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Original article

Conservative surgery with combined high dose rate brachytherapy for patients suffering from genitourinary and perianal rhabdomyosarcoma

Jörg Fuchs [a,1,*], Frank Paulsen [b,1], Martin Bleif [c], Ulf Lamprecht [b], Nicola Weidner [b], Daniel Zips [b], Felix Neunhoeffer [d], Guido Seitz [a,e]

[a] Department of Pediatric Surgery and Pediatric Urology, University Children's Hospital; [b] Department of Radiation Oncology, University Hospital, Tuebingen; [c] Department of Radiation Oncology, Goeppingen; [d] Department of Pediatric Cardiology and Intensive Care, University Children's Hospital, Tuebingen; and [e] Department of Pediatric Surgery, University Hospital Marburg, Germany

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ABSTRACT

Background and purpose: Outcome of patients with genitourinary rhabdomyosarcoma has been improved in the past, but organ preservation rates are too low. Conservative surgery with LDR-brachytherapy has been advocated, but LDR-brachytherapy is often not available. We wanted to establish a novel treatment modality combining HDR-brachytherapy and conservative surgery.

Material and Methods: We performed an organ preserving tumor resection with intraoperative placement of brachytherapy tubes. Suitable patients were selected following assessment of response to neoadjuvant chemotherapy where organ preserving surgical resection was deemed feasible. In bladder-prostate rhabdomyosarcoma, only tumors located below the bladder neck could be treated by brachytherapy. After surgery, high dose rate brachytherapy was carried out for 30–36 Gy total dose.

Results: A total of 11 patients were treated up to now (embryonal histology $n = 10$, alveolar histology $n = 1$) with a median follow-up of 18 months [4–80]. All patients were IRS group III. There were no significant side effects. One patient had local relapse and was successfully treated with re-excision. All other patients are in the first complete remission. One patient developed a neurogenic bladder and required creation of a Mitrofanoff stoma.

Conclusion: Combined conservative surgery and high dose rate brachytherapy is a treatment option for selected rhabdomyosarcoma patients. The paper highlights the essential technical challenges and clearly shows limitations of this treatment approach.

Rhabdomyosarcoma is the most common soft tissue sarcoma in children [1]. It accounts for approximately 2/3 of all sarcomas and for 7–8% of all solid malignant tumors in the pediatric population [1]. The genitourinary tract is the second most common localization accounting for 15–20% of all RMS patients [2,3]. Most of these tumors are of embryonal histology [4]. In general, the outcome of patients with bladder-prostate RMS (BPRMS) is satisfactory with overall survival rates around 80% in different international trials [2,5–6] and even better in patients with vaginal RMS (VRMS) [7]. Perineal/perianal RMS (PRMS) has a worse prognosis with an overall survival rate of approximately 47% in the CWS trials and a higher proportion of alveolar histology [8].

Therapy consists of a multidisciplinary treatment approach including chemotherapy, radiation therapy and/or surgery [2]. The optimal local treatment remains unclear as radiotherapy and surgery may both have severe side effects. Surgery might lead to loss of organs and organ function or mutilation. Radiation therapy might induce secondary malignancies after years and in pelvic tumors a dysfunction of growth plates might occur in the radiation field. Decision for local control depends on age, tumor size and tumor extension. In general, the bladder preservation rates are still too low [2,5–6]. Therefore, novel combined approaches using conservative surgery and brachytherapy have successfully been introduced for BPRMS in the past especially by the Paris group [9]. The authors described avoidance of mutilating surgery in tumors not extending above the level of the trigone with sufficient local control [9]. They actually reported a long-term follow up demonstrating a normal quality of life in 76% of their male long term survivors with normal urological function in most patients [10].

* Corresponding author at: Department of Pediatric Surgery and Pediatric Urology, University Children's Hospital, Hoppe-Seyler-Strasse 1, 72076 Tuebingen, Germany.

E-mail address: Joerg.fuchs@med.uni-tuebingen.de (J. Fuchs).

[1] Jörg Fuchs and Frank Paulsen contributed equally to the first authorship of this paper

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Conservative surgery and brachytherapy has also been successfully described for patients with VRMS. Over the years with a more precise adjustment of the brachytherapy penetration depth, better indications for surgery and more efficient chemotherapy, improved results could be achieved [11]. In PRMS, intensity modulated radiotherapy (IMRT), protons and conformal radiotherapy are used for the treatment of these patients [8].

As already mentioned, the colleagues from Paris described the method of conservative surgery in combination with brachytherapy. Their technique is based on low dose rate (LDR)-brachytherapy [9]. Typical treatment times for continuously LDR-brachytherapy are 3 to 5 days. Implants are manually loaded [12]. The continuous LDR-brachytherapy seems to have positive radiobiological effects [12]. High dose rate (HDR)-brachytherapy is widely available and has very high activity sources such as a 370 GBq ^{192}Ir source seems to be an alternative [12]. Treatment is given in a very short period of time within minutes [12], but often delivered for several days. Translation of LDR experience into HDR dosage is difficult due to different physical properties and consequential radiobiological effects without established calculation models.

The aim of our study was to introduce a combined treatment approach for GU-RMS and PRMS using conservative surgery and HDR-brachytherapy focusing on technical details, outcome and urological function of the patients.

