1 Introduction

Cancer is a relatively rare disease in children with an annual frequency of 13-14 in 100,000 children up to 15 years. (3) It accounts for less than 1% of all cancer in industrialised countries. However, cancer represents the second leading cause of childhood death in children 1-14 years old in developed countries, following accidents. In developing countries, infections still represent the major cause of childhood death, as it was 100 years ago in the industrialised countries.

Leukaemia and lymphoma represent the most frequent paediatric malignancies (about 35% and 12%), followed by tumours of the CNS (central nervous system) (about 17%). All other entities are less frequent - bone tumours (5%), soft tissue tumours (7%), neuroblastoma (8%), nephroblastoma (7%), and germ-cell tumours (about 4%). (3,22) Several types of these malignancies are specific to children, in particular the "blastoma"- type.

Cure rates have improved significantly during the last three decades in the majority of paediatric malignancies reaching a 5 year overall survival rate of 70%. (3,22) This progress was mostly due to the introduction of chemotherapy into multimodal treatment protocols in these chemosensitive tumours during the 70ies and 80ies. Surgery and radiotherapy, however, still play a major role in achieving local control. Radiotherapy nowadays plays a major role in the treatment of Hodgkin’s disease, CNS tumours, Ewing’s and soft tissue sarcoma. During the last decade, the intensity of systemic and local treatment has been increasingly tailored according to certain risk groups. In low and medium risk groups, the overall burden of treatment has been reduced in order to reduce long term morbidity in the large population of long term survivors.

The growing normal tissue in the child is very radiosensitive, in particular soft tissue and bone. Therefore, one of the main goals in treating paediatric malignancies with a high cure rate is to avoid radiation related long term morbidity. (5,6,9,16) The development of radiation morbidity is associated with several risk factors: sequelae are more pronounced the younger the child at the time of treatment, the higher the radiation dose, and the larger the volume of healthy tissue included in the radiation field. (22)

Treatment strategies directed towards the reduction of late side effects have significantly increased interest in brachytherapy, in particular of soft tissue sarcoma and clear cell adenocarcinoma, as in these malignancies often only a limited target volume needs to be treated by a significant radiation dose. Radical surgery does not play a major role, as this usually leads to mutilation. These requirements closely match the major advantage of brachytherapy which is to deliver a high radiation dose to a well defined limited volume with a sharp dose fall-off. This results in a reduction of the treated and also the irradiated volume compared to external beam therapy (even conformal therapy) and can thus minimise late side effects, especially radiation induced impairment of bone and soft tissue growth in these young children (mostly aged under 10).

The clinical experience mainly collected by the IGR group (10,16,20,26) and some other groups (2,4,7,23,25,28,29,31) has shown that it is feasible to adapt brachytherapy procedures used in adults to clinical situations which are relevant for paediatric malignancies (gynaecology, head and neck, urology, soft tissue). Taking into account radiobiological considerations and the experience collected so far, LDR brachytherapy seems to be most appropriate for paediatric malignancies, helping to
reduce the probability of late effects to normal tissue close to the target volume. PDR brachytherapy may replace LDR brachytherapy as it demonstrates comparable advantages and allows for more flexibility due to the stepping source technology. With HDR brachytherapy little experience has been collected so far; it should be used with great caution and only with small doses per fraction. (27,29,30)

Due to the favourable results, this experience is now being enlarged as brachytherapy has been introduced at least as one treatment option into the organ sparing multidisciplinary treatment protocols for soft tissue sarcoma of the large trial groups in North America (Intergroup Rhabdomyosarcoma Study (IRS), (22) in Europe (SIOP Malignant Mesenchymal Tumour Study (MMT), (33) and in German speaking countries (GPOH Cooperative Weichteilsarkom Studie (CWS). (31) These treatment protocols address brachytherapy as a treatment option within primary treatment. However, in locally recurrent disease the role of brachytherapy may be even more important according to the experience of IGR and of the German CWS Recurrence Trial. (10,16,18,31)

2 Anatomical Topography

For sites relevant for brachytherapy, the anatomy and topography in tumours of children are comparable to those in adults. However, depending on the age of the patient, the dimensions are of course much smaller, which is specifically important for the shape and size of the target volume and for the relationship of critical organs to the target volume.

Furthermore, radiosensitivity in the growing child is dependent on the period of development (most pronounced in the young child) and on the tissue involved. Detailed study of the different anatomical sites with their different tissues involved and their specific radiosensitivity is essential. (22) Anatomical descriptions for a given site found elsewhere in this book should be studied in detail (e.g. head and neck, gynaecology, prostate, trunk and limb).

The very high radiosensitivity of tissues in growing children may lead to significant long term sequelae (after years and decades), in particular to severe growth, cosmetic and functional impairment. However, it is beyond the scope of this chapter to give details for the different tissues at risk; the reader should study a comprehensive textbook. (22)

Some basic parameters must be considered in the development of late effects with regard to different critical organs: the treated volume, the total delivered dose, and the dose rate.

- It has been clearly demonstrated that volume treated plays a crucial role in the expression of late effects, but no precise data have been published for paediatric malignancies to date.
- There is clear correlation between the amount of radiation dose and the induction of late effects. Different treatment protocols and different tumour sites must be studied in detail to determine the most appropriate therapeutic window. The tolerance dose is different from organ to organ and also depends on the age of the child and the developmental status of the respective organ. Furthermore, it must to be kept in mind that most radiation tolerance doses have been derived from long term experience after classical external beam radiotherapy.
- For the dose rate, the radiobiological advantages of LDR brachytherapy in minimising late effects must be taken into account. Late effects increase with dose rate. For HDR brachytherapy, the delivered dose must be therefore well fractionated with a low dose per fraction as in external beam therapy, to try to improve the tolerance of normal tissues and to reduce the potential for late sequelae. For PDR brachytherapy, the total dose, the dose per pulse and the dose rate should be chosen in the light of experience with LDR brachytherapy and external beam irradiation.
3  Pathology

3.1  Soft tissue sarcoma

Soft tissue sarcomas are divided into rhabdomyosarcoma (RMS) and soft tissue sarcomas other than rhabdomyosarcoma. (22) 80% of rhabdomyosarcomas are of the embryonal subtype and 20% alveolar which carry a worse prognosis. Prognosis is also defined by an international grouping classification.

