International Journal of **Medicine Research**
ISSN: 2455-7404
Impact Factor: RJIF 5.42
www.medicinesjournal.com
Volume 3; Issue 4; October 2018; Page No. 104-113

Conservative surgical treatment in bilateral neuroblastoma (Rétrospective study of 8 cases)

Mounir Kisra[1*], Driss Hanine[2], Zakaria Aboulam[3], Jaouad Bouljrouf[4]
[1-4] Visceral Pediatric Surgery Department « A » - Children Hospital of Rabat, Faculty of Medicine of Rabat, Morocco

Abstract
Neuroblastoma is the most common extracranial solid tumor in children under 5 year of age. Adrenal bilateral involvement is rare and characterized by an extraordinary clinical heterogeneity, ranging from spontaneous regression to metastatic progression resistant to all treatment. Prognostic factors that explain this variability is dominated by age, stage, and a set of biological characteristics that which allow the grouping of neuroblastoma into groups of risk, which affect different therapeutic strategies in which surgery retains an important place.
This work provides a particular perspective of the role of surgery in the management of bilateral neuroblastoma and examines the interest of conservative surgery in this particular localization.
In this study, we report 8 cases of bilateral adrenal neuroblastoma treated between 2001 and 2014, the median age at diagnosis is 9 and a half months with a male predominance, discovery circumstances are most often due to the presence of metastases.
The therapeutic management consists of neoadjuvant chemotherapy followed by conservative surgery followed by postoperative chemotherapy. All operated patients received this regimen, with a low incidence of relapse and excellent survival. The combination of chemotherapy to surgery reduced the tumor volume thus allowing a satisfactory surgery with minimal risk and minimal postoperative morbidity. The low incidence of relapse and the risk of adrenal failure if radical surgery is performed, argue against an aggressive surgical approach.
In the future, it will be necessary to study the biological profile of these bilateral tumors, to characterize the differences between the unilateral neuroblastoma, if they exist, and understand the physiopathology of this bilateral involvement.

Keywords: bilateral neuroblastoma, therapeutic management, conservative surgical treatment

Introduction
Neuroblastoma is a malignant tumor derived from the cells of the neural crest. It is the most common extra-cranial solid tumor in childe under 5, which accounts for 8 to 10% of child hood cancers and 15% of all pediatric cancer deaths.
Bhind the term neuroblastoma, are hidden different entities whose présentation and evolution are extremely variable: some forms may regress spontaneously, others heal after surgery and / or chemotherapy and others have a poorer prognosis despite intensive therapeutics. Neuroblastomas are in fact probably several different diseases. What gives even more interest to the study of this disease is the fact that the neuroblastoma is the first tumor whose molecular characteristics were used to guide the therapeutic management, by adapting the treatment according to the specific characteristics of the patient and tumor.
In about 70% of cases, neuroblastomas are abdominal, including 45% in the adrenal and 25% in sympathetic ganglia.
The bilateral abdominal involvement is rare, very few cases are reported in the literature.
In the last two decades, advances in the diagnosis and treatment of neuroblastoma have been made. Medical imaging methods have been developed. Histological criteria, biological, genetic and chromosomal markers were also defined and allowed the establishment and gradual improvement of classification of patient groups. Protocols combining chemotherapy with surgery, radiotherapy and even autologous stem cells have been developed with therapeutic strategies adapted to risk groups, in which surgery retains a central role.
The concept of operability is a major element in the choice of neuroblastoma therapeutic strategy, even if the need for surgery is well established and the quality of excision is important, the benefits of a complete excision are to be made to balance with the risk of complications and postoperative sequelae. New approaches are being developed to reduce the side effects associated with current therapies and to allow the healing of patients with the most aggressive forms of pathology, including antiangiogenic.

Materials & methods
The general aim of this work is to study the clinical, biological, radio logical, histologique, prognostic and therapeutic characteristics of a series of 8 patients followed for bilateral neuroblastoma at the service of pediatric visceral surgery "a", in collaboration with the department of pediatric hemato-oncology at the children's hospital of ibn sina hospital, rabat, during the period between 2001 and 2014.
The specific goal is to analyze the surgical treatment strategies used in bilateral adrenal neuroblastoma, as well as their results while comparing them with the other cases reported in the literature. An update is made on the interest of conservative surgical treatment in the case of this rare pathology.

Results

Our series consists of 5 boys and 3 girls with a slight male predominance, a sex ratio of 1.66. The average age at the time of diagnosis is 30 months or 2.5 years with extremes ranging from 2 months to 8 years. The geographical distribution of the patients is of no particularity while the socio-economic level is low.

The clinical presentation at diagnosis was most often related to the presence of metastases: the diagnosis was evoked by the discovery of a mass or two abdominal masses isolated in one case (case 1), associated with

Peripheral adp in 2 cases (case 2, case 6), and associated with hutchinson's syndrome in 2 cases (case 3, case 7).

In 2 patients (case 4, case 5) the diagnosis was made on signs in favor of pepper syndrome, with as an initial symptomatology, abdominal distension that is life-threatening in one case (case 4) due to respiratory distress.

In addition, one child (case 8) presented with nonspecific abdominal pain associated with anemia and thrombocytopenia.

No diagnosis has been made on a routine pregnancy ultrasound.

All patients in our series received abdominal ultrasound and abdominal or abdominopelvic ct on several occasions for diagnosis and monitoring of therapeutic efficacy, as well as chest x-ray.

Biologically, the determination of urinary catecholamines was performed in 7 of our patients, only the result of a patient could not be retained (case 3). For the other patients at least one of the dosages is high.

Lactic dehydrogenase (ldh) was measured in 6 patients (cases: 2.3.4.6.7.8), and was always high except for one patient (case 6). While the determination of ferritinemia was only reported in 5 patients (cases: 2.3.6.7.8), it was elevated in 2 patients (cases: 3.7) and normal in the 3 others.

Regarding the extension assessment, all our cases benefited from a medullogram of the 2 peaks, while only 4 cases benefited from bone scintigraphy.

Four out of eight of our cases received a biopsy specifying the anatomopathological type of the tumor (cases: 1.2.6.7); it focused on the abdominal mass in 3 cases, and on the mass and the peripheral ganglion in one case.

None of our patients sought the amplification of the nmyc oncogene by default of the laboratory and its high cost.

A total of 7 of our patients could be classified after extension assessment by the pre-therapeutic classification "evans": 4 patients are stage iv; 2 patients are of stage iv s; and a patient is stage iii.

All of our cases who completed their treatments received neoadjuvant chemotherapy for tumor reduction followed by surgery followed by postoperative chemotherapy.

