TREATMENT EFFICIENCY, OUTCOME AND SURGICAL TREATMENT PROBLEMS IN PATIENTS SUFFERING FROM LOCALIZED EMBRYONAL BLADDER/PROSTATE RHABDOMYOSARCOMA: A REPORT FROM THE COOPERATIVE SOFT TISSUE SARCOMA TRIAL CWS-96

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INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common pediatric soft tissue sarcoma. About two thirds of all sarcomas and 7–8% of all solid malignant tumors in childhood are rhabdomyosarcomas [1]. Approximately 10–15% of all RMS cases are located in the bladder/prostate with a predilection to the trigone of the bladder [2] making the genitourinary tract the second most common primary site [3–5]. The main histological subtypes are embryonal and alveolar [6]. The embryonal subtype including the botryoid variant is the most prevalent in bladder/prostate-RMS (BPRMS) [4,7]. Cardinal symptoms are obstructive voiding symptoms, constipation, hematuria, and abdominal mass [4,8]. A multidisciplinary treatment approach including surgery, radiotherapy, and chemotherapy is used in these patients depending on the clinical trial [2,9]. Up to now it remains unclear, which treatment strategy is optimal for local control in BPRMS. Radiotherapy might help reduce tumor volumes and therefore might avoid radical surgery at the expense of high post-treatment morbidity [2]. Surgery might require radical approaches to perform a complete tumor resection. Therefore, treatment approaches focus now on less aggressive management with the aim of preservation of the bladder function. The main treatment problems are local relapse, metastatic disease and malfunction of the bladder and other pelvic structures following radiotherapy and surgery.

The aim of this study was to evaluate treatment efficacy, outcome and surgical treatment problems in patients with BPRMS treated on the CWS-96 trial of the Cooperative Soft Tissue Sarcoma Study Group CWS.

METHODS

Patients

Seven hundred and seventy-nine patients with a centrally reviewed (IL) histological diagnosis of rhabdomyosarcoma (RMS) were treated at 42 participating institutions in Germany, Austria, Poland, Switzerland, and Sweden and were enrolled on the Cooperative Soft Tissue Sarcoma Study CWS-96 of the Society of Pediatric Oncology and Hematology (GPOH) conducted between 1996 and 2002. Eighty-five patients suffered from BPRMS. Twenty-two patients were excluded from this analysis because of alveolar subtype (n = 5), metastatic disease (n = 11), or incomplete data (n = 6). The trial was approved by the appropriate ethical committee (EK LAK 105/95). Written informed consent for participation on the trial was given by the patients, guardians or parents, or both.

Conflict of interest: All authors disclose a conflict of interest.

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Study Design

Risk stratification for systemic treatment. All patients with BPRMS received multiantiagent chemotherapy with at least three drugs including alkylators, dactinomycin, and vincristine (Fig. 1). Patients in the standard risk group received treatment with IVA (ifosfamide, vincristine, dactinomycin) and patients in the high-risk group were randomized to receive chemotherapy with VAIA (vincristine, ifosfamide, doxorubicin, dactinomycin) or CEVAIE (carboplatin, epirubicin, vincristine, dactinomycin, ifosfamide, etoposide). Neoadjuvant chemotherapy was prescribed for the majority of patients with macroscopic residual tumors after initial biopsy (IRS-Group III) [10]. In this group, radiological response was assessed after nine weeks using computed tomography (CT) or magnetic resonance imaging (MRI) as local treatment depended on the proportion of tumor volume reduction (Fig. 1).

Radiotherapy

According to the treatment protocol, radiotherapy was to be limited to a maximum dose of 32 Gy in children younger than 3 years of age. In children younger than 1 year, radiotherapy was not envisioned by the protocol in general. Protection of pelvic and hip growth plates was recommended in order to avoid growth disturbances of these regions. The planning target volume included the initial tumor volume on MRI plus a 2 cm margin. The radiation dose was stratified on the response to chemotherapy, IRS group and histology. After complete tumor resection with no residual microscopic disease, patients received no radiotherapy. Patients with radiographic complete response (CR) or good response (GR) and favorable (embryonal) histology should receive hyperfractionated, accelerated radiotherapy (HART) of 32 Gy to the primary site (1.6 Gy twice daily). Patients with radiographic poor response (PR) received a total dose of 44.8 Gy HART. Patients, who could not undergo hyperfractionated radiotherapy (due to young age that required anesthesia or involvement of liver or gut) received conventional fractionation with 1.8 Gy/day (overall dose: 39.8 or 50 Gy). Lower dose was used for irradiation of the abdomen or if a dose reduction was necessary due to patient’s age or tumor location.