In RMS the classical distinction is made between the embryonal subtype accounting for approximately 80% of all RMS and the alveolar subtype for about 15 - 20%. Botryoid RMS and a spindle-cell variant are both related to embryonal RMS and the solid alveolar variant to the alveolar RMS.

Recently, an international classification has been introduced which groups the different histological subtypes according to prognosis. (33) Group I has a superior prognosis and includes botryoid RMS and spindle-cell RMS; group II has an intermediate prognosis and includes embryonal RMS; group III has a poor prognosis and includes alveolar RMS and undifferentiated sarcoma.

Soft tissue sarcoma other than rhabdomyosarcoma are much less frequent and comprise a large variety of different histologies, often similar to soft tissue sarcoma in adults (Synovial Sarcoma, neurogenic sarcoma, fibrosarcoma, malignant fibrous histiocytoma, alveolar soft part sarcoma, epitheloid sarcoma, extraosseus Ewing’s sarcoma and primitive neuroectodermal tumours, sarcoma not otherwise specified. (22))

Most brachytherapy experience has been with RMS, but soft tissue sarcomas other than rhabdomyosarcoma in principle also qualify for brachytherapy if the essential indication of brachytherapy is met which is a well defined limited volume.

3.2  Clear cell adenocarcinoma

Clear cell carcinoma has an identical histopathological appearance in the different tumour localizations in the gynaecological tract. The macroscopic tumour aspects are comparable to those noted in adult patients with glandular carcinoma of the cervix.

Histopathology typically shows clear cells or tubulo-cystic structures surrounded by typical flat cells. (“clou de tapissier”) (34)

Clear cell adenocarcinoma can be detected on a smear but cannot be differentiated from a non specific adenocarcinoma. Detection may therefore be difficult; up to 25% of PAP smears are negative in the presence of a clear cell carcinoma. (15) Electron microscopy appearances are similar to those of conventional microscopy but show intra-cytoplasmic glycogen and apical microvillocities. (34)

4  Work Up

As primary chemotherapy is used in most chemosensitive paediatric soft tissue sarcoma protocols, tumour extent must be assessed at diagnosis, after surgery and after tumour shrinkage due to chemotherapy, usually at the start of local radiotherapy. Different diagnostic procedures are necessary for different tumour sites (e.g. gynaecology, urology, head and neck…). Clinical examination is an important part of tumour assessment at the time of diagnosis, after surgery and after induction chemotherapy and may be assisted by endoscopy.
Magnetic Resonance Imaging nowadays represents the most important imaging tool for tumour assessment in soft tissue sarcoma, in the head and neck, pelvis, trunk and extremities.

In selected cases, ultrasound and/or computed tomography may also play an essential role. A biopsy of the soft tissue mass is taken to confirm the diagnosis of a malignant tumour and to arrive at a definitive histology including histological subtyping. If appropriate, surgery is carried out to remove the tumour mass completely, or to reduce the tumour volume as much as possible. Surgery which would lead to significant long-term morbidity is avoided whenever possible. Wide or radical resection, relevant for adult soft tissue surgery, is usually not performed in paediatric RMS. Surgery as local resection may be performed at diagnosis and/or after induction chemotherapy as secondary or delayed surgery for residual tumour.

Chest radiograph, CT scanning and radionuclide bone scanning are needed to detect any distant metastases.

The work-up defines a tumour stage at diagnosis in every case and an additional TNM assessment after primary or secondary surgery (pathological stage).

4.1 Clinical stage at diagnosis

The stage at diagnosis (clinical stage), derived from the SIOP experience, (33) is nowadays mainly related to the extension of the tumour (T1: confined to anatomic site of origin; T2: extension beyond), the size of the tumour (a: < 5 cm, b: > 5 cm), presence/absence of lymph nodes and distant metastases (TNM system). Stage, tumour site and histology are the major prognostic factors at diagnosis. The favourable tumour sites are orbit, non-parameningeal head and neck, genitourinary non-bladder, non-prostate. The current pretreatment staging system is based on the recommendations of an international rhabdomyosarcoma workshop and includes the following: (22)

**Stage 1** includes any T, any N, and M0 in favourable tumour sites as orbit, head and neck (non-parameningeal), genitourinary (female genital organs, paratesticular, etc.) and carries an excellent prognosis.

**Stage 2** includes small tumours (T1/2a) with N0/Nx, M0 in bladder/prostate, in an extremity, in head and neck (parameningeal), and in others (trunk, retroperitoneum, anus-rectum, thorax-abdomen) and carries a good prognosis.

**Stage 3** includes larger tumours T1/2 b with or without lymph node involvement (N0/N1), also T1/2a N1 without distant metastases at the same sites as in stage 2 and carries an intermediate prognosis.

