RHEUMATOID ARTHRITIS AND INTERSTITIAL LUNG DISEASE

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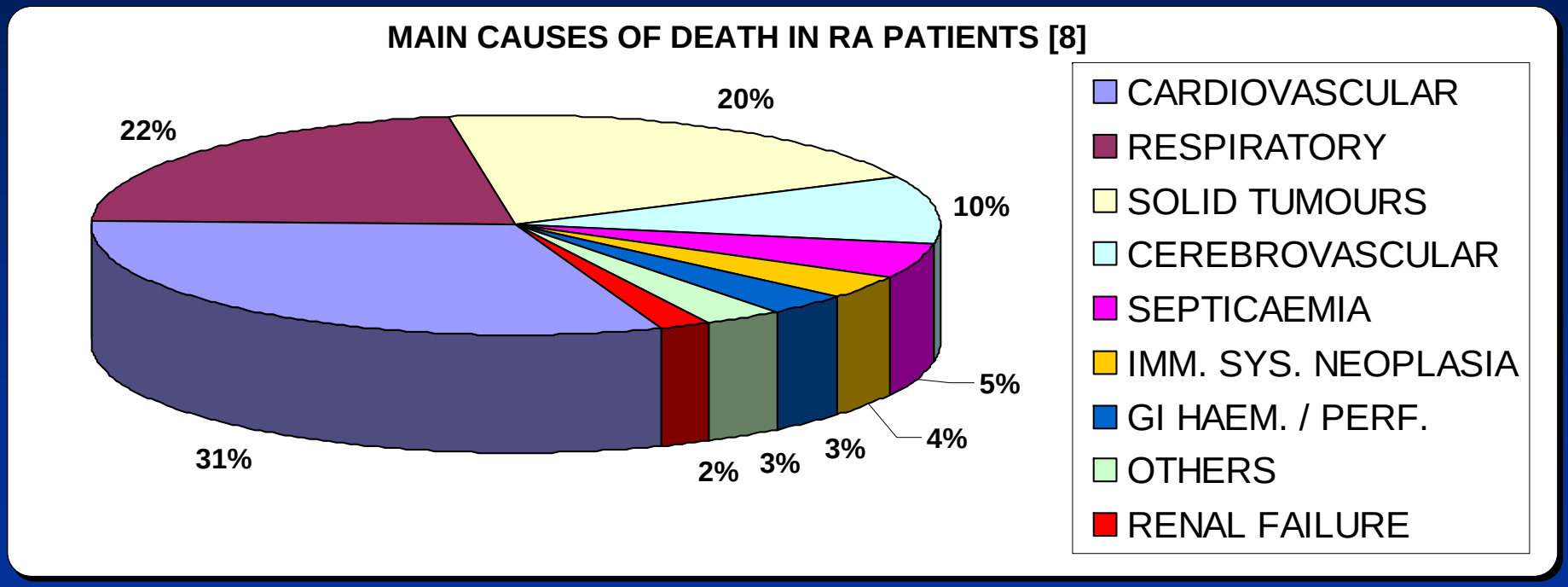
RA-ILD – epidemiology

- Recognised for over 50 years
- Present in up to 40% established RA patients at post-mortem
- Evident in up to 25% on HRCT
- Clinical prevalence of 3-5% in RA – lifetime risk calculated at 7.7% by Bongartz et al 2010.

Causes of mortality in RA



Primary respiratory causes:

1. Chest infection (9%)
2. Pulmonary fibrosis (6%)

Young A (ERAS) Rheumatology 2007

RA - epidemiology

- Large multi centre study of prevalence of several systemic complications of RA
- All found to be decreasing over the last two decades with the exception of ILD
- Due to increased awareness and sensitivity of tests, or to true increase?

Bartels et al Rheumatology Sept 2010

RA-ILD – predisposition

- Male sex
- Increasing age
- Presence of erosions
- Other extra-articular features eg nodules
- Rheumatoid factor positivity
- Smoking

Natural history of ILD

- The natural history of interstitial lung disease (ILD) is known to be poor with overall median survival from diagnosis of 3 years
- Conflicting evidence exists as to whether the prognosis of ILD associated with rheumatoid arthritis (RA) is any different

Hubbard 2002, Park 2007, Kelly 2006

Survival

- Found to be better in RA-ILD patients when compared to CFA patients matched for age, gender and symptom duration
- Mean survival was 4.9 years in RA-ILD as compared to 3.0 years in the CFA group
- Most deaths occurred in the first two years in both groups with some long term survivors – mainly among RA patients

FOLLOW UP

- Absence of finger clubbing, preserved gas transfer and active alveolitis were good prognostic factors
- Death was due to respiratory failure in 7 patients with CFA and to lung cancer in 3.
- Death in RA patients was less often due to respiratory failure (2) but more frequently a result of lung cancer (5).

