**A SUMMARY OF THE PAPERS PRESENTED AT THE 2010 PROS MEETING**

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The 2010 PROS meeting took place in Boston. As I have done for all of our previous meetings, what follows are my summaries of the presentations at the meeting that I was able to attend. Unfortunately, neither my rapidly typing fingers nor my overall strength were sufficient to attend every single session and take notes at all of the talks – but I did attend most of them. EC Halperin Educational Sessions on Wednesday October 20, 2010 Ependymoma Lorenza Gandola of Italy speaking. Post operative irradiation compared to surgery alone improves the survival of these children by 2 to 3 fold. Chemotherapy by itself is not curative. Chemotherapy has the potential for improving the possibility of resection. The role of adjuvant chemotherapy is an object of clinical study. There has been a debate over the role of spinal irradiation. In properly staged patients without spinal seeding, spinal irradiation is not necessary. There is a dose response relationship for local control with evidence for improved results with local doses >45 and now up to 59.4 Gy. BID irradiation, however, is not an improvement over QD. Conformal radiotherapy shows high local control rates. A slightly lower dose (54 Gy) is appropriate for children One irradiates the gross tumor volume and the CTV puts a 1 cm margin around that and the PTV is another 0.3-0.5 cm. The results are quite good. (See Lancet Oncology 2009 Merchant et al.) You should achieve a local control of about 87%. Local failure remains a problem. Maintenance of IQ is associated with tight treatment margins and precision delivery of therapy. Factors predicting a drop in IQ include hydrocephalus, pre-existing conditions, pre-RT chemotherapy. Image registration is useful for radiotherapy treatment planning. Current techniques of treatment focus on the post-operative tumor volume as the treatment target. This requires high quality imaging. The criteria for CTV and PTV significantly influence the volume of brain irradiated. IMRT has been described in relatively small series. The median dose is on the order of 54 Gy. The results look good compared to historical series. Some children with residual disease after surgery have been treated with radiosurgery to the residual tumor. A few papers suggest that this is promising – albeit in papers with very few subjects. The AIEOP 03 study gives 59.4 Gy @ 1.8 Gy/fraction. In patients with residual tumor after surgery a radiosurgical boost of 4 Gy x 2 is given on top of the 59.4 Gy. Obviously great attention must be given to protect critical adjacent structures. The preliminary results of AIEOP 03 show 78% local control. Fifteen of the 110 patients received the radiosurgical boost. There is no difference in survival in patients with or without residual disease! Proton therapy for ependymoma also appears to achieve local control in about 86% of patients. See MacDonald et al. IJROBP 2008. Questions from the audience: Is 59.4 Gy really better than 54-55 Gy? Some of the members of the audience are really not sure. Another speaker pointed out that it is hard to tell if late effects are different between the two doses. Dr. Habrand expressed concern about irradiating tumors which extend down to the spinal canal to such a high dose. Another questioner asked about the use of constraints. The speaker said that the brain stem constraint was about 54 Gy. Yet another questioner commented that a lot of the results attributed to radiotherapy are the result of the quality of surgical resection i.e. the ability to achieve local control. The questioner observed that sometimes re-resection is in order. Finally, a questioner wondered if we have “plateaued” at 85% local control and if other chemo- or biologic agents can help move us beyond that. High Grade Gliomas Speaking was David Ebb of the United States. High grade gliomas of childhood constitute about 10-15% of the 50% of all childhood tumors which are brain tumors. This means there are about 300 pediatric high grade gliomas per year in the U.S. This contrasts with 15,000 adult high grade gliomas per year in the U.S.. The outcome is generally very poor. These tumors are usually highly vascular and very invasive. The biology of these tumors in children is not the same as in adults. Pediatric low grade gliomas are much more common than high grade – the opposite of what you see in adults. In children, 1/3rd of high grade gliomas are supratentorial. Leptomeningeal spread at the time of diagnosis takes place in 2-3%. 