives.[1,3,4,5] The interrelationship is complex as the latter three factors are also related to sexual behaviour. The implicated sexually transmitted agent has variously been thought to be: gonorrhoea, syphilis, trichomoniasis, basic sperm proteins, herpes simplex virus (HSV) type 2, Chlamydia trachomatis, cytomegalovirus and human papillomavirus (HPV)[3,4,6,10,12]. Recent DNA hybridization studies have tended to discount the importance of HSV[3,10,12] and the sexually transmitted agent currently felt to be most directly related to the development of cervical carcinoma is HPV, in association with an undetermined cofactor or cofactors.[9-13]

Survival in the individual patient with invasive carcinoma of the cervix is not uniform and is dependent on a number of factors, which can be termed prognostic factors. Overall survival rates are meaningless in the

individual or in discrete groups unless corrected for these prognostic variables. The overall, global, 5-year survival rate for invasive carcinoma of the cervix is between 50 and 55%.[1,7] This may vary between 0% and 100% depending on certain prognostic factors. Throughout the Western world there has been noted to be a marked rise in the mortality rate (of the order of 2 to 4 times greater) in young women, i.e. women aged 15 to 34 years, during the years 1960 to 1980.[1]

Recognised independent prognostic factors are: tumour stage, tumour type, tumour grade, tumour size, channel invasion status, depth of tumour invasion into the cervix and lymph node metastases.[4,7,8,22-29,48,80] Even in this conservative listing there is still much controversy. For example, there are studies which show no difference in outcome by tumour type or tumour grade.[30-32] There are also many more prognostic variables under investigation. These include evidence of extension into the uterine corpus and patient age.[23,33] There are certain variables of importance in radiotherapy, e.g. prior subtotal hysterectomy or uterine position; also pretreatment haematocrit or pretreatment neutrophil count.[34] Coexistent pregnancy and endocervical geographical site are said not to be of independent prognostic significance, but there is room for doubt in both cases.[36,37] Race, Parity and menopausal state have been investigated in the past and are not accepted prognostic variables.[58,37,38,48] The

same applies to duration of symptoms.[40] Recent negative cytology (i.e. within 1 year of diagnosis) might indi-cate a rapidly progressive or fast growing tumour.[41-46]

It is clearly difficult to separate out one factor from all the other potential influences. It would seem that tumour size, site and invasiveness, together with host resistance must be the important conceptual aspects of the problem of prognosticating in the individual case.

Treatment with either surgery or radiotherapy gives equal survival, although there is room for doubt in the individual case, particularly for non-squamous and/or bulky endocervical tumours.[22,25,49] Neither surgery nor radiotherapy nor their combination is adequate for disease which has spread (including microscopically) beyond the pelvis and there is increasing interest in adjuvant (or adjunctive) chemotherapy in cervical carcinoma.[22] Cervical adenocarcinoma seems to have an added tendency to spread beyond the pelvis.[47] For carcinoma of the cervix in general there is a levelling off in mortality after 2 years and by 3 years for irradiated squamous carcinomas, 94% of pelvic recurrences will have occurred.[48,49] By 7 years the survival rate is equivalent to that of the general population.[48] Distant metastases occurred in 21% of squamous carcinomas in a large series treated by radiotherapy.[49] With better control of the disease in the treated area,

more patients will show evidence of disseminated cancer because of their longer survival. There are complications of treatment by radiotherapy or by surgery with some evidence that radiotherapy complications are more serious.[83] Sexual function following surgical therapy may furthermore be significantly better.[50]

There is evidence that in certain Western countries there has been a significant increase in the incidence of preinvasive carcinoma of the cervix during the time period 1960 to 1980.[51,52] Furthermore, the overall rate of decrease in invasive carcinoma appears to be levelling off and an actual increase has been evident in younger women.[52,55,56] With continuing follow-up of these women it becomes clear that a cohort effect is present and the increased incidence will spread to the older age groups with time.[52,53,56,57] The increased incidence of invasive carcinoma of the cervix in the young in the United Kingdom, the United States, Australia and New Zealand has been of the order of twofold or more.[55,56]

Evidence of the effectiveness of screening for preinvasive cervical carcinoma is available from a number of countries.[52] In those patients who develop carcinoma of the cervix there is a disturbing lack of utilization of the available screening services.[54]

1.2 HUMAN PAPILLOMAVIRUS INFECTION

The Human Papillomavirus (HPV or Wart Virus) is currently the object of much interest as a possible aetiological agent in cervical carcinoma.[9,10] At present it is felt to be the most important single factor in the multifactorial genesis of the disease.[11,12,13]

The papillomaviruses belong to the Papovaviridae family, together with the polyoma (or SV40) viruses, and are a deoxyribonucleic acid (DNA) virus. The DNA occurs in a double-stranded circle and there is a 72 capsomere icosahedral protein shell. The papillomaviruses infect both man and a variety of animals, e.g. the cow and the rabbit, and induce epithelial proliferations.[13]

The papillomaviruses show marked heterogeneity as well as remarkable host specificity. There are currently well over 50 types of human papillomavirus as detected by DNA hybridizations, with each new papillomavirus designated a different type if it shares less than 50% sequence homology with any other.[15] (There are, however, antigens common to the entire genus.) Host specificity is illustrated in the human by the fact that Type 1 is found in the common deep plantar wart, Type 2 in the common hand wart and yet other types in the genitalia. Types 6 and 11 make up 90% of genital HPV infection although 15 of the viral types

can infect the genitalia. Certain of the latter viruses have an enhanced oncogenic potential, in that they are regularly found incorporated in the DNA of cervical carcinomas. They include the virus Types 16 and 18, and, less commonly, 31, 33 and 35.[12-14]

Although the epidemiological evidence demonstrates a sexually transmitted agent in the aetiology of cervical cancer (which currently is felt to be HPV by exclusion of the other contenders) and although the 5 types mentioned above are regularly incorporated into cervical carcinoma DNA, and although malignant transformation occurs commonly in bovine and rabbit papillomavirus infections, there is not yet adequate evidence that HPV infection in humans causes malignant transformation.[9,11-13] (It can be shown, for example, that HPV 16 is also found in the normal cervix.[9]) It may be postulated that there is intracellular control of incorporated HPV DNA expression by cellular genes, in which case malignant transformation is viewed as a failing host cell control of persisting viral genes. Factors modifying cellular gene function might then <u>initiate</u> the malignant transformation which is promoted by the HPV infection - the classic Zur Hausen hypothesis.[12] The initiating events are at present thought to be multifactorial and poorly defined, but certainly include cigarette smoking.

Compromised immune state plays a major role in HPV infection in the cervix and leads to a very high incidence of cervical intraepithelial neoplasia.[35]

Almost all cervical carcinomas are found to contain incorporated papillomavirus DNA (typically 90%[10]) if subjected to DNA extraction and molecular cloning, with subsequent DNA hybridization analysis. This technique can also be performed *in situ* on paraffin-embedded biopsies or cytological specimens.[18,20] With the recent advent of the polymerase chain reaction (PCR), which is a technique to amplify the target DNA sequence, this figure of 90% should improve still further.[14] There should also be more adequate demonstration of the ubiquity and type of papillomavirus infection in the female genital tract in general than is possible with current techniques such as cytology and histology which already show an up to 80% synchronous HPV infection rate for cervical-vulval or vulva-cervical papillomavirus lesions.[16]

Besides the definitive but highly complex DNA hybridization techniques, evidence of HPV infection can be obtained by immunocytochemistry, electron microscopy, cytology, serology, colposcopy and histology.[10,13,18-21]

Colposcopy probably has a similar (poor) sensitivity to that of cytology. One study calculated a sensitivity of 35%.[21] Serology is of no value in genital papillomavirus infection because the concentration of virus particles is extremely low.[13] Electron microscopy is said to show a sensitivity

better than that for conventional histology, but is a complex procedure.[18] Immunocytochemistry for papillomavirus group-specific capsid antigens with a peroxidase-antiperoxidase procedure is well described.[10] The frequency of localization of antigens diminishes in relation to the severity of the lesion and none are found in cases of carcinoma. The assembly of virions within the nucleus is linked to the maturation of the squamous cell. The sensitivity of immunocytochemistry seems relatively poorer than that of histology in the more severe lesions.[18]

Cytology has been widely used to detect HPV infection. There is a 1 to 2% HPV infection rate in routine cervical cytology.[20] The cytological features are well described and confirmed by studies using other modalities for HPV detection. Features include koilocytosis (perinuclear cytoplasmic vacuolation), binucleation, degenerative nuclear changes, dyskeratosis and increased density of the peripheral cytoplasm.[10,20] A number of studies comparing cytology to DNA hybridization techniques show that cytology has a good specificity but a poor sensitivity in detecting HPV infection.[19-21] Typically the sensitivity is in the region of 40% of that achieved by DNA studies. There is evidence, as with immunocytochemistry, of a declining ability to detect HPV infection as the lesion becomes more severe.[10]

Histology suffers from the same decline in HPV detection rate as the lesion approaches malignancy. Figures from a series of 500 biopsies showing CIN give an HPV detection rate of 80% for CIN I versus 63% for CIN III.[10] In another study by Sato et al[18] figures were 89% and 20% with an average of 66%. In this latter study DNA hybridization showed an overall 98% detection rate. In a study of 98 cases of CIN by McNicol et al[21] histology and DNA hybridization proved equally sensitive in detecting HPV infection (80 versus 81% overall). Histology is not useful for detecting HPV in malignant tissue.

The histological features of HPV infection, which were first reported by Meisels and Fortin in 1976 and were not widely taught until the early 1980's, are extensive and well described. They include koilocytosis, nuclear wrinkling, binucleation, multinucleation, dyskeratosis, prominent metaplastic parabasal cells and epithelial spikes.[10,18]

1.3 CARCINOMA OF THE CERVIX IN YOUNG WOMEN

The mean age, at diagnosis, of the patient with invasive carcinoma of the cervix depends on the sample analysed. The same applies to any breakdown of the age distribution of the disease. In a large, population based study of 10,022 cases of invasive carcinoma in the United Kingdom (10% of all cases in England and

Wales) covering the years 1957 to 1981[59], the age distribution was as follows:

Under 20	6 cases, i.e. 0,06%
Under 35	7,8%
75 and over	8,3%
Peak incidence	age group 55 - 59

Older figures for the United States 1914-1946[60] based on 4 652 patients and corrected for the female population of the state of New York give the following age distribution for invasive carcinoma of the cervix:

Under 20	0,05%
Under 35	7,4%
75 and over	6,1%
Peak incidence	age 57

Many hospital-based studies have been done on the younger patient group. By convention these have been the under 35 group, although some have used under 30 groups and others under 40 groups. The under 35 grouping seems to have the most merit, as the incidence of the disease is still rising rapidly at this point while at the same time sufficient numbers are obtained for analysis and a patient under the age of 35 years is still clearly young. The group of under 20 patients forms a special group of rarities of the case report type.

As discussed in section 1.1 of the Introduction, the incidence of invasive cervical carcinoma has in-

creased in certain Western countries in the young age group. This is clearly seen in age distribution studies done over time, although these figures are often skewed by referral patterns in hospital-based studies. In the British population-based study of Meanwell et al the under 35 year group in 1965 had 13 cases; in 1975 there were 33 and in 1980 there were 64[59]. Because of a falling incidence in older women there is no obvious overall increase in the incidence of invasive carcinoma of the cervix in the United Kingdom. A hospital-based study in the west of Scotland found that the number of patients under 35 referred to them doubled between 1974 and 1984[61]. In Brighton the mean age of referred patients with cervical cancer fell from 50 years in 1967 to 35 years in 1977.[62] In a study of 385 new patients at the Royal Marsden hospital the number of patients less than or equal to 35 years of age rose from 2% for the triennium 1970-1972 to 18% for 1982-1984.[63] Of 1 451 patients seen at the Mayo Clinic from 1940-1949, 11,6% were 35 years of age or younger.[64]

As mentioned earlier, invasive carcinoma of the cervix in those below 20 years of age must be classed as exceedingly rare. There have been a number of reviews of this subject with a review in 1968 finding only 32 cases in girls under the age of 17 in the world literature since 1888.[65,66,67] A review by Dekel et al[67] in 1982 found only 11 cases of squamous carcinoma

in the age group under 20 in the world literature for this century.

Quite apart from the issue of a rising incidence of cervical cancer in young women is the empirical observation that the mortality for this group has risen markedly. Yule in 1978 showed that while the overall mortality had decreased in England and Wales by 11,8%, the mortality in the group under 35 had doubled in the 6 years 1970 to 1976[68]. Green in New Zealand demonstrated a similar doubling of the mortality for this group (1941-1974), in the face of an overall marked decline in mortality rates[55].

The reason for these changes is unknown.[33,69] The main debate revolves around the issue of whether there has been a fundamental change in the nature of cervical carcinoma or whether the increased mortality is explainable purely on the grounds of an increased incidence of the disease; and if the latter holds true what then the cause of the increased incidence is.[41] This has become a major issue in cervical carcinoma, with enormous implications for screening and treatment of the disease as well as for understanding its fundamental aetiology. The issue is compounded by the possibility of smaller but simultaneous changes in <u>both</u> the nature and incidence of the disease.

Numerous studies have been done to determine if there is less survival, in the young group, i.e. a more

virulent disease, and there is considerable evidence that this may indeed be so.[24,70-79] Evidence for an increase, in the young group, of the prognostic variables associated with a poorer prognosis is as follows: more non-squamous tumour types; more poorly differentiated (high grade) tumours; more cases of a short preinvasive phase; more recurrent disease; more lymph node metastases; more false negative cervical cytology screening; and a longer delay in making the diagnosis.[24,40,61,64,70,72-75,86,88,96] There is however no evidence that the young group avails itself less of screening cytology services or presents with later stage disease.[69] Indeed, there is a large body of evidence to show that the disease is found at an earlier stage in the younger group.[61,63,81,82,85,92,95] There is no obvious explanation for this latter common finding. There are also no studies in the literature comparing human papillomavirus (HPV) infection rates or types in young versus older patients with invasive cervical carcinoma.

The undoubted fact of an increased number of deaths from carcinoma of the cervix in the younger age group has been shown, in contrast to the above quoted evidence, to be unrelated to a decreased survival in the young in an impressive number of studies spanning most of this century.[27,37,39,40,48,59,61,63,64,81-95] The increased deaths relate rather to an increased incidence of the disease.

The consensus of opinion of major reviews of the problem is that Age is a prognostic factor of uncertain significance.[33]

The role of HPV infection in any shift in disease virulence, should this be present, or in a relative increase in incidence in the younger group is unexplored.