TREATMENT

- Immunosuppressive drugs were used in 12 patients, more often in RA > CFA patients
- Nine of the 10 survivors had received steroids +/- azathioprine /cyclophosphamide
- Lung cancer was more common in those patients treated with these drugs (33%) than those who were not (17%)

Recent work

- Relative risk for dying early was 3.0 in patients with RA-ILD: Bongartz 2010
- UIP had worse mean survival than NSIP (3 years vs 6 years): Kim 2010
- Increased cellular activation in alveoli of RA-ILD involving T and B cells: Nannini 08
- CCP may exist in ILD without RA and predict later articular disease: Invi 2008

Ongoing clinical research

- We prospectively identified all cases of ILD in RA patients over a 10 year period from 2000
- Defined ILD on radiological grounds – assessed clinically, then all with dyspnoea or chest crackles had PFTs & Chest x ray
- Those with abnormalities in either assessment proceeded to HRCT

Prevalence

- Population of 250,000 people in and around Gateshead
- Database identified approx 1,600 RA patients from December 2000
- Within last decade we have confirmed the presence of ILD on HRCT in 49, equating to ***minimum*** prevalence of 3.125%
- Likely to be a significant underestimate

Demography

- Female: male ratio = 27:22 = 1.25:1

  - significantly lower than that seen in the RA population as a whole (3.1:1)

- Median age at identification of ILD was 74 years (46 – 87 years)

- Median duration of RA at diagnosis of ILD was 6 years (0 - 24 years)

