Use of Brachytherapy to Preserve Function in Children With Soft-Tissue Sarcomas

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Pediatric soft-tissue sarcomas are managed with a multimodality treatment program that includes surgery, chemotherapy, and external-beam radiotherapy (teletherapy). The use of teletherapy in young children can

Introduction

Of the approximately 8,000 new malignant neoplasms diagnosed in the United States annually, 2% occur in children. Soft-tissue sarcomas comprise 6.5% of pediatric malignant tumors.

The management of pediatric soft-tissue sarcomas is a therapeutic challenge. Treatment of this disorder has undergone a revolution during the past 2 decades with the initiation of the prospective Intergroup Rhabdomyosarcoma Study (IRS). Combined-modality treatment is the standard approach for soft-tissue sarcomas, and one of the main therapeutic goals is preservation of function.

Current IRS IV guidelines call for the use of external-beam radiation therapy, or teletherapy (4,140 to 5040 cGy; or, alternatively, 5,940 cGy hyperfractionated at 1.1 Gy twice daily) in all patients, except those classified as group I within stages I and II (ie, those with localized, completely resected disease and no regional node involvement). According to the guidelines, this latter group should not receive teletherapy. The standard planning target volume encompasses the gross tumor volume, with a 2-cm margin to allow for microscopic spread, internal organ movement, set-up error, and patient movement.[1-3] This results in the delivery of the prescribed dose to a large tumor volume. In addition, since the radiation is delivered from outside the child's body, teletherapy results in the delivery of a moderate radiation dose to a large volume outside of the planning target volume (Figure 1). This may cause severe late morbidities, especially growth retardation problems, which can be devastating in a developing child.[4-6] Hence, radiation therapy is often eliminated from the treatment program, with resultant decreased survival in the very young child.[6] The IRS I and II guidelines recommended limiting teletherapy doses to 40 Gy in infants. Doses of 50 to 60 Gy were recommended for older children, depending on the extent of disease. The analysis of local control revealed a higher local failure rate for infants in groups I through IV, although this difference was only statistically significant (P = .02) for group III patients (ie, those with gross residual disease at the start of treatment).[6]

Brachytherapy refers to treatment of a tumor at a short distance using sealed radioisotopes placed inside or close to a tumor. It has been used to treat childhood cancers in some centers.[7-32] The planning target volume for brachytherapy is smaller than that for teletherapy and closely approximates the clinical target volume, since there is no need to allow for internal organ movement, patient movement, or set-up errors (Figure 2). Furthermore, since the dose from brachytherapy falls off at a rate that is inversely proportional to the square of the distance, the volume of normal tissues that is irradiated outside of the planning target volume is minimized (Figure 2), thereby reducing long-term morbidity. Compared with teletherapy, brachytherapy has a shorter time course (7 to 8 days) and can be started soon after surgery. The shorter time course also expedites the integration of systemic chemotherapy, which is of prime importance in childhood soft-tissue sarcoma.

Techniques Used

The brachytherapy techniques used in children are modified from those employed in adults. Brachytherapy can be divided, according to the placement of the radioactive material, into intra-cavitary (inside body cavities) and interstitial (within tissues). Brachytherapy can be further subdivided, according to its duration, into temporary (the radioactive material being withdrawn after
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A specified dose has been delivered) and permanent (the radioactive material is left to decay in the body).

Brachytherapy can also be classified according to the prescribed dose rate: high-dose rate (HDR) techniques (> 12 Gy/h); medium-dose-rate (MDR) techniques, 2-12 Gy/h; and low-dose-rate (LDR) techniques, < 2 Gy/h. Finally, pulsed-dose rate (PDR) brachytherapy is the administration of remote afterloading brachytherapy in small pulsed doses of 1 to 2 Gy per interval (1 to 4 hours), over a few days. Table 1 summarizes the differences between the various radiation techniques.

