

# Proceedings of Congress

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### Acute Lymphoblastic Leukaemia in Hong Kong Children

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The Hong Kong Paediatric Haematology and Oncology Study Group (HKPHOSG) started the first Acute Lymphoblastic Leukaemia (ALL) collaborative study in 1993 based on the United Kingdom ALL treatment protocol. However the treatment result was inferior to many contemporary clinical trials with 6 years event-free survival of only 60%. Since 1997, the HKPHOSG changed to the German treatment approach, BFM based, and adopted the treatment backbone. The major differences of HKALL 97 study from UK studies were: (1) including 7 days prednisolone prophase at the start and assess the early treatment response (Blast count in peripheral blood on day 8 for risk stratification), (2) re-induction chemotherapy at around week 20 of chemotherapy, (3) reduction of cranial irradiation as CNS prophylaxis to less than 20% of patients. The study was a joint study with 2 Singapore hospitals, and this HK-SG 1997 Study ran from 11/1997 to 12/2002. A total of 265 patients were recruited and the treatment outcome is shown in Table 1. Fifty-one patients developed relapses and 2/3 were of isolated bone marrow relapse. Only 6 patients (2.3%) had isolated CNS relapse. Forty-two

patients died and mostly after relapse of leukaemia, 4 were due to early death during induction chemotherapy and 4 died of complications during first complete remission.

From 2002, HKPHOSG joined in the Inter-continental BFM ALL 2002 Study. This was the first paediatric oncology study that the Hong Kong hospitals participated in a multi-centre randomised study. This IC-BFM ALL Study is the largest international ALL study with over 5000 patients recruited from more than 10 countries from Europe and South America. The study was conducted from 01/2003 to 04/2008 and total of 169 patients recruited. The treatment backbone was similar to the previous HK-SG 97 Study. However the 2002 Study included new stratification criterion which was Day 15 bone marrow assessment for blast counts. Molecular genetic study was also included as stratification criteria. Up to end of 2010, 16% patients developed relapse and mostly were isolated bone marrow relapse, while isolated CNS relapse only occurred in 0.6% of all patients. The treatment outcome is shown in Table 2. During this study, our local investigators also started to test the Flow Cytometry and PCR methods to monitor the minimal residual disease (MRD) which could detect minute quantity of leukaemia cells in the bone marrow.

Year 2008 marked the first Hong Kong – Mainland institutions collaboration on clinical trial of childhood ALL. With 17 hospitals from 9 cities formed the Chinese Children

**Table 1** HK-SG ALL 97 study

Overall survival (OS) Event-free survival (EFS)	Follow-up duration	Whole group	By treatment arm		
			Standard risk (39%)	Intermediate risk (50.5%)	High risk (10.5%)
OS	5 years	86.7% (2)	97.1% (2)	84.9% (3)	57.1% (9)
EFS	5 years	78.8% (3)	88.3% (3)	76.7% (4)	53.6% (9)
OS	7 years	86.0% (2)	96.1% (2)	84.2% (3)	57.1% (9)
EFS	7 years	78.0% (3)	87.4% (3)	76.0% (4)	53.6% (9)

**Table 2** IC-BFM 2002 study (Hong Kong)

Overall survival (OS) Event-free survival (EFS)	Follow-up duration	Whole group	By treatment arm		
			Standard risk (39%)	Intermediate risk (50.5%)	High risk (10.5%)
OS	3 years	92.9% (2)	94.8% (3)	96.7% (2)	68.4% (11)
EFS	3 years	82.7% (3)	87.8% (4)	84.6% (4)	57.9% (11)
OS	4 years	88.8% (3)	90.8% (4)	92.9% (3)	62.7% (11)
EFS	4 years	82.7% (3)	87.8% (4)	84.6% (4)	57.9% (11)

Leukaemia Group (CCLG) and the CCLG 2008 ALL Study was started from April 2008. Up to end of December 2010, 63 patients were recruited. This study adopted the MRD assessment approach to classify risk groups. Standard or low risk patients received a reduced intensity chemotherapy, while high risk patients received more intensive chemotherapy. The study is still on-going and the treatment outcome is closely monitored.