- Initial chemotherapy was administered to all our patients to reduce tumor volume, make the tumor operable and / or regression of metastases. The protocols used were studied according to the age and stage of evans.
- The number of courses and cycles administered is variable depending on the protocol and response to treatment.
- Surgery was only possible in 4 of our patients; 2 patients were lost to follow-up and another died early in treatment before surgery, and one patient with pepper syndrome developed well on initial chemotherapy, did not require surgery, and was referred to palliative chemotherapy. 'Endoxan.
- It is a bilateral adrenalectomy in 3 of our patients: total for the large tumor and partial for the smallest; partial unilateral adrenalectomy in only one of our patients.
- Post operative chemotherapy was administered to all our 4 operated patients.
- The prognosis of 4 of our patients is excellent; 2 of our 8 cases were lost before surgery; one case died early in initial chemotherapy; and one case relapsed and required a second surgical cure and then died.

Discussion

Bilateral neuroblastoma is a rare entity with an incidence <10% [1, 2]. This is consistent with data from our cohort, which shows the rarity of the bilateral form of neuroblastoma and estimates it to be 2.11% of all neuroblastomas.

For neuroblastoma in all localizations, it is the second most common solid tumor in children after brain tumors, it represents 8 to 10% of pediatric cancers and nearly 50% of newborn cancers.

The median age at the time of diagnosis of bilateral neuroblastoma is 9 months in the study of kushner *et al* [3], 4 months in the study of sfce (french society of childhood cancer) and 3 month in the other articles of the literature [4].

In our series of bilateral neuroblastoma the median age is 9 months and half, of which more than 50% of cases were diagnosed before the age of one year.

As regards sex, bilateral neuroblastoma is predominantly female in the majority of articles [4, 5, 6], whereas all-site neuroblastoma is slightly more common in boys than in girls, with a sex ratio of 1, 2: 1,0 [7, 8]. In our series there is a slight male predominance with a sex ratio of 1.66.

The etiology of neuroblastoma in all localizations is not completely defined. For bilateral adrenal neuroblastoma or multiple primary neuroblastoma, up to 20% of patients with familial neuroblastoma have been described [3]. However, among the published cases as well as in our cohort, no cases of familial neuroblastoma have been reported. Also the appearance of multiple primary tumors in young children has been described and may underline a genetic predisposition of this disease [9-11]. And as for maris and his colleagues, they reported evidence of a hereditary predisposition locus of bilateral neuroblastoma on chromosome 16p12-13 [12].

There has been some controversy whether these bilateral tumors are double synchronous primary metastases or contralateral metastases of a unilateral tumor [13] reflecting the multicentric origin of this tumor [14, 15]. However, most reported cases were synchronous [6, 16] and to date, only 2 asynchronous cases have been reported in the literature [15, 16], for the first asynchronous case, the author thinks it is possible that the administration of cyclophosphamide after excision of the first adrenal tumor affected the growth of the second tumor in his patient and that the chemotherapy had inhibitory effects on the growth of neuroblastic elements in the second adrenal gland, and that their growth has been resumed after stopping treatment [15]. While for the second case, the author believes that since there is no histopathological information on the first adrenal tumor, there is no evidence that this bilateral

nb represents a multifocal or metastatic primary dissemination [16].

The pathogenesis of primary bilateral adrenal neuroblastoma is considered to be multicentric growth of neuroblastic nodules or neuroblastoma in situ at both adrenal glands [17, 18].

- In the antenatal period, the diagnosis is evoked by the ultrasound of the third trimester of pregnancy which shows a supra-renal abdominal mass. The differential diagnosis that must be considered in this period is the bilateral hematoma of the adrenal glands, which has a very favorable spontaneous evolution under the guise of surveillance [19, 20]
- In the postnatal period, the clinical signs revealing are extremely variable, either in relation to the primary tumor, or in relation to the metastases, which are most often hepatic in infants and osteomedullary in children over one year old. [21].

Patients with a tumor site at the abdominal level are likely to develop a visible or palpable abdominal mass that is hard, lumpy, deep-set, painless, voluminous with systematic discovery, or with signs of gastrointestinal compression. Arterial hypertension is possible in these patients, due to compression of the renal artery by the tumor or hypersecretion of catecholamines.

While patients with metastatic disease, may have a general state of deterioration with paleness related to anemia indicative of bone marrow invasion, localized or diffuse bone pain with often lameness associated with metastases osteomedullary, a periorbital hematoma sometimes associated with an exophthalmitis characterizing the hutchinson syndrome and which is due to orbital metastases, not to mention liver metastases discovered on ultrasound or causing in the small infant monstrous hepatomegaly realizing the classic pepper syndrome.

Very rarely, paraneoplastic syndromes specific for neuroblastoma are associated, such as opso-myoclonic syndrome (ataxia, myoclonus during voluntary movements and eye shaking) and kerner-morisson syndrome which results in prolonged watery diarrhea with dehydration and loss of potassium due to the secretion of the vasoactive intestinal peptide (vip) [22]. Some patients with bilateral presentation of neuroblastoma have other associated syndromes such as congenital hypoventilation syndrome with total colonic aganglionosis [23], fanconi anemia and vacterl syndrome [24] or microcephaly [25].

An hourglass tumor, that is to say, compressing the spinal cord, can cause paralysis of the lower limbs and sensitivity disorders [21] but also more discreet disorders such as urination and defecation disorders which are more difficult to interpret in these young children.

The determination of catecholamines gives important indications, in fact the secretion of dopamine, the hva, the vma which are specific markers is directly proportional to the tumor mass [26].

Although urinary catecholamine dosages are often normalized before complete remission of the disease, they are routine tests for the diagnosis and follow-up of these tumors [26].

A high ldh level is observed in more than three quarters of neuroblastoma cases, and significantly associated with lower survival in these tumors. However, its prognostic value is discussed, identified by some [27] and not found by others in multivariate analysis [28].

Ferritinemia is elevated if neuroblastoma is metastatic (stage 4) or with locoregional extension (stage 3). Its prognostic value is most often erased by its correlation with other biological factors [28].

On the radiological level, ultrasound is the first-line examination when the tumor is abdominal or pelvic [29].

This examination often guides the diagnosis but must be completed by a ct scan or an mri [29].

Nearly 60% of patients with neuroblastoma have metastases at the time of diagnosis. Their seat is medullary, bone or both, in 82% of cases [29].

Mibg scintigraphy is a sensitive and specific examination. When the tumor is fixed mibg, which is the case for 95% of neuroblastomas, makes it possible to map the disease [29].

It is only when the primary tumor does not fix the mibg (mibg scintigraphy is negative) that a technetium 99 scintigraphy is performed in search of bone metastases. However, this examination is not specific to the disease, it is less sensitive and makes it possible to evaluate the response to treatment less finely [29].

Medullary metastases are sought by myelograms and bone marrow biopsies that are taken from different sites, two different sites must be evaluable with two different techniques [29].

We are satisfied with the standard image of the face of the lungs, looking for possible pulmonary or pleural localizations, but pulmonary metastases are exceptional.

The diagnosis of neuroblastoma is strongly suspected on all the clinical, biological and radiological arguments previously described. It must be confirmed by histological analysis of a biopsy or by the presence of typical tumor cells in the bone marrow (aspiration or biopsy).

Nmyc is a proto-oncogene located on the short arm of chromosome 2, which in neuroblastoma can be amplified up to several hundred gene copies per cell [30]. Amplification of this oncogene of more than 10 copies is strongly associated with adverse histology, advanced pathology, aggressive tumor behavior and high risk of relapse [31, 32].

