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**Hodgkin’s Disease: Technical Aspects (Chaired by Drs. P. Thomas and S. Wolden)**

In a presentation on target delineation in Hodgkin’s Disease, Dr. K. Dieckmann (Vienna) reviewed the German-Austrian studies from 1978 through 2007. She described the historical evolution in the treatment of Hodgkin’s disease from total lymphoid irradiation (TLI) to MOPP chemotherapy to chemotherapy with involved field irradiation, (IFRT), chemotherapy alone, and IFRT alone.

Dr. Dieckmann began by citing the 1976 study by Donaldson et al. which utilized 40 to 46 Gy of extended field radiation therapy and achieved an overall survival rate of 89 to 95%. The utilization of chemotherapy with IFRT (20 to 40 Gy) yielded a 90 to 95% event free survival. Chemotherapy alone, however, also generated a 90 to 95% event free survival.

The German-Austrian Pediatric Hodgkin’s Studies now separates patients into three treatment groups (TG): 1 - Early Hodgkin’s disease constituting 40% of the population; 2 - Intermediate Group Hodgkin’s Disease constituting 27% of the population; and 3 - high risk Hodgkin’s disease constituting 34% of the population.

The basic treatment strategies were codified in HG studies 82, 85, 87, 90, 95, and 2000. In TG 1 there has been progressively declining radiation therapy dose and the chemotherapy has either been OPPA or OEPA. In TG 2 children have been treated with alternating OEPA/OPPA or COPPIC/COPP with 20 Gy of IFRT. In TG 3 the same forms of chemotherapy were used, utilizing either IFRT or more extensive chemotherapy.

The summary paper for this work is Doerffel et al. from 2003. It described how radiation therapy field size experienced a progressive volume reduction. The procarbazine dose has involved progressive dose reduction over each study to decrease the risk of fertility injury. Extended field irradiation in the German-Austrian studies has evolved to IFRT to cover the involved nodes with a small margin.

In the HD90 study the German-Austrian group demonstrated no increase in local failure as a result of radiation field size reduction. It now appears reasonable, after the evolution of study HD90 to HD95, to treat the involved nodes with a 2 cm margin. It may be appropriate to irradiate, for example, half the vertebrae in order to miss the heart.

A topic currently under debate is whether it is necessary to irradiate a PET negative spleen with positive pariortic nodes. For disease sites after chemotherapy that are CT positive and PET negative, in Euronet PHLC1, no radiotherapy is given for TG1-3 studies if the CT or MRI volume response is >75%. (This is a way of implementing the use of PET in assessing CR vs. no CR.) The COG is also looking at the role of PET scanning.

In GPOH-HD95 they found that, in TG1-3, those children having a complete response to chemotherapy do not need irradiation but those without a complete response need 20 to 30 Gy. Radiotherapy does not appear to be necessary in most children within TG 1. Because of the increased relapse rate in TG 2 and 3 without radiotherapy, radiotherapy is used in for TG2-3.
For disease sites after chemotherapy that are CT positive and PET negative, in Euronet PHLC1, no radiotherapy is given for TG1-3 studies if the CT or MRI volume response is >75%. (This is a way of implementing the use of PET in assessing CR vs. no CR.)
There remains a significant risk of second malignant neoplasms and cardiac dysfunction in long term survivors of Hodgkin’s disease, including valvular disease. This later ill effect is probably related to the mediastinal dose.

Open questions for future studies concern whether or not you can decrease the risk of infertility by replacing Procarbazine with Etoposide and whether you can avoid radiotherapy in PET negative patients (such as 66% of TG1 and 20 to 30% of TG2-3 after chemotherapy). Over time the role of radiotherapy will probably decrease. Some speakers noted that growth factor administration may increase the possibility of a falsely positive PET.
In discussing the volume of irradiation in IFRT, Dr. Kortmann said that the cranio-caudal dimension relied on the prechemotherapy volume whereas the width of the field was that determined status post two cycles of chemotherapy.
In staging, a PET positive bone scan with a CT negative scan and a plain film negative is ignored.

The next presentation was by Dr. R. Kortmann (Leipzig) who discussed the evolution of ideas in the treatment of Hodgkin’s disease. Dr. Kortmann described attempts to decrease late effects in the treatment of Hodgkin’s disease by progressively decreasing the dose of radiation from 36 to 40 Gy down to 20 Gy, limiting the irradiated volume, and utilizing PET scanning.
The speaker cited the importance of quality assurance in studies of pediatric Hodgkin’s disease. There was an increased relapse rate in the German-Austrian studies in radiation therapy protocol violation patients. The current study for TG1 patients (1A-B, IIA) is to administer two cycles of an OEPA. If you are PET negative you receive no radiotherapy, if you are PET positive you receive radiotherapy. The complicated question is whether to give radiotherapy for PET negative patients who are not complete responders on CT or MRI (unless they are using the cut off of >75% anatomic response as described by Dr. Dieckmann). The Eruonet PHLC1 study has an extensive radiotherapy quality assurance data base. They are analyzing the margin necessary for 3D planning in Hodgkin’s disease.

The COG is also looking at the role of PET scanning.
The German study shows no influence on prognosis of the presence of “bulk areas”. It has little role in staging except for the need for a 10 Gy radiotherapy boost; although the COG is no longer using the boost.
Patterns of failure in reference to field size have been evaluated in the HD90 and HD95 studies. The smaller fields appear to be satisfactory. The current German-Austrian study uses these smaller field sizes.

Dr. L. Constine (Rochester) discussed “consensus in [Hodgkin’s disease] treatment? I doubt it!” He began by reviewing the role of radiation therapy (RT) in the current era and cautioned against the substitution of additional chemotherapeutic agents or cycles for low dose involved field RT. Modern approaches for treating pediatric Hodgkin’s disease are risk adapted or response driven therapy, and the rapidity or completeness of response to chemotherapy can be used to define subsequent adjuvant radiotherapy. Dr. Constine also noted that “involved lymph node irradiation” is being tested for its efficacy and morbidty compared with “involved field radiation therapy” which is the current standard of care. Dr. Constine cautioned that one should be careful not to get into a situation where, in the hopes of reducing late effects, one reduces the radiotherapy dose and volume but increases the toxicity of the chemotherapy.
Dr. Constine then presented a series of cases designed to illustrate current debates in the treatment of Hodgkin’s disease. There were several take away messages from this exercise:

