BLADDER FUNCTION AFTER CONSERVATIVE SURGERY AND HIGH-DOSE-RATE BRACHYTHERAPY FOR BLADDER-PROSTATE RHABDOMYOSARCOMA.

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Abstract

Background: Conservative-surgery (CS) brachytherapy (BT) techniques for local therapy in bladder-prostate rhabdomyosarcoma (BP-RMS) seeks to retain organ function. We report bladder function after high-dose-rate (HDR) BT combined with targeted CS for any vesical component of BP-RMS. Procedure: Prospective cohort of all BP-RMS patients between 2014-19 receiving HDR-BT (Iridium-192, 27.5Gy in 5 fractions) with/without percutaneous endoscopic-polypectomy (PEP) or partial cystectomy (PC). Functional assessment included frequency-volume-chart, voided volumes, post-void residual, flow studies, continence status and ultrasound scanning; abnormalities triggered video-urodynamics. Results: Thirteen patients (10 male), aged 9 months to 4 years (median 23 months), presented with localised fusion-negative embryonal BP-RMS measuring 23-140mm (median 43mm) in cranio-caudal extent. After induction chemotherapy, local treatment consisted of PC+BT in three, PEP+BT in four and BT alone in six. At a median $3\frac{1}{2}$ years (range $1\frac{3}{4}$-7 years) follow up, all were alive without relapse. At a median age of 6 years (4-9 years), the median bladder capacity was 86% (47%-144%) of that expected for age, including 75% (74-114%) after PC. There was no relation to radiation dose to the bladder. Complications occurred in two: one urethral stricture and one vesical decompensation in a patient with pre-existing high-grade VUR. The remaining patients are dry by day; five with anticholinergic medication for urinary urgency. Three patients are enuretic. Conclusions: Day-time dryness at a median $3\frac{1}{2}$ years after CS-HDR-BT was achieved in 92%, with 85% voiding urethrally, and 62% attaining day-and-night continence aged 4-9 years. We report reduced open surgery, with minimally-invasive percutaneous surgery with HDR-BT or brachytherapy alone being suitable for many.

Introduction

With over 80% long-term survival after bladder-prostate rhabdomyosarcoma (BP-RMS), attention has turned to reducing the long-term consequences of treatment while maintaining outcomes. Management has moved away from upfront radical surgery in the 1970s to initial biopsy, systemic chemotherapy and surgical resection and/or radiation therapy for local control. The goal of simple organ preservation has also progressed to functional maintenance. In the 1990s, the impact of external beam radiotherapy (EBR) on bladder function was exposed. Yeung et al observed normal bladder dynamics only in those managed without EBR for pelvic RMS. Raney et al and Hays et al documented bladder dysfunction in 30% and 47% of those receiving EBR compared to 11% treated without radiation for BP-RMS. Newer approaches, such as brachytherapy (BT), seek to reduce the long-term impact of radiotherapy on the surrounding normal organs, while still delivering high doses of radiation to the target volume. Today, conservative surgery-brachytherapy (CS-BT) is the

preferred local therapy for BP-RMS[6,7,8,9], where suitable. A deliberate incomplete surgical resection is combined with brachytherapy to sterilise the remaining tumour cells, but preserve organ function.

Different BT regimens have evolved. The total dose of radiation may be delivered in one treatment or as two or more fractions depending upon dose rate. Low-dose-rate (LDR-BT) delivers the radiation dose continuously over several days[6], but for children compliance and parental radiation exposure are challenging. Pulsed-dose-rate (PDR-BT) exposes the source in hourly pulses[11] and has similar challenges to LDR-BT in the paediatric population. High-dose-rate (HDR-BT) involves briefly passing a radioactive source via flexible cannulae into the tumour to deliver the radiation dose over just a few minutes[10]. Because the rate of delivery is rapid it is potentially more damaging to surrounding normal tissues and therefore has to be delivered in several exposures (fractions) to allow normal tissue repair between fractions.

Following conservative surgery and LDR-BT or PDR-BT, day- and night-time dryness is reported in 72% of those aged more than 6 years, who did not require cystectomy for vesical failure after completing treatment for BP-RMS[7]. The aim of this study is to report the medium-term bladder function after CS-BT in a prospective cohort of children treated for BP-RMS using fractionated HDR-BT.

Methods

With institutional approval, all BP-RMS patients treated by interstitial HDR-BT from 2014 to 2019 were included. Case records were prospectively collected. Patients were treated on the EpSSG RMS 2005 protocol[12]: after 3 cycles of chemotherapy (iFosfamide, Vincristine, Actinomycin D with or without Doxorubicin), the response to chemotherapy is appraised and local therapy options are considered on a case by case basis.

