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Nuclear medicine in pediatric oncology

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Introduction

Pediatric malignancies are relatively rare and account for 0.5% of all cancers. The annual incidence varies between 110 and 150 per million children, which means that the chance for a child to develop a cancer during the first 15 years of life is 1:450–600. Leukemias and tumors of the brain and spinal cord have the highest relative incidence rates, followed in frequency by neuroblastoma, lymphomas, Wilms tumor and bone tumors. Other tumor types are less frequent. Pediatric tumors arise as a result of disturbance of genetic material. In very young children predominantly blastemal tumors (e.g. nephroblastoma, neuroblastoma, medulloblastoma) occur, whereas in the age group 10–25 years sarcoma's (e.g. osteosarcoma, EWING sarcoma) are dominating. Carcinomas are typically adult-type tumors (> 30 years of age).

The overall survival rate for childhood cancers has improved significantly over the years (from 25% in the 1960's to 75% in the 1990's). This means that the pool of children and adults, who have survived childhood cancer and who are in follow up and being studied for potential late effects, is continuously increasing [1].

In recent years the contribution of nuclear medicine has been of increasing interest to pediatric oncology, in particular in imaging for diagnosis, staging and follow-up, in quantitative function analysis of organs at risk during oncological therapy, as well as in radionuclide therapy [2–5]. Nuclear medicine studies in children require special considerations regarding the performance of the procedure and the attitude of the attending staff [6].

In tumor imaging the trend has been to use more or less specific tumor-seeking radiopharmaceuticals. A great number of these agents are available, exploiting various metabolic and biological properties of individual tumors. Parallel to these developments radionuclide therapy becomes more widely used, whenever its success is envisaged on the basis of a good and selective uptake and long retention of the radiopharmaceutical in the tumor. Table 1 shows a list of tumor seeking radiopharmaceuticals, which are currently available for diagnosis and therapy of pediatric tumors. The major indications, in which nuclear medicine has a role, are discussed below.

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Table 1. Tumor-seeking radiopharmaceuticals and indications in pediatric oncology

Purpose	Radiopharmaceutical	Indications
Imaging	^{67}Ga-citrate	Lymphoma
	^{201}Tl-chloride	Differentiated thyroid ca.
		Lymphoma
		Osteosarcoma
		Brain tumors
		Rhabdomyosarcoma
	^{99m}Tc-sestamibi	Lymphoma
	^{99m}Tc-tetrofosmin	Lymphoma
	^{99m}Tc-diphosphonate	Osteosarcoma
	^{99m}Tc-pentavalent DMSA	Medullary thyroid ca. (M.E.N. II syndromes
	^{123}I/^{131}I-MIBG	Neuroblastoma
		Pheochromocytoma
		Ganglioneuroma
	^{111}In-pentetreotide	Neuroendocrine tumors
		Lymphoma
	^{99m}Tc-HIDA derivatives	Hepatoblastoma
	^{111}In-antimyosin Fab	Rhabdomyosarcoma
	radiolabeled antibodies	Neuroblastoma
	(3F8, ch14.18, chCE7)	
PET	^{18}F-deoxyglucose	Lymphoma
		Neuroblastoma
	^{124}I-MIBG	Neuroblastoma
	^{124}I-3F8 antibodies	Neuroblastoma
	^{11}C-hydroxyephedrine	Neuroblastoma,
		Pheochromocytoma
Therapy	^{131}I-iodide	Differentiated thyroid ca.
	^{131}I-MIBG	Neuroblastoma
	^{125}I-MIBG	Neuroblastoma
	^{131}I-3F8 antibodies	Neuroblastoma
	^{131}I-Rose Bengal	Hepatoblastoma
	^{131}I-antiferritin antibodies	Hepatoblastoma
	^{89}Sr-chloride	Osteosarcoma
	^{186}Re-HEDP	Osteosarcoma
	^{153}Sm-EDTMP	Osteosarcoma
	^{131}I-anti CD20 antibodies	Lymphoma
	^{90}Y-anti CD20 antibodies	Lymphoma

Tumor imaging

Bone tumors

The principle bone tumors in children are osteosarcoma (incidence rate 1.6–2.6/10^6 children per year) and EWING sarcoma (incidence 0.6/10^6/year). The peak incidence is between 10 and 20 years of age and etiological factors include rapid growth, trauma, radiation and previous chemotherapy. Patients generally present with bone pain, swelling of bone with or without functional impairment. The distribution of the sites of the primary tumor is different for both tumor types.