33% are disseminated at recurrence. PDGFRA promotes gliomagenesis in children whereas in adults EGFR plays the major role. Amplification of EGFR is relatively infrequent in pediatric high grade gliomas. There are different gene expression patterns in children v. adults with high grade gliomas. There are also differences in gene copy numbers in children v. adults. Pediatric patients more often have mutations on chromosomes 1 and 16 than in adults but less often mutations on chromosomes 7 and 10 than adults. Compared to adults, p53, RTK/P13K, and RB are less often abnormal in pediatric high grade gliomas than in adults. PTEN mutations in pediatric high grade gliomas are less common than in adults. RAS activation in children does occur. Inactivation of RAS may be associated with a better outcome in children. The prognostic factors for these children include extent of resection, histology, p53 expression, PTEN deletion, MGMT status, location, MIB-1 index. Unfortunately, gross total resections are achieved only about 25% of children with these tumors. For anaplastic astrocytomas gross total resection doubles survival whereas in GBMs it improves survival six fold. Grade clearly correlates with survival. WHO 1 at 15 years has a 95% 5 year survival v. 20-25% for WHO IV. Overexpression of p53 worsens survival. Survival is better when PTEN is not mutated. MGMT is a DNA repair enzyme. If it is overexpressed then the survival is worse. Infants with high grade gliomas ( In the French BBSFP study the prognosis was also better in younger children. TP53 mutations are rare in children RAS/AKT is of prognostic importance. When it is inactive, the children do better. Maximal safe surgical resection in the first step. After surgery, chemoradiotherapy and chemotherapy are typical. Usually 54 Gy + chemotherapy is given followed by chemotherapy. CCG 943 was a study which was reported in 1976 and indicated that RT was worse than RT + chemotherapy. Stupp et al. showed the usefulness of temozolamide in adults (NEJM 2005 and also Stupp et al. in JCO 2007)/ Some of the pediatric studies are contaminated by including other tumors in the series. Upon pathology review, some of the patients in the CCG studies turned out not to have high grade gliomas. This changes the reports survival rates. If MGMT is hypomethalated and highly expressed, there is little benefit to temozolamide. If MGMT is methylated, the prognosis is better, if it is unmethylated the outcome is worse. The results in unmethylated patients are worse, but in pediatric patients the temozolamide still seems to help a bit in the unmethylated tumors. Of interest regarding new techniques is the targeting of VEGF in high grade gliomas. Avastin and irinotecan have been employed in an adult study from Duke in adults and produced a 63% response rate and these findings have been replicated in Cleveland. In children, however, the 2010 JCO report described no responses for recurrent malignant gliomas or in pontine gliomas. Now there is a study of the use of xrt/tmz followed by tmz + ccnu. There may be a “slight benefit” compared to historical controls but not too impressive i.e. about 20% event free survival. Also a recent study by Wolff et al. Cancer 2010 of xrt concurrent with cddp/vp16/vcr followed by cddp/vp16/ifos showed no benefit compared to historical controls except in those children with gross total resections. New candidate agents include targeting pdgfr, ras, mTOR, VEGFR, integrins, HDAC-SAHA, and PKC. (See Idbaih et al. The Oncologist 13, 2008) The current COG study is xrt + vorinostat v. xrt + tmz v. xrt + bevacizumab and post-xrt maintenance, in all arms, of bevacizumab + irinotecan. Turning to diffuse intrinsic pontine gliomas, xrt + tmz is not better than xrt alone. The medial survival is Questions from the audience: The COG studies will use 60 Gy as the standard xrt dose. If age is a prognostic factor, when do you consider a patient as having an adult tumor? At what age? No one really knows. What is the role fur functional imaging? The speak thinks it will have a major impact in the future. Supratentorial PNET The speaker is Dr. Roger Taylor of the U.K. These are 20% of PNETs and 2-3% of pediatric brain tumors. The survival is worse than medulloblastoma. There are significant long term morbidity issues for these children. These tumors have heterogenous radiological characterictics and can present with large masses. They are large, vascular, and hemorrhagic. On MRS they have elevated choline, decreased N-acetyl aspirate, and a small taurine peak. Synaptophysin may be prominent. The molecular characteristics suggest that medulloblastoma and supratentorial PNETs are cytogenetically distinct. Pineal tumors have a survival that is consistently better than non pineal supratentorial tumors. M status predicts outcome. There has been no difference in event free survival produced by the use of chemotherapy. The predominant site of relapse in the randomized study was local. A tumor The St. Jude Children’s Research Hospital PNET study gave 23.4 Gy to the spine in lower risk patients and 36-39.6 Gy in higher risk. The tumor bed got 55.8 Gy. The overall survival was 73% at five years with many pineal patients in the study. A Canadian retrospective study was based on physician questionnaires. 