* There is evidence that in Stage 1-2 Hodgkin’s disease the use of a response adapted radiation therapy dose guidelines, after four cycles of VAMP chemotherapy (15 Gy for complete responders and 25.5 Gy for partial responders), produces satisfactory results. [Journal of Clinical Oncology 20:3081, 2002].
* The risk of second malignant neoplasms in long term survivors is probably 5 to 15% but there is a continued upward force of morbidity in the second malignant neoplasm curves with a risk of >20% at 20 to 25 years of follow up using historic treatment approaches.
* Fertility preservation in males with four cycles of AVBD is >90% but is approximately 10% with 6 months of MOPP.
* Female fertility preservation is a function of either the number of oocytes or the functional activity of the oocytes, explaining why younger females are at lesser risk RT-induced infertility.
* Many clinicians now treat Stage 1A lymphocyte predominate Hodgkin’s disease with Rituximab but this is probably not durable in sustaining a response.
* The event free survival for Stage IIA nodular sclerosing Hodgkin’s disease, with bulky disease, is now probably 85 to 95%.
* Erythrocyte sedimentation rates “probably still matter in the prediction of outcome but we’re not sure what the real extent is of its importance.”
* The breast cancer second malignant neoplasm risk following radiation therapy may be 5 to 15%. It is probably dose related and is also probably related to pubertal status – although this last point is controversial.
* Hypothyroidism risk after radiation therapy is dose related and time related. It is probably 15 to 20% after 21 Gy of irradiation.
* Cardiomyopathy risk with mediastinal irradiation is about 15% at 30 years. The fatal myocardial infarction risk is clearly increased and anthracyclines plus mediastinal radiotherapy have an additive effect.
* Growth factors will increase the spleen PET activity. In an interesting study (Picardi et al. Leukemia and Lymphoma 2007) patients with negative PET scans but who had a CT with >1.3 cm nodes were randomized to 32 Gy IFRT vs. no radiotherapy. The radiation therapy arm of the study did better.
* There was a debate over the importance of pleural effusions in Hodgkin’s disease, particularly small ones which may be the result of obstruction.
* It is unknown whether to give IFRT during consolidation for a bone marrow transplantation for Hodgkin’s disease and whether it is best given before or after the infusion of stem cells.
* There is another debate concerning the role of whole lung irradiation in adolescent females with lung involvement in Stage IV disease. There is, of course, a substantial increased risk of lung local failure.

The next lecture on Hodgkin’s disease, in a session chaired by Drs. Goddard and Sanchez de Toledo, was by Dr. Oberlin (Villejuif). She discussed late effects of Hodgkin’s disease treatment.

Dr. Oberlin observed that growth impairment from radiotherapy is worse in patients who were irradiated at 35 Gy. The relative risk in long term survivors of Hodgkin’s disease of any cardiac disease was 30 times that of controls and the estimated acute MI risk was two times that of controls. Cardiac problems included pericardial and valvular disease, cardiomyopathy, and coronary artery disease.
Dr. Oberlin observed that anthracyclines produced myocyte injury which leads to left ventricular wall thinning. Risk factors for this injury are young age, female gender, and the accumulative dose administered.

Turning her attention to lung complications, patients treated with 6 cycles of ABVD/MOPP and 15 to 20 Gy of irradiation have observable late effects. Forty percent will have a decrease in pulmonary function and 55% of patients will have diffusion capacity abnormalities. Studies of Dexrazon, intended to decrease lung toxicity (POG studies 9246 and 9425), showed an increased risk of second malignant neoplasms with Dexrazon (3.5% vs. 1%; the drug is a topoisomerase inhibitor).

Acute myelocytic leukemia is a second malignant neoplasm that occurs after treatment of Hodgkin’s disease and has a relatively short latency and is associated with anthracyclines. Non-Hodgkin’s lymphoma has a long latency period and is associated with radiotherapy. In general, the risk of second malignant neoplasms is increased in females because of the breast cancer risk.

The 2003 study of the Late Effects Study Group showed a 34 year risk of leukemia of 2% and of solid tumors of 24%. In general the risk was 23% for the second malignant neoplasms following treatment with radiotherapy alone, 8% with chemotherapy alone, and 68% with chemoradiotherapy. The risk of leukemia was a function of alkylating agent dose. The mean age of occurrence of second malignant neoplasm breast cancer is 32 years of age with a mean mantle dose of 35 Gy.
The risk of breast cancer as a function of age at the time of follow up was 2% at 30 years of age, 14% at 40 years of age, and 20% at 45 years of age. Overall the relative risk of a second malignant neoplasm was inversely related to the age at the time of diagnosis of Hodgkin’s disease.
The risk of sterility in males with < 2 cycles of MOPP was low. With 3 cycles of MOPP/ABVD it is 25%, and with >4 cycles of MOPP it is 75%. The risk of an abnormal FSH is a direct function of Procarbazine or Cyclophosphamide dose.
The ovaries appear to be less sensitive to alkylating agents than the testes. Fatigue and psychosocial distress are relatively common late effects.
Dr. Oberlin recommended an ultrasound of the thyroid be done once a year for up to ten years after radiotherapy. Chemical thyroid abnormalities can show up quite late and ultrasounds have lots of false positives. She described an increased risk, at very long term follow up, of second malignant neoplasms of the bowel.

In a presentation on anthracyclines vs. radiation therapy by Drs. H. Wallace (Edinburgh) and R. Taylor (Swansee), Dr. Wallace began by presenting the data of Schellong et. al. showing a 94% overall survival at 20 years in Hodgkin’s disease patients treated on the German-Austrian study. He then described the paper by DeBruin M. et. al. which described 3,105 five year survivors of Hodgkin’s disease. There was a 30% incidence of breast cancer at 45 years of age for patients treated in childhood. There was also an increased risk of premature menopause as a function of the Procarbazine dose. Dr. Wallace also cited data from Germany indicating an 18% risk of second malignant neoplasms in Hodgkin’s disease survivors at 20 years of follow up with a particular increased risk for children who received doses of radiotherapy >35 Gy.
He then went on to discuss hormonal long term effects including how, in males, pathologic FSH values were correlated with the dose of Procarbazine administered and, in females, premature menopause was correlated with a dose of Procarbazine.
Next turning to the data of Sklar et. al. (JNCI 98:890-6, 2006), he described the relative risk of 13 for non-surgical premature menopause in long term cancer survivors with cumulative incidences of 18% vs. 0.8% in controls.