**Manually Afterloaded LDR Removable Brachytherapy**
This is the most common type of brachytherapy used in children. Nylon catheters inserted into the target volume with the aid of hollow needles are then loaded with radioactive sources. A variety of templates can be used to aid the accurate positioning of the sources inside the target volume. Custom-built intracavitary vaginal applicators are generally used for gynecologic sites (standard sized applicators are usually inappropriate for young girls with soft-tissue sarcoma). Afterloading of radioactive sources (usually iridium-192 or cesium-137) is most often done 3 to 5 days after surgical excision to allow healing to begin.

There is a potential radiation hazard for the nursing staff and parents associated with the release of radiation in LDR brachytherapy, particularly in the treatment of younger children and infants who require constant monitoring. For patients implanted with cesium-137 or iridium-192, visitor restrictions are required to minimize radiation exposure of the parents and medical caregivers. These restrictions can be minimized if a low-energy radioisotope, such as iodine-125, is used. In these cases, thin sheets of lead applied over the treated area or standard lead aprons (0.25 mm lead equivalent) can adequately shield visitors.

**Permanent Interstitial Brachytherapy**
For permanent brachytherapy, low-activity iodine-125 seeds are commonly used. These are usually embedded at 1.0 cm intervals in vicryl suture material and directly sewn into the tumor bed. If there are gross palpable tumors in the target volume, the iodine-125 seeds are inserted into the tumor through hollow needles.

The low-photon energy of iodine-125 (28 KeV) makes hospitalization, a shielded room, and strict visitor restrictions unnecessary. Nevertheless, it is prudent for the patient to avoid prolonged contact with pregnant women and children below 18 years of age during the initial few months of therapy.

**Remote Afterloading Brachytherapy**
With remote afterloading brachytherapy, the catheters (or applicators) are inserted into the tumor site, as in the manually afterloaded technique. They are then connected to the afterloader for remotely controlled radioactive loading. High-dose-rate, PDR, and remote LDR techniques eliminate radiation exposure hazards to parents and medical caregivers. In addition, the radioactive sources in this equipment are retracted into the main safe during planned interruptions or in the event of accidental entry into the treatment room.

The treatments are performed over a few days in PDR and LDR brachytherapy and over a few minutes in HDR procedures. The short treatment time of HDR brachytherapy obviates the need for prolonged immobilization and sedation of these young children and infants. Furthermore, hospitalization is not mandatory, and the procedure can be done on an outpatient basis. In most remote-controlled afterloaders, the tumor is irradiated by a single radioactive source (stepping source) that moves in discrete steps through the tumor. The dose given is directly proportional to the time (dwell time) the source spends at a particular position (dwell position). The dwell times can be adjusted (decreased to minimize “hot spots” or increased to minimize “cold spots”) to optimize the treatment. Hence, the use of the stepping source in remote afterloaders allows for treatment optimization through the use of variable dwell times.

**Intraoperative HDR Brachytherapy**
Intraoperative HDR brachytherapy is a method of delivering a single large dose of HDR brachytherapy to a surgically exposed tumor site. Hollow plastic catheters are inserted into special flexible applicators and connected to the HDR machine. The treatment is delivered using a single, high-activity iridium-192 source. Normal tissues are either displaced from the irradiated area or shielded, if clinically applicable.

The tumor bed is visualized directly, thereby avoiding a geographical miss. Risk of catheter displacement is also reduced, since the treatment is given over a short time to an anesthetized patient. The need for an appropriately shielded operative suite, or alternatively, the need to transport the anesthesized patient to the radiation oncology suite limits the use of this modality to very few centers.
Results

**Table 2** outlines the results of the major trials of pediatric brachytherapy.

**Experience With LDR Brachytherapy**

The Institute Gustave Roussy (IGR) in Villejuif, France,[26] has the largest experience with this modality. From 1972 to 1990, 127 children (mostly with soft-tissue sarcoma) were treated with LDR interstitial and intracavitary brachytherapy. Tumors were noted in the following sites: pelvis (57%), head and neck (33%), and other soft tissues (10%). Histologically, rhabdomyosarcomas and undifferentiated sarcomas comprised 60% of the cases.

