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Radiotherapy in nephroblastoma. Pre- and postoperative combination treatment. Radiotherapy in localized (stage II, III, IV) and metastatic disease. Acute and long-term side effects.*

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Nephroblastoma, an embryonic type of malignant tumor in the kidney found in infancy and early childhood is sometimes associated with congenital anomalies. In recent years the research in genetics of this tumor has been extremely active. For decades radiation has generally been accepted as a valuable supplement to surgery in the treatment of nephroblastoma. Unfortunately it may produce undesirable late effects. With the survival rates steadily improving from about 25% before up to 80% and more, the problem of late sequelae is becoming the most important one. With the aim to diminish late sequelae with adjustment of treatment to known variables several clinical trials have been conducted in Europe, USA and Great Britain. The results of these are presented together with adverse effects and second malignancies. Further prospects are discussed. The success of therapy for children with nephroblastoma has resulted in growth to adulthood of a large population of former patients. Radiation therapy is considered responsible for a great deal of early and late toxicities. However, the number of children at risk for this has certainly diminished.

Key words: nephroblastoma-radiotherapy

General aspects

Nephroblastoma is a term used for an embryonic type of malignant tumor in the kidney, found in infancy and early childhood, seldom seen beyond the age of 10 and very rarely in adult life.

Wilms suggested in 1899 that the tumor arises from undifferentiated mesoderm. This was accepted and his name has been associated with the tumor ever since. Nephroblastoma comprises 10% of malignant diseases in children and afflicts one in 10.000 children.

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Nephroblastoma is sometimes associated with congenital anomalies. Children with aniridia, genito-urinary malformations and mental retardation (WAGR), Denys-Drash syndroma or Beckwith-Wiederman syndroma are considered to run a higher risk for nephroblastoma.[1]

In Wilms' tumor associated with specifical congenital syndromes, WT 1 germ-line mutations are frequently detected, while in sporadic Wilms' tumor WT 1 - DNA mutations are present only in 6% of the cases. Possible molecular markers for prognosis, using DNA techniques, are being developed. The loss of heterozygosity for chromosomes in Wilms' was seen for chromosomes 11 p, 16 q and 1 p in 33,17 and 12% respectively. Patients with loss of heterozygosity for chromosome 16 q had mortality rates 12 times higher than those without it. However, the correlation of chromosome 16 q and poor prognosis seems related to tumor progression rather than initiation, as there is no constitutional deletion

of the chromosome in Wilms' tumor. Whether IGF binding protein -2- levels will be a useful serum marker of Wilms' tumor activity is no yet established.[2,3]

Radiation treatment - development

The first cure of a child with nephroblastoma was reported in 1894, the report on the first child treated for nephroblastoma by radiation therapy (RT) alone in 1916 and in 1945 the first cures of children with nephroblastoma treated with RT were reported. It has since then been generally agreed upon that RT is a valuable supplement to surgery for nephroblastoma.

A beneficial effect of preoperative radiation has been first shown in 1947 and later by many others. Opponents, however, warned of the delayed surgery and thereby risk for metastases. They also denied that preoperative shrinkage of the tumor was of importance for the surgeon. The discussion on whether radiation should be used preoperatively or postoperatively has been continued until 2 decades ago, when more systematical studies provided evidence of the value of preoperative radiation and of the value of preoperative treatment of nephroblastoma in general. This experience is still not generally used outside Europe, preoperative chemotherapy (ChT) is at present widely accepted as a mode of treatment for the great majority of children with malignant solid tumors.

The optimal dose of radiation for nephroblastoma was also a matter of discussion for decades. It was shown more than 20 years ago that 20 Gy to the tumor bed postoperatively was sufficient for tumor control. The decision, that in the great majority of cases not more than that is necessary, was made only after the introduction of Actinomycin D. A significant influence of preoperative RT in locally advanced tumors on the cure rate was shown in a retrospective multivariate analysis in 1973 and was the basis for the first study to determine whether preoperative radiation improves survival as compared to postoperative radiation, in a prospective randomized trial.[4] Postoperative radiation was still much more in use.