Relevant diagnostic procedures are X-ray, CT, MRI, bone scintigraphy and SPECT, alkaline phosphatase (osteosarcoma) and LDH (EWING sarcoma). The diagnosis is confirmed by histology and immunocytochemistry. Osteosarcoma is treated by surgery (i.e. resection/amputation/rotationplasty) after preoperative chemotherapy, followed by postoperative chemotherapy, prosthetics and rehabilitation therapy. EWING sarcoma is treated by radiotherapy or surgical resection of an expendable bone and chemotherapy [1].

Bone scintigraphy is highly sensitive to detect EWING sarcoma and bone metastases.

In differentiated osteosarcoma, bone scintigraphy/SPECT using ^{99m}Tc-diphosphonate may, as a result of its targeting the tumor-produced osteoid, visualize not only the primary bone tumor and its skeletal metastases with great intensity and 100% sensitivity, but also the extraosseous metastases in the majority of cases, regardless their localization [7, 8]. SPECT can be helpful to distinguish extraosseous from skeletal metastases, particularly in the thorax and pelvis [9]. To study the effect of preoperative chemotherapy in osteosarcoma also Thallium-201 scintigraphy has been used with success [10].

Lymphoma

The 3rd most common childhood malignancy (16.4/10^6 children) occurs as Hodgkin's disease or (more often) as non-Hodgkin lymphoma of the B-cell- or T-cell type. The diagnosis is based on histopathology and immunocytology of lymph nodes, bone marrow, cerebrospinal fluid or effusions [1]. Structural (anatomical) diagnostic imaging is done by X-ray, ultrasonography of the abdomen, CT-scan of chest/abdomen (poor for bone marrow) and MRI (good for bone marrow). Nuclear medicine provides functional imaging, i.e. bone scintigraphy and tumor imaging (planar scintigraphy/SPECT/PET) using ^{67}Ga-citrate, ^{201}Tl-chloride, ^{99m}Tc-sestamibi, ^{111}In-pentetreotide and ^{18}F-FDG.

^{67}Ga-citrate has been used for decades in the detection and staging of lymphoma [11]. ^{67}Ga-SPECT is better than planar scintigraphy (sensitivity 97% vs. 67% for lymphoma in the chest) [12]. More recently it is also used for early recognition of response to chemotherapy or radiotherapy: failure of a positive ^{67}Ga-scan to convert to negative is associated with a poor prognosis. In follow up ^{67}Ga-scintigraphy is better than CT-scan in differentiating residual tumor from fibrosis.

^{201}Tl-chloride scintigraphy and emission tomography and positron emission tomography (PET) using ^{18}F-deoxyglucose can also be used for this purpose. Especially in low grade non-Hodgkin lymphoma ^{201}Tl-chloride scintigraphy is superior to ^{67}Ga-imaging [13].

More recently ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin have been used for imaging lymphoma; these tracers add the aspect of tumor characterization, because of their association with p-glycoprotein, which plays a role in multi-drug resistance [14].

Thyroid carcinoma

Thyroid carcinoma is rare in childhood (0.5–1.5% of pediatric malignancies); 72% are of the papillary type, 18% follicular and around 10% medullary carcinoma. The diagnostic and therapeutic approach in children is not essentially different from that in adults: diagnosis by ultrasonography, thyroid scintigraphy and fine needle aspiration, treatment by surgery and postoperative ^{131}I-therapy. Subsequently, diligent surveillance of the tumor marker thyroglobulin (should not be detectable after adequate surgery and ^{131}I-ablation) and ^{123}I- or ^{131}I-scintigraphy either at regular intervals or whenever a rise in serum Tg is detected, is mandatory [1].