80% of the patients had M0 disease and the remainder had M1-3. The 4 year overall survival was 38% and there was a 2% toxic death rate. The German HIT 88/89 and HIT 91 studies had a 48% overall survival at 3 years. The 3 year survival was 49% if the radiotherapy was correctly administered and 7% if there was a major deviation. The pineal patients, once again, did better than the non pineal. In infants with supratentorial PNET there were German HIT-SK 87 and HIT – SK92 studies for patients 3-37 months. Some patients with chemotherapy complete responses didn’t get xrt. The 3 year overall survival is 17%. The Milan hyperfractionated accelerated radiotherapy (HART) study had 3 pineal and 12 nonpineal patients. The patients got mtx, etoposide, cyclophosphamide, carboDDP prior to xrt with HART. The 3 year event survival was 34% and a 61% overall survival. Current protocols include COG ACNS 0332High risk study Supratentorial PNET and high risk medulloblastoma. The target is 300 patients to be accrued. The randomization is XRT + Vincristine v. XRT + Vincristine and Carbo DDP and then plus or minus retinoid. The dose will be 36 Gy CSI and 55.8 Gy to the primary and a boost to metastases of 45-50.4 Gy. The chiasm dose will be less than 50.4 Gy. The German HIT-2000 study gives 1 Gy b.i.d. to 36 Gy CSI and 68 Gy to the tumor bed and then a further boost to residual tumor. If age is Biological studies are needed to assess the impact of biological markers on outcome. Local control remains a problem. Detailed patterns of relapse studies are needed. Late effects studies are also necessary. The questions for this speaker included: Isn’t 23.4 Gy often adequate for the lower risk patients? Proton Therapy in Childhood Brain Tumors Dr. Tarbell of the U.S. was the speaker. Protons decrease the normal volume of tissue treated and may decrease the risk of second malignant neoplasms. There is no exit dose. The prospective phase II trial of protons in medulloblastoma, study 99-271, has closed from the Massachusetts General Hospital. This study was reported at ASCO in June and was summarized again in this talk. Protons in the treatment of medulloblastoma spare the organs anterior to the spinal cord. They also seem better at sparing the cochlea and supratentorial brain. The treatment was 23.4 GyE craniospinal irradiation (CSI) and 54-55.8 GyE to the tumor bed. Proton CSI in children >14 years of age was thecal sac irradiation only and didn’t cover the entire vertebral body. See the illustration in Krejcarek et al. in IJFOBP 68:646, 2007 that shows the beam stopping in the posterior 1/3rd of the vertebral body. A proton boost can spare a lot of the hypothalamus. The patients had extensive follow up for late effects. Sixty patients were enrolled on the study and 59 were evaluable. Most were standard risk. The 3 year progression free survival was 80% and overall survival 90%. The baseline full scale IQ was 107.26 patients had baseline and follow up testing. The follow up full scale IQ was 103. No other indices fell except for processing speed which did drop. The cochlea dose was lower with protons than what you get with IMRT. 16% of the proton patients had grade 3 or 4 ototoxicity. Hearing loss starts around year 1 and gets worse as the years go by. The cumulative dose of administered cisDDP was higher than is usually reported. So, the lower mean dose to the cochlea does not translate into fewer patients with grade 3 or 4 ototoxicity. CisDDP can cause substantial high frequency hearing loss. Endocrine results look better. They have, overall, treated about 1000 children with protons at the older and new proton facilities. (With fractionated treatment, not radiosurgery). Protons are more expensive and more labor intensive. Every patient has their own brass aperture. Lucite is used for depth dose modification. This also accounts for tissue inhomogeneity. They have on line portal imaging. Protons can be used for whole ventricular irradiation for germ cell tumors. Esophagitis occurred in an early proton patient. They have now pulled back the range of the protons in the upper cervical spine because of it. Questions: Do protons produce more skin ill effects and prolonged alopecia? With three fields for brain tumors, Dr. Tarbell said, no. For superficial rhabdomyosacromas there may be more trouble with skin injury. The thicker the tumor and the closer the tumor is to the skin, the harder it is to have sparing. They intentionally try to keep the skin dose lower. Sometimes, with combined modality therapy, you have to do a treatment break because of skin effects. Also, sometimes they combine photon and protons for chordomas and rhabdomyosarcomas. With protons, you have to be careful not to treat too small a volume. Daily treatment with anesthesia is a 20-30’ session for ependymoma. Craniospinal irradiation is 1.5 