This genetic anomaly present in 20 to 25% of neuroblastomas [30] and considered today as the reference biological marker, is generally associated with a metastatic tumor, at 2 years of age at diagnosis, and is correlated with a prognosis very unfavorable in terms of survival [33, 34].

The status of the nmyc oncogene has become an essential prognostic factor, decision-making for treatment [30]. And a future perspective will be to seek amplification of this oncogene in the serum of patients, as has already been proven [35, 36].

Our work sheds special light on the role of surgery in the management of bilateral adrenal neuroblastoma but with minimal risk. In other words: how can we remove bilateral adrenal tumors by preserving the adrenal glands and avoid the risk of adrenal insufficiency?

The extreme heterogeneity of neuroblastomas leads to a therapeutic strategy based on stratification according to the

prognostic evaluation, thus a management in favor of two strategies:

- In the case of tumors with favorable prognosis: the lightening of the therapy is recommended with the sometimes only use of surgery.
- In the case of aggressive tumors: the trend is to intensify management with the use of surgery combined with chemotherapy, radiotherapy and sometimes autologous stem cell transplantation.

1. The management of **bilateral neuroblastoma according to the risk group**

This classification into three risk groups will enable us to plan a well-targeted treatment combining as needed surgery alone or surgery more or less associated with chemotherapy and radiotherapy. There are three risk groups: low risk group, intermediate risk group and high risk group.

The low risk group is summarized as above described in any localized neuroblastoma (stage 1 or 2) with favorable biology and histology (ie without amplification of the nmyc oncogene, no hyperploidy and well on a histological type little or in the process of differentiation) or children with a 4s stage with a favorable biology and histology.

This group requires minimal therapy, and the majority of children can be treated by surgery alone. Surgery is the first line of therapy for localized disease when the mass is operable and the goal is total resection of the tumor mass without leaving a residue.

A low dose of chemotherapy provides an excellent prognosis for low-risk, localized tumors that are ineffective [37].

The intermediate risk group consists of patients of any age with stage 3 or patients under 18 months of age with a stage 4 condition for both that the biology is favorable.

Management in this second group consists of moderate-dose chemotherapy aimed at reducing the size of the tumor and making it operable [38].

Vincristine, cyclophosphamide, etoposide, ifosfamide, doxorubicin, cisplatin and carboplatin have appeared in many therapeutic protocol. The pediatric oncology group states in one study that the prognostic drug results are excellent in intermediate-risk neuroblastomas without nmyc oncogene amplification, and with hyperploidy, while in diploid and oncogene nmyc study showed less favorable results [39].

The high-risk group, under this term are grouped localized tumors with adverse biological factors and stage 4 neuroblastomas after 18 months.

The therapeutic strategy is complex, involving an induction phase by intensive chemotherapy and primary tumor surgery, consolidation by a myeloablative treatment (high-dose chemotherapy then bone marrow autograft), and treatment of residual disease. Minimal by maintenance treatment (13-cis retinoic acid) [40-44].

2. The management of **bilateral neuroblastoma according to ingr (international neuroblastoma group risk)**

A new pre-therapeutic classification system based on 13 prognostic factors; clinical, biological, genetic and histological; was recently developed by ingr [45], a panel of international experts, to develop risk-based pretreatment protocols applicable worldwide [12].

For patients at low risk, surgical excision of the tumor is usually curative and avoids the risks associated with chemotherapy.

Intermediate-risk patients are usually treated with surgery and chemotherapy. Studies to minimize therapeutic regimens for these groups of patients are ongoing [12].

The poor prognosis of high-risk patients justifies a much more intense therapeutic regimen, including the combination of chemotherapy followed by complete surgical excision (if possible), radiotherapy to achieve local control, myeloablative treatment with graft bone marrow, and biological therapy [12].

Surgery is a key element in the treatment of neuroblastoma.

This is the most important element in the treatment of localized neuroblastomas, as it may be the only treatment required [29].

The criteria of operability were defined thanks to an important work of cooperation between radiologists and pediatric surgeons. The surgical decision must be taken after consultation with oncology physicians, radiologists and surgeons accustomed to this type of pathology to ensure the absence of potential morbidity [29].

In tumors that are initially inoperable, surgery will be performed after tumor volume reduction by neo-adjuvant chemotherapy, which increases the possibility of complete excision [46] and limits surgical complications.

In metastatic tumors, the place of surgery is controversial [47]. It will be performed secondarily after obtaining a good regression of metastases [29].

In ivs neuroblastoma, where surgery plays only a marginal role [48], it can be understood that an attempt at excision is recommended only in the absence of major operative risks.

The objective of the intervention remains a complete resection, to balance with the risks of complications and postoperative sequelae. The decision must be taken in the overall context of the other prognostic elements (age, biology, localization of the primary tumor), because unlike other embryonic tumors, neuroblastoma has the histological peculiarity of being able to regress or to undergo a maturation [49] thus microscopically complete excision is not always essential. This question arises all the more because they are localized tumors, occurring in infants where we know the possibility of regression or spontaneous maturation of the tumor.

So the surgical procedure is always subject to a benefit / risk assessment, and the main risk induced by extensive surgery of an extensive abdominal neuroblastoma is primarily vascular, as this tumor usually includes large vessels, excision is a problem important technique [50]. In its bilateral adrenal localization, neuroblastoma in addition to vascular risk, presents a risk of adrenal failure if radical surgery is performed so several studies argue against an aggressive surgical approach [4].

The surgical technique used is edward kiely [50]. This technique has been designed to minimize the risk of vascular injury and to achieve optimal tumor elimination.

- **Principle of the technique**: to expose the vessels interested in the tumor, to dissect them to remove the whole tumor.
- **Basis of the technique:** neuroblastomas do not invade the media tunic of blood vessels. So plane of dissection

between the tumor and the media in sub-adventitial.

- **Three phases of the procedure:** presentation of the vessel, clearance of the vessel and removal of the tumor

The first phase consists in exposing a part of the wall of each vessel that crosses the tumor, in continuity. The vessels are then circumferentially disengaged and mobilized from the tumor, after which the tumor can be removed. As with any operation, these phases are not distinct during a long operation.

In our series all our patients received first chemotherapy; this has helped to reduce bilateral adrenal tumors in all cases, to make operable a case, and to put in remission of metastases in the other cases.

Four out of six patients, ie all those who completed their treatment (two lost in early chemotherapy), had adrenal surgery: 1 unilateral adrenalectomy and 3 subtotal bilateral adrenalectomies with total adrenalectomy. Larger tumor and enucleation or partial resection of the smallest tumor, thus conservative surgery aimed at preserving adrenal function and avoiding the morbidity of adrenal insufficiency to the patient, this is consistent with the literature which suggests that the preservation of adrenal function is and that total bilateral adrenalectomy should be limited to cases with irretrievable glands, while unilateral adrenalectomy with enucleation

Contralateral or partial resection is an acceptable option [13, 51,52]. Pedérivia *et al.* [6] concluded that bilateral neuroblastoma has exceptional behavior, variable nmyc amplification, widespread metastasis, and a high mortality rate, so they require individually tailored therapeutic strategies based on size, extent of tumor, and prognostic markers. Bilateral adrenalectomy is sometimes unavoidable, but unilateral adrenalectomy with contralateral enucleation, partial resection, or surveillance are valid alternatives [6].