Addressing the role of PET scanning in Hodgkin’s disease, Dr. Wallace said that negative predictive value was 81 to 100% and false positives are frequent. In the Euronet pediatric Hodgkin’s disease pilot study, if the PET scan is positive or negative and the lymph node is 2 cm on CT scan whether the PET scan is positive or negative, the lymph node is considered to be involved with lymphoma, and if the node is 1 to 2 cm on CT scan then, if the PET scan is positive, it is considered to be involved with lymphoma but if the PET scan is negative, it is considered to be uninvolved. So far, on this study, 30% of patients in TG1 will require radiotherapy and 60% of those in TG2.

Dr. R. Taylor began his remarks by describing the ability of the prone position in radiotherapy to decrease the amount of breast in the field. (Vuong et. al. IJROBP). He then cited a Journal of Clinical Oncology study (12: 2160-6, 1994), producing a 10 year survival of 96% with alternating cycles of MOPP/AVD and radiotherapy. CCG study 5942 described an event free survival of 92% vs. 87% with IFRT.
Amongst the long term ill effects, second malignant neoplasm leukemia is rarely survivable whereas second malignant neoplasm breast cancer is. In a United Kingdom study (International Journal of Cancer 120: 384-391, 2006) there was a 10 to 12% 25 year follow up risk of breast cancer. The lower risk, as compared to other studies, may be because of the lower radiotherapy doses administered in the United Kingdom vs. the United States. Dr. Taylor said that the breast cancer risk is a function of the dose and volume of irradiation but the risk of death from breast cancer induced by radiotherapy is low. The risk of bilateral breast cancer is high and there may be a genetic predisposing factor.
Both speakers also mentioned that, perhaps, the decreased risk of sterilization with modern treatment programs in Hodgkin’s disease will lead to an increased risk of breast cancer.

**Guest Lecture**

Dr. S. Lasker (Mumbai) discussed the challenges of pediatric radiation therapy in the developing world. He cited, as particular challenges: inadequate infrastructure, an inadequate number of cancer centers, inadequate rehabilitation facilities, and failure of practitioners to adhere to evidence based medicine.
Reviewing the pertinent data, Dr. Lasker pointed out that the generally accepted standard for cancer care are two cobalt 60 machines or linear accelerator teletherapy units per one million population. In India, the ratio, instead of 2.0, is 0.33. The country has 337 teletherapy units, many more than 20 years of age. Instead of the generally accepted standard of one radiation oncologist for 250 new consultations, the ratio in India is one per 715. There is also a severe shortage of medical physicists and radiation therapists. At the Tatta Memorial Hospital in Mumbai, 400 patients receive external beam radiotherapy per day. There are 15 attending physicians treating patients on 7 machines. There are 25,000 new cancer consultations per year and 1,000 new pediatric cancer cases per year. For example, there at 15 pediatric nasopharyngeal carcinoma cases seen per year at this one hospital.
The survival rates in Mumbai for Ewing tumor are quite comparable to those in the western world. They are currently doing a randomized trial with 55 vs. 70 Gy for local therapy. An interesting program is an evaluation of extracorporeal irradiation of 50 Gy in one fraction for bone tumors since the cost of a prosthesis is so high.

In his response to Dr. Lasker’s talk, Dr. D’Angio (Philadelphia) talked about the challenges of radiotherapy in the Ivory Coast. A cobalt 60 unit has been promised but not installed. There are no glass slides available to prepare pathology specimens. Often there is no supply of Cyclophosphamide. A significant proportion of patients get no follow up care for their cancer unless they are hospitalized. Dr. D’Angio speculated that, in some sense, we would do a service to cancer care in the developing world by “going back to the 1940’s” i.e. administering routine postoperative radiotherapy for all Wilms tumor cases and using more frequent radiotherapy than in the western world and simpler techniques. While this would not meet the standard of care in western medicine, it would elevate the standard of cancer care in the developing world.

**Free Papers**

In the free papers on Hodgkin’s disease, the first presentation was by Dr. Raslawski (Buenos Aires) who discussed her results with combined modality therapy for high risk Hodgkin’s disease. Fifty-six patients were registered and 45 were eligible with mediastinal bulky disease (Stages 2-4) or Stage 4 disease. Eleven patients were lost to follow up. Patients received either 6 cycles of COPP/ABV or 6 cycles of ABVD or COPP/ABV; then, for complete responders, 21 Gy of IFRT was administered and for partial responders 36 Gy. In the COPP/ABV group, after chemotherapy, 59% were complete responders and 41% were partial responders. After radiotherapy 94% were complete responders and 6% were partial responders. There was an 88% ten year survival rate. For those patients treated with ABVD, there was a 50% complete response rate after chemotherapy and a 46% partial response rate. After radiotherapy the complete response rate was 93% and the partial response rate was 4%. At 68 months of follow up there was a 96% survival rate.

The next presentation was by Dr. Chafe (Alberta). She discussed thyroid cancer in childhood and adolescence. In this review of 45 years of experience in Alberta, the ten year survival rate for these patients was 96%. From 1961 to 2006 there were 78 cases seen and 53 charts were reviewed. The mean follow up was 12 years. There was a high rate of local regional tumor recurrence in children but survival was excellent; albeit with all manner of surgery, with or without I-131, and with or without external beam therapy. Papillary carcinoma, female gender, and nodal involvement were more common in children than in adults. She did not report any long term ill effects of I-131 or thyroid feeding.
Dr. Raslawski returned to the podium (Buenos Aires) discussed whether or not radiotherapy is needed in childhood early stage Hodgkin lymphoma. She described patients at her institution with Stage 1 and 2A Hodgkin’s disease without bulky disease. Fourteen received COPP and ABV from 1996 to 2000 and 22 received 4 cycles of ABVD. In children who are complete responders, no radiotherapy was administered. In partial responders 21 to 36 Gy was administered.
After chemotherapy 94% were complete responders although 2 relapsed and eventually got combined modality therapy. Six percent were partial responders. The survival rate of these children was 93%.

The next presentation was by Dr. Kamer (Istanbul) on the results of the modified version of the GPOH-HD-95 study in children with Hodgkin disease treated at her institution. She described 76 patients who received 4 to 6 cycles of ABVD or MOPP and 25 to 35 Gy IFRT. Since 2000 they have restricted the study to HD-95 and had 37 patients in TG1, 22 in TG2, and 17 in TG3. The complete response rate was 40% and the partial response rate 60%, overall survival 98%, and disease free survival 82%. She emphasized the importance of improved diagnostic imaging for selecting the tumor volume for radiotherapy and also pointed out that Turkish patients may, on average, more often be Epstein Barr virus positive.

