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Radiotherapy in pediatric head and neck tumours

I. Rutten, J.-M. Deneufbourg

Department of Radiotherapy, Centre Hospitalier Universitaire, B-4000 Sart Tilman Liège, Belgium

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Abstract. *Radiotherapy in pediatric head and neck tumours.* According to international protocols, radiotherapy remains a part of the treatment of several pediatric ear, nose and throat tumours. The role of radiation therapy in the treatment of rhabdomyosarcomas, non-Hodgkin's lymphomas, nasopharyngeal carcinomas, osteosarcomas and juvenile nasopharyngeal angiofibromas is reviewed. The main complications of this type of treatment in children, as well as their management, are described. Finally, we discuss how several technical advances (increased fractionation of the dose, various types of stereotactic radiotherapy, use of tridimensional treatment planning systems) help the radiation oncologist to minimize the toxicity of the treatment for healthy tissues.

Introduction

In some tumours, such as rhabdomyosarcomas, nasopharyngeal carcinomas and malignant schwannomas, radiotherapy is very useful to obtain a local control, which is mandatory for survival.

The efficacy and complications of radiotherapy are the result of the action of ionizing radiation on cell DNA. Dividing cells are the main targets. The difference between the toxicity of the treatment for the tumour versus healthy tissues is therefore lower in children than in adults. This explains the great sensitivity of the child to radiotherapy. It is important in this respect to distinguish between two types of toxicity of irradiation in children (1). Complications related to delayed necrosis are comparable to those encountered in the adult and are usually seen with high doses. On the other hand, "developmental toxicity" is usually seen at doses equivalent or inferior to those needed to treat tumors.

Irradiated healthy tissues will become hypotrophic and their function will be altered. The severity of these effects will depend on the age of the child, the dose of radiation, previous and concomitant treatments (surgery and/or chemotherapy), and the technique which is possible to use according to the clinical situation.

We will first discuss the role of radiotherapy in the most common pediatric head and neck tumours, with the exception of most orbital cancers and of thyroid cancers. Secondly, complications of the treatment will be considered. Finally, new techniques in this field will be described.

Role of radiotherapy in head and neck tumours

Rhabdomyosarcomas

Guidelines for the treatment of rhabdomyosarcomas are based on studies performed by

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the Intergroup Rhabdomyosarcoma Study Group and by the International Society of Paediatric Oncology (2). Radiotherapy is able to control both microscopic and gross tumour. Although one early study suggested little benefit from radiotherapy on survival in the group with no microscopic residual and no lymph node disease, an analysis performed later showed a high relapse rate in the patients with unfavorable histology which had not received radiotherapy. Therefore, a large proportion of children with a diagnosis of rhabdomyosarcoma are currently irradiated (3), especially when complete remission is not obtained with chemotherapy (2).

There is general agreement that the total dose used should be at least 45 Gy, although associated chemotherapy may turn out to allow a reduction of this dose. A dose of at least 55 Gy should be used when gross residual disease is present. A margin of 3 to 5 cm around the tumour volume is often used because of the high ability of these tumours to infiltrate healthy tissue. However, it is possible to use the so-called "shrinking field" technique, in which a progressively smaller volume is irradiated above a certain dose. This allows to minimize damage to surrounding tissues (3).

Combined treatment of head and neck rhabdomyosarcomas with surgery, multidrug chemotherapy and radiotherapy has allowed to increase the overall 5-year survival to 74%, as shown by KRAUS *et al.* (4). This study showed that local failure was mainly responsible for the death of 14% of the patients at 5 years. In the case of residual or recurrent disease after chemotherapy, a preliminary report suggests the usefulness of a new approach which includes surgical ablation, embedding of a mould with subsequent brachytherapy and reconstructive surgery (5).

Techniques of irradiation of these tumours should be adapted for each site. Orbital RMS are not classified as parameningeal tumours because of their good prognosis (see Fig. 5 of Ref. 2). However, because of the tendency of these tumours to extend posteriorly, an adequate coverage at the optic canal region is critical.