The death of a young woman from carcinoma of the cervix makes a strong impression on her medical attendants and there is a feeling, from personal experience, amongst many workers in the field that there may indeed be an issue of decreased survival in younger women.[22]

1.4 STUDY OBJECTIVES

The aim of the study, as stated in the official protocol, is as follows: "To obtain objective information on the natural history of invasive carcinoma of the cervix in women under 35 years of age and to compare it to the disease in women aged 35 years and older to see if there are any significant differences".

Aspects of the natural history of carcinoma of the cervix in each of the two groups considered important for comparison are as follows:

(a) Survival;

(b) Miscellaneous Patient Characteristics, e.g. Race, Parity, Pregnancy State.

(c) Prognostic Factors:

- Disease Stage
- Tumour Size
- Tumour Geographical Site
- Tumour Grade
- Tumour Type
- Lymph Node Involvement
- Recurrence Time and Site
- Length of the Preinvasive Phase
- False Negative Cytology

(d) Treatment Type and Complications

(e) Evidence of Human Papillomavirus Infection

It is planned to study these issues in a scientifically valid way, within the resources of a single investigator engaged also in full-time clinical work, so that clear conclusions can be reached on the matter of whether or not a difference exists between cervical carcinoma in young versus older women.

A secondary goal will be to use the data to check for any change in the relative proportions of young and older patients to see if there is evidence of an increased incidence in younger women locally, in keeping with the findings in Western nations.

In view of the epidemiological nature of the data under investigation - which precludes the experimental approach[97,99] - the overall study design chosen is ob-

servational, with an unbiased comparison of the previously mentioned aspects being made between a group of young patients with the disease and a group of older controls with the disease, ensuring that the two groups are fully comparable.[97,99] In order to study the natural history of the disease this comparison is a follow-up or cohort study.[98,99] As it would be beyond the resources of the study to institute follow-up over 10 years or more concurrent with real time, the well described non-concurrent prospective format is chosen, allowing analysis of recorded data.[98,99]

2. MATERIALS AND METHODS

2.1 RESOURCES

The treatment of invasive carcinoma of the cervix is highly complex and in general involves radiotherapy or radical surgery or a combination of both. The result of this complexity is that treatment is centralized to special centres based in large hospitals. In the city of Cape Town there are two such treatment centres, each based at an academic teaching hospital group, i.e. Groote Schuur Hospital and Tygerberg Hospital.

The two teaching hospitals are referral centres for a large, poorly defined section of the Cape Province. They are either natural referral centres for country areas to which they are in closest geographical proximity or special referral centres for some of the treatment centres with lesser facilities. The closest treatment centre to Cape Town is found in Port Elizabeth.

Radical pelvic surgery is seldom performed in private and if so is invariably done by a senior gynaecologist associated with a teaching hospital.

The department of radiotherapy issues a radiotherapy number to every patient with a malignant tumour registered by any of its clinics. This applies even if the treatment of the tumour has been purely surgical. About 3000 numbers are allocated per year. Numbers are

allocated at registration on a daily basis, for the entire radiotherapy division on a first come first served principle.

All cases of invasive cervical cancer at Groote Schuur Hospital are registered and assessed by a combined assessment clinic (CAC) consisting of both Gynaecological Radiotherapists and Gynaecological Oncologists, in close association with a Gynaecological Pathologist. All staging is by combined decision and the same applies to treatment recommendations. The details of each case are fully recorded and include comprehensive follow-up notes. The gynaecological CAC makes use of a special summary control sheet (See figure 2) for follow-up purposes. The patients's home address is also entered on the form.

Follow-up of patients is usually on a lifetime basis. A few patients are discharged if they have survived 10 or more years but in general this is not policy and such patients return for checkups every two years.

In all cases, when a given follow-up appointment is missed there is a routine mechanism for pursuit of the matter. In almost all cases an explanation is obtained and entered in the records and if the patient is still alive further follow-up arrangements are made.

Certain country cases, especially those who live more than a day's journey to and from Groote Schuur

Hospital have follow-up done locally. Their control sheets are periodically updated by letters of enquiry.

These records have been regularly computerized since 1982.

All cases of cervical carcinoma have a histopathological diagnosis, with the specimen usually taken by punch biopsy of an obvious clinical lesion. The histology report may not always have originated at Groote Schuur Hospital.

The department of pathology stores all slides of malignant tumours which it has processed in its archives and these can be recovered if the relevant histology numbers are known. A screening cytology laboratory also forms part of the gynaecology oncology service.

The cytology service also stores its abnormal slides which can be located by cytology number and year.

During the earlier part of the study (1974 to 1979) the Department of Radiotherapy used a modified (higher dose) form of radical radiotherapy as part of a British Medical Research Council trial in some of the patients allocated for radiotherapy. This protocol did, however, result in a higher incidence of radiation bowel injury and was ultimately abandoned.

2.2 DATA SELECTION

As mortality in young women has at least doubled in the West (See section 1.3), it is felt that a study with 80% power to detect a 50% difference in survival at the 95% confidence level will be adequate to allow a clinically meaningful conclusion.[100]

The Gynaecological CAC registered approximately 150 cases of carcinoma of the cervix per year during 1974 - 1983. To achieve an adequate number of young patients it was decided that a 10-year study would be required. This was based on the following reasoning and calculations.

A type II error is likely to be the limiting factor in any comparison with older patients using limited numbers (if α is chosen as 0,05 and β as 0,20 as is usually done)[98,101].

For the most important comparison, namely survival, the value pC (or the probability of survival in the controls) is chosen as 0,5 (i.e. 50% 5-year survival; see Section 1.1). The minimum difference to be detected is 50% (see Section 1.4) which translates into a factor 0,5x(1-0,5) or 0,25. A value pE (i.e. the probability in the test group at the given difference) is then calculated as pE = pC + clinically important difference or pE = 0,5 + 0,25 or 0,75. From the value pE = 0,75 a graph can be used to determine study power at various sample sizes. If 80% power is chosen for this calculation a sample size of 70 is required.[100] A 10-year study is expected to yield 1,500 patients of whom ±7.5% at least (see Section 1.3) should be under the age of 35 years. This gives 112 patients, thus

allowing some leeway for study losses. A 5-year study (66 patients) would yield too few patients.

It was decided furthermore that the study group or "cases" should include if possible all young patients over the 10-year period.

As the data collection and analysis began on 1 January 1989, the follow-up part of the study was ended on 31 December 1988. To allow the possibility of at least a 5-year follow-up on all cases for survival curves, the 10 year period selected for study became 1974 to 1983 inclusive.

In view of the overall design strategy, which is an unbiased comparison of a cohort of younger women with a cohort of older women (see Section 1.4), the selection of the older women or control group next required attention. Both groups need to be fully comparable.

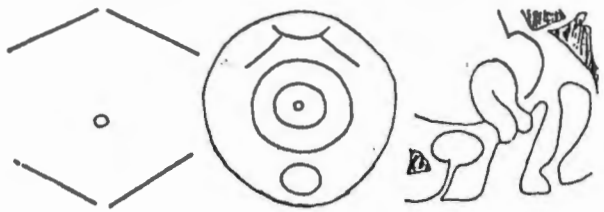
The possibility of analysing the entire older group, i.e. about 1400 patients (or 1500-112) could not be entertained due to the limited resources of the study. The alternative method, i.e. that of a random sample of the control group, was therefore used. For ease of comparison a sample size equal in size to that of the study group (or young cases) was decided upon. To achieve this and at the same time make an unbiased or random selection from the older group the following method was used: for each radiotherapy number of a

Figure 1: Gynaecological CAC Follow-up Control Sheet.

TP. 3484.

SITE	T N M	HISTOLOGY	POLICY	CHANGE OF POLICY	TREATMENT	NAME NUMBER
		Grade: Type:			S R Cx	AGE RACE SEX

REF. DR. DATE: HISTORY: INVESTIGATIONS



Chest x-ray
IVP
Cytoscopy
Cytology
W.R.
UREA:

L.M.P.
OBSTETRIC HISTORY
FAMILY HISTORY
HISTOLOGY/ COMPLICATIONS
OTHER

SURGICAL PROCEDURES:

YR	J	F	M	A	M	J	J	A	S	O	N	D

young patient a further radiotherapy number from cases of carcinoma of the cervix was selected which was the next highest number and did not in itself belong to another young patient. Seeing that radiotherapy number allocation is a stochastic procedure, this method allows a random sampling of older women. This method has been used in other similar studies of the problem.[95]

The selection of cases and controls was done manually and was facilitated by the existence of the Follow-up Control Sheets (see Figure 1). Once selected, the patients' radiotherapy folders and, if necessary, the hospital folders were drawn and further examined.

Two facts became evident at this stage. Firstly, the proportion of younger women was greater than that expected for population studies (see Section 1.3) and secondly, a number of biasing factors were potentially present. These factors related either to the unfair weighting of one group against the other or to an invalid assessment of survival in carcinoma of the cervix. A total of 11 exclusion criteria were developed, details of which appear in Section 2.3 and patients were only selected for each group if these did not apply, i.e. if they were eligible. The exclusion criteria were applied equally to both cases and controls. Thus the study included all eligible young women, with the controls being a random sample of the

Figure 2: Data Record Sheet

C A C E R V I X I N T H E Y O U N G

D A T A S H E E T

HOSPITAL STICKER

Sheet No.: |__|__|__|

Radiotherapy No. |_____|

Histology No. |_____|

Cytology No. |_____|

CAC Date of diag. |___|___|___|

CARCINOMA OF THE CERVIX 34 YEARS AND UNDER VERSUS 35 YEARS AND OVER

1.	CASE OR CONTROL	|___|	1
2.	AGE AT DIAGNOSIS	|___|	2
3.	RACE	|___|___|	3
4.	PARITY	|___|___|	4
5.	PREGNANCY STATUS AT DIAGNOSIS	|___|___|	5
6.	TUMOUR STAGE	|___|	6
7.	TUMOUR VOLUME	|___|	7
8.	MODE OF 1° TREATMENT	|___|	8
9.	LYMPH NODE STATUS AT PRIMARY SURGERY	|___|	9
10.	MAJOR LATE COMP.OF 1° TREAT. (_____)	|___|___|	10
11.	TIME TO RECURRENCE CONFIRMED	|___|___|___|	11
12.	SITE OF RECURRENCE (_____)	|___|	12
13.	RECURRENCE TUMOUR TYPE	|___|	13
14.	MODE OF TREATMENT OF RECURRENCE	|___|	14
15.	TUMOUR STATUS AT DEATH	|___|	15
16.	DIRECT CAUSE OF DEATH (_____)	|___|___|	16
17.	10 YEAR RECORDS STATUS	|___|	17
18.	KNOWN SURVIVAL TIME	|___|___|___|	18
19.	FOLLOW-UP STATUS	|___|	19
~~20.~~	~~TUMOUR TYPE~~ Clinical Endocervical Nature	|___|	~~20~~
21.	MUCIN STAIN STATUS	|___|	21
22.	RECURRENT TUMOUR TYPE CORRESPONDENDE	|___|	22
23.	TUMOUR DIFFERENTIATION/GRADE	|___|	23
24.	TUMOUR TYPE (_____)	|___|	24
25.	ANGIOLYMPHATIC PERMEATION STATUS	|___|	25
26.	ADJACENT NON-NEOPLASTIC EPITHELIUM STATUS	|___|	26
27.	HPV STATUS ON HISTOLOGY	|___|	27
28.	CYTOLOGY ABNORMAL RESULT MOST DISTANT FROM DIAGNOSIS	|___|	28
29.	CYTOLOGY RESULT AT DIAGNOSIS	|___|	29
30.	COMPLETE CYTOLOGY STATUS	|___|___|	30
31.	LENGTH OF KNOWN PREINVASIVE PHASE	|___|___|___|	31
32.	HPV STATUS ON CYTOLOGY	|___|	32

next highest eligible radiotherapy number as described above.

To be eligible for the study each patient from either group had to have newly diagnosed, properly staged, invasive carcinoma of the cervix in an intact uterus. The patient had to accept treatment and be free of a second primary carcinoma. The histology on which the diagnosis was based had to have been processed by the local Groote Schuur Pathology Department and the patient had to have her permanent home address (domicile) in an area which made Groote Schuur Hospital the normal first point of referral. Any specially referred cases within this area were also not eligible. By confining the study to the geographically associated population it was hoped to make the data on the study groups generalizable.[102]

In this way the total number of eligible cases amounted to 82. This was balanced by a random sample of 82 eligible controls. The cases and controls were not matched or pre-stratified in any further way.

Data collection on each patient was in keeping with the study objectives outlined in Section 1.4. A standardized form (Figure 2) was drawn up and used to record the data from each case. This data was coded into numerical form to allow computer processing if necessary.

Figure 3: Histology data sheet.

PATHOLOGY

Sheet No.: |_|_|_|

Histology No.: |_____|

HOSPITAL STICKER

CARCINOMA OF THE CERVIX 34 YEARS AND UNDER VERSUS 35 YEARS AND OVER

MUCIN STAIN USED YES / NO

NORMAL ADJACENT EPITHELIUM YES / NO

EVIDENCE OF HPV YES / NO

Figure 4: Cytology data sheet.

CYTOLOGY

Sheet No.: |_|_|_|

Cytology No.: |_____|

HOSPITAL STICKER

Ca.△(date) _____

CARCINOMA OF THE CERVIX 34 YEARS AND UNDER VERSUS 35 YEARS AND OVER

DATE	RESULT

EVIDENCE OF HPV YES/NO

Part of the data collected from the folder was the histology number in every case. This was then supplied, in the form of a further data sheet (Figure 3) to the Department of Pathology where the relevant archival slides were drawn and reviewed by a single, blinded, gynaecological histopathologist (Professor A J Tiltman). Apart from the data displayed, the tumour grade and type were also recorded.

Similarly, a cytology sheet was supplied to the Cytology Laboratory for each case (Figure 4). Cytology numbers were not available for each case as a lack of Groote Schuur cytology was not an exclusion criterion for the study. Because a great many of the cytology results were reports from other laboratories, the cytology results are as reported and not based on a review (except for the search for HPV on Groote Schuur slides). This search was conducted by a single, blinded senior technologist.

The date of registration of the patient with the CAC was taken as the date of entry into the study. The only exceptions were cases of retrospective registration of greater than one month's delay following treatment. This applied to a few cases of radical hysterectomy that were registered post-operatively to facilitate speed of treatment. In these few cases (<5) the date of entry into the study was taken as the date of operation.

The key to the data sheet (Figure 2) is as follows:

Question 1. Case or Control

1 = Case

2 = Control

This is self-explanatory and makes for ease of analysis.

