For many years, after each PROS international meeting, I place a summary of the meeting on our web site. I am, therefore, pleased to do so for the 2017 meeting.

Edward C. Halperin MD MA

**Wednesday session**

The meeting began with interactive case presentations utilizing a sophisticated cell phone/pad app. Members of the audience could "vote" in response to questions posted on the slides. I will report some of the take-home messages from each presentation.

**The Medulloblastoma Case - Indelicato**

Medulloblastoma has tightly packed cells and shows high signal on MRI. Intraoperative MRI can be used to assess extent of tumor resection. Molecular biological staging is now quite important in assessing the prognosis and therapy of medulloblastoma.

WNT subtype is rare in infants. Usually fits with classic histopathology. Rarely has metastatic disease and the prognosis is relatively good.

About 2/3rds of those in attendance at the meeting do not incorporate molecular staging into their clinical decision-making outside of a protocol.

Most of those in attendance feel that 42 days post-op is the maximum interval to begin radiotherapy in the absence of induction chemotherapy. The speaker showed some evidence showing that this opinion is evidence-based.

In a M0 case, WNT positive, most people would give 23.4 Gy CSI with a tumor bed boost to 54 Gy. The Michalski et al paper in average risk disease favored 23.4 Gy over 18 Gy and found that you don't have to boost the entire posterior fossa; just boosting the tumor bed is fine.

If a pseudomeningocele occurs, should you include it in the CSI volume? Most of the audience would. The speaker agreed with that view.

Most members of the audience would not compromise cribiform plate coverage to spare the lens. The cribiform plate region can be contoured with a CT scan to plan the radiotherapy fields.

Most members of the audience recommended proton therapy. That is what the speaker uses in order to, it is hoped, reduce long term ill-effects of radiation therapy.

**Low grade glioma - Hess**

The speaker presented a 4 year old with radiographic evidence of a low grade glioma who was treated with induction chemotherapy without biopsy.
For progressive disease after chemotherapy the speaker showed a case wherein a biopsy was done and therapy was given based on molecular markers. There are multiple drug-able targets in low grade gliomas.

What do you do if the patient progresses after therapy based on molecular markers? The speaker described using a 5 mm CTV and a 3-5 mm PTV. The patient's family, however, having become very fearful of radiotherapy, declined it.

A common treatment strategy for these tumors is to delay radiotherapy with chemotherapy in an attempt to reduce the risk of side effects. The five year overall survival is about 95-98% whereas the event free survival is about 50%. Radiation appears to produce better progression free survival and visual preservation, but at what cost?

There can be injury to emotional and cognitive function as well as hormonal function.

Ependymoma - Gandola

Complete resection is a recognized positive prognostic factor.

The radiotherapy fields have moved from CSI to large cranial fields to tumor bed fields. GTV is the post operative tumor bed and gross residual tumor with a CTV of 1 cm and PTV of 0.3-0.5 cm. In the SJCRH series the local failures were within the 95% isodose line volume.

A case was presented of a 4 year old male with a 4th ventricle Ependymoma who underwent a subtotal resection and had measurable residual tumor. The histology was Anaplastic Ependymoma with no spinal metastases. In the current SIOP trial completely respected children are observed v. Chemotherapy. For subtotal resection > 12 months of age it is chemotherapy first (randomization is between two types of chemotherapy).

There is a role for 2nd look surgery after induction chemotherapy. The AIEOP protocol results show the prognostic importance of complete resection after 2nd or 3rd look surgery.

In the presence of residual disease after surgery, most of the audience would administer a boost dose of radiation to the residual after the radiotherapy to the full tumor volume. The speaker showed a retrospective study which supports the value of the boost.

Wilms Tumor - Kalapurakal

A Stage III ruptured Wilms tumor was presented, favorable histology, after nephrectomy. Most of the audience would give whole abdomen irradiation to 10.5 Gy and would not block the opposite kidney.

A year later the child had a lung metastasis with involvement of the chest wall. The speaker favored whole lung irradiation rather than chemotherapy first and assessment of response. 12-15 Gy.

Two years later the child developed a recurrent nodule in the left lung, resected with positive margins. Most of the audience would give local IGRT but the speaker preferred whole left hemithorax irradiation followed by a boost.

Then another 2 years later there was a metastasis next to the opposite kidney. It was resected.
Ewing Sarcoma - Constine

The speaker presented a 9 year with a paraspinal Ewing sarcoma with a left pleural effusion. There were malignant cells in the effusion.

About 6% of Ewing tumors arise in the spine.

About 5-10% of patients with rib and spine tumors will have a pleural effusion at presentation.

Need to give local therapy and systemic therapy.