**Stage 4** includes all patients with distant metastasis in any tumour site and carries a poor prognosis.

4.2 Post-surgical pathological stage

The post-surgical histopathological classification (pathological stage), derived from the IRS experience, (22) is related to the tumour extent at diagnosis (T1/T2) and the amount of residual disease after surgery. In addition, T0 is introduced which applies if there is no evidence of tumour found on histological extension. Clinical stage cT1 and cT2 translate into pathological stage pT1 and pT2, if the excision was complete and the margins are histologically tumour free. Pathological stage pT3 applies for cT1 and cT2 if the excision was incomplete and is divided into pT3a for microscopic residual disease and into pT3b for macroscopic residual disease. The majority of patients are attributed to pT3.
After induction chemotherapy the amount of response is documented using the appropriate diagnostic tool.

In order to tailor the treatment to the overall prognosis, the response to treatment and the post surgical stage are added to the prognostic factors known from the time of diagnosis (clinical stage, site, histology). Based on these parameters, specific treatment groups are determined at diagnosis and after re-staging defining the overall risk of failure: low risk, standard (intermediate) risk, high risk. The amount of treatment with regard to systemic and local therapy is stratified according to these risks. (3,22,33)

In non-chemosensitive paediatric soft tissue sarcoma which represents a part of the soft tissue sarcoma other than rhabdomyosarcoma (in particular grade 1 sarcoma), the work-up is similar to that described for brachytherapy of soft tissue sarcoma in adults.

4.3 Clear cell adenocarcinoma

The work-up for clear cell adenocarcinoma of the cervix and of the vagina in children or adolescent patients is comparable to that indicated in adult patients (see chapter on Gynaecology). Nevertheless, the treatment should be as conservative as possible. A very precise local and locoregional evaluation must be performed of the size and shape of the vagina and the cervix, the tumour volume and possible spread to adjacent structures, and the lymph node status. (12,15,16) Ultrasound, CT scan and MRI are essential.

First, surgery is performed with exploration of the abdominal cavity, iliac lymph node excision completed by para-aortic lymphadenectomy when pelvic nodes are involved, and ovarian transposition. Conventional laparotomy should be replaced by a laparoscopic approach whenever possible. (16,17)

5 Indications, Contra-indications

The place of radiotherapy and more particularly brachytherapy differs according to the chemosensitivity of each tumour and the possibilities of a non mutilating surgical procedure. Soft tissue sarcomas, in particular rhabdomyosarcomas, and the majority of germ cell tumours are chemosensitive and radiosensitive, whereas for example clear cell adenocarcinoma of the cervix or vagina is very insensitive to chemotherapy. Therefore, radiation therapy plays the major role in the treatment of clear cell adenocarcinoma.

5.1 Soft tissue sarcoma

For soft tissue sarcoma, there has been a long tradition of multicentric trials in paediatric oncology, both in North America and in Europe. In Europe, there have been trials from the different national groups (Germany: CWS 81/86/91/96, Italy: RMS 79,87) and the International Society of Paediatric Oncology (SIOP), representing mainly the French and British national groups (MMT 75,84,89,94). Dependent on these different trial traditions, the place of radiation therapy in these protocols has been defined differently. (33,35)

Multiagent combination chemotherapy plays a major role in the treatment of all rhabdomyosarcomas. Initial chemotherapy consists of one of the following chemotherapeutic agents (Vincristine (V), Actinomycine D (A), Cyclophosphamide (C), Ifosfamide (I), Adriamycine (A), Etoposide (E)) in different combinations according to the risk from low to standard and to high risk: VA, VAC, VAI, VIE, IVA, VACA, VAIA, EVAIA. The European trial tradition has been based on initial chemotherapy
followed by a local conservative treatment to the residual tumour, partly with simultaneous chemotherapy, followed by a multiagent chemotherapy regimen for several months. (33,35)

For this conservative treatment, brachytherapy was integrated as one of the possible treatment options for residual disease after induction chemotherapy, which in these sites represents a significant risk for local failure. Brachytherapy was in particular indicated if a limited surgical resection would lead to mutilation and/or if external beam irradiation would lead to major long term sequelae. The main sites, shown to be suitable for brachytherapy are: head and neck (non-parameningeal: nasolabial sulcus, tongue, soft palate, floor of the mouth, neck…), gynaecological (vagina, uterus, vulva), urological (prostate, bladder), anus-rectum, tumours of the trunk and of the extremities, and eye-orbit in recurrent disease.

From trial results (IRS, SIOP, CWS, RMS), groups at high or intermediate risk of local relapse can be defined. (3,22,32,33). This risk is determined by combinations of the following parameters: the clinical stage at diagnosis (stage II or III), the site (non favourable), the histological subtype (alveolar or non RMS), the response to chemotherapy (partial remission or no response), and the postsurgical stage (pT3).

If there is local relapse after primary treatment, local treatment is crucial, as the tumour has been proven to be insufficiently chemosensitive. Radiotherapy and brachytherapy have a major role in this situation. As brachytherapy may be regarded as superior to external beam irradiation for limited disease, it should be used if possible in recurrent disease at least for the sites listed above. Brachytherapy to a limited volume may even be considered, if external beam therapy has been used within primary treatment.

5.2 Clear cell adenocarcinoma

For clear cell adenocarcinoma of the cervix and the vagina the role of brachytherapy is essential for the treatment of the primary tumour, as no other conservative treatment is available, except in very small tumours accessible to limited conservative surgery. Dependent on the findings of explorative surgery (involvement of lymph nodes, tumour extension) additional external beam irradiation is indicated. (5,17,24)

6 Target Volume

6.1 Soft tissue sarcoma

The target volume in soft tissue sarcoma is affected by various factors, but mainly by the overall risk group (low, intermediate, high risk). These factors are the following: tumour site including topography of the tumour itself (infiltrative growth/well defined borders) and its relation to organs at risk; tumour stage at diagnosis and after surgery (amount of residual disease); histological subtype (good, intermediate, poor prognosis); response to chemotherapy (complete/partial remission, no response); age of the child.

