ENDOCRINE AND NEUROENDOCRINE TUMORS

Neuroendocrine
Lanreotide 1 mg/tid sc vs IFN alfa 3x5 MIU/wk sc vs both: No CR, NC 40-50% at 1 y; combination do not add (ASCO 2000)
CDDP+VP, OR 50% neuroendocrine. First line therapy (ASCO 2000)
5FU 500 mg/m2 + DTIC 200 mg/m2 + EPI 30 mg/m2 d1-3 q 3wks. OR 26% (ASCO 2000)
TXT in carcinoid: 13% MR, 5HIAA response 37% (>50%) & 63% (<50%). Use in combination (ASCO 2000)
Merkel ca responds to Octreotide 2/2 PR (ASCO 2001, 235)
Merkel ca in Mayo Clinic experience: Wide excission, Adj RT improves 5 yOS, adj chemo ?. CPA based ChT>CDDP based ChT. 5y OS in the 60%range (ASCO 2001,252)
Neuroendocrine: Sandostatin LAR 20-120 mg q 4 wks (ASCO 2001) (2342)

Medullary Thyroid
90 Y-MN-14 antiCEA (20 mCi/m2 to 50 mCi/m2) + DOX 60 mg/m2 + PBSCT (when 90Y <3 mCi/m2) 2 mR, 4 NC, 7 P among 14 pts with moderate toxicity (ASCO 2001,20)

Tratamiento con meta-yodo-benzil-guanidina-I 131: La captacion como trazador es alta en tumores de la cresta neural: feocromocitoma 90% (RO 60%), neuroblastomas 90% (RO35%), carcinoides 70% (RO 50%), y medular de tiroides 35% (RO 50%).

Phaeochromocytoma NCI series: CPA+VCR+DTIC+ q 3-4 wks in 18 pts (9 adrenal) CR 11%+PR 44%+mR 16%+ Biochem response 71*, MST OR 3.8 y, and non responders 1.8 y. Largest serie published (ASCO 2001, 678)

THYMOMA

Masaoka staging: I Macro encapsulated & micro no capsular invasion (48% and 10yos 90%); II Microinvasion fat tissue/pleura &/or microinvasion capsule (13% and 10yOS 80%); III Macro invasion of organs (pericardium, vessels, lung) (32%, 10yOS 35%); Iva Invasion pleura-percardium (13%, 10yOS 20%); Ivb Distant metastases.

A Vincent (Lancet 2001;357:2122-8). Review myasthenia gravis. Thymic tumor found in 10% of the cases, representing 60-70% of thymic tumors. Ab to acetylcholine receptor of muscle (AchR) present in 85%. Neurophysiology evpked muscle potential with stimulus 3Hz. Tensilon test (showing improvement in 2 minutes but with a respiratory arrest danger (it has false

positive/negative cases). Therapy: Oral anticholinesterase (pyridoestigmine) or thymectomy. In Lambert-Eatn there are Ab to calcium channel in the nerve synapsis and therapy is 3,4 diaminopyridine +/- anticholinesterase +/- corticosteroids (Ab control) +/- carbamacepine/Phenytoin (membrane stabilizers).

P Loehrer et al (Cancer 2001;91:2010-5). N=35, Mfup 43 mo. VP 75 mg/m2/ x 4 + IFX 1.2 g/m2/d x 4 + CDDP 20 mg/m2/d x 4, q 3 wks x 4. No CR, 32% PR fo 28 eval. patients. MDR 11.9 mo, MOS 31.6 mo, 2 yOS 70%. Moderate activity.

Thymoma in progression to chemotherapy: Octreotide 1.5 mg/d sc (alternative LAR) + PDRNS 0.6 mg/kg/d x 3 mo: OR 37% (Abstract G-9 IIINatl Cancer Congress Med Oncol, 4-7 Nov 2001, Naples (Ann Oncol 2001, Abstract Proceedings, Nov 2001)

Thymoma multimodal approach largest series: CPA 500 mg/m2 d 1, DOX 20 mg/m2 civi d1-3, CDDP 30 mg/m2 d1-3, PRDN 100 mg po qd d1-5 x 3, then surgery, then RTx 50 Gy no residuum and 60 Gy residuum, then chemotherapy again x 3: Initial OR 77%, pCR 4, pPR 17 of 22 pts, MFU 50 mo, 18/19 DFS, 20/22 alive so far; 5 y OS 95%, 7 y OS 77%. Good approach (ASCO 2001,1236)

Tandem trasnplant in relapsed thymoma: 5 pts, 3 ANED 21+ to 32+ mo (ASCO 2000)

M Okumura et al (Cancer 2002;94:624-32). WHO Classification: A Spindle /oval shape epithelial cells, few lymphocytes, no atypia: 8%, 11% invasion, 0 great vessel invasion, 20 y OS 100%; AB: 21%, invasion 41%, great vessel invasion 4%, 20yOS 87%; B1 dendritic/plump epithelial cells, lymphocytes, similar to thymus: 15%, invasion 47%, great vessel invasion 7%, 20 yOS 91%; B2 more lymphocytes, perivascular spaces scattered cells: 36%, invasion 69%, great vessel invasion 17%, 20 yOS 59%; B3 atypia and more epithelial component with less lymphocytes;: 12%, invasion 84%, great vessel invasion 19%, 20 yOS 36%; C Thymic carcinoma excluded from analysis.

G Palmieri et al (Cancer 2002;94:1414-20). N 16 advanced thymic ca resistant, MFup 43 mo. Octreotide 1.5 mg/d sc (LAR 30 mg q 2 wk)+ PRDN: OR 6% CR + 31% PR & 6 NC. MST 15 mo.

K Ogawa et al (Cancer 2002;94:1405-13). N=103 treated with resection + RT 40 Gy whole mediastinum. According to Masaoka I encapsulated N 17, 10y OS 100%; II1 microcaps invasion & II2 extracps invasion & II3 pleural invasion N 61, 10 yOS 90%; III neighboring organs invasion N 25, 10yOS 48%. Plaeural invasion was a factor of pleural recurrence (=/71 vs 12/32, 38%). RT is required...

K Yoh et al (Cancer 2003;98:926-31). CDDP 25 mg/m2 wkly + VCR 1 mg/m2 wk 1, 4, 6 & 8 + DOXO 40 mg/m2 wk 1, 3, 5, 7 & 9 + VP 80 mg/m2x 3 d wk 1, 3, 5, 7 & 9. Results: 5/12 PR, MPFS 5.6 mo, MST 46 mo.

P Loeher et al (JCO 2004;22:293-9). Octreotide o.5 mg sc tid. Results: 2 CR (5.3%) & 10 PR (25%). Modest activity.

P Ströbel et al (JCO 2004;22:1501-9). N=228 surgery, MFup 5 y. + additional RT N 42 + additional chemotheraopy N 33. WHO A, AB and B1 N=86, 88% only surgery, 3 relapses. 12/67 B2 & B3, Stages I & II Masaoka, surgery and RT, no recurrences; 75 patients with B2 & B3, Stage III, recurrence 34% with RT+ChX and 78% without adjuvant therapy.

