Is there a role for High Dose Interleukin-2 ?

Robert Hawkins

MANCHESTER 1824

The Christie NHS Foundation Trust

YES!!

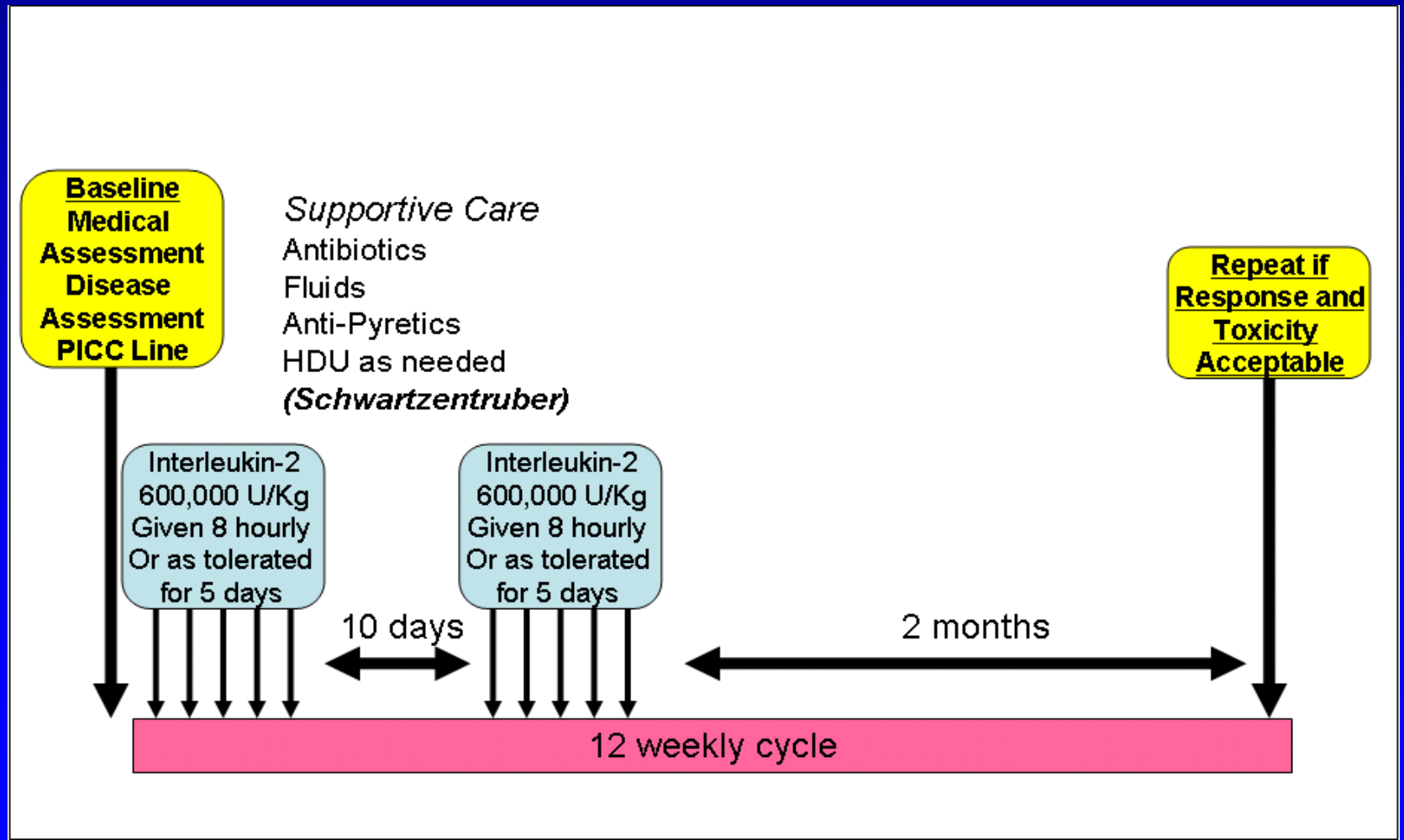
- It is the **only** systemic therapy offering a chance of long term remission/cure
- In carefully selected patients the outcome is excellent
- ALL PATIENTS should be considered for high-dose interlekin-2
  - *Although only a small minority will be treated*

Overview

- What is high dose IL2?
  - How is it given
  - Side Effects
- The Outcome of Treatments
  - Historical Use
  - Selection of patients
  - Latest Results
- Where can / should it be used?