For pages *et al* [4], the therapeutic strategy for this particular group of tumors could be similar to that used for unilateral neuroblastoma, with the exception of surgery. However, the low incidence of relapse and the risk of adrenal insufficiency if radical surgery is performed, argue against an aggressive surgical approach. For this author treatment of bilateral tumors with the same therapeutic strategy of unilateral tumors gave similar results in terms of survival [4].

Hiyama *et al* [52] recommend conservative surgical excision because most multifocal neuroblastomas have low malignancy potential and generally have good prognosis. Total bilateral adrenalectomy is not required and attempts should be made to maintain adrenal function with minimal invasion [52].

Our two patients with stage ivs with pepper syndrome were initially treated with chemotherapy alone even in the absence of signs of threat in one case. While in the literature initial abstention is a therapeutic approach conventionally used in non-threatening ivs neuroblastomas, given the possibility of spontaneous regression, and chemotherapy is used secondarily in case of tumor progression or nonoperability before performing the surgical gesture. The surgical modalities used in stage 4s neuroblastoma (unilateral and bilateral), especially in infants, have not been clearly standardized.

In france and according to the attitude recommended by suarez *et al* [53] and martinez *et al* [54], it is usual when resection is possible and does not involve a vital risk, to resect the primary tumor in the ivs stages in order to avoid local recidivism, but this attitude remains controversial.

Indeed, according to haas *et al* [55], gluglielmi *et al* [48] and nickerson *et al* [56], resection of the primary tumor would have no influence on survival. Thus, for some authors, a favorable result seems to be related to complete tumor resection [57], while for others, excision is not considered decisive [48]. Because stage 4s may spontaneously regress [56, 57], we suggest that bilateral adrenalectomy in 4s disease should be avoided to prevent potential adrenal insufficiency [5; 58-60]. Primary bilateral surgical excision could be avoided in tumors that do not amplify nmyc given the low incidence of local relapse with their favorable outcome [61].

Our stage iv patients were treated with chemotherapy first until the remission of metastases, followed by surgery. This is similar to the literature in which the excision of the primary tumor is only considered after having obtained the control of metastases. Moreover, in stage 4 neuroblastoma, surgical excision is not a major prognostic factor [47]; conversely, complete remission of metastases remains one of the main prognostic factors [42, 62]. The benefit / risk balance should be evaluated according to the age of the child and the presence of nmyc amplification in the tumor. Hsu *et al* suggest that complete resection is not performed at all costs if the tumor amplifies nmyc [63]. As a result, the risk of local recurrence increases in the presence of amplified nmyc and radiotherapy of the tumor bed has been proposed to prevent local recurrence [64].

Thus, in the published cases of bilateral neuroblastomas, the evolution of the iv stages appears much more related to the biology of the tumor than to the bilaterality of the excision [4, 14, 65] and the bilateral excision should be avoided, except in the case of nmyc amplifying tumors [4].

It has been shown that the majority of children with localized neuroblastoma of inss 1 and 2 can recover by surgery alone, and that the quality of surgical excision does not influence survival [66, 67]. This is true even for bilateral forms [52].

In children with a more advanced neuroblastoma (even non-metastatic) inss 3 or stage iii of evans, all locations included, the benefit of extensive excision was evoked [66]. In bilateral forms, our patient as well as the only stage 3 case published in the literature [52], have undergone conservative surgery with subtotal bilateral adrenalectomy and good results (both cases are alive), so the quality of excision does not seemed to have no significant influence on survival.

In our series 2 of our 8 cases died, one stage 4s case with pepper syndrome complicated respiratory distress, and the other case was more than one year old with stage 4 disease. Only one case relapsed, he it is a local recurrence of the partially recaptured adrenal, requiring total adrenalectomy of the remaining gland with development of adrenal insufficiency and initiation of hormone replacement therapy, this case has died.

In the literature, it has been pointed out that multifocal neuroblastomas generally have favorable biological characteristics and a good prognosis [52]. However, a considerable number of reported cases of tumors

Bilateral adrenal glanders died of the disease [14, 23, 59, 68, 69], and some had generalized and particularly aggressive metastases [23, 59, 65, 70]. Pederivia *et al* concluded that the prognosis of this

particular group of neuroblastomas is uncertain and mortality is high [6].

While pages *et al* showed good overall survival (79% at 5 years) concluding that the majority of bilateral neurblastomas have a favorable prognosis, except those with risk factors, such as the amplification of nmyc [4] and that these are comparable to cases of high-risk unilateral neuroblastoma with the same characteristics of poor prognosis.

The prognosis of bilateral adrenal neuroblastomas with pepper's syndrome is favorable because of the age of less than one year, the absence of bone metastases and the absence of amplification of the nmyc gene in the majority of cases [5].]. In cases reported in the literature, many infants with stage 4s disease died promptly after diagnosis [4, 59]; they all had pepper's syndrome with respiratory distress. This joins our case with pepper's syndrome complicated with respiratory distress, who died a month after the diagnosis.

In previous series the relapse is too weak, indeed only 5 cases have relapsed among published cases of bilateral neuroblastoma, 3 of them have died [4, 58]. At death, the majority of the deceased children had tumors that amplified nmyc [4, 6, 59]. Unfortunately in our population, we have not been able to carry out this examination since we do not have this facility in our institution, also because of its high cost and the lack of means of the families.

Radical surgery in bilateral adrenal neuroblastoma is likely to produce significant functional sequelae, including adrenal insufficiency.

Only one case in our series developed adrenal insufficiency after a total bilateral adrenalectomy performed in 2 times and none of our cases having undergone bilateral subtotal adrenalectomy had this morbidity.

In the literature, one case out of four who underwent total bilateral adrenalectomy had adrenal insufficiency [60]. The remaining 3 died a few weeks after diagnosis [6, 14]. And only 2 of the 13 cases who had bilateral subtotal excision developed this sequelae insufficiency requiring long-term hormone replacement therapy, both patients are alive [4].

Overall, our results suggest that bilateral neuroblastomas have a good prognosis, and our data show excellent survival of children treated for metastatic bilateral neuroblastoma highlight the risk of long-term sequelae after radical surgery. The effectiveness of the strategy based on preoperative chemotherapy suggests that the question of operability should be considered very carefully at the diagnosis, rather than considering surgery from the outset sometimes random results and with a risk of potentially heavy sequelae. Considering the excellent prognosis of children in complete or partial remission and the low incidence of relapse, leaving a postoperative residue appears acceptable when significant morbidity seems necessary to achieve a complete excision.

And the goal of surgery in bilateral adrenal neuroblastoma is to try to preserve adrenal function by using conservative surgery.