The treatment regimen for the majority of patients consisted of combination chemotherapy, conservative surgery, brachytherapy, and, in some cases, teletherapy. Brachytherapy doses were 45 to 65 Gy when used as a sole modality and 15 to 25 Gy when used as a boost. Brachytherapy was performed employing the LDR (0.4 to 0.6 Gy/h) technique.

The overall 5-year disease-free survival rate for the entire population was 75%. Patients who received brachytherapy as primary treatment had a local control rate of 81%, as opposed to a 57% rate when brachytherapy was delivered for recurrent disease. Also, patients with disease in the limb and trunk sites had poorer local control than those with disease in other sites.

The overall complication rate was 22%. This increased rate of complications was noted in the earlier cases and was thought to be related to the delivery of high doses to large treatment volumes. With better brachytherapy techniques and chemotherapy regimens in later cases, the rates of long-term toxicity were found to be acceptable.

A total of 24 patients with soft-tissue sarcoma (predominantly rhabdomyosarcoma) were treated at the St. Jude Children’s Research Hospital and were followed for a median period of 39 months.[11]. Nine patients received brachytherapy as the sole radiation modality. The total implant dose ranged from 25 to 56 Gy delivered at a dose rate of 30 to 120 cGy/h. No local recurrences were detected. Four patients developed significant complications, consisting of soft-tissue necrosis, impaired joint mobility, and wound dehiscence.

Brachytherapy was administered in conjunction with teletherapy in six patients. Teletherapy doses ranged from 40 to 44.5 Gy, and brachytherapy doses ranged from 10 to 50 Gy given at a rate of 30 to 71 cGy/h. Three patients attained local control. However, no patient with microscopic residual disease suffered a local treatment failure. No long-term complications were noted in this group.

Overall, 10 patients were treated for recurrent disease or second malignant tumors that appeared in previously irradiated sites or for metastatic disease. All but two of these patients received teletherapy. The brachytherapy schedule was 30 to 50 Gy at 30 to 88 cGy/h. Local control was maintained in eight patients. Side effects, namely, enteric fistula, joint stiffness, hemorrhage, and soft-tissue necrosis, developed in four individuals.

Healey et al from the Joint Center for Radiation Therapy[12] reported their 10-year experience with LDR brachytherapy in 18 children. Of seven patients with soft-tissue sarcomas, four received permanent iodine-125 implants, and the remaining three were treated with removable implants. The dose range for removable implants was 40 to 50 Gy. Prior to brachytherapy, the majority of patients received teletherapy to a median dose of 54 Gy. Unfortunately, although the local control rate was 100%, the majority of the patients died of metastatic disease.

Other, smaller series also have demonstrated the value of LDR brachytherapy in children.[13-23]

**Experience With HDR Brachytherapy**

Nag et al from The Ohio State University (OSU) published their results with HDR brachytherapy in 12 children with soft-tissue sarcoma (including 9 with rhabdomyosarcoma) whose median age at diagnosis was 18 months.[28] The children received combination chemotherapy, as per the IRS III and IV guidelines, conservative surgery, and HDR brachytherapy. Teletherapy was avoided in this very young patient population. Ten patients had microscopic residual disease at the time of brachytherapy. High-dose-rate brachytherapy was delivered in 300-cGy fractions twice daily, to a total dose of 36 Gy in 8 days. The dose was prescribed at a depth of 0.5 cm for a single plane implant.

The patients were followed for a median of 61 months. The 6-year actuarial local control rate was 91% and the overall survival rate was 81%. One patient developed a local recurrence and distant metastases to the lungs. Morbidity was seen in 50% of patients and was acceptable (Radiation Therapy Oncology Group [RTOG] grade 1 or 2) in most cases. Severe complications were noted in two children (subcutaneous fibrosis and delayed dentition, respectively).

