Example of how end of rotation hand-out should be done:

Developing a Prognostic System for Therapy in Metastatic Renal Cell Carcinoma (mRCC)

Overview of RCC:

-Classic presentation includes triad of hematuria, flank pain, and palpable abdominal mass

-Other symptoms may include: wt loss, fever, HTN, hypercalcemia, varicocele, night sweats

-Initial treatment for both local and metastatic disease is cytoreductive nephrectomy

-Immunotherapy with IL-2 and IFNα have been utilized for the last 20 years for mRCC with potentially severe side effects (e.g.- capillary leak syndrome) and variable outcomes

Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Stratification Model

-Motzer et al. aimed to develop a method of stratifying patients to determine which patients would respond to immunotherapy. Retrospective study w/ 463 pts who received IFNα as first line systemic tx for mRCC.

-Predictive factors considered:

- -number/site of metastases
- -prior nephrectomy, prior radiotherapy
- -levels of serum albumin, alkaline phosphatase
- -criteria listed below, which were found to have greatest prognostic value

Divided patients into three risk groups: favorable risk (0 criteria), intermediate risk (1-2 criteria), and poor risk (>3 criteria)

1) Low Karnofsky performance status (<80%)
2) High lactate dehydrogenase (>1.5 times upper limit of normal (ULN))
3) Low serum Hemoglobin (variable cut-off levels used)
4) High corrected serum calcium (>10 mg/dL)
5) Time from RCC dx to start of IFNα of less than one year

Median time to death using MSKCC stratification model:

Favorable risk: 30 mo

Intermediate risk: 14 mo

Poor risk: 5 mo

Limitations of study: Did not consider histologic subtype, genetic factors, or immunologic or inflammatory markers for immune-mediated therapy.

The drug armamentarium for mRCC has increased w/ the advent of drugs targeting VEGF/tyrosine kinase and mTOR. Is stratifying patients based on the MSKCC criteria appropriate for evaluation of newer drugs?

The European Association of Urology recommends the 2002 MSKCC risk group stratification be used to determine the indications for targeted therapies.

Applying the MSKCC model to other treatments:

1) Favorable risk:
Similar median survival time between sunitinib (fewer adverse side effects, slightly longer survival) and IFNα (more cost effective)
2) Intermediate risk:
Studies have suggested sunitinib or combination of bevacizumab+IFNα (Ljungberg et al 2009)
3) Poor risk:
Temsirolimus phase III multicenter trial (Hudes et al, 2007) showed temsirolimus (10.9 mo), an inhibitor of rapamycin kinase, was more effective in prolonging median survival than IFNα (7.3 mo) or combined IFNα+temsirolimus (8.4 mo). Sunitinib may be a good alternative, yet no studies have compared temsirolimus w/ sunitinib.

Newer drugs are being evaluated using the MSKCC model but there are limitations of using this stratification scheme. Should new stratification models be developed? Should various models be combined?

For example, LDH is regulated by the PI3K/AKT/mTOR pathway; thus, if this were the only criteria met (putting the patient in the intermediate risk category), the pt would be likely to receive either sunitinib or bevacizumab+IFNα but biochemically temsirolimus (acts on mTOR) may be more appropriate.

Possible future biomarkers/stratification models:
-serum levels of VEGF-receptor
-VHL status
-carbonic anhydrase 9 (high levels associated w/ better response to IL-2)

One study (Choueiri TK et al, 2007) suggested the following stratification criteria for use of VEGF-targeted treatment (with more criteria met→worse response to tx). Results have yet to be externally validated:

-Corrected calcium (<8.5mg/dL, >10mg/dL)
-Absolute neutrophil count (>4,500/μL)
-Platelet number (>300,000/ μL)
-ECOG performance status (>0)
-Time from dx of mRCC to treatment (>1 yr)

References:

Atkins MB. Treatment selection for patients with metastatic renal cell carcinoma: identification of features favoring upfront IL-2 based immunotherapy. Med Oncol. 2009;26 Suppl 1:18-22. Epub 2009 Jan 23.

Choueiri TK, Garcia JA, Elson P, Khasawneh M, Usman S, Golshayan AR, Baz RC, Wood L, Rini BI, Bukowski RM. Clinical factors associated with outcome in patients with metastatic clear-cell renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. Cancer. 2007 110:543–550.

Gore ME, Griffin CL, Hancock B, Patel PM, Pyle L, Aitchison M, James N, Oliver RTD, Mardiak J, Hussain T, Sylvester R, Parmar MKB, Royston P, Mulders PFA. Interferon alfa-2a versus combination therapy with interferon alfa-2a, interleukin-2, and fluorouracil in patients with untreated metastatic renal cell carcinoma (MRC RE04/EORTC GU 30012): an open-label randomised trial. The Lancet. 375: 9715, Feb 20 2010, 641-648**.**

Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, Sosman J, McDermott D, Bodrogi I, Kovacevic Z, Lesovoy V, Schmidt-Wolf IG, Barbarash O, Gokmen E, O'Toole T, Lustgarten S, Moore L, Motzer RJ. Temsirolimus, interferon alfa, or both for advanced renal cell carcinoma. N Engl J Med. 2007 May 31;356(22):2271-81.

Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, Patard JJ, Mulders PF, Sinescu IC. EAU guidelines on renal cell carcinoma: The 2010 update. Eur Urol. 2010 Jul 13 [e-published ahead of time]

Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol. 2002 Jan 1:20(1):289-96.

Rini BI, Campbell SC, Escudier B. Renal Cell Carcinoma. The Lancet. 2009 March 6: (373): 1119-32.

Volpe A, Patard JJ. Prognostic factors in renal cell carcinoma. World J Urol. 2010 Jun: 28(3): 319-27.