The next presentation by Dr. Lunaczek-Motyka (Vancouver) concerning the factors associated with second malignant neoplasms in pediatric Hodgkin disease. In this population based study there were 238 patients with Hodgkin disease who were treated when they were

Among the controversies addressed in the discussion on this paper was whether or not you should begin screening mammography at 25 years of age in Hodgkin disease survivors or at 8 to 10 years post treatment? Is it appropriate to replace mammography with MRI in this population?
Dr. Zaletel (Slovenia) also discussed second malignant neoplasms after treatment of Hodgkin disease. From 1960 to 2000 there were 1,577 patients Dr. Claude (Lyon) discussed the incidence of second malignant neoplasms after conditioning with total body irradiation (TBI). She described how, in neuroblastoma, there were second malignant neoplasms in 6 of 32 patients treated with TBI. Kulkarni described a 6% incidence of second malignant neoplasms at 10 years of age. In her particular study there were 250 patients of whom 101 had acute lymphoblastic leukemia and 82 had neuroblastoma. The TBI program was 12 Gy in 6 fractions administered to 204 patients. With follow up of 9 years there were 9 second malignant neoplasms for a 10 year risk rate of 12%. The most common were thyroid and parotid.
Dr. Claude then went on to present a paper on the toxicity of high dose chemotherapy followed by radiotherapy in Ewing axial tumors. She described an unusual number of late ill effects in axial Ewing sarcoma patients including a paraplegic (43 Gy), Brown Sequard syndrome (36 Gy), a myelitis (44 Gy), and three lethal digestive toxicities (dose >54 Gy). She recommended waiting 8 to 10 weeks between Busulfan, Melphalan, and radiotherapy to minimize the risk of late effects.

Dr. Casal (Barcelona) discussed the comparative dosimetry of dynamic conformal arc therapy, conformal beam, and intensity modulated radiosurgery for arterio-venous malformations. Six patients were in the series with a mean volume of 2.3 cc and a mean dose of 17.6 Gy. He found that intensity modulated radiotherapy gave higher conformality than alternative techniques but more integral dose.

The next paper was by Dr. Arguis (Madrid) on chemoreduction and external beam radiation therapy for advanced retinoblastoma. The treatment program consisted of 6 cycles of CVE and either local radiotherapy, external beam radiotherapy, or enucleation. The external beam radiotherapy was 40 Gy at 2 Gy per fraction. The treatment series included 32 eyes and 23 patients. There was a 30% local failure rate, 70% eye preservation rate, and a 6% retinopathy rate. Four weeks was the average interval between the conclusion of chemotherapy and the initiation of radiotherapy.

The last platform presentation of the day was by Dr. Woo (Houston) on the management of secondary cancers after Hodgkin disease. He described a 2 to 2.5 increased relative risk for second malignant neoplasms of her Hodgkin disease with breast and lung cancer being the most frequent solid tumors. He speculated that it is possible that alkylating agents might decrease the risk of breast cancer by hormonal suppression. MRI or ultrasounds are considered by some as alternative to mammography for screening these populations. Mastectomy is generally the preferred therapy since most physicians would be hesitant to use irradiation. When chest wall irradiation is called for, one usually relies on electrons. Dr. Woo stated in the management of lung cancer the role of screening CT is highly controversial in the general population and it is unknown if it is useful in Hodgkin disease survivors. He commented that the risk of second malignant sarcoma development is dose dependent and that, for lung cancer, following Hodgkin disease treatment, smoking is a significant precipitant factor.

**Innovative Approaches**

On June 28, 2007, the second day of the meeting, the program began with a presentation regarding the results of the work of the Pediatric Brain Tumor Consortium of the United States. Dr. Larry Kun wasn’t able to attend because he has undergone recent surgery. Therefore, Dr. Nancy Tarbell (Boston) was kind enough to fill in for him and present his slides.
Dr. Tarbell reported that the Pediatric Brain Tumor Consortium (PBTC) was pursuing major projects in the treatment of brain tumors in infants, brain stem gliomas, and molecular targeted strategies.

The programs in brain stem gliomas involve the use of primary radiotherapy plus novel agents. There is also a neuro imaging research arm of the studies. There are currently 7 trials including a study of Gleevec and one of anti platelet derived growth factor.
Dr. Tarbell reported there had been some concerns about reports of 5 cases of intra tumoral hemorrhage in brain stem glioma – ultimately rising to 11 cases. An analysis by Broniscer (Cancer 2006; 106) looked at the baseline rate and found that Gleevec probably did not increase the risk of hemorrhage over the background rate. Intratumoral hemorrhage is a recognized entity in brain stem gliomas at presentation. It is different from intralesional necrosis. The one year event free survival with the use of Gleevec was 24%.

A study on the use of radiotherapy plus Iressa in brain stem gliomas is based on the fact that this EGFR tyrosine kinase inhibitor might be active because EGFR is expressed in high grade pediatric gliomas. The study is identifying the MTD. The brain stem glioma trial of radiotherapy plus Zarnestra (a farnesyltransferase inhibitor) is also being analyzed to determine the MTD. There is, so far on the study, an overall survival of 36% at one year. There are also ongoing studies of radiotherapy with Bevacizumab plus Temezolomide and/or Ernlinotib.
The PBTC has developed a central computer imaging archive at Children’s Hospital of Boston. They found that the pre and post radiotherapy FLAIR MRI volumes differs significantly in brain stem gliomas. Radiotherapy also lowers the diffusion ratio.
During the discussion period the point was made that infants with glioblastoma multiforme may be sometimes cured by surgery plus chemotherapy. They probably have a better prognosis than older children.

The next speaker was Dr. Timmermann (Villingen, Switzerland). Dr. Timmermann discussed the roles of tomotherapy, cyberknife, and stereotactic therapy. Data was presented to show that the temporal lobe dose in the treatment of posterior fossa ependymoma can be reduced by the use of more conformal therapies. One must be cautious, however, because IMRT improves dose conformality but increases the “dose bath” to normal tissue. There is very little IMRT clinical data and what exists is equivocal for change in late effects.
Dr. Timmermann commented that IGRT may allow minimization of safety margins but it may increase the amount of time a child must be under immobilization. The need for image acquisition will increase the total dose.

Tomotherapy involves a combination of IMRT plus IGRT. A 6 MV linac is used with a collimator and a beam stopper. There is a helical beam path which can create a highly conformal beam. Simply stated, tomotherapy is the helical delivery of dynamic CT image guided IMRT. Dr. Timmermann displayed a craniospinal irradiation plan as well as a total marrow irradiation plan. There is, however, a considerable amount of “dose spread”.