The speaker addressed the long-standing debate about the role of radiotherapy v. Surgery for local control. The speaker addressed the problem of case selection bias which often appears in retrospective reviews.

He favored the use of hemithorax irradiation because of the presence of a positive pleural effusion. There is a risk of pneumonitis for this patient in the short run and, in the long run, second malignant neoplasms, cardiac dysfunction, lung fibrosis, and chest wall asymmetry.

Rhabdomyosarcoma - Mandeville

He presented a 17 year old with left forearm (10 cm) and left buttock masses (5 cm) with generalized symptoms, thrombocytopenia and renal impairment. Biopsy of the forearm mass showed alveolar rhabdomyosarcoma, fusion gene positive.

FDG PET-CT is used for assessment of metastatic disease along with bone marrow biopsy. In this case it showed positive marrow and widespread bony metastases. Induction chemotherapy is VAC+Ifosfamide, Doxorubicin or VAC+ Ifosfamide.

After 6 cycles of chemotherapy the patient had a radiographic CR. The speaker then irradiated the primary tumors, involved lymph nodes, and soft tissue extension of the primary tumors.

When radiotherapy was administered, the audience favored 50.4 Gy to the primary and 41.4 Gy to the metastatic sites. The speaker showed a European trial which favored 30 Gy to metastatic sites, if feasible.

The speaker showed a proposed European trial which will randomize children in order to ascertain the role of radiotherapy to metastatic sites.

The group then retired to the end-of-the-day reception.

Thursday sessions

Symposium on neuroblastoma

Imaging - Voss

Staging is a combination of cross sectional imaging and functional imaging. No further role for bone scan. Functional imaging is very important in neuroblastoma. A variety of new functional imaging agents are under development for this disease. For example, 68 Gallium dotatate which
is related to somatostatin receptors in neuroblastoma. There are established criteria for assessing response from the IDRF. Quantitative measurements of MIBG uptake with SUV is an excellent way to assess response. There is a copper 64 agent which binds to neuroblastoma somatostatin receptors. This may be useful for PET imaging in neuroblastoma.

131 I - MIBG is used for therapy. It gives a highly localized dose.

**Surgery - La Quaglia**

This talk was devoted to surgical management of high risk neuroblastoma. Neuroblastoma constitutes 8-9% of all childhood cancers. While there have been improvements in survival in neuroblastoma there has not been as much improvement in high risk disease.

Serum ferritin, LDH, urinary catecholamines all help to identify the risk group of the patients. Biological variables are Mycn amplification, ploidy, 11qdel.

INSS Shimada classification predicts outcome. You can split the patients into risk groups based on the assortment of markers.

Gross total resection is important after maximum chemotherapy response. You usually get the maximum response after 2-3 cycles. These tumors are typically tucked under the diaphragm. A thoraco-abdominal approach is used to get adequate exposure and a controlled resection in an attempt to get negative margins. For tumors in the cervical-thoracic junction the speaker uses a "trap-door thoracotomy".

The ability to get a gross total resection is a function of how many vessels are encased. Local progression and survival are related to extent of resection. He showed a meta-analysis which supports this assertion. Mycn amplification is related to overall survival.

COG A3973 for high risk patients correlated completeness of resection of the primary tumor with overall survival and event free survival. SIOPEN found the same thing.

Almost all patients got external beam radiotherapy.

1-2% reoperation rate for adhesions after neuroblastoma surgery.

**Radiotherapy, Europe - Mandeville**

He discussed SIOPEN high risk neuroblastoma 1 study - a very complicated study with use of local radiotherapy to the primary tumor site.

Busulfan and melphelan seems to give better survival and less toxicity than carboplatin, etoposide, and melphelan.

What is the evidence for local radiotherapy in high risk disease?

Doses vary widely.

Local RT seems to reduce the local relapse rate.

In European study they give local RT 60-90 days after high dose chemotherapy. They give 21 Gy in 14 fractions. 1.5 Gy qd. No systematic irradiation of distant metastases. No TBI.

GTV is the post chemotherapy volume.
Radiotherapy QA reviewed in 100 patients out of the >2000 patients in this study. Only 48 were treated as per protocol.
29 justifiable deviations.
1 non justifiable deviation.
5 justifiable deviations where adverse affects were likely
17 non justifiable deviations where adverse affects are likely.
Local control was worse in patients with deviations. Quality of the radiotherapy clearly does matter.

New randomized trial will compare 21 to 36 Gy. It will have 50 patients. It is a two year pilot. They will continue to assess the need for local radiotherapy and for metastatic disease. They are considering a randomization to no RT when there is no macroscopic residual disease after surgery on surgical report and MIBG. For those with macroscopic disease they are considering a randomization of 21 v 36 Gy.