In addition to the above ALL studies, HKPHOSG also joined in another two international ALL studies involving rare subtypes ALL, namely Infant ALL below age of 1 year (Interfant 99 Study and Interfant 2006 Study), and Philadelphia chromosome study (EsPhALL Study). Our group contributed some cases in these large international studies and the results have been published in international journals.

#### **Outcome of NOPHO-AML 2004 Study for Children with Acute Myeloid Leukaemia (AML)**

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**Objective:** We reviewed the treatment outcome of NOPHO-AML 2004 study for children with acute myeloid leukaemia which was implemented prospectively in Hong Kong involving 5 regional hospitals from 2007 to 2011 (4 years).

**Method:** The Hong Kong Paediatric Haematology & Oncology Study Group (HKPHOSG) joined the NOPHO-AML 2004 study since November 2007. The

protocol stratifies patients according to cytogenetics and chemo-responsiveness into different risk group. Sequential block will be given immediately if D15 marrow shows increased blast after first course. The treatment protocol consists of 6 courses of combination chemotherapy as single arm therapy. Allogeneic stem cell transplantation (SCT) is offered to patients in the high-risk group. Mylotarg is given at the end of treatment as a randomised controlled study. Subsequent modification of the protocol included termination of Mylotarg study due to withdrawal of the drug from the market and excluding 11q23 rearrangement as high risk parameter.

**Results:** A total of forty one cases of AML were recruited within the study period. Age ranged from 4 months to 17.9 years (median: 11.1 year). There were twenty-four boys and seventeen girls. M2 and M5 were most frequently seen, accounting for 22% and 24% of the cases respectively. There were thirty standard-risk patients and eleven high-risk patients. Forty patients (98%) achieved complete remission after chemotherapy. Three patients (7%) died during treatment. Fourteen patients (34%) had marrow relapse. Eight patients in high-risk group, one patient in standard-risk group and another seven relapsed patients underwent bone marrow transplant (6 matched sib or parent donors, and 10 matched unrelated donors). Ten (62%) out of the sixteen transplanted patients are surviving with no disease while the rest died either of transplant-related toxicities or relapse of leukaemia. The overall survival (OS) and event-free survival (EFS) at 2 years for the whole group are 73.4% and 52% respectively with median follow-up of 18.6 months.

**Conclusion:** The current AML protocol in Hong Kong yielded treatment results comparable to other groups. Further improvement in outcome may be made by reducing treatment toxicities and relapse rate.

### Treatment Outcome of Neuroblastoma: The Hong Kong Experience

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**Background:** Neuroblastoma is now known as a group of heterogenous diseases with different biological behaviour and outcome. Different classifications tried to stratify the good from poor risk neuroblastoma and manage them differently. We reviewed our experience in treating neuroblastoma based on the INSS classification approach.

**Patients and Method:** This is a prospective cohort study. The patients were recruited from 5 regional hospitals which take care of almost all children with cancer locally. The data were collected by 2 data managers sponsored by Children Cancer Foundations. Children with INSS stage I neuroblastoma were treated with surgery alone. INSS stage 1&2 neuroblastoma patients without poor prognostic features such as *MYCN* amplification or unfavourable Shimada histological pattern were treated with either surgery alone or with low intensity chemotherapy (modified POG protocol). Stage 3 patients used to be treated with intensive regimen (modified MSKCC N7 protocol) in the past but were changed to low/intermediate risk protocol after 1999 if they have no high risk features. Stage 4 patients were treated with modified MSKCC N7 regimen plus local RT and autologous haematopoietic transplant with anti-ganglioside antibody immunotherapy (anti-GD2). *MYCN* was evaluated by FISH and amplification was defined as >10 copies.

**Results:** From January 1996 to December 2010, there were 20 stage 1 patients, only one received chemotherapy; 13 stage 2 patients, 12 of them received low intensity chemotherapy, the patient who did not receive chemotherapy were stage 2a patients (tumour completely excised but with positive ipsilateral lymph nodes at diagnosis). For stage 3 and 4 patients, we only included those from January 1999 till December 2010 for analysis because we adopted the immunotherapy since 1999. There were 25 stage 3 patients and 9 were treated with intensive N7 regimen. There were 42 stage 4 patients and 38 were treated with anti-GD2 containing regimen. None of our stage 1&2 patients had *MYCN* amplification and only one stage I patient had

unfavourable Shimada features. All patients survived without major complications with a median follow up of 7 years (range 1.26-10.45 years). Our stage 3 patients had a 5 years progression free survival (PFS) of 87.5% including 3 with amplified *MYCN* status (median follow-up was 5.2 years, range 1.43-10.59 years). For our stage 4 patients, overall survival of 52.4% was achieved by those who received anti-GD2 in comparing to that of 11.8% of those who did not have anti-GD2 (historical control). The median follow up period was 42 months (range 1.04-10 years).