Question 2. Age at Diagnosis

1 = 30 - 34

2 = 20 - 29

3 = <20

4 = 35 - 49

5 = 50 - 75

6 = >70

The actual age of each patient was also entered. The correctness of the age was checked both against the hospital registration details and the CAC proceedings.

Question 3. Race

2 = European

4 = Coloured

6 = Asian

8 = Black

This numerical code matches that of the Hospital. Although race independent of other factors is not considered to be of importance in cervical carcinoma

(see Section 1.1), a difference in proportions between the two groups might indicate that a new factor is present in one of the racial groups.

Question 4. Parity

The number equals the actual parity.

Parity was chosen rather than gravidity as estimation of the latter by patients is clearly less reliable. Although parity is not thought to relate to prognosis (see Section 1.1), determination of the parity of a modern young cohort of patients with cervical carcinoma is considered to be relevant. Are they still of high parity as in the case of their classic counterparts?

Question 5. Pregnancy Status at Diagnosis

1 = Non-pregnant by at least 6 months

2 = Pregnant, or within 6 months of delivery

Pregnancy is not felt to be a prognostic factor although some dispute this (see Section 1.1). The time limit after pregnancy for inclusion in the pregnancy group varies in the literature, typically from 3 months to 12 months. Six months was therefore chosen as a compromise. It was decided to include this factor to see if pregnancy is a particularly common or uncommon event in this particular study group as the factor may be controversial.

Question 6. Tumour Stage

1 = 1B

2 = 2A

3 = 2B

4 = 3

5 = 4A (Bladder or Rectum)

6 = 4B (Distant)

Only an official multi-parity FIGO staging by the CAC was accepted as valid.[106] Microinvasive disease (Stage 1A) was not included, nor was any type of post-surgical staging. If positive lymph nodes were found at an attempted radical hysterectomy the case was included under its original clinical stage, i.e. usually stage 1B. Stage 3 disease was not differentiated further into A or B as there were no cases of stage 3A that were not also stage 3B.

Question 7. Tumour Volume

1 = Clearly > 3 cm diameter

2 = Clearly < 3 cm diameter

3 = Unclear

There is no clarity yet in the literature on this topic beyond the fact that large size is a bad prognostic factor (see Section 1.1). There is no consensus on the exact method of measuring the tumour. Usually diameter is measured and not volume. In this study, diameter was estimated from the tumour description in the

CAC notes. Often this was clear, especially that it was larger than 3 cm. As the study and control groups were subjected to the same estimation process, the results are felt to be comparable.

Question 8. Mode of Treatment

1 = Radical Radiotherapy

2 = Radical Radiotherapy following Surgery

3 = Radical Radiotherapy plus Salvage Hysterectomy

4 = Palliative Radiotherapy

5 = Palliative Radiotherapy and Defunctioning Surgery

6 = Palliative Radiotherapy and Chemotherapy

7 = Radical Surgery

8 = Radical Surgery and Adjuvant Chemotherapy

9 = Palliative Surgery

0 = Nil. Patient Terminal.

The purpose of this long list of permutations is to identify those in each group that were not treated with curative intent. If all other factors are equal, patients treated with radical radiotherapy and radical surgery should have an equal survival rate (see Section 1.1). Factors such as failed surgery, salvage hysterectomy, chemotherapy and adjuvant chemotherapy are of interest to document although the numbers in the study will be very small.

Question 9. Lymph Node Status at Primary Surgery

1 = Negative

2 = Positive

0 = Not Applicable (i.e. no primary surgery)

The proportion of patients with positive lymph nodes at surgery is well known in the literature. Is the young group at any special risk as has been suggested? (see Section 1.3)

Question 10. Major Late Complications of Primary Treatment (After 1 year)

1 = None

2 = Required bowel surgery due to radiotherapy

3 = Required urinary diversion due to radiotherapy

4 = Required urological surgery due to radical surgery

5 = Permanent urological injury due to surgery

6 = Chronic lymphocyst formation

7 = Death

8 = Significant other (by name)

9 = Residual tumour or recurrence within 1 year

0 = Unknown due to poor follow-up

Significant treatment complications might have a more serious impact in the younger patient who would be expected to live on for a longer time if cured. Long term survival studies show that after between 7 and 10

years the survival of patients with treated cervical carcinoma is the same as that of the general population.[48]

Question 11. Time to Confirmed Recurrence

The number equals the time in months from CAC registration to confirmation of tumour recurrence at the official follow-up clinic. Part of a month greater than 15 days was recorded as a month, while 15 days or less was not counted. Confirmation of recurrence was seldom based on histology in practice and was usually a clinical assessment. The recorded judgement of the attending doctor that recurrence had occurred was taken as confirmation (i.e. time was not measured from voiced patient suspicions or vague symptoms).

0 = No recurrence or no follow-up

1 = Residual tumour present

To determine recurrence sites and times accurately one also has to know the follow-up status of each group.

Question 12. Site of Recurrence

1 = Contiguous

2 = Non-contiguous

3 = Both

4 = Not applicable (no recurrence or unknown)

Contiguous encompasses the entities of local, central, pelvic or regional recurrence and is best defined

by its alternative, non-contiguous. The latter is equivalent to distant metastases. This includes inguinal lymph nodes, malignant ascites, bony destruction or nodular enlarged liver and any more peripheral manifestations.

Question 13. Recurrent Tumour Type

1 = Squamous carcinoma

2 = Adenocarcinoma

3 = Adenosquamous carcinoma

4 = Other (as stated)

5 = Not biopsied - histology unknown

0 = Not applicable (no recurrence or no follow-up)

This section was included in an attempt to see if certain tumour types recurred more often.

Question 14. Mode of Treatment of Recurrence

0 = Not applicable (no recurrence or no follow-up

1 = Radical radiotherapy

2 = Chemotherapy alone

3 = Nil

4 = Palliative surgery

5 = Exenteration

6 = Full irradiation at a distant site

7 = Palliative radiotherapy

The purpose of this section is to check if there is a difference in intensity of treatment of recurrent disease between the young and the older groups.

Question 15. Tumour Status at Death

0 = Definitely alive

1 = Died of ca. cervix, contiguous only

2 = Died of another cause, no ca. cervix present

3 = Died of another cause, ca. cervix present

4 = Died of ca. cervix, non-contiguous only

5 = Died of ca. cervix, contiguous and non-contiguous

6 = Definitely dead from ca. cervix, site uncertain

7 = Condition unknown, i.e. may be alive

This provides data on death from unrelated disease and loss to follow-up as well as giving further information on tumour site in the two groups.

Question 16. Direct Cause of Death

1 = Haemorrhage

2 = Sepsis

3 = Uraemia

4 = Other

5 = Died in unknown way

0 = Not applicable (alive or lost to follow-up)

What are the direct causes of death and are they any different between the two groups?

Question 17. Ten-year Records Status

1 = Not available

2 = Available

This section was included for ease of analysis in the event of a late or long-term study using this data, e.g. a study of proportional changes between two consecutive 5-year groupings (i.e. 1974-1978, 1979-1983).

Question 18. Known Survival Time

The number given is the time in months from date of entry into the study to the date of death, loss to follow-up, intercurrent death of known alive status at the conclusion of the study on 31 December 1988. Fractions of months are ignored if less than 16 days and counted as 1 if greater than 15 days. The actual date of the event, i.e. one of the four possibilities mentioned above, is also recorded. This is the data required to construct a survival curve of the Kaplan-Meier type.[104,105]

The handling of the data at the conclusion of the study requires comment. Many patients who are not dead, lost or dead from intercurrent disease will have had their last follow-up visit some time prior to the 31 December 1988 cut-off date, making their status on that date not accurately known. To avoid this problem two mechanisms were used: firstly, because the data collection took place through most of 1989 and most of

the patients had a follow-up visit in 1989, their status on 31 December 1988 could be retrospectively determined. Secondly, in those few patients who did not have a follow-up appointment in 1989, there were patients with a previously perfect follow-up record (see Question 19). These patients were assumed to be alive on 31/12/1988 if the time for their next appointment had not yet come e.g. was due in early 1990. Patients with poor follow-up, on the other hand, were presumed lost on their last follow-up appointment prior to 31/12/1988.

Question 19. Follow-up Status

1 = No default

2 = Defaulted < 3 months

3 = Defaulted > 3 months but status known

4 = No follow-up

Patients often attend follow-up for a while and then default, although their ultimate status remains known (by telephone, letter or other reports). Follow-up is thus comprehensive (1 + 2), crude (3) or non-existent (4).

Question 20. Endocervical Tumour Clinically

1 = No

2 = Yes

A tumour predominantly in the endocervical geographical site might have a greater tendency to be

clinically understaged or to be an adenocarcinoma, both of which may have an effect on survival (see Section 1.1). The purpose of this section is to check if there is a different distribution of endocervical tumours in the two groups.

Question 21. Mucin Stain Status

1 = Not used

2 = Used

There are claims in the literature that if mucin staining is not done routinely then for every adenosquamous tumour diagnosed two are missed.[24] As mucin production may be associated with a poorer prognosis, especially in younger patients, it was felt worthwhile to document the actual use of mucin stains during 1974-1983 in the two groups (mucin stains have been done routinely at Groote Schuur Hospital since 1989).

Question 22. Recurrent Tumour Type Correspondence

1 = Corresponds

2 = Not the same as the original

3 = Unknown (no biopsy)

4 = Not applicable (no recurrence or no follow-up)

The purpose of this section corresponds with the previous question, i.e. in the light of further histology was there any error in the original his-

tology? What is the distribution of these errors in the two groups?

Question 23. Tumour Differentiation/Grade

1 = Grade I

2 = Grade II

3 = Grade III

Tumour grade, of which differentiation is only part of the assessment[32], is felt by many to be of prognostic importance (see Section 1.1). What is the grade distribution between the two groups?

Question 24. Tumour Type

1 = Squamous carcinoma

2 = Adenocarcinoma

3 = Adenosquamous carcinoma

4 = Other (specify)

Tumour type is thought by many to be of prognostic importance (see Section 1.1). A great many cell types have been described, some of which are extremely rare. This section makes use of a simple, everyday classification of clinical importance.

Question 25. Angiolymphatic Permeation Status

1 = Not commented on

2 = Definitely present

3 = Definitely not present

Angiolymphatic permeation or "channel invasion" is probably equivalent to lymphatic micrometastases and as such is of prognostic importance (see Section 1.1). To assess a specimen for this feature one requires more than a cervical punch biopsy.

Question 26. Adjacent Non-neoplastic Epithelium Status

1 = Not present

2 = Present

The accuracy of histological assessment of the presence or absence of HPV infection is inversely related to the degree of neoplasia and to be truly accurate requires non-neoplastic epithelium (see Section 1.3). This section controls for this variable in the two groups.

Question 27. HPV Status on Histology

1 = Not present

2 = Present

If there was any doubt whether HPV was present or not it was recorded as not present. The presence of HPV was only recognised by histological means in 1976 (see Section 1.3) and was not regularly reported at Groote Schuur until the early 1980's. Thus re-examination of the archival histology for HPV provides new data.

Question 28. Cytology Abnormal Result Distant from Diagnosis

1 = CIN I

2 = CIN II

3 = CIN III plus adenocarcinoma-in-situ

4 = Possible microinvasive carcinoma

5 = CIN III plus severe endocervical atypia

6 = CIN III only

7 = Severe endocervical atypia (only)

8 = Adenocarcinoma-in-situ

9 = Negative cytology

0 = No previous cytology

These results were at least 3 months prior to the diagnosis of malignancy. They represent the most distant result known if there are more than two abnormal results. This section has the purpose of seeing how many preinvasive lesions escaped adequate management or were possibly false negative for malignancy in each group.

Question 29. Cytology Result at Diagnosis

1 = Invasive carcinoma (squamous)

2 = Microinvasive carcinoma (squamous)

3 = CIN I or II

4 = Adenocarcinoma

5 = Severe endocervical atypia only

6 = CIN III

7 = CIN III plus adenocarcinoma-in-situ

8 = CIN III plus severe endocervical atypia

9 = Negative cytology

0 = Cytology not done

These were results at the time of registration with the CAC for cervical carcinoma and up to 3 months prior to this. The purpose of this section is to see how many smears were falsely negative in each group.

Question 30. Complete Cytology Status

1 = Complete by not more than 1 year

2 = Complete by not more than 3 years

3 = Complete by not more than 5 years

4 = Totally incomplete at 5 years

5 = Partly incomplete

By complete is meant a negative result at a date (as given in years) prior to an abnormality being found. This gives an indication of the longest possible time a lesion could have been present prior to registration with the CAC and gives a measurement of the speed of progression of the tumour, i.e. length of the pre-invasive phase. Totally incomplete cytology in this context means no cytology baseline in the last 5 years. Partly incomplete means that only a previous abnormal result is known. This section analyses the screening adequacy of patients who develop cervical carcinoma.

Question 31. Length of Known Pre-invasive Phase

The number given is the time in months from the date of the last normal cytology result to the date of registration with the CAC or invasive cytology date (if earlier). This gives the longest time the pre-invasive phase could possibly have been (excepting false negative cytology). Is the preinvasive phase shorter in young women?

Question 32. HPV Status on Cytology

1 = Not present on reviewed slide

2 = Present on reviewed slide

3 = Cytology by report only

4 = No cytology from any source

HPV can be detected by cytology (see Section 1.3). This has been routinely reported only since about 1983 and is therefore new data on the reviewed slides. Cytology numbers, as gleaned from various reports in folders, are not unique to the Groote Schuur laboratory, making the exact retrieval rate of archival material difficult to determine.

The method used to determine the relative proportion of young women in the study from 1974 to 1983, and also in the ensuing time period 1984 to 1988, was a geographically based one, thus making the measured proportions generalizable by correcting for referral bias. For the study period, the exact number

of young women and their domiciles as well as the total number of women was known. Also known was the exact percentage of sampled older women not eligible because of a domicile outside the Cape Town natural geographical area. From this the total number of older women living in the correct area could be estimated and the relative proportion of young women could then be calculated.

A comparison of computer-generated data with data from the manual study shows that programming became reliable for carcinoma of the cervix by 1982. In this way all young patients could be traced from a 1984-1988 patient list (excluding stage IA). The total patient number could also be determined for this time period. A sample of older women was obtained using the next highest numbers system and, finally, all the domiciles were checked manually using the summary control sheets (Figure 1).