Although brachytherapy alone is effective in treating patients with selected localized tumors, patients with extensive tumors frequently need teletherapy to enhance local control. Nag et al[29]
combined a single, 10- to 12.5-Gy dose of HDR brachytherapy given intraoperatively with modest doses (27 to 36 Gy) of teletherapy given postoperatively. Six children treated with this protocol are currently alive, and five are without evidence of disease after 40 months (range, 22 to 62 months). One child developed ureteral stenosis, and another had delayed orbital growth.[29]

Potter et al from Austria described their experiences with HDR brachytherapy.[30] Of the 12 children with soft-tissue sarcoma, 7 received HDR brachytherapy as the sole radiation modality, to a dose of 15 to 43 Gy in 3 to 16 fractions, or, alternatively, HDR of 15 to 25 Gy in 3 to 10 fractions as a boost after teletherapy. The other children received 20 to 36 Gy of PDR brachytherapy with or without teletherapy (18 to 50 Gy). Rates of local control and 2-year survival rates were both 100% with no significant morbidity.

The group at Memorial Sloan-Kettering Cancer Center have reported on the results of intraoperative HDR brachytherapy in 10 children with primary or recurrent solid tumors at various sites and with different histologies.[31] After gross surgical resections, 12 Gy was delivered at a depth of 0.5 to 1 cm in the tumor bed with intraoperative HDR. Supplemental teletherapy (10 to 54 Gy) was used in five patients.

The 2-year actuarial local control rate was 80%. Actuarial absolute survival rates at 1 and 2 years were 64% and 32%, respectively. One patient developed a perirectal abscess with fistula formation, and another patient died of chemotherapy-related sepsis. No other treatment-related complications were observed.

**Discussion**

The current standard treatment for soft-tissue sarcomas in pediatric patients is conservative organ- or limb-preserving surgery, aggressive combination chemotherapy, and radiation according to IRS guidelines. This treatment regimen has markedly enhanced the survival of these children, resulting in many long-term survivors. A multidisciplinary treatment approach (involving the pediatric surgeon, pediatric oncologist, and radiotherapist) has been instrumental in attaining the present treatment results. In addition, involvement of various collaborative groups, such as the IRS, in establishing and coordinating trials has also contributed to the excellent outcome.

Teletherapy has been the traditional mode of radiation therapy in pediatric patients. However, the adverse effects of ionizing radiation on growing soft tissue and bone are well documented. Furthermore, the treatment duration ranges from 5 to 6 weeks, and this radiation modality often requires sedation or general anesthesia.

Brachytherapy is an alternative modality that has been tried in children, either as sole therapy or in conjunction with teletherapy. It has distinct physical and radiobiological advantages over teletherapy and may avoid or decrease the long-term morbidity associated with external radiation.

**Patient Selection**

Careful selection of patients is essential for a successful outcome of brachytherapy in children with soft-tissue sarcomas. As a sole modality, brachytherapy is ideally suited for patients with microscopic or small-volume residual disease at accessible tumor sites who have responded well to chemotherapy and surgery. Patients with locally advanced disease or those who have had a poor response to systemic therapy may do better with teletherapy alone or in conjunction with brachytherapy. This may particularly be relevant to older children, who are less vulnerable to the effects of radiation on normal growth and development.[11]

**Treatment Volumes**

Sarcomas tend to spread via fascial planes, and, therefore, radiation fields have been planned with generous margins. These margins are not fixed, but rather, vary depending on the site, extent of surgery, and histology. In adults, the margins range from 5 to 10 cm. Sarcomas are chemosensitive in children, and chemotherapy can achieve appreciable tumor shrinkage and sterilization of subclinical disease. Hence, irradiating the post-chemotherapy volume alone may suffice without compromising local control.[28]

**Brachytherapy: HDR vs LDR vs PDR**

The bulk of the worldwide experience has been with LDR manually afterloaded brachytherapy, which has produced acceptable local control and complication rates.[7-21] The major disadvantages of this modality have been the necessity for isolation and other measures to protect the family and medical caregivers from radiation exposure, the need to immobilize and sedate the child during treatment, and the psychological trauma associated with separation from the parents.