High dose IL-2 regimen

- Immunotherapy
  - Activates T cells, NK cells to kill cancer cells



Treatment Effects

IL2 Infusion
Paracetomol
Chlorpheniramine
Ranitidine

Rigors
Pethidine
Increase IV fluids

Increase
IV fluid

Decrease IV fluid
Paracetomol
Chlorpheniramine

IL2 Infusion
Paracetomol
Chlorpheniramine
Ranitidine

0 | 3 hours | 6 hours | 10 hours

39°C

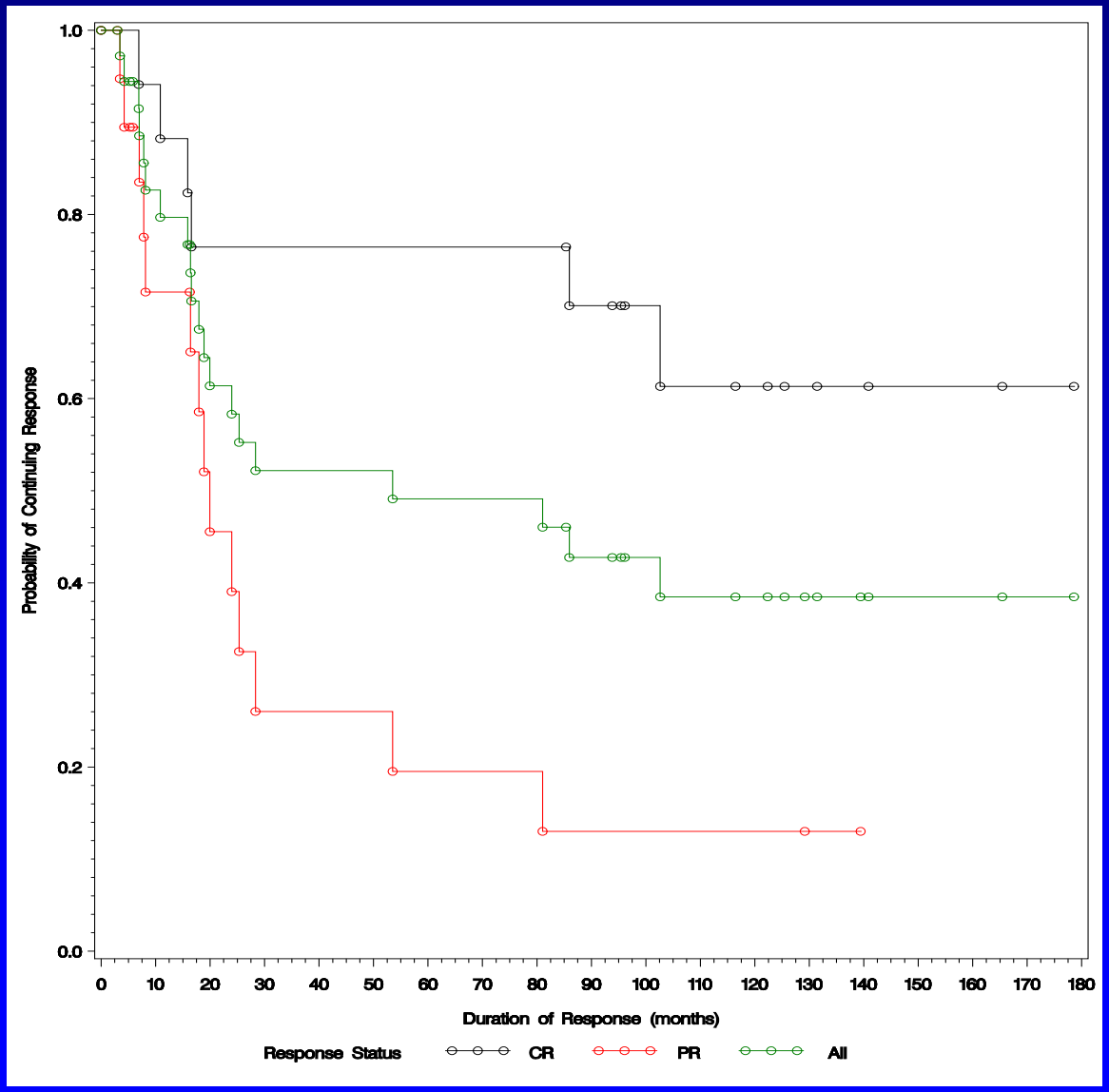
37°C

BP

120

80

High-dose IL-2 therapy: response durations – 255 pts



FDA approval 1992

15% response rate with durable responses in a small percentage of patients

Median response duration – 50 months

But:

Significant toxicity and cost

Application limited to selected patients treated at only a few centers

Prerequisites for IL2

- Few symptoms from cancer / reasonably fit
- Normal Lung Function
- Cardiac Assessment
  - All patients > 55 or prior history or previous Sunitinib have Stress ECHO
- Routine blood tests near normal
- Preferably limited metastatic sites

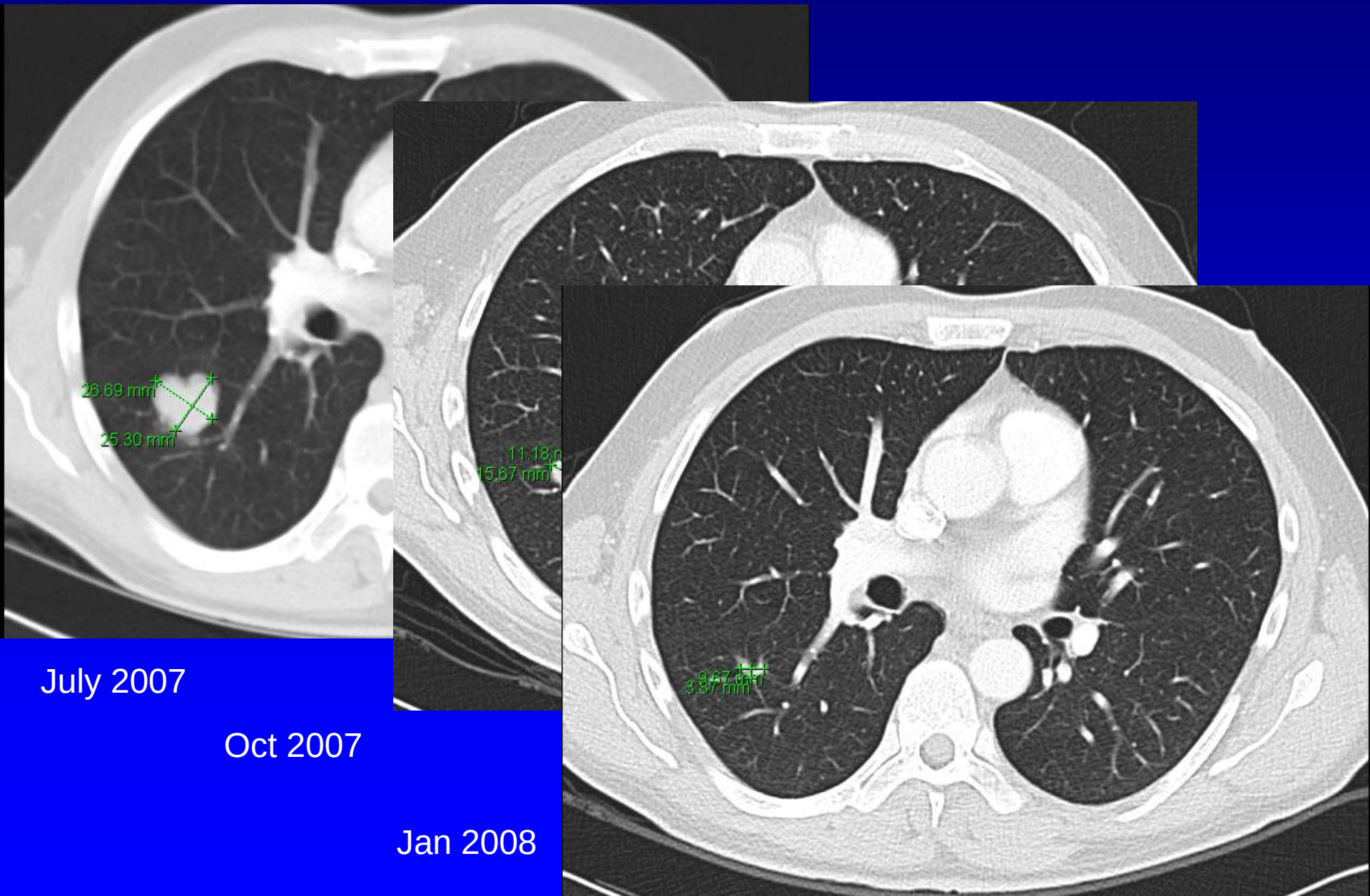
Our Experience

- Manageable on Medical Ward
- Rarely need ITU
  - Most cases due to unrecognised line infection
- Generally achieve about 8/9 doses
  - Range 4 – 14 per cycle
  - Generally consistent for individual patient
- Reasons for stopping
  - Renal impairment
  - Hepatic impairment
  - Arrhythmias – one due to acute hyperthyroidism
  - Patient preference