As therapeutic perspectives, anti-angiogenic therapies target tumor angiogenesis, a preliminary step to metastatic dissemination. These novel therapies acting at a late stage of tumor development are of interest in these patients diagnosed at stage iv and may represent one of the future therapies in the management of these patients.

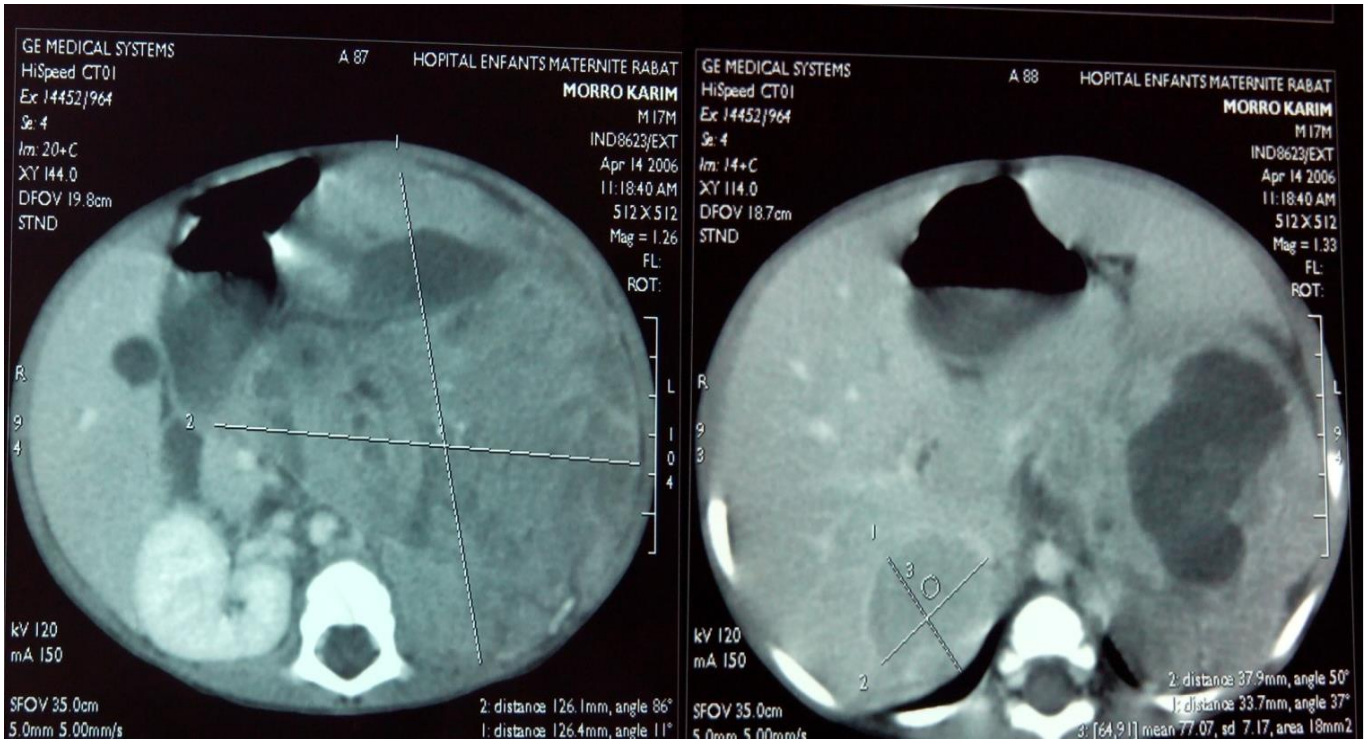

Fig 1: ct transverse cuts without injection made with the admission of a child showing the bilateral process adrenal: on the left it is voluminous exceeding the median line and on the right it is limited to the adrenal box

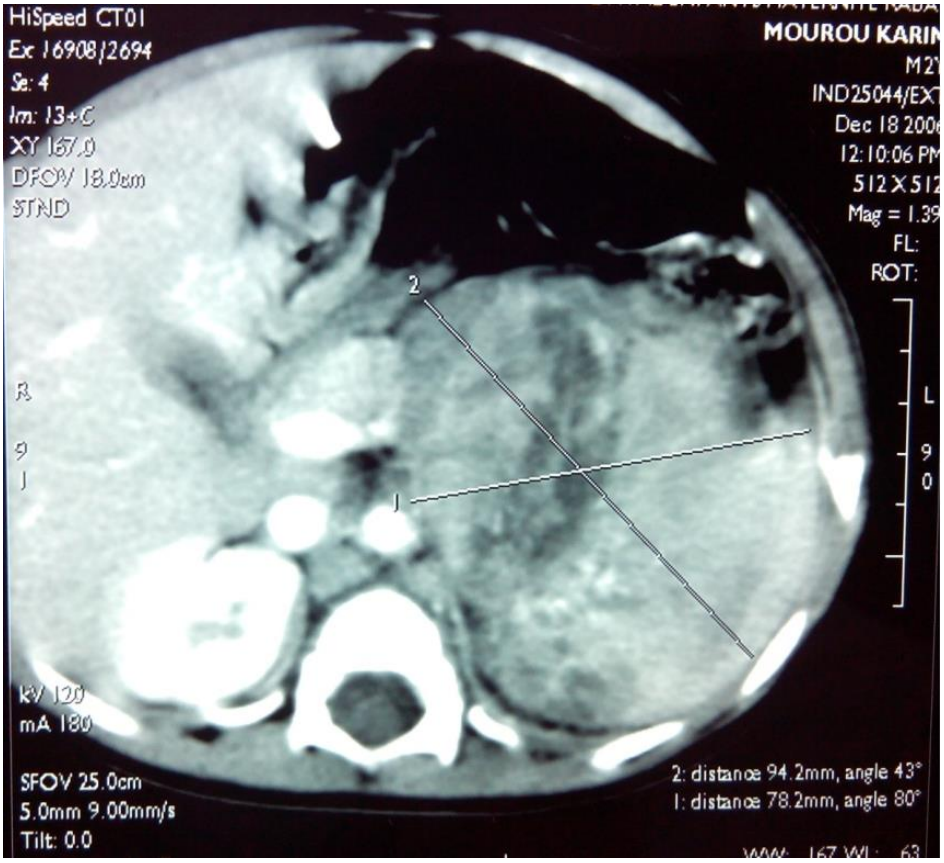

Fig 2: ct transverse cuts after injection showing: a regression of the left adrenal process which arrives near the median line and disappearance of the right process after preoperative chemotherapy.