D Ionescu (Cancer 2005;103:630-6). EGFR overexpression 69% thymomas (N=32).

A Manchewsky et al (Cancer 2008;112:2780-8). Review literature and propose to joint thymomas types A/AB/B1 and leave only 3 groups: Early A/AB & B1 (incidence 30.50%, survival 90-97%), B2 (incidence 30-40%, survival 75-80%) and B3 (incidence 15-20%, survival 60-70%).

THYROID CANCER

Low iodine diet for intervals of scan and therapy at www.lightoflifefoundation.org

TG Kroll et al (Svcience 2000;289:1357). T(2;3)(q13;p25) PAX8 (thyroid transcription factor) fused to PPARg1. Present in 5/8 follicular ca, 0/20 follicular adenoma, 0/10 papillary ca and 0/10 hyperplasia.

Combretastatin A4 prodrug (tubulin binding and antiangiogenesis) DLT 90 mg/m2 q 3 wks, 1CR thyroid ca anaplasic type (ASCO 2000)

A Stojadinovic et al (JCO 2001;19:2616-25). Hürthle cell ca, M Fup 8 y. Pathologic classification: Unknown malignant behavious (UMB) N=17, incomplete + capsular invasion, no vasc invasion; Minimally invasive (MIC) N=23, one focus complete capsular invasion and vascular invasion + 1 focus; Widely invasive (WIC) N=33, > 1 focus capsular invasion and > 1 focus vascular invasion. UMB and MIC no relapses. WIC 73% relapsed and 55% died. Prognostic factors were: extrathyroid disease, + margin, + ly no, and slid growth pattern.

Y Fukui et al (Cancer 2002;92:2868-74). Correlation of SLNB with regional metastases 90.5%.

C Barden et al (Clin Ca Res 2003;):1792-800). Gene profiling array to differentiate follicular adenoma, follicular carcinoma and undifferentiated carcinoma of thyroid: interesting genes c-met, EMMPRIN, adrenomedullin, autotaxin, TGFBIIR.

L Lopez-Penabad et al (Cancer 2003;97:1186-94). Hürthle cell carcinoma N=127, 38% I^{131} uptake and benefit from I^{131} adjuvant therapy. Older age group and larger tumor size worst results.

G Garaz-Rostan et al (JCO 2003;21:3226-35). Ras mutation (H, k, N) in thyroid carcinoma: 4/49 well differentiated (8.2%) (2/30 papillary and 2/19 follicular), 16/29 poorly differentiated (55.2%) mad 15/29 undifferentiated. Independent prognostic factor: 74% mut ras died vs 32% wt ras.

S Sherman (Lancet 2002;361:501-11). Differentiated tumors: Initial surgery bilateral thyroidectomy and ly no resection (+ in 80% papillary ca). Post op adj I131 (drop thyroxin & TSH to 25-30 mU/L for maximum uptake during 4-5 wks). Residual disease treated with 2.778-5.556 MBq (dosimetric studies have shown 30.000 cGy are required). Maintain TSH <0.1 mU/L (<0.01 in high risk, double MST). Use TG as a control, sensitive to elevation of TSH (sensitivity 85-95% at withdrawal but only 50% sensitivity during TSH suppression). Mets disease treated with I131: 80% OR with 80.100 Gy for < bulky disease (5yOS 60% lung, treated with 5.556-6.481 mBQ), CR 10% and PR 35%. ChX: DOXO, TXL, TMX, Octreotide, TNP470.
Anaplastic tumors: Mortality 100% (>50 yo, 50% prior differentiated tumor, p53 mut observed. Treated with preop RT + Surgery + postop RT + ChX. 2yOS 70% in localized disease. Usual MST 1 y with combined therapy.

S De Falco et al (Clin Ca Res 2006;12:1623-9). B-Raf mutated in 44% papillary thyroid and 24% anaplastic thyroid cancer. V600E mutation caused papillary to anaplastic transition in trasnegnic mice.

JH Lee et al (Cancer 2007;110:38-46). BRaf V600E mut in 49% (N=1168 patients with papillary thyroid cancer. Mutation associated with extrathyroid extension, papillary disease histology and higher stage.

S Metso et al (Cancer 2007;109:1972-9). Increased incidence of cancer after I131 treatment for hyperthyroidism: gastric cancer HR 1.75, RCC HR 2.32, breast cancer HR 1.53.

P Zanotti-Fregonara et al (Europ J Nucl MedMol Imag 2008;35:1392-9). Recombinant hTSH useful to detect elevation TG (pathol >2 ng/ml) and for follow up scan. Not useful for therapy because it is less I131 uptake in tumor after hTSH as compared to hypethyroidism and also for treatment of remnant thyroid ablation ij high risk patients.

ANAPLASTIC THYROID CANCER

D Giuffrida et al (Ann Oncol 2000;11:1083-9). N=84. Aggressive multimodal locoregional therapy with Surgery + RT + ChX (CDDP, TXL, 5FU, HOUrea, Bleo, CPA). MST 6 mo.

G Pellegrito et al (cancer 2002;95:2076-85). Insular thyroid cancer: <5%, intermediate differentiation, median age >60yo, mets 50% (ly no & hematogenous) compared to similar age papillary and follicular cancer. Only 7.7% NED at 10 y, compares to 46% and 44% respectively. Distant mets 84% insular. Poor response to I^{131}.

K Mizutani et al (Cancer 2005;103:1785-90). OEATC-1 (Over expressed in anaplastic thyroid cancer), 15q22.1. Found overexpressed in all ATC lines and primary tumors. When silenced with siRNA tumor groth was suppressed.

E Kebebew et al (Cancer 2005;103:1330-5). Reviewed 516 patients of 12 cancer registries in the USA. Med age 71.3 yo, male 171:female 345, 8% intrathyroid, 38% regional, 43% metastasic. Operated/resected 64%, 63% only RT. Mortality 68.4% at 6 mo, 80.7% at 12 mo. Multivariate prognostic factor analysis: <60 yo, intrathyroidal, surgery + RT had lower mortality.

V Gupta-Abramson et al (JCO 2008;26:4714-9). N=30 refractory thyroid carcinoma. Sorafenib 400 mg bid, PR 23% lasting 18+ to 84 wk & 53% NC (Benefit 77%). TG response 17/19 with a mean decrease 70%. MPFS 20 mo.

EW Cohen et al (JCO 2008;29:4708-13). Axitinib (AG 013736) VEGF 1, 2 & 3 inhibitor, 5 mg bid. N=60. PR 30% + NC>16 wk 38%. OR all subtypes, MPFS 18.1 mo. Hypertension 12%. Very active.

PARATHYROID CANCER

K Sekiyama et al (Int J Urol 2003;10:7-11). Primary hyperparathyroidis imaging dtection rate of parathyroid adenomas: US 70%, CT 67%, MRI 38% and MIBI 78%. One month thyroxin therapy increased localisation of adenomas.