^{201}Tl-chloride scintigraphy, in conjunction with thyroglobulin assays in serum, has become a reliable alternative to the use of ^{131}I-iodide in the follow-up of differentiated thyroid carcinoma, particularly as the procedure and radiation dose to the child compares favorably with that of ^{131}I [15]. ^{131}I maintains its role in radionuclide therapy of thyroid carcinoma. In case of iodine-non-avidity of metastases, alternative tumor-seeking radiopharmaceuticals may be used, e.g. ^{201}Tl-chloride, ^{99m}Tc-sestamibi, ^{111}In-pentetreotide, ^{67}Ga-citrate and ^{18}F-FDG.

Medullary thyroid carcinoma arises from the parafollicular or C-cells and may present as sporadic cases or as a familial disease in association with other endocrine tumors (25%). In the latter form, children may become involved in the family screening of MEN 2 syndromes. A variety of tracers can be used to demonstrate medullary thyroid carcinoma: ^{201}Tl-chloride, ^{99m}Tc-pentavalent DMSA, ^{99m}Tc-sestamibi, ^{123}I- or ^{131}I-MIBG, ^{111}In-pentetreotide, ^{131}I-labeled anti-CEA antibodies and ^{18}F-FDG. Both ^{201}Tl- and ^{99m}Tc(V)-DMSA scintigraphy have a high sensitivity (> 80%), but are aspecific tracers, whereas MIBG and antibodies are highly specific, but have a low sensitivity (35% and 60% respectively) [16].

Neuroblastoma

Neuroblastoma is a malignant tumor of the sympathetic nervous system, occurring most frequently in early childhood: 50% of patients are younger than 2 years, 75% are younger than 4 and the disease is rare after the age of 14. The incidence in US children is 5/10^6 population per year, with a slight preponderance of males and white-skinned people. The site of the primary tumor varies: 70% of all tumors originate in the retroperitoneal region, including around 30% in the adrenal gland and 10% in the abdominal sympathetic side chain, and 8% occur in the cervical, 17% in the thoracic and 5% in the pelvic sympathetic side chain.

The diagnosis is suspected on clinical symptomatology, which varies with the site and size of the tumor and the amount catecholamines, which more than 90% of these tumors produce in excess, and is confirmed by increased levels of catecholamines and metabolites in urine and by MIBG scintigraphy [1].

Specific targeting of neuroblastoma may be achieved either via the metabolic route (MIBG), via receptor binding (peptides) or via the immunological route (antibodies).

An active uptake-1 mechanism at the cell membrane and neurosecretory storage granules in the cytoplasm of neural crest tumours are responsible for the specific uptake and retention of ^{131}I-MIBG respectively. As nonadrenergic tissues rely on passive

Table 2. Medication interfering with MIBG-uptake and/or retention (mechanism: a — uptake-1 inhibition, b — depletion, c — transport inhibition, d — uncertain)

Drugs known to interfere	Drugs expected to interfere
Labetalol [a, b]	Adrenergic blocking agents [b]: e.g. bretylium, guanethidine
Reserpine [b, c]	Sympathicomimetics [b]: e.g. amphetamine, dopamine, isoproterenol, terbutaline
Calcium-channel blockers [d]: e.g. nifedipine, verapamil	Phenothiazides [a]: e.g. chlorpromazine, promethazine
Tricyclic antidepressants [a]: e.g. amitryptiline, imipramine	Butyrophenones [a]: e.g. droperidol, haloperidol,
Sympathicomimetics [b]: e.g. ephedrine	Thioxanthines [a]
Cocaine [a]	Maprotiline, trazolone [a]

diffusion only, this results in high tumor/non-tumor ratio's. A number of drugs may interfere with the uptake and/or retention of ^{131}I-MIBG (Table 2) [17].

Bone scintigraphy may reveal increased uptake at the site of the primary tumor and is a sensitive, but aspecific technique to demonstrate bone metastases, especially when these are located in/near the epiphyses.

As ^{123}I- or ^{131}I-MIBG scintigraphy has a cumulative sensitivity of 92% and is a highly specific procedure in children, this has become the procedure of choice for detection, staging and follow up of neuroblastoma. It can detect the primary tumor, residual or recurrent disease and nodal or distant metastases, regardless their localization, in a single procedure [18, 19]. Due to the high specificity, it can also establish the diagnosis of neuroblastoma, ruling out other pediatric tumors [20]. Moreover, ^{123}I-MIBG scintigraphy can assist in probe-guided surgery of tumor residu or recurrence, and MIBG tracer studies can identify patients who are likely to benefit from therapy using ^{131}I-MIBG. For diagnostic scintigraphy both ^{123}I-MIBG and ^{131}I-MIBG are available: a comparison of these tracers showed that results are not essentially different, but, as the image quality of ^{123}I-MIBG images is generally better, this agent is preferred for diagnosis and follow up scans [21]. ^{131}I-MIBG allows delayed imaging which may be preferred for assessing both the tumor uptake and retention prior to therapy.