Patients recover very rapidly after stopping

Reviewed day 5 post treatment - usually getting back to norma

Speed of Response



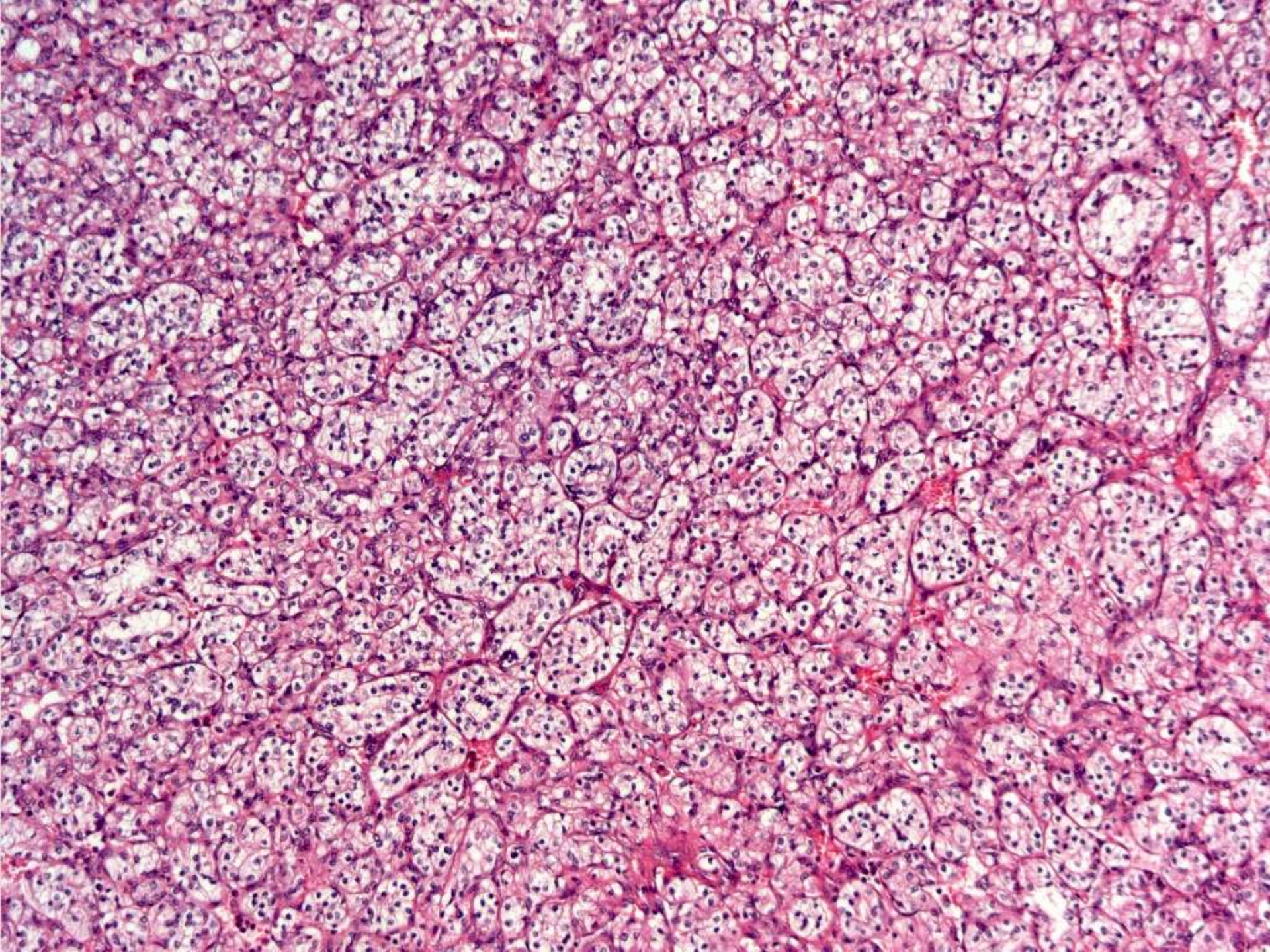
July 2007

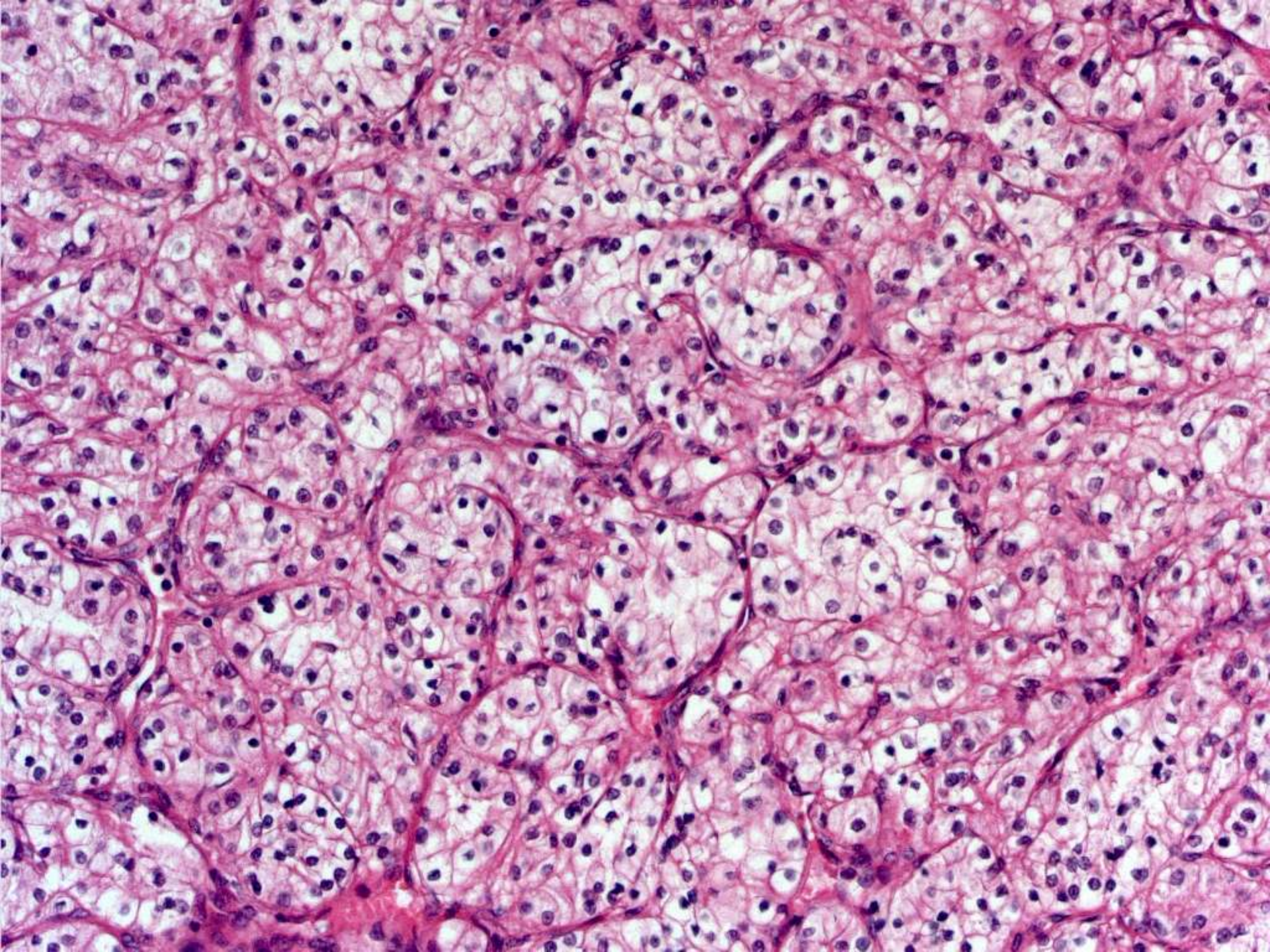
Oct 2007

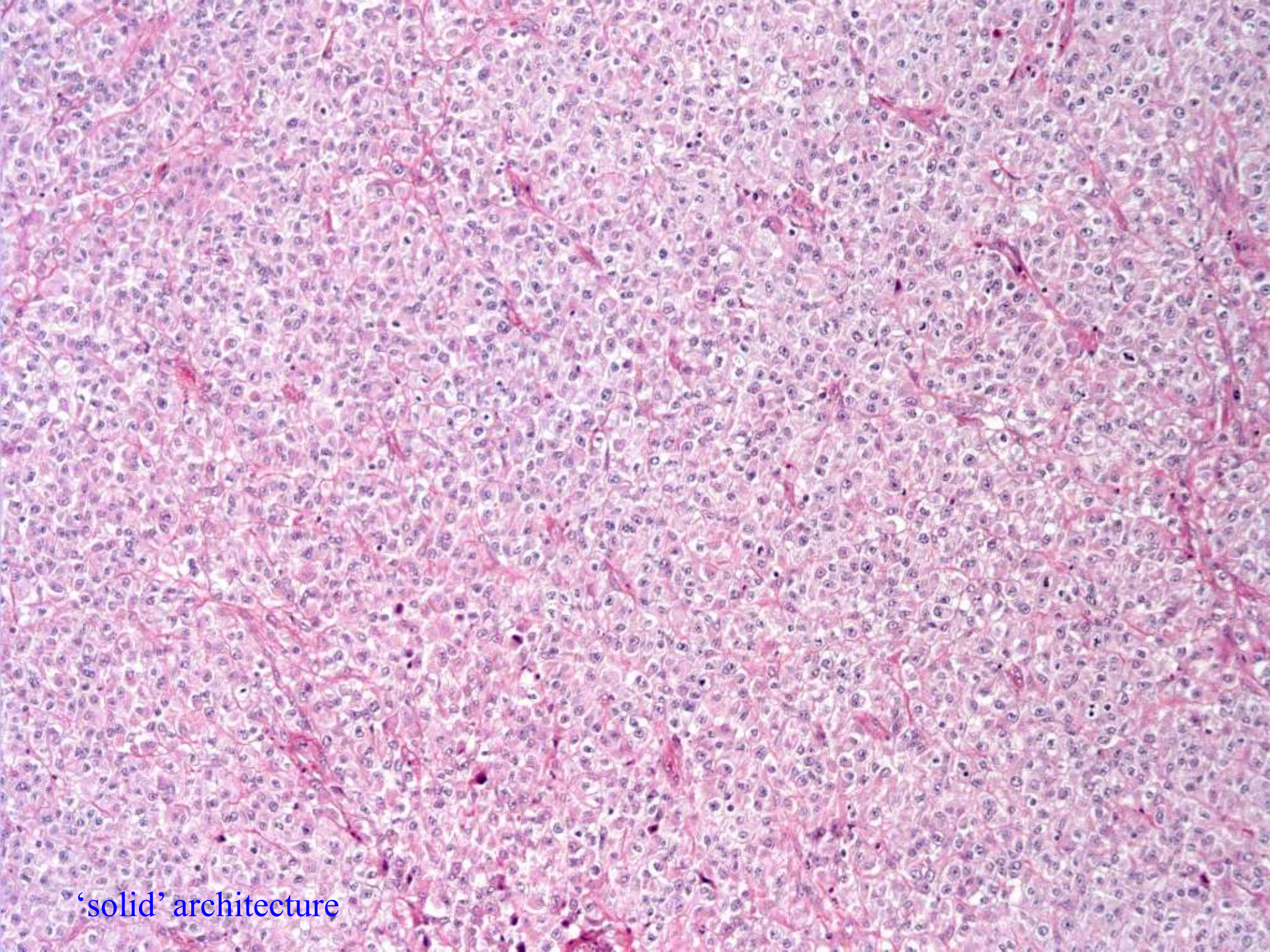
Jan 2008

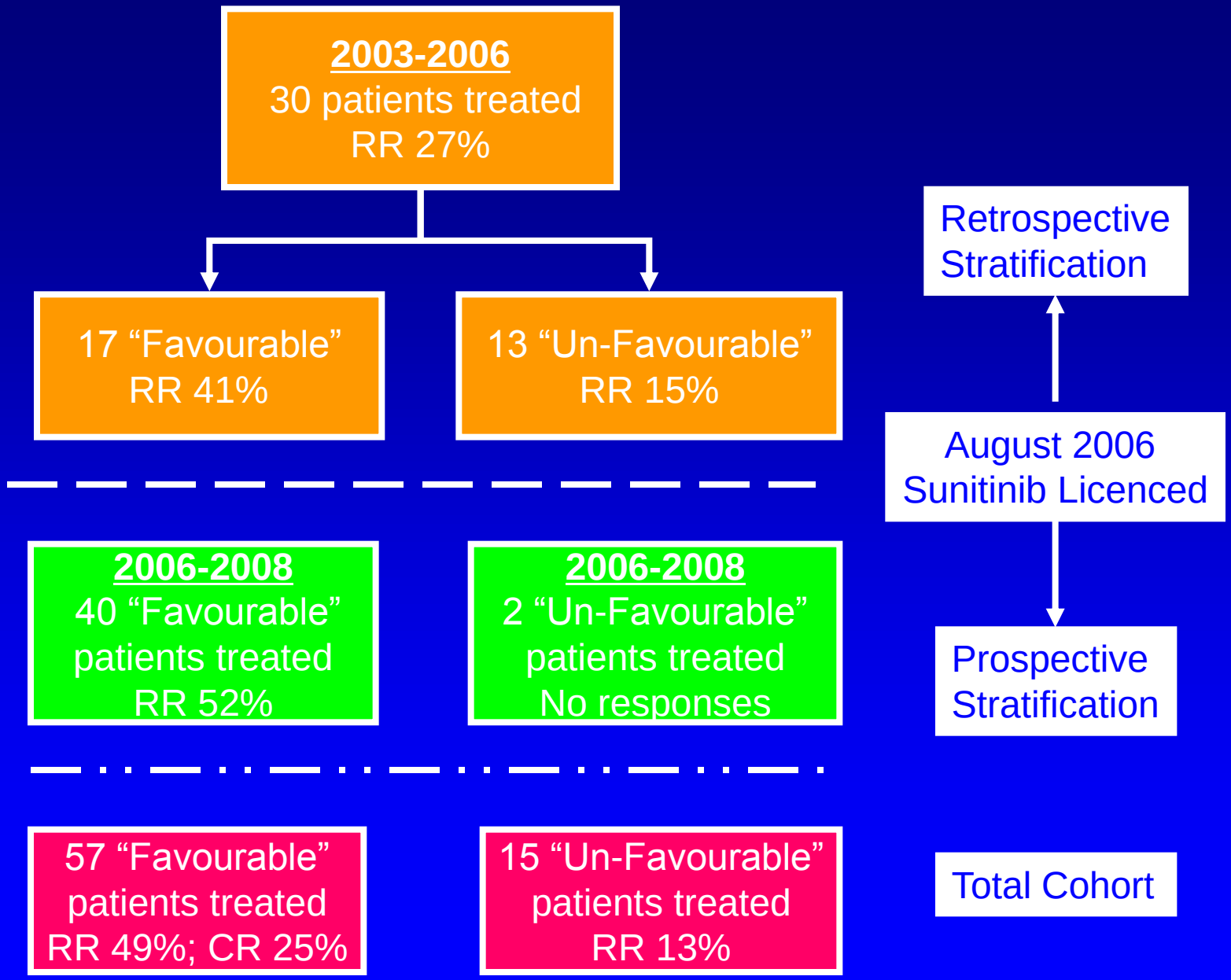
IL-2 treatment Predictors of Response

- Performance status 0 *
- One site of metastasis *
- Interval from diagnosis to treatment *
- Histology (Upton MP *et al J Immunother* 2005;28:488-495. Histological predictors of Renal Cell Carcinoma Response to Interleukin-2- based Therapy)