**Conclusion:** Early stage neuroblastoma without poor risk feature has extremely good outcome with low intensity therapeutic approach. Our stage 3 patients also had excellent outcome but some might be over-treated. Stage 4 neuroblastoma achieved significant improvement in their survival with multi-modality intensive therapy plus anti-GD2 approach.

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### The Epidemiology and Treatment Outcome of Childhood Brain Tumours in Hong Kong

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**Objective:** Brain tumour is the 2nd commonest malignancy in childhood and there was no population based study on its incidence and treatment outcome in Chinese children. We reviewed our local data and compared them with the existing data from the SEER of USA.

**Materials and Methods:** Prospective collection of childhood paediatric brain tumours data from the 5 major Public Hospitals was performed since 1999. These 5 hospitals are the only institutes with paediatric oncology service in our locality. Standard data entry sheet was used and the data collection and entry was performed by designated data managers. The data was further crosschecked with the Hong Kong Cancer Registry database which collected all the pathology reports of cancer in the territory. Except for brainstem tumours, brain tumours with no histological or tumour markers (i.e. AFP in germ cell tumour) proof were not included in this analysis.

**Results:** From January 1999 to December 2009 (11 years), a total of 357 cases of childhood ( $\leq 18$  years) brain tumours were diagnosed. Excluding 45 patients age  $>15$  years, the incidence of brain tumour was 28.4/million  $\leq 5$  years children/year. There may be slight underestimation because low grade brain tumours diagnosed by imaging alone without tissue diagnosis were not included in this analysis. Compared to the SEER data (1975-95), we noted a lower frequency of astrocytoma (SEER vs HK = 49.6% vs 33.3%) and similar frequency of primitive neuroectodermal tumour (PNET, including medulloblastoma) (22.9% vs 23.2%) in our cohort. The differences in other tumour subtypes differed even more strikingly. We have a lower frequency of other glioma (15.4% vs 5.3%) and ependymoma (9.3% vs 6.7%) but a much higher frequency of germ cell tumour ( $<2\%$  vs 20.7%). The incidence of intracranial germ cell tumours (GCT) was almost 6 times higher than the Western data. In addition, even within each tumour types, the histological subtypes also differed. Such as in medulloblastoma, 93% belonged to classical medulloblastoma and desmoplastic type is relatively uncommon. For the treatment outcome, low grade astrocytoma (WHO Gr I & II) accounted for almost 70% of all astrocytoma and they have good prognosis even when unresectable. Low intensive chemotherapy could suppress the progression of a significant proportion of them. However, high grade astrocytoma and intrinsic brainstem glioma still have extremely poor prognosis in our cohort with no long term survivor. Our standard risk PNET patients have slightly poorer outcome (5 years EFS 75% compared to 83% of Packer et al.). Lower compliance to radiation therapy and error in initial staging might account for such difference. For intracranial GCT, the 2 chemotherapy protocols (BEP and SFOP) have similar efficacy and both could achieved around 90+% and 75+% 4 years event free survival for germinoma and non-germinoma respectively. But around 5% of these survivors subsequently developed laminar cortical necrosis as a deliberating long term neurological complications due to radiation therapy.

**Conclusion:** A different distribution pattern of brain tumours types is found in our Southern Chinese patient cohort as compared to the SEER data. What accounts for such ethnic difference remains to be explored. In general, Chinese childhood brain tumour patients have excellent outcome and long term survival. Further efforts should aim to improve the outcome of high grade glioma and minimise severe long term complications.

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## Long Term Outcome of Conventional High Grade Osteosarcoma in Children and Adolescents

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**Objective:** The objective of this report was to estimate the long-term outcome in children and adolescents with osteosarcoma treated with a standard region-wide protocol.