T Shattuck et al (NEJM 2003;349:1722-9). HRPT2 gene sequenced in 21 carcinoma/15 patients without family history of primary hyperparathyroidism or HPT-JT (hyperparathyroidism-jaw tumor

syndrome) which carries a high risk of parathyroid cancer: 10/15 had HRPT2 mut (inactivated parafibromin protein) and 3 patients had germ line mutation identified.

CARCINOID TUMORS

H Connolly et al (Cancer Control 2001;8:454). Carcinoid right side heart disease: development of right side valvular failure. Early detection by US study, follow up until right heart symptoms develop. Operate for valvular diagnosis (retraction/ fixation) if required, before liver surgery/clinical management. MST after surgery 1.5 y, medical therapy MST 1 y (3y OS 30% surgery and 12% medical therapy). Alternatives: bioprosthesis (premature degeneration risk due to serotonin) & mechanical prosthesis (risk of anticoagulation & 4% thrombosis yearly).

****Rayson et al (Cancer 1997;79:605-11). 4 patients with right side heart failure due to >2y carcinoid syndrome with liver metastases underwent prosthetic valve replacement and had an objective partial regression of carcinoid syndrome (reduction 5HIAA) and CT liver metastases for a median of 24 mo. Cause unknown. Suggest that Atrial Natriuretic Peptide produced by the failing myocardium and has modulatory growth properties can be the cause. It is reduced after surgery. It has been found secretion of ANP by the carcinoid cells. Another explanation is regularization of hepatic blood flow after surgery.

D O'Toole et al (cancer 2000;88:770-6). N=33. Randomized to Octreotide 200 ug/bid/tid x 1 mo → Lanreotide 30 mg imq 10d x 1 mo; vs Cross over design. No differences in QOL: 68% preferred Lanreotide. Improvement of carcinoid syndrome 68% & 54%; diarrhea 50% & 45%, abdominal pain and nausea 29% & 14% for octreotide and lanreotide. Similar efficacy.

P Tomassetti et al (NEJM 2000;343:551-4). Gastric carcinoid: Type I associate with chronic gastritis & hypergastrinemia; Type II (multiple carcinoid tumors) associated with MEN1 and ZES and Type III sporadic. Types I & III respond to octreotide. Type II Laso HAD EVENTUAL RESPONSES TO OCTREOTIDE.

BG Taal et al (Ann Oncol 2000;11:1437-43). I131 MIBG in 10 patients with no or weakly positive tracing with 1 mCi (37 MBq, 5 mg MIBG).Treatment 200 mCi (7.4 MBq) I131-MIBG following a pharmacologic predose of 20-40 mg/m2 MIBG.. This is followed by 2 cycles of I131-MIBG. Results: Improvement in 5 patients, MDR 6-12 mo and biochemical response in another 3 patients. Predosing improved I131-MIBG tumor targeting, because I131-MIBG when imaging is positive gives a 60% response rate.

D Granberg et al (Ann Oncol 2001;12:1383-91). N=31 lung carcinoid and metastases at dx. MST 25 mo. ChromoA marker 93%. IFNa (NC 4/27, MDR 15 mo); Octreotide only clinical benefit; Streptozotocin + 5FU 7/7 PD; Streptozot + DOX NC 2/2, 8 & 10 mo respectively; CDDP+VP 2/8 PR (6 & 8 mo, respectively).

D Walther et al (cancer 2002;94:3135-40). 7 hydroxytryptophan is metabolized by tryptophan hydroxylase (present in carcinoids secreting serotonin) into a potent toxin, 5,7-dihydroxytryptamine. (This step is blocked by parachlorophenylalanine, a tryptophan hydroxylase inhibitor). Highly specific target therapy because otherwise is an inoffensive substrate.

I Modlin et al (cancer 2003;97:934-59). Review SEER & NCI data on 13.715 carcinoids (1950-1999). Largest serie published. GI 67.5% (small intestine 41.8%, appendix 5 yOS 71%, metastases 38.8%; rectum 27.4%, 5yOS 88.3%, metastases 3.9%, and stomach 8.7%). Bronchpulmonary

25.3% (5yOS 73.5%, metastases 27.5%). Distant metastases at diagnosis 12.9%. Overall 5yOS all tumors 67.2%. Trend of incidence appeared to be increasing.

S Safford et al (cancer 2004;101:1987-93). N=98. I131-MIBG, 401+/-202 mCi I131-MIBG dose. MST 2.3 y. Patients with symptomatic improvement MST 5.76 Gy. Results better when initial therapy >400 mCi. OR did not predict survival.

D Kwekkeboom et al (JCO 2005;23:2754-62). Octreotate-Lu177-DOTA for somatostatin endocrine gastroenteropancreatic tumors: individual doses of 100-200 mCi for a cumulative 600-800 mCi Lu-Octreotate dosing. N=131 with Octreotide receptor + tumors. Toxicity 2 renal failure and 2% haematological. CR 3 (2%), PR 26%, mR 19%, NC 25%, PD 18%.

J Soga et al (cancer 2005;104:1180-7). Carcinoids of the pancreas represent 30-40% of neuroendocrine pancreatic tumors and 1.4% of carcinoids. Mets 66.7%, median size 6.8 cm, carcinoid syndrome 23.3%. 6yOS 29%, very low.

W. Sun et al (JCO 2005;23:4897-904). N=249. Randomized to DOX+5FU (OR 15.9%, PFS 4.5 mo, MOS 15.7 mo) vs STZ + 5FU (OR 16%, PFS 5.3 mo, MOS 24.3 mo, best results); with cross over to DTIC after PD (OR 8.2%, MOS 11.9 mo).

S Gupta et al. N=69 carcinoids, 54 pancreatic islet cell ca. Hepatic arterial embolization and chemoempolization: OR 66.7% PFS 22.7 mo, OS 33.8 mo for PNET and OR 35.2%, PFS 16.12 mo, OS 23.2 mo for carcinoids (better pancreatic neuroendocrine tumors)

***MH Kulke et al (JCO 2006;24:401-6). N=29 carcinoids. Phase II TMZ 150 mg/m2 x 7 qowk + Thalidomide 50-400 mg qd. Chromogranine A response 40%; OR 25%. MDR 13.5 mo, 1yOS 79%, 2yOS 61%. Quite active.

TM Katona et al (ca Res 2006;66:4936-42). 16 carcinoid with multifocal tumors : 15/16 LOH concordance, and 8 pancreatic endocrine multifocal tumors 7/8 LOH concordance. Multifocality…

JC Yao et al (Clin Ca Res 2007;13:234-40). N=27. Imatinib 400 mg bid clinical trial: 1 PR + 17 NC + 9 PD, 7 Biochemical responses. MPFS 24 wk, MOS 36 mo.