The use of low-energy radioisotopes, such as iodine-125, does reduce radiation hazards to some extent. The advent of remote-controlled LDR, PDR, and HDR machines has eliminated radiation...
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exposure hazards to the patient’s family and medical personnel.[22-32] In addition, HDR has the advantage of delivering the dose in minutes, thereby reducing the duration of sedation and immobilization. If the child’s hospital does not have facilities for brachytherapy, the catheter insertion and continued care can be performed there, and then the daily HDR treatments can be done in the radiation oncology unit of an adult cancer care facility. Because of these advantages, HDR is the preferred form of brachytherapy in young children. In the pediatric group, there has been a long-standing concern that the high-dose rates used could lead to excessive morbidity. However, the radiobiological disadvantage of HDR can be overcome if the treatment is well fractionated, although a fractionated schedule is more personnel-intensive. In contrast, LDR can be given as a single treatment over several days and is probably easier to administer in older children.

Intraoperative HDR brachytherapy is an attractive option in children for several reasons. High doses can be accurately delivered intraoperatively to the directly visualized tumor bed, while normal tissues can be displaced or shielded during the irradiation. Furthermore, there is no risk of catheter displacement, since the treatment is given while the child is anesthetized, and the catheters are removed immediately afterward. However, since only a single dose is given, modest supplementary doses of teletherapy are required. Hence, we prefer to use intraoperative HDR brachytherapy only in older children. Long-term follow-up data are needed to establish the role of HDR vs that of LDR brachytherapy.

Morbidity

Brachytherapy minimizes but does not eliminate the morbidities of teletherapy. Acute radiation-induced toxicity, depending on the site, consists of skin or mucosal reaction (RTOG grade 1 or 2) and is usually self-limiting. However, in some patients, RTOG grade 3 reactions may occur 2 to 3 weeks after brachytherapy.

If the patient is receiving concomitant chemotherapy with anthracycline drugs (eg, doxorubicin), exacerbation of radiation morbidity may result [12,27] and rescheduling of the chemotherapy drugs is mandatory. In addition, the Institute Gustave-Roussy group[10] reported excessive toxicity in patients treated with irradiation doses greater than 60 Gy and at dose rates above 100 Gy/h. Other long-term complications, such as menstrual irregularities, gonadal dysfunction, psychosocial problems, and possible second malignancies, have been noted and will assume greater importance as cure rates improve. Thus, it is prudent for us to continue to closely follow children who receive brachy-therapy for longer periods to look for growth retardation and potential second malignancies.

Limitations of Brachytherapy

Since brachytherapy treats small volumes, there is the potential for a marginal miss, especially if extensive tumors are treated. Radioisotopes, techniques, and equipment facilities for brachytherapy vary in different institutions, and there is limited availability of brachytherapy facilities and expertise in pediatric institutions. Intraoperative HDR brachytherapy, a relatively new technique, is performed in only a few centers worldwide. Quality assurance can be difficult to attain with brachytherapy. All of these factors have hindered the initiation of multi-institution trials, in which adherence to strict treatment protocols and quality assurance are required.

Conclusions

The use of brachytherapy, if feasible, is an attractive alternative when radiotherapy is needed for the treatment of pediatric soft-tissue sarcomas. When used as a first-line treatment in conjunction with surgery, brachytherapy increases local control and decreases the probability of late complications (especially growth retardation of bones and organs), as compared with teletherapy. Aggressive chemotherapy achieves systemic control and tumor shrinkage, thereby facilitating conservative surgery and use of optimal radiation technique.

Low-dose-rate brachytherapy with manually afterloaded removable iridium-192 is commonly used. Low-energy radionuclides (iodine-125) and remote afterloading technology have been employed to reduce radiation exposure hazards. The use of HDR, PDR, and intraoperative HDR brachytherapy has extended treatment to younger children and infants, but the long-term effects of these techniques need to be addressed.

Long-term morbidity is a concern that requires close surveillance. Further efforts are needed to develop novel regimens with equivalent therapeutic efficacy but lower potential for long-term sequelae.
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