**Methods:** Children and adolescents diagnosed with conventional high grade osteosarcoma between 1 November 1993 and 31 December 2010 were included. The patients were treated according to the Study Group Osteosarcoma 1993 protocol that included neoadjuvant and adjuvant chemotherapy with wide margin local tumour resection at week 10. Patients were defined as good responders if there were  $\geq 90\%$  tumour necrosis after neoadjuvant chemotherapy. Good responders would receive a total of 27 weeks of chemotherapy consisted of cisplatin, adriamycin and methotrexate. Poor responders would receive a total of 40 weeks of chemotherapy with methotrexate to be replaced by ifosfamide and etoposide from week 16.

**Results:** Total of 118 patients (66 males and 52 females; median age at diagnosis 12.3, range 0.6-20, years) were treated at five paediatric oncology centres in Hong Kong. The 3 commonest primary sites were the distal femur (56%), proximal tibia (21%) and proximal humerus (9%). One patient had multifocal bone disease. Ninety-eight patients (84%) had localised disease at diagnosis. Of the 20 patients with metastatic disease, 15 had pulmonary metastases, 2 had skip bone lesions and 2 had both bone and pulmonary metastases. Wide-margin tumour resection could be performed in 108 patients. Fourteen patients (12%) had disease progression on treatment. Twenty-eight (24%) patients developed relapses at the median time of 1.84 years from diagnosis (range 0.48-12.74). The commonest sites of relapses were the lungs (n=19) and distant bone (n=5). With further surgery with or without chemotherapy, 8 relapsed patients were salvaged and alive without diseases. Total of 35 patients died, 32 with disease progression or after relapses, 1 died from cardiomyopathy, 1 died from early post-operative complication and 1 from an unrelated cause. The 5-year Overall survival (OS) and event-free survival (EFS) for the whole group were 68% and 61.5%. OS and EFS of patients without metastases were 77.2%

and 68.2%, while OS and EFS of patients with metastatic diseases were 26.9% and 28.1%. Good responders had a better OS and EFS: Localised good responders, 88.9%, 81.4%; Localised poor responders, 73.7%, 62.8%; Metastatic good responders, 75.0%, 75.0%; Metastatic poor responders, 10.0%, 10.0%.

**Conclusions:** The current Hong Kong paediatric osteosarcoma treatment protocol yields results comparable with other international groups. Children and adolescents with localised osteosarcoma who receive multiagent chemotherapy and wide-margin tumour resection have a favourable outcome. However, new chemotherapeutic agent and strategy need to be explored for the group of patients with metastatic diseases and poor chemotherapy responses.

### A Multi-centre Treatment Protocol for CNS Germ Cell Tumours

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**Background:** The treatment and outcome depend on the type of germ cell tumours (germinoma vs non-germinomatous tumours), site, localised or metastatic disease, the resectability and the treatment (operation, chemotherapy and radiotherapy).

**Methods:** Hong Kong Paediatric Haematology and Oncology Study Group started this clinical trial involving five regional public hospitals in Hong Kong since 1st January 2008. Patients who were suspected to have germinoma received a biopsy, followed by chemotherapy with carboplatin (600 mg per m<sup>2</sup> on day 1) and ectoposide (150 mg per m<sup>2</sup> per day, day 1 to 3), alternating with ifosfamide (1.8 mg per m<sup>2</sup> per day and etoposide 150 mg per m<sup>2</sup> per day, day 1 to 5). They were assessed with MRI every 2 cycles. A total of 4 cycles of chemotherapy were given, followed by radiotherapy. The dose and volume of radiotherapy depend on the response and site of involvement. Patients with non-germinomatous germ cell tumours received operation to remove the tumour (if possible), chemotherapy as above for 6 cycles, reassessed by MRI once in two cycles, and cranio-spinal radiotherapy. The patients may need a second look operation and

autologous stem cell transplant if necessary.