For defining the target volume for brachytherapy, the tumour volume at diagnosis, (after surgery,) and after induction chemotherapy must be taken into consideration. A precise clinical examination, if necessary under general anaesthesia, is done by the physicians who play an essential role in the treatment, i.e. the radiation oncologist who performs the brachytherapy and. e.g. the gynaecologist or urologist. The findings from this examination are integrated with information about tumour volume and topography from the different imaging procedures. For a gynaecological implant, e.g. considering the CTV to be treated, MRI should be performed before and during the implant with the (moulded)
vaginal applicator in place. Tumour thickness and the exact topography of the residual disease can be evaluated, and can be compared to the initial findings including the vaginal imprint.

If a surgical procedure is associated with brachytherapy the target volume is defined by the radiation oncologist together with the surgeon and the pathologist. With an intraoperative procedure, the target volume is more easily defined because of the direct view of the structures to be treated. Frozen sections obtained during surgery may lead to more appropriate management.

For children the target volume must be as small as possible because of the high risk of radiation morbidity, in particular the impairment of soft tissue growth and its possible adverse impact on cosmetic and functional outcome (Fig. 31.8 and 31.9). However, for reasons of local tumour control, it is also necessary to consider the initial tumour volume. In fact, the target volume is a compromise between initial and residual tumour volume taking into account the different variables listed below. For multimodal treatment (induction chemotherapy, surgical resection) there are in principle three situations that are most important for target volume definition:

* Residual macroscopic gross tumour: CTV is defined including at least the gross tumour volume after induction chemotherapy plus a considerable safety margin. In any case the initial GTV must also be taken into account.
* Residual microscopic disease (confirmed by pathology): For CTV the region of microscopic disease is included with some safety margin, also considering the dimensions of GTV at diagnosis. The volume can in principle be smaller than that for gross residual disease.
* No residual tumour as found out by clinical examination, imaging, or biopsy: if brachytherapy is considered, which is controversial, a target volume is defined, which will most likely prevent local recurrence without inducing major morbidity (e.g. prostate, cervix, tongue).

If radiotherapy (brachytherapy) is combined with surgery, the major first line treatment to the primary tumour in non chemosensitive soft tissue sarcoma, the situation in the paediatric patient is much more comparable to the situation in adult patients with soft tissue sarcoma (compare chapter 27 on soft tissue sarcoma). Nevertheless, the specific characteristics of the paediatric patient and of the paediatric malignancy must be taken into account.

In conclusion, in children, target volume must be defined as accurately as possible even more carefully than in the adult patient because of the potential induction of major radiation induced morbidity in normal tissue. Therefore, even if specific examinations or techniques for CTV determination cannot be used on a daily basis in adults, they must be introduced systematically in the target volume definition for brachytherapy in children (e.g. MRI at diagnosis, after chemotherapy and with the applicator in place).

6.2 Clear cell adenocarcinoma

Target volume in clear cell adenocarcinoma is defined as for cervix and vaginal tumours in adult patients treated by radical radiotherapy (brachytherapy alone or combined with EBRT). The aim of the treatment is to cure but also to preserve the different organs and to preserve as much as possible their integrity and their functions.

The target volume is therefore established according these different goals; the safety margin around the GTV must be limited to 10 mm anteriorly and posteriorly, but is larger laterally or in the vagina (15 - 20 mm). These dimensions for establishing the CTV are adapted to the GTV but also to the anatomy and to the age of the child.
7 Technique

In principle, there is no difference in the technique of brachytherapy between the adult and the paediatric patient. The major practical difference is caused by the dimensions of a child for which the specific technique which is typical for the specific tumour and site in the adult patient has to be adapted.

The following examples for brachytherapy techniques are described according to major locations which have been treated: head and neck (nasolabial sulcus, oral cavity, oropharynx, neck), eye-orbit, trunk, limbs, bladder-prostate, cervix/vagina/vulva, anus-rectum. These examples include different methods of brachytherapy (interstitial, endocavitary). Some procedures are or can be performed intraoperatively (bladder, prostate, trunk, limbs). Only a short description is given here; for detailed description we refer to the respective chapters in this book.

7.1 Head and Neck

The details for the techniques to be applied in oral-cavity, oropharynx, cheek and neck tumours are to be derived from the respective chapters in head and neck which should be adapted because of the small dimensions of the young child.

Nasolabial sulcus

Two sorts of manual afterloading systems can be used: plastic tubes and silk threads. The first uses a remote afterloading system, the second makes it possible to treat very superficial lesions or fragile structures. Both systems can be used together in the same implant (Fig 31.1A).

Usually, 3 to 5 lines are implanted when possible with 3 or less in one plane, otherwise in 2 planes; in the latter case, the different lines are alternatively placed parallel, creating an ideal equilateral triangle in the perpendicular central plane (Fig 31.1B)

Fig 31.1: RMS of the nasolabial sulcus (compare also Fig 31.8 (late effects in this patient)): A: Interstitial brachytherapy with a double loading system: 3 plastic tubes in the deep plane, two silk threads in the superficial plane. B: The 5 Iridium wires are checked on the AP radiograph to be used for the computerised dosimetry.
When three lines are disposed in one plane, the central line is parallel to the nasolabial sulcus basting it, the other two framing it.

In all cases, the different lines are parallel and equidistant to each other, the spacing between them is from 0.8 to 1.2 cm, and the length of the radioactive sources usually are from 2.5 to 3.5 cm.