********D Campana et al (JCO 2007;25:1967-73). Chromogranine A cut off 18-19 U/l (sensitivity 85.3%, specificity 95.8%) distinguished NET and normal patients. Chromogranine A cut off for chronic gastritis and NET is 31-32 U/l (sensitivity 75%, specificity 84%) and 84-87 U/L (specificity 95% and sensitivity 55%). In chronic gastritis with hyperplasia of neuroendocrine cells recommend to use the higher cut off.

J Zhang et al (Cancer 2007;109:1478-86). VEGF expression is levated in tumors (32% strong and 54% weak) and correlates with growth and short PFS & metastases.

M Rugge et al (Clin Ca Res 2008;14:149-54). Prognosis of bronchopulmonary carcinoid. N=67, 30 male and 37 female, med age 45.9 +/-19.1. Six recurrences and time from recurrence to death 46 mo. There were: 86.6% low grade typical carcinoid, 20yOS 95% and 13.4% intermediate grade with atypia, 5yOS 50%. M F up 85 mo. Intermediate grade had peripheral location, vascular invasion and ly no mets. All tumors expressed neuroendocrine markers but not TTF1. Mib-1 <5.4% cutoff and Bcl2 <2% cut off distinguished patients with recurrences.

J Yao et al (JCO 2008;23:1316-23). N=44, treated with octreotide 30 mg q 3 wk. were randomized to BV (OR 4 PR and 17 NC (95%), PFS-18 wk 95%, MPFS 63 wk, decreased tumor flow) vs

PegIntrona (15 NC (68%), PFS-18 wk 68%,and MPFS 63 wk; all with BV+PegIntron at the time of PD (at least 1 PR). BV>IFN?.

****K Koopmans et al (JCO 2008;26:1489-95). C11-HTP (Hycroxytryptophan)-PET optimal for islet cell tumors, more sensitive than somatostatin and CT & also 18F-DOPA-PET (100% vs 80%). 18F-DOPA (Dyhydroxyphenylalanine)-PET optimal for carcinoid, more sensitive than somatostatin and CT & 11C.5HTP-PET (100% vs <90%).

I Kayani et al (cancer 2008;112:2447-55). 68Ga-DOTA-TATE (DOTA-D Phe-1Tyr-3-Octreotate (obtained by generator) PET-CT > 18FDG. Sensitivity 82% vs 66% (combined 92%), SUV 29 vs 2.9. Quite good .

D Kwekkeboom et al (JCO 2008;26:2124-30). N>500. 177Lu- DOTA-D Phe-1Tyr-3-Octreotate, 780-800 mCi (27.8-29.6 GBq) in 4 cycles (repeat q 6-10 wks). Hematological toxicity grade 3-4 in 3.6%, liver toxicity 3, MDS 3. Results: CR 2%, PR 28%, mR 16%. MTTP 40 mo, MOS 46 mo. Benefit in survival 40-72 mo.

J King et al (Cance 2008;113:921-9). N=34. Syrtex Y90 microspheres. N=34 NET (carcinoid 24). Symptomatic OR>6 mo 55% , RX OR: 18% CR + 32% PR, MOS 29 mo. Chromogranine A response 45% at 6-30 mo. Long term OR and CR were observed.

M Kulke et al (JCO 2008;26:3403-10). N=109, carcinoid 41, PNET 66. Sunitinib 50 mg/d x 4-6 wk. OR pancreatic-NET 16.7%, NC 68%, MTTP 7.7 mo, 1yOS 81.1%. OR Carcinoid 2.4%, NC 83%, MTTP 10.2 mo, 1yOS 82.4%.

PANCREATIC NEUROENDOCRINE TUMORS

RT Jensen et al (cancer 2008;113:1807-43). Review.
GENETIC SYNDROMES WITH NET (Genes not in common for all tumors):
MEN-1: 11q13, Wermer syndrome.
Parathyroid hyperplasia 95-100%.
Pancreatic ET 60%, symptoms 40%, non functional 70%. Gastrinoma 54%, insulinoma 15%, glucagonoma 3%, Vipoma 3%, GFRoma <1%, somatostatinoma <1%. Median age 30 yo, sporadic 40 yo. OS PET 50%, Non functional 50%, gastrinoma 70%, insulinoma 92% (mostly benign and operated when detected, ly no mets do not affect survival. Gastrinoma: Omeprazol, Whipple operation (large, identified, diffusse) controversial, because 80% are duodenal.
Hypophysis 40%;: Prolactinoma 21%ther 10% (ACTH, Growth hormone).
Adrenal adenoma 25%
Carcinoids (gastric 10%, symptoms <5%, lung 5%, thymus 1%.
Thyroid adenoma 10%
Skin angiofibroma 70%
CNS: hemangioma, paraganlgioma, meningioma, schwannoma, ependymoma
Smooth muscle leiomyosarcoma 5%.
MEN-2: THYROID MEDULLARY CA + PHEOCHROMOCYTOMA + PHPT
CARNEY SYNDROME: PITUITARY + CORTICAL ADRENAL + THYROID papillary/follicular ca

VHL: 3p25. Hemangioblastoma cerebellum, retina or brain stem 60%, RCC 40%, Pheochromocytoma 10%, Pancreatic ET 10%, Angiomyolipoma. Cysts liver, pancreas, skin. Groups Type I not pheochromocytoma; Type IIa low risk RCC, Type Iib high risk RCC; and Type Iic only pheochromocytoma.
VON RECKLINGHAUSEN NF-1: 17q11.2. Diagnosis base in:>6 café au lait freckles, benign iris hamartoma (Lisch nodules), optic glioma, dysplasia sphenoid bone and first relative with NF1) asscoiated with Pancreatic ET 15% periampullary somatostatinoma, Pheochormocytoma, PHPT, Bronchus/thymus carcinoid, neuroectodermal tumors + GI Carcinoid, AMM leukemia, malignant nerve sheat/sarcoma.
FAMILIAL PARAGANGLIOMA
TUBEROUS SCLEROSIS BOURNEVILLE DISEASE TSC1 hamartin 9q34 and TSC2 tuberin 16p13.: PANCREATIC NET uncommon.

E Bajetta et al NCI Milan (Cancer 1999;86:858-65). Chromogranin A sensitivity 67.9%, specificity 85.7%, best marker for accuracy and clnical follow up. NSE sensitivity 32.9%, specificity 100%. CEA sensitivity 15.4%. 5HIAA, sensitivity 35.1%, specificity 100%. N=177.

S Ricci et al (Ann Oncol 2000;11:1127-30). N=15, with PD after slow release LANREOTIDE 30 mg q 2 wk for a median time of 8 mo and Octreotide scan + in 13/15. Treated with Octreotide acetate long acting release (LAR) im 20 mg q 4 wk: Median duration therapy 7 mo, mild side effects, Results: 1 PR (7%) + 6 NC (MDNC 7.5 mo)(40%) + 5 PD (53%). Biochemical OR 41% (33% CR + 8% PR), MDR 7.5 mo. Symptomatic response 82%, MDR 6.5mo. Active

C Waldherr et al (Ann Oncol 2001;12:941-5). 90Y-DOTATOC (90Y-DOTA)-D-Phe1-Tyr3-Octreotide. N=41, 82% resistant . Received 6000 MBq/m2 Y90-DOTA_TOC q 6 x 4. M F up 15 mo. OR 24% (2%CR + 22%pr + 12% mR + 49% NC + PD 15%. MDR >26 mo; 2yOS 76%. Very good survivial, response and symptom control.