‘solid’ architecture


2003-2006
30 patients treated
RR 27%
17 “Favourable”
RR 41%
13 “Un-Favourable”
RR 15%
Retrospective Stratification
August 2006
Sunitinib Licenced
2006-2008
40 “Favourable”
patients treated
RR 52%
2006-2008
2 “Un-Favourable”
patients treated
No responses
Prospective Stratification
57 “Favourable”
patients treated
RR 49%; CR 25%
15 “Un-Favourable”
patients treated
RR 13%
Total Cohort

Summary of Responses

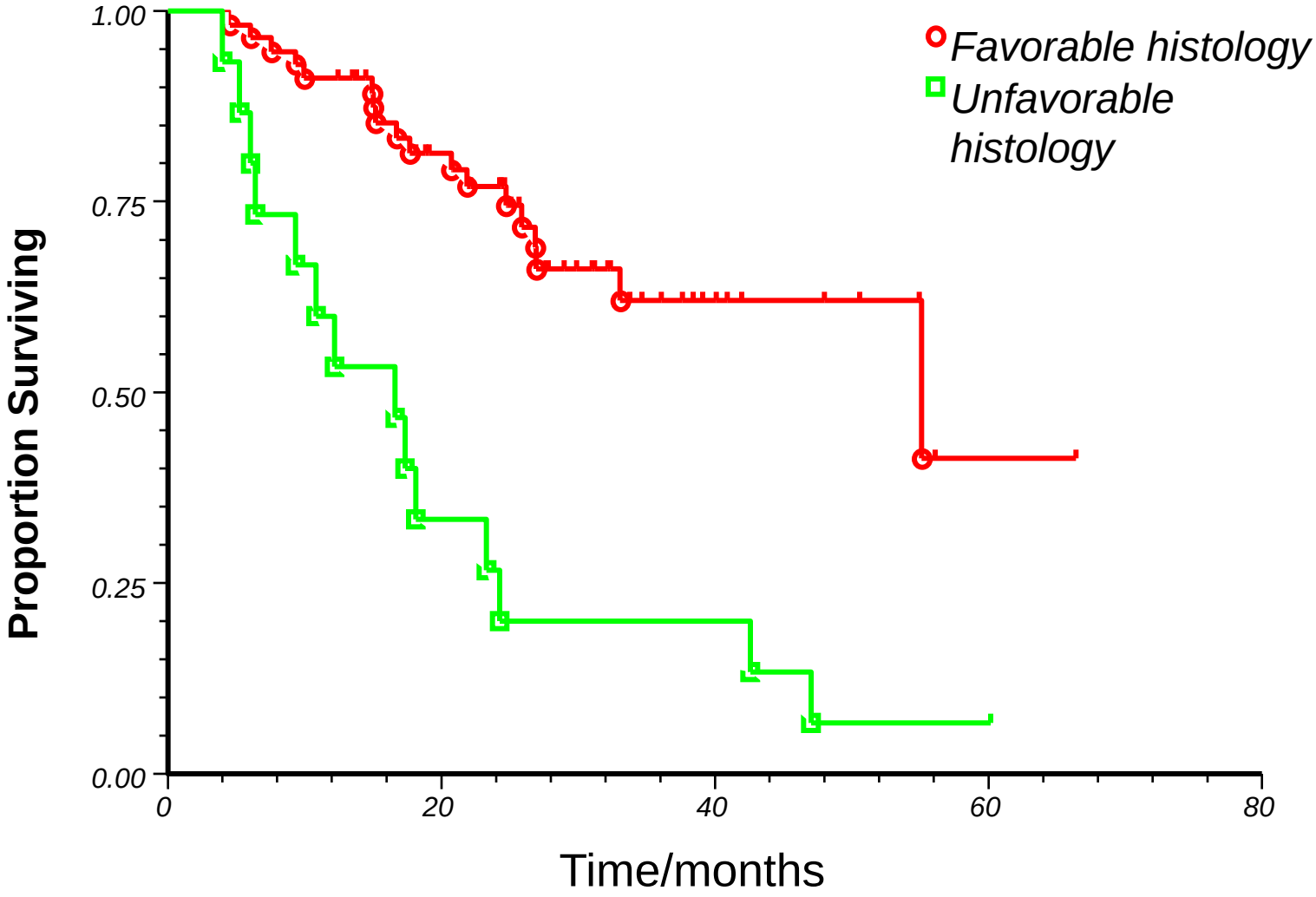
- Overall Responses 49%
- Complete Responses 25%
- Further 9% had surgical resection of remaining disease to Complete Response

Clinical Factor	Response Rate
Sex	
Male	20/41 (49%)
Female	8/16 (50%)
Age	
<55	14/24 (58%)
>55	14/33 (42%)
Prognostic Score	
Good	23/42 (55%)
Intermediate	5/15 (33%)
Organs of Metastases	
1	14/25 (56%)
2	11/18 (61%)
≥3	3/14 (21%)