**Results:** Until 31 December 2010, there were 29 patients included in this clinical trial. The male to female ratio was 3.8:1. The median age was 12.6 years of age (0.4 to 18.7). The pathology was germinoma (n=18; 62.1%) and non-germinomatous germ cell tumours (n=11; 37.9%). The locations of the tumours were suprasellar (n=6; 20.7%), pineal gland (n=15; 51.8%), suprasellar & pineal gland (n=3; 10.3%) and basal ganglia (n=3; 10.3%) and others (n=2; 6.9%). Four patients (12.9%) had metastatic diseases at presentation. After treatment with chemotherapy and radiotherapy, 23 patients (79.3%) achieved complete remission, 3 patients (10.3%) had partial response, 1 (3.5%) had progressive disease and 2 patients had just started therapy. Two patients (6.9%) had relapse. One patient died after recurrence. Twenty eight patients (96.6%) were alive. The median follow up time was 22.8 months (0.7 to 36.4).

**Conclusion:** With a uniformed treatment protocol and multi-disciplinary approach, a better outcome was achieved though the follow up period was short.

### Treatment of Wilms Tumour in Hong Kong

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**Background:** Wilms tumour is an uncommon cancer of the kidney in childhood.

**Methods:** The treatment of this cancer requires a multi-disciplinary approach. The Hong Kong Paediatric Haematology & Oncology Study Group started to use a uniformed treatment protocol since 1 January 1990, with operation, chemotherapy, with or without local radiotherapy.

**Results:** Until 31 December 2010, there were 53 patients from the five regional hospitals. The male to female ratio was 1.2:1. The mean age at diagnosis was 38 months old (range 3 to 176 months). The right kidney was affected in 22 (41.5%), and the left one in 24 (45%). Bilateral sides were affected in 5 cases (9%) at presentation. Two cases (2%) presented as extrarenal mass in abdomen which as confirmed to be Wilms' tumour by histopathology. Twenty-

two patients (41%) had stage one disease, 10 patients (19%) had stage 2 disease, 13 patients (24%) had stage 3 disease, 4 patients (8%) had stage 4 disease, and 4 patients (8%) had stage 5 disease. Histopathology was favourable in 41 (77%), unfavourable in 4 (8%) and 8 (15%) cases were not classified. Thirty-seven patients (70%) received immediate nephrectomy followed by post-operative chemotherapy, while 16 (30%) patients received pre-operative chemotherapy followed by nephrectomy and further chemotherapy. Sixteen patients received local radiotherapy to the tumour beds. All patients had complete response to treatment. Six patients (11%) had relapse in the lungs (n=3) and tumour beds (n=3). Two patients died after relapse of Wilm's tumour, while two patients died in first complete remission (pneumonia or rupture of AVM). The five years event free survival was 85% and the overall survival was 96%. The event free survival according to stages were 94% (stage 1), 77% (stage 2), 91% (stage 3), 53% (stage 4) and 75% (stage 5) respectively. The median follow up duration was 9.2 years (9 days to 20.8 years).

**Conclusion:** The treatment outcome was good and comparable with the published data.

### **Treatment Outcome of Extra-cranial Germ Cell Tumours in Chinese Children in Hong Kong**

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**Objective:** We reviewed the treatment outcome for children with Extra-cranial Germ Cell Tumour (GCT) treated in five paediatric oncology centres from 1995 to 2010.

**Materials and Method:** It is a prospective territory-wide cohort study of the children suffered from GCT treated in five paediatric oncology centres in Hong Kong from January 1995 to December 2010. All patients were treated with a unified protocol (HK-GCT-96.4 protocol). Surgery was the only treatment for non-malignant GCT or early stage malignant GCT. Chemotherapy consisted of Carboplatin, Etoposide and Bleomycin (JEB) was directed to advanced stage diseases.

**Results:** There were 138 patients enrolled. Patients with mature or immature teratoma without malignant elements were eligible. There were 68 males and 70 females. Age ranged from (1 day to 18.6 years) with median age of 2.5 years. Histological types included Teratoma: 65 cases (47.1%); Yolk sac tumour: 41 (29.7%); Germinoma: 9 (6.5%); Mixed GCT: 18 (13%) and other histology types: 5 (3.6%).