L Dogliotti et al (Ann Oncol 2001;12:105-9). Octreotide 1.5 mg qd: 30-70% symptom improvement and 10-30% OR, biochemical OR 70%. Lanreotide 12-30 mg/d: 40% symptom control and 50-60% biochemical response, 40% OR. LAR-Octreotide 20 mgq 2wk: 80% symptom, 50% biochemical, and 40% OR, with some of the responses after failure to Octreotide and Lanreotide.

ML Fjall et al (Cancer 2001;92:1101-7). N=36 (18 carcinoid & 15 PNET) CDDP 45 mg/m2 x 2 + VP 100 mg/m2 x 3 q 4 wks. PR 10/18 carcinoid & 7/14 PNET.

K Ramanathan et al (Ann Oncol 2001;12:1139-43). N=50. DTIC 850 mg/m2 2 h q 4 wk. OR 33%, MOS 19.3 mo.

F Que et al Mayo Clinic (Ca Control 2002;9:67). Review hepatic surgery in NET GI origin. Series of cytoreductive surgery >150 patients, mortality <3%, recurrence 80%, MST >7y. Response 90%, MDR 2 y. Many patients with simultaneous primary surgery. Series of liver transplant >80 patients, mortality 14%, recurrence 70%.

S Hochwald et al (JCO 2002;20:2633-42). N=136. Pancreatic endocrine tumors pathology review: Factors: Mitosis < 2/50 hpf or higher and necrosis present/absent. Both helped to differentiate low and high grade more accurately and had OS correlation.

H Shojamanesh et al (Cancer 2002;94:331-43). Mest gastrinoma: Octreotide 200 ug bid → LAR Octreotide 20-30 mg q mo. OR 53% (PR 6% + NC 47%), MDR 25 mo. Slow growing OR 86% vs 0% fast growing. It should be considered standard therapy.

S Faiss et al (JCO 2003;21:2689-96). N=80, mixed GI & functional status. Randomized to Lanreotide 1 mg tid (N=25, OR 1, NC-12 mo 7 and PD 14) vs IFNa 5 MU tiwk (N=27, OR 1, NC-12 mo 7 and PD 15) vs Lanreotide + IFNa (N=25, OR 1, NC-12 mo 7 and PD 14). Combination did not improve upon the results.

J Teunissen et al (JCO 2004;22:2724-9). 177Lu-DOTA-Tyr3-octreotate 660-800 mCi. N=50, M Fup 3 mo. OR 24 + NC 19 + PD 6. QOL improved from 69 score to 78.2 score.

M Kouvaraki et al mDACC (JCO 2004;22:4710-9). N=61 male and 23 female. 5FU 400 mg/m2 iv bolus x 4 d + DOX 40 mg/m2 d 1 + STREPTOZOTOCIN 400 mg/m2 iv bolus x 4. OR 39%, MDR 9.3 mo, 2yPFS 41%; 2y OS 74%.

B Asgharian et al (Clin Ca Res 2004;10:869-80). N=74 with MEN-1. MRI-CNS to screen for meningioma: 8% had meningioma as a late event (median age 51 yo, 18 y after diagnosis).

E Bajetta et al (Cancer 2006:107:2474-81). N=60, low grade well differentiated neuroendocrine tumors. Randomized to Lanreotide microparticles (LAN-MP) 60 mg q 3 wk IM (OR 55% markers, 68% size) vs LAN autogel (LAN-ATG) 120 mg q 6 wk x 3 sc (OR 59% markers and 66% size). Cost similar.

J Hainsworth et al (JCO 2006;24:3548-54). Poorly differentiated NET except lung cancer. N=78. TXL 200 mg/m2 d 1 + CBDCA AUC 6 + VP 100 alternating 50 mg/m2 qd, d 1-10 & then 24 wk of wkly TXL 70 mg/m2/wk x 6 q 8 wk if an OR is observed. Results: OR 53% (CR 15%),, NED 5 patients from 18+ to 66+ mo. MST 14.5 mo, 3y OS 24%.

C Ferrone et al MSKCC (JCO 2007;25:5609-15). N=183 operable PNET. M age 56 yo, M Fup 44 mo. Grade based on necrosis and mitosis: low grade 56% a(normally <2cm 83%). T<2cm 19%, T>2cm 52% and N/M metastases 29%. Tumors >2cm low grade 5yDSS 97% and intermediate 5yDSS 80%, no metastases 5yDSS 93%, with metastases 5yDSS 62%.

J Yao et al (JCO 2008;26:4311-8). N=30 carcinoid & 30 islet cell, low and intermediate grades. Everolimus 8RAD001) 10 mg/d + LAR 30 mg q 4 wk. OR 20% intent to treat. Final PR 22% + NC 70% + PD 8%. MPFS 60 wk, MOS >3y, 3yOS 78%, Chromo A OR 70%. OR correlated with increase in LDH. Promising.

M Kulke et al (Clin Ca Res 2009;15:338-44). MGMT deficiency in 97 archival cases: 19/37 pancreatic and 0/60 carcinoid. TMZ OR 18/53 (34%) PNET (of those 4/5 ORs had MGMT deficiency and no ORs were observed in 16 with a normal MGMT) and 1/44 (2%) carcinoid. TMZ response only in MGMT defficient tumors.

MEN-2

RET MUT 10q11.2, exons 10 and 11, 14; codons 609, 611, 618, 620, 634 frequently; 768, 804 rarely.

MEN-2A TRIAD: MEDULLARY THYROID CARCINOMA 95%, PHEOCHROMOCYTOMA 50%, HYPERPARATHYROIDISM OR ADENOMA 15-30%. COUNSELING AT 6 YO
MEN-2B: NO PARATHYROID, WITH MUCOSAL NEUROMAS (MARFANOID HABITUS, CAVUS, EXCAVATUM, WEAKNESS, CONSTIPATION. COUNSELING BEFORE 6 YO. MTC early and PHEOCHROMOCYTOMA late occurrence.
FAMILIAL MTC

E Kebebew et al (Cancer 2000; 88:1139-48). MTC or FMT Classification of EORTC reflected better the prognostic factors than TNM and others: N=104. Scoring: Male +12, less differentiated +10, anaplastic +45, extrathyroid invasion +10, one distant mets +15, more than 1 distant mets add +15. Group 1 <50 mortality 0; G2 50-60: 8.7%; G3 66-83: 33.3%; G4 84-108: 40%; G5 >109: 100%.