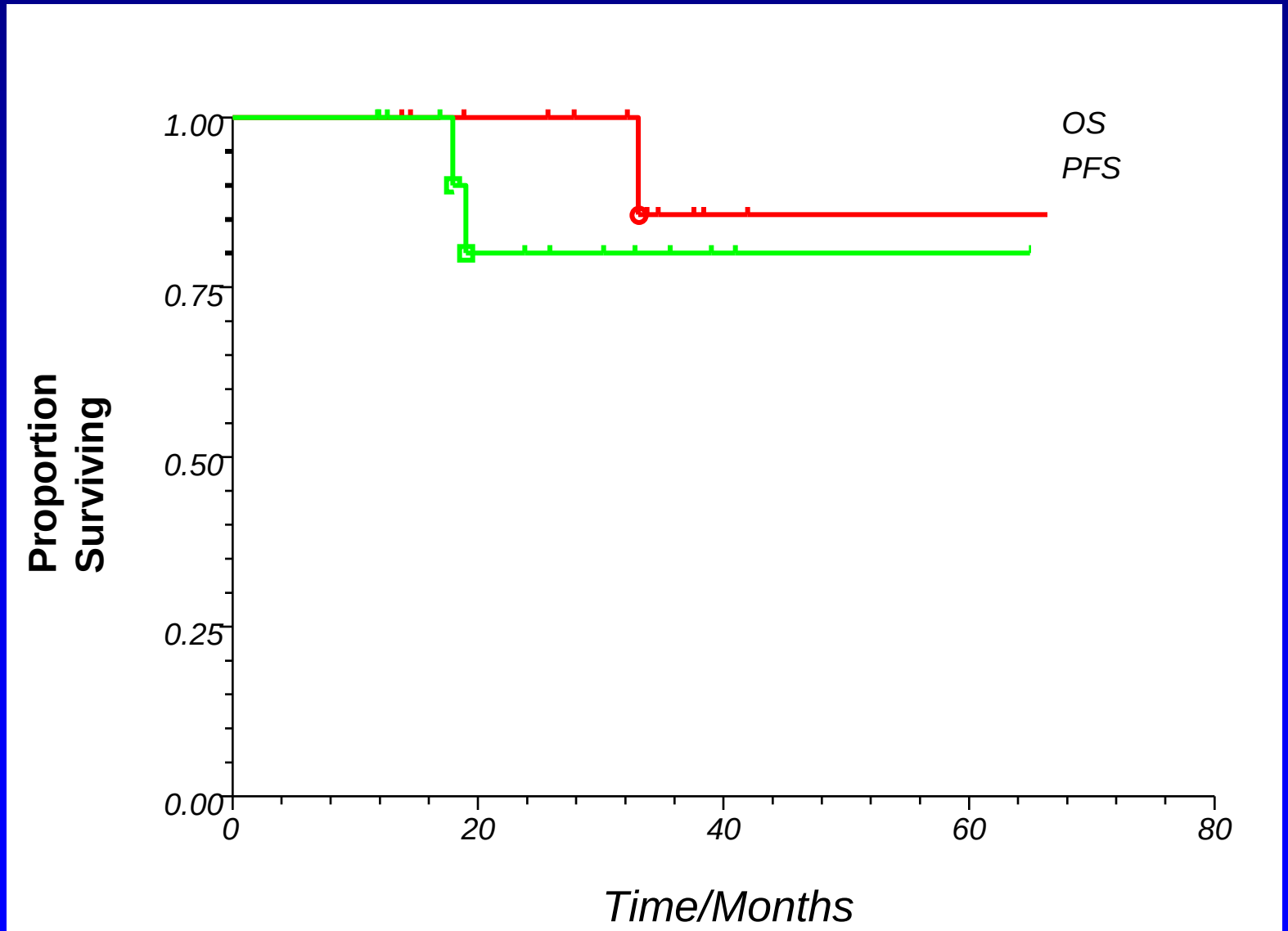
Predictors of Response to Interleukin-2

- Generally Good Prognosis patients
- Lung Metastases / Limited organ sites
- Histology
  - Classic Clear Cell Cancers
    - Pattern
      - » Alveolar
      - » Solid
    - Cellular Staining
      - » Non-granular (or high CAIX)
    - CAIX polymorphisms

OVERALL SURVIVAL BY HISTOLOGY

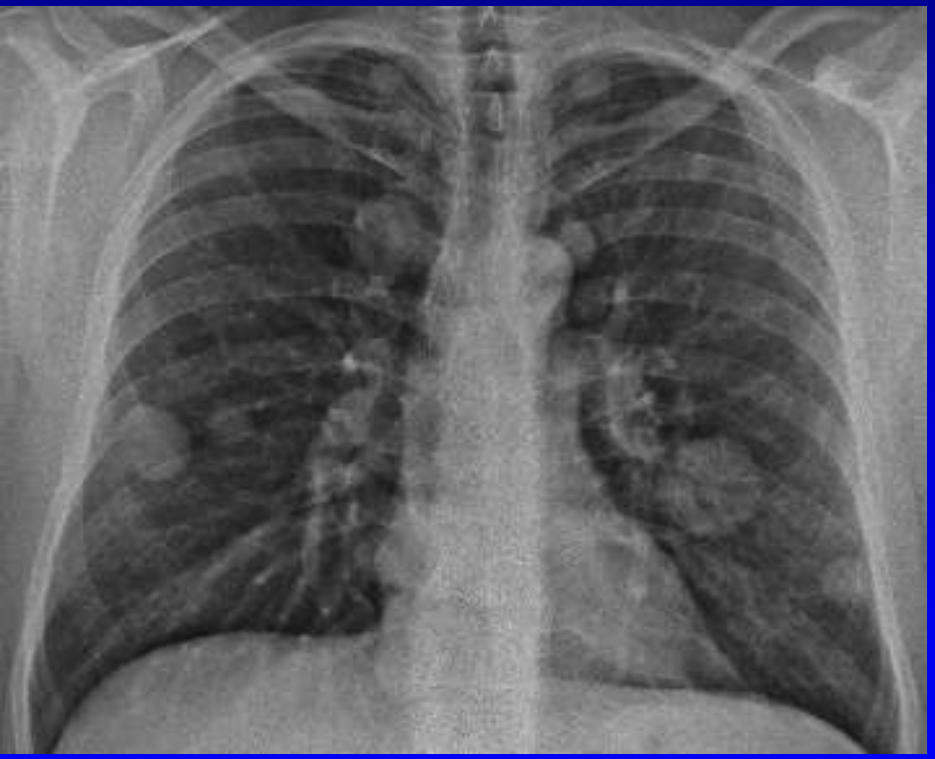


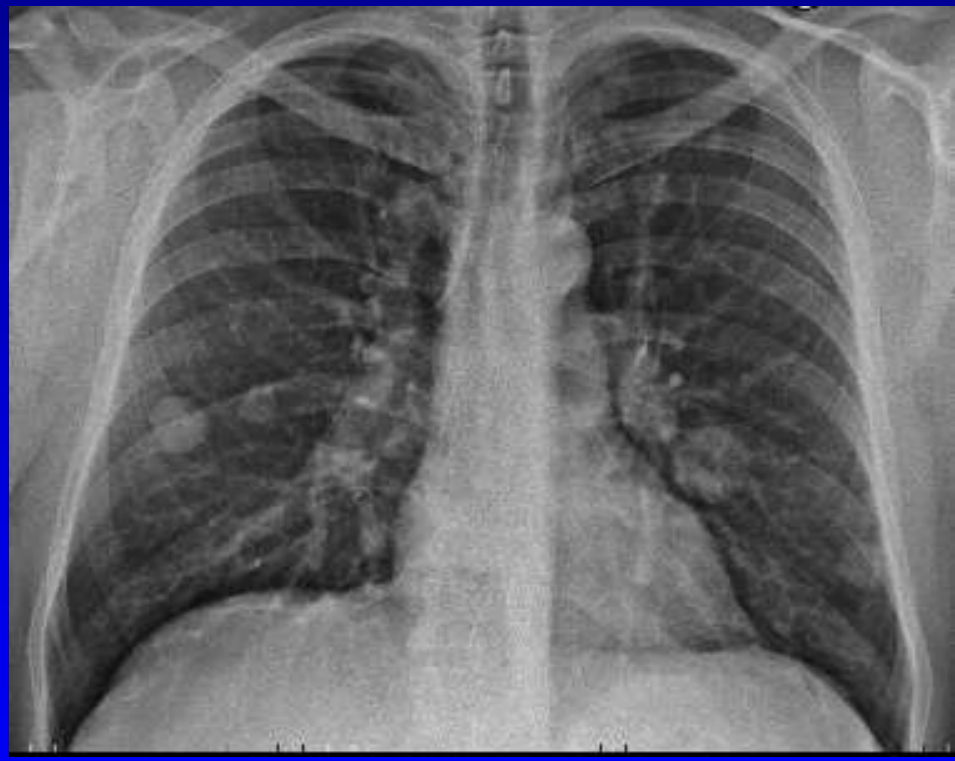
Survival / PFS of patients achieving Complete Remission