Surgery

The extent of tumor resection was defined in the following way: \( R_0 = \) complete tumor resection without microscopic residual disease, \( R_1 = \) tumor resection with microscopic residual disease, and \( R_2 = \) tumor resection with macroscopic residual disease. The surgical guidelines did not recommend primary resection unless the tumor was located at the bladder dome and a primary \( R_0 \) resection was feasible. In all other patients, a primary biopsy (open, trucut, or endoscopic) was performed. Secondary surgery was only undertaken if a residual tumor mass was detected at the time of response reassessment. If residual disease remained after radiotherapy, radical surgery was permitted and was defined as cystectomy and/or prostatectomy with supravesical urinary diversion. Bladder substitution was permitted after tumor resection.

Definition of Treatment Groups and Response to Preoperative Chemotherapy

For the analysis of the local treatment, patients were assigned to four different treatment groups: In group 1, patients underwent chemotherapy and tumor resection (Surgery). In group 2, patients were treated with preoperative radiochemotherapy followed by tumor resection (RT plus Surgery). In group 3, patients underwent incomplete tumor resection followed by postoperative radiochemotherapy ([R1/2 resection plus RT). In group 4, patients were treated solely with radiochemotherapy (RT). CR was assumed if there was a lack of visible tumor on CT/MRI imaging or no evidence for viable tumor during second look surgery. GR was defined as a reduction of tumor volume of more than 2/3, PR was a tumor volume reduction between 1/3 and 2/3. Objective response (OR) was presumed if the reduction was less than 1/3 or more than baseline. Progressive disease (PD) described any tumor progression.

Statistical Methods

Survival analysis was performed using the Kaplan–Meier method. Kaplan–Meier estimates of the overall survival (OS) and event-free survival (EFS) were calculated and are expressed as 5-year survival rates. For OS, the time from primary diagnosis to death (therapy related or other reason) or last follow-up (censored observations) was recorded. For EFS, the endpoint was defined as the time from diagnosis to first relapse. Survival estimates are given with log–log-transformed 95% confidence intervals [11], and the log rank test was used to test the difference between survival curves. Patient age and length of follow-up are reported with the median and standard deviation. The complication rate between primary biopsy and surgery was calculated using the Mann–Whitney rank-sum test. The statistical analyses were carried out with the SAS 9.1.3 software (SAS Institute, Cary, NC) A \( P \)-value of 0.05 was considered significant.

RESULTS

Patients

The characteristics of the 63 analyzed patients with localized BPRMS are shown in Table 1. In 14 patients of the IRS III group, response to chemotherapy was not assessable as imaging was not performed according to the protocol. Reasons therefore were the wrong time point of imaging or failure to measure tumor size properly.
Patients (38/63; 60.3%) were irradiated. Assignment to the different local treatment groups is shown in Table II. Incomplete tumor resection without preoperative radiotherapy was not envisioned by the study protocol. The radiation doses ranged from 32 to 50 Gy. Two patients were irradiated with a lower dose (18 Gy: termination due to severe bladder infection; 24 Gy: irradiation of the whole abdomen). Doses <36 Gy (low dose group) were used in 19 patients (HART: 10, conventional fractionation: 5, no data: 4). Doses ≥36 Gy (high dose group) were applied in 19 patients (HART: 6, conventional: 11, no data: 2). Six of 13 patients following R1/2 resection were irradiated with doses ≥36 Gy. Since the irradiation dose was risk adapted, EFS and OS, as expected, did not differ between the low and high dose irradiation group (Fig. 2 A,B). Early complications of radiotherapy were reported in 50% of the patients including local infections, urinary retention, cystitis, leucopenia, thrombocytopenia, strictures of the urinary tract, diarrhea, burns, sepsis, colitis, and skin reactions up to loss of skin.

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Surgery

Primary surgery. Fifty-one patients underwent initial tumor biopsy (open biopsy: n = 16; cystoscopy: n = 23; punch biopsy of the prostate: n = 3; needle biopsy: n = 2; data not assessable: n = 7).

Twelve patients underwent primary tumor resection. Treatment modalities and outcome are shown in Table II. The following surgical complications occurred: bleeding (n = 3), abscess formation (n = 1), urinary tract infections (n = 3), as well as injury of the ureter and rectum (n = 1). The complication rate was higher in patients undergoing primary tumor resection (25%) than in patients receiving a tumor biopsy (9.8%) (P = 0.205).

