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Long-term Survival in Endometrial Cancer with Special Reference to Age as a Prognostic Factor

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ABSTRACT

Long-term survival was evaluated in 13 586 patients with cancer of the endometrium, constituting 97 % of all cases diagnosed in Sweden 1960-1978. Survival rates corrected for the expected mortality revealed that age at diagnosis is an important predictor of prognosis, with a constant trend towards a more favourable course in younger women. Thus, the cumulative relative 15-year survival rates ± 95 % confidence limits were 90 (86.1-93.7) %, 89 (87.4-91.3) %, 72 (68.9-74.3) %, 50 (44.9-54.7) % and 32 (18.3-45.6) % at ages 35-44, 45-54, 55-64, 65-74 and 75+ years respectively. Patients younger than 55 years deviated from the general pattern by having an excellent survival and virtually no excess mortality after 7 years of observation.

INTRODUCTION

Cancer of the endometrium constitutes an important medical problem in Sweden. This tumour has become increasingly common in the last decades with age-standardized incidence rates rising at a mean annual rate of 1.1 %, from 16.7 cases per 100 000 women in 1960 to 20.7 per 100 000 in 1980. Endometrial cancer at present rates as the fourth most common and accounts for 5.4 % of all female malignant tumours. It is the second most frequent of gynaecologic neoplasms with over 900 cases reported in 1980, next to ovarian cancer with about 1 000 cases (3).

The prognosis of endometrial cancer is generally considered favourable (15). In case materials from Sweden, Norway and Finland, the overall crude 5-year survival rates have ranged from 68 to 75 % (4, 13, 14, 22). Studies of large series of patients with endometrial cancer in the USA have shown overall

relative survival rates in the order of 72 % at 5 years and 69 % at 10 years of follow-up (12).

When interpreting or comparing the outcome of treatment with regard to survival in different materials, a number of problems must be considered. Firstly, survival figures reported from small and selected case materials represent specifically the outcome of treatment practised at the individual oncologic department during the time period of the study. Secondly, the distribution of prognostic factors such as age at diagnosis and tumour characteristics may differ between case series. Thirdly, the presented figures may represent non-identifical survival measures: Thus, in some instances survival is expressed as the crude rate, and in others as the corrected rate. Correction may be made either with regard to intercurrent disease after individual follow-up or in relation to the survival of the underlying population. Fourthly, the estimation of outcome is frequently based on an observation period limited to 5 years.

Here, we report on the age-related crude and corrected (relative) long-term survival of 13 586 patients with endometrial cancer constituting a total and unselected material of cases with a nearly complete follow-up.

We chose to analyse age as a prognostic factor for several reasons. Firstly, information on age is a prerequisite for valid comparisons of survival figures from materials with differing age distributions. Secondly, a finding of age-related differences in prognosis might help to clarify heterogeneity in tumour biology related to age. Lastly, there is a further need to separate patients into different prognostic groups in order to facilitate the choice of the most efficient methods of treatment.

MATERIAL AND METHODS

The Swedish National Cancer Registry was established in 1958. All physicians in hospitals and other centres for medical treatment under public administration in Sweden are under obligation to report all cases of diagnosed cancer to the Registry. Pathologists and cytologists also have to report every cancer diagnosed on the basis of surgically removed tissues, biopsies or cytological specimens and at autopsies. In 95 % of all cases the National Cancer Registry is provided with reports from both these sources. The non-reporting rate to the Cancer Registry has been estimated to be about 5 % (17).

The cancer file is linked annually with the Causes of Death Registry, and dates of death and causes of death are transferred. In addition, a last date of contact is obtained by linking the registry data with a continuously updated registry that holds information on vital status and covers the total Swedish population. Patients with incomplete follow-up through the linkages -i.e. neither identified in the Causes of Death Registry nor in the national population register - were excluded from the present analysis.

For all cases the closing date of this analysis was December 31, 1979. In the 19-year period 1960 to 1978, reports were made to the Cancer Registry in Sweden of 14 039 cases of endometrial cancer that were diagnosed as first and primary cancers in these patients. Of these, 203 (1.5 %) cases were excluded from the survival analyses since the diagnosis was based on autopsy. Furthermore, the follow-up of 250 cases (1.8 %) was not complete and they were excluded from the calculations. As a result, the analysis comprised 13 586 patients with the age distribution shown in Table 1. The median age of the patients was 61.9 years.