The distal ends of the plastic tubes are maintained in good parallelism by a preperforated catheter placed perpendicularly to the tubes. When using the silk thread technique, they are knotted two by two, to maintain their position throughout the treatment. (1,9,11,13,16)

**Fig 31.2:** Interstitial PDR brachytherapy in a six year old girl with a soft palate rhabdomyosarcoma. Tumour size at diagnosis was 2.5 x 6 cm, which was partly exophytic and resected. After induction chemotherapy (VAIA) there was only microscopic residual disease at the basis of the former exophytic tumour at the soft palate. This CTV was implanted through the nasal cavity with two plastic needles and treated with 40 Gy by PDR brachytherapy with 50 cGy per pulse per hour (dotted line on lateral X-ray and coronal CT). After 7 years there is continuous complete remission with only a small deviation of the uvula with no functional impairment.

### 7.2 Eye-Orbit

**Fig 31.3:** Perioperative interstitial brachytherapy in RMS of the orbit (courtesy of G. Kovacs)  
A: CT control with 4 plastic tubes; B: Treatment plan with addition of EBRT and brachytherapy
Experience has been mainly collected with recurrent tumours after radiotherapy given in the primary treatment. Usually plastic tubes are implanted during an intraoperative procedure in which an attempt is made to remove tumour macroscopically as much as possible (Fig 31.3A,B).

### 7.3 Soft Tissue Sarcomas of the Extremities and the Trunk

A major goal is to avoid mutilation (enucleation, exenteration). Therefore, wide excision with generous safety margins can often not be achieved. The plastic tubes are implanted into the tumour bed and are often located along and parallel to the walls of the orbit towards its top in one or two planes (3 - 6 tubes). As the orbit is funnel shaped, there is no parallelism of the tubes towards the top. This disadvantage can be mostly overcome in using stepping source technology adapting the dwell times and positions to avoid major over- and/or underdosage.

Only the plastic tube technique can be used for this perioperative brachytherapy. After partial, or, if possible, total removal of the tumour, plastic tubes are implanted perpendicularly to the length of the operative bed, parallel and equidistant to each other. Usually they are implanted in one plane. The number of lines is a function of the target volume. The spacing between the lines is 1 to 1.5 cm. When closing the wound it is essential to maintain the tubes in an appropriate position according to the clinical and pathological parameters and also to respect the rules of implantation of the Paris system. (13,16,19)

In some situations e.g. for tumours at the inner surface of the thoracic wall or in the pelvis where only the surface tissue is at risk for recurrence a flap technique may be used. However, as this technique can only be used as an intraoperative procedure, HDR brachytherapy must be undertaken during surgery. Therefore, this technique must be used with great care (see below paragraph 9). (27,30,31)

### 7.4 Bladder-Prostate

In perioperative brachytherapy the surgeon uses a suprapubic approach. The plastic tubes can be implanted by this route or through the perineum. In both situations the afterloading system is the plastic tube. The plastic tubes are always parallel and equidistant to each other. They are generally in one plane for suprapubic procedures (Fig 31.4), and more often in two planes for perineal implants where the goal is to perform loops. (13,21)

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![Fig 31.4: Perioperative implant of a bladder tumour, the implant is done suprapublically. A: Check AP radiograph after the plastic tubes were loaded with iridium wire B: Check radiograph, lateral view](image-url)
This perioperative brachytherapy is a complex procedure and necessitates excellent collaboration not only between experienced surgeon and radiation oncologist, but also with the pathologist and radiologist.

Nowadays a perineal rectal ultrasound guided approach may be considered as used for brachytherapy of prostate cancer in the adult patient with plastic or steel needles. (13,21) Brachytherapy of the bladder requires a perioperative approach, comparable to that in the adult patient (Fig 31.4 A,B).

### 7.5 Vagina/Cervix (rhabdomyosarcoma), Vagina/Cervix (clear-cell adenocarcinoma)

In both situations, the use of a personalized moulded applicator is recommended as used for adult patients with gynaecological cancer (Fig 31.5A). Nevertheless, in children the cervico-vaginal impression is made under general anaesthesia often using a condom introduced into the vaginal cavity for easy removal of the impression from the vagina which is too small to receive liquid paste and strips. It is also more often necessary to push the impression out of the vagina with an intrarectal finger.

The following steps are identical to making a mould in adult patients: impression into plaster, rough mould, positioning of the catheters according to the anatomy and the CTV, making appropriate perforations including four small holes to suture the applicator with silk thread to the inferior lateral parts of the vagina (Fig 31.5B and C).

*A: Determination of the GTV on the vaginal impression; first step in making the applicator.*

*B: Personalised vaginal applicator containing four plastic tubes.*

*C: Check radiograph, lateral view, with 5 iridium wires: 1 in the uterine catheters, 4 in the vaginal applicator.*

*Fig 5: Vaginal RMS, residual tumour after chemotherapy: Intravaginal and intrauterine brachytherapy with a personalised mould applicator*
Based on the mould technique different techniques of application may be used with plastic tubes that can be afterloaded. (11,12,15) For clear-cell adenocarcinoma the same technique is used (Fig 31.6A-C).

**Fig 31.6:** Clear cell adenocarcinoma of the vagina
A/B: vaginal impression, perfectly showing tumour site and size (posterior and lateral views)
C: corresponding applicator with plastic tubes and delineation of GTV and projection of one radioactive source line on the surface of the applicator

### 7.6 Vulva

The same interstitial-brachytherapy technique used in adult patients can be employed for children.

### 7.7 Anus-Rectum

Almost one half of the circumference was involved. Brachytherapy was performed for microscopic residual disease after salvage combination chemotherapy with a specific applicator (A) based on X-ray (B) and MRI assisted treatment planning (C, see next page). A dose of 44 Gy was applied in multiple fractions of HDR brachytherapy.
Fig 31.7 (continued) After 11 years continuous complete remission with no impairment of anorectal function.