It has been demonstrated, according to Dr. Timmermann, that you can treat children with fractionated stereotactic radiotherapy. The Gamma knife has limits in the size of the target volume. Stereotactic radiosurgery has been tested in the treatment of ependymoma where residual disease, after external beam radiotherapy to 59.4 Gy, has been treated with 4 Gy per fraction x 2 fraction boosts in the AEOIP Study.

Cyberknife therapy might be thought of as a combination of stereotactic radiosurgery and IGFT. It offers on line tracking of moving targets. The drawbacks are that it involves many fields, a longer duration of therapy, often hypofractionation, and an increased dose for image acquisition. This technology is often used in single fraction treatment. Dr. Timmermann also commented on a few new techniques that are evolving. One involves the combination of a linear accelerator with MRI and IGRT. It is referred to as the “Renaissance System”. Dr. Timmermann also discussed the use of proton tomotherapy and, more briefly, the generation of highly localized beams with protons.

During the discussion period members of the audience discussed the difference in price between the different technologies, their requirements for physics support, and differences in the need for quality assurance and machine commissioning time.
The next speaker was Dr. Tarbell (MGH-Boston) who discussed the use of proton therapy. She asserted that, on average, protons deliver approximately half the normal tissue dose of photon irradiation and would be predicted to reduce the risk of second malignant neoplasms. Additional promise is likely to be associated with the development of pencil beam proton therapy.
Dr. Tarbell discussed several open protocols for proton therapy including that for medulloblastoma. This study is designed to reduce the neurocognitive, ototoxic, and hormonal toxicities of radiotherapy. It will explore the question of whether or not proton therapy will affect the quality of life of patients. The COG study is currently comparing 18 vs. 23.4 Gy of craniospinal irradiation. In proton therapy in Boston, they continue to use match lines for the spinal irradiation (they have not treated any CSI in Swiss program to date). To date, in Boston, they have treated 35 patients with medulloblastoma with protons. Twenty-six of the children are standard risk and 9 are high risk. So far one patient has had grade 3 esophageal toxicity. The proton beams are angled to cover the cribiform plate and miss the lens and proton beam therapy decreases the skin dose compared to tangential photons. She also noted that one still needs to use Zofran with proton craniospinal irradiation but that there is clearly less acute toxicity. The current COG trial uses 18 vs. 23.4 Gy of craniospinal irradiation while comparing whole posterior fossa boost therapy to involved field boost therapy.

Proton therapy for craniopharyngioma has been used in 17 children in Boston. The medium dose was 52.2 cGE. The GTV equals the CTV and the PTV is the CTV plus a 3 mm margin. A four field technique was generally used with daily portal imaging. Three of the 17 children needed to be replanned because of growth of the cyst during the course of radiotherapy. They recommend using MRI’s during irradiation. Cyst growth during radiotherapy is described as occurring in about 20% of patients.

Dr. Tarbell reported that the retinoblastoma study for protons is not accruing well.
In COG trials protons are permitted in the treatment of rhabdomyoscaroma and medulloblastoma. It was reported, during the discussion session, that the MD Anderson Hospital has treated 12 patients with medulloblastoma with protons using a supine technique.
Late in the morning free papers were presented. The first was by Dr. Carrie (Lyon). He described medulloblastoma study MSFOP 98. This is a protocol for standard risk medulloblastoma in which the children received 36 Gy of craniospinal irradiation at 1 Gy b.i.d. The posterior fossa is boosted to 68 Gy at 1 Gy b.i.d. No chemotherapy is administered. In this study there were 55 children. Seven were excluded for inappropriate pathology or metastases. The median follow up is 77 months. Progression free survival is 75% and overall survival is 78%. Fourteen children need growth hormones. It appears that posterior fossa syndrome was relatively infrequent compared to the COG trials in which is stated to have occurred in 30% of patients. There have been no frontal lobe relapses and there were 9 major protocol deviations which were detected and corrected before radiotherapy.

IQ results from this study show that the verbal score is better and the score IQ is worse than when 25 Gy was given q.d. However, one should remember that the treatment volume is also smaller than in a q.d. study. One might speculate that this study helps to define a potential new standard in medulloblastoma therapy and it may be demonstrating that chemotherapy has more severe neurocognitive ill effects than b.i.d. irradiation.

The next speaker was Dr. Saran (Sutton). He described a series of children with craniopharyngioma treated from 1994 to 2000. The treatment technique was a stereotactic box system with a mean GTV of 11 cm3 and a PTV of 37 cm3. The treatment margin was 5 to 8 mm. The mean dose was 58 Gy and the fraction size was 1.6 Gy. In 39 patients (3 to 69 years of age) the median follow up was 14 months. Acute cystic enlargement occurred in 38% of the patients. A radiologic partial response was seen in 41% of the patients and there was stable disease in 59%. The 5 year progression free survival was 92% and the overall survival 100%. Dr. Saran remarked that in the Royal Mardsan Hospital series of 188 patients the 5 year survival was 90% and the 20 year survival 80%.

Dr. Saran commented that acute cystic degeneration during the course of radiotherapy is not of prognostic import. Half of the patients in his series were primary treatments and half were relapsed. He recommends a complete resection of the tumor if the hypothalamus is not involved and to do “as much resection as reasonable”. He also remarked that there can be very late relapses and that the number of operations is related to the probability of cognitive injury.
The next speaker was Dr. Alapetite (Paris) who described a series of patients treated with protons for craniopharyngioma. The target was delineated by CT and MRI fusion and the mean tumor dose was 54 cGE at 1.8 Gy per fraction. The chiasm dose was kept at

The last speaker in the free papers was Dr. Habrand (Orsay). He discussed the role of proton therapy in pediatric skull base and cervical canal sarcomas. He described 30 children with chondrosarcomas and chordomas who are between 7 and 17 years of age treated between 1996 and 2006. Sixty percent were males and all were treated post resection; none with biopsy alone. All cases had some residual disease. The mean dose between the combination of protons and photons was, for chondrosarcomas, 69.1 Gy and for chordomas 62.6 Gy. He demonstrated the ability to improve radiotherapy technology by missing brain stem during this form of irradiation. There were 5 local failures out of 30 patients with a median follow up of 27 months. The 5 year disease free survival in chordomas was 77% and in chondrosarcomas it was 100%. The program is looking forward to having spot scanning and isocentric beams by 2009.
The next speaker was your correspondent, Dr. Halperin (Louisville). The slides for my Keynote talk are attached.

