Mortality and causes of death in a Swedish series of systemic sclerosis patients

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Abstract

***Objectives*—To analyse survival rates and the causes of death in a systemic sclerosis (SSc) population, and to evaluate the occurrence of fatal malignant neoplasms and their possible association with oral cyclophosphamide (CYC) treatment.**

***Methods*—Survival was calculated for 249 SSc patients followed up for up to 13 years. Mean (SD) follow up was 5.8 (4.2) years. The 49 deceased patients were subdivided according to causes of death and its relation to SSc. Fatal malignancies in CYC treated patients were compared with those occurring in non-CYC treated patients.**

***Results*—The overall 5 and 10 year survival rates were 86% and 69% respectively. There was a 4.6-fold increased risk of death, as compared with the general population. Prognosis was worse in the diffuse cutaneous involvement (dSSc) and male subgroups than in the limited cutaneous involvement (lSSc) and female subgroups. Of the 49 deaths, 24 were attributable to pulmonary complications such as pulmonary fibrosis, pulmonary hypertension, pneumonia or pulmonary malignancy. Treatment with oral CYC did not increase the risk of dying of cancer.**

***Conclusions*—Mortality is increased both in the SSc population as a whole and in its different subsets (dSSc and lSSc). Prognosis is worst among male patients with dSSc. However, the 5 year survival rate was better than those reported from earlier studies. Most patients die of cardiopulmonary disease. Five of seven fatal lung cancers were adenocarcinomas, possibly caused by chronic inflammatory disease of the lung. In this study, CYC treatment was not associated with an increased incidence of fatal malignant neoplasms.**

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Systemic sclerosis (SSc) is a systemic connective tissue disease characterised by immune abnormalities, fibrosis, microvascular injury, and inflammation.[1 2] Possible pathogenic mechanisms have been delineated[2] but the aetiology still remains unknown. The prognosis is highly variable[3] and in several studies SSc has been associated with an increased mortality. During the past decade Lee and coworkers reported an overall 9 year survival rate of 61%[4] and similar results were presented by Lally *et al*[5] and by Silman.[6] Both Barnett and coworkers[7] and Abu-Shakra *et al*[8] found death rates to be dependent on the degree of skin involvement.

An increasing number of factors of prognostic importance in SSc have been reported, and sex, age at diagnosis, and organ involvement (of kidney, heart or lung) are generally accepted determinants of survival.[4 9] Based on the distribution of skin sclerosis, subgroups with different prognosis have been identified.[7 10] Within these subsets, the specificity of the antinuclear antibodies in serum has been reported to be useful in predicting organ involvement, and in predicting long term outcome.[11–13]

Interpretation of the results of mortality studies may be difficult, as selection bias may work in different directions and the patient populations at centres specialising in SSc may not be representative. The exclusion of those with rapidly fatal disease already deceased before referral will improve survival rates, whereas survival will be deteriorated if patients with less severe disease are not referred and identified. In a survival study, the survival rate will differ according to the juncture at which patients are included in the study. For example, survival may be increased when patients are entered retrospectively—that is, at the onset of symptoms instead of at the time of diagnosis. In the first approach survival is 100% during the interval between onset of symptoms and diagnosis, and if the interval is long, the 5 year survival may well be better than that in the general population.

The purpose of this study was to analyse survival rates and the causes of death in a Swedish SSc population as a whole, and in different subgroups. Survival was studied with two different methods, the Kaplan-Meier method of computing survival rates over time for different subgroups, and the standardised mortality ratio for comparing survival with that in the general population. As SSc patients have been reported to be characterised by an increased incidence of malignancy, in particular lung and breast cancer,[14 15] we also wanted to study the occurrence of fatal malignant neoplasms and their possible association with oral cyclophosphamide (CYC) treatment.[16]

Methods

The study population comprised 249 consecutive patients (248 white, one Asian), all fulfilling the American College of Rheumatology criteria for SSc,[17] and referred from hospitals throughout Sweden during the 13 year period 1983–95. The disease was classified as diffuse cutaneous systemic sclerosis (dSSc) if truncal scleroderma was present, or limited cutaneous systemic sclerosis (lSSc) if truncal