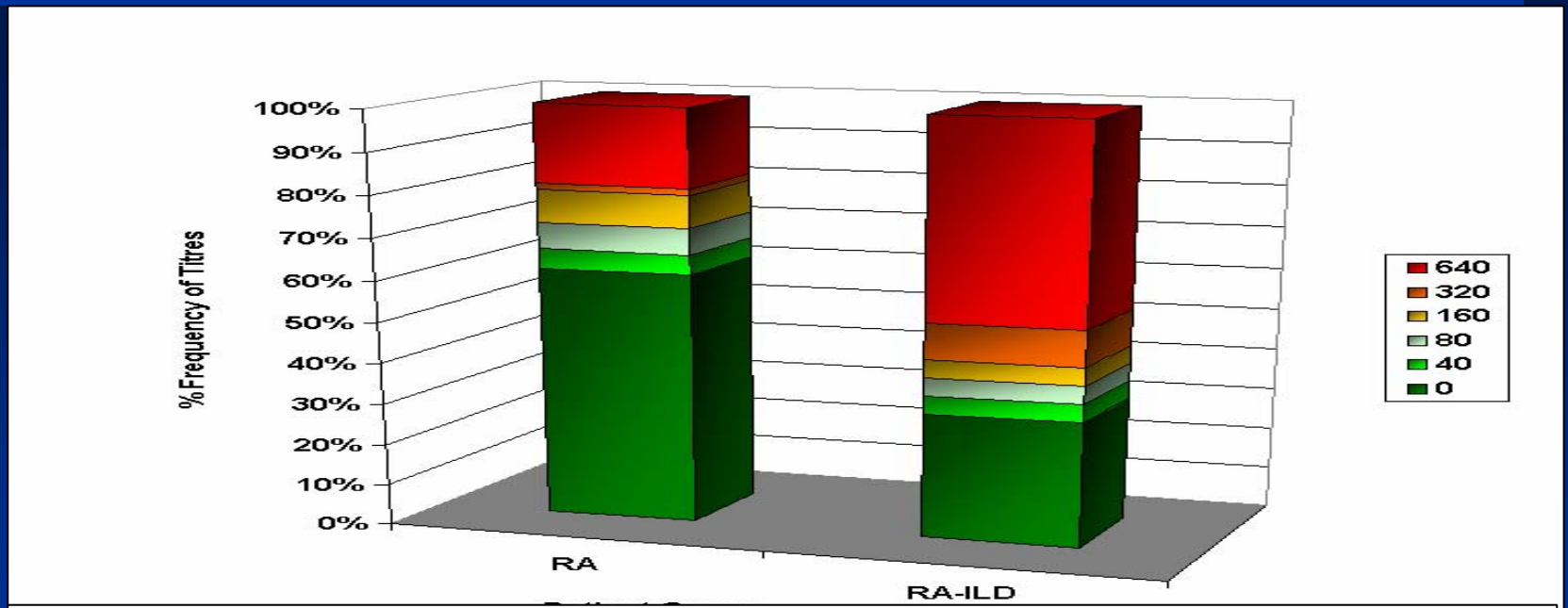
RA-ILD subtypes on HRCT

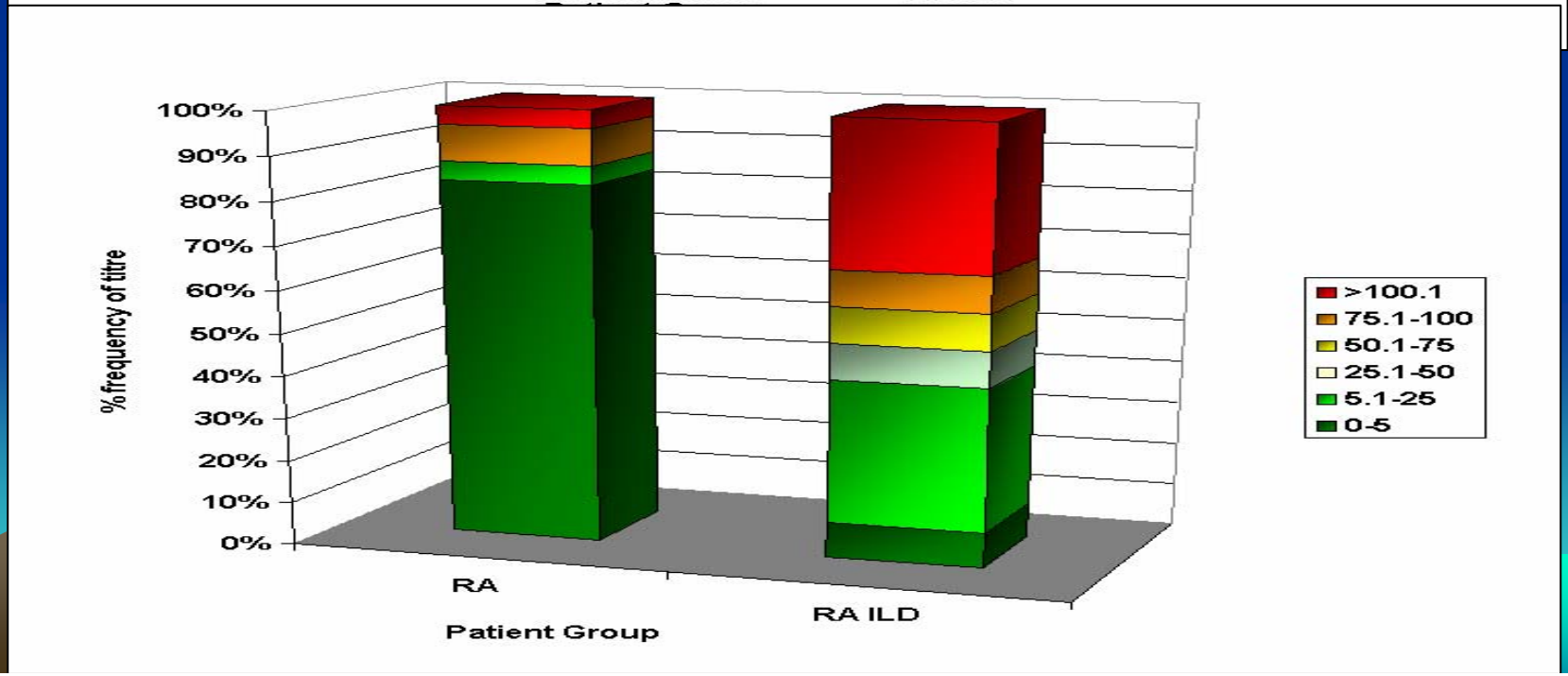
- Usual interstitial pneumonia 44%
  - carries worse prognosis
- Non specific interstitial pneumonia 36%
  - more responsive to early therapy
- Cryptogenic organising pneumonia 10%
  - better prognosis (if diagnosed!)
- Mixed or indeterminate pattern 10%
  - variable outcome

