REVIEW

Scleroderma and survival

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Scleroderma (systemic sclerosis) is a multisystem disorder which can often be confined to the connective tissues outside the major organ systems. The morbidity, and ultimately the mortality, risk from scleroderma stems, however, from the possible involvement of the lungs, heart, or kidneys. The disease itself is rare and often fatal when one of a number of different combinations of internal organs is affected. As a consequence, overall survival rate is a useful measure of outcome, which can be applied across groups of patients in studies of natural history. This is different from the situation with other connective tissue disorders, such as systemic lupus erythematosus, which have a relatively low mortality[1] and for which other outcome indicators are more appropriate.[2 3] The other advantages of adopting survival as the standard measure of outcome are the relative ease of obtaining mortality data and the standardisation in data collection between centres.

There are a number of problems in interpreting survival data from the various centres. Firstly, as mentioned above, scleroderma is a rare disease with an annual incidence of under 10 per million population in both the United Kingdom[4] and other countries.[5] Inevitably, therefore, expertise at managing patients with scleroderma becomes concentrated in a few tertiary referral centres, and it is from such centres that the natural history data emerge. Such centres, however, are likely to receive the more severe cases and thus their experience might overestimate the true mortality from scleroderma. Secondly, there is often a long delay between clinical onset and referral due to the nature of the early features,[6] and calculating survival from first attendance ignores that referral gap. Thirdly, retrospective studies of survival in patient attenders using their recalled date of disease onset are biased owing to the study cohort being, by definition, a surviving cohort who were selected for study on the basis that they had not died before referral—the so called 'immortality bias'.[5] Some studies have attempted to overcome these problems by concentrating only on locally referred patients identified early in the course of the disease.[7] Finally, there is a problem in some studies of loss to follow up with incomplete ascertainment of vital status at the end of the follow up period.[8] This introduces bias if there is a selective difference (which there normally is) in the likelihood of death between those with and without follow up data. The direction of such a bias varies. In some study designs, using population death registers, deaths are preferentially notified. By contrast, where patients or their doctors are contacted for follow up, deaths are preferentially missed.

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Survival from scleroderma

There have been a number of studies of survival in the past 50 years (tables 1 and 2). The disease definition used is unlikely to have remained constant and indeed the American College of Rheumatology (ARA) criteria were only introduced in 1980,[20] too late for most of the long term studies reported. The figures by Tuffanelli and Winklemann, based on a large series of patients seen at the Mayo Clinic between 1935 and 1958, are likely to be overestimates given the large number of subjects for whom follow up data were unavailable.[11] The data from Farmer *et al* are also derived from the Mayo Clinic population, but a more restricted sample (those diagnosed between 1945–52), and interestingly show a lower five year survival rate of around 50%.[9] The surprising aspect about the data from the numerous studies presented in table 1 is the relative consistency of survival reports between centres and countries despite the long time period covered by these studies. There have only been two studies from the United Kingdom,[8 14] both on relatively small numbers of cases, but both showing a higher

Table 1 Survival after presentation with scleroderma

First author	*Ref No*	*Country*	*Period*	*Number studied*	*% Survival at year:*			
					1	*5*	*7*	*10*
Tuffanelli	11	US	1935–58	727		70		59
Farmer	9	US	1945–52	236		51		
Sackner	10	US	1957–64	65	73	34	27	
Bennett	8	UK	1947–70	67		73		50
Medsger	12	US	1947–68	86	68	48	35	
Medsger	12	US	1955–70	210	78	51	35	
Medsger	13	US (men)	1963–70	358	70	44	35	
Rowell	14	UK		84				74
Barnett	15	Australia	1953–78	118		70		55
Eason	7	New Zealand	1970–80	47		60		42
Wynn	16	US	1970–84	64	98	69	59	51
Bulpitt	17	US	1984–89	52	90	64		

Table 2 Survival after scleroderma by extent of skin sclerosis at presentation (results from two studies)

Extent of skin sclerosis	*n*	*% Survival at years:*		
		5	*10*	*15*
Digits alone				
Giordano *et al*[18]	28	84	47	33
Barnett *et al*[19]	86	79	75	43
Intermediate				
Giordano *et al*[18]	25	75	22	10
Barnett *et al*[19]	66	77	61	48
Truncal				
Giordano *et al*[18]	37	50	26	17
Barnett *et al*[19]	25	48	22	—

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survival than results from other centres would suggest. In all studies survival decreases with increasing follow up, which is not solely a feature of increasing age.[12] The average age at the start of follow up in these series was between 40 and 50 and the general population survival rates over a 10 year period in this age group would be expected to be high. The increased mortality is almost linear over time, and in those studies with 15 or more years of follow up[18 19 21] shows no signs of reaching a plateau. Although anecdotally there are clinical observations of patients whose disease runs a benign course for many years, the conclusion from studying groups is that even prolonged survival does not protect against an increased mortality risk.