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Table 1 Demographic characteristics of 249 SSc patients

	lSSc	*dSSc*	*Total*
	Number (%)		
Total	186 (75)	63 (25)	249 (100)
Male	45	26	71 (29)
Female	141	37	178 (71)
	Mean (SD) (y)		
Age at onset	43.4 (13.7)	49.4 (16.3)	44.9 (14.6)
At enrolment	48.5 (13.2)	52.7 (15.3)	49.6 (13.8)
Disease duration			
At enrolment	5.1 (6.4)	3.3 (4.1)	4.6 (5.9)
At end of study	10.9 (7.7)	9.1 (6.4)	10.4 (7.4)
Follow up	5.8 (4.2)	5.7 (4.3)	5.8 (4.2)

Table 2 Survival rates estimated from enrolment (%)

	Male		*Female*		
	lSSc	*dSSc*	*lSSc*	*dSSc*	*Total*
5 year	83	61	91	90	86
10 year	66	40	85	52	69

scleroderma was absent.[1] Six patients had additional symptoms compatible with other connective tissue diseases such as systemic lupus erythematosus (n=2), mixed connective tissue disease (n=1) or dermatomyositis (n=3). The onset of disease was defined as the time of development of cutaneous sclerosis. The time of entry into the study (that is, the beginning of follow up) was the time of the first SSc related visit to our department. In the majority of cases this was also the time of diagnosis.

In 27 of the 49 deceased patients the cause of death was determined by necropsy. Deceased patients were subdivided according to the cause of death and its relation to SSc, the following four categories being created: I definitely SSc related, death caused by organ insufficiency verified by biopsy, for example, renal crisis, or by a manifestation (for example, pulmonary hypertension, restrictive lung disease, or intestinal perforation based on subileus), attributable to no other cause or predisposing factor than SSc; II probably SSc related, death caused by a complication caused or aggravated by SSc related organ injury or treatment (for example, infection in an immunosuppressed patient or pneumonia in a patient with severe pulmonary fibrosis); III possibly SSc related, death caused by a manifestation reported to occur at increased frequency in SSc, for example, malignancy[14 15] or suicide[18]; and IV unrelated, death unrelated to SSc related organ involvement or treatment.

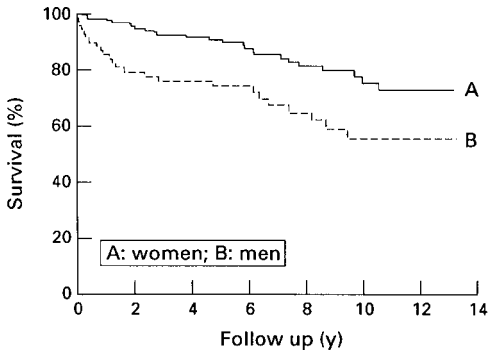

Figure 1 Sex as a determinant of survival in systemic sclerosis (p<0.0001). Differences analysed by a proportional hazards model using the Breslow test.

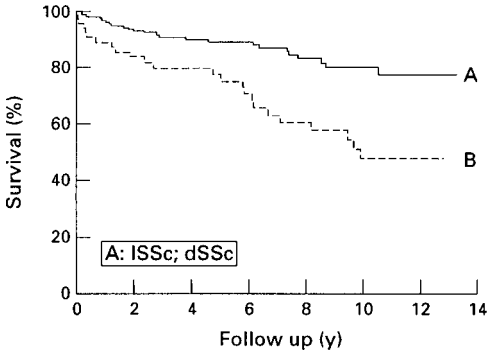

Figure 2 Skin involvement as a determinant of survival in systemic sclerosis (p<0.0005). Differences analysed by a proportional hazards model using the Breslow test.

Of the series as a whole (n=249), 71 patients were given daily oral CYC treatment started 10.8 (20) months (mean (SD)) after entry into the study.