On the other hand, nasopharyngeal RMS are classified as parameningeal tumours and frequently invade bones. The CNS is sometimes invaded as well. Treatment mainly includes chemotherapy and locoregional radiotherapy. In some cases, the irradiated volume should include cranial meninges at the base of the skull, using adequate margins. Three dimensional treatment planning (see below) allows to improve coverage of the tumour and sparing of critical structures (6). When extensive bone destruction is present, the risk of local failure is high, even with a total dose of 60 Gy. Hyperfractionation regimens (see below) may be useful in this case. There is no reason to use prophylactic whole-brain irradiation when there is no clear evidence of CNS invasion.

Similar problems of bone and CNS invasion are encountered with middle ear RMS. Large margins need to be used. However, in order to minimize damage to various structures, it is often necessary to use shrinking fields.

Non-Hodgkin's lymphoma

Recommendations about the treatment of localized non-Hodgkin's lymphoma in children have changed over time. Although radiotherapy was generally used in addition to chemotherapy in the eighties, an influential randomized study performed by the Pediatric Oncology Group showed no benefit of adding radiotherapy to chemotherapy (7). Radiotherapy is therefore rarely used in extranodal head and neck non-Hodgkin's lymphoma, although it has been recently suggested that it may be useful in tumors of intermediate and high malignancy, at least in a general population of patients (8).

Nasopharyngeal carcinoma

Although this tumour is rare in Western countries, its incidence is much higher in some areas of Africa and Asia because of virologic

(Epstein-Barr virus), environmental (salt-cured fish and meat) and genetic factors.

Radiotherapy is an essential part of the treatment of this disease, even if the addition of various schemes of chemotherapy is clearly beneficial (9, 10). Treatment of NPC by radiotherapy in children is similar to the one in adults. The target volume encompasses the nasopharynx and often the base of skull. Until now, chemotherapy does not allow a dose reduction in areas of gross disease. The dose for definitive radiation therapy is in the range of 65-70 Gy (11). Data in adults suggest that brachytherapy, radiosurgery or twice daily fractionation could have a role in the localized "boosting" of the dose.

Osteosarcomas

Primary osteosarcomas of the mandible and maxilla have a better prognosis than those at other sites (12). Moreover, in a study comprising 33 patients out of which 11 were children, the latter had a better outcome, 10 of them being long-term survivors (13). Most early studies showed a beneficial effect of radiotherapy on survival. However, because chemotherapy protocols are increasingly effective, its use is currently being questioned.

Juvenile nasopharyngeal angiofibroma

These are histologically benign but locally invasive tumours. Their preferred treatment is surgical, although this surgery is very difficult and needs to be performed by an experienced team. Radiotherapy is used when the initial size of the disease is too large for a safe excision. Based on the available studies, doses of 40 Gy or more should be used. Responses of this tumour to irradiation are typically very slow. A recent study also suggests the usefulness of radiotherapy (30 Gy) when a recurrence is demonstrated (14). The authors, however, stress the fact that tumor remnants in symptom-free patients should only be monitored by CTscan because they are likely to involute over time. Such a situation was encountered in 20% of the patients.

Rare pediatric head and neck tumours

Radiotherapy is used in subgroups of patients with neuroblastoma, esthesioneuroblastoma, Langerhans cell histiocytosis or giant cell tumours. It is usually not indicated in childhood parotid tumours (15).

Complications of radiotherapy

The main types of toxicity which are observed are the following (see RUBIN *et al.* (16) for a review).

First, musculoskeletal abnormalities can be induced. They include fibrosis of soft tissues and bone atrophy, which leads to various types of abnormalities (17). To minimize their visibility, a symmetrical technique has to be used (1). Complications of growth and development are especially frequent in rhabdomyosarcoma because young children are affected. In few cases, cosmetic surgery may be performed later.

Hyposialorrhea and its consequences (caries and other dental problems) are observed if at least part of the salivary glands cannot be spared. Recent reports show that the use of pilocarpin, either in a systemic or in a topical form, efficiently decreases xerostomia in these patients (18, 19), thereby confirming results of earlier studies. In addition, radiotherapy causes abnormalities of dental development. Toothbuds have to be shielded if this does not interfere with the efficiency of the treatment. Intensive fluoride treatment and specialized dental care have to be applied.