Serology

- 81% of RA-ILD patients seropositive for RA with a median titre of 1/320
- Significantly greater than overall RA population where 65% RF ‘+’ @ titre of 1/160
- 97% of RA-ILD patients were CCP positive with median of 223 units (negative= 0-7)
- Significantly greater than overall RA population – 67% ‘+’ @ median 89 units

Rheumatoid Arthritis Auto-Antibody Measurements and Associated Interstitial Lung Disease





Serology and RA-ILD

- Suggests CCP may be associated with RA-ILD, both in presence and titre
- Previous work has suggested link between RA and systemic manifestations

  (Alexiou 2008)
- May be other links between CCP and systemic complications eg. lymphoma

Effect of anti rheumatic drugs

- All anti TNF agents have been reported to be associated with acceleration of death from underlying ILD

Hagiwara, Ostor, Collins 1997-2008;

- BSRBR data suggests that the presence of RA-ILD is associated with shorter survival but does not necessarily attribute this to anti-TNF therapy
- Patients with prior ILD have a tenfold increased risk of developing pneumonitis on Methotrexate

Kelly Rheumatology 2004

Therapeutic philosophy

- To try and treat the individuals' major symptoms, be they articular or respiratory, without adversely affecting the other aspects of disease
- Meant using selected DMARDs where joint disease dominated
- Experimenting with immunomodulation where lung disease major concern
- Trying monoclonal anti B cell therapy in patients where both lung and joint disease a major issue