A Maschens et al (NEJM 2003;349:1517-25). Recommendations for hereditary MTC. N=207/145 families, grouped according to mutation site. Consensus:
Mut codons 634, 618, 620, & 611: Thyroidectomy > 5yo, & ly no dissection only if malignant cells, not in C cell hyperplasia.
Mut codons 609, 768, 790, 791, 804, & 891: Thyroidectomy 5-10 yo.
Findings: MTC 100% at age 20, earliest case a >5yo. For group mut codons 634 and others: no ly no mets <14 yo, about median 6.6y after malignant transformation. For group mut codons 609 and others: Never tumor < 10yo and ly no dissection at 20 yo.

A Stift et al (Clin Ca Res 2004;10:2944-55). N=10. Dendritic cell vaccination. Mature CD14+ cells with magnetic selection of PBL cultured with IL4, GM-CSF, TNFa & IFNg. DC loaded with tumor lysate and injected in the groin. Results: 3 PR + 1 mR + 2 NC. All patients had Elispot + reactivity.

G Cuccuru et al (JNCI 2004;96:1006-14). RET is a protooncogene coding for a TK. RPI-1 is an indolinone analog inhibitor of RET-KI, active in mice…

M Skinner et al (NEJM 2005;353:1105-13). N=50, >19 yo, RET mutation (MEN2a) underwent total thyroidectomy. F up 5-10 y after surgery, 44/50 serum calcitonin <0.88. Two patients with stimulated test were positive (iv calcium and pentagastrin) above normal and four were stimulated but remained within the normal limits. No progression of the disease. Mut in codon 883, 922 and 918 justify surgery in infancy (<5 yo), while codon 804 might wait. Mut codons 609-634 very common, 80% of the cases.

F Carlomagno et al (JNCI 2006;98:326-34). BAY 43-9006 inhibits cells carrying RET V804L and V804M which are resistant to anilin quinazoline and pyrazolopyrimidines

JF Chatal et al (JCO 2006;24:1705-11). N=29. Short calcitonin doubling time. 39 patients historical control. AntiCEA-DTPA-I111 tracer → 5 days later I131 labeled bivalent hapten (73 mCi). 47% OR, MOS 159 mo (vs 109 mo non responders and vs 61 mo non treated). Long term disease stabilization and longer survival.

F Iten et al (Clin Ca Res 2007;13:6696-702). 90Y-DOTA-Tyr3-Octreotide (TOC), median 12.6 GBq, Phase II. N=31. OR 9 (29%); OS HR=0.20 (for OR). Hematologuical toxicity 12%, renal toxicity 22%.

PHEOCHROMOCYTOMA

Originally described by F Frankel 1886, the first was a MEN2. Actually 4 living relatives with mut RET descendants of the first described patient (H Neumann et al, NEJM 2007;357:1311-5).

B Rose et al (Cancer 2003;98:239-48). N=12, 5 prior therapy. High dose I131-MIBG 800 mCi, 2-3.5 usual doses associated to prolonged survival. M F up >45 mo. 3CR + 7PR.(median cumulative dose 1015 mCi).

J Bryant (JNCI 2003;95:1196-204). Pheochromocytoma associated syndromes representing >20% of tumors: 6% VHL, Isolated paragangliomas succinate dehydrogenase genes SDHD 8% and SDHB 4%, RET 1% (MEN2). Genetic counseling is always required.

HJLM Timmers et al (JCO 2007;25:2262-9). FDG-PET is the best study for metastatic paraganglioma and pheochromocytoma as compared with MIBG, CT, MRI, 123I-MIBG, 131I.MIBG, In111-pentreotide, Tc99-diphodphonate and Fdopamine-PET.

J Lenders et al (Lancet Oncol 2005;366:665). Rule out 10% bilateral, extradrenal, familial and metastasic pheochromocytoma. Triad: Headache, palpitations, sweating in 90% with ortosthatic hypotension. Biochemistry: Urinary/plasma catecholamines; urinary metanephrines (normetanephrine and metanephrine), urinary VMA, no Chromogranin A. Clonidine suppression test distinguish activated sympathetic vs phechromocytoma. Suppression of normetanephrine no chromocytoma (97%). Preferred Imaging FDG-PET.
(Urine norepinephrine >1180 nmol/24h, epinephrine >170 nmol/24h, HPLC normetanephrine >6550 nmol/24h, HPLC metanephrine >2880 nmol/24h, for a total metanephrines >12.7 nmol/24h).
(Blood HPLC: noradrenaline >7.7 nmol/l, adrenaline >1.2 nmol/L, normetanephrine >1.4 nmol/l, metanephrine >0.42 nmol/L

MALIGNANT PARAGANGLIOMA

H Huang et al (Cancer 2008;113:2020-8). N=18, NCI series. CPA 750 mg/m2 + VCR 1.4 mg/m2 + DTIC 600 mg/m2 d 1 & 2, repeat q 3-4 wks. CR 11% + PR 44%. MOS 3.8 y Ors vs 1.8 y non-Ors. Active chemotherapy.

N Hahn et al (JCO 2009;27:460-3). Case report of ine patient responding to Sunitinib malate. Two other cases in the literature.

ALDOSTERONOMA

ADRENAL CORTICAL CARCINOMA

B Allolio et al (Dtsch Med Wochenschr 1989;10:381-4). Describe a case report of a CR afteer suramin in a patients previously treated with Mitotane, CDDP/VP/Bleo.

TS Khan et al (Ann Oncol 2000;11:1281-7). N=40, median age 44 yo. Therapy: O,p'DDD 1-4 g/d (+Hydrocortisone 25-100 mg qd) + STREPTOZOTOCIN 1 g/d x 5 d → 2 g q 3 wk + MAXIMAL SURGERY (adrenal tumor). CR+PR 36.4%; 2y OS 70%; 5yOS 32.5%; MOS 47+/- 9 mo. Adjuvant postoperatory MOS 8y (otherwise MOS 3 y. Well tolerated low dose Mitotane. Propose randomized study for a new standard.

E Baudin et al (Cancer 2001; 92:1385-92). O,p'DDD levels correlate with the response. N=13, Mitotane 6-12 g/d. 58% levels >14 mg/L (6 patients) → 1 CR + 3 Biochemical response. No responses seen among 7 patients not abtaining these levels. In adjuvant therapy 2/8 NED with good levels vs 1/3 without levels. Toxicity seen only with levels above 14 mg//L.