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Time point of surgery</th>
<th>No. of patients</th>
<th>Resection status at the time of primary or secondary surgical resection</th>
<th>EFS (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative chemotherapy followed by tumor resection (Surgery)</td>
<td>Primary tumor resection followed by chemotherapy</td>
<td>7 (including 2 pts. with primary and secondary surgery)</td>
<td>R0: 3; R1: 2; R2: 2</td>
<td>71.4 [25.8–92]</td>
</tr>
<tr>
<td>Preoperative radiochemotherapy followed by tumor resection (RT + Surgery)</td>
<td>Secondary tumor resection after chemotherapy</td>
<td>18 (+2 patients, who received primary and secondary surgery)</td>
<td>R0: 10 (bladder preservation: 3); R1: 2; R2: 4; no data: 2</td>
<td>88.9 [62.4–97.1]</td>
</tr>
<tr>
<td>Incomplete tumor resection followed by postoperative radiochemotherapy (R1/2-ressection + RT)</td>
<td>Secondary surgery after RT</td>
<td>17</td>
<td>R0: 9 (bladder preservation: 2); R1: 4; R2: 3; no data: 1</td>
<td>82.3 [54.7–93.9]</td>
</tr>
<tr>
<td>Solely radiochemotherapy (RT)</td>
<td>No surgical treatment</td>
<td>8</td>
<td></td>
<td>38.5 [14–62.8]</td>
</tr>
</tbody>
</table>

RT, radiotherapy; 95% CI, 95% confidence interval; R0, complete tumor resection without microscopic residuals; R1, tumor resection with microscopic residuals; R2, tumor resection with macroscopic residuals.

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Secondary resection. Forty-five patients underwent secondary surgery. Treatment modalities and outcome are shown in Table II. In the 19 patients who underwent complete tumor resection (R0) after neoadjuvant chemotherapy or radiochemotherapy, the EFS was 89.5% to 97%. Operative procedures performed are listed in Table III. Preservation of the bladder was not possible in 17 patients. Surgical complications occurred in 28.8% of these patients. The following complications were found: bowel perforation, development of fistula (gut), abscess formation, adhesive ileus, urinary tract infections, stricture of the ureter, erectile dysfunction, severe tumor bleeding, peritonitis, and development of a neurogenic bladder. In four patients receiving preoperative radiotherapy, complications like development of fistula, stricture of the ureter or erectile dysfunction were possibly associated with the preoperative treatment.

Surgical Treatment Failures

Twenty-three patients underwent incomplete primary tumor resections or incomplete secondary tumor resections without preoperative radiotherapy (Table II). These procedures were not done according to the study protocol. The authors reviewed all 23 cases and found 16 cases where protocol recommended surgical guidelines were not followed (e.g., avoidance of primary biopsy, intended incomplete resection). In the remaining seven cases, the surgical procedure was correct and an avoidance of incomplete resection was not feasible (e.g., no radiotherapy due to very young age of children). Surgical treatment failures may have been caused by misjudgment of tumor resectability by the surgeon. Ten of 16 patients died during follow-up, 9 from disease progression and 1 of a second malignancy.
The outcome of patients younger than 3 years was comparable to other groups treated according to the protocol. Figure 2C,D shows the Kaplan–Meier curves of the different treatment groups. The outcome of patients younger than 3 years was comparable (OS: 76.2 ± 7.9%, n = 30) compared to patients older than 3 years (OS: 76.3 ± 8%, n = 33).

Local Relapse

Local relapse occurred in 14 of 63 patients, of which 6 patients underwent incomplete primary or secondary tumor resection without radiotherapy. Two children underwent complete surgical tumor resection after neoadjuvant chemotherapy and two were treated with radiochemotherapy alone, respectively. Four patients developed a local relapse after combination of radiochemotherapy and tumor resection.

Discussion

Management of genitourinary rhabdomyosarcoma has changed over the years emphasizing bladder preservation as a goal of treatment. Survival rates, however, had not been improved from IRS-I (78%) to IRS-IV (82%) [2]. In 1972, during the first Intergroup Rhabdomyosarcoma Study, most patients with BPRMS were treated with primary pelvic exenteration, chemotherapy for 2 years and local radiotherapy [2,12]. Today, less aggressive surgical treatment regimens focusing on bladder preservation have been established [2]. Rates of cystectomy decreased from 78% in IRS-I to 9% in IRS-IV [2]. The cystectomy rate in the CWS-96 was 27%.

A combination of radiotherapy and conservative delayed surgery was advocated for the IRS-IV study [2,12]. Similarly, the concept of the Cooperative Soft Tissue Sarcoma trial CWS-96 envisioned preoperative radiotherapy in all cases, except in patients where a R$_0$ resection seemed to be feasible or in children younger than 3 years of age. Bladder preservation was preferred whenever possible.

The primary diagnosis must be established by tumor biopsy. In our trial, primary tumor resection risked incomplete resection with 2.5-times higher complication rates and unfavorable outcome. This corresponds to the observation of Cecchetto et al. [13], who promoted initial tumor biopsy in locally advanced RMS instead of tumor debulking. One of the essential challenges in the local treatment of BPRMS is the assessment of feasibility of complete tumor resection without loss of organ function.