They are going to emphasize quality assurance to assure reproducible radiotherapy and imaging and perform research on QA. They are going to do prospective radiotherapy QA.

Radiotherapy, US - Panoff

For high risk disease they give 5 to 6 cycles for radiotherapy. Site based radiotherapy to local and metastatic sites.

CCG 3891 10 Gy in 3 fractions and 10-20 Gy local RT

COG A 3973 - 21.6 Gy locally

ANBL 0032 - stopped early due to efficacy. Immunotherapy showed superior EFS and overall survival.

ANBL 0532 compared tandem thiotepa, cyclophosphamide and CEM v CEM alone and assessed value of toptotecan consolidation. Also studied increased local dose of RT to 36 Gy. Tandem myeloablative chemotherapy was better. No significant toxicity difference. Tandem is superior to single transplant.

ANBL 09P1 Can you add therapeutic MIBG with BU/Mel consolidation?

ANBL 12P1 Is it safe to use the BU/MEL?

SIOPEN HR-NBL 1. Two different induction regimens were studied and two different consolidation regimens were studied. High rate of sinusoidal obstructive syndrome.

ANBL 1531 will be a five arm study designed to accrue 800 patients. Stratify MIBG non avid v avid. If the patient has ALK aberration get crizotnib plus chemotherapy. If you are MIBG avid there are randomizations to see if 131IMIBG is beneficial. The patients continue to get local RT. ANBL 1531 RT changes are based on what was learned from previous studies. They updated normal tissue constraints. Clarified vertebral body coverage. Now, if the tumor is close to the vertebral body, cover the whole vertebral body. Decreased CTV1 from 1.5 cm to 1 cm.

Proton therapy. Use a posterior beam when treating the retroperitoneum because of dose uncertainty in air absorption. Don't have proton dose heterogeneity in the vertebral body.
Lymph node coverage. Effects of extent of lymph node irradiation were neither clinically nor statistically significant.

Radiotherapy for metastatic disease - Lucas

Do high risk patients benefit from metastatic site radiotherapy? What are the late effects? Are we picking the right target? Does the degree of MIBG avidity influence the local radioresponsiveness?

Retrospective reviews suggest a benefit for metastatic site control with local RT. Most are bony sites rather than soft tissue sites. Most of those bony sites are axial and extremity.

Who do you consolidate? Persistently MIBG avid post induction is generally agreed upon. Curie scores select for event free survival.

It is probably not worth doing consolidation radiation for metastatic sites not present a diagnosis.

The speaker presented a retrospective review of SJCRH experience with treatment of metastatic sites. Two populations: high curie score at presentation v not. New metastatic site failure does worse than old metastatic site failure. Curie score was not predictive of failure type. Post induction curie score most predictive of failure curie score. Curie score was correlated with propensity for new site failure. Curie score may predict for those patients with refractive/progressive disease.

Extent of systemic therapy positively affects metastatic site control.

Predictors of new v. Old metastatic site failure. Lung mets at diagnosis predicted for new but not old metastatic site failure.

MIBG avidity post induction or post transplant predicts for a bad outcome.

Persistent MIBG avidity metastatic disease is insufficiently controlled with 21-23 Gy.

Proffered Papers

Veno-occlusive liver disease after hall liver radiotherapy - Hall

This was a PENTEC report.
The authors did a systematic literature review. Most patients were treated for hematological malignancy, some Wilms, some lymphoma. Lots of TBI patients. All were whole liver irradiation.

Radiation Dose, use of non alkylating chemotherapy were significant predictor, age < 20 years of age borderline significant. 6% incidence of the complication at 10 Gy and 15% at 20 Gy.

Partial liver dose will be studied in an upcoming PENTEC report.

Difference in treatment related facial growth deformity between AMORE and EBRT for orbital RMS - Hol

Speaker is from Amsterdam. She discussed a comparison of photon irradiation v. Ablative surgery plus mouillage technique with brachytherapy plus reconstructive surgery.
60% of both groups have skeletal abnormalities.

This is a retrospective review over a period of 24 years comparing patients treated at Great Ormond Street and Amsterdam. Detailed 3D imaging was done of the face. There are 29 patients in the study. There is a mean of 18 years of follow up. The EBRT has smaller facial surface areas and a higher probability of abnormal facial curvature.

The next study will explore other treatment options such as proton patients and surgery plus EBRT.

There may have been selection bias.

Can you correlate the mean dose to different facial compartments and the degree of deformity?

**Brain stem tolerance guidelines - Indelicato**

Rationale for proton therapy for posterior fossa is to reduce the exposure of normal tissue such as the brain stem. Pediatric Ependymoma is the most patient treated with protons at the University of Florida.