hours per session. This is an issue if you still need to use anesthesia. (That’s not common with medulloblastoma – the children are usually old enough that anesthesia isn’t necessary.) They infrequently do re treats because of beam access issues. A representative of another proton center made a similar comment. They are studying the issue of the induction of second malignant tumors with protons – largely in a series of patients treated at the Harvard Cyclotron Laboratories with a minimum of five years of follow-up. Afternoon Educational Session Wilms Tumor The speaker was Dr. Kalapurakal. The mortality rates for childhood cancers in the U.S. are improving significantly. Wilms tumor is the poster child for the improvement in survival. Wilms tumor is also illustrative of our interest in both improving survival and improving the quality of survival. There are about 500 cases annually in the U.S. The peak incidence is in 3-4 year olds. 12% are multifocal and 7% involve both kidneys. The tumor is typically soft and friable and can be easily ruptured. There are favorable and unfavorable histologies. 90% are favorable. The important genetic issues are WT1 on 11p13, WT2 on 11pl5.5, and WTX on the X chromosome. There are also a variety of tumor suppressor and promoter genes. LOH at 1p and 16q were assessed for prognostic value in NWTS-5. Relative risk for relapse or death are both elevated with LOH at both sites. 16q only LOH is not of prognostic significance. This tumor is often localized at diagnosis and may be cured by surgery or RT in as many as 50% of cases. Clinical presentation: a healthy appearing child with an abdominal tumor or compared to neuroblastoma which is characterized by a sick child with an abdominal tumor. Rhabdoid tumors of the kidney are associated with posterior fossa ATRT. They no longer recommend a staging chest x-ray; rather they do a chest CT. With the advent of good imaging, exploration of the opposite kidney at the time of surgery is no longer recommended. Tumor spillage upstages to Stage III. Stage III and IV anaplasia still have relatively poor survival rates. (He pointed out the distinction between diffuse and focal anaplasia and how stage II diffuse anaplasia did better than stage I diffuse anaplasia; because of the employment of chemotherapy in Stage II.) The COG study will use stage, histology, and LOH in stratifying patients for therapy. Thus in the new COG study, they will split the patients into very low risk, low, standard, and higher risk. Very low risk are surgery alone patients that are For CT only metastases, 3 drug chemotherapy is adequate without irradiation if the tumor responds. About 40% of the patients can be spared whole lung irradiation. For those patients who still get abdominal irradiation, use 10.8 Gy except for higher risk patients who get 19.8 Gy. They still recommend irradiation at 9-14 days. For bilateral disease they seek to improve the 4 year event free survival beyond 73%. In syndromic Wilms tumor they are seeking to increase renal parenchymal sparing surgery. In the future, gene expression analysis will likely be used to predict relapse in favorable histology Wilms tumor. A panel of genes are used and this concept will require prospective evaluation. These gene expression classifiers may help to decide which patients are extremely unlikely to relapse. They find that liver metastases patients do as well as lung metastases patients. Therefore, they should be able to reduce the liver radiation dose from 20 to 10 Gy. There is a feasibility study of using IMRT to do cardiac sparing whole lung IMRT in those patients when whole lung irradiation is indicated. This might have the potential to reduce the risk of heart failure. The threshold dose for CHF with chemotherapy is about 5 Gy. CHF is the leading cause of morbidity and mortality at 10 to 20 years after treatment. This makes it important to try and minimize heart radiation dose. The pilot study will assess practicality, efficacy, and toxicity. All cases will be pre-reviewed by QARC. If you want to see how to do the contouring, look at the QARC web site. Participating institutions will have to irradiate a special phantom to get credentialed to be in this study. By giving the lungs 12 Gy, you can get the heart dose down to about 6 Gy. Most of the lung movement is superior/inferior – it is on the order of 1 cm. With 4D volume measurement, with IMRT and gated scan, you can treat more lung. Because we don’t use lung correction, there are hot spots in the lung with AP/PA techniques. These are reduced with 4D IMRT. The DVH can be created for each of the crucial targets in the heart i.e. coronary arteries v. myocardium. What is to be done about sequential whole lung irradiation and abdominal irradiation concerning the overlap? Can IMRT improve the amount of tissue in the overlap area? It looks like IMRT is better than AP/PA for reducing the volume of overlapped tissue. In general, he believes that IMRT is likely to improve the therapeutic radio in the radiotherapy of Wilms tumor. They got an excellent breathing pattern in these young children for the pilot study. Neuroblastoma The speaker was Dr. FH Saran of the U.K. He began with a bit of apology over the relative lack of data for treatment of this tumor. The principles of radiotherapy for neuroblastoma: It is about 6% of childhood tumors. That is about 100 cases per year in the UK. Median age is 22 months. 