M Boscaro (Lancet 2001;357:783-91). Review Cushing syndrome & Hypercortisolism: Corticotropin dependent Cushing 60-80% from pituitary adenomaand rest ectopic production. Corticotropin independent autonomous tumors. Diagnosis: Urinary 24 h free cortisol (sensitivity 95-100%). Low dose dexamethasone suppression test (1 mg at 11pm) exclude if at 8.00am plasma cortisol is <50nmol/L. Dexametahsone 0.5 mg q 6 h x 8 & 1 mg/kg CRH 2 h after last dose of dexamethasone→ then cortisol >39 nmol/L diagnosis of Cushing. Desmopressin response 10 ug+/- 100 ug CRH. Rule out pseudoCushing (obesity, depression, alcoholism, HIV infection). Therapy: Transesphenoidal selective adenomectomy, Pituitary RTX, Bilateral adrenlectomy, Drugs active in hypothalamic-pituitary axis: Bromocriptine, Cyproheptadine, valproate, ritanserin, ketanserin (occassionally are active). Drugs inhibiting steroid synthesis: Mitotane 2-10 g/qd, Metyrapone, Aminogluthetimide, Ketokonazole 600-800 mg qd, mifepristone 20 mg/kg/d.

J Abraham et al (Cancer 2002;94:2333-43). N=35. DOXO 10 mg/m2 d1+ VP 75 mg/m2 x 4 d civi + VCR 0.4 mg/M2 d1 + Mitotane. Results 8/35 OR (22%), MDR 12.4 mo, MST 34.3 mo ORs vs 11.6 mo non-ORs. Mitotane antagonizes pGP at >10ug/ml levels (achieved in 69% of the patients in this study).

A Stojadinovic et al MSKCC (JCO 2002;20:941-50). N=124, M Fup 4.7 y. Factors of prediction of DSS: Distant mets at Dx; Invasion vein, capsule or adjacent organ; Tumor necrosis, mitosis or atypia; mdm2 overexpresssion. Score 1-2: 84%; 3-4:37%; >4: 9% 5yDSS.

E Michalkiewicz et al (St' Jude's) (JCO 2004;22:838-45). International Pediatric Adrenocrotical Tumor Registry Jan 1990- Dec 2001. N=254 <20 yo, Females 1.6:1
Vierilization 84.2%, Cushing without virilization 5.5%, non fuctional 10.2%. Complete resection 83%, residual Dx treated with Mitotane, CDDP, VP, DOX. Stage I:112, 5yOS 90%. Stage II:40%, Stage III-IV 20%. M Fup 2.5 y, 61.8% alive NED and 38.2% deaths; 5yEFS 54.2%. Prognostic factors: Stage I, Virilization alone, and age <4 yo.

M Terzolo et al (NEJM 2007;356:2372-80). N=177 after radical surgery, secreting tumors 50%, tumor size 10 cm, median age 42-47 yo. Adjuvant Mitotane N= 47 (MRFS 42 mo, HR=2.91, Deaths 25%), Control N=120 (MRFS 10-25 mo), Deaths 41-54%). Dose reduction 13% (3-5 g/d high dose and 1-3 g/d low dose). Support adjuvant Mitotane (non randomized study).

YY Xiao et al (AJR 2002;190:105-110). Percutaneous ethanol in lesions <3cm and acetic acid (50% iodized oil) in lesions > 3 cm. Volume 4 Π(R+0.5)3. N=37 with 46 tumors: 11 adenoma, 6 functioning adenoma, 9 aldesteronoma, 20 mets). At 2 y: CR 92% + PR 7.7% in primary tumors and CR 30% + PR 70% in mets. No complications.

A de Reynies et al (JCO 2009;27:1108-15). N=153 adrenocortical tumors: Microarray/RT-PCR 2 gene predictors: DLG7 and PINK-1 to predict benign adenoma or carcinoma (100%). In

adreniocrotical carcinoma BUB1B and PINK1 predict for OS better than staging: HR=32 (10yOS 90% vs 5yOS 10%).

PITUITARY TUMORS

WHO Classification Functional: Endocrine: Acromegaly, Cushing, Hyperthyroidism, elevation FSH/LH, Multiple. Pathology: Adenoma (typical, atypical, expansive-invasive), carcinoma.

PJ Trainer et al (NEJM 2000;342:1171-7). N=112 with acromegaly, ranmdomized to Placebo (IGF-1 decrease 4%, Normal concentration 10%); vs Pegvisomant x 12 wk (GH-receptor antagonist, 191 aa) 10 mg sc/d (IGF-1 decrease 26%, normal concentration 54%); 15 mg sc/d (50% and 81% respectively) and 20 mg sc/d (62% and 89% respectively).

AJ Swerdlow et al (Lancet 2002;360:273-7). N=1848 patients treated with piyuitary growth hormone in childhood-early adulthood. Cancer incidence increased overall OR=2.8. (CRC 10.8, HD 11.4). Keep evaluation...

J Schlechte (NEJM 2003;349:2035-41). Review prolactinoma. Secretion and release of prolactin are mediated by dopamine, and processes that disrupt dopamine secretion or its delivery to the portal vessels may cause prolactinemia. Normal prolactine 20-25 ug/L, pysiologicalincrease in pregnancy x 10. Physiscal or psychological stimulus rise to 40 ug/L.
Microadenoma (<1cm) treat only if dismenorrhea/or whishing a pregnancy. Therapy is bromocriptine (effective in >85%, safe in pregnancy), begin with 0.625 at night time and increase weekly up to 5 mg. Daily 5-7.5 mg restore menses and normalize prolactin level. Nausea, hypotension and depression are minimal if given at night time and dose incrementes are slow. After 2 normal menses try conception and stop it after one missed menstruation. Symptomatic enlargement during pregnancy 1%. 95% of microadenoma do not increase in size. Alternatively cabergoline, effective in 70% not responding to bromocriptine. Begin at 0.25 mg biwk and increase up to 0.5 mg tiwk. After 2 y therapy it can be discontinued without any further porlactin increase.
Macroadenoma: specially suprasellar extension, 15-35% increase in pregnancy. Require bromocriptine during pregnancy (surgery is an aggressive alternative for pregnancy patients) up to high doses 7.5-10 mg/d. Some times combine bromicriptine and surgery.

A Colao et al (NEJM 2003;349:2023-33). Series: 25 non tumoral hyperprolactinemia, 105 microprolactinoma and 70 macroprolactinoma. Stop cabergoline with a normal prolactin, a reduction >50% in size, or >5mm from optic chiasm. Recurred (only biochemical progression, never tumor growth) 24% non tumoral, 31% micro and 36% macroadenoma. Try to discontinue cabergoline in selected patients.