2.3 EXCLUSIONS AND LOSSES

Exclusion criteria were applied uniformly to all cases prior to entry into the study. All young women were examined and 91 were excluded and 82 accepted. Random sampling (as described in Section 2.2) was then performed on the older group. If an exclusion was made, it was recorded and the next highest number was proceeded to. In this way 93 older women were excluded by

the time the random sample of 82 was obtained. A total of 1 522 cases of invasive carcinoma of the cervix were registered by the CAC over the period 1974 to 1983 inclusive. Of these, 173 were in the young group and 1 349 in the older group. A total of 82 out of 173 (47,4%) young women were eligible. In the older group, 82 out of 175 (82+93) were eligible, i.e. 46,9%. This translates to 633 patients (i.e. 46,9% of 1 349). Thus the sample size of 82 out of 633 amounts to 13%.

TABLE 1. STUDY EXCLUSIONS.

		YOUNG	OLDER
1	Domicile not in correct area	46	48
2	No Groote Schuur biopsy	25	22
3	Post-surgical (unstaged)	7	6
4	Double primary malignancy	1	10
5	Stump carcinoma	0	1
6	Partly treated elsewhere (1°)	0	1
7	Recurrent carcinoma from elsewhere	1	0
8	Referred from Tygerberg Hospital	1	1
9	Patient refuses treatment	9	3
10	Untreatable	1	1
11	Vault recurrence (after CIN)	0	0
		91	93

The exclusion criteria and the numbers excluded for each group are listed in Table I1. Some of the exclusions in Table I require comment:

1. Domiciles beyond Springbok, Beaufort West and George were excluded for reasons described in Section 2.2.

2. During the 1970's histology from other institutions or private pathologists was not regularly reviewed by Groote Schuur Gynaecological Pathology.

4. It seemed justified to exclude these cases even though there is a vastly different occurrence of double primaries (not necessarily synchronous) in the young and older groups. It is impossible in these cases to judge the true influence of cervical carcinoma on patient survival. Any bias thus resulting (from a possible artificial prolonging of survival in the older group) would tend to make any decreased survival in the young group slightly more obvious.

9. More young patients refused treatment than older patients. These patients were excluded because the study applied to patients who accepted the treatment recommendation for the disease. Any bias (from an artificial prolonging of survival in the young group) would tend to make any decreased survival in the young group slightly less obvious.

10. The untreatable patients consisted of a patient with a single pelvic kidney and advanced disease and another patient with a permanent sigmoid colostomy unrelated to malignancy and advanced disease.

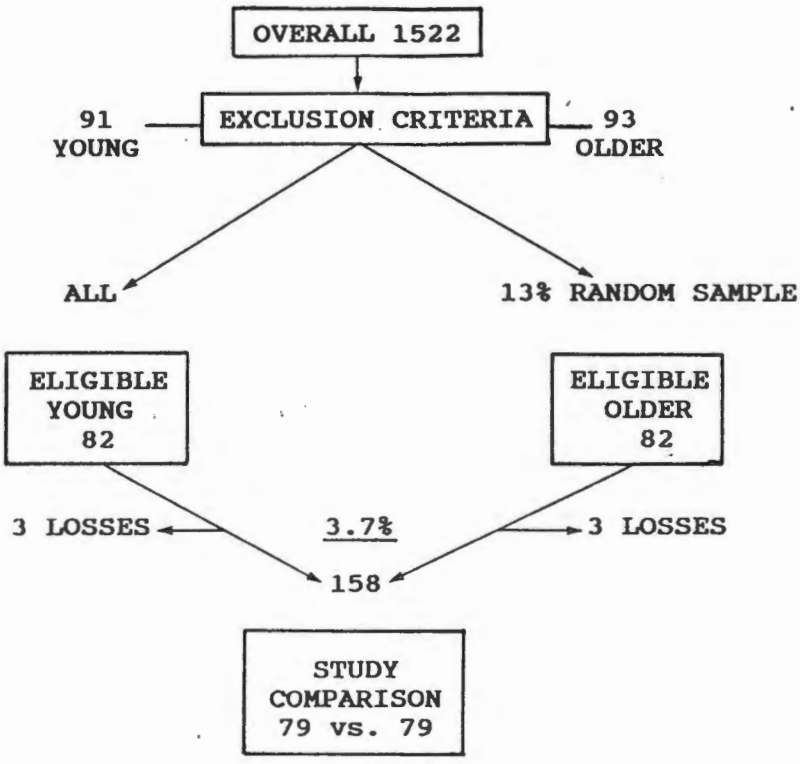


Figure 5. Study Numbers

A total of 164 patients (82 + 82) were entered into the study. Of these, 6 were lost for technical reasons, comprised of 3 losses in each group and leaving 79 patients in each group. The loss amounted to 6\164 or 3,7% of the study. Not a single patient was lost due to lack of information, i.e. all patient records were obtainable. It was possible to obtain 160 satisfactory archival slides out of 164 of the cervical biopsies and other specimens from 1974 to 1983. A total of 2 patients were felt on review of the histology not to have cervical carcinomas, i.e. they had been misdiagnosed in the past. The 6 losses are further detailed in Table II.

TABLE II. STUDY LOSSES.

NO.	AGE	DESCRIPTION
55	27	Yolk sac tumour. Probably secondary spread to the cervix. Palliative radiotherapy. Stage 4.
96	44	Archival material untraceable at the GSH Laboratory. Radiotherapy. Stage 1B.
99	25	Archival material untraceable at the GSH Laboratory. Stage 2B.
106	47	Archival material untraceable at the GSH Laboratory. Stage 2B.
118	59	Serous carcinoma with probable secondary to the cervix. Radical surgery. Stage 1B
143	24	Archival material of biopsy untraceableat GSH Laboratory. Radical surgery. Stage 1B.

The overall study numbers are illustrated in Figure 5.

3. RESULTS

3.1 MISCELLANEOUS PATIENT CHARACTERISTICS

3.1.1 Age

The mean age of patients in the young group was 29,9 years. There were no patients in the under 20 group, 27 patients in the 20-29 group and 52 patients in the 30-34 group. This "doubling up" distribution matches that seen in the literature.[59,60] The two youngest patients were 22 years old (Patient Nos. 43 and 149). The first patient had a Stage 3 Grade 2 squamous carcinoma and she died after 8 months with extensive distant metastases; the second patient had a Stage 2B Grade 2 squamous carcinoma and she was lost to follow-up at 27 months while disease free.

The mean age of patients in the older group was 53,4 years. The oldest patient (No. 78) was 85 years old. She had a Stage 3 squamous carcinoma. There were 32 patients in the 35-49 age group, 42 patients in the 50-75 group and 5 patients older than 75 years. The 42 patients in the 50-75 year group were listed for possible use as a "classical cancer of the cervix reference set" for comparison with the under 35 group in terms of survival.

3.1.2 Race

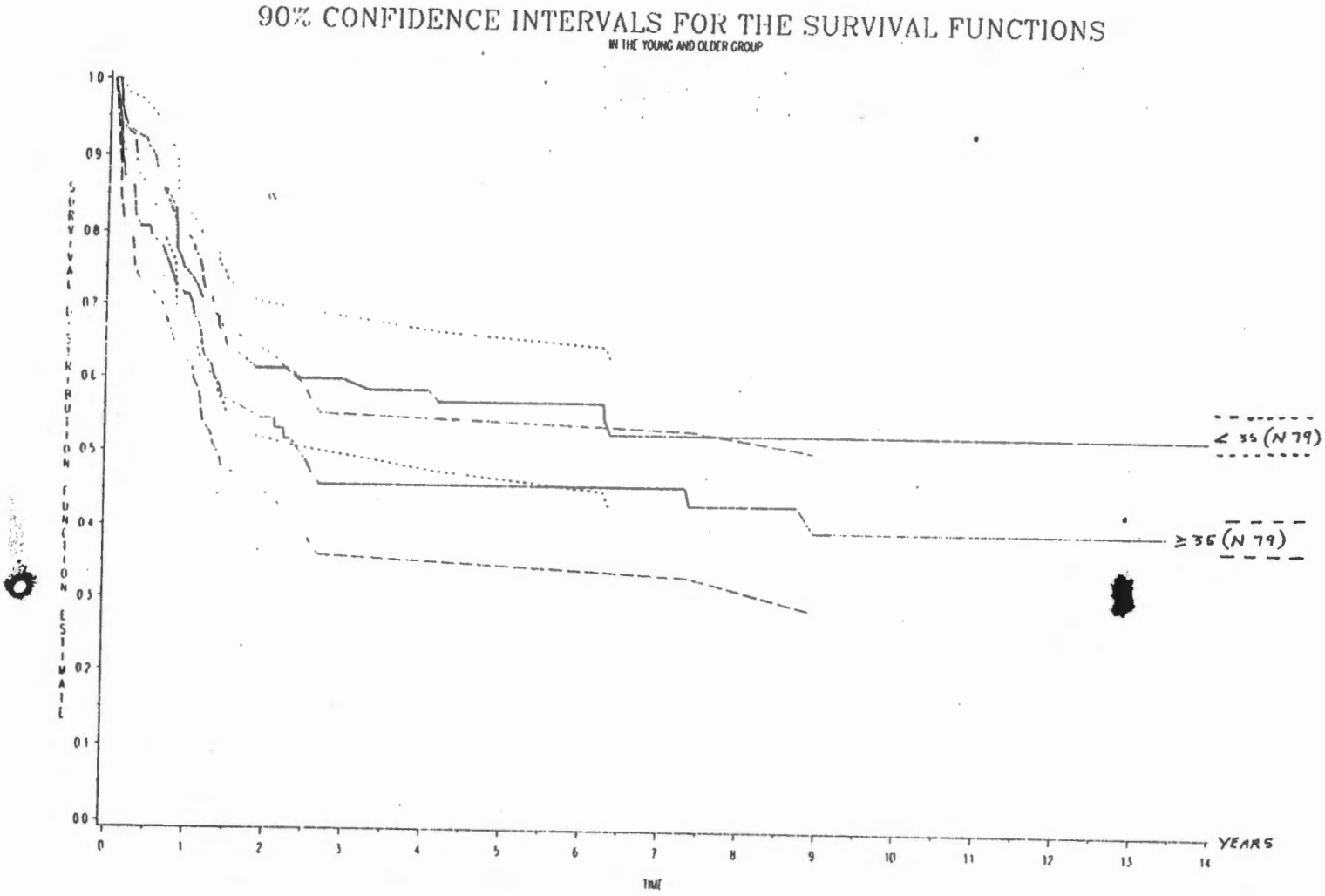
By far the majority of the patients were of the Coloured race group. This group amounted to 76% of

the patients in the older age group and 82% of the patients in the young age group. The proportion of Europeans was respectively 13% and 11% in the two age groups and of Blacks it was 11% of the older and 6% of the young. There was no statistically significant difference in racial distribution between the young and the older patients (Chi-square 1,395 and p = 0,498). See Table III.

TABLE III. RACE DISTRIBUTION

RACE FREQUENCY PERCENT ROW % COL %	GROUP <35 (n=79)	 ≥35 (n=79)	 TOTAL
WHITE	9 5.70 47.37 11.39	10 6.33 52.63 12.66	19 12.03
COLOURED	65 41.14 52.00 82.28	60 37.97 48.00 75.95	125 79.11
BLACK	5 3.16 35.71 6.33	9 5.70 64.29 11.39	14 8.86
TOTAL	79 50.00	79 50.00	158 100.00

Figure 6: Overall survival curves for the two groups.



3.1.3 Parity

An analysis of parity gives the following result: total births in the young group 262; total births in the older group 424. Mean parity in the young group 3,32. Mean parity in the older group 5,37. In the literature the mean parity in cervical carcinoma is between 3 and 4 (for all age groups combined).[58]

3.1.4 Pregnancy

Patients pregnant at diagnosis (including patients up to 6 months post-delivery) amounted to 12, of which 11 were in the young group (92%). The case numbers of these patients are as follows: 15, 21, 41, 61, 63, 77, 85, 93, 105, 107, 151. Of the total number of young patients (i.e. 79), 13,9% were pregnant. This compares with the 17% found by Stanhope et al in 265 young women.[77]

3.2 OVERALL SURVIVAL

A computer generated survival curve based on information from the data record sheet (Figure 2; Questions 18, 15) is shown in Figure 6. This illustrates the overall survival data for the young group versus the older group based on date of entry and date of termination due to death from disease, death from unrelated causes, loss to follow-up or alive at end of study as described by Kaplan and Meier in 1958 and further described by Peto et al.[104,105] Also displayed are the confidence intervals for the data.[107] It can

be seen that the upper 90% confidence interval for the older group is approximately on the survival curve for the young group. The young group has a better survival throughout by 10 to 12%; at 5 years it is 57% in the young and 46% in the older group. It can be seen that for both groups survival stabilizes markedly by 3 years and from between 6 and 9 years onwards there are few deaths.

The events at the termination of the study were distributed as shown in Table IV. As can be seen, follow-up was achieved in almost 80% of the patients. The quality of this follow-up varied but from Question 19 of the data record sheet, selection of numbers 1 and 2 show that 50 out of the 79 young patients (63%) and 57 out of the 79 older patients (72%) had completely adequate follow-up. This difference is not statistically significant ($x^2 = 1.0423$; $p = 0,3073$).

TABLE IV. EVENTS AT TERMINATION OF THE STUDY. (N = 79)

	ALIVE	DIED		LOST	TOTAL
		Ca. Cx.	Other		
<35	24 (30%)	35 (44%)	2 (3%)	18 (23%)	79(100%)
≥35	19 (24%)	42 (53%)	2 (3%)	16 (20%)	79(100%)

Statistical analysis of the two survival curves in Figure 6 using the Mantel Haenszel (or Logrank) test gives a chi-square value of 1,6583 and a p-value of

0,1978[104]. There is thus no significant difference in survival between the two age groups. In the young group the proportion surviving at 5 years is 0,584 and the proportion surviving at 3 years is 0,569. In the older group the proportion surviving at 3 years is 0,455 and the proportion surviving at 5 years is 0,455. At 5 years the observed difference is 0,569-0,455 or 0,114 (11,4%). The power of the logrank test for the observed proportions at 5 years is 0,2912 or 29%. (At 3 years the power is 36%)[108].

3.3 PROGNOSTIC FACTORS

As there is little doubt in the literature that stage is the most powerful of the prognostic factors,[7] the stage distribution of the two groups was tabulated (Table V) to see if an explanation could be found for the overall survival results of Figure 6.

TABLE V. STAGE DISTRIBUTION (N = 79)

STAGE	≤35 YRS (N = 79)	>35 YRS (N = 79)	TOTAL
* 1B	34 (43%	12 (15%)	46
2A	4 (5%)	5 (6%)	9
2B	12 (15%)	11 (14%)	23
3	24 (30%)	41 (52%)	65
4A	4 (5%)	5 (6%)	9
4B	1 (1%)	5 (6%)	6

*Chi-square = 14,994; p = 0,01 for Stage 1B

It can be seen that there is more early stage disease in the young group. Some of the stage groups are very small with 5 or less members. It was therefore decided to combine the stages to give a distribution for early stage disease and late stage disease - a concept with well accepted clinical validity.[27,84] Early stage disease is taken as 1B and 2A and late stage disease as all the rest. Early stage disease indicates operability and late stage disease to a greater extent signifies sytemic disease. This distribution is illustrated in Table VI.