54-59.4 Gy
No more than 58 Gy to 0.1 cc of brainstem. Some of the CTV, therefore, gets between 54 and 59 Gy because of this very firm dose constraint.

They are seeing no brain stem necrosis with this new constraint. Also, however, in the past more patients have gotten chemotherapy before they were irradiated.

Overall survival is 86% at 3 y. Local control is 83%. No significant change in local control in spite of the tighter brain stem tolerance constraints.

Time to symptomatic necrosis v. Intratumoral necrosis was discussed

They did not formally look at the influence of pseudomeningocele.

**Audiometric guidelines - Jyoti**

Proton therapy may allow for greater sparing of the cochlea.

This paper was a retrospective review of hearing loss in patients treated with protons at the University of Florida.

Subjective hearing loss was more common that objective hearing loss (4% v 16%). The probability of hearing loss rises with dose and the 5% rate is about at 39 Gy. These statistics are at a mean follow up of 3 years.

Hearing loss is greater in children younger than 3 years of age when irradiated and it is also exacerbated by the receipt of oto-toxic chemotherapy.

If you use cisDDP, perhaps it is best to keep the mean cochlear dose less than 30 Gy.
There was a discussion of whether to make the definition of objective hearing loss of 20 dCb or a drop from baseline before treatment.

Palliative radiotherapy for pediatric patients, acute toxicity - Marcus on behalf of Lee

This is a retrospective study. Most common diagnoses were neuroblastoma, re-irradiation of intrinsic pontine gliomas, Ewing.

Indications for treatment 40% were for radiologic progression without symptoms.

About 60% had symptomatic improvement with radiotherapy.

85% of the parents denied any symptoms from palliative radiotherapy.

Hypothalamic pituitary dysfunction after cranial irradiation - Zadravec

This is a retrospective study on brain radiotherapy patients. They analyzed dysfunction in 10 year survivors. 76 patients were studied. This is a subset of the entire treated population. The patients studied were the long-term survivors who had undergone regular testing. They got 30-80 Gy, median 50 Gy.

35 had dysfunction. 34% of them were panhypopituitary. Growth hormone followed by adrenal insufficiency followed by hypothyroidism followed by hypogonadism were the most common individual hormone abnormalities. The incidence of abnormalities rises with time.

Most of the patients with adrenal insufficiency were assymptomatic and were picked up on screening. These patients may be less able to respond if stressed by trauma or infection later in life.

Total marrow irradiation with tomotherapy - Engellau

“TBI is a remarkably non-uniform treatment modality.” When you compare TBI at different institutions you observe different techniques of positioning. With and without junctions. No consensus of total dose or dose per fraction.

While 12 Gy in 6 fractions is the most commonly used fractionation. In Lund they do 12 Gy in 6 fractions, ap/pa, and lung shields, bid

What is the target? Red bone marrow? Spleen? CNS? Testes?

People are concerned about TBI toxicity and many strive to use less TBI because of it.

They have been doing tomotherapy in Lund for 1 3/4 years.

Junction at thighs with collapsing penumbra technique. Target delineation is determined.

The speaker described fifteen patients. BMI has an effect on treatment planning.

Compared to TBI there is a reduction in dose to organs at risk and more homogeneous coverage of the targeted tissue. Lung doses are only 5% less than with TBI. Sparing is as good in pediatric
as in adult patients. Treatment time is relatively short. TBI takes about one hour TMI takes, on average, 23 minutes. They use surface scanning for assuring positioning.

Amount of red marrow varies with age.

He treats the whole skeleton. He uses a 5-10 mm expansion on the CTV.

Dose rate 0.4 Gy for TBI and for tomotherapy it is 8 Gy/min.

None of his patients required sedation.

In leukemia patients they include the spleen and the CNS

Symposium on medical physics

Breath motion - Bel

Motion can be measured and quantitated with a 4D CT. Diaphragm motion is less under anesthesia than awake breathing. It is also far more predictable and regular.

Diaphragm motion poorly correlates with organ motion. It is mildly correlated with height. The magnitude of motion is less in children than adults.

How to control breath motion?

Tracking (have the machine move such as cyberknife or vero system) or gating (can improve this by coached breathing) or control breathing (voluntary breath hold using a computer screen for visual feedback for the patient) or abdominal compression (the later is not appropriate for children).

Even during a breath hold you can still see the diaphragm moving on a real time MRI. Most of the motion occurs in the first 10-20 seconds of the breath hold. If you do gating combined with a breath hold you have to have a margin around the target volume. You need more margin when you have more respiratory amplitude.

Children breath more regularly than adults and 4DCT for treatment planning might be more accurate than for adults

Particle therapy - Bolsi

The speaker, from Switzerland, showed the typical dose distributions for protons v photons for Ependymoma and craniospinal irradiation.