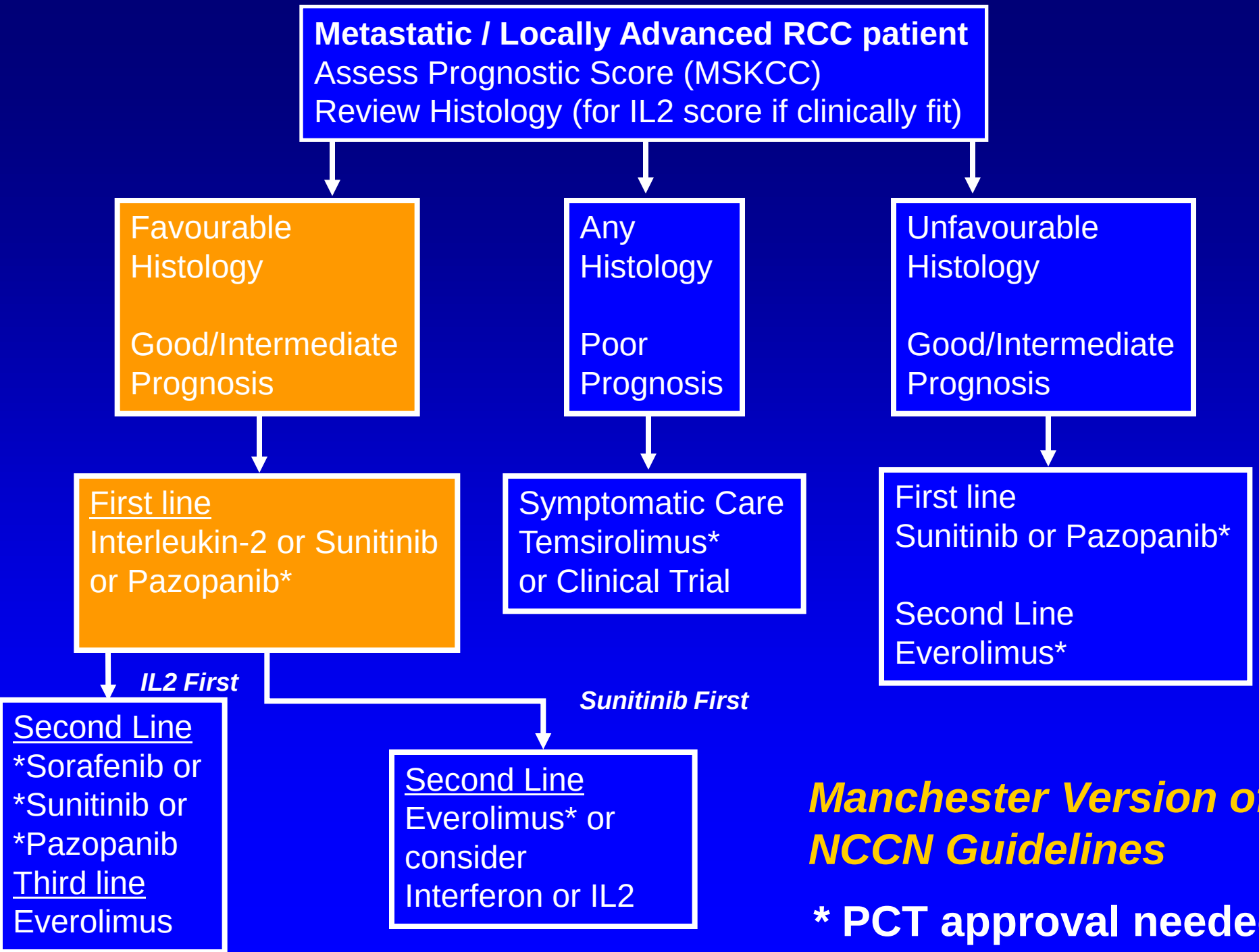
Treatment after Sunitinib?

- Concern about cardiac toxicity of sunitinib
- Can be safely given if wait at least 6-8 weeks





- Can give after failure of other available treatments
- Can be given after electively stopping sunitininb with good response


Metastatic / Locally Advanced RCC patient
Assess Prognostic Score (MSKCC)
Review Histology (for IL2 score if clinically fit)
Favourable Histology
Good/Intermediate Prognosis
Any Histology
Poor Prognosis
Unfavourable Histology
Good/Intermediate Prognosis
First line
Interleukin-2 or Sunitinib or Pazopanib*
Symptomatic Care
Temsirolimus*
or Clinical Trial
First line
Sunitinib or Pazopanib*
Second Line
Everolimus*
IL2 First
Sunitinib First
Second Line
*Sorafenib or
*Sunitinib or
*Pazopanib
Third line
Everolimus
Second Line
Everolimus* or consider
Interferon or IL2
Manchester Version of NCCN Guidelines
* PCT approval needed