Table 1. Age distribution.

Age at diagnosis	Number	%
15 - 24	3	0
25 - 34	50	0.4
35 - 44	507	3.7
45 - 54	3 334	24.5
55 - 64	4 218	31.1
65 - 74	3 550	26.1
75 +	1 924	14.2
	13 586	100.0

The observed and relative survival rates were calculated by means of the actuarial or life table method (9). The observed survival rate is the proportion of persons alive at a specified time after diagnosis. The relative survival rate is the ratio between the observed survival in the patient group and the expected survival for that group if they had the same mortality as the total Swedish population with respect to age, sex and year of investigation.

For calculation of the expected survival rates, death rates from life tables by sex, 1-year age groups and 5-year calender periods were used.

The expected figures were based on the mortality of the total Swedish population. No correction was made for the endometrial cancer mortality which

contributes only to a negligible extent to the overall death rate of the female population.

The survival measures may have been influenced by sampling error. The 95 % confidence limits are therefore given as a measure of the confidence that must be taken into account when interpreting the results. The standard error was computed from Greenwood's formula (10).

RESULTS

The overall cumulative observed survival rates with 95 % confidence limits for patients at all ages were 69.1 (68.3-70.0) % at 5 years, 57.6 (56.6-58.5) % at 10 years, 48.2 (47.0-49.3) % at 15 years and 37.8 (35.6-40.0) % at 20 years respectively. The median survival time was 13.9 years. The observed survival rates were highly related to age at diagnosis and varied after 15 years of observation between 87.5 (78.0-97.1) % at ages 25-34 years and 3.4 (2.0-4.9) % in women 75 years or older (Fig. 1).

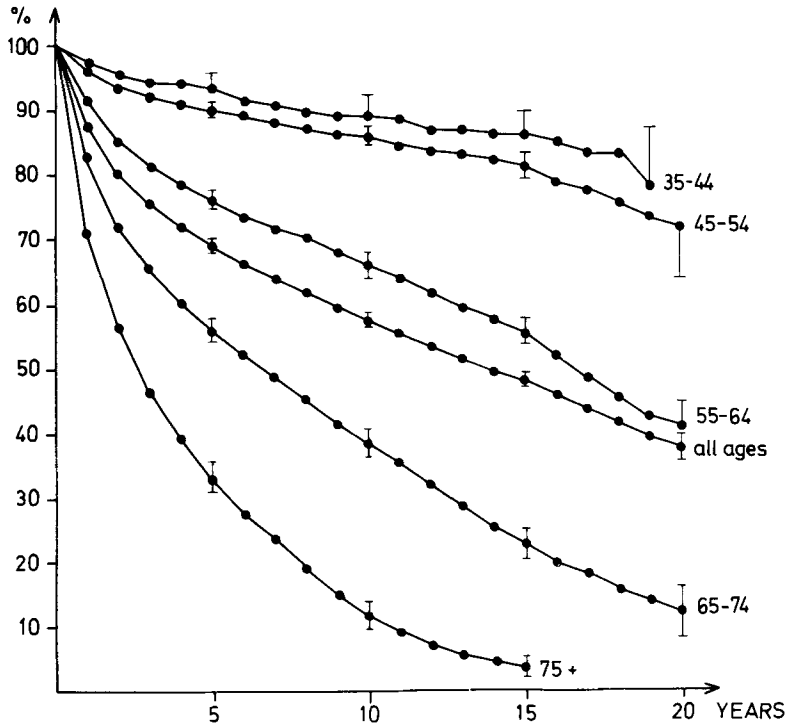

Fig. 1. Observed cumulative survival rates with 95 % confidence limits, by age at diagnosis, in 13 586 patients with endometrial cancer diagnosed in 1960-1978.

The differences in survival related to age at diagnosis remained pronounced after correction for the expected mortality. Patients younger than 55 years at diagnosis showed virtually the same relative survival, both at short- and long-term. After the age of 55, however, the survival rates were constantly lower with increasing age. These differences were significant already during the first years of observation (Table 2) and increased during the whole period of observation (Fig. 2). Among patients younger than 55 years at diagnosis the relative survival remained fairly constant at about 90 % after seven years of observation, indicating that the excess mortality was almost eliminated and hence that a large fraction in these age groups was cured. Women older than 55, on the other hand, displayed a continuing decrease in relative survival and this trend was most pronounced in the oldest age group.