Parallel scanning gives you, effectively, a seamless field whereas divergent scanning requires beam matching.

The speaker showed techniques to maximize the quality of proton treatment planning for Ependymoma. One must be cognizant of differences in the RBE at the distal edges.

The RBE rises at the distal end of the beam because the LET rises.
There are multiple factors which produce range uncertainty at the distal end of the beam such as energy, patient motion, tissue heterogeneity factors.

Models for second malignant neoplasms - Stokkevag

SMN appear decades after treatment and there is a continued upward force of morbidity.

The speaker cited the classic Cahan criteria for SMN. She next cited the major studies which demonstrate the incidence of SMN after radiotherapy. Then she turned to the life span studies of the Japanese atomic bomb survivors.

There are multiple factors which contribute to the risk of SMN such as dose, gender, diet, tobacco use, age at exposure (risk increases at decreasing age at the time of exposure), attained age, or use of chemotherapy.

The concept of organ equivalent dose (OED).

This modeling shows, in general, a lower risk of SMN with proton therapy rather than photon therapy.

You can convert a 3D dose to a risk equivalent dose.

There are also uncertainties related to leakage dose, neutrons, scatter dose, CT dose, and genetic predisposition.

MRI guided radiotherapy in children - Perkins

Why do this? Tumor localization, tracking/gating, adaptive radiation therapy (ART; this is about day-to-day changes in the tumor's proximity to normal structures and changes in the tumor itself)

Inter v intra fraction variability

The unit is a 3.5 tesla with 3 Co60 heads with MLCs. They are adding a unit with a LinAc. (Brand name is viewray)

Some MRIs, if the magnet is very powerful, can create dosimetric changes. That's why they use 3.5 tesla.

For RT you need MRI compatible monitoring and sedation equipment and ear protection

The unit opened in 1/14 and they have treated 450 patients.

She showed an example of how normal tissue can be closer or farther away from the tumor volume on a day-to-day basis.

This technique has almost never been used in children so some of the talk addressed possible applications of the technique.

On Thursday night there were two social activities. Some attendees went to a Broadway show and some went to a New York Yankees baseball game.
Friday sessions

Education in pediatric radiation oncology

PROS/ESTRO teaching courses - Kortman

Dr. Kortman described the educational courses in pediatric radiotherapy run by PROS/ESTRO. He showed data on the variability of contouring by course participants and the nature of their practices (most see relatively few children, have limited access to protons).

The IAEA approach - Anacak

This international organization is a major player in radiation oncology. They perceive pediatric cancer a major priority. They run training courses, publications, patterns of care studies. They regularly run free-of-charge courses for physicians in less economically developed countries for training in pediatric radiotherapy. They arrange for the exchange of fellows, survey of practices, patterns of care studies, and technical meetings for the establishment of guidelines. They are promoting a telemedicine network. They have a library of recorded lectures.

Proffered Papers

Treatment of infants with localized rhabdomyosarcoma - Bradley

Local failure is a bit higher for infants than older children and local failure is lower with protocol therapy than with individualized therapy.

Patterns of failure with proton therapy for head and neck rhabdomyosarcoma - Ludmir

Local control is comparable to other series but there was a high rate of regional nodal recurrences, particularly in alveolar patients, this raises the possibility of needed elective nodal irradiation.

Impact of radiobiological models on medical decision making for photon and proton therapy - Bondiau

Mathematical models show a lower predicted normal tissue complication probability with protons v photons for Medulloblastoma

Vaculopathy after proton therapy for treatment of base of skull tumors - Hall

3 year incidence of any vaculopathy was 8% and there was a 3% incidence of serious vaculopathy.

Predictive factor was >54 Gy to the optic chiasm

Only three years of follow up

Timing of radiotherapy for parameningeal rhabdomyosarcoma with intracranial extension - Ludmir

Proton treatment
5 year OS 51%
9 of 15 had recurrences. All local failures were in-field. No marginal misses
The big predictor was that if the radiotherapy was begin by week four or earlier after the initiation of chemotherapy. Primary reason is referral delay (some of this delay may have been the result of referral of patients from great distances). Sometimes the medical oncologists want to hold off on radiotherapy by seeking to ascertain if there is going to be more a response to chemotherapy. One questioner pointed out that some of the local relapses may have been the result that the chemotherapy dose was de-escalation.

**Hypofractionated radiotherapy for DIPG - Zaghloul**

The speaker described the hyperfractionated data. Then he described a randomized trial of Hypofractionated (39Gy in 13 fractions) v 54 Gy in 30 fractions. No difference in survival or progression free survival or complication rates.