Fig. 31.7C: MRI based treatment planning with the applicator in place and an overlay of isodoses

The brachytherapy technique follows the principles used in the adult patient for anal cancer. However, the dimensions of the applicator must be especially adapted. One layer of plastic or steel needles (3 - 5) is implanted depending on the CTV. Specific care must be taken to keep the contralateral side of the rectal wall as far away from the needles as possible (with an obturator). (Fig 31.7A and B) (10)

8 Dose Calculation and Treatment Planning

The main goals of paediatric brachytherapy must be carefully considered in treatment planning. These are to achieve local control and preserve the function of the organ involved at the same time as reducing long term adverse side effects, in particular minimising functional and cosmetic impairment. Therefore, computer assisted dose calculation is always performed and treatment planning is systematically based on sectional images, preferably MRI.

For interstitial implants the computer assisted dose calculation is based on data from sectional imaging (PTV, organs at risk) with the implant in place taking into account the rules of the Paris system. The homogeneity criteria are carefully to be considered (reference isodose should be 85% of the mean central dose) and no large high dose volumes should be allowed. Dose-volume relations for organs at risk (including soft tissue and bone) are accurately assessed.

For intracavitary brachytherapy the calculation of dose distribution is complex and comparable to the situation in the adult woman. Computer assisted dose calculation is based on sectional image assisted assessment of the PTV and of critical organs with the applicator in place and leads to a dose distribution related to certain points and to certain volumes (PTV, rectum, bladder, bowel, bone). It is inadequate to prescribe the dose only to point A and B. The dose distribution at different levels (points, planes, volumes) according to the situation of the child must also be considered.

Computerized treatment planning systems are routinely used to obtain a better individualization and optimization of the dose distribution. Each source in LDR brachytherapy is regarded as independent in terms of radioactive length, time schedule, allowing for an individually designed brachytherapy. If a stepping source technology is used (PDR, HDR), the different locations and dwelling times of the sources must be carefully selected taking into account the dose distribution in the target and in the organs at risk.
9 **Dose, Dose Rate, Fractionation**

Total dose varies according to the aim of radiotherapy within the specific treatment protocol applied. Total dose in the treatment of recurrent disease is usually higher than for primary treatment.

**For interstitial or intracavitary brachytherapy alone,** the total dose varies from 32 to 45 to 60 Gy: 32 Gy for favourable prognosis disease, 45 Gy for standard prognosis (e.g. residual microscopic disease), > 50 up to 60 Gy for poor prognosis (e.g. gross residual disease) (CWS, SIOP, IRS). Decisions about dose depend on the individual prognosis of the child according to the specific risk group. The factors mentioned previously also influence the decision about total dose: tumour site, tumour stage at diagnosis and after surgery (amount of residual disease), histological subtype (good, intermediate, poor prognosis), response to chemotherapy (complete/partial remission, no response), dose volume relations in organs at risk, age of the child, place of brachytherapy within the treatment programme.

When given with external beam radiotherapy the dose delivered by brachytherapy is 15 - 20 Gy depending on the dose of external beam radiotherapy.

For gynaecological tumours in the majority of the patients, the brachytherapy is performed in one session; for other patients - for bulky tumour or where it is difficult to adapt the treated volume to the CTV - two, or sometimes even three sessions are necessary.

The greatest experience relates to LDR brachytherapy which is performed in one session in 80 - 90% of cases. The dose rate is low (0.4 - 0.6 Gy/h) to minimise late sequelae. The overall treatment time varies between one day and 5 - 6 days depending on total dose and dose rate.

There is scanty experience with PDR and HDR brachytherapy. If PDR brachytherapy is used, the dose per pulse per hour should be similar to the classical dose rate used in LDR brachytherapy with 0.4 - 0.6 Gy/h. In case of HDR brachytherapy high doses per fraction should be avoided, as they may lead to unacceptable long term morbidity. There has been some experience, with a fractionation schedule using fraction sizes similar to conventional fractionation in external beam therapy with 2 Gy per fraction and an 8 hour interval between each fraction allowing for sufficient repair of normal tissue.

For **clear cell adenocarcinoma** the preferred treatment protocol is the following:

In all cases, the treatment of the primary tumour includes a LDR brachytherapy, preceded by pelvic external beam irradiation of 20 to 30 Gy for bulky tumours and up to 40 to 45 Gy if there is nodal involvement. The dose of LDR brachytherapy is 60 Gy delivered to the PTV for brachytherapy alone, or 60 Gy minus the dose of EBRT if given in combination. In both cases the dose and consequently the CTV is adapted to the dose to the critical organs.

10 **Monitoring**

During irradiation, regular checks must be carried out as for adult patients, but specific checks are mandatory dependent on the age of the child and the support of the family. The bedroom is equipped with TV monitoring and viewing facilities.

First, to preserve the quality of the implant, it is necessary to check clinically twice a day that there is no displacement of the plastic tubes or needles (radioactive sources) in an interstitial brachytherapy
or of the applicator (mould) in endocavitary brachytherapy. X ray or sectional image control is always mandatory when there is any suspicion of movement of the material. The major problem during continuous or pulsed irradiation for a time period of several days is the compliance of the young child. The whole team including the brachytherapist, nurses, technologists, anaesthesiologist, psychosocial staff, family and paediatric oncologist must collaborate closely to support the child in coping with the various situations creating discomfort.

To minimize pain and psychological problems related to isolation, a “preventive” anaesthesiological programme is usually set up including some sedation and pain treatment and thus reducing discomfort. The continuous support of the family and the care of the nurses is crucial throughout the day and night and in particular during meals. With regard to other forms of supportive and “preventive” care (e.g. anti inflammatory treatment, antibiotics), these depend on the site, the procedure and the specific risks. In general, they are similar to those in adults (see the respective organ chapters).