Gonads were the most commonly involved sites, with testis involved in 36 cases (26.1%), ovaries 35 cases (25.4%). Twenty-two cases (15.9%) were found in mediastinum; 19 cases (13.8%) occurred in sacrococcygeal region; 14 cases (10.1%) in abdomen; 5 cases (3.6%) in pelvis, 1 case (0.7%) in head/neck region and 6 cases (4.3%) were found outside the above common sites. Eighty-five patients (61.6%) had stage I disease; stage II: 9 (6.5%); stage III: 24 (17.4%) and stage IV: 20 (14.5%)

Seventy-six patients were treated with surgery alone, 61 patients received JEB protocol and 1 patient did not have any treatment. Median follow-up time was 7 years 9 months. There were 113 patients (81.9%) alive and remained disease-free. Eleven cases relapsed (8%), 8 patients died (5.8%), 12 patients lost to follow-up (8.7%), 2 patients (1.4%) developed second cancer. The 5-year overall survival (OS) for mature teratoma was 100% whereas 5-year event free survival (EFS) was 96%. The 5-year OS for other GCT was 94%, 5-year EFS was 86.3%.

**Conclusions:** The current treatment of Extra-cranial GCT in Chinese children is effective. The high cure rate is comparable to the Western studies. Treatment protocol according to risk groups is efficient and rational.

### Treatment Outcome of a Multi-centre Clinical Study of Hodgkin Lymphoma

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**Background:** Hodgkin's lymphoma is an uncommon childhood cancer.

**Methods:** The 5 regional hospitals in Hong Kong started to use a uniformed treatment protocol for children with Hodgkin's lymphoma from 1st February 2000. The clinical data were collected prospectively.

**Results:** Up till 31 December 2010, thirty-five children were diagnosed to have Hodgkin's lymphoma. The median age was 13.7 (2.8 to 17.7). Male to female ratio was 1.2 to 1. The clinical stages were 20% for stage 1 (n=7), 46% for stage 2 (n=16), 11% for stage 3 (n=4), and 23% for stage 4 (n=8). Seven patients (20%) had B symptoms. Twelve cases (34%) got bulk diseases. The histological subtypes were nodular sclerosis (n=21; 60%), lymphocyte predominant (n=5; 15%), mixed cellularity (n=4; 11%), lymphocyte rich (n=1; 3%), and unclassified (n=4; 11%). The organs involved by the disease were combination of sites in 68% of patients (n=24), 23% in head and neck regions (n=8), and 9% in peripheral area (n=3). COPP/ABV chemotherapy was given to the patients. Twelve patients had low-dose involved field radiotherapy. Thirty-three patients had complete remission after treatment. Three patients had relapse of the disease. Autologous stem cell transplantation was performed in one patient with progressive disease and in two patients after relapse. The 5-year overall survival (OS) rate was 100% and event-free survival (EFS) rate was 90.4%.

**Conclusion:** The treatment outcome was good and the results were comparable to the published literature.

### Treatment Outcome of a Multi-centre Clinical Study of Rhabdomyosarcoma

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**Background:** Rhabdomyosarcoma is the commonest soft tissue sarcoma in children.

**Methods:** The 5 regional hospitals in Hong Kong started to use a uniformed treatment protocol for children with rhabdomyosarcoma from 1 August 1995. The clinical data were collected prospectively.

**Results:** Up till 31 December 2010, seventy-three children were diagnosed to have rhabdomyosarcoma. The male to female ratio was 1.2:1. The median age was 6.3 years of age. The primary sites involved were head and neck region in 23 patients (32%), genito-urinary area in 13 patients (18%), extremities in 8 patients (11%), chest and diaphragm in 7 patients (n=10%), retroperitoneum in 5 patients (7%), pelvic area in 6 patients (8%), back in 4 patients (5%), liver and bile duct in 3 patients (4%). The clinical stages were 29% for stage 1 (n=21), 9% for stage 2 (n=7), 29% for stage 3 (n=21), and 33% for stage 4 (n=24). The histological subtypes were embryonal (n=43; 59%), alveolar (n=23; 31%), pleomorphic (n=2; 3%), and undifferentiated (n=5; 7%). Forty-three patients (59%) had excision of the tumour, while 26 patients (36%) had biopsy of the tumours only. Fifty-eight patients (79%) received radiotherapy. Chemotherapy was given according to the Intergroup Study IV in USA. It consisted of vincristine, actinomycin D and cyclophosphamide. There were 15 relapses and 30 deaths. The 5 years event free and overall survivals were 59.5% and 46.5% respectively. The median follow up duration was 8 years.

**Conclusion:** The treatment outcome was less favourable because of advanced diseases in presentation (stage 3 and 4).