**Proton Therapy Seminar**

The first speaker, Dr. Carrie (Lyon) discussed the calculation of cost adjusted quality of life data for carbon ion therapy and made an argument in favor of its use.
Next, Dr. Timmermann(Villlingen) described spot scanning proton therapy. She reported the treatment of over 5,000 choroidal melanoma patients since 1986 using a moving pencil beam. She contrasted the effects of passive proton beam scattering vs. spot scanning and indicated that the principle difference was in the proximal edge of the beam and reduction in neutron scattering. Spot scanning is highly sensitive to patient motion, however. The most common pediatric proton therapy cases in Switzerland are brain tumors and sarcoma patients. She emphasized the use of proton therapy at “non-moveable anatomic sites” and the use of sedation. Her facility is now adding second gantry.
The use of proton therapy poses the complexity of deciding “what to spare”. With beams being highly localized, one could consider, for example, in the treatment of a midline brain tumor whether it is more important to spare the hippocampus or the temporal lobe. Dr. Timmermann said that down time with her proton therapy unit was rare.

The next speaker was Dr. Claude (Lyon) who addressed the high precision and increased RBE of carbon ion therapy. She indicated that fractionation is less important in this form of therapy and that the mean duration of curative therapy with carbon ions is 13 fractions. Carbon ions produce positron emission at the end of the Bragg peak which is suitable for beam imaging and quality assurance. The carbon ion therapy unit in Lyon will emphasize the treatment of “radioresistant tumors”. The expense of carbon ions is two to three times that of photon IMRT i.e. on the order of 20,000 euros per patient. Multiple carbon ion units are open or are opening in Europe. The possible pediatric indications are osteosarcoma, chordoma, chondrosarcomas, Ewing tumor, and rhabdomyosarcoma. The speaker acknowledged, however, that these constitute a very small number of patients and that dosimetry is, to some extent, uncertain.

The next speaker, Dr. Tarbell (MGH-Boston) stated that the most common indications for proton therapy in childhood cancer are sarcomas, brain tumors, and in particular, medulloblastoma.. She described the treatment of 17 patients with parameningeal rhabdomyosarcoma. As a late effect there is often some facial asymmetry. In the treatment of orbital rhabdomyosarcoma the local control data with proton therapy is equivalent to that of photon irradiation. She emphasized the importance of reducing time delay in the institution of radiotherapy.

**Business Meeting**

At the end of the second day of the meeting, the PROS business meeting was conducted. It was reported that there were 136 members who had joined the society from 26 countries, 84 members who were in attendance at the conference, and that there were 140 total attendees at the Congress. At the SIOP meeting that will take place in conjunction with PROS in Mumbai in 10/08, the principal topic will be Ewing sarcoma.

 **Neuroblastoma**

On the third day of the conference we began with a discussion of the management of neuroblastoma. Session chairs Drs. D’Angio (Philadelphia) and Laprie (Toulouse), in conjunction with Dr. Gauthier (Paris) and Evans (Philadelphia) discussed the new staging system.
Drs. D’Angio (Philadelphia) and Evans (Philadelphia) reported on the treatment of neonatal neuroblastoma with special emphasis on stage 4S disease. Approximately 10% of metastatic neuroblastoma falls in this category and some cases can spontaneously regress. The liver with metastatic disease usually grows in the child up to 3 months of age and there can be, with extreme hepatic enlargement, obstruction of the inferior vena cava.
The indications for therapy in Stage 4S neuroblastoma include respiratory distress, regurgitation, decreased urine output, and coagulopathy. Treatment options include Carboplatinum, radiotherapy, or creation of a surgical defect in the abdominal wall with a silastic sheath to allow room for hepatic expansion.

One can assess the severity of symptoms in Stage 4S disease by measuring the volume of emesis for GI symptoms; tachypnea or the need for C-Pap for respiratory symptoms; leg and scrotal edema for assessing venous return; oliguria for assessing renal toxicity; and thrombocytopenia or DIC for assessing hepatic disease. In general, the prognosis for Stage 4S babies is much better if they are older than 3 to 4 months of age.

Dr. D’Angio described the use of hepatic irradiation (1.5 Gy x 3 fractions) with a 5 degree anterior angulation and a half beam block to avoid the kidneys with lateral beams. This program may be repeated if necessary and there is an 80% response rate. The speakers noted few long term sequelae of low dose lateral field irradiation.
The speakers took note of a recent poster at the 2000 SIOP meeting by Bruining et al. reporting the treatment of 4 girls with 50 mCi of MIBG for Stage 4S disease. All of them were responders.

Dr. Gauthier described the surgical management of neuroblastoma. He pointed out that broad based population screening did not decrease the mortality in neuroblastoma and probably lead to over treatment. Neuroblastoma constitutes about 25% of neonatal tumors and is the most common type of neonatal tumor after germ cell tumors. He described the cystic variant of neuroblastoma and also pointed out that one can see pulmonary sequestration or compression of the upper renal pole in neuroblastoma.

Dr. Evans discussed, in detail, the new international risk group system for staging neuroblastoma. This system was developed in 2006 and relies on “image defined risk factors”. Staging studies include plain films, CT or MRI, MIBG if the skeletal survey is negative, and bone marrow biopsy. The new system does not incorporate biological factors.
The prognostic factors which have been assessed include age >18 months, INSS Stage, presence or absence of MK1, grade if the child is older than 18 months, NMyc, 1P loss of heterozgosity, 11Q loss of heterozgosity, or 11Q aberrations, feritin levels, LDH levels, the primary site, metastatic sites, and ploidy. Combining these factors one can come up with risk groups of low and high.

The new staging system will focus on feritin levels, LDH, the primary site, metastatic sites, and ploidy. Combining these factors one can come up with risk groups of low and high. The new staging system will focus on central radiographic review.
There is high local control in Stage IV neuroblastoma with local irradiation. In bone marrow transplantation there may be an increased risk of second malignant neoplasms when total body irradiation (TBI) programs are used but there is probably a lower risk of dental complications than with high dose chemotherapy programs. The current SIOP neuroblastoma study (HR-NDLI-ESIOP) for >1 year of age with Stage II-III disease, N-Myc elevated, or with Stage IV disease, utilizes 1.5 Gy of irradiation per day to 21 Gy to the preoperative volume for local field irradiation.