The technique of RT as regard the design of the treatment volume, fractionation schemes, daily dose and planning has not changed much during the decades. Two opposing fields are used to cover the tumor bed. After recognizing the risk for scoliosis, when irradiating only one half of the vertebral body, the 2 opposing fields were enlarged to cover the whole vertebral bodies. Fields for treatment of the whole abdomen or the whole lung in disseminated tumors have also remained essentially the same, although the dose had to be reduced because of additional ChT. Nephroblastoma being a rare condition; studies have been conducted in cooperative groups: The National Wilms' Tumor Study (NWTS) [5] started in 1969 in the USA by the Children Cancer Study Group (CCSG). The Nephroblastoma SIOP 1 in Europe in 1971[6] and in 1979 the United Kingdom Children's' Cancer Study Group Wilms' trial (UKW) in Great Britain and Norway.[7]

The stage of the tumor and its histological type have been recognized as the most important factors for the prognosis in nephroblastoma. Consequently, the criteria applied for randomization were mainly the same in the three trials, the questions asked, however, varied, as they were based on previous experiences and traditions at the 3 different regions. Recognizing the importance of lymph node involvement for prognosis[8], the staging has been slightly modified, from that which was first accepted by the NWTS 1, and in the SIOP 1 Study trial.

The significant difference in the outcome of tumors with favourable histology (FH) and unfavourable histology (UH) (10% of all cases), has been confirmed in the trials.[9] For further randomization, only localized stages with FH were included; infants and stage IV, Stage V and all tumors with UH were dealt with in other ways.[10] In the course of these studies several histological subtypes have been recognized e.g. the Stockholm histological classification of nephroblastoma (Table 1).

Table 1. The Stockholm working classification of renal tumors of childhood (1994).

I. LOW RISK TUMOURS ("FAVOURABLE")
– Cystic partially differentiated nephroblastoma
– Nephroblastoma with fibroadenomatous-like structures
– Nephroblastoma of highly differentiated epithelial type
– Nephroblastoma - completely necrotic (after preoperative chemotherapy)
– *Mesoblastic nephroma*
II. INTERMEDIATE RISK TUMOURS ("STANDARD")
- Non-anaplastic nephroblastoma with its variants
– Nephroblastoma - necrotic but some features left (< 10%)
III. HIGH RISK TUMOURS ("UNFAVOURABLE")
– Nephroblastoma with anaplasia
– *Clear cell sarcoma of the kidney*
– *Rhabdoid tumour of the kidney*

Groups of patients with very good prognosis have been identified; e.g. children younger than 2 years with tumors of FH, not greater than 550 ccm (NWTS) or stage I tumors[11] in which after preoperative chemotherapy no vital tumor cells were found (SIOP). In such cases postoperative treatment could possibly be omitted. Also, groups with very poor prognosis have been identified; those with advanced tumors and UH. For those, more aggressive treatment schemes were designed.[12]

By increasing the rate of Stage I tumors with preoperative chemotherapy in the ongoing SIOP trial, postoperative radiation is given only to 20% of children as compared to 80% in the first SIOP study.[13] The number of children receiving postoperative RT has diminished in the UKW when the study confirmed that omittance of postoperative RT for Stage I tumor is safe and RT was given to Stage II and Stage III tumors only if at the second look operation no residual tumor was found. Fewer children receive RT in the NWTS as well and also the doses in general are lower.

After the most important questions were resolved: on the value of preoperative treatment in the SIOP, on the effect of chemotherapy combinations VCR, VCR - AMD, VCR + AMD + Doxo in the NWTS, on the safe omittance of postoperative RT for Stage I tumors in the UKW, the main goal, that is, to decrease the number of children receiving postoperative radiation seemed to be achieved.