It is important to point out that radiotherapy enhances cis-platinum ototoxicity, in particular if the drug is given after the radiation.

Several types of toxicity can be observed in the eye if it is close to the tumour site (cataracts, corneal and retinal lesions, optic neuritis). They should be managed by a specialist.

Finally, the CNS and pituitary gland have to be protected as well as possible. However, because of the extension of the tumour, protection is often impossible in children with

nasopharyngeal carcinoma. This implies a careful and lifelong follow up of hypothalamic-pituitary hormonal function in cured patients.

New techniques

Research is being carried out in many fields of radiotherapy in order to minimize the toxicity to healthy tissues.

Ongoing studies examine the possible usefulness of increasing the fractionation of the total dose (e.g. two daily sessions instead of one). According to radiobiological models, giving the same total dose in more small fractions should be as efficient but less toxic in terms of late sequelae. This prediction has been confirmed clinically in a large population (n = 941) of adult patients treated for nasopharyngeal carcinoma (20). The use of 2.5 Gy instead of 4.2 Gy fractions produced a four-fold decrease (from 18.6 to 4.6%) in the incidence of temporal lobe necrosis in this group. Theoretically, these very encouraging results could allow an increment of dose without a parallel increase in complications. Some clinical studies are addressing these questions in pediatric malignancies.

It is now possible to better focalize the beam on the tumour, in part thanks to improvements of imaging techniques and of tridimensional treatment planning systems. The interaction of a software with a virtual patient defined by a CT scan allows a greater anatomic and dosimetric accuracy. Treatment planning may be performed directly on the CTscan matched with other imaging techniques (MRI, positron emission tomography). This is called "virtual simulation" (Fig. 1). This type of simulation does produce clinical benefits, as shown in a recent study on 78 (mostly adult) patients treated for nasopharyngeal carcinoma (21). Patients who underwent virtual simulation were found to have significantly less severe xerostomia than those who had had a conventional simulation. Currently, an effort is also made to conform the dose distribution

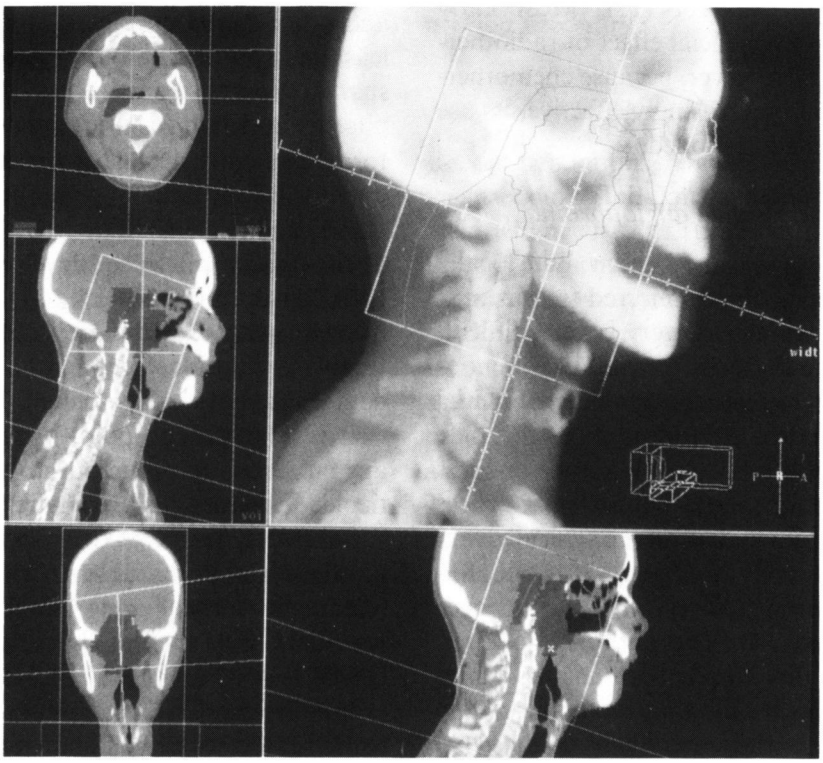

Fig. 1
Example of tumour localization by imaging.

to the shape of the tumour, using so-called "multileaf collimators".