Of the 49 deceased patients, 23 had been treated with CYC, one with methotrexate, two with azathioprine, and seven with penicillamine, whereas the remaining 16 received no immunosuppressive treatment. Eight patients were given ACE (angiotensin converting enzyme) inhibitors, and 23 were treated with calcium channel blockers as monotherapy or in combination with ACE inhibitors. The reasons for treatment with ACE inhibitors were arterial or pulmonary hypertension, impaired kidney function and scleroderma renal crisis, the latter being diagnosed in five cases, two of dSSc and three of lSSc.

Survival curves were plotted with the Kaplan-Meier method, subgroup differences in survival (men *v* women, dSSc *v* lSSc) being analysed with a proportional hazards model using the Breslow test. Other subgroup differences were analysed with the Mann-Whitney U test or the χ^2 test. In the standardised mortality ratios (SMRs), the expected number of deaths were calculated as the sum of person years multiplied with the age specific mortality rate for each age group. The expected death rates were calculated from official Swedish census data for life expectancy and the risk of death during the period 1988–92.[19]

Results

Table 1 shows the demographic characteristics of the 249 patients. Patients with lSSc were younger at onset than those with dSSc ($p<0.01$). The proportion of patients with dSSc was higher among men compared with women ($p<0.01$). No significant differences were found between lSSc and dSSc regarding age at entry, disease duration, or follow up time.

At the end of the study, 49 patients were deceased (table 2). The 10 year survival rate was based upon 54 patients. As reflected in the Kaplan-Meier survival curves, there were manifest sex related (fig 1) and disease form related differences (dSSc *v* lSSc; fig 2) in survival, indicating prognosis to be significantly worse among men ($p<0.0001$) and among those with dSSc ($p<0.0005$).

Table 3 Estimated risk of death in the 249 SSc patients compared with the general Swedish population

	Observed number of deaths	*SMR*	*95% CI*
lSSc	25	3.72	2.41, 5.32
Women	14	3.97	2.17, 6.66
Men	11	3.46	1.72, 6.18
dSSc	24	6.06	4.09, 9.02
Women	11	5.22	2.61, 9.34
Men	13	7.02	3.74, 12.00
Overall	49	4.59	3.48, 6.07
Women	25	4.44	2.87, 6.34
Men	24	4.77	3.21, 7.09

SMR: standardised mortality ratio.

SMRs showed mortality to be increased among SSc patients, both in the series as whole and in the various subgroups (table 3), the overall risk of death being 4.6 times greater than that in the general population. The risk of death was significantly greater in the dSSc than in the lSSc subgroup ($p<0.05$), but there was no sex related difference in this respect.

Fifteen deaths were considered to be definitely related to SSc, 10 probably, 14 possibly, and 10 unrelated to SSc (table 4). The predominant definitely related cause of death was pulmonary fibrosis with respiratory insufficiency (n=6), isolated pulmonary hypertension (n=2) or a combination of the two (n=2). However, the pulmonary arterial pressure was not known in all cases. Only one patient died of renal insufficiency after scleroderma renal crisis. Of another four patients who developed scleroderma renal crisis, one died of myocardial infarction, one of pulmonary fibrosis with respiratory insufficiency, and two are still alive. Of six patients who died of infections probably related to SSc, all had severe pulmonary fibrosis and pneumonia. Most deaths because of causes only possibly related to SSc were attributable to cardiovascular disease or cancer, two of the cardiovascular deaths occurring in patients with antiphospholipid antibodies. One patient, belonging to the miscellaneous cause of death category, suffered from angioimmunoblastic lymphadenopathy and died of haemolytic anaemia.

Twenty four deaths were attributable to pulmonary complications such as pulmonary fibrosis, pulmonary hypertension, pneumonia or pulmonary malignancy. Of the 12 patients who died of cancer, seven had a primary lung tumour and the remaining six breast, liver, pancreas, uterus or ovarian malignancy.

Patients who died of cancer and those who died of other causes did not differ significantly in sex, degree of skin involvement, age, treatment with oral CYC, or smoking habits (table 5). Of 23 diseased patients treated with CYC, four (17.3%) died of cancer, as compared with eight of 26 (30.8%) not treated with CYC. Among those treated with CYC, the mean (SD) cumulative dose was 25.6 (14.0) g in the four patients who died of cancer and 16.6 (12.1) g in the 19 patients who died of other causes (NS). The four deaths in the CYC treated group were attributable to ovarian malignancy in one patient and to lung cancer in three patients of whom all were smokers and had pulmonary fibrosis.