Some authors, who favour HDR brachytherapy, point out the disadvantages of the LDR technique which also partly apply to PDR brachytherapy: sedative treatment for children, risk of displacement of the implants, radiation exposure to the staff and the parents, psychological impairment. Of course, all these considerations must be taken into account at the time when the dose rate is chosen. However, the great experience with LDR brachytherapy shows that these different problems have been managed successfully in different institutions, and they seem to be of relatively minor importance when compared with the long term results, in particular in terms of minimizing late side effects.

11 Results

11.1 Local control, survival

The largest and most recent study was done in the Institut Gustave-Roussy (18) including 131 patients (no retinoblastoma, CNS primary malignancy and clear cell adenocarcinoma) with a mean age of 4.8 years. The main tumour sites were: head and neck 35.1%, trunk-limbs 12.3%, lower gynaecological tract 24.4%, bladder-prostate 19.1%, other pelvic organs 9.1%. LDR brachytherapy was combined with other treatment modalities including chemotherapy, conservative surgery and in few cases external beam irradiation (13.6%). Brachytherapy was done as salvage treatment in more than one third of patients. Overall the 5 year results (Kaplan-Meier) were: survival 70%, local failure 23.7%, metastases 24.6%; complications 28.2% (Gr 1 3%, Gr 2 12.9%, Gr 3 12.2%); among causes of death there were only 8.4% local failures. Results for different tumour sites are given below.

Gynaecological tract (RMS): Most patients (24/30) were treated with endocavitary brachytherapy as part of the primary treatment. The survival rate was 80% and local control rate close to 90%. (12,18) According to a long term analysis (5) in patients treated before 1978 with a minimum follow-up of 10 years the pubertal growth spurt occurred in virtually all children if prior ovarian transposition was performed. (14,16,20) An active sexual life was possible in more than half. Two women gave birth to three healthy children. (16) In children receiving less than 60 Gy at low dose rates in this historical series the long terms side effects were much less obvious.

Bladder-prostate: Among 18 patients who were exclusively treated by brachytherapy, there were 5 local, 2 nodal and 1 local and nodal recurrence. Among 5 patients treated for recurrence, 3 were in continuous complete remission after 4 to 11 years. No serious long term complications were observed. (18,20)

Head and Neck (nasolabial sulcus): Among 16 patients treated with brachytherapy alone, there were 2 local recurrences, one of these a combined local and nodal recurrence. Among 3 patients
treated for recurrence, there was one nodal recurrence. 13/19 patients are alive after a mean follow-up of 12 years. Among the causes of death, 4 were due to nodal progression and 2 to metastatic disease. Significant cosmetic side effects in the soft tissues of the face (Fig 31.9A-B (same patient as in Fig 31.1A-B); Fig 31.10A-D) and bone have been observed in 4 children requiring cosmetic surgery. (1,18)

**Trunk and Limbs:** The results of soft tissue sarcomas of the trunk and limbs were the worst observed in the Gustave Roussy series when compared to those obtained in other tumour sites. The 3 year survival rate was 68%, the local failure rate 31% ± metastases 50%. (13,16,18)

The Institut Gustave-Roussy results are comparable to those published by other groups. Fontanesi et al (7) report about 48 children treated at St. Jude Hospital with 62 LDR implants: at 5 years disease-free survival was 75%, local control rate 86%, complication rate 26%. All other series report small patient numbers, but similar results.

For **PDR and HDR brachytherapy** there is very limited experience reported in the literature. Nag et al. (29) and Pötter et al. (31) report on small patient numbers at different sites (head and neck, pelvis, trunk, limbs) with local control in 11/13 and 9/12. As follow-up is short, no data on late side effects are given.

**Clear-cell adenocarcinoma:** The largest number of patients were treated at the IGR. (12,15,16,17) In this series of fifty patients who underwent brachytherapy (cervix 28%, vagina 25%, combined 47%) there were 20% in FIGO stage I, 40% in stage II, 25% in stage III, 15% in stage IV and overall 32% with positive pelvic nodes. The 2-year survival rate was 83 - 95% for stage I and II, 57% for stage III and IV, 90% for those with negative nodes and 50% for those with positive nodes. Complete conservative organ sparing treatment was achieved in 70% and each of two patients gave birth to a healthy child (Fig 9). (15,16)

### 11.2 Adverse side effects

The problem of tolerance, early reactions, late effects and complications in children irradiated for cancer, constitutes a crucial point. As was said before, the normal tissue of a child is very radiosensitive, and the radiation morbidity is correlated to the age of the patient, to the delivered dose and to the irradiated volume. It is difficult to analyze the complications induced by different therapeutic strategies, particularly in a multidisciplinary approach and therefore to define the specific role of brachytherapy.

Since few publications reported in detail the complications and the different grading systems used, a retrospective study is even more difficult. Complication rates, including definitive late sequelae grade 2 and 3, range from 20 to 30%. This range is high, but must be compared to the complication rates after EBRT or from radical, non conservative surgery.