TABLE VI. DISTRIBUTION OF EARLY AND LATE DISEASE

FREQUENCY PERCENT ROW % COL %	GROUP <35 yrs	 ≥35 yrs	 TOTAL
1 & 2A	38 24.05 48.10	17 10.76 21.52	55 34.81
2B - 4B	41 25.95 51.90	62 39.24 78.48	103 65.19
TOTAL	79 50.00	79 50.00	158 100.00

It can be seen that about half (48%) of the young group have early stage disease compared to 22% in the older group (Chi-square 12,300; p = 0,001, 95% intervals 0,1388 to 0,6253 on odds ratio).

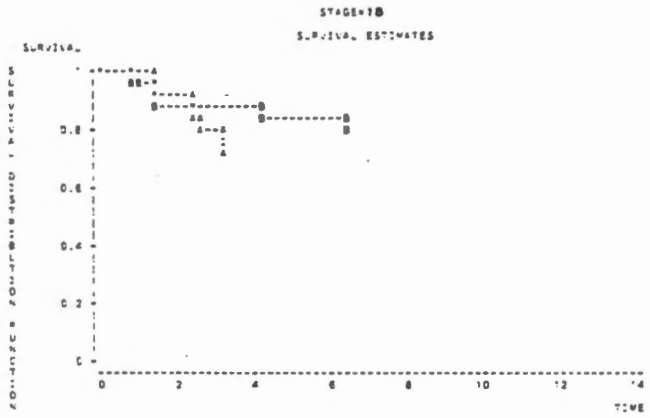


Fig. 7:
Survival comparison for Stage IB.

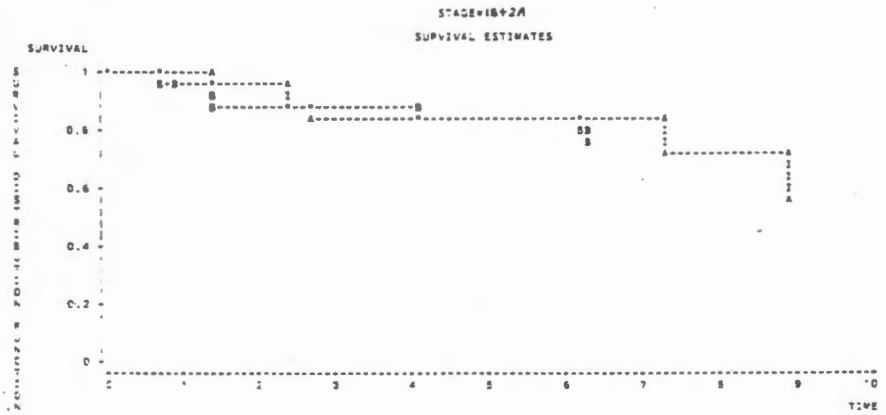


Fig. 8:
Survival comparison for early stage disease.

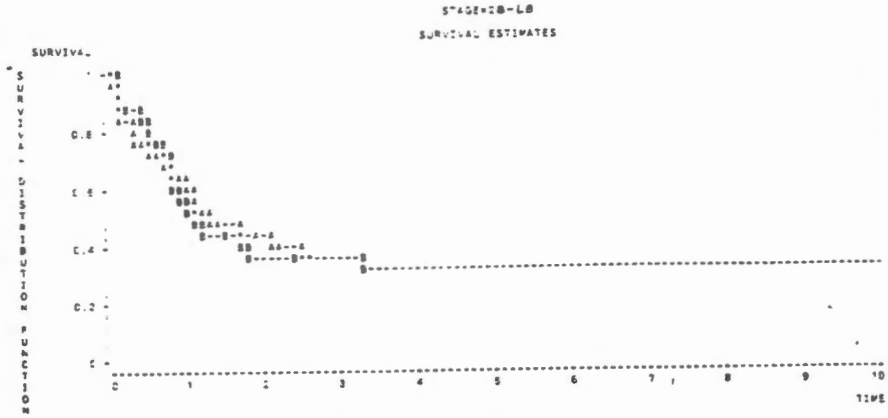


Fig. 9:
Survival comparison for late stage disease.

To remove the confounding effect of stage from the survival estimations of the two age groups, survival curves were computer generated for Stage 1B in the young versus Stage 1B in the older group (Figure 7), early stage disease (1B+2A) in the young group versus early stage disease in the older group (Figure 8) and late stage disease (2B-4B) in the young group versus late stage disease in the older group (Figure 9). As mentioned before, the broader stage grouping into early and late is to increase numbers in the group and enhance the statistical power of the comparisons.

In all three illustrated survival estimates, time is given in years. Curve A is for the older group and curve B marks the young group. The points A or B represent the product limit survival estimates generated by the data (see Section 3.1 for the principle involved)[105]. The asterisks mark points where the curves cross each other. The curves do not cover the full 15 years because of limitations by the censored data.[105]

The next prognostic factor considered was <u>tumour size</u> (Question 7 of Figure 2). In the young group 8 tumours were of unclear size and in the older group 7 were unclear in size, while in the young group 17 tumours were less than 3 cm diameter compared to 8 in the older group. When this difference was corrected for stage it was found that all 17 small tumours in the young group and all 8 small tumours in the older group

were in early stage disease. If one considers that there are 38 early stage tumours in the young group and 17 in the older group (Table VI) there is clearly no significant difference in the distribution of tumour size between the two groups.

There were a total of 25 clinically endocervical tumours, 17 in the young group and 8 in the older group. Of these, 9 occurred in early stage disease in the young versus 3 in the older group. Two stage-stratified contingency tables are presented for this data (Table VII).

TABLE VII. ENDOCERVICAL TUMOUR DISTRIBUTION BY AGE.

	<35 YRS	≥35 YRS	TOTAL
EARLY STAGE	17	38	55
Endocervical	3 (18%)	9 (24%)	12
Not endocervical	14	29	43
LATE STAGE	62	41	103
Endocervical	5 (8%)	8 (20%)	13
Not endocervical	57	33	90
TOTAL	62	41	103

Fisher's Exact Test: p = 0,0806

Of these 25 tumours 7 were non-squamous (4 in the young group (24%) and 3 in the older group (38%).

Tumour grade was the next prognostic factor to be analysed (Question 23, Figure 2). It was noted that 20 patients were inadvertently not graded during the his-

tological review and therefore they were not included for analysis. Of these, 9 patients were in the young group and 11 in the older group. These were all squamous tumours. The remaining squamous tumours in the study (125) were comprised of 62 in the young group and 63 in the older group (note that these figures are derived after removal of the non-squamous tumours - see next paragraph). It was felt that Grade III tumours might carry a worse prognosis and a distribution for these tumours was obtained for the two groups. The result are shows 22 Grade III tumours out of 62 (35%) in the young group versus 17 Grade III tumours out of 63 (27%) in the older group - clearly there is no significant excess of high grade tumours in the younger age group (Chi-square = 0,6929; p = 0,4051).

There were 13 <u>non-squamous tumours</u> out of 158; 8 in the young group (10%) and 5 in the older group (6%). These tumours can be tabulated as follows: (Table VIII).

TABLE VIII. NON-SQUAMOUS TUMOURS

STUDY NO.	<35 YRS	STUDY NO.	≥35 YRS
45	Adenocarcinoma	10	Adenocarcinoma
53	Adenocarcinoma	30	Adenocarcinoma
63	Adenocarcinoma		
73	Adenocarcinoma		
95	Adenocarcinoma		
97	Adenocarcinoma		
		52	Adenosquamous
83	Adenosquamous	110	Adenosquamous
119	Adenosquamous	126	Adenosquamous

It is of interest to note that in the entire study of 158 patients a mucin stain was only used 9 times (6%) (4 times in the young group and 5 times in the older group). Three of these 9 proved mucin positive (1 in the young group and 2 in the older group). Also of interest is the fact that 4 of the 8 (50%) non-squamous tumours were endocervical in the young group and 3 out of 5 (60%) in the older group. If one considers only adenocarcinomas the figures rise to 67% and 100% respectively.

To determine if the excess of adenocarcinomas in the young group represents a significant difference, a contingency table was drawn up (Table IX) and Fisher's Exact Test performed.

TABLE IX. ADENOCARCINOMA BY AGE GROUP.

	YOUNG <35 YRS	OLDER ≥35 YRS	TOTAL
Adenocarcinoma	6 (8%)	2 (3%)	8
Not adenocarcinoma	73	77	150
TOTAL	79	79	158

Fisher's Exact Test: p = 0,1381

Lymph node involvement by cervical carcinoma was the next prognostic factor examined (Question 9, Figure 2). Analysis was made difficult by the stage skewing in the two groups. Far more lymph node sampling was done in the young group, i.e. 33 versus 7. In the young group 7 out of the 33 samples proved positive (21%) and in the older group 2 out of the 7 (29%). The young group comprised 30 Stage 1B's and 3 Stage 2A's. Of the latter, 1 patient had positive nodes. Thus, for Stage 1B in the young age group, 6 out of 30 sampled patients had positive lymph nodes (20%). All the sampled patients in the older group were Stage 1B. (See Table X).

TABLE X. STAGE IB POSITIVE NODES BY AGE GROUP

SAMPLED STAGE IB	YOUNG <35 YRS	OLDER ≥35 YRS	TOTAL
Nodes Positive	6 (20%)	2 (29%)	8
Nodes Negative	24	5	29
TOTAL	30	7	37

Fisher's Exact Test: p = 0,4793

Tumour recurrence data (Questions 11, 12, 13, 14; Figure 2) showed, firstly, that complete tumour regression was not achieved in all patients by the completion of treatment. In the young group there were 14 (18%) residual tumours and in the older group 20 (25%) residual tumours. All these occurred in late stage disease. As the proportion of late stage disease in the old versus the young is 3 to 2 (i.e. 62 cases v. 41 cases, see Table VI) there is no significnt difference in residual disease between the two groups. The number of tumour recurrences recorded for the young group is 20 and for the older group 18, while the mean time to recurrence is 22 months in the young and 23 months in the older group. This latter data is dependent on follow-up information. Table IV shows that 61 (77.2%) in the young group and 63 (79.7%) in the older group had follow-up information. Recurrence data (Question 11 of Figure 2) were not entered except for these

cases. This gives 20 out of 61 in the young group and 18 out of 63 in the older group having disease recurrence, i.e. 33% versus 29%. This difference is not significant. It is possible that recurrence data in the older group is under-represented because of old patients in the lost group who conceivably "give up" when the disease recurs and do not return for follow-up. In general, survival in patients who develop recurrent disease ranges from 3,5 to 11% and recurrence is equivalent to death from disease.[23]

In the young patients there were 11 peripheral recurrences (i.e. distant metastases) out of 20 (55%) compared to 6 out of 18 (33%) in the older group. Of these, 4 occurred in early stage disease in the young group and 2 in early stage disease in the older group. The distribution of distant metastases (non-contiguous recurrent disease or both; see Question 12) between the age groups is given in Table XI. The actual sites of metastases are shown in Table XII.

TABLE XI. DISTANT METASTASES BY AGE GROUP

RECURRENCE	YOUNG <35 YRS	OLDER ≥35 YRS	TOTAL
Distant	11 (55%)	6 (33%)	14
Contiguous	9	12	21
TOTAL	20	18	38

Chi-square = 1,0292; p = 0,3103

TABLE XII. SITE OF DISTANT METASTASES.

NO.	YOUNG GROUP	NO.	OLDER GROUP
7	VT node	6	VT node
9	VT node	16	Hepatic
13	VT node + hepatic	32	Hepatic + pulmonary
29	VT node + brain	92	Brain + pulmonary
33	VT node + pericardium	108	Brain + pulmonary
43	Hepatic	150	Bone
59	Malignant ascites		
65	Brain + pulmonary		
105	Pericardium		
127	Pulmonary, breast, bone		
157	Pulmonary + bone		

The histological type of the recurrent tumour corresponded with that of the primary tumour in all the 5 biopsies that were done in the older group and in 10 of the 11 biopsies in the young group. Individual inspection of the non-corresponding case (29) shows it to be from a 33 year-old patient with a Stage 3 squamous carcinoma as the primary tumour. The tumour was Grade 2. A mucin stain was not used. The tumour recurred 28 months later as widespread distant metastases (pulmonary, breast, bone). Biopsy at that stage revealed a poorly differentiated adenocarcinoma. She died 11 months later.

Of the 20 recurrences in the young group, 7 occurred in early stage disease (35%) and of the 18

recurrences in the older group 4 occurred in early stage disease (29%).

Of the 38 recurrent tumours in the overall study, 16 were biopsied - 11 in the young group (55%) and 5 in the older group (28%). (See Questions 13 and 22, Figure 2). This distribution is shown in Table XIII.

TABLE XIII. BIOPSY OF RECURRENCE BY AGE GROUP

RECURRENCE	YOUNG GROUP	OLDER GROUP	TOTAL
Biopsied	11 (55%)	5 (28%)	16
Not biopsied	9	13	22
TOTAL	20	18	38

Fisher's Exact Test: p = 0,5275

The results of the evaluation of the length of the preinvasive phase in the two age groups as detected by cytology are now presented (Question 32; Figure 2). Of the 158 patients only 14 had results of negative cytology performed in the preceding 5 years. Of these, 8 were in the young group and 6 in the older group. The mean time from negative cytology to diagnosis of carcinoma was 20 months in the young group (range 7-36 months) and 24 months in the older group (range 4-53 months). In a total of 4 patients in the young group this preinvasive phase was 12 months or less, while in the older group 3 patients fell into this category.

Of the remaining 144 patients, 7 (3 young, 4 older) had partially incomplete screening results (See Question 3, Figure 2) and 137 had no cytology result available prior to diagnosis (i.e. 87%). A total of 95 patients had cytology results available at diagnosis (Question 29) (51 young, 44 older). Of these, 75 (78,9%) gave the diagnosis of an invasive lesion. In the young group there were 37 and in the older group 38; with corresponding false negative results of 14 (27%) and 6 (14%). Only 4 in the young group and 1 in the older group were totally negative (i.e. not even a preinvasive lesion detected), giving truly false negative rates of 8% in the young and 2% in the older group. See Table XIV.