One of the speakers noted that the preliminary results for bone marrow transplantation without irradiation show a fair number of local relapses. Among the complete responders, if radiotherapy was avoided, 5 out of 46 children relapsed, 6 out of 28 with microscopic residual, 4 out of 21 with macroscopic residual, and 2 out of 5 with unresectable disease. Age and histology are of prognostic importance. The speakers concluded that one should consider irradiation for lymph node negative N-Myc amplified patients. The role of PET scanning remains uncertain.
Dr. Buschbaum (Hershey) presented a talk on the use of TBI on childhood malignancies. The most typical dose scheme is 12 Gy in 3 to 4 days. He summarized the clinical data by stating that TBI seems to be better than chemotherapy in transplant procedures for childhood acute lymphblastic leukemia, acute myelocytic leukemia, myelodysplasia, Fanconi’s anemia, and adult acute lymphoblastic leukemia. There is a risk, however, of an increased incidence of second malignant neoplasms utilizing TBI and at risk does not plateau over time. There are also risks associated with TBI for cardiac problems, cataracts, thyroid nodules. About 50% of long term survivors of bone marrow transplantation have psychological problems (although the background number is not known). There is also a high frequency of fertility problems. TBI is also associated, in long term survivors, with an increased risk of spontaneous abortion, preterm babies, and low birth weight.

Among the controversies in the use of TBI is the role of the central nervous system boost or the testicular boost. A recent review from Michigan showed no significant impact of boost field for cranial irradiation. Testicular boosts are often used but the data is mixed.

**Free Papers**

Dr. Goddtard (Vancouver) described a study of the rate of hospitalization due to late effects, excluding second malignancies, in long term survivors of central nervous system tumors. She studied patients who were 1 hospital admission. The most common causes of admission were dental problems (9%), seizures (8%), endocrinopathy (7%), infection (5%), and needs for rehabilitation, respite care, or palliation (5%).

The next speaker was Dr. Kim (Seoul) who discussed his observation that chemo/radiotherapy produced more relapses than extended radiotherapy in intracranial germinomas. In his retrospective comparison of craniospinal irradiation CSI vs. CRT from patients treated from 1981 to 2003 with pure germinoma proven by biopsy, there were 81 patients with a median follow up of 68 months. Thirty-two were treated with craniospinal irradiation (CSI) and 42 with chemoradiotherapy (CR). The failure rate was 0 out of 39 patients with CSI of 26 Gy with a 54.6 Gy boost whereas the relapse rate was 4 out of 41 in patients who received CR with CSI consisting of 24 Gy and a 54 Gy boost although a fair number of patients received no irradiation. There were several Grade III and IV chemotherapy related toxicities and Dr. Kim suggested that if one uses a combined CR protocol one should use whole ventricle plus involved field irradiation rather than just involved field irradiation.

The next speaker was Dr. Kortmann (Leipzeig) who discussed the high risk medulloblastoma study (MET/HIT-2000) conducted from 2000 to 2007. For children >4 years of age they administered chemotherapy and then hyperfractionated irradiation, 40 Gy CSI with boosts ranging from 60 to 72 Gy. For children

There were 12 children 4 years of age in this study. There are a fair number of protocol deviations regarding the duration of therapy and the dose. The mean follow up was 24 to 32 months. Eleven of the 12 children 4 years of age have relapsed.

Dr. Douglas (Seattle) discussed the role of intensity modulated radiotherapy in medulloblastoma. For 34 children with MO disease the CSI dose was 23.4 Gy and the boost dose was 55.8 Gy. The 5 year local control rate was 94% and the failure free relapse was 87%. There were no failures in the posterior fossa outside the local field of irradiation. He indicated that he “didn’t see much difference” in IMRT vs. 3-D planning. IMRT may increase anesthesia time and increase the amount of low dose normal tissue exposure.

Dr. Dieckmann (Vienna) described the quality assurance system being used in the German-Austrian neuroblastoma trial. While they will be focusing on N-Myc amplified patients, very little data has so far been uploaded. They offer the promise of studying local control rates in the future and pursuing a randomized radiotherapy question.

**Brain Tumors**

The final session was chaired by Drs. Perilongo (Padova) and Wharam (Baltimore).
The speakers began by reviewing the distribution of tumors of the central nervous system in the germ cell tumor category. Citing SIOP-CNS-GCT Study 96 and SIOP-CNS-GCT Study 11, 5% of the tumors were teratomas, 40% were non-germinoma germ cell tumors, 51% were germinomas, and 4% were mixed malignancies. A total of 511 patients were evaluated and 319 were evaluable for protocol. Non-germinoma germ cell tumors were treated with 4 cycles of PEI chemotherapy and focal irradiation, germinomas were treated with chemotherapy and focal irradiation vs. CSI. The definitions utilized in the SIOP trials were that non-metastatic disease had either one focus or two foci (pineal and suprasellar) whereas metastatic disease included macroscopic tumor, >1 foci except for those cited under non-metastatic disease, or positive CSF cytology.

As regards the treatment of non-germinomatous germ cell tumors, 28% had an elevation of AFP and β HCG, 33% had an elevation of βHCG, 39% had an elevation of AFP, and 42% had no biopsy and the diagnosis was made by markers only. In this category tumors were treated, for focal disease, with 4 cycles of PEI chemotherapy and 54 Gy of focal irradiation; for metastatic disease 4 cycles of PEI chemotherapy and 30 Gy of CSI followed by a 24 Gy boost.
In these studies most relapses were local. AFP >1,000 predicted for poor outcome. Therapy induced complete response predicted for good outcome.
In the new SIOP Germ Cell Study 11 there will be no change in the metastatic or non-metastatic disease treatment but, for the poor prognosis group with elevated AFP and residual disease, they will be treated with 2 cycles of PEI and 2 cycles of high dose PEI and local radiotherapy or CSI as appropriate.

In the 196 patients in these studies with germinomas there was no clear agreement on how to treat. They were either treated with 24 Gy of CSI and a boost to 40 Gy or 2 cycles of Carboplatinum EI and focal radiation to 40 Gy. The 7 year event free survival in the CSI group was 94% and in the chemotherapy and focal irradiation group it was 84%. Most failures were infraventricular. A prognostic factor was in complete staging. The absence of residual disease was not a prognostic factor.
In SIOP Study CNS-GC2 non-metastatic disease was treated with 4 cycles of Carbo PEI, 24 Gy of whole ventricle irradiation, and a 16 Gy boost. Metastatic disease got 24 Gy of CSI and a 40 Gy boost.