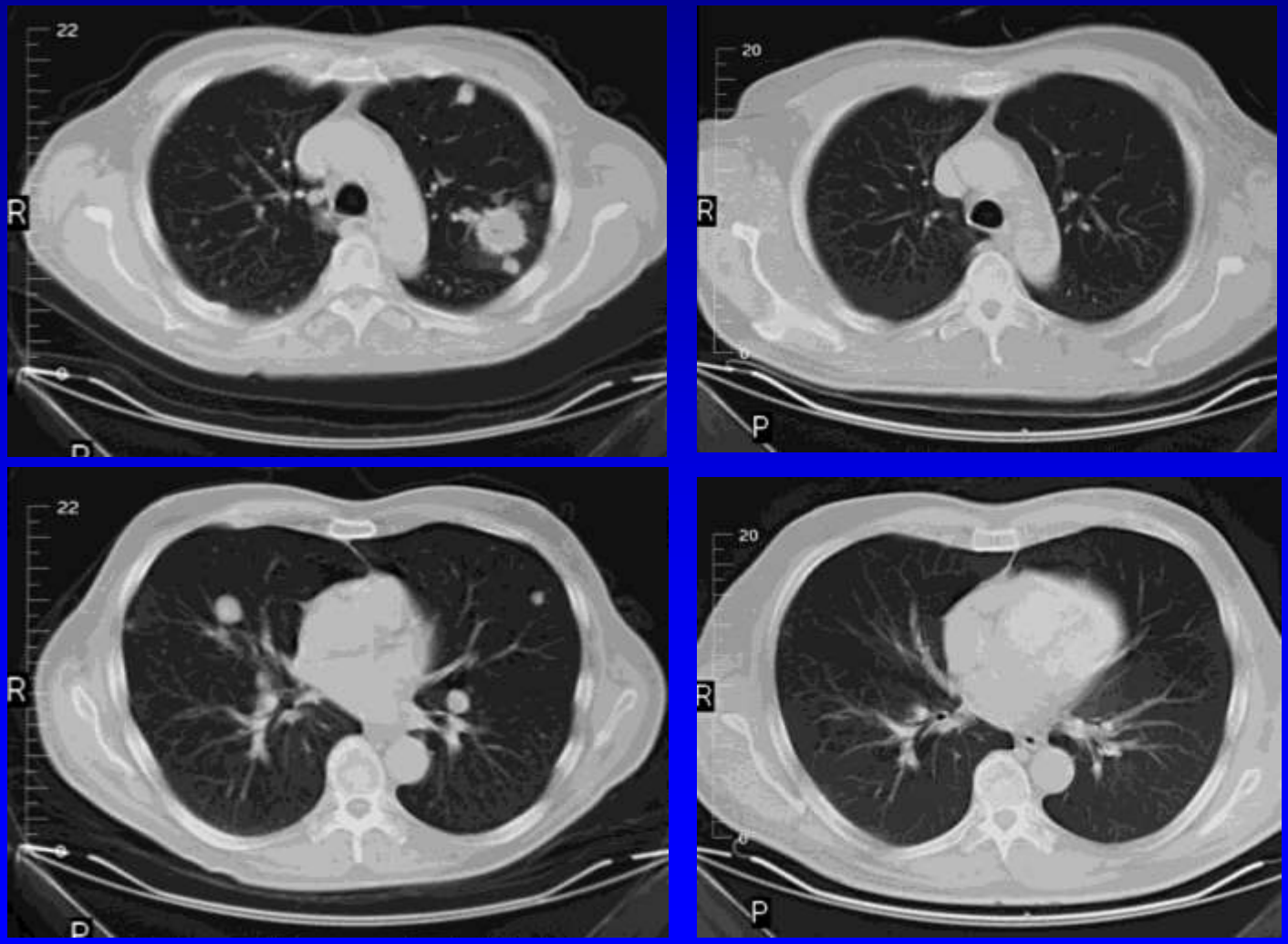
Conclusion

- Should not forget Immunotherapy in RCC in general
- Patients with high response rate to IL2 can be selected
  - Favourable Clinical Prognosis
  - Favourable Histology
  - Around 50% respond; Around 25% achieve a CR.
    - Appear Durable – some Cured?
- Safe on normal wards with experienced staff
- IL2 should not be forgotten as first line therapy for suitable patients
  - Offers a real chance of long term benefit for short term treatment
- Combinations with other active agents should be fully explored to see if durable CR rate can be extended
  - Other Immunotherapies – Vaccines / Antibodies
- Preliminary Evidence IL2 can be effective after sunitinib

Opening of Cellular Therapy Unit

Guess who's on Interlukin 11 ?

Even larger tumours



Patient History

- 51 year old female
- Presented painless haematuria
  - Staging 3 x lung metastases, breast metastases
  - 10 cm primary with renal vein involvement
- Attempted surgery
  - Inoperable
  - Very extensive nodal disease, enormous collateral vessels, tumour thrombous in IVC

Referred for Immunotherapy

- Embolisation undertaken
- Post Embolisation
  - >10 small volume lung metastases
  - 1.4 cm breast mass
  - Large renal mass invading peritoneum and pancreas

IL2 therapy

Course 1

- Cycle 1: 9 doses
  - Most given approx 12 hourly
  - Severe skin rash/peeling
  - PICC line infection
- Cycle 2 – 7 doses

Course 2 – 5 received on average 7 doses per cycle

Generally stopped due to Oedema and Skin toxicity

Outcome

- After 2 Courses – Lung Metastases CR
  - Breast Mass PR
  - Reduction in Renal Mass
- After 4 courses
  - Further reduction in renal mass
  - Breast mass reduced
  - Lung metastases remain CR
- Nephrectomy undertaken
  - Clear Cell – Fuhrman Grade2
- Then breast lump excised
- Remains in ongoing CR

Modified Histological Groups

- Anything more than trace (>10% of Papillary Tumour) is a poor prognostic sign
  - regardless of other features
- Good prognostic features for Clear cell carcinoma for response to Interleukin-2 are:
  - Alveolar (or Solid or both) > 50%,
  - Granular <50%
- Classify as 0, 1, 2 good features

Checklist on admission

Requirement		√					
Baseline Disease Assessment	YES						
Motzer 0 or 1	YES						
No Steroids > 2 weeks	YES						
Stopped anti-hypertensive drugs	YES						
No recent infections (<7 days)	YES						
Fbc / Clotting returned to normal / baseline	YES						
Chemistry returned to normal /baseline	YES						
ECG normal / baseline	YES						
Exercise ECG normal if aged over 50	YES		Cycle 1 only				
CXR - no infiltrates / no effusion	YES						
CHECK DRUGS WRITTEN UP							
Regular							
Paracetomol 500 mg QDS	YES						
Ibuprofen 200-400 mg 8 hourly	YES						
Ranitidine 150 mg BD	YES						
Ondansetron 8 mg BD	YES						
Levofloxacin 500 mg iv daily	YES	if have central line					
Regular iv fluids 150 ml/hr initially	YES						
PRN							
Pethidine 25 mg iv prn	YES						
Piriton 4 mg po or 10 mg iv 6 hrly prn	YES						
Loperamide 2 mg prn	YES						
Gaviscon 5 -10 ml prn	YES						
Temazepam 10 - 20 mg prn	YES						
Haloperidol 1-5 mg iv prn	YES						
N Saline 1 L iv over 2 hours	YES						
Dopamine 2 mcg/kg/min	YES	if urine output low					
Dobutamine 2 - 5 mcg/kg/min	YES	if BP low inspite of fluid challenge					
Nursing Obs							
4 hourly T,P,R,Sats	YES						
1 hourly if problems	YES						
Cardiac Monitor if low BP or inotrophs							
Fluid Balances							
Consider Catheter if urine output < 120 mls in 6 hours							
DAILY WTS - VERY IMPORTANT	YES						

Monitoring during IL2

Table 1. Patient Monitoring Guidelines		
	Not requiring	**Requiring**
	vasopressors	**Intensive care unit/vasopressors**
Vital signs	Every 4 h	Every 1 h
Intake and output	Every 4 h	Every 1 h
Weight	Daily	Daily
Mental Status	Every 8 h	Every 8 h
Intravenous site	Every 8 h (change arm	Every 8 h
	intravenous line every 3 days)	
Laboratory tests		
Complete blood cell count	Daily	Twice daily
Electrolytes, blood urea nitrogen, creatinine, glucose	Daily	Twice daily
Alanine aminotransferase, aspartate aminotransferase, total bilirubin	Daily	Daily
Ca +++, Mg ++, phosphorus	Daily	Daily
Prothrombin time, partial thromboplastin time	Daily after day 2	Daily
Creatine kinase, total	Daily	Daily
Thyroid stimulating hormone, free T4	Each cycle	Each cycle
Urinalysis	Each cycle	Each cycle
Electrocardiogram	Each cycle	Each cycle
Chest X-ray or chest radiograph	Each cycle	Each cycle