Potential pitfalls in MIBG scintigraphy in neuroblastoma are abnormalities which are located in or close to normal structures that normally take up MIBG (^{123}I-MIBG SPECT may be helpful in these cases [22]), hyperplasia of the residual adrenal gland after contralateral adrenalectomy, hydronephrosis, contamination, activity in the reservoir of an administration system or in intravenous lines or in drains, inadequate blockade of the thyroid, and uptake in benign or malignant tumors other than neuroblastoma which can concentrate MIBG.

On the basis of peptide receptor binding (somatostatine receptors have been found in 86% of neuroblastomas and VIP receptors in 57% [23]), the cumulative sensitivity of ^{111}In-pentetreotide is 77% [19].

In the eighties murine monoclonal antibodies ^{131}I-UJ13A and ^{131}I-3F8 were used for diagnosis and treatment of neuroblastoma. More recently, chimeric antibodies, e.g. ch14.18 and chCE7 have been developed yielding high specific tumor uptakes in neuroblastoma-bearing nude mice and initial results of scintigraphy in patients are promising [24].

As most neuroblastomas are highly differentiated tumors, positron emission tomography (PET) using ^{18}F-deoxyglucose (FDG) has a lower sensitivity than MIBG-scintigraphy [25], however the more specific ^{11}C-hydroxyephedrin (HED) has been used with success to image neuroblastoma [26] and ^{124}I-labeled MIBG and 3F8 antibodies for dosimetry prior to therapy.

Rhabdomyosarcoma

Eight percent of pediatric malignancies are rhabdomyosarcomas, which occur in two peaks, one between 1 and 7 years of age, the other between 15 and 20 years. The primary location is most frequently in the head&neck area (36%) and the genitourinary tract (25%). The diagnosis is confirmed by a biopsy with immunohistochemical staining of the myosin, which is characteristic for this tumor and forms the basis for radioimmunoscintigraphy. Treatment consists of preoperative chemotherapy or radiotherapy, followed by surgery of the primary tumor and regional lymph nodes and postoperative chemotherapy [1].

Aspecific tracers, e.g. ^{67}Ga-citrate, ^{201}Tl-chloride and ^{18}F-deoxyglucose (PET), can be used to image rhabdomyosarcoma [27, 28]. Specific targeting of rhabdomyosarcoma is provided by radioimmunoscintigraphy using ^{111}In antimyosin Fab fragments [29], however this radiopharmaceutical is no longer commercially available.

Hepatoblastoma

Liver tumors are rare in children and the incidence and distribution of tumor types vary with geography. The most frequent type is hepatoblastoma, which usually presents with abdominal distension, palpable mass or hepatomegaly. Serum assays of α-foetoprotein, produced by the tumor, serve as a tumormarker. Treatment is by surgery (hepatic lobectomy, which is better tolerated by children than adults) and chemotherapy (either systemic or intra-arterial); inoperable or recurrent tumors may also be treated by hepatic arterial embolization and intra-arterial radionuclide therapy [1].

^{67}Ga-citrate scintigraphy and SPECT may be used for (aspecific) tumor imaging. Some hepatoblastomas have retained their capability to take up hepatobiliary agents, such as ^{99m}Tc-HIDA derivatives, and tumor retention of these agents may be demonstrated by hepatobiliary scintigraphy [30].

Miscellaneous

Apart from tumor imaging, scintigraphy of organs, e.g. of bone, bone marrow, thyroid lungs, kidneys, brain, liver/spleen and lymphnodes, is also widely used in pediatric oncology. Scintigraphy using ^{99m}Tc-labeled autologous erythrocytes may be helpful to differentiate hemangioma from other tumors.