The relative survival was virtually stable after 15 years in patients aged 65-74 at diagnosis. The number of women at risk was small, however, and the confidence limits accordingly wide (Table 2).

When interpreting relative survival at all ages, it should be recognized that this curve represents an increasing proportion of young surviving patients with increasing length of the observation period (Table 2).

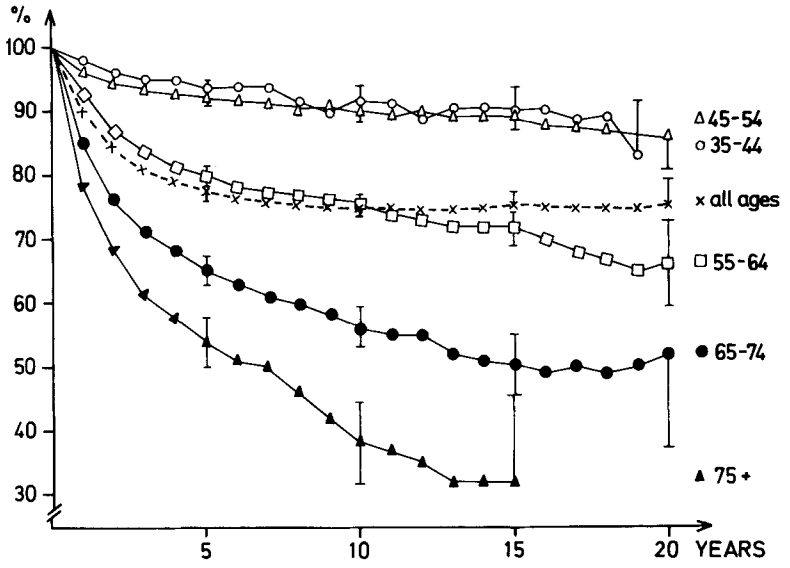

Fig. 2. Relative cumulative survival rates with 95 % confidence limits, by age at diagnosis.

Table 2. Number of patients at risk (N), cumulative observed survival (OS)% and cumulative relative survival (RS)% with 95 % confidence limits (RS±95%CL)%, by age at diagnosis[1].

Age at diagnosis	Category	Years after diagnosis				
		1	5	10	15	20
25-34	N	50	42	27	16	2
	OS	96	90	88	88	-
	RS	96	90	88	89	-
	RS±95%CL	90.4-101.5	81.8-98.7	83.6-97.9	79.7-98.8	-
35-44	N	507	409	276	159	20
	OS	97	93	89	86	-
	RS	98	94	91	90	-
	RS±95%CL	96.2-99.0	92.0-96.5	88.0-94.1	86.1-93.7	-
45-54	N	3334	2536	1566	766	92
	OS	96	90	86	81	72
	RS	97	92	90	89	86
	RS±95%CL	95.9-97.2	91.0-93.1	88.8-91.7	87.4-91.3	80.8-91.2
55-64	N	4218	2635	1467	643	76
	OS	92	76	66	56	40
	RS	93	80	75	72	66
	RS±95%CL	91.2-93.4	78.3-81.2	72.9-76.7	68.9-74.3	58.5-72.6
65-74	N	3550	1749	736	221	19
	OS	83	56	38	23	12
	RS	85	65	56	50	52
	RS±95%CL	83.3-85.2	62.9-66.9	53.6-59.3	44.9-54.7	36.8-67.7
75+	N	1924	576	126	20	1
	OS	71	33	12	3	-
	RS	78	54	38	32	-
	RS±95%CL	75.4-79.8	50.1-57.6	31.6-44.3	18.3-45.6	-
All ages	N	13856	7950	4199	1826	210
	OS	88	69	58	48	38
	RS	90	78	75	76	76
	RS±95%CL	89.1-90.3	77.6-78.6	73.7-76.2	73.9-77.6	71.6-80.3

[1] Three women aged 15-24 at diagnosis are not included.