Risk factors

DEMOGRAPHIC FACTORS

Survival in the general population is higher in women than in men and declines with increasing age. It is thus difficult to interpret those reports which suggest an increased mortality from scleroderma in men[12 14 15] and in those aged over 40 at presentation.[8 12 13 16] Few reports have adjusted survival rates for population experience, but where this has been done it does seem that the male excess risk (15% at nine years) and the age >45 *v* age <45 excess risk (34%) are both substantially greater than would be expected after considering the effects of these variables on population death rates.[12] In the small subgroup of patients with presentation in the eighth and ninth decades the prognosis seems good with internal organs rarely affected.[22 23] Undoubtedly, part of the explanation for that observation lies in the selective survival of those with limited disease whose diagnosis might have been missed for many years.

Black races in the United States have a lower survival at one year than white races, but this disadvantage does not widen with follow up.[12] Both alcohol and cigarette consumption in men correlate with poor survival,[13] but this might reflect the general health risks associated with such exposures.

EXTENT OF SKIN SCLEROSIS

The extent of skin sclerosis has been traditionally taken as a useful marker both of current severity and future prognosis. The extent of skin sclerosis is normally divided into limited (distal to wrists and ankles with or without the face) and diffuse.[24] Others have subdivided the diffuse group into those with and without truncal disease.[6] Those with limited disease have a higher incidence of positivity for anticentromere (antikinetochore) antibodies, whereas those with diffuse disease are more likely to be positive for antibodies to scleroderma-70 (topoisomerase-1) and antinucleolar antibodies.[19] It is the latter group that has more internal organ disease,[24] and it is thus reasonable to compare survival in groups defined by extent of skin sclerosis. In two recent studies there seemed to be a strong association between the extent of skin sclerosis and survival, with consistent 10 year survival rates below 25% in those with truncal disease and substantially higher rates in patients with digital disease alone (table 2).[18 19] It is also apparent from the data that even limited skin disease at presentation is associated with a high mortality risk and that this risk increases with time. A recent small study found that the extent of skin sclerosis did not explain the mortality risk at five years,[17] but this result is at odds with the experience of others.

SCLEROSIS IN OTHER ORGANS

There is absolutely no doubt that sclerosis of the kidneys, lung, or heart is a bad prognostic sign. In one large study of 646 patients from Pittsburgh none of the 24 patients with kidney disease at onset survived for six years, and even the one year survival was only 25%.[21] Similarly, those with the heart affected, in the absence of kidney disease, had a three year survival of 50% and none survived for more than nine years. By contrast, the presence of isolated lung disease was consistent with a 10 year survival of over 50% and those with none of these major organ systems affected had a 10 year survival of 70%. Numerous other studies report similar findings.[7 13 15] It is perhaps too early to judge whether the advent of the use of angiotensin converting enzyme inhibitors for the treatment of scleroderma renal crisis will improve the prognosis from scleroderma kidney disease, but this therapeutic advance seems the only likely possibility of substantially altering mortality.[25]

OTHER MARKERS

There have been two reports suggesting that anaemia is a bad prognostic sign[9 13] which may be independent of any renal effect on blood. Similarly, there have been a number of studies suggesting that the erythrocyte sedimentation rate at presentation is a predictor of future mortality,[9 13 17] with a rise as modest as 32 being important. Others have found no effect on mortality of the sedimentation rate or other serum markers, including antinuclear antibody positivity and immunoglobulin concentrations.[8 12] Anecdotal reports suggest that better delineation of the specific staining pattern when testing for antinuclear antibodies may be more valuable as a predictor than just the presence or even the titre of antinuclear antibodies (Jablonska, personal communication).

Comorbidity

Mortality from any disease reflects the summated risk of death as a direct consequence of that disease plus the risks (excess or not) of death from an apparently unrelated cause. The problem of defining a 'related' cause is a real one and the distinction is not always clear. In one early series 21 of 42 deaths were due to scleroderma related renal disease, nine to scleroderma related heart disease, and the remainder to a variety of diverse causes.[26] By contrast, a more recent series from Australia of 86 deaths had only 16 (19%) due to renal disease with only half the deaths being 'scleroderma

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related'.[19] This proportion ranged, however, between 36% for those with limited skin sclerosis to 76% for those with truncal skin disease. There are no comparative data to suggest whether patients with scleroderma do have a higher mortality from all causes (excluding scleroderma related deaths) than the general population, a situation which probably applies to rheumatoid arthritis.[27]

There have been some interesting suggestions of specific cancer risks with scleroderma. One report of an unexpected cluster of breast cancer cases in women with scleroderma[28] was followed by a formal epidemiology study that could not confirm an excess of breast cancer but did suggest a temporal relation between the onset of the two diseases in some women.[29] More relevant in that study was the increased rate of lung cancer in patients with scleroderma. This seems to be independent of cigarette smoking but related to the presence of pulmonary fibrosis.[30] This is perhaps not a surprising result given the association of lung cancer with pulmonary fibrosis from occupational causes. Thus it is perhaps likely that part of the excess mortality from scleroderma is not only primarily attributable to the scleroderma but also due to secondary associated pathological changes, though the exact magnitude of any increased risk in 'unrelated' deaths is unknown.

Conclusion

Scleroderma has a high excess mortality, which continues over time for at least 15 years. The magnitude and continuing time course of this excess mortality are similar to those noted in some cancers, such as that of the breast. Survival has altered little in the past 50 years, which might reflect the lack of any treatment that has been shown to improve prognosis. The extent of skin sclerosis, although an imperfect marker, is perhaps the best current guide to future prognosis.

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