In conclusion, it is encouraging to note that girls treated for cancer in childhood are able to give birth to a child when they are adult. Among the patients treated for gynaecological tumours by a multidisciplinary approach in the IGR series, 5 children were born during the last decades. The first healthy birth of a child to a woman previously treated for a clear cell adenocarcinoma by conservative surgery and brachytherapy at the IGR was in 1992. The determination of the GTV with the support of modern imaging, the technical progress of brachytherapy, the advances in chemotherapy and in conservative surgery, and the expertise of some dedicated groups makes it possible for brachytherapy to play an important role in the
### Table 31.1: Results for the treatment of Paediatric Malignancies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Pts N.</th>
<th>Primary tumour</th>
<th>Treatment</th>
<th>BT</th>
<th>Survival %</th>
<th>Local control %</th>
<th>Complications %</th>
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<tbody>
<tr>
<td>Cherlow (2)</td>
<td>11</td>
<td>Sarcoma 9, carcinoma 1, Wilm’s 1</td>
<td>FBT 6 SBT 5</td>
<td>LDR</td>
<td>82 (3y)</td>
<td>82 (3y)</td>
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<tr>
<td>Curran (4)</td>
<td>12</td>
<td>pelvic, HAN, Limbs, retroperitoneal</td>
<td>FBT 8 SBT 4</td>
<td>Ir, I, Cf</td>
<td>FBT 78 SBT 1/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fontanesi (7)</td>
<td>46 pts</td>
<td>RMS 14, STS 10, Retinoblastoma 10</td>
<td>FBT: 11 SBT: 23 EBRT+BT: 16</td>
<td>LDR</td>
<td>DFS 75</td>
<td>85</td>
<td>Gr3: 26</td>
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<tr>
<td>Fontanesi (8)</td>
<td>16</td>
<td>Synovial Sarcoma</td>
<td>BT±EBRT</td>
<td>LDR mould</td>
<td>OS 80 DFS 72 N’96 N’61</td>
<td>I 100 II 92 III 40 IV 4</td>
<td>Gr 1: 25 Gr 2: 20 Gr 3: 15</td>
</tr>
<tr>
<td>Gerbaulet (17)</td>
<td>53</td>
<td>Gyn: CCA I 34% II 35% III 17% IV 9%</td>
<td>S+BT±EBRT</td>
<td>LDR mould</td>
<td>Os 80 DFS 72 N’96 N’61</td>
<td>I 100 II 92 III 40 IV 4</td>
<td>Gr 1: 25 Gr 2: 20 Gr 3: 15</td>
</tr>
<tr>
<td>Gerbaulet (18)</td>
<td>131</td>
<td>A HAN B Trunk-limb C Gyn: no CCA D Bladder-Prostate</td>
<td>FBT 64% SBT 36% EBRT+BT 14%</td>
<td>LDR</td>
<td>A 76 B 68 C 84 D 56 Tot 70</td>
<td>A 80 B 69 C 90 D 56 Tot 76</td>
<td>A 37 B 13 C 34 D 12 Tot 28</td>
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<tr>
<td>Haie-Meder (21)</td>
<td>23</td>
<td>Bladder Prostate I/II 18, III 4, IV 1</td>
<td>CT+BT S BT 5</td>
<td>LDR IOBT: 22/23</td>
<td>F BT61 S BT 60</td>
<td>F BT 56 S BT 60</td>
<td>15</td>
</tr>
<tr>
<td>Healey (23)</td>
<td>18</td>
<td>Gyn, brain, kidney, liver, pancreas</td>
<td>CT+BT S BT 5</td>
<td>PI 16 TI 3 IOBT 14</td>
<td>76</td>
<td>Gr 3-4 12</td>
<td></td>
</tr>
<tr>
<td>La Quaglia (25)</td>
<td>13</td>
<td>Bladder-prostate</td>
<td>CT+BT SBT±BT</td>
<td>HDR</td>
<td>77 (FU 1-5 yrs)</td>
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<td>Martelli (26)</td>
<td>38</td>
<td>RMS Gyn</td>
<td>S+CT±BT±EBRT</td>
<td>LDR</td>
<td>Os 91 DFS 78</td>
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<td></td>
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<tr>
<td>Merchant (28)</td>
<td>31</td>
<td>Gr 2-3 STS (excluding RMS – Ewing)</td>
<td>BT 12 EBRT+BT 19</td>
<td>I or Ir</td>
<td>F BT 29 S BT 2</td>
<td>81 (3-yr) 89 (3-yr)</td>
<td>20</td>
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<tr>
<td>Nag (29)</td>
<td>13</td>
<td>STS</td>
<td>CT+BT SBT 11 CT+BT+EBRT 2</td>
<td>HDR IOHDR</td>
<td>77</td>
<td>84</td>
<td>G2-3: 23</td>
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<tr>
<td>Potter (31)</td>
<td>18</td>
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<td>FBT 4 SBT 8 EBRT+BT 6</td>
<td>HDR – PDR IOBT</td>
<td>STS 75 (1yr) Ew 100 (2yr)</td>
<td>RP</td>
<td></td>
</tr>
</tbody>
</table>

**Table 31.1 Legends:**
- **FBT:** first-line brachytherapy  
- **SBT:** salvage brachytherapy  
- **IOBT:** intraoperative BT  
- **S:** Surgery  
- **CT:** chemotherapy  
- **RMS:** Rhabdomyosarcoma  
- **HAN:** Head and Neck  
- **CCA:** Clear Cell Adenocarcinoma  
- **PI:** permanent Implant  
- **TI:** temporary Implant
Fig 31.8: RMS of the nasolabial sulcus (patient Fig 31.1):
A: Cosmetic results at 1 year       B: Cosmetic results at 3 years

Fig 31.9: GTV, Brachytherapy and late sequelae in RMS of nasolabial sulcus

A: GTV at the time of diagnosis

B: AP radiograph with CTV drawing

Fig 31.9C: Cosmetic results at 2 years

Fig 31.9D: Cosmetic results at 20 years
multidisciplinary conservative management of paediatric malignancies. We recommend, however, to refer children amenable to this treatment to a limited number of highly specialised and experienced centres.

Fig 31.10: Patient treated for a clear-cell adenocarcinoma of the vagina (consecutive approach with LDR brachytherapy IGR method). Three years later she was cured and had a baby. This young girl is now 8 years old. Mother and child are in excellent health.

12 References