Of the 249 patients, 71 were treated with CYC at a mean (SD) cumulative dose of 27.3 (15.6) g. They were all carefully instructed to drink no less than two litres per day and after a mean (SD) follow up of 4.6 (3.8) years there has been no case of bladder cancer, and only one case of haemorrhagic cystitis. The frequency of fatal malignancy was 5.6% among the 71 CYC treated patients, as compared with 4.5% among those not treated with CYC (NS).

Table 4 Causes of death in realtion to SSc in 49 patients

	Relation with SSc				
Cause of death	*Definite*	*Probable*	*Possible*	*None*	*lSSc/dSSc*
Pulmonary disease	10				7/3
Renal disease	1				0/1
Cardiovascular	1	1	4	4	1/9
Gastrointestinal	3	1			4/0
Cancer			7	5	9/3
Infection		7	1	1	2/7
Suicide			2		1/1
Other		1			1/0
lSSc/dSSc	10/5	4/6	8/6	3/7	25/24

Table 5 Comparison of cancer and other causes of death

	Cause of death	
	Cancer (n=12)	*Other than cancer (n=37)*
Male/female	6/6	18/19
lSSc/dSSc	9/3	16/21
	Mean (SD) (y)	
Age at onset	48.6 (18.2)	53.7 (14.5)
At entry	57.1 (15.1)	59.0 (13.2)
At death	62.7 (14.6)	62.3 (13.0)
Disease duration	14.1 (8.5)	8.6 (7.0)
Smoker/non-smoker	6/6	11/26
CYC/no CYC	4/8	19/18

Discussion

As mortality studies generally deal with ethnically heterogeneous populations and few have been performed on an unselected population, the results need to be interpreted with caution.[4 5 8 9 20 21] Higher survival rates have been reported from more recent studies, possibly because of the selection of more patients with less severe and earlier disease, as well as to improved management.

The female preponderance of 71% in the present series is consistent with corresponding figures of 60–90% reported for all SSc studies published to date.[20 22] Published figures for the proportion of patients with diffuse skin involvement have varied from 25% to 67%, the discrepancy probably being because of differences in classification criteria or in the frequency of dSSc referrals.[5 23] The proportion of dSSc cases of 25% in the present series is consistent with figures reported from epidemiological studies,[23 24] which suggests that our series may be more representative of the SSc population as a whole than are series with a higher proportion of dSSc cases.

In this study, 249 patients with SSc were followed up prospectively over a period of up to 13 years. At the end of study, 49 patients were deceased, and the overall 5 and 10 year survival rates were 86% and 69% respectively. Compared with Lee *et al*,[4] who reported a 3 year survival rate of 86%, and with Lally and coworkers,[5] and Kaburaki and coworkers,[21]

who reported a 5 year survival rate of 77% and 78% respectively, we report a more favourable result in the overall 5 year survival rate, while the 10 year survival rate is consistent with those of earlier reports.[4 5 13] The more favourable 5 year survival rate in the present series may be explained by a higher proportion of lSSc patients or possibly by early therapeutic intervention. An improvement in 10 year survival was reported by Bryan and coworkers,[25] but their series consisted exclusively of patients with disease onset after 1 January 1982, and survival was calculated from the onset of disease and not from the first attendance, as in the present series, which complicates comparison with our results. When applying the same procedures on our series, our 5 and 10 year survival rates are 92% and 78% respectively, whereas the series of Bryan *et al* found 5 and 10 year survival to be 87% and 75% respectively.

Using life table analysis or Kaplan-Meier curves to elicit cumulative survival rates, male sex[7 20] and diffuse cutaneous skin involvement[8 20 26] have been found to be associated with more severe prognosis. Our results, with similar SMRs for men and women are consistent with those reported by Abu-Shakra and coworkers,[8] but this method is statistically less powerful in comparing different subgroups and will underestimate existing differences. The more powerful method, the Breslow test, indicated highly significant survival differences to exist with respect to sex and skin involvement. However, this method tends to overestimate these differences, as both patients with diffuse skin involvement and male patients were older at entry and therefore had shorter life expectancy for reasons unrelated to SSc. This is further aggravated by the fact that in Sweden, male sex in itself is associated with shorter survival.