TABLE XIV. TRULY FALSE-NEGATIVE CYTOLOGY DISTRIBUTION

	YOUNG GROUP	OLD GROUP	TOTAL
FALSE NEGATIVE	4	1	5
TRUE POSITIVE	47	43	90
TOTAL	51	44	95

Fisher's Exact Test: p = 0,2303

3.4 TREATMENT TYPE AND COMPLICATIONS

The mode of primary treatment (Question 8, Figure 2) is highly dependent on both disease stage and patient age. Overall, 103 patients received radical radiotherapy as

the primary mode of attempted cure and 30 patients received only radical surgery. It should be noted (from Section 3.3 on lymph node sampling) that a total of 40 patients were initially subjected to a surgical attempt at cure. In only 31 cases (78%) was a curative procedure possible. In 14 patients in the study, palliative treatment only was given and in 11 cases no treatment was recommended. A breakdown of the primary treatments according to disease stage (i.e. early stage or late stage) and patient age (young or older) is given in Table XV.

TABLE XV. TREATMENT ACCORDING TO AGE AND STAGE

	YOUNG GROUP (<35) Stage		OLDER GROUP (≥35) Stage		TOTAL
	Early	Late	Early	Late	
RR	13 (16%)	34 (43%)	12 (15%)	44 (57%)	103
RS	25 (32%)	0 (0%)	5 (6%)	0 (0%)	30
PR	0 (0%)	4 (5%)	0 (0%)	8 (10%)	12
PS	0 (0%)	1 (1%)	0 (0%)	1 (1%)	2
NT	0 (0%)	2 (3%)	0 (0%)	9 (11%)	11
	38	41	17	62	158

RR = Radical Radiotherapy; RS = Radical Surgery
PR = Palliative Radiotherapy; PS = Palliative Surgery
NT = No Treatment

There appear to be clear differences in the young and older group with regard to use of radical surgery in early stage disease (32% versus 6%). Reference to Table VI shows that there are 38 early stage cases in

the young group versus 17 in the older group. A contingency table shows the following distribution (Table XVI).

TABLE XVI. RADICAL SURGERY BY AGE GROUP

YOUNG GROUP	OLDER GROUP	TOTAL	
SURGERY	25	5	30
NO SURGERY	13	12	25
TOTAL	38	17	55

Chi-square = 4,8877; p = 0,0270

It can also be noted from Table XV that more of the older patients were not offered any primary treatment (9 patients v. 2 patients), probably in keeping with the more advanced nature of the disease in this group (see Table V). Of the older group 51 had Stage 3 or 4 disease compared to 29 in the young group; more importantly, 10 had Stage 4 compared to 5 in the young group.

Treatment of recurrent disease (Question 14, Figure 2) was assessed to see if there was any difference in intensity of secondary treatment in young versus older patients. Reference to Table XI shows 20 recurrences in the young group versus 18 in the older group. The distribution of treatment is shown in Table XVII. No patient in the study had pelvic exenteration

performed. Chemotherapy was not systematically or extensively used during the study period (1974-1983) but was sometimes combined with other secondary treatment modalities; recorded here are those cases where it was used alone. (Table XVII).

TABLE XVII. TREATMENT OF RECURRENT DISEASE

SECONDARY TREATMENT	INITIAL STAGE			
	Young Group		Older Group	
	Early	Late	Early	Late
Nil	2	7	2	9
Full dose irradiation	4	2	1	2
Palliative surgery	1	0	0	0
Chemotherapy only	0	2	0	1
Reduced dose irrad.	0	2	1	2
TOTAL	7	13	4	14

Examination of the table does not show any apparent bias towards younger women except in full-dose irradiation for recurrent early stage disease - which would be expected because of the increase use of surgery as primary treatment in this group.

Returning to primary therapy, the relative major complication rates of the various treatment modalities were assessed after one year (see Question 10, Figure 2).

In the young group, 26 (51%) patients out of 51 treated had no treatment complications worth mentioning after one year compared to 23 (49%) out of 47 treated

patients in the older group. (In both groups patients with residual disease or recurrent disease before 1 year were excluded as were those lost to follow-up). In the remaining patients there were 9 major complications requiring surgery, 5 in the young group and 4 in the older group (See Table XVIII).

TABLE XVIII. TREATMENT COMPLICATIONS AFTER 1 YEAR.

	YOUNG GROUP (n = 51)	OLDER GROUP (n = 47)
POST SURGERY	Laparotomy for chronic lymphocyst	Nil
	Hot flushes x3 Bladder symptoms x2 Chronic wound sinus x1	
POST RADIOTH.	Nephrectomy	Bowel resection
	Urinary diversion	Bowel resection
	Death (rectal necrosis)	Death (sepsis from bowel obstruction)
	Hot flushes x2	Hot flushes x1
	Bladder symptoms x1	Bladder symptoms x2
	Vaginal stenosis x7	Vaginal stenosis x8
	Chronic bowel symptoms x4	Chronic bowel symptoms x9
	Total 25	Total 24

It can be seen that there were two deaths, one from each group, both resulting from radiotherapy. If one compares the complications of surgery versus radiotherapy in the young group where 32% had radical surgery (see Table XV), it appears that radiotherapy

gives more serious complications. Note that the complications which are recorded are the ones that caused real problems for the patient and dominated the follow-up visits. The single most troublesome complaint was selected.

If one compares the radiotherapy complications in the two groups, there are few differences. What is of note in the young group is the large vaginal morbidity of radiotherapy.

3.5 EVIDENCE OF HUMAN PAPILLOMAVIRUS INFECTION

The histology slides of all 158 patients in the study were examined for histological evidence of HPV infection (see Section 1.2). This information was not reported before in the original filed reports. Analysis of Questions 26 and 27 (Figure 2) gives the following results:

There were 18 cases positive for HPV in the young group and 7 positive in the older group. However, there were also more evaluable cases (i.e. cases with non-neoplastic epithelium present on the slide) in the young group, i.e. 46 versus 25. To determine if a significant difference was present in the distribution of HPV between the young and the older group in the 71 evaluable cases, a contingency table was drawn up (Table XIX). Evidence of HPV was found in one case of adenocarcinoma and in a case of adenosquamous carcinoma - both in the young group. The overall HPV pickup rate

for all the 71 evaluable cases was 25 (or 35%). In the entire study of 158 cases of cervical carcinoma, 25 cases (16%) could be found to have HPV present.

TABLE XIX. DISTRIBUTION OF EVALUABLE HPV

	YOUNG GROUP <35 YRS	OLDER GROUP ≥35 YRS	TOTAL
HPV Present	18 (39%)	7 (28%)	25
HPV Not Present	28	18	46
TOTAL	46	25	71

Chi-square = 0,4593; p = 0,4979

Examination of cytology data in Section 3.3 showed that only 7 patients had abnormal cytology results available prior to diagnosis and a further 90 had abnormal results available at diagnosis. (Note that the cytology laboratory stores only abnormal slides). Thus there were potentially 97 slides available for review, an unknown proportion of the 97 reports being from outside cytologists. A total of 48 slides were ultimately obtained after a full search of the cytology archival material, 1974-1983. (Unlike the histology section, lack of cytology done at Groote Schuur Hospital was not made an exclusion criterion for the study). There were 23 slides available in the young group and 25 slides available in the older group. A total of 10 slides (21%) were positive for HPV by cyto-

logical criteria, 6 in the young group and 4 in the older group. These results are displayed in Table XX.

TABLE XX. HPV AT CYTOLOGY

	YOUNG GROUP <35 YRS	OLDER GROUP ≥35 YRS	TOTAL
HPV Present	6 (26%)	4 (16%)	10
HPV Not Present	17	21	38
TOTAL	23	25	48

Fisher Exact Test: p = 0,307

To determine the correlation between histology and cytology, the 10 HPV-positive cytology cases were cross-referenced with the histology result. The result is shown in Table XXI.

TABLE XXI. CASES WITH POSITIVE CYTOLOGY VS. HISTOLOGY

CASE	CYTOLOGY	CYTOLOGY HPV	HISTOLOGY HPV WITH COMMENT
46	Malignant	+ve	-ve Not evaluable
47	Malignant	+ve	+ve Evaluable
51	Malignant	+ve	+ve Evaluable
61	Malignant	+ve	-ve Evaluable
67	Malignant	+ve	-ve Evaluable
78	Malignant	+ve	-ve Not evaluable
111	Malignant	+ve	-ve Not evaluable
144	Malignant	+ve	-ve Evaluable
153	Malignant	+ve	-ve Evaluable
154	Malignant	+ve	-ve Not evaluable

Table XXI shows that 7 of the cases with HPV-positive cytology could be checked against the

histology (i.e. adjacent non-neoplastic epithelium was present in 7 of the corresponding histology specimens). In these, the majority, i.e. 5 out of 7, were negative, demonstrating a lack of positive correlation between cytology and histology in the detection of HPV infection.

3.6 THE PROPORTION OF YOUNG PATIENTS

This was determined on a geographical basis, making use of the patient's usual home address as the inclusion or exclusion factor; otherwise all registered cases of invasive carcinoma of the cervix were included in the calculations (see Section 2.2).

The total number of young patients for 1974-1983 was 173. Of these 46 did not live in the correct area and 127 did (73,42%). (see Section 2.3). The total number of older patients was 1349. Of these a sample of 175 was taken (of which 82 were ultimately eligible for the study and 93 were excluded). Of these, 48 did not live in the correct area and 125 did (71,43%). Applying the latter proportion to all the older cases gives 71,43% x 1349 = 964 older patients in the correct geographical area.

The proportion of young women is given as 127 in 964 + 127, i.e. 127 in 1091 or 11,6%.

To see whether the proportion of young women changed during the subsequent 5-year period directly

following the study and included in its follow-up period, i.e. 1984 to 1988 inclusive, calculations were made as follows: a computer printout was obtained of all cases of invasive carcinoma of the cervix for this time period (Comparison of computer data with manual data over the years 1981, 1982 and 1983 showed that the computer data was fully reliable in terms of registration data by 1982). This yielded a total of 879 patients. Of these, 122 were less than 35 years of age and 757 equal to or older than 35 years of age. The patient's usual home address could not be obtained from the computer. A manual sample was therefore taken of the patient records and the data obtained from here (see Section 2.2) is as follows: (Table XXII).

TABLE XXII. DISTRIBUTION OF USUAL DOMICILE

DOMICILE	YOUNG GROUP	OLDER GROUP	TOTAL
Correct area	83 (68%)	101 (83%)	184
Incorrect area	39	21	60
TOTAL	122	122	244

Chi-square = 6,3873; p = 0,0149

In the 1984 to 1988 period, the correct (local) domicile in the young was 68% (compared to 73% for 1974-1983), while the correct domicile in the older patients was 83% (compared to 71% for 1974-1983).

Applying these new proportions to the patient list of 1984 to 1988 yields 83% x 757 = 628 older patients from the correct geographical area.

The proportion of young women is given as 83 in 628 + 83, i.e. 83 in 711 or 11,7%!

3.7 STATISTICS AND MULTIVARIATE ANALYSIS

The statistical analyses have mostly been reported simultaneously with the results. The results have been mostly categorical data.

The main body of these statistics involves the parameter of rate, known also as proportion. A rate is obtained for the young group of a certain event and a rate is obtained for the older group of a certain event and the two rates are then compared after being displayed in a contingency table. The statistical method of comparing rate is the chi-square test.[109] There are a number of modifications of this test to accommodate numbers smaller than 10 per cell, e.g. the Yates continuity correction for cell frequencies of 5 to 9 and the Fisher exact probability test for cell frequencies of less than 5. The alpha value has been taken as 0,05 throughout and it has been used for a two-tailed phenomenon.

The survival curves have been constructed and interpreted in the standard way described by Peto et al.[104] The curves have been generated using the

standard method of nonparametric estimation from incomplete observations of Kaplan and Meier.[105]

Statistical comparison of survival curves is by the standard logrank method (the Mantel-Haenszel test[104]). These complex mathematical functions were conducted for this study by the Institute for Biostatistics of the Medical Research Council in Parow. All the numerical data for the graphs and statistics are in the possession of the investigator. The chi-square computations were conducted on a personal computer by the investigator using the "Epistat" statistics program.

Further analysis of the survival data for confounding variables is described further below but essentially it involved (a) stratifying the data for unconfounded logrank comparisons (smaller studies within a study); (b) a proportional hazards general linear model procedure.[98] (Multivariate Analysis).

As described in Section 3.1, there is no significant difference in survival between the young and the older groups even when compared stage for stage. There is the possibility that other confounding factors are obscuring a significant difference, e.g. type of treatment or type of tumour.

A survival curve was generated for treatment type and displayed according to early stage of late stage

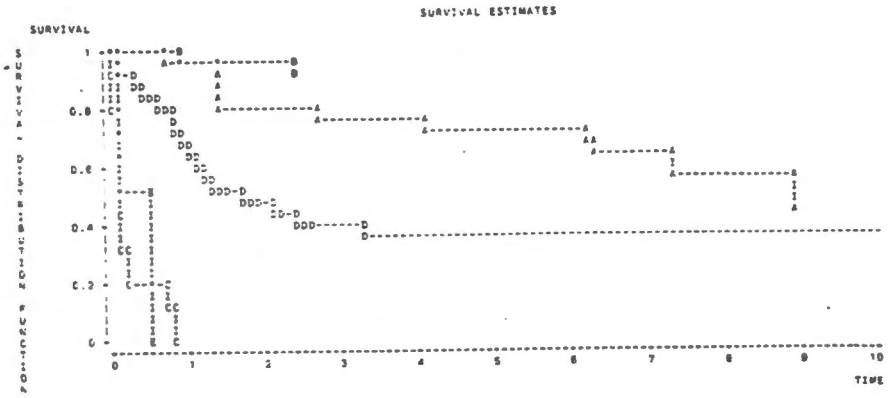


Fig. 10:
Survival comparison for treatment type by stage.

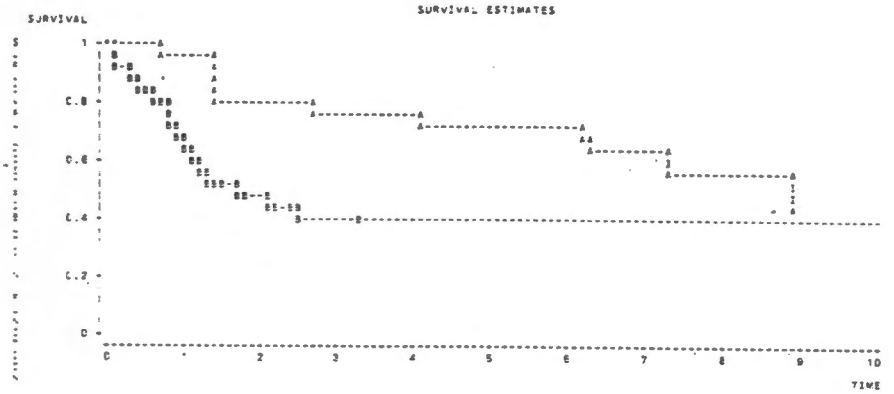


Fig. 11:
Overall survival estimates for radiotherapy in squamous carcinoma.