In our series, we could document 16 patients with inadequate primary or secondary surgical treatment resulting in incomplete tumor resection (Table II). These patients had an inferior survival. This observation is consistent with a report from Filipas et al. [14], who observed that involved surgical margins increased the risk of local relapse. Postoperative radiotherapy seems not to compensate for inadequate surgery in this group [15]. Central surgical and radiographic review of tumor response prior to definitive local therapy might help to reduce the rate of incorrect assessment of resectability. The surgical approach of primary tumor resection seems to be a bigger problem. Inadequate primary surgery was often performed prior to enrollment on the trial. Therefore, the study group had no influence on the initial surgical treatment. Since the CWS trials register over 95% of patients diagnosed with RMS in Germany with the goal of nationwide inclusion, patients were not excluded from registration despite inadequate primary surgery.

There is an obvious need for a better education of surgeons who come in primary contact with a child with BPRMS and who has not yet been evaluated at a study center. The optimal secondary local control for bladder/prostate-RMS remains disputed with regard to survival as well as optimal functional outcome.

The major role of chemotherapy in this tumor location is the reduction of the primary tumor mass in order to assist with local therapy as well as to avoid tumor progression and the development of distant metastases [10].

There is a major difference in radiation dose between the IRS-IV trial and the CWS-96 study. In the IRS-IV protocol, the radiation dose and fractionation was randomized (50.4 Gy conventional vs. 59.4 Gy accelerated) and was 18.4–27.4 Gy higher in this tumor location than in the CWS-96 trial. The radiotherapy dose was not randomized but stratified in our study. Lower radiation doses seemed to not have a negative impact on the outcome in a selected group of patients with favorable characteristics compared to higher dose (5-year-OS < 36 Gy: 78.3 ± 9.6%; ≥36 Gy: 65.6 ± 11.7%; 5-year-EFS < 36 Gy: 73.7 ± 10.1%; ≥36 Gy: 57.9 ± 11.3%). Radiochemotherapy alone as a local treatment seems to be optimal especially in patients with smaller tumors and a GR to neoadjuvant chemotherapy [16]. Besides the major role of radiotherapy on local tumor control, there are several relevant concerns. There was a high early complication rate of 50% after RT causing severe morbidity or termination of therapy in these patients as well as late sequelae. Fryer [9] reported that radiation therapy contributes to post-treatment morbidity. Another disadvantage is the fact that surgery is even more complicated after radiotherapy. Besides hindering dissection due to fibrotic and fragile tissue, wound healing is problematic after radiotherapy. Sufficient wound healing is essential for good surgical outcomes of BPRMS, which often requires complex reconstructive procedures such as bladder substitution or augmentation with reimplantation of ureters. Late effects are commonly described in the literature after irradiation of pelvic organs.
RMS. There were a significantly higher number of patients with late effects after irradiation of the pelvis (short stature, ovarian hormone failure, intestinal complications such as strictures and fistulas, gynecologic problems, secondary malignancy) compared to patients, who were not irradiated [3]. Therefore, a risk adapted reduction of the radiation dosage might have a positive influence regarding late effects. Brachytherapy might be an alternative treatment approach for patients with BPRMS. Martelli et al. promote the use of conservative surgery (incomplete tumor resection) followed by low dose rate brachytherapy in children suffering from prostate and/or bladder neck RMS. They found that this therapy seems to be effective in terms of survival, anatomical preservation of the bladder/prostate as well as continence. But one limitation that they report is that this therapy can only be used in children with tumors located in the prostate or the bladder neck. Tumor extension into the bladder must not be above the level of the bladder trigone [17]. A direct comparison with the results to the CWS-96 trial is not possible as low dose brachytherapy was not envisioned by the protocol and most of the tumors in our study were located at higher levels within the bladder. However, brachytherapy appears to be a promising option for a selected group of patients.

The number of local relapses was higher in our study than in the IRS-IV trial [2]. Most local relapses occurred in patients treated with incomplete resection and postoperative radiotherapy. Most of these tumors were located at the bladder neck or the prostate. The reasons therefore seem to be multifactorial, including incorrect primary surgical approach or improper assessment of secondary resectability.

Further analysis evaluating bladder function using video urodynamic examinations and quality of life interviews will follow in order to clearly describe the effects of different treatment modalities.

In conclusion, BPRMS require a multidisciplinary treatment approach. Biopsy is the recommended primary surgical approach in patients with these tumors. Primary tumor resections should be avoided. A risk adapted secondary local control therapy is essential for optimal outcomes. The surgeon must be certain whether a R0 resection is feasible prior to attempting a tumor resection. If there is doubt of a possible R0 resection, preoperative radiotherapy should be administered. Patients who underwent preoperative radiochemotherapy followed by surgical tumor resection, and patients who underwent only radiotherapy or surgery plus chemotherapy had a similar good outcome with an OS of over 80%. Radiation alone for local therapy is a good treatment option especially in patients with favorable prognostic factors like small tumors and GR to chemotherapy.

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