35% This is a small, round, blue cell tumor. On diagnostic imaging you see intrinsic calcification. He demonstrated an image of a dumb-bell shaped tumor. These tumors can be positive on MIBG imaging. n-myc, 1p-, trk expression are biologic prognostic factors. Randomized prospective trials in INSS 2B + 3 with 62 patients shows an improvement in event-free and overall survival with radiotherapy (Castelberry JCO 1991 9:789). The local relapse rate in stage 4, age >1 year, is about 40%. This lead to studies which show that radiotherapy can reduce the local relapse rate - either the use of TBI or involved field irradiation. The local failure rate of 21 Gy in 14 fractions with b.i.d. treatment of tumor at diagnosis + 3 cm + regional lymph nodes + metastases in the Memorial Sloan Kettering publication was 10%. He next described a complex European stage IV study which integrated 21 Gy in 14 fractions over 14 working days. They use the pre operative post chemotherapy primary tumor volume + the involved regional lymph nodes as the treatment volume. He recommends the use of abdominal lymph nodes atlases (Martinez-Morque) to map out the nodes you wish to treat. He emphasized the importance of sparing the opposite kidney. Highly conformal treatment plans can be achieved with proton fields. He next turned his attention to radioisotope therapy. MIBG can be used both for diagnostic evaluation with I125 or I131 or for therapy with I131. A tumor cell is roughly 10u in diameter. An alpha particle can reach about 10-100u. A low energy B ray can reach rather farther than that. If you get heterogeneous uptake of MIBG in a tumor, only about 1/1000 MIBG molecules will have the radioisotope. You still are likely to get enough cross-fire in the tumor to have a biological impact. The overall neuroblastoma response rate to MIBG is 58%. There are interesting potentials for improving the efficacy of MIBG by using higher activity, fractionating it, maintaining oxygenation, and/or use of concomitant chemotherapy (in animal model experiments, this appears promising). Questions: What is the role of treatment for microscopic/macroscopic residual abdominal disease? In older practice, a graded radiotherapy dose plan was used with higher doses for bulkier disease i.e. 35-40 Gy. He irradiates post-chemotherapy post-operative volumes in high risk disease. Hematological reserve is important if you give MIBG. It can cause thrombocytopenia. The combination of chemotherapy + MIBG can be marrow ablative and may require stem cell rescue. After this session, the group adjourned to the tour of the proton facility and the social program. Thursday, October 21, 2010Educational Session Greetings from the President of PROS, Christian Carrie of Lyon, France He opened the session and greeted the attendants. He thanked the local organizing committee. What’s New in Rhabdomyosarcoma (RMS)? The Australian Approach – Dr. Verity Ahern of the University of Sydney There are small patient volumes in Australia. The country is geographically isolated and the radiation oncologists are scattered. There are 8 PROS members for a country of 25 million. Australia has universal health care. In the Australia + New Zealand (ANZ) data bases there were 1892 pediatric cancer cases There are no Australian radiotherapists with a practice restricted to children. Adolescents are particularly problematic and only 4-8% of 16-24 year olds are treated on protocol. New Zealand has a better system to get adolescents on study. (The problem of adolescent oncology is a general one.) Very few RMS papers are published from Australia. There are Australian studies that show that centers treating fewer patients are less compliant with XRT protocols. (Peters et al. JCO 28:2996, 2010). She cited Halperin’s paper showing that protocol deviations in ALL C2 whole brain were related to the number of patients treated but that they fell over time as experience accumulated. She next cited data that showed that survival in Wilms tumor is associated with a center participating in a cooperative trial. Uniform quality control is important in improving outcome in a clinical study. This has been shown in RMS. In Australia, just over ½ of children with RMS were enrolled in a clinical trial. They used to use SIOP trials and now, mostly, COG trials. They have largely given up on Australian trials for children because of the small pati