New tracers

The recent trend in oncology to tailor therapy to the individual patient has led to the development of specific tracers which allow characterization of the tumor rather then detection. Using such tracers, a negative result, which in terms of tumor detection would be considered a "false negative", may be just as meaningful as

a positive result. Although most of these agents are undergoing clinical investigation in adult patients, they will in time be used in pediatric oncology too.

^{99m}Tc-sestamibi, a cationic complex which is taken up in mitochondria, may be removed from the cell by P-glycoprotein which is associated with multiple drug resistance; in children with lymphoma, inability of the tumor to retain ^{99m}Tc-sestamibi was found to be correlated with a poor response to chemotherapy [14].

Other examples (in adults) of scintigraphic tumor characterization are the use of ^{123}I-estradiol which binds to estrogen receptors, ^{123}I-IAZA, ^{18}F-misonidazole and ^{99m}Tc-labeled metal-complexes highlighting tumor hypoxia, and ^{99m}Tc-annexin V indicating apoptosis.

New techniques

Positron emission tomography using ^{18}F-deoxyglucose is gradually gaining recognition in pediatric oncology, although in children special considerations and preparations are required to ensure a flawless i.v. injection of the tracer, sufficient patient rest prior to and after the tracer administration and immobilization during the entire acquisition time. Pediatric indications for ^{18}F-FDG PET include brain tumors, osteosarcoma, EWING sarcoma, rhabdomyosarcoma, WILMS tumor and lymphoma [31]. Neuroblastoma can better be detected with a highly specific single photon tracer such as ^{123}I-MIBG than with the aspecific ^{18}F-FDG [25]. However, as specific agent, ^{11}C-hydroxyephedrine can be used for PET of pheochromocytoma and neuroblastoma [26].

Positron emission tomography is particularly useful for the staging prior to surgery or radiotherapy, for the planning of radiotherapy by 3-dimensional matching of functional and anatomical parameters, and for monitoring response to therapy. One must be aware that, in children, ^{18}F-FDG uptake in normal thymus tissue may cause false-positive results in the mediastinum.

Other new technology is the intraoperative use of gamma-probes and minicamera in pediatric surgery to facilitate tumor resection. E.g. after previous surgery of neuroblastoma, resection of tumor residu or recurrence may be difficult: radioguided surgery after administration of ^{123}I-MIBG may allow the detection of the lesion and determination of the completeness of resection [32]. The same principle applies to the use of other tumor seeking agents for other malignancies.

Function monitoring

As a functional modality nuclear medicine is well suited to monitor the function of organs at risk during treatment in pediatric oncology, in particular cardiac, pulmonary, renal and salivary function. Anthracycline- or radiation induced cardiomyopathy is studied monitoring the ejection fraction by gated analysis and myocardial damage has been assessed using ^{111}In-antimyosin antibodies. Pulmonary ventilation and perfusion studies and ^{111}In-pentetreotide scintigraphy are used to detect radiation lesions to the lungs and monitor the success of their treatment with corticosteroids. Renography with ^{99m}Tc-DTPA or ^{99m}Tc-MAG3 and renal uptake studies using ^{99m}Tc-DMSA can monitor radiation nephropathy and renal consequences of Ifosfamide and Cisplatin treatment [33]. Radiation lesions to the salivary glands after ^{131}I-therapy or external beam radiotherapy to the neck can be monitored by measuring salivary gland ^{99m}Tc-pertechnetate secretion and excretion.

Radionuclide therapy

Considerations

As an oncological treatment modality, radionuclide therapy combines the advantages of being systemic, like chemotherapy, with that of delivering local radiation to tumors, like radiotherapy. Apart from attaining objective response, radionuclide therapy can provide excellent palliation, as it is associated with limited side effects and few late effects.

However, handicaps for this modality are the need of isolation of patients and storage of radioactive waste, the insufficient availability of suitable isolation facilities and the high cost of the newer therapeutic agents [34].

Multiple mechanisms for targeting radionuclides to tumors prevail; in children, current indications are differentiated thyroid carcinoma, neuroblastoma, osteosarcoma, painful skeletal metastases and, in future, lymphoma. Contraindications are severe myelosuppression and renal function disorders, as well as an instable patient condition not allowing isolation therapy or lack of understanding of or cooperation with guidelines for radiation protection.