PARANEOPLASTIC ENDOCRINE-METABOLIC SYNDROMES

ACTH Precursor (propiomelanocortin POMC) commonly screted by tissues/tumors with action as a growth factor, rarely activated to ACTH (Cushing). Gene is a POMC promoter, P1 the more effective in transcription. When Rb is inactivated, FOS is increased and POMC is subsequently increased.
Ectopic ACTH is different from pituitary dependent Cushing in: Higher ACTH/POMC in cancer, hypokalemia common in cancer, ACTH not suppressed by 8 mg at 10AM dexamethasone in cancer, higher serum/urine cortisol in cancer, no elevation of ACTH after corticotropin releasing hormione

stimulation in cancer. Some tissues do not follow this pathway (ie carcinoid). Treatment recommended: Ketokonazole.
Hypercalcemia: (Cancers: Breast, lung, kidney, ovary and others), It is due to PTH like or prostaglandin secretion (these are few but usually respond to ASA). Now it is demonstrable a PTH-related protein (PTH-RP), a 141 aa protein homologous to PTH in the NH2 terminus, and it is increased in hypercalcemia. Other mechanisms involve the production of 1,25 OH-D and cytokines.
Hypoglycemia (Tumors: mesenchymal, hepatic, adrenal, gastrointestinal, and others). Usually very large tumors (> 1 Kg) and sometimes beningn tumors. It is due to IGFII and suppression of GH secretion. Treatment: Surgery or somatostatin analog + glucagons or glucose. GH + Somatostatin can work and should be tried.
HCG (alfa subunit shared by TSH, LH, FSH, & HCG, but Beta subunit uis unique to each one). Produced by most tumor cells.
Arginine vasopressin (ADH). Common in oat cell and other NSCLC, Hodgkin disease. The syndrome requires not only ADH production but inappropriate water intake (low Na, hypervolemia and renal Na loss).
GH & GH-RH (Acromegaly). Carcinoids and pancreatic islet cell tumors. Rare, not ectopic.
EPO: Renal cell carcinoma, HCC and others.
Hypophosphatemia (oncogenic osteomalacia), hyperphosphaturia and low 1,25OH-D (pleomorphic carcinoma, oat cell, prostate)
Prolactin: Variety of tumors. Rarely amenorrhea/galactorrhea in premenopausal women. In man no symptoms. Also in postmenopausal women no symptoms.
Renin: Hypertension and hypokalemia, increased aldosterone and highly increased rennin. Tumor of the juxtglomerular apparatus, hemangiopericytomas, Wilms and others.

CANCER- ANOREXIA- CACHEXIA SYNDROME

Rats triple therapy: GH 1000 u/kg/d + Somatostatin 150 ug/kg/d + Insulin 5 u/kg bid, increase wt without tumor effect by inhibiting growth kinetics.

**4494. Randomized study for cachexia >200 patients. Only L-carnitine and MPS/MA+ L carnitine had effect on IL6 and TNFa reduction. Phase III consited in 5 randiomized arms including Thalidomide, Vits, EPA/nutrition, etc. Proc AACR 49 Meeting, San Diego, April 12-16, 2008

PARANEOPLASTIC LIMBIC ENCEPHALITIS

Subacute onset (85%), altered mental status(short term memory loss, confusion, and psyciatric symptoms, seizures and somnolence. **CSF**: mild pleocytosis (normally first symptom before a cancer diagnosis), elevated protein & normal glucose, oligoclonal bands or IgG elevation, normal cytology. **EEG**: slow waves & temporal lobe epileptifor activity. **MRI**: FLAIR and T2 bilateral temporal abnormalities, abnormal limbic structures. **Associated Tumors**: Ab AntiHu (ANNA-1) Oat cell; AntiCV2 (CRMP5) Oat cell, thymoma, germ cell testes; AntiMa (Ma1, Ma2): Germ cell testes, lung cancer, breast cancer; Anti-Amphiphysis: Oat cell; Anti PCA-2: Oat cell; AntiVGKC: Thymoma, oat cell; Other anti-neuropil: Thymoma, germ cell medistinal, thyroid cancer.

MERKEL CELL CARCINOMA

D Smith et al (Ca Control 2000;7:72-83). Review: Epidermal tumor of the skin, originates in neural crest and express neuroendocrine markers. Mean age 65 yo, affect H&N, extremities and trunk, only in whites. It is ahigh grade aggressive tumor, local recurrence 26-44%, median interval 4 mo, mest ly nodes 55-66%, med time 7-8 mo. Mortality with ly no mets 66% at 5y. Distant mets 50%, mortality 75%. Surgery and 2 cm margin plus sentinel ly no biopsy + RT 40-60 Gy primary and regional ly no. ChX PE, CDDP-5FU.

P Tai et al (JCO 2000;18:2493-9). N=204, 25% widespread mets (Reviewed 25 series). Chemoradiation is an option: CPA+ADM+VCR+PRDNS (OR 75%), VP+CDDP/CBDCA (OR 60%), others Bleo, MTZ, IFX. MOS 29 mo, MDFS 9 mo.

T Inone et al (J Dermatol Sci 2000;24:203-11). TIL active in Merkel ca regressing spontaneously (T8).

K Marno et al (BJ Dermatol 2000;142:1184-9). Regressing Merkel showed replacement of tumor cells by macrophages (foamy cells).

M Poulsen et al (JCO 2003;21:4371-6). N=53, high risk Merkel disease (recurrent, ly no +, tumor >1cm, gross residual disease, occult ly no mets) treated with adjuvant chemotherapy with CBDCA AUC 4.5 + VP 80 mg/m2 x 3 + RT 50Gy. MF up 48 mo. 3yOS 76%, regional control 75%, distant control 70%. Recommended.

PJ Allen et al MSKCC (JCO 2005;23:2300-9). N=215. Prognosis relates to Stage I 5yDFS 81%; II 67%, III 52%, and IV 11%. Node biopsy improves OS 23% had ly no mets. Lymphadenectomy improves survival avoiding nodla recurrences (44% vs 11%).

W McAfee et al (Cancer 2005;104:1761-4). N=34 RT alone, N=32 RT + Surgery, and N=9 adjuvant ChX. Results overall series: 5y local control 94%, 5y loco-regional control 80%, 5y mets free survival 60%, 5yOS 37%.

P MOjica et al (JCO 2007;25:1043-7). Adjuvant RT after Merkel skin cancer (SEER Data 1973-2002) N=1665. Stage I 55%, II 31%, III 6%, unclassificable 8%. Surgery 89%, MST 49 mo (M F up 40 mo). Adjuvant RT 40%, MST 63 mo, usually lesion >2cm.

CK Bichakjian et al (Cancer 2007;110:1-12). Guidelines for early disease Merkel cancer. Surgery: < 2cm wide local 1 cm margin and SLNBx & > 2cm wide local, 2 cm margin, SLNBx, and adjuvant chemotherapy. When SLNBx negative only observation; if positive complete ly no dissection + Adj RTx +/- ChX. When systemic disease: ChX + RTx + Surgery.

A Andrea et al MSKCC (Cancer 2008;113:2549-58). N=156 MCC, 5yOS 67.5%. Prognostic factors: Tumor thickness (<1cm 5yOS 85% vs >1cm 55%); tumor size (<20 5yOS 85% vs >20 50%); deepest anatomical involvement skeletal muscle (5yOS 17%); TIL (present 5yOS 78% absent 60%); solar elastosis (present 5yOS 76%, absent 60%); Lymphovascular invasion (absent 5yOS 90%, present 55%). Multivariate analysis: Stage, thickness and lymphovascular invasion (nodular vs infiltrative also).

H Feng et al (Science 2008;319:1096). Merkel cell cancer polyoma virus in 8/10 patients. Confirmatory data lacking.