DISCUSSION

Our results are based on an unselected material including virtually all cases with cancer of the endometrium reported to the Swedish Cancer Registry from the whole country during a 19-year period from 1960 and with an observation period of up to 20 years.

The size of the material permitted a detailed age classification. This was considered advantageous, since it meant that the survival among those patients in pre- or perimenopausal age groups could also be evaluated.

Data concerning expected mortality were based on the total Swedish population and adjusted for changes with time.

Three possible sources of error that might have influenced the internal validity of the study were considered.

1. A bias of the results due to the exclusion of patients who were lost to follow-up is unlikely. Firstly, the proportion of patients excluded for this reason was low (1.8 %), and secondly, there is no reason to suspect that there is a relation between having an erroneous national registration number, which was the major reason for losses in the follow-up, and the outcome of the disease.

2. Furthermore, exaggerated differences in survival rates between age groups may occur as a consequence of this particular method of survival analysis. The use of relative survival implies that patients with endometrial cancer are assumed to have a mortality pattern equal to that in the background population except for the mortality associated with the endometrial cancer. The present findings of age-dependent differences in relative survival may be confounded if: a) other disease states associated with endometrial cancer enhance mortality, and b) the prevalence of such conditions increases proportionately more with age among the cancer patients than among women in the background population. Thus, three such factors, namely diabetes, hypertension and obesity, were taken into consideration.

Data on the age-related prevalence of such factors were derived from a material of 1 000 cases of endometrial cancer from the northern part of Sweden treated at the Department of Gynaecologic Oncology in Umeå during the period 1963 to 1981 (2). The prevalence of manifest diabetes, ascertained through the case histories, rose markedly with age, from 2.3 % in the age group 45-54 years to 20.2 % in those older than 75 years. The diastolic blood pressure level increased with age from an average of 83 mm Hg in the age group 35-44 years to 95 mm Hg in the oldest patients. The mean body weights also showed an increasing trend with age, from 65 kg among patients in the age group 35-44 years to 73 kg in the 65-74-year group. No comparable information is available on the age-related prevalence of diabetes and

the distributions of blood pressure levels and weights in the background population. Each of these factors has been found to be associated, however, in previous studies, with a moderate increase in the risk of endometrial cancer, with relative risk estimates in the order of 3, 2 and 3 for diabetes, hypertension and obesity respectively (16). These findings suggest that the risk factors are slightly more frequent among cancer patients than among healthy women and could thus only explain excess mortality to a limited extent in the older age groups.
Moreover, from the findings that the age-related differences in survival in the present material were substantial and that the differences appeared already within the first years of observation, it seems probable that the results are not confounded to any major extent.
3. Lastly, a lead-time bias might be present, with, on the average, an earlier diagnosis in younger women. This, however, would lead to survival curves slightly shifted to the right for the younger age groups rather than to a steadily increasing, age-dependent difference in relative survival.

To summarize, we were unable to identify any factor that could have biased the results substantially. It was therefore concluded that the influence of age on long-term survival in patients with endometrial cancer is real and that this finding is representative for the Swedish population.

The present report gives the overall and age-dependent cumulative survival rates obtained by life-table calculations. The crude (uncorrected) survival rates (Fig. 1) show marked differences between age groups. Such differences are expected, simply on account of increasing mortality with age. These crude rates permit comparisons with other materials. In two Swedish reports, comprising 320 and 500 cases diagnosed and treated in the 1960s, the crude 5-year survival rates were 75 % and 71 % respectively (14, 4). In a more recent study covering 1 113 cases of endometrial cancer treated in three oncologic departments in Finland during the period 1970-1974, the overall crude 5-year survival rate was 71 % (13). The corresponding figure in the present material is 69 %. Such comparisons must be interpreted with caution, however, as the materials may differ with regard to distributions of age and tumour characteristics.
Examination of the relative survival rates reveals an interesting pattern. Patients whose cancer was diagnosed before the age of 55 clearly had a better relative survival than those diagnosed at an older age, and 90 % of them seemed to have been permanently cured. In the age groups from 55 years and older, however, the relative survival rates decreased markedly with age and showed a continuing downward trend during the 15 years of

follow-up. Thus, in these age groups relative mortality was increased even after 5 years, which is the period of follow-up usually given in reports on the outcome of treatment.