Material and methods

Patients

Eleven children with diagnosis of BPRMS ($n = 8$), VRMS ($n = 1$) or PRMS ($n = 2$) were treated in our institution between 2009 and 2015. Suitable patients were selected following assessment of response to neoadjuvant chemotherapy where organ preserving surgical resection was deemed feasible. All BPRMS were located in the prostatic region with tumor extension toward the bladder. All tumors were located below the level of the trigone except in one patient with extension above the level of the trigone. One girl with VRMS had an initial tumor infiltration of the uterus and the vagina. At the time of surgery, tumor remnants were found at the vaginal wall as well as in the cervix uteri extending into the vagina. The two patients with PRMS had tumors located in the perineum with extension toward the rectum and the urethra. All patients were treated with neoadjuvant chemotherapy according to the CWS-2002P-trial or the CWS-Guidance in the high risk group including alkylators, dactinomycin and vincristine. Patient's details are shown in Table 1. Brachytherapy tubes were placed following preoperative and intraoperative interdisciplinary definition of surgical and radiation strategy.

Surgery

The basic principle of our approach is on the one hand to carry out a macroscopically (R1) or microscopically complete (R0) tumor resection and on the other hand to avoid mutilating surgery such as cystectomy or prostatectomy. This surgical principle in these pelvic tumors regularly results in remnant tumor tissue especially around the urethra and the prostate. All patients underwent diagnostic cystoscopy prior to the actual procedure. After placement of a transurethral catheter, the skin is incised using a large Pfannenstiel incision. For a better exposure of the surgical field, we carry out a transection of the symphysis in all children with BPRMS. After mobilization of the bladder it is opened and the spatial relationship between the ureteral orifices and the tumor is evaluated. If one or both ureteral orifices are infiltrated by the tumor, the affected part of the ureter is resected and reconstructive procedures such as reimplantation of the ureter or transverso-ureteroureterostomy is carried out. Tumors above the level of the trigone are treated with a R0 resection as brachytherapy would not be helpful in this localization due to unfavorable distribution of the radiation field. The ureteral orifices are intubated with ureteral tubes (Ch 6). These tubes are left for the whole brachytherapy period in order to avoid lower urinary obstruction. A suprapubic catheter is placed and the bladder is closed with interrupted sutures. The former tumor bed is marked by clips, which are later used for brachytherapy planning. Four to seven brachytherapy tubes are brought through the perineum and placed around the urethra in a circumferential fashion (Fig. 1). Tubes are fixed with Vicryl 5-0 sutures. Care is taken that the distance between the tubes is not exceeding 8 to 10 mm in order to allow a homogeneous dose distribution. In selected cases, such as a small circumscribed tumor extension in the upper urethra involving the trigone of the bladder, the placement of a transurethral brachytherapy tube can be helpful for the application of a small amount of the total radiation dose. At the end of the procedure, the symphysis is readapted either with PDS sutures in small children below 1 year or with wire in older children.

In patients with VRMS, our surgical approach intends to avoid mutilation of the vagina and the uterus. Surgical procedures may include partial resections of the vagina and conisation of the cervix. A single individual vaginal mold (Fig. 2) is used for brachytherapy, which is removed after each brachytherapy session.

PRMS normally requires microscopically complete tumor resections. Encasement of the urethra or the sphincter complex of the anus may lead to mutilation. Therefore, we performed macroscopically complete tumor resections without resection of the sphincter or the urethra. 5–6 brachytherapy tubes are placed into the tumor bed through the perineum (Fig. 3).

After surgery, BPRMS and PRMS patients were transferred to the pediatric intensive care unit and were mechanically ventilated for the duration of brachytherapy in order to avoid dislocation of the brachytherapy tubes.

HDR-brachytherapy

On the first day after surgery, a planning CT scan of the tumor region is carried out (1.5 ml/kg contrast media i.v. (Ultravist®-370, Bayer, Leverkusen, Germany), scanning 1 min thereafter, 100–120 kV, 40–80 mAs, slice thickness 1 mm). Based on the pretherapeutic and preoperative MRI imaging, intraoperative findings including clips and the planning CT scan, 3-dimensional brachytherapy planning using the Brachyvision software (Varian, Medical Systems, Haan, Germany) is done. Clinical target volume (CTV) was treated and encompasses the tumor bed below the level of the trigone in its preoperative extension with expected subclinical local spread and is adapted to the postoperative changed anatomy. Care is taken to avoid high radiation dosage at the rectum, growth plates, uterus, ovaries, testicles, the urethra and the bladder. Local dose distribution was individually shaped considering maximal dose and dose-volume effects. Radiation dosage was calculated using the linear-quadratic model based on recommendations for percutaneous radiation therapy of the Cooperative Soft Tissue Sarcoma Study (CWS) group, adapted for HDR-brachytherapy estimating an effect of acceleration. Exemplary HDR-brachytherapy for BPRMS planning is shown in Fig. 4. For the VRMS patient, an individual vaginal mold was manufactured. Prior to brachytherapy, X-rays with dummy sources were performed in order to ensure integrity and proper localization of the tubes. The correct position of the brachytherapy tubes was assured before each session by measuring of the external length of each catheter with a caliper rule. Additionally, a fluoroscopic evaluation of the BT tubes was carried out every second day for quality

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