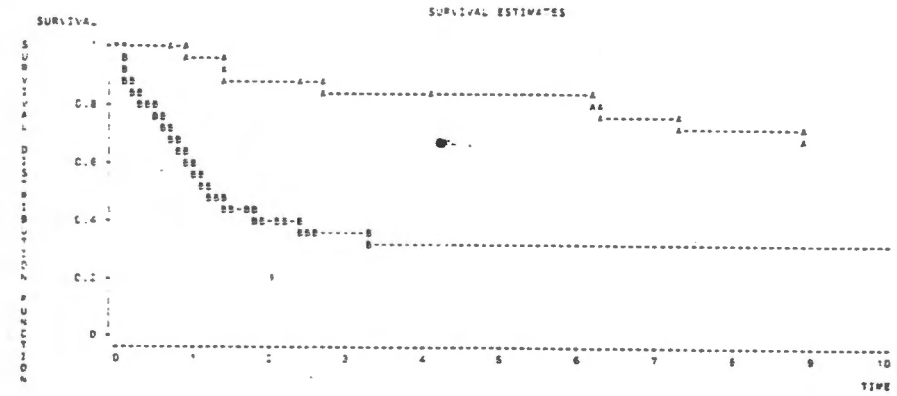


Fig. 12:
Overall early stage versus late stage survival.

(Figure 10). Refer to Section 3.4, Table XV for the relevant numbers.

To remove the possible confounding effect of tumour type on survival, a homogeneous treatment modality was selected (Radiotherapy, to give the largest patient numbers) for a specific tumour type (squamous carcinoma to give the largest patient numbers) and survival was then compared in the two age groups. See Figure 11). Using this data and also previous stage distribution data (see Section 3.3.) for covariate correction of the Mantel-Haenszel test a chi-square of 1,9312 and a p-value of 0,1646 were obtained. This gave the best evidence so far in the study that a difference might be present, but it was not significant.

To graphically illustrate the effect of stage, the study patients were divided into early stage disease (n = 55) and late stage disease (n = 103), irrespective of age group. The survival graphs are illustrated in Figure 12. The difference in survival is highly significant: chi-square - 28,703842 and p = 0,0001.

Using all the illustrated covariate information generated so far by stratifying the information in the Mantel-Haenszel equations, the following results can be tabulated (Table XXIII):

TABLE XXIII. SIGNIFICANCE OF PROGNOSTIC VARIABLES

VARIABLE	CHI-SQUARE	p-VALUE
Disease stage	28,7038	0,0001
Age group	1,9312	0,1646
Treatment type	2,3900	0,1221
Tumour type	2,4405	0,1182

All the previous statistical work has, by univariate stratifications, diminished the power of the study to detect a real difference (by effectively reducing comparison numbers). The univariate analysis is not able to test the simultaneous effect of all the covariables on all the data. This effect can be achieved by multivariate analysis,[98] which, in dealing with survival data, makes use of the proportional hazards method best described by Cox. By using this method the confounding effect of the disease stage difference between the two comparison groups (young and older) is effectively removed and the only factor affecting study power now becomes study number. The full effect of the large study number of 79 + 79 can be used.

A multivariate analysis was performed on the data by the Medical Research Council Institute for Biostatistics based on the general formula:

$\lambda(t : z) = \lambda o\ (t)\ e^{z\beta}$

where

$\lambda(t : z)$ is the hazard function (i.e. instantaneous rate of failure at $T = t$), z denotes the covariates, ß the regression parameter, and $\lambda o(t)$ an arbitrary baseline hazard function.

The result of the multivariate analysis shows that, as in the logrank analysis earlier, the age effect is non-significant (p = 0,8498). The estimated 95% confidence interval for ß is -0,502 <ß<0,414. This interval includes 0 and supports the hypothesis-test result (i.e. p-value). The obtained value for ß (excluding the given confidence intervals is -0,04430092. This indicates that the older age group has a decreased hazard function (being a negative sign), although this finding is not significant. In other words, the older age group has a non-significant, relatively decreased hazard of death. This is discussed further in Section 4.

The key statistical findings of the multivariate analysis are displayed in Table XXIV.

TABLE XXIV. MULTIVARIATE ANALYSIS OF AGE GROUP AND DISEASE STAGE IN DEATH FROM CERVICAL CARCINOMA.

Chi-square	0,04
p-value	0,8498
Age ß	-0,04430092
95% Confidence	-0,502 <ß>0,414

DISCUSSION

The study was motivated by the conflicting evidence in the literature on the nature and prognosis of cervical carcinoma in young women. A number of reports have concluded that there are important differences in disease characteristics and/or survival in young women compared to their older counterparts.[24,40,42,61,64,69,70-79,80,96] Conversely, there is a considerable body of evidence that no such differences exist in young women.[27,37,39,48,59,63,81-95]

The personal feeling of those working closely with the disease prior to the study was that there may well be important differences in the disease in young women and in particular that their survival might be worse, especially in early stage disease. The study had the added motivation of resolving the issue in a local context where patient populations differ from those reported in the literature.

List of Findings

The study generated a large number of findings. For ease of reference they are given below in list form.

There is no significant overall difference in survival between young and older women, they have a similar follow-up attendance, there is a significantly different stage distribution between the groups, there is no significant difference in tumour size for stage or

endocervical tumour site between the two groups or any significant excess of high grade tumours or adenocarcinoma or non-squamous tumours in general in the young group, as well as no significant difference in metastasis to lymph nodes. There is no difference in residual disease following correction for stage, no significant difference in rate of recurrence or mean time to recurrence, no predilection for early stage recurrence in the young and no significant difference in rate of distant metastasis or site of metastasis. Recurrences are treated with a similar intensity in the two groups and there is no significant difference in the number of recurrences biopsied. There is no evidence of a significantly shorter preinvasive phase of the disease in young patients or a higher false negative cytology rate.

There is a significant difference in type of treatment given in the two groups with surgery being more favoured in the young. There is no difference between the age groups in the overall number of patients with treatment complications.

Compared to radiotherapy, the complications of surgery seem less severe in the young. Vaginal stenosis occurs with similar frequency in both groups following irradiation. Evidence of Human papillomavirus (HPV) is found in 35% of evaluable histology slides and in 21% of cytology slides of cervical carcinoma. There is no significant excess of HPV in the young group. There is a lack of positive correlation between histological and

cytological assessment of HPV. Invasive cervical carcinoma is fairly common in women between 20 and 35 years of age. There is no recent increase in the local proportion of young patients with cervical carcinoma; however, a greater number of young patients are being specially referred to Groote Schuur Hospital. Analysis of survival in the two groups corrected for the confounding variables of stage, tumour type and type of treatment shows no significant difference in survival rate, even after formal multivariate analysis. In the latter analysis the older group shows a small, non-significant reduction in the hazard of death.

Further notable findings are that the overall survival curves have a long term shape compatible with that found in the literature, while the age distribution in the young group is similarly compatible, as is their pregnancy rate. The race distribution in the two study groups is similar. A mucin stain was used in only 6% of cases, while in 1 out of 11 biopsied recurrences of squamous carcinoma in young women a previously undiagnosed adenocarcinoma was found. The study patients have sparse previous cytology results. Tumour type and treatment type do not significantly affect survival, while stage has a profound effect on survival.

A summary of the positive findings of the study is as follows: There are significantly more stage 1B tumours in the young group ($p = 0,01$), surgery is used significantly more often in young patients ($p = 0,027$)

and the difference in survival between disease stages is highly significant (p = 0,0001).

STUDY ACHIEVEMENTS

It can be seen from the study findings that the study objectives (Section 1.4) have largely been achieved. As most of the findings were of a negative or "no difference" nature, any further division of the study into smaller "studies-within-a-study" as originally envisaged in the study protocol, e.g. "comparison of the group under 35 with a classical group aged 50 to 75", etc., was resisted, and instead the analytical method of multivariate analysis was resorted to conserve the study's power to detect a real difference[98] (thus achieving the stated objective of maximizing the chance of finding a real difference). For similar reasons some of the very extensive subcategorization in the data collection sheet was ultimately avoided in the data analysis. A few aspects of the data (i.e. Questions) were not used at all as it became clear during the practical collection of the data that the information sought was incomplete or non-objective. Thus, results are not presented for Question 16 (Direct cause of death) or Question 25 (Angiolymphatic permeation status). In the former case this is seldom described in recorded information beyond vague terms and in any case death often ultimately occurred at home. In the latter case the assessment of angiolymphatic space (i.e. preformed space, or channel)

invasion could not be done on punch biopsy histological material and this precluded most of the study subjects.

STUDY DESIGN

The overall study design (Figure 5) follows a well recognized format.[98,99,101] Of note is that a random sample is used for the older group. All sampling is subject to an inherent random sampling error, i.e. the mean of the sample will not fall exactly on the mean of the population; however, a greater than 10% sample, as in this study which used 13%, can generally be considered to be adequate.[109] In the Materials and Methods section it may further be noted that various exclusion criteria were used (Table I), some of which have a skewed distribution between the two age groups. The effect of excluding the many older patients with a second malignancy, although making for a more accurate estimation of survival in cervical carcinoma, will possibly tend to reduce the hazard of death in the older group thereby making any decreased survival in the young group more obvious.

PATIENT SURVIVAL

The major result of the study is the survival analysis, as this is the practical measure of any difference in cervical carcinoma in young versus older women. Any significant difference detected in survival would have major implications for screening programs, treatment protocols and aetiological analyses. It is not sufficient to display survival data as a mean value, e.g. "mean sur-

vival 37 months", as this is notoriously inaccurate.[104] The Life Table method, which is a graph or table giving an estimate of the proportion of a group of patients that will still be alive at different times after randomization, calculated with due allowance for incomplete follow-up, is the only generally accepted way to present and analyse such data.[104]

This study fails to show a significant difference in survival between the two age groups. Comparing the two survival curves uncorrected for confounding variables gives a p-value of 0,198. As the observed difference between the groups is low (of the order of 10 to 12%), the power of the logrank test (at its maximum 3-year value) is only 36%.[108] Therefore, this study shows that for the actually observed data the 98% chance of being 80% sure of showing a significant difference is only 36% (at α = 0,05 and ß = 0,20). On the other hand, as the pre-study power calculation (see Section 1.4 and 2.2) showed, an 80% chance of finding a real difference would have occurred if the difference in survival between the two groups had been observed to be in the region of 50%. This study might therefore be missing a real difference in survival if this difference should be less than 50%, even though the achieved result shows "no significant difference in survival". Alternatively, it is highly improbable, given the actual results of this study, that the difference in survival between young and older patients is <u>greater</u> than 50%.

Most of the studies in the literature support the conclusion that there is no worse survival in young versus older patients with cervical carcinoma[27,37,39,40,48,59,61,63,64,81-95]. One of the most important of these studies, that by Meanwell et al, 1988. was done on 10 022 patients to determine the prognostic effect of age[59]. They divided patients into under 40 years and greater than or equal to 40 and found 5-year survival for the young group to be 69% and for the older group to be 45%. The overall survival difference, unlike the present study, was found to be significant (logrank p-value <0,0001); however multivariate analysis for 9 covariables showed that age was, if anything, a small but favourable factor. Similarly, another modern study on 2011 patients using adequate statistics including multivariate analysis with the Cox proportional hazards model (Junor et al 1989) showed no significant difference in survival in young versus older patients.[61] All the patients in that study received identical radiotherapy. A study similar in design to the present one (Carmichael et al), in which 121 patients under 35 years of age were compared to a random sample of 242 older patients, showed a significant difference in overall survival which disappeared after correction for stage.[95]

In the present study it was felt that further analysis controlling for the confounding effect of covariables would possibly find a significant difference in survival not seen in the overall results. For example, a true de-

crease in the survival of young patients might be obscured by an excess of early stage young patients compared to the older group, or possibly the young patients had better treatment.

Curves comparing survival in the young and older age groups stage for stage, by stratified logrank analysis (Figures 7-9) show p-values of 0,425 for 1B versus 1B, 0,714 for Early Stage versus Early Stage and 0,714 for Late Stage versus Late Stage. Comparing survival stage for stage thus shows even less likelihood of a significant difference in survival than the overall comparison. Using the full numbers of the study, i.e. 79 versus 79, a multivariate analysis controlling for the effect of stage shows that the effect of age on survival is non significant. The p-value here is only 0,850. The effects of treatment type and tumour type on survival are non-significant. The effect of stage is highly significant ($p = 0,0001$).

Seeing that no significant difference in survival could be found between the two age groups in this study (and the power constraints have been discussed), the question arises of whether the two groups really are comparable or whether there is some as yet unmentioned bias masking a true difference in survival. One of the most common sources of bias in a case-control type comparison is the so-called prevalence-incidence or Neyman bias[103] by which is meant that the most acutely ill patients, who do not get into the proper management channels, may be

missed in an institutional study. In the specific instance of cervical carcinoma, this bias would seem to play a minimal role as the disease is not usually acutely fatal and would almost always be referred into a regional centre for further management. Another common bias, the admission rate or Berkson bias[103], would not apply in this study as all patients in both groups would be registered (admitted). There is, however, the small possibility that some patients who had initial radical surgery might have escaped subsequent registration by the CAC. If this were so, the observed survival of the young in the present study might be too pessimistic.

Survival curves, to be truly accurate, need to be adjusted for population national mortality rates[104]. These rates are age-dependent and will affect survival curves for older patients more than for young patients. The survival curves used in this study could not be mortality rate adjusted by the Medical Research Council as the race-specific national mortality rates are not accurately known in South Africa. The nett result is that survival in the older group will appear better than it is in reality.

Analysis of 24 articles in the literature which support a conclusion of no worse survival in young patients shows the following breakdown of numbers studied in approximate increasing order of <u>young</u> patients for study.