On the other hand, we can now use stereotactic radiotherapy, which may be indicated for example in skull base tumour relapses. A unique dose can be used (radiosurgery), but a fractionated treatment seems more attractive from a radiobiological point of view in a lot of circumstances (but see below). In short, a stereotactic frame is fastened on a repositionable, non-invasive mask on the head of the patient. The fiducials of this frame constitute a three-dimensional reference system which is used for imaging, dosimetry and treatment. Arcs allow to concentrate the dose at their convergence point (Fig. 2). Reasonable sparing of surrounding brain tissue is obtained.

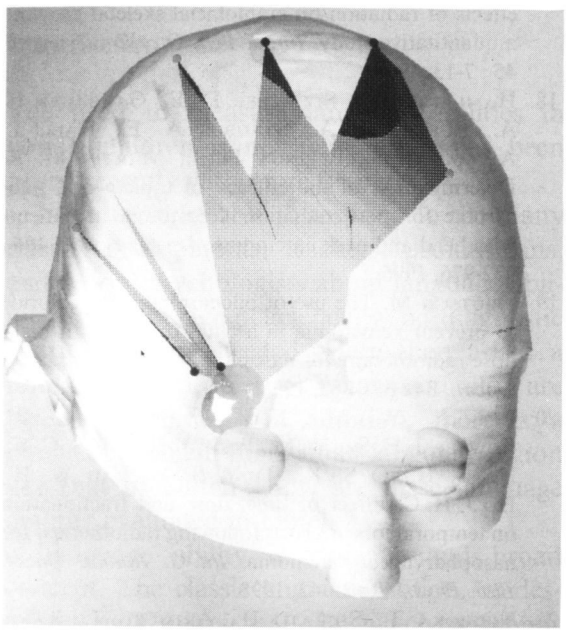

Fig. 2
Example of the use of arc-therapy on a skull base target, which is localized stereotactically.

Radiosurgery was used successfully in 13 patients who had malignant tumors of the skull base (22). These patients had had repeated tumor resections or irradiation and could not anymore be treated by surgery or conventional radiotherapy. Five patients had sarcomas (of which one child) and all of them responded to the treatment, with four of them alive after a follow up of 2 to 5 years. This study suggests that radiosurgery may be an effective tool in such a clinical situation.

Another example of technical research is the modulation of the beam intensity as a function of healthy organs that the beam meets in the different directions (Fig. 3).

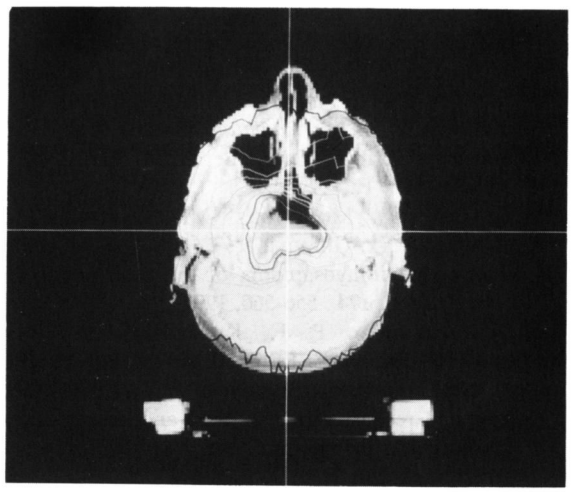

Fig. 3
Example of dose distribution when using intensity modulation.

Finally, the effectiveness of brachytherapy has been well documented in the adult. This surgical implantation of radio-active wires is used for well-localized irradiations (e.g. see Ref. 5).

Conclusion

Although many technical advances are being made in the field, radiotherapy still induces important sequelae in children. Further multidisciplinary effort is needed to find less toxic, yet effective protocols for the treatment of pediatric tumours. Furthermore, there is a need for a classification of this group of tumours according to their behaviour and their aggressiveness. It is likely that this will be possible with the development of modern histopathological techniques and will help to better delineate the indications of the various irradiation techniques that are available.

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Isabelle Rutten, M.D.
Department of Radiotherapy
Centre Hospitalier Universitaire
B-4000 Sart Tilman Liège, Belgium