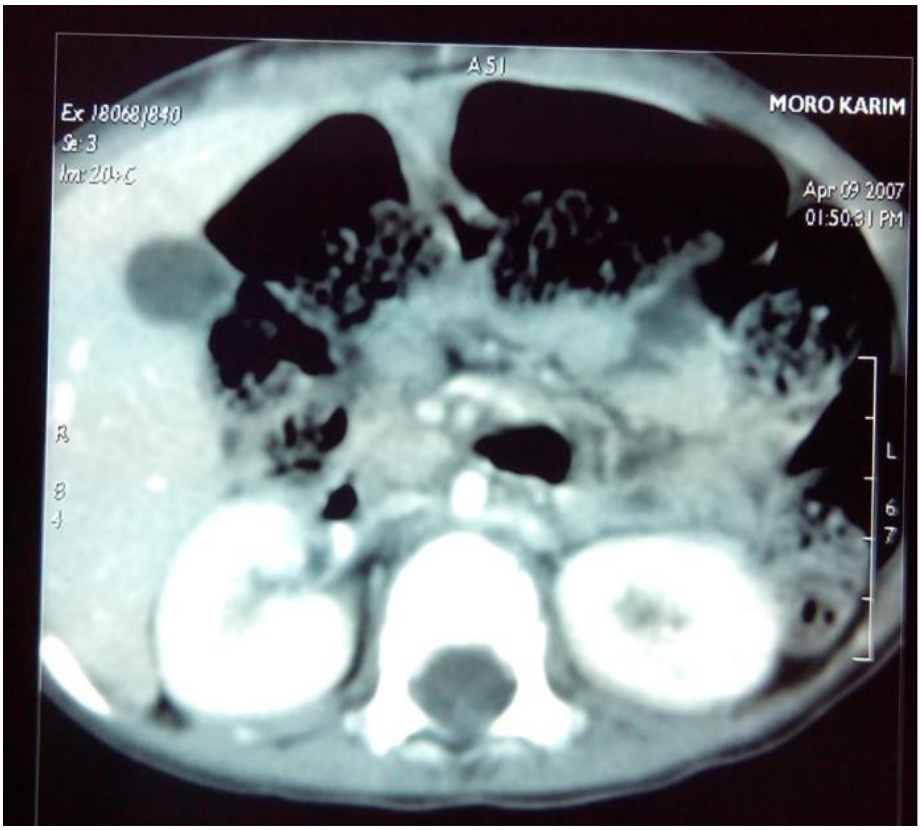

Fig 3: ct transverse cuts after injection showing an absence of the adrenal tumor residue after surgery and postoperative chemotherapy.

Table 1: Table summarizing all the observations collected

cas	Sexe âge	Types de métastases	Stade Evans	Chimiothérapie préopératoire	Type De chirurgie	Chimiothérapie postopératoire	rechutes	Insuffisance surrénale	évolution
1	F 8 m	????? Bilan d'extension Non fait	????	-1 cycle CADO_VP16_CISPLT					Perdue De vue
6	M 6ans Et 4m	ADP	III	-2 cycles CADO_VP16_CARBO -1 cure CADO en attendant chirurgie	Bilatérale Surrénalectomie Totale gauche et partielle droite	-1cure VP16_CARBO -1cycle CADO_VP16_CARBO			Rémission complète
2	M 11m	ADP OS	IV	4 cycles CADO_VP16_CISPLT	Bilatérale : Surrénalectomie Totale gauche et partielle droite	1 cycle CADO_VP16_CISPLAT			Rémission puis Perdu de vue
3	F 8ans	OS MOELLE	IV	1 cure d'endoxan : 4cp et demi/j 1semaine/2					Perdue de vue
7	M 4m	OS MOELLE	IV	-1 cure CO (en attendant pec dg) -5 cures du protocole HR_NB MAROC_2010	Unilatérale : Surrénalectomie Partielle gauche	-1 cycle CADO_VP16_CISPLAT -C3 ET C4 du prot HR_NB MAROC_2010			En cours de Rémission
8	F 3 A et 1 /2	OS MOELLE	IV	-5 cures du protocole HR_NB MAROC_2010 -1 cure CADO en attendant chirurgie	-chirurgie n°1 : Bilatérale Surrénalectomie Totale gauche +néphrectomie gauche et partielle droite -chirurgie n°2 : Surrénalectomie droite	2 cycles CADO_VP16_CARBOP	Locale au niveau surrénal droit	oui	décédée
4	M 2 m	FOIE	IV S	-2 cures CO					décédé
5	M 5 m	FOIE MOELLE	IV S	-3 cures CO -2 cycles CADO_VP16_CARBO					Rémission complète

Conclusion

Surgery retains a central place in the treatment of bilateral neuroblastoma, and the objective of the intervention remains a complete excision, to be weighed against the risks of complications and postoperative sequelae. The decision must be made in the overall context of other prognostic elements, and complete excision is not always essential.

Some older studies show that children can be cured by surgery alone and regardless of the quality of the excision, it was primarily a recognition of the major impact of age and clinical stage on the prognosis. It now appears that it is indirectly the weight of the favorable biological factors that explains why the extension of the surgery does not have a prognostic impact in certain cases. This notion of incomplete resection was acceptable, and patients could be cured by partial resection, which helped to parasitize the message about the role of surgery.

After a period when many localized tumors presenting risk factors were operated from the outset, with significant morbidity, the "pedagogical" message of the interest of a neo-adjuvant treatment was widely disseminated to the surgical community. The message inherited from the studies carried out during the 90s broadcast indeed 3 reasons:

1. Incomplete resection may be preferable to complete resection with complications.
2. Surgery immediately exposes the occurrence of complications that can be avoided by neo-adjuvant chemotherapy.
3. First-line chemotherapy improves the operability of certain tumors with surgical risk factors.

It seems that the pediatric oncological surgery teams have now largely assimilated these notions, and that fewer interventions are now realized from the outset in the presence of factors of inoperability.

It appears that the surgical procedure is always subject to an evaluation benefit / risk, and the main risk in the bilateral localization of this tumor, other than vascular risk, is the risk of adrenal failure if radical surgery is performed so several studies argue against an aggressive surgical approach.

Our work on bilateral adrenal neuroblastomas shows that incomplete excision provides excellent survival while limiting the risk of adrenal insufficiency. It is especially the recognition that the bilateral location is a favorable location.

Conflict of interest

All the authors declare that they do not have any conflict of interest.

Author's contribution

All authors contributed to the writing of this manuscript. All have read and approved the final version of the latter.

References

1. Nickerson HJ, Matthay KK, Seeger RC, Brodeur GM, Shimada H, Perez C, *et al*. Favorable biology and outcome of stage IV-S neuroblastoma with supportive care or minimal therapy: a Children's Cancer Group study. J Clin Oncol. 2000; 18:477-486.
2. Lo Cunsolo C, Casciano I, Gambini C, De Bernardi B, Tonini GP, Romani M. Molecular alterations in a case of bilateral adrenal neuroblastoma. Med Pediatr Oncol. 2001; 36:491-493.
3. Kushner BH, Gilbert F, Helson L. Familial Neuroblastoma: Case Reports, Literature Review and Etiologic Considerations. Cancer. 1986; 57:1887–1893.
4. Perle Maliszewicz Pagès, Christelle Dufour, Sylvie Fasola, Jean Michon, Patrick Boutard, Jean claude Gentet, Olivier Hartmann. Bilateral adrenal neuroblastoma. Pediatr Blood Cancer 2009; 52:196-202.
5. Kerdudo C, Corradini N, Michon J, Leverger G. Neuroblastome surrénalien bilatéral et syndrome de pepper: à propos de quatre observations Arch Pediatr 2004; 11(12):1450-6.
6. Pederiva F, Andres A, Sastre A, Alves J, Martinez L, Tovar JA. Bilateral adrenal neuroblastoma is different Eur J Pediart Surg. 2007; 17:393-396.
7. Brodeur GM. Neuroblastoma. Biological insights into a clinical enigma.Nat Rev Cancer. 2003; 3:203-216.
8. Grosfeld JL. Risk based management of childhood solid tumors. J Am Coll Surg. 1999; 189:407-425.