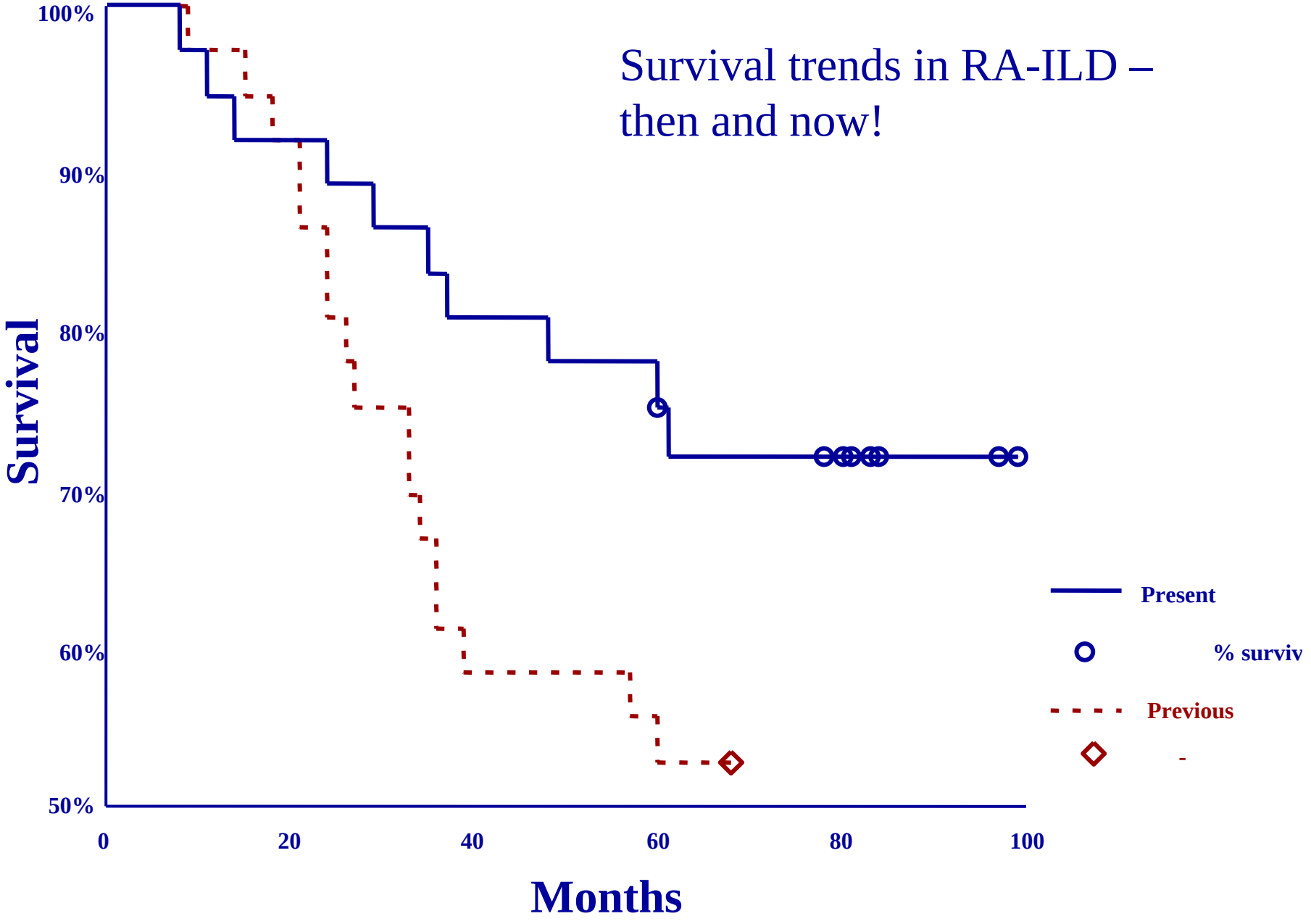
Treatment - DMARDs

Azathioprine / 6 MP	24
Prednisone	12
Myocrisin	16
Salazopyrin	11
Leflunomide	10
Penicillamine	4

Immunomodulation

Mycophenolate 1 – 2 gms daily	28
Rituximab 1 gm x 2 doses 6/12ly	12
Cyclophosphamide IV 15 mg / kg x 6	8
Methylprednisone IV 500 mg x 6	8

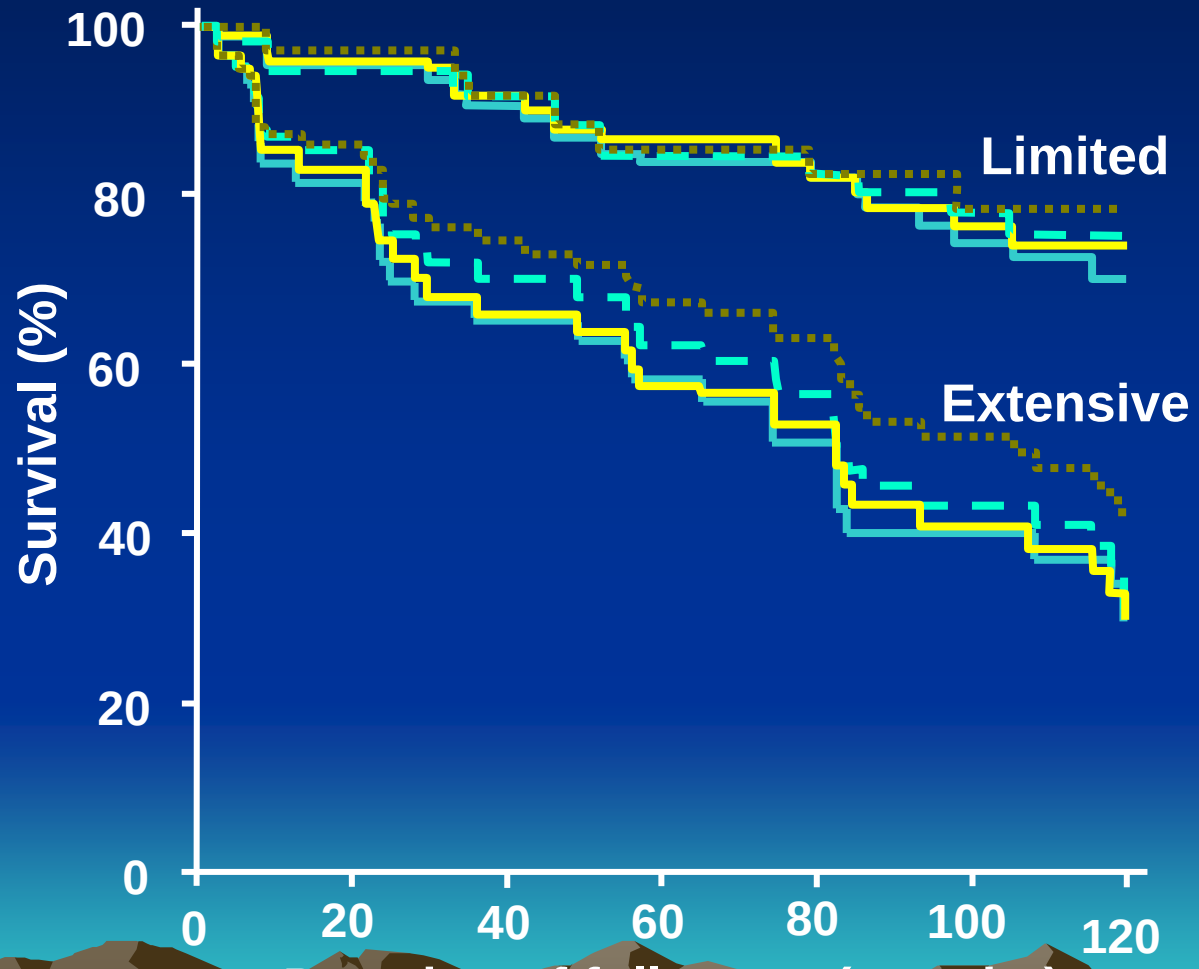
Survival trends in RA-ILD – then and now!