In other studies relating age to the outcome, it has been shown that younger patients have a more favourable prognosis than older ones (1, 5, 8, 21). In one study by Nielsen and Koller (1959), the crude 5-year survival rate in patients aged 40-49 years was 92.1 %, versus 60.9 % in patients over 70 years (18). In that study, data showed that younger patients also had more favourable tumour characteristics, with a higher frequency of stage I and superficially invasive cancers than older patients. Since both the stage of the disease and the depth of myometrial invasion are related to the prognosis, it might not be age per se that determines the outcome but rather age-related differences in tumour characteristics.

The prognosis may be influenced not only by tumour characteristics but probably also by the particular treatment modality. Combined treatment including both surgery, i.e. hysterectomy and salpingo-oophorectomy, and radiotherapy has been reported to lead to a better outcome than radiotherapy alone (14). The presence of conditions such as cardiovascular disease sometimes precludes the use of surgical therapy. As the prevalence of such disease increases with age, it is possible that the excess death rate among the elderly may be explained to some extent by a lower frequency of surgical treatment.

The present registry-based data include no clinical or histopathological information. To estimate the influence of age-dependent tumour features on our results, data were obtained from two Swedish case materials.
One comprised 574 cases of endometrial cancer admitted to and treated at the Department of Gynaecological Oncology in Uppsala during the period 1970-1975 (20). Regarding the extent of the disease, it was found that 82 % of the patients younger than 50 years had tumours in stages 0 or I, compared with 76 % of those above 50 ($p<0.3$). Furthermore, highly differentiated cancers (grade 1) were found in 58 % of the patients younger than 50 years of age, versus 39 % of those of higher ages ($p<0.01$).
A similar pattern was seen in the data from another series of 1 000 cases from the northern part of Sweden treated at the Department of Gynaecological Oncology in Umeå during the period 1963-1981 (2). Tumours in stage I were found in 89.8 % of the patients younger than 55 years, and in 79.7 % of those older ($p<0.004$). Significant differences were found in the whole material, with a more advanced stage with increasing age ($p<0.0008$).

Grade 1 cancers occurred in 50.2 % of the subjects younger than 55 years and in 27.5 % of those at higher ages ($p<0.003$). Higher grades (lower differentiation) became significantly more frequent with age ($p<0.00001$).

These data support the view that a significant influence of age on long-term survival probably reflects age-dependent variations in tumour biology. This theory may be explained in different ways.

Firstly, cancer of the endometrium may differ between younger and older women with respect to aetiological factors, hormonal control, or immunological or other host factors. In younger patients, endogenous estrogens unopposed by progesterone, either in connection with anovulation or obesity or with exogenous substitution, may play a role in promoting initiated cell clones that show the least deviation from normal cells. Such a process could lead to the occurrence of less aggressive tumours at lower ages (7). In elderly patients, on the other hand, the endogenous estrogen production is low or negligible and the use of exogenous estrogens infrequent. The lesser influence of estrogens as selective promotors, together with a greater genetic instability and possibly impaired immunological defence in patients of higher ages may, hypothetically, lead to a greater risk of development and progression of cell clones with a highly malignant potential.

Secondly, there might be trends towards changing patterns of exposure to various aetiological factors as a function of time rather than of age per se. Treatment with exogenous estrogens, which became increasingly popular during the late 1960s and 1970s in Sweden (20), might be one such factor. The use of estrogens has been associated with an increased risk of endometrial cancer, the risk being significantly elevated after only 2-4 years of exposure and rising with increasing treatment duration (11). Cancer cases occurring after the intake of estrogens have been shown to be clinically of an early stage and histologically of a highly differentiated grade and to be associated with a superior survival rate compared to non-exposed cases (6). Since estrogen treatment is started mostly in the perimenopausal period, it is possible that the introduction of this exposure in recent years has, to some extent, contributed to the favourable outcome of the cancer cases diagnosed at young ages.

Further analyses of incidence and mortality rates within and between subsequent birth cohorts will hopefully elucidate the possibility of changing aetiological influences with time.

We conclude that age at diagnosis is an important predictor of long-term survival in patients with endometrial cancer and has to be taken into account when different materials are compared. Further studies on the impact of age

on prognosis might improve our understanding of the aetiology and natural history of endometrial cancer.

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