Special considerations apply for the treatment of children with radionuclides [35].

Problems of isolating a child may be minimized by inviting parents or other relatives to become actively involved in the care of the child. They can stay in an adjacent room with closed circuit television and intercom and must be instructed about issues of radiation protection: to wear disposable gown, gloves and shoes and carry a pocket dose-meter, when entering the isolation room; to restrict the time of exposure, keep as much distance as feasible, not to drink or eat in this room and how to handle any radioactive waste; in case of ^{131}I-containing treatment, the carer uses potassium iodide (200 mg daily orally) for thyroid blockade. If these conditions are met, participation of relatives is both feasible and safe, with measured and estimated radiation doses varying 0.4–3 mSv.

The child must be kept busy and amused, e.g. by drawing/ /reading material, toys, (computer) games, video-films, etc. Child and parents should be made aware, that items which become contaminated may have to be stored for radioactive decay.

In general, both the radionuclide therapy and the isolation are well tolerated by children. Potential hazards are acute radiation effects, like nausea, vomiting, sialoadenitis or temporary swelling of tumor localizations; or side effects due to the targeting agent, e.g. allergic reactions and HAMA response to antibodies, vasoactive reaction to MIBG. Potential long-term effects are hematological effects, xerostomy, induction of leukemia or other malignancies; it should be emphasized, however, that long-term follow up studies have demonstrated that radionuclide therapy carries a much lower risk of leukemia and second cancers than chemotherapy and external beam radiotherapy.

Thyroid carcinoma

As in adults, radioiodine therapy is indicated in children with differentiated thyroid carcinoma, either for ablation of thyroid remnants after (near)total thyroidectomy or for treatment of tumor recurrence or metastases.

^{131}I-therapy of metastatic thyroid carcinoma has proven efficacy, both in terms of objective response and survival rates. Following the Chernobyl accident in 1986, the incidence rates of pediatric

Table 3. Pooled results of ^{131}I-MIBG therapy in neural crest tumors (EANM Radionuclide Therapy Committee Workshop, Barcelona, October 1999)

Disease	Patients	Objective response: Tumor volume	Objective response: Biochemical	Subjective response: Palliation
Pheochromocytoma	77	51%	68%	68%
Paraganglioma	34	48%	51%	70%
Neuroblastoma	229	51%	NA	Most patients
Medullary thyroid ca.	29	23%	60%	60%
Carcinoid	159	8%	24%	60%
Other	6	2/6	NA	NA
TOTAL	534			

NA — not available

thyroid cancer have risen significantly in countries affected by fall out. Many of these children presented with stage T4 tumors, multifocal tumors, and metastases in lymph nodes and lungs. In a group of patients from Belarus, treated with ^{131}I in Germany under a cooperative project of the European Commission, the overall percentage of complete remission was 64%, i.e. 95% for lymph node metastases, but only 40% for pulmonary metastases [36].

In long-term follow up of surviving young thyroid carcinoma patients, induction of second malignancies and fertility disorders are rarely seen. Girls treated with ^{131}I at young age generally have normal pregnancies and healthy offspring later on.

In children with recurrent or metastatic medullary therapy carcinoma radionuclide therapy (by targeting with MIBG, peptides or antibodies) may also be considered.

Neuroblastoma

Since 1984 therapeutic doses of ^{131}I-MIBG have been administered to children with metastatic or recurrent neuroblastoma failing conventional treatment [35]. Pooled results of major centers indicate an objective response rate of 51% (Tab. 3). Most patients had stage IV, progressive and intensely pretreated disease and were only treated with ^{131}I-MIBG when other treatment modalities had failed. Both the ^{131}I-MIBG therapy and the isolation are generally well tolerated by children; hematological side effects may occur. For patients with recurrent and progressive disease after conventional treatment ^{131}I-MIBG therapy is probably the best palliative treatment, as its invasiveness and toxicity compare favorably with that of chemotherapy and external beam radiotherapy [37, 38].

The therapeutic effect of ^{131}I-MIBG may be increased by combining it with chemotherapy and/or total body irradiation, but this is associated with severe toxicity. Less toxic is the combination of ^{131}I-MIBG therapy with oxygen treatment under hyperbaric conditions, by which the tumor cell is exposed to the toxic effect of hydroxyl radicals in addition to the radiation effect [39].