Survival trends in RA-ILD

- Definite trend towards longer survival among those patients treated in the last decade than in the previous ten years
- May reflect the change in treatment approach – is it all benefit from newer agents or is some from avoidance of harm from older ones?
- Is response related to the subtype of RA-ILD, or to other factors – eg disease extent

Disease extent determines mortality



Goh NS, *et al. Am J Respir Crit Care Med.* 2008 Mar 27;

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Assessment of the individual

1 Mild asymptomatic disease (incidental) - stable lung volume; preserved gas transfer

2 Limited pulmonary disease – gradually progressive dyspnoea & falling gas transfer

3 Extensive disease, often with other systemic manifestations

Tailoring treatment…

1 No specific treatment, but avoid anti TNF therapy and Methotrexate. Monitor yearly.

2 Oral therapy with Azathioprine 200mg, 6 Mercaptopurine 100mg daily or Mycophenolate (MMP) 1 – 2 gms daily

3 IV treatment with Cyclophosphamide 15 mg / Kg and methylprednisone 10 mg/Kg given x6 a month apart with MMP maintenance therapy for responders

Other therapeutic considerations

- Exclude infection –consider BAL if in doubt
- Exclude drug induced disease – eg MTX
- N acetyl cysteine 600 mg tds may be useful in presence of alveolitis
- Low threshold for suspecting pulmonary emboli – CTPA. Anticoagulate if unsure
- Role of transplantation in younger patients

 - refer early if under 55 years

- Oxygen and opiates are often effective palliation

Newer therapeutic developments

- N – acetylcysteine 600 mg tds
  Demedts 2005
- Anticoagulation with INR of 2.5 - 3.0
  Hubbard 2007
- Mycophenolate 500mg – 2 gm daily
  Swigris 2006
- B cell antagonists – Rituximab 2 x IV

Other thoughts

- Antıbıotıc therapy
  - Co-trımoxazole
  - Tetracycline
  - Azıthromycın
- Poster on combınatıon therapy wıth IV Ig. Cyclosporın and Cyclophosphamıde
  - ın partıcular role of IV Ig

Mycophenolate

- Useful as an alternative to Azathioprine in maintenance of response in scleroderma and SLE
- Comparisons suggest equipotency with cyclophosphamide in remission induction
- Initially used mainly in renal disease but found to be useful in lung manifestations
- Early evidence of efficacy in RA-ILD now

Rituximab

- Used for over a decade in treatment of lymphoma, including many RA patients
- CD 20 B cell markers identified in small bronchi and airways of patients with RA-ILD suggesting targeted therapy may work: Atkins 2006
- Rituximab now known to be most effective in strongly seropositive patients – and our data confirms this is the case in almost all RA patients with ILD

RA-ILD collaboration (UK)

- Multicentre database of all cases of RA-ILD – 33 centres interested now
- Examine epidemiological, clinical, radiological, immunological, biochemical and genetic factors predicting outcome
- Record drug regime for disease subtype, together with survival trends

OUTCOME MEASURES

- Survival curves
- Stabilisation of pulmonary function
- Stabilisation of HRCT findings
- Drug related toxicity

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