The experience of the different trials was constantly exchanged and incorporated into treatment schemes. Preoperative treatment is used in the ongoing SIOP trial for all cases, in the USA it is given to children with "unresectable" tumors and its beneficial effect is reported in selected groups of patients with intracaval and intraatrial tumor extension.[14] Also, in the UKW study, preoperative treatment is given to individually considered unresectable tumors. The main drawback, according to the opponents of preoperative chemotherapy, is the difficulty of histological classification. They accept, however, a 100% tumor response to preoperative chemotherapy as a good prognostic sign. There is still no known effective treatment for some of the tumors of UH, especially if disseminated. For these children with poor prognosis, RT is still used to reduce the risk of abdominal recurrence, while new chemotherapeutic agents or new combinations are being introduced to reduce the risk for metastases.

In the majority of cases, radiotherapy has been replaced by chemotherapy. For advanced tumors and those with UH, Doxorubicin is usually added. It has also been a part of treatment for UH and recurrent tumors, often in combination with RT. Fatal late effects of cardiotoxicity have been observed after treatment with Doxorubicin. The answer to the question how best to balance the merits and demerits of chemotherapy vis-a-vis those of RT has yet to be found.

Adverse effects of treatment

With the survival rates of Wilms' tumor steadily improving from about 25% before the introduction of chemotherapy, with the amounting knowledge and treatment tailored to age, stage, histology type, the survival rates are now up to 80% and more in some good risk groups; the problems of late sequelae are becoming the most important ones.

The tolerance for RT of different organs has been agreed upon after decades of experience and observation, the late effects of chemotherapy are still being recognized and the effects of combination of chemotherapy and RT are a rather new chapter of radiobiology.

Radiation nephrotoxicity

In general, the tolerance to radiation of the kidney in the child is similar to that in the adult. It is about 20.0 Gy when radiation has been delivered to both kidneys in 3-5 weeks, using reduced daily fractions, when delivered without chemotherapy. The duration of follow-up is critical, signs and symptoms of late radiation damage to the kidney may not develop for years. The underlying process of late radiation damage is progressive nephrosclerosis.

It has been suggested that renal function compatible with clinical health in nephrectomised patients can be preserved as long as the remaining kidney has received less the 12.0 Gy. It has been reported that one child out of four, who received 14-15 Gy, experienced transient nephropathy, and one child in the NWTS has developed fatal nephropathy. Thus, the dose of 14 Gy appears relatively safe even on a long-term basis. An excess of diastolic hypertension has been reported in the long-term survivors (5 years from diagnosis) of the NWTS, notably among younger children. The results of this retrospective study have to be taken with caution for several reasons.[15]

It has been suggested that moderate doses of radiation (14.5 - 20.0) may reduce or eliminate the

ability of a remaining kidney to hypertrophy. The enhancing effect of AMD on radiation nephropathy is controversial, but in animal experiments BCNU, cisplatinum and Doxorubicin showed this effect. Iphosphamide may produce nephropathy, but it is not clear if it enhances the effects of RT.[16]

Radiation hepatotoxicity

Hepatotoxicity is one of the major acute reactions to combined postoperative treatment in nephroblastoma patients. 30.0 Gy is considered a safe RT dose to the whole liver. The tolerance of the liver varies a great deal depending on the volume irradiated and on additional chemotherapy. Hepatotoxicity identical in presentation and course to radiation hepatitis occurred in children who received postoperative chemotherapy only, in about 10%. In the SIOP group of patients who received postoperative radiation and AMD it occurred in 11 out of 58 children (19%) who had major parts of the liver or whole liver within the irradiation fields. Four of them had veno-occlusive disease (VOD). The dose range was 12.0 - 22.5 Gy with a few who had a boost up to 30 Gy. All four patients who had VOD had received doses > 20 Gy and AMD on 5 consecutive days (15 y/kg). None of the patients who received a single dose of AMD (0/13) developed liver toxicity but 11/24 with AMD on 5 consecutive days did. All children recovered from toxicity with conservative treatment and dose reduction of AMD.[17, 18]

Radiation pneumonitis

Radiation induced interstitial pneumonitis and pulmonary fibrosis are common complications of treatment for lung metastases in Wilms' tumor patients. A safe dose to the whole lung is considered to be 20 Gy when given in conventional fractionation and without chemotherapy; 1400 Gy in 10 fraction in combination with ChT have resulted in no complications. In the NWTS, however, with 14 Gy to the whole lung plus AMD and VCR, pneumopathy was found in 10 - 13%.