More recently, ^{131}I-MIBG therapy has been integrated in the treatment protocol as the initial therapy instead of preoperative combination chemotherapy in children presenting with advanced disease/inoperable neuroblastoma. The objective is to reduce the tumor volume, enabling adequate surgical resection and to avoid toxicity and the induction of early drug resistance. Chemotherapy is reserved to treat minimal residual disease postoperatively. Initial results demonstrated the feasibility and effectiveness of this approach: a higher objective response rate (> 70%) and considerably less toxicity compared to ^{131}I-MIBG therapy after conventional treatment [40]. ^{131}I-MIBG is equally effective as chemotherapy in attaining operability of neuroblastoma and the 5 year survival rate is not worse. Two new multicenter studies integrate upfront ^{131}I-MIBG therapy in the treatment protocol of neuroblastoma: patients with unresectable stage II and III neuroblastoma receive 2 cycles of ^{131}I-MIBG only prior to surgery; in patients over 1 year of age, with stage IV and unfavorable prognostic parameters (high risk group), the ^{131}I-MIBG therapy is intensified and combined with the topoisomerase I inhibitor Topotecan to enhance the radiation induced cytotoxicity.

Phase I studies of radioimmunotherapy using ^{131}I-UJ13A or ^{131}I-3F8 in small series of patients with stage IV neuroblastoma resulted in few objective responses and stabilization of disease, but this was associated with severe side effects and the induction of HAMA response limited the usefulness of repeated application. New developments in radioimmunotherapy of neuroblastoma include the use of chimeric antibodies, such as chCE7 and ch14.18. In nude mice with SK-N-SH neuroblastoma xenografts the therapeutic efficacy of ^{131}I-labeled anti-L1-CAM antibody chCE7 compared to ^{131}I-MIBG was demonstrated; the complementarity of these agents, as shown by comparative scintigraphic studies in patients, underline the heterogeneity of this disease and may have implications for radionuclide therapy of neuroblastoma in the future [24].

Osteosarcoma

Therapeutic bone-seeking radiopharmaceuticals, such as ^{89}Sr-chloride, ^{186}Re-HEDP and ^{153}Sm-EDTMP, may be indicated for the palliation of painful skeletal metastases of various tumors, provided that bone scintigraphy shows intense ^{99m}Tc-diphosphonate uptake at metastatic sites which are painful. In case of metastatic osteosarcoma, this treatment may be directed at both the skeletal and extraskeletal metastases (e.g. lung or painful pleural lesions) [41]. Theoretically, bone seeking agents may also been used preoperatively in patients with inoperable osteosarcoma, but in practice chemotherapy is used.

Lymphoma

Although, at this time, radioimmunotherapy of recurrent lymphoma is not practiced in children, it should be noted that this treatment is attaining overall objective response rates of around 70% in adults with recurrent B-cell lymphoma [42]. Several protocols are undergoing clinical investigation: either immunotherapy using unlabeled anti-CD20 antibodies, or radioimmunotherapy with non-myeloablative doses of ^{131}I- or ^{90}Y-labeled anti CD20 or with myeloablative doses of ^{131}I-anti CD20 antibodies,requiring autologous bone marrow or peripheral stem cell reinfusion. The reported objective response rates of radioimmunotherapy are better than those of immu-

notherapy, and with myeloablative therapy higher than with non-myeloablative therapy. It may therefore be a matter of time before such protocols become active in pediatric oncology too.

Conclusions

The role of nuclear medicine in pediatric oncology is expanding:

— in tumor imaging the focus of interest is shifting from tumor detection to tumor characterization and early prediction of response;
— digital matching of functional parameters (SPECT/PET) with anatomical parameters (CT/MRI) provides greater accuracy in detection, staging, follow up and radiation therapy planning;
— as a functional modality nuclear medicine is highly suited for monitoring the function of organs, which are at risk during oncological therapy;
— also in children therapeutic nuclear medicine can provide an effective, systemic, but relatively noninvasive treatment, which is associated with limited toxicity and few long-term effects;
— pediatric nuclear oncology requires a close collaboration between pediatricians and nuclear medicine physicians.

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