<10% of the patients were biopsied

New trial is 54 Gy/1.8 Gy f or 39 Gy/3 Gy f or 45 Gy/(I couldn't make out what he said regarding fractionation, maybe 2.5 Gy/f?).

No difference in overall survival or event free survival. Prognosis a bit better for children five years of age or younger. Hypofractionated irradiation seems equivalent.

Some of the questions from the audience concerned the development of knowledge regarding genetic markers in DIPG and whether such data will eventually lead to new prognostic markers or drugable targets.

**Proton therapy for Ependymoma - Peters**

82% tumor control; 97% survival

**Local control and outcomes from pediatric palliative irradiation - Madden**

2/3-3/4 of patients had symptomatic relief or pain relief from palliative irradiation

**Patterns of care for intracranial germ cell tumors - Goddard**

She did a questionnaire in Canada which included a scenario of a germinoma and a nongerminoma tumor.

72 of the 119 invited physicians answered.

Most respondents would treat the localized germinoma would give chemotherapy (carboplatin and etoposide) and whole ventricle radiation (24-5 Gy) and pineal boost (to 45 Gy). 96% of doctors working in pediatrics would give chemotherapy v. 54% of those working in adults. For non-germinoma most would give CSI (36/54-60 ) and chemotherapy.

**Challenging brain tumors**

**DIPG - Janssens**

The speaker reviewed the hyperfractionated literature and the Hypofractionated studies.
Prediction model: longer symptom duration, use of chemotherapy, age older than 3, MRI ring contrast enhancement

Genome characteristics: Histone H3 K27 mutation. There appears to be a prognostic influence of certain subtypes of this mutation.

Role of re-irradiation at the time of first progression. It may buy an additional average 3 1/2 months of survival.

Now there is a randomized trial of re-re irradiation (54 Gy v 36 Gy + 19.8 Gy + 9 Gy)

Comments were made regarding convection enhanced delivery to circumvent blood-brain barrier

High grade glioma - Bandopadhayay

She showed an excellent slide which summarized (slide from Wu et al, Nature Genetics 2014) the massive number of genetic aberrations in DIPG and high grade gliomas among histones, growth promoting genes.

She described targeted genetic DNA sequencing of brain tumors by a consortium of Boston hospitals to create a data bank. They look at copy numbers and mutations.

For many pediatric brain tumors, there are NOT a lot of aberrations or copy number changes.

% genomic disruption is highest for embryonal tumors > HGG > LGG but, still, pediatric tumors are genetically quieter than in adults.

Molecular profiling trial of DIPG (trial PI is Dr. Mark Kieran, Dana Farber Cancer Institute)

Biopsy, RT+Bevacizumab, Additional agents based on molecular diagnostics: MGMT promoter methylation - temozolomide, EGFR - erlinotib,

60% of children with DIPG don't have markers.

Low grade glioma - Harrabi

Surgery. If compete resection then watch and wait. If not complete resection then if there are symptoms then, in <8 years, chemotherapy; >8 year radiotherapy.

Overall survival at 10 years 90% and 50% event free survival.

Some molecular targets are being sought after but, so far, this has not had an impact on clinical management.

RT can impact event free survival but it is associated with significant long term ill effects.

AT-RT - Timmerman

Very young patients, rare disease, high risk for toxicity, little RT data available

A MD Anderson retrospective review and a SEER database review indicate a benefit to RT.
The use of highly focal irradiation such as protons makes one more sanguine about the use of RT in very young children.

For M0 disease give 54/59.4 Gy and CSI for M1 disease but an unpublished review from Essen that there is no benefit from CSI in either M0 or M+ disease (small numbers)

There is a proposal for a European trial of HDCT v CT with RT

**Adult tumors in children**

**Melanoma - Chard**


She showed the "slip, slop, slap" Sidney the seagull health education campaign

Ban on commercial solariums

No hat, no play policy

Australia and NZ have the highest melanoma rates in the world

The rates are falling for young adults now - perhaps as a result of the health education program

**ABCDE criteria (asymmetric, border, color, diameter, evolving)**

Survival is strongly a function of depth of penetration and nodal involvement. Treatment is wide local excision. Sentinel lymph node biopsy. Adjuvant therapy include IFN-alpha. Ipilimumab. Targeted therapies include drugs which are BRAF inhibitors.

If you can't get a negative margin on a local excision for technical reasons then consider adjuvant RT. For regional disease to the nodes it can be used to reduce the risk of lymph node relapse but won't affect survival. Also it has a role for palliation.

**Rental tumors - Ladra**

This talk is about renal cell carcinoma, not Wilms.