9. Brodeur GM, Pritchard J, Berthold F, *et al*. Revision of the international criteria for neuroblastoma diagnosis, staging and reponse to treatment J Clin Oncol. 1993; 11:1466-1477
10. D'Angio GJ, Evans AE. Multifocal neuroblastoma Med Pediatr Oncol. 1990; 18:234-235.
11. Knudson AG, Strong LC. Mutation and cancer: neuroblastoma and pheochromocytoma Am J Hum Genet 1972; 24:514-522.
12. Barrie SR, Michael P, La Quaglia. Neuroblastoma (chapter 31) Pediatr Surg. 2012; 7:441-458.
13. Ishiguro Y, Lio K, Seo T, Nagaya M, Ito T. Bilateral adrenal neuroblastoma Eur J Pediatr Surg. 1994; 4:37-39.
14. Kramer SA, Bradford WD, Anderson EE. Bilateral adrenal neuroblastoma Cancer. 1980; 45(8):2208-12.
15. Suzuki H, Honzumi M, Funada M, Tomiyama H. Metachronous bilateral adrenal neuroblastoma Cancer 1985; 56(6):1490-2.
16. Kwan Jong-lee, Tomonari U, Masahiko K, Tadashi A, Fumio E, Yukihiro I. Heterochronous bilateral adrenal neuroblastoma: stage 4S in early infancy following resection of stage I lesion in the neonatal period Pediatr Surg Int. 2012; 28:59-62.
17. Beckwith JB. Perrin EV. In situ neuroblastomas: a contribution to the natural history of neural chest tumors. Am J Pathol 1963; 43:1089-1104.
18. Turkel SB, ltabashi HH. The natural history of neuroblastic cells in the fetal adrenal gland Am J Pathol 1974; 76:225-236.
19. Ho PT, Estroff JA, Kozakewich H, *et al*. Prenatal detection of neuroblastoma: a ten-year experience from the Dana-Farber Cancer Institute and Children's Hospital Pediatrics. 1993; 92(3):358-64.
20. Araujo EJ, Sanchez Ayub E, Costa Santos EM, Moraes DJ, Rodrigues Pires C, Filho Sebastiao MZ. Diagnostico prenatal ultrasonografico de neuroblastoma adrenal Ginecol Obstet Mex. 2005; 73(8):451-5.
21. IGR, (2004), http:// www. igr. fr/ service. php? p_ m= downloadpfile=pediatriesite/neuro/neuroblastome_pro.pdf (consulté le 26 juin 2012)
22. Chu CM, Rasalkar DD, Hu YJ, Cheng FW, Li CK, Chu WC. Clinical presentations and imaging findings of neuroblastoma beyond abdominal mass and a review of imaging algorithm. Br J Radiol. 2011; 84:81-91.
23. Stovroff M, Dykes F, Teague WG. The complete spectrum of neurocristopathy in an infant with congenital hypoventilation, Hirschprung's disease, and neuroblastoma J Pediatr Surg. 1995; 30:1218-1221.
24. Berrebi D, Lebras MN, Belarbi N, *et al*. Bilateral adrenal neuroblastoma and nephroblastma occuring synchronously in a child with Fanconi's anemia and VACERL syndrome J Pediatr Surg. 2006; 41(1):11-14.
25. Park WS, Chi JG. Bilateral neuroblastoma in situ associated with microcephaly J Korean Med Sci 1993; 8:99-103
26. Monsaingeon M, Perel Y, Simonnet G, Corcuff JB. Comparative values of catecholamines and metabolites for the diagnosis of neuroblastoma Eur J Pediatr. 2003; 62:397-402.
27. Verma UM, Yankelevich B, Hodgson J, Mazumder A. Effect of the in vivo priming regimen for peripheral blood stem cells (PBSC) mobilization on in vitro generation of cytotoxic effectors by IL-2 activation of PBSC in a murine model. Bone Marrow Transplant. 1997; 19:265-73.
28. Mora J, Gerald WL, Qin J, Cheung NK. Evolving significance of prognostic markers associated with treatment improvement in patients with stage 4 neuroblastoma Cancer. 2002; 94:2756-65.
29. Couanet D, Valteau-Couanet D. Neuroblastome EMC (Elsevier Masson SAS, Paris), Pédiatrie, 4-100-E-80, 2006.
30. Plantaz D. Neuroblastome. un siècle après pepper: Quels sont les gènes ? Archives pédiatr. 2001; 8(9):917-21.
31. Bagatell R, Beck-Popovic M, London WB, *et al*. International Neurobalstoma Risk Group. Significance of MYCN amplification in international neuroblastoma staging system stage 1and 2 neuroblastoma: a report from the Inernational Neuroblastoma Risk Goup database J Clin Oncol. 2009; 27:365-70.
32. Ambros PF, Ambros IM, Brodeur GM, Haber M, *et al*. International consensus for neuroblastoma molecular diagnostics: report from the International Neuroblastoma Risk Group (INRG) biology committee Br J Cancer 2009; 100:1471-82.
33. Shimada H, Stram DO, Chatten J, *et al*. Identification of subsets of neuroblastomas by combined histopathologic and N-myc analysis. J Nat Cancer Inst. 1995; 87:1470-6.
34. Seeger RC, Brodeur GM, Sather H, *et al*. Association of multiple copies of the N- myc oncogene with rapid progression of neuroblastomas. N Engl J Med. 1985; 313:1111-6.
35. Combaret V, Audoynaud C, Lacono I, *et al*. Circulating MYCN DNA as a tumor-specific marker in neurobalstoma patients Cancer Res. 2002; 62(13):3646-8.
36. Gotoh T, Hosoi H, Lehara T, *et al*. Prediction of MYCN amplification in neuroblastoma using serum DNA and real-time quantitative polymerase chain reaction J Clin Oncol. 2005; 23(22):5205-10.
37. Rubie H, Coze C, Plantaz D, *et al*. Localised and unresectable neuroblastoma in infants: excellent outcome with low-dose primary chemotherapy. Br J Cancer. 2003; 89:1605–9.
38. Mathay KK, Perez C, Seeger RC, Brodeur GM, Shimada H, Atkinson JB, *et al*. successful treatment of stage III neuroblastoma based on prospective biologic staging: a children's Cancer Group study. J Clin Oncol 1998; 16(4):1256-64.
39. Bagatell R, Rumcheva P, London WB, *et al*. Outcomes of children with intermediate-risk neuroblastoma after treatment stratified by MYCN status and tumor cell ploidy. J Clin Oncol. 2005; 23:8819-27.
40. Pritchard J, McElwain TJ, Graham-Pole J. High-dose melphalan with autologous marrow for treatment of advanced neuroblastoma. Br J Cancer. 1982; 45(1):86–94.
41. Matthay KK, Villablanca JG, Seeger RC, *et al*. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation and 13-cisretinoic acid. N Engl J Med. 1999; 341:1165-73.