Whether Doxorubicin addition increased the rate of late pulmonary dysfunction is not clear. Radiation pneumonitis has been seen as a "recall effect" of AMD after RT.[19]

Cardiac toxicity

Congestive heart failure is a known complication of therapy with antracyclines. Its frequency is directly proportional to the cumulative dose of doxorubicin, with a reported incidence of congestive heart failure of about 5% in patients who received a cumulative dose of 400-500 mg/m2 or more. Although the initial reports of cardiac failure were limited to the first year after completion of therapy, reports of heart failure and dysarrhytmias, leading in some cases to sudden death, are now appearing in patients treated 4-20 years earlier. In patients from the NWTS 1, 2 and 3, 8 cases (1.7%) were found of congestive heart failure after doxorubicin treatment. Additional risk factors included whole lung irradiation and concurrent therapy with cyclophosphamide. Only further follow-up will define the magnitude of the risk for different combinations of chemotherapy and RT.[20]

Reproductive system

Damage to the male and female reproductive system caused by cancer therapy may result in infertility or hormonal dysfunction. Up to 12% of female survivors of childhood cancer who received abdominal radiation have ovarian failure. In males, gonadal radiation may result in temporary azoospermia and elevated levels of follicle stimulating and luteinizing hormones. A study of pubertal development in children treated for Wilms' tumor found that 3 out of 10 girls and 1 out of 6 boys had delayed development associated with elevated hormone levels. The relative fertility of the 20 Wilms' tumor survivors was 1.49%. Serious adverse pregnancy outcomes have been observed in women who had received abdominal radiation for Wilms' tumor. Perinatal mortality has been estimated to be eight times higher than among USA white women in general and the rates of low births weight 4 times higher. Similar observations regarding the effect of abdominal radiation on low birth weight have been made in babies born to other childhood cancer survivors. The risk for children born to Wilms' tumor patients who had chemotherapy, but no RT, is not known.

Second malignancies

Children treated for cancer are at increased risk for both malignant and benign second tumors. Cyclophosphamide, doxorubicin and cisplatin currently used to treat high risk Wilms' tumor patients, or those who had recurrences, have been implicated in leukemogenesis and carcinogenesis. Radiation and chemotherapy in combination may be more onco-

genic than either agent alone. Studies of second malignant neoplasms in Wilms' tumor survivors have documented a 1% cumulative incidence at 10 years from diagnosis and rising thereafter. All but 2 of the 26 SMN identified in 2 studies occurred in irradiated patients, most within the radiation field.

In the NWTS, among 5415 patients treated, 46 developed SMNs, 34 of these had RT and 12 had no RT. Radiation, doxorubicin and recurrence, alone or in combination appear to account for 86% of the SMN cases recorded.[21] These 46 cases represent a 8.5 times higher rate than excepted. One possible cause of SMN might also be related to genetic predisposition; there are some observation that suggest such correlation: patients with congenital anomalies have an increased risk of SMN, the patients who experienced SMN were relatively young (5 out of 7 less the 2 years old and in one study of 36 patients with SMN after Wilms', eight had first degree relatives with Wilms' tumor or congenital anomalies associated with Wilms' tumor.[22]

How much the risk for SMNs has decreased by decreasing the use of RT only time will show. Much work is still needed to define the risks depending on treatment modality, doses of RT and particular chemotherapy agents.

The success of therapy for children with Wilms' tumor has resulted in growth to adulthood of a large population of former patients. The quality of their lives and the lives of their offspring must be our first concern after saving their lives.

RT is considered responsible for a great deal of early and late toxicities and the most serious late sequelae - second malignant tumors. The number of children at risk for this has certainly diminished.

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