TOTAL PATIENTS

27	Berkowitz et al[88]	(<35 years)	1975-1978
28	Kahanpaa[94]	(<30 years)	1936-1945
210	Gusberg & Herman[37]		1960-1968
218	Spanos et al[81]		1972-1984
305	Smales et al[63]		1970-1984
107	Mann et al[83]	(Stage 1)	1956-1974
59	Kyriakos et al[94]	(<30)	1957-1968
100	O'Brien & Carmichael[27]	(Early) (Young Better)	1970-1984
762	Van Voorhis[85]		1951-1962
185	Alvarez et al[84]	(Early Stage Young Better)	Not stated
820	Blomfield et al[39]		1945-1953
94	Futoran & Nolan[87]	(Stage 1)	1942-1972
988	Baltzer[93]		1958-1974
103	Le Vecchia et al[86]	(<35)	1970-1979
1125	Gilmour et al[40]		1925-1939
121	Carmichael et al[95]	(<35)	1950-1984
1418	Dodds & Latour[82]		1926-1959
1451	Decker et al[64]		1940-1949
168	Gerbaulet et al[91]	(<35)	1975-1985
1863	Pejovie et al[48]		1950-1963
2001	Kjorstad[89]		1963-1968
2011	Junor et al[61]		1964-1984
2870	Russel et al[92]	(Young do better)	1971-1978
10022	Meanwell et al[59]	(Young do better)	1957-1981

Note that it is the number of young patients in a study that is important as it is their prognosis which is uncertain. The present study, which is based on 79 young women, is a middle ranking study in terms of the surveyed literature which shows no significant difference.

OTHER NATURAL HISTORY CHARACTERISTICS

Turning now to other aspects of the present study, the numerous negative findings of comparisons between the young and older groups for differences in natural history characteristics deserve comment. Often these contingency table numbers relate to subgroups of the study and are much less than 79 on each side, e.g. Table X which has 30 in one group and 7 in the other; with 6 events in the one and two in the other. To have an even chance of detecting a difference of 1 : 3 or more, one needs about 20 events; while for a 2 : 3 difference one needs at least 100 events.[110] The various negative findings should be interpreted in this light. There is, nevertheless, ample support in the literature for all the findings of this study as listed at the start of the discussion.

It has become increasingly clear that tumour size (or more correctly, tumour volume) may relate to the risk of lymph node metastasis and thus to prognosis;[22,28,23] studies by O'Brien & Carmichael[27] and Alvarez et al[84] are in agreement with the findings of this study that young women do not have an excess of large tumours. There has been speculation that young women might have a greater proportion of high grade tumours.[69] Both Gilmour et al[40]

and Hall & Monaghan[80] provide evidence for this and although the present study found 35% high grade tumours in the young versus 27% in the older group, this could not be shown to be significant. Chang et al[26] on the other hand, in a major study of grade and prognosis, did not even consider an association between grade and age.

There were 8 non-squamous tumours in the young group versus 5 in the older group. The study could not detect a significant difference; however, it is of interest that a full 10% of cervical carcinoma in the young group was not squamous. As a mucin stain was used in only 6% of the cases in the study, this proportion might be even higher, as Buckley et al[24] have pointed out. There is much evidence in the literature[70,73], summarized by Crowther and Shepherd,[33] that there has been an increase in the proportion of adenocarcinomas, particularly in the young. Adenocarcinoma might have a poorer prognosis than squamous carcinoma,[48] but there is also much evidence that this is not so.[30,31]

There have been claims that spread to lymph nodes is more common in young patients. Elliott et al[73], who studied 2628 women between 1953 and 1986 claimed that pelvic lymph nodes were being found positive more commonly in the young in the later years of the study. La Vecchia et al[86], in a study of 103 young women, found lymph nodes positive in a very high 40% of Stage 1B (45 cases). The present study found positive lymph nodes in 20% of Stage 1B in young women which is in keeping with classic teaching.

Although the older group in the present study had more residual disease following primary therapy than the young group (25% versus 18%), the recurrence rate (29% versus 33%) and time to recurrence (23 months versus 22 months) were very similar. Unlike Dattoli et al[74] and Mendenhall et al[72], who showed increased disease recurrence in young women, this study could not show a significant difference.

Analysis of cytology factors in the two groups in the present study was hampered by the poor cytological screening histories of the study patients - an understandable problem seeing that all the patients had developed a cervical carcinoma. Thus only 13% of the patients had any prior screening cytology results, which is in agreement with findings by Carmichael et al[54], who showed that 71,4% of 245 patients with cervical cancer in Canada had not been screened and Paterson et al[42], who found similar results. Paterson also found a higher false negative cytology screening rate in young women who developed carcinoma. The present study found that the diagnosis of carcinoma was missed on cytology in a higher proportion of young women than older women (27% versus 14%), but this could not be shown to be significant; similarly, a significant difference in the length of the preinvasive phase could not be found. Paterson provides evidence that it may be shorter.[42]

Treatment is shown in the present study to vary according to the age of the patient; thus significantly

more young women with early stage disease received radical surgery than older women with early stage disease (p-value 0,027). This result is entirely expected as it has always been a general policy to prefer radical surgery in the patient who is younger and fitter; another reason to favour surgery in the young is to preserve vaginal and ovarian function. Mann et al[83], in a series of Stage 1 patients under the age of 40, found 81 had surgery versus 26 with irradiation; this compared to 56 with surgery versus 43 with irradiation in an older group. The treatment of recurrent disease is shown in the present study to be of equivalent intensity, corrected for stage, in both age groups.

Assessment of complications of treatment in the two age groups showed that an equal proportion of patients (±50%) had complications after one year following treatment. The type of post-radiotherapy complication was very similar in both groups, where substantial numbers (59% in the young and 72% in the old) received this form of treatment in radical doses. The young patients, despite their presumably greater sexual activity, had definite problems with vaginal stenosis post-radiotherapy. Seibel et al[50] in a study on sexual function after surgical and radiation therapy for cervical carcinoma found that patients in the irradiation group had significantly less sexual enjoyment, controlled for age. An impression which is gained is that the late complications of surgery are less severe than those of radiotherapy.

Mann et al[83] had a similar finding that the complications of radiotherapy seem more serious than for surgery. In his study there were also two treatment related deaths, both following radiotherapy.

Human papillomavirus infection can be found in 90% or more of cervical carcinomas by means of DNA hybridization studies[10] and this figure will probably approach 100% with the advent of the polymerase chain reaction.[14] (See Section 1.2). Histology is not able to detect HPV infection in carcinoma cells but has a sensitivity as high as 80% in non-malignant epithelium.[21] In intraepithelial neoplasia the detection rate is inversely proportional to the severity of the lesion.[18] Cytology has a probable sensitivity for HPV of about 40%[20,21] in non-malignant specimens and this declines when the disease is present, in a manner inversely related to severity.[10] In the present study, HPV was detected in 35% of the histologically evaluable cervical malignancies and in 21% of the malignant cytological material. The purpose of examining the archival material in this way in the present study was to see if HPV was as prevalent in older women in 1974 - 1983 as it is today. The suspicion that there was a relatively lower prevalence in older women and thus a greater prevalence of HPV in the young group in previous times, indicating that HPV plays a new and undefined role in carcinoma of the cervix, could not be proven. The difference in HPV detected histologically in the young versus the old (39% versus 28%) had a p-value

of 0,498 and for cytology (26% versus 16%) the p-value was 0,307.

PROPORTION OF YOUNG PATIENTS

The study finding that there is no recent increase in the proportion of patients under the age of 35 years differs from many findings in Western countries. Smales et al, in a United Kingdom hospital-based study, found the proportion of young women to increase from 2% to 18% in 15 years[63] and Elliott et al, in an Australian hospital-based study, saw an increase from 9% to 25% over 20 years[73]. The British 10 022-case population-based study of Meanwell et al gave figures of 3,6% under 35 in 1960 and 14,5% under 35 in 1980[59]. The present study found the proportion of those under 35 to be constant at 11,6 and 11,7% (in a hospital-based geographically corrected study for 1974-1983 versus 1984-1988). An explanation of why the figures have not increased as in Meanwell et al might be that local patients did not experience the relative rise in sexual promiscuity seen in the West some 20 years ago. Alternatively, local patients are not having the diagnosis made at any earlier stage than before. Factors related to smoking in young people and to the use of the oral contraceptive may also be of importance[4,5]

DISEASE STAGE

One of the significant and surprise findings of the present study was the fact that more young patients have

early stage disease (p = 0,01 for excess of Stage 1B). Junor et al found 48% of patients under 45 years of age to have Stage 1 disease and they state that "We cannot explain the increased frequency of earlier presentation in younger women"[61]. The finding that young women have earlier stage disease is widely confirmed in the literature. Carmichael et al in Canada found 64,5% of women under 35 to have early stage disease versus 43,0% (p <0,002)[95]. Similar results are reported by Russel et al[92], Spanos et al[81], Smales et al[63] and Dodds and Latour[82]. The latter report is of interest because it is based on a patient series from 1926 to 1959, i.e. before cervical screening was widely current. Most of the studies mentioned above, including the latter, conclude that this discrepancy in stage distribution "may be partly explained by the tendency of younger women to seek screening procedures and by older women to disregard symptoms"[82] Although not stated in the literature, it seems clear that the true explanation might be rather more simple: All carcinoma of the cervix in any individual patient must start as Stage 1 disease and then progress through time (which may be in years) to Stage 4, at which time the patient will be older. A population of such individuals will have Stage 1 disease at a younger mean age than Stage 4 disease (or Stage 2 disease). Thus, instead of a case of "young patients more often have early stage disease" it is rather a case of "early stage disease is found more often in younger patients"

Having considered most aspects of the study, it remains to discuss the literature which gave rise to the motivation for the present study, i.e. the literature which claims that carcinoma of the cervix in younger women has a worse prognosis than in older women (and therefore might be a different disease). Once again, it is salient to consider the study numbers - ranked in terms of the number of younger patients:

Total Number			
72	Yeoh & Spittle[71]		1979-1983
254	Gynning et al[76]		1952-1974
131	Dattoli et al[74]	(Stage 1B)	1974-1985
220	Adcock et al70	(Stage 1B)	1970-1979
55	Chapman et al[70]	(<35)	1951-1985
264	Mendenhall et al[72]	(Early Stage)	1964-1980
561	Prempree et al[75]		1969-1974
246	Buckley et al[24]		1979-1985
5258	Lindell[78]	(210 under 31)	1910-1944
1085	Stanhope et al[77]	(265 under 35)	1960-1970
2628	Elliott et al[73]		1953-1986

The study by Elliott et al, which is Australian and hospital based, contains a group of 418 younger women - the largest in this listing[73]. Multivariate analysis was performed and it was found that the younger group had significantly more early recurrence and more lymph node metastases; when node state was allowed for, age lost its significance for death. This suggests that there is

more occult advanced disease in the young group. Another large study by Lindell early in the century was the first serious work to raise the suspicion that young women have a worse prognosis.[78] The difference, however was small (10 to 12% reduction in 5-year survival). The most significant current study prior to Elliott et al was the work in 1980 of Stanhope et al from the M D Anderson hospital in Texas, who found survival in the young group to be significantly less ($p = 0,005$).[77] The article has several potential methodological problems including choice of controls and an absence of primary data. Another article with wide influence was that by Buckley et al in 1988 where evidence was presented that mucin secretion in tumours is more common in the younger patient and that mucin secretion carries a worse prognosis.[24] This data is not accurately quantified statistically. Chapman et al[79] and Prempree et al[75] do not provide actuarial survival curves; the latter article finds the decreased survival in the young group to have a p-value of 0,03. Gynning et al[76] find a value of less than 0,05 and Adcock et al[70] find a value of 0,025 based on 26 patients. Yeoh and Spittle have only 6 young patients in Stage 1 and have a p-value of 0,01.[71] The largest difference in survival between the two age groups is found by Dattoli et al (1989).[74] There were 43 young patients in the study and the p-value was 0,0001.

The literature claiming a worse prognosis in the young patient can be seen to be open to doubt, especially

in the light of the work reviewed earlier showing an opposite conclusion. The present study provides results very much in keeping with the world literature experience and contributes to the evidence that there is in fact no difference between carcinoma of the cervix in the young versus the older patient beyond a natural fact that early stage disease is seen more often in the young patient ($p = 0,01$) and that surgical treatment is used more often in the young patient ($p = 0,027$).

FUTURE STUDIES

A future direction of study to explain the clinical impression that at least some young women do badly after treatment might lie in the entity of occult advanced disease. Perhaps the young women who do badly have in fact late stage disease (and are surrounded by women who do very well). Seeing that young women conceivably have a different cervical stromal response to a cervical neoplasm than older women, it is possible that what appears to be disease confined to the cervix in some young women may in fact be advanced disease. This sort of occult advanced disease in the young could explain the "so called" Stage 1B case with a poor prognosis. As hypothesized earlier, this situation might be more common in the young patient. Research efforts should be directed at identifying those patients with occult advanced disease. A related aspect which has been poorly explored in this regard is the role of the immune state. With the advent of the AIDS era, the technology for

assessing cellular immune status is well developed and could be employed to answer this question. It is also conceivable that the hormones play a role in cervical stromal immunoregulation at a local level. Progesterone, for example, only occurs in the younger premenopausal woman; it is also associated with oral contraceptive use.

Age, immune state and steroid hormone state may all relate to occult advanced disease, a concept which deserves further study.

5. CONCLUSIONS

As a result of the present study the following general conclusions can be drawn about invasive carcinoma of the cervix in local young women:

1. General Patient Characteristics

   The general characteristics of local young women with the disease are compatible with findings in the literature. This applies to age distribution within the young group, mean parity and rate of disease seen during pregnancy.

2. Prevalence

   The disease is fairly common in women between the ages of 20 and 35 years. There has been no recent local increase in the proportion of young women with the disease.

3. Disease Stage

   Early stage disease is seen significantly more often than in older patients.

4. Pathology

   There are no major differences in the pathological features of the disease compared to older women, excluding those which might have been detected by a routine mucin stain.

5. Cytology

   There are no major differences in cytology results compared to the older group, within the context of a

generally very poorly utilized modality in patients destined to develop invasive disease.

6. Treatment

Radical surgery is used significantly more often than in older patients, even if corrected for stage. The young do not receive better treatment than the older group, neither do they experience less treatment complications. Vaginal morbidity following radiotherapy is common and death may also be a complication of radiotherapy; surgery should be offered to the young patient if possible.

7. Evidence of Human Papillomavirus

HPV was not significantly more prevalent than in older women during the years 1974 to 1983. This suggests that it is not a new factor in cervical carcinoma. There is a lack of positive correlation between histology and cytology diagnosis of HPV.

9. Survival

There is no overall statistically significant difference in survival compared to older patients. The young patients do not have a worse prognosis even if the survival data is corrected for confounding factors by multivariate analysis.

10. Policy Recommendations

Young women should be recognized to be at risk of having invasive cervical carcinoma. The treatment should be the same as in older women except that

surgery should be specifically favoured. Occult advanced disease should be looked for in patients of all age groups and treatment modified accordingly.

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