42. Hartmann O, Valteau-Couanet D, Vassal G, Lapierre V, Brugieres L, Delgado R, *et al*. Prognostic factors in metastatic neuroblastoma in patients over 1 year of age treated with high-dose chemotherapy and stem cell transplantation: a multivariate analysis in 218 patients treated in a single institution. Bone Marrow Transplant 1999; 23:789-795
43. Hartmann O, Benhamou E, Beaujean F, Kalifa C, Lejars O, Patte C, Behard C, *et al*. Repeated high-dose chemotherapy followed by purged autologous bone marrow transplantation as consolidation therapy in metastatic neuroblastoma. J Clin Oncol. 1987; 5(8):1205-11.
44. Coze C, Hartmann O, Michon J, *et al*: NB87 induction protocol for stage 4 neuroblastoma in children over 1 year of age: a report from the French Society of Pediatric Oncology J Clin Oncol. 1997; 15(12):3433-40.
45. Cohn SL, Pearson AD, London WB, *et al*. The International Neuroblastma Risk Group (INRG) classification system: An INRG Task Force report J Clin Oncol. 2009; 27:289-97.
46. Rubie H, Michon J, Plataz D, *et al*. Unresectable localized neuroblastoma: improved survival after primary chemotherapy including carboplatin-etoposide Br J Cancer 1998; 77:2310-2317.
47. Castel V, Tovar LA, Costa E, *et al*. The role of surgery in stage IV neuroblastoma J Pediatr Surg. 2002; 37:1574-8.
48. Guglielmi M, De Bernardi B, Rizzo A, *et al*. Resection of primary tumor at diagnosis in stage IVs neuroblastoma: does it affect the clinical cours? J Clin Oncol 1996; 14:1537-44.
49. Jereb B, Tournade MF, Lemerle J, Voute PA, Del emarre JF, Ahstrom L, *et al*. Lymph node invasion and prognosis in nephroblastoma Cancer. 1980; 45(7):1632-6.
50. Edward Kiely. A technique for excision of abdominal and pelvic neuroblastomas Ann R Coll Surg Engl 2007; 89(4):342-348.
51. Shaw A, Sabio H. Bilateral adrenal neuroblastoma Am J Pediatr Hematol Oncol. 1984; 6:41-43.
52. Hiyama E, Yokoyama T, Hiyama K, *et al*. Multifocal neuroblastoma: biologic behavior and surgical aspects. Cancer. 2000; 88(8):1955-63.
53. Suarez A, Hartmann O, Vassal G, Giron A, *et al*. Treatment of stage IVS neuroblastoma: a study of 34 cases treated between 1982 and 1987 Med Pediatr Oncol 1991; 19:473-7.
54. Martinez DA, King DR, Ginn-Peaz ME, Haase GM, Wiener ES. Resection of de primary tumor is appropriate for children with stage IVS neuroblastoma: an analysis of 37 patients J Pediatr Surg. 1992; 27:1016-20 discussion1020-1021
55. Haas D, Ablin AR, Miller C, Zoger S, *et al*. Complete pathologic maturation and regression of stage IV-S neuroblastoma without treatment Cancer. 1988; 62:818-25
56. Nickerson HJ, Matthay KK, Seeger RC, Brodeur GM, Shimada H, Perez C, *et al*. Favorable biology and outcome of stage IV-S neuroblastoma with supportive care or minimal therapy: a Children's Cancer Group study. J Clin Oncol. 2000; 18:477–486.
57. Schleiermacher G, Rubie H, Hartmann O, *et al*. Treatment of stage 4s neuroblastoma –report of 10 years' experience of the French Society of Paediatric Oncology (SFOP) Br J Cancer. 2003; 89(3):470-6.
58. Lo Cunsolo C, Casciano I, Gambini C, De Bernardi B, Tonini GP, Romani M. Molecular alterations in a case of bilateral adrenal neuroblastoma. Med Pediatr Oncol. 2001; 36:491–493.
59. Zaizen Y, Suita S, Yamanaka K, Nagoshi M, Tsuda T. Bialteral adrenal neuroblastoma Eur J Pediatr Surg. 1997; 7(5):304-7.
60. Brouard J, Nivot S, Deschrevel G, *et al*. Neonatal Pepper's syndrome with bilateral adrenal tumor Arch Fr Pediatr. 1990; 47:543.
61. Hero B, Simon T, Spitz R, *et al*. Localized infant neuroblastomas often show spontaneous regression; Results of the prospective trials NB95-S and NB97 J Clin Oncol. 2008; 26:1504-1510.
62. Bastian PJ, Fleischhack G, Zimmermann M, *et al*. The role of complete surgical resection in stage IV neuroblastoma World J Urol. 2004; 22:257-260.
63. Hsu WM, Jen YM, Lee H, *et al*. The influence of biologic factors on the surgical decision in advanced neuroblastoma Ann Surg Oncol. 2006; 13(2):238-44.
64. Laprie A, Michon J, Hartmann O, *et al*. High dose chemotherapy followed by locoregional irradiation improves the outcome of patients with international neuroblastoma staging system stage II and III neuroblastoma with MYCN amplification Cancer. 2004; 101(5):1081-1089.
65. Yanai T, Okazaki T, Yamataka A, *et al*. A rare case of bilateral stage IV adrenal neuroblastoma with multiple skin metastases in neonate: diagnosis, management, and outcome J Pediatr Surg. 2004; 39(12):1782-3.
66. Evans AO, d'Angio GJ, Koop CE: the role of multimodal therapy in patients with local and regional neuroblastoma. J Pediatr surg. 1984; 19:77-80.
67. Matthay KK, Sather HN, Seeger RC, *et al*. Excellent outcome of stage II neuroblastoma is independent of residual disease and radiation therapy. J Clin Oncol. 1989; 7:236-44.
68. Lee SY, Chuang JH, Huang CB, Hsiao CC, *et al*. Congenital bilateral cystic neuroblastoma with liver metastasesand massive intracystic haemorrhage Br J Radiol. 1998; 71:1205-1207.
69. Pinarti FG, Danaci M, Tander B, Dagdemir A, *et al*. Bilateral adrenal cystic neuroblastoma with superior vena cava syndrome and massive intracystic haemorrhage Pediatr Radiol. 2004; 34:746-749.
70. Koksal Y, Varan A, Kale G, *et al*. Bilateral adrenal cystic neuroblastoma with hepatic and splenic involvement in a new born J Pediatr Hematol Oncol. 2005; 27(12):670-671.