Usually clear cell with papillary features in adults. In children about half are translocation subtype (transcription factor E3). About 1/5th are papillary. About 1/10th are renal medullary, often associated with sickle cell trait.

Some renal cell carcinomas are associated with genetic syndromes like Von hippel lindau but these are rare in children.

Geller Cancer 2015 is a good review article

**AREN03B2**

Most children undergo radical nephrectomy and some undergo nephron sparing surgery. Just over half have surgical evaluation of lymph nodes and half of them have positive nodes.
Pediatric 5 year survival by stage I-92%, II-83%, III-73%, IV-14%

There is a long list of reported active agents in renal cell carcinoma - some are chemotherapy and some are immunotherapies.

RT is good for pain palliation

Good local control for single fraction radiosurgery for palliation of metastatic renal cell carcinoma

**Lung - Goddard**

Most common types of adult lung cancers in children are Carcinoid (40%), mucoepidermoid, adenocarcinoma

The population of British Columbia is about 4.5 million and they have had 9 Carcinoid lung tumors in children over > 20 years.

Of the carcinoid tumors 90% are typical and 10% are atypical. Both can metastasize.

Diagnosis is often delayed. They usually present with obstruction and infection.

Carcinoid syndrome is rare in carcinoid tumors and is usually associated with extra pulmonary carcinoid disease.

The mainstay of treatment is surgery. Late recurrences are well known.

Mucoepidermoid cancer can occur and are usually low grade. Optimum management is complete resection.

Adenoid cystic cancer can occur. They need to be resected. They frequently engage in perineural spread.

Pediatric lung cancers have been described as being associated with prior treatment for another pediatric malignancy.

**Stereotactic radiation therapy**

**Lung metastases - Van Dijk**

Stereotactic radiation therapy has been used in adults for lung metastases but rarely in children - but it certainly could be. A maximum intensity projection CT is used to identify the volume to treat. We have already heard, earlier in this meeting, that there will be less average distance of organ motion in children than adults.

Cone beam CT for image guidance.

Typical fractionation schemes are 3 X 18 Gy or 5 X 11 Gy (near chest wall) or 8 X 7.5 Gy (near spinal cord and heart) for adults. For children they use 5 X 6.5 Gy.
Bone - Eaton

Fractionation schemes in children: 10 Gy X 3

SBRT for Ewing and osteosarcoma. Median is 8 Gy X 5 but a variety of schemes were used (Brown et al. Sarcoma 2014). 85% two year local control.

There are two papers on treating primary or metastatic spine sarcomas. 10 Gy X 3 or 16 Gy X 1 or 8 Gy X 3 or 5 Gy X 5. Good pain relief.

Non-spine bone metastases. 24 Gy X 1 or 16 Gy X 1 or 10 Gy X 3 or 8-10 Gy X 5. (Owen et al PRO 2014). Pain flair in 10%.

Brain - Gandola

Typically use 6 MV photons.
Acute toxicity is small.
No more than 2.5 Gy/f to the chiasm.
Don't treat lesions within 5 mm of the chiasm or optic nerves
There can be transient tumor oedema.

For low grade glioma 11-15 Gy X 1 have been given. It takes, on average, a year for the tumor to decrease in size. PR in 50-75% and CR in 20%. Main complication is transient symptomatic edema. Recommended marginal dose to avoid necrosis is 12-14 Gy.

The speaker said that the optic nerve tolerance to a single fraction is 8 Gy.

Craniopharyngioma

Be at least 3 mm from the optic apparatus and the lesion shouldn't be more than 2.5 cm. Marginal doses given are 11-14.5 Gy. Of course, these patients can also be treated with 1.8 Gy/fraction X 30.

Radiosurgery has been used for recurrent/retreatment of Medulloblastoma

Can protons replace SRT? - Liu

X-rays are more conformal and adaptable to tumor size whereas protons are more homogeneous. Protons have dose uncertainty in these very small volumes.

RBE with protons rises in the 6 mm from the Bragg peak

Private insurance and higher income correlates with the receipt of protons

Immunology and the abscopal effect - Vatner

Anti-tumor immunity is a complementary mechanism for radiation induced tumor control and contributes to the abscopal effect of radiotherapy.

The local effect of RT is dependent on T lymphocytes.
Irradiated tumor cells are immunogenic - they become a vaccine.

Abscopal effect is an impressive but rare phenomena.

Why is the abscopal effect rare? In part it is because tumors are quite good at suppressing their own antigenicity. Investigators have tried immunomodulators like check point inhibitors. In mouse models they can accentuate the abscopal effect as seen by tumor response and lymphocyte infiltration of the tumor.

Radiation may make tumor cells appetizing for dendritic cells which heightens the antigenicity.