Most teratomas are resected and locally irradiated. Twenty-five patients were in the study and half were resected and half were resected with adjuvant therapy. The 9 year overall survival was 80% and event free survival was 44%. Most relapses are local.
Dr. Wharam discussed the COG ACNS-O232 Phase III Study which includes 225 patients. The study compares radiotherapy vs. chemotherapy plus response based radiotherapy for germinoma.

Dr. Wharam discussed the historical data where the 10 year survival is 94%. Patients will be eligible if the AFB is negative and the βHCG is <50, there is a negative spinal tap and a negative MRI. Dr. Wharam pointed out that the definition in the COG Germinoma Trial for M+ are sites of involvement in the pineal and suprasellar region or multiple midline tumors. The study will include a comprehensive post radiotherapy neuropsychological testing. Low risk disease is treated with whole ventricle irradiation to 24 Gy and a 21 Gy boost. Moderate risk disease received 24 Gy whole ventricle irradiation and a 21 Gy boost and M+ disease receives 24 Gy of CSI and a 21 Gy boost - all at 1.5 Gy per fraction. Patients in a chemotherapy arm will receive Cisplatinum, Cyclophosphamide, Carboplatinum, and Etoposide. In those patients who are receiving risk adjusted response based radiotherapy and you have a complete response and M0 disease there will be involved field irradiation to 30 Gy. A complete response and moderate risk disease will receive will receive 21 Gy of whole ventricle irradiation and a 9 Gy boost. M + disease will receive 29 Gy of whole ventricle irradiation and a 9 Gy boost.
They will attempt to salvage failures after chemotherapy and local irradiation with chemotherapy and CSI.

Low grade gliomas were described by Dr. Wharam as largely pilocytic astrocytomas. The 3 to 5 year progression free survival of optic path gliomas is 34 to 68 Gy and they are typically treated with Vincristine and Carboplatinum. There appears to be no plateau on the survival curves until six years. Prognostic factors are age Dr. Scarzello (Padova) discussed the management of low grade gliomas. He stated that they constituted 1/3 to ½ of pediatric central nervous system tumors. There is often a very long natural history with progression sometimes taking several decades.

Addressing the role of radiotherapy in low grade gliomas, Dr. Scarzello talked about how the EORTC Study in adults showed an increase in progression free survival but not overall survival after immediate postoperative radiotherapy. The increase in progressive free survival was seen at approximately 2 years after therapy but we do not know how this treatment impacts on the quality of life. He indicated that radiotherapy can stabilize or improve vision in about 80 to 90% of cases and that local failure is the predominant pattern of failure. The consensus dose is 45 to 54 Gy at 1.8 Gy per fraction.
Summarizing the Children’s Oncology Group data, Dr. Carolyn Freeman (Montreal) stated that in the United States and Canada about 94% of children with brain tumors are registered on studies and 50% are treated on studies.

The POG 9130 Low Grade Glioma Study had children with complete resections followed without further therapy and those with less than complete resections randomized to follow up or radiotherapy or chemotherapy if they were

In the discussion of the management of ependymoma, Dr. Freeman described a CNS Study 0121. In children with gross total resection, low grade and supratentorial located tumors it is appropriate to watch. For subtotal resection of any histology in any location it was the plan to give chemotherapy and then determine if the tumor was resectable or not resectable. Ultimately 59.4 Gy was administered.

In medulloblastoma/PNET, average risk, residual disease In high risk medulloblastoma, survival has improved from 0 to 40% - 60%. In POG Study 9031 advanced medulloblastoma was treated with 36 Gy of CSI, an 18 Gy boost, Vincristine, Carboplatinum, and Cyclophosphamide. The 3 year overall survival was 81% in this study of 58 patients. The current study for high risk disease, (ACNS0332) is 36 Gy of CSI and a boost to 55.8 Gy and comparison concurrent Vincristine to concurrent Vincristine plus Carboplatinum. There is also a subsequent randomization to plus or minus Isotretinoin.

In ependymoma, for gross total resection, infratentorial tumor; any histology or high grade supratentorial tumor; or any tumor within complete resection, 59.4 Gy is administered.
For non-germinomatous germ cell tumor, chemotherapy is given. If the child has a complete response then 36 Gy of CSI is given with a boost to 54 Gy. If they have less than a complete response they undergo secondary surgery and, if they are then rendered to a complete or partial response, they are given the same dose of CSI. For those with stable or progressive disease, they undergo bone marrow harvest and high dose therapy as rescue followed by CSI.
In infants with brain tumors and low grade gliomas one tries to avoid radiotherapy up to 10 years of age. In ependymoma, radiotherapy is only given if a child is >1 year of age. In M0 medulloblastoma, conformal radiotherapy is given along with chemotherapy and stem cell rescue. There is about a 50% survival at 5 years for M0-1 patients. For M0 only disease about 75% are long term survivors. In the upcoming study they will test the role of radiotherapy.
In high grade gliomas in children MIB is associated with poor prognosis. For brain stem gliomas the baseline is a 17% 1 year survival and they are now going into Phase I and II studies including radiotherapy with Gadolinium, radiotherapy with Timezolemide, and radiotherapy with Topotecan.

The next speaker, Dr. Taylor (Swansea) discussed the treatment of intracranial germ cell tumors. In germinomas CSI produces a 94% long term survival whereas the combination of Carbo PEI and 40 Gy of focal irradiation produces a long term survival of 84%. In non-germinomatous germ cell tumors, a prognostic factor is AFP is >1,000.
The next SIOP ependymoma study will treat children with no residual disease with focal irradiation to 59.4 Gy and then randomize to treatment with or without chemotherapy. Children with residual disease will get an upfront chemotherapy window, focal irradiation to 59.4 Gy, radiosurgery of 4 Gy x 2, and then be randomized to treatment with or without chemotherapy.
The SIOP PNET IV Study for children with M0 disease will begin with surgery and then randomize children to 36 Gy of bid CSI followed by a 60 to 68 Gy boost vs. q.d. CSI to 23.4 Gy and a 54 Gy boost. All children will then get Vincristine, CCNU, and Cisplatin. The target for accruals was around 320 patients and 340 were accrued. This study is now closed and the 5 year event free survival is 77%. Therapy interruptions occurred in about 30% of q.d. and b.i.d. patients. The acute toxicity was slightly worse in q.d. patients. Major quality assurance deviations occurred in 27% of the patients and minor deviations in 59% of patients.

There are now discussions about a SIOPP/COG Infant Brain Tumor Study in low grade gliomas in children who are completely resected.