Our findings confirm previous observations that pulmonary[4 9 20] and cardiac[4 20] involvement are common causes of death, while in our series only one of 49 deaths was attributable to renal involvement. The improved prognosis of renal crisis after the introduction of ACE inhibitors probably has contributed to the overall decrease in 5 year mortality. Both internal organ involvement and biochemical evidence of inflammation[5 9 21 22] have been associated with shortened survival. Therefore treatment with CYC, which may result in improved pulmonary function among patients with increased biochemical activity and pulmonary involvement,[27–30] is another possible contributing factor for the improved prognosis among our patients.

Previous studies have yielded evidence of an excess both of SSc related deaths and of deaths unrelated to SSc.[8 25] There is no plausible explanation for this excess of deaths unrelated to SSc. In our study, 25 deaths were considered to be definitely or probably related to SSc, whereas 24 deaths were considered to be only possibly related, or unrelated to SSc. It is sometimes impossible to estimate the exact relation of death to SSc, for example in ischaemic heart disease, as SSc patients may have both microvascular[31] and macrovascular changes[32] that reasonably might aggravate the disease. We consider lung cancer to be possibly related, because SSc has been reported to be characterised by an increased incidence of malignancy, pulmonary in particular.[14 15] The two suicides in our study were patients with no known psychiatric illness before the advent of SSc, and were therefore considered to be possibly related. Most deaths unrelated to SSc occurred in the dSSc subgroup, whereas the majority of deaths definitely related to SSc occurred in the lSSc subgroup, which may indicate an underestimation of the relation in cardiovascular deaths.

When comparing male and female Kaplan-Meier curves it seems that increased mortality in men compared with women, occurs within the first two years. During these two years five men, but no women died from myocardial infarction. This accumulation of early myocardial infarctions in men is only seen in the first two years after entry and the mechanism is unclear. When comparing dSSc and lSSc Kaplan-Meier curves, it seems to be a constantly increasing difference in survival, which is expected because dSSc patients are more severely ill in terms of more involved organs, and involved organs being more severely damaged.[33]

The increased risk of cancer among first degree relatives of SSc patients, raises the possibility that genetic factors may predispose both to SSc and to the development of cancer.[34] In this study, lung cancer was the most frequent type of malignancy, a finding in accord with those of earlier studies.[14 15] In epidemiological studies of lung cancer, squamous cell carcinoma has been found to be the most frequent form of the tumour (30–35% of all cases), followed by adenocarcinoma, and small cell carcinoma.[35] Smoking affects all the major types of lung cancer, in particular squamous and small cell carcinomas. Chronic inflammatory disease of the lung, such as interstitial fibrosis, on the other hand is associated with the occurrence of adenocarcinoma.[35] This may explain why five of our seven lung cancers were adenocarcinomas, and only two were squamous cell carcinomas although six of these seven patients were smokers. Five of these patients manifested radiological signs of pulmonary fibrosis at a mean of four years before the cancer was diagnosed. The occurrence of chronic inflammatory disease of the lung may thus be the pathophysiological basis of the increased incidence of cancer among SSc patients.

The CYC treated patients were not comparable to the untreated patients according to disease severity, but the absence of increased cancer mortality in particular, and the absence of bladder cancer and leukaemia in the CYC treated group is encouraging, although the observation time is only 4.6 years and bladder malignancy may occur 20 years after treatment.[16] However, SSc patients may be at risk of dying of causes more related to the disease before they develop cancer. The risk of inducing malignancy by CYC has yet to be evaluated.

To conclude, these findings confirm mortality to be increased among SSc patients, especially among men with dSSc. However, survival rates were better than those reported from earlier studies. The most common cause of death is cardiopulmonary disease. The increased incidence of lung cancer may be caused by chronic inflammatory disease of the lung. In this study, CYC treatment was not associated with increased incidence of fatal malignant neoplasms.

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