Radiation makes tumor cells better targets for the immune system. (This is not uniformly true amongst varying experimental models.)

There are several attempts to see what fractionation scheme is best at provoking an immune response. Perhaps higher doses/fraction inhibits the local immune response.

The immune modulator works better if you give it right before or during the radiation.

There are now some open clinical trials.

After this talk the PROS General Assembly met.

Then, in the evening, the gala dinner took place.

**Saturday morning**

Proton therapy - Merchant

Scanning beam technology has become the preferred technology. It is very important to have enough space set aside for anesthesia support. Quality assurance is done with both planar imaging and cone beam CT.

Larger part of the proton practice is Medulloblastoma and Ependymoma.

The speaker reminded the audience of the risks and complexities of CSI. Planning CSI proton therapy is very labor intensive. He showed a technique of proton field junctioning for spinal field CSI irradiation.

Protons in CNS tumors, pros and cons - Claire Alapetite

The speaker made the usual argument that we strive to improve the therapeutic index on the treatment of brain tumors and minimize the risks to brain function. Imaging now allows delineation of individual brain structures.

Proton therapy may also reduce risks to non target structures.

There are, however, uncertainties regarding the dose at the distal end of the beam and, with a rising RBE at the distal end of the beam; uncertainties with the dose at the distal end of the beam
as a result of tissue heterogeneity. The scattered dose is different with passive beam scattering v pencil beam.

In Europe RMS, Ependymoma, low grade glioma, craniopharyngioma are among the common uses of protons for pediatric radiotherapy.

In Medulloblastoma there appears to be equivalent survival.

Questionnaire studies favor proton therapy in many of the pediatric brain tumors but not, for example, in Wilms tumor.

One must be cognizant that as new agents are introduced into the treatment of brain tumors there will be new combined modality toxicities.

If prognosis is poor, not routinely treated with proton therapy.

There are marked access disparities to protons throughout the world. As proton unit become more widely available, the cost will be closer to photon therapy.

**Reduction in late effects with proton therapy - Eaton**

The speaker showed multiple slides based upon reviewing papers in the published literature asserting lower incidence of late term ill effects of radiotherapy with protons v photons. These slides included data on endocrine (the effects of protons v photons differ for different hormone end-points ie thyroid function and sex hormone function are more often damaged than growth hormone, or adrenal) and other forms of neurocognitive function, vascular and cardiac injury, second malignant neoplasms, and general quality of life metrics.

There was a question about the thyroid dose with proton CSI therapy. Even with full coverage of the vertebral body during CSI with protons the thyroid dose is about zero.

**Best poster session**

**Social health-related QOL in proton therapy patients - Nanda**

This is a retrospective review of QOL metrics in U of F proton therapy patients receiving skull base and brain tumor treatment. Parents of children who were <8 years of age when treated showed the most decline in social quality of life.

**Dose based approach for Inter observer variation in target declination**

This study looked at not only difference in target delineation but what was the impact of those variations upon the dose. A graphical display was used to show the impact on dose using a Hodgkin disease case.

**Retrospective review of white and gray matter changes after focal radiotherapy for pediatric brain tumors - Cavorta**

At least two years of follow up with no evidence of relapse. The dosimetry was registered with the diffusion tensor imaging MRI in order to extract the mean dose value and inside each region of interest and correlative cognitive testing. Three were significant associations (P<0.01) between
cognitive test score and absorbed dose in 46 regions of interest. The most significant associations were in cerebellum and occipital lobes.

Comparing pediatric to adult patients with rhabdomyosarcoma - Lin

The speaker was looking at differences in prognostic factors in children vs adults. She used the SEER database and did univariate and multivariate analyses.

Children more often had smaller tumors, earlier stage. They more often had radiotherapy and surgery.

Race, stage, primary site were associated with survival in pediatric group. Race was not significant amongst the adults.

Pediatric patients had superior survival and were more likely to get irradiation and surgery. There is probably less use of protocols in adult patients.

Dose-volume approach to surveillance for radiotherapy related late effects - Olch

This is a report of an attempt to provide automated patient-specific dose-Volume data for the relevant organs at risk (OAR) to optimize risk-assessment and correlative organ surveillance for patients followed longitudinally in the cancer survivorship clinic. Each child's electronic medical record has a table showing the organs contoured, the dose, and whether a "threshold to warrant concern" was exceeded.

Multicenter treatment planning inter-comparison for a case of parameningeal RMS, alveolar, of the skull base

Ten centers planned the case with either IMRT, tomotherapy, or proton therapy to identify possible dose distributions. The optimization strategies selected by the planners played a key role in the delivered dose to the OAR. While proton therapy seemed to reduce the dose to the OAR the results were highly dependent on human factors.

The meeting concluded.