Review article

Brachytherapy in paediatric malignancies – review of indications

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Abstract

Paediatric malignancies are relatively rare, with an annual frequency of 13-14 in 100 000 children up to 15 years, and account for less than 1% of all cancer in developed countries. Paediatric tumours are generally managed with a multimodality treatment programme that includes surgery, chemotherapy, and external beam radiation therapy (EBRT). 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. Current indications for brachytherapy in paediatric malignancies are presented briefly in this study.

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Key words: paediatric malignancies, brachytherapy, LDR, HDR.

Purpose

Paediatric malignancies are relatively rare, with an annual frequency of 13-14 in 100 000 children up to 15 years, and account for less than 1% of all cancer in developed countries [1]. Paediatric tumours are generally managed with a multi-modality treatment programme that includes surgery, chemotherapy, and external beam radiation therapy (EBRT). Although the cure rates in paediatric malignancies have improved significantly during the last three decades, mostly due to the introduction of chemotherapy into multimodal treatment protocols, radiotherapy still plays a major role in achieving local control.

The use of EBRT in children can potentially result in growth retardation of bones and other organs or adversely affect organ function. 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.

Brachytherapy (BRT) may be used to deliver high doses of radiation in a localized volume, thereby reducing the probability of radiation-related side effects that are likely to occur when children are treated with external beam irradiation. In some paediatric malignancies the dose required to control the tumour is higher than that prescribed for the more common solid paediatric tumours. In such a case, BRT as a highly conformal technique can potentially minimize the toxicity of radiation therapy and preserve function without compromising local control or overall survival. BRT can reduce the dose of radiation to normal tissues and shortens the overall treatment time while maintaining a comparable high rate of local control. Thus, reductions in normal tissue doses decrease the probability of growth deformity, radiochemotherapy interactions, and theoretically, the risk of second tumour induction [1,2].

Treatment strategies directed towards the reduction of late side effects have increased interest in brachytherapy, in particular in those malignancies where only a limited target volume needs to be treated by a significant radiation dose.

Technical considerations

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

Considering the effect of the dose rate, the radiobiological advantages of LDR BRT in diminishing late effects should be taken into account. For PDR BRT, 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.

For HDR BRT, the delivered dose must be fractionated with a low dose per fraction as in external beam therapy,

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to try to improve the tolerance of normal tissues and to reduce the potential for late sequelae [1].

Clinical indications by tumour site

The most common tumours in which BRT can be used are soft tissue sarcoma and clear cell adenocarcinoma in gynaecological localization.

Soft tissue sarcoma

Although randomized trials comparing BRT and EBRT in STS have not been published, hypothetically, brachytherapy offers several advantages for paediatric patients with soft tissue sarcoma (STS) over EBRT. In the conservative treatment, BRT is 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. BRT is 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. BRT may also allow a reduction in the EBRT dose required [2, 3].

The main sites which can be suitable for BRT are: the head and neck region (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. The risk for local failure is determined by combinations of the following parameters: the clinical stage at diagnosis (stage II or III), the site (unfavourable), the histological subtype (alveolar or non-RMS), the response to chemotherapy (partial remission or no response), and the post-surgical stage (pT3).

Radiotherapy and brachytherapy have a major role if there is local relapse after primary treatment. BRT to a limited volume may be considered if EBRT has been used within primary treatment. The target volume in soft tissue sarcoma depends on the following factors: 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, histological subtype, response to chemotherapy, patient's age.

To define the target volume for BRT the tumour volume at diagnosis and after induction chemotherapy must be taken into consideration. For a gynaecological implant, MRI should be performed before and during the implant with the (moulded) vaginal applicator in place in order to define tumour thickness and the exact topography of the residual disease [1].

The target volume is a compromise between initial and residual tumour volume. CTV is defined including the gross tumour volume before and after induction chemotherapy with a considerable safety margin. The region of microscopic disease is included with some safety margin, also considering the dimensions of GTV at diagnosis.

Clear cell adenocarcinoma

The role of BRT is essential for the treatment of primary clear cell adenocarcinoma of the cervix and the vagina. Depending on the histological findings (involvement of lymph nodes, tumour extension) additional EBRT is indicated.

The target volume in clear cell adenocarcinoma is defined as for cervical and vaginal tumours in adult patients treated with radical radiotherapy (BRT alone or combined with EBRT). The principal aim of treatment is permanent cure, but function preservation is also an important goal [1]. 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 [1].

Technique

There is no great difference in the technique of BRT between the adult and the paediatric patient, except the implant volume and proximity of normal tissues.

In vaginal or cervical rhabdomyosarcoma or clear-cell adenocarcinoma, the use of a personalized moulded applicator is recommended as used for adult patients with gynaecological cancer. In children the cervico-vaginal impression is often made under general anaesthesia. The moulds and catheter positioning should be checked with orthogonal X-ray. In interstitial brachytherapy the tumour bed should be jointly outlined by the surgeon and radiation oncologist. Permanent radiopaque clips should be placed at the margins of the tumour bed. After loading, catheters are sutured into the tumour bed. One or both ends of the afterloading catheters exit the site percutaneously at a distance of 2 cm from the tumour bed. On the first postoperative day orthogonal plain films should be taken and the dosimetry of the treatment determined [2].

The dose rates should be selected according to age, anatomical site and EBRT total dose received. BRT alone can be used when tumour resection is complete with negative margins. The combination of EBRT and BRT should be considered for patients with involved margins [2].

Total dose, dose rate and fractionation

For interstitial or intracavitary LDR BRT alone, the total dose varies from 32 to 45 to 60 Gy:

1) 32 Gy for favourable prognosis disease,
2) 45 Gy for standard prognosis (e.g. residual microscopic disease),
3) 50-60 Gy for poor prognosis (e.g. gross residual disease).

The dose rate is low (0.4-0.6 Gy/h) to minimise late sequelae. The overall treatment time varies between 1 day and 5-6 days [1].

When given with EBRT the dose delivered by BRT is 15-20 Gy depending on the dose of EBRT.

Until the early 1990s, the studies enrolled patients treated with LDR BRT. The local control rates were effective, but the technical difficulties to treat children with LDR BRT sources made this approach restricted to a few institutions. The value of HDR BRT for STS has been demonstrated in adults with a local control advantage of BRT over wide local excision alone for adults with high-grade tumours [2-7]. In children, limited data are available from series that

include relatively small numbers of patients with different tumour types [8-12].

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 the 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 2-3 Gy per fraction and an 8-hour interval between each fraction, allowing for sufficient repair of normal tissue to a total dose of 36 Gy during 8 days. The advantage of fractionated HDR BRT is the hypothetical reoxygenation and redistribution of residual cancer cells [2, 13, 14]. If the BRT is started within days of surgery and delivered through catheters implanted during surgery, repopulation is also limited.

For clear cell adenocarcinoma the treatment of the primary tumour includes LDR BRT, preceded by pelvic external beam irradiation of 20-30 Gy for bulky tumours and up to 40-45 Gy if there is nodal involvement. The dose of LDR BRT 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.

The rate of complications, both acute and chronic, ranges from 10 to 48% depending on the series [14, 15]. The most common side effects of HDR BRT are radiation local erythema, telangiectasia and fibrosis, which are likely to occur when children are treated with external beam irradiation alone [2].

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