Selection criteria

Patients' suitability for a conservative approach was determined by a combination of imaging, digital and cysto-urethroscopic examination under anaesthesia and histology. An initial MDT reviewed the pathology, diagnostic and re-assessment imaging for tumour size, location and extent, histological subtype/fusion status and lymph node involvement. Likely candidates underwent examination under anaesthesia jointly by the surgeons and oncologists. The vesical extent of the tumour was specifically assessed histologically by endoscopic biopsies mapped to different sites in the bladder, using a cysto-urethroscopic or percutaneous approach (described below). All patients were discussed at National Advisory Panel. Involvement of more than a third of the bladder above the trigone or tumour size greater than 5 cm following induction chemotherapy and surgery (if required), lymph node or distant metastases were contra-indications for a conservative procedure. There were three forms of CS-BT: partial cystectomy of the vesical component and brachytherapy (PC+BT), percutaneous endoscopic polypectomy and brachytherapy (PEP+BT) or interstitial HDR-BT alone.

Partial cystectomy

For tumours involving the bladder cranial to the trigone, partial cystectomy was required for this portion of the tumour as it is not consistently covered by the interstitial HDR-BT system described below. Through a Pfannenstiel incision the bladder was opened. While surgery sought to achieve a microscopically tumour-free ("R0") margin cranially, a deliberate macroscopically incomplete ("R2") resection was intended at the trigone/bladder neck. Surgery avoided dissection to the level of the prostate, in the knowledge that this area could be reliably treated by HDR-BT and in order to prevent the genitourinary sequelae of radical surgery at the bladder neck. Ureteric reimplantation was not required. Regional lymph nodes were sampled as part of the procedure.

Percutaneous Endoscopic Polypectomy

For patients with BP-RMS confined to the prostate and baldder neck up to the level of the trigone, open surgery was not required. However, those with large exophytic tumour polyps, which risk obstructing voiding, were offered percutaneous endoscopic laser polypectomy. Under cystoscopic vision (9.5Fr cystoscope, Storz®), a suprapubic needle puncture into the bladder above the tumour allowed placement of a 0.035Fr Sensor PTFE-Nitinol guidewire (Boston Scientific®). The tract was dilated by 7Fr rigid dilator (Cook®)

followed by a Nephromax balloon (Boston Scientific®). Via a 18Fr or 30Fr Amplatz sheath (Boston Scientific®), a 15Fr or 20.8Fr R.Wolf® nephroscope allowed any tumour polyps to be assessed in terms of their potential to create a ball-valve effect over the bladder neck and posterior urethra. Holmium:YAG laser (Cook®) at 0.5-1J and 5-15Hz long-setting allowed the stalk of the polyp to be coagulated and divided. The polyp was extracted via the Amplatz sheath preventing contamination of the tract. This suprapubic access was also used to obtain bladder "mapping" biopsies for patients whose urethra was too narrow to accept the biopsy cystoscope.

High-rate-dose brachytherapy

For brachytherapy alone or after conservative surgery, cannulae were inserted percutaneously through the perineum under general anesthesia with ultrasound guidance. Post-implantation computed tomography (sometimes supplemented by fusion with pre-procedural magnetic resonance imaging (MRI)) was used for 3-dimensional treatment planning with accurate delineation of the clinical target volume (CTV) and the organs at risk (OAR). Following optimisation of treatment plans and quality control, 27.5Gy in 5 fractions were administered over three days using HDR Iridium-192 afterloading via the temporary cannulae[13,14,15].

For this study, the doses are reported based on the day 1 post-implantation CT scan. CTV and OAR were contoured by the oncologist and radiation doses calculated using the Nucletron Oncentra treatment planning system (TG-43 dose calculation method[16]). The doses reported were the D90 (the minimum dose to 90% of the volume) for the CTV, D2cm^3 doses (the minimum dose received by the two cubic cm of tissue that receives the highest dose) for the bladder, and D0.1cm^3 doses (the minimum dose received by 0.1 cubic cm of tissue that receives the highest dose) for the urethra. All doses were converted to EQD2 doses, taking 2.8Gy as the alpha beta ratio for the CTV and 3Gy for OAR[15].

If the likely proximity of radiation field justified, an oophoropexy was offered to female patients before brachytherapy.

Post-treatment Assessment

On completing treatment, patients commenced surveillance imaging as per RMS2005 protocol[12] for recurrence and complications. In addition, a multidisciplinary clinic was established by the surgeons and oncologists to jointly review BP-RMS patients. A full history, examination and a systematic bladder function assessment were obtained for all, including frequency-volume-chart, voided volumes, post-void-residual (PVR) volume, flow studies, continence status and ultrasound scanning of the upper tracts and bladder. If a problem was identified, invasive video-urodynamics were performed. The expected bladder capacity for age (EBCA) was calculated based on the formula 30ml + (30ml times age in years) for children above 2 years of age[17] and 38ml + (2.5ml times age in months) for children less than 2 years[18]. Patients underwent serial bladder assessments as part of their follow-up. Variations in the documented functional capacity were oberved but only the most recent assessment reported.

Statistical analysis

Categorical data are presented as numbers and percentages, and continuous variables presented by median and range. Patients after PC+BT were compared to age-matched PEP+BT or BT alone.

Due to the small size of the study population, non parametric tests were used: Kruskal-Wallis-test, Mann-Whitney test and Spearman test ($p<0.05$ considered statistically significant), using IBM SPSS 24.0.

Results

During the study period, 13 patients (10 male), aged 9 months to 4 years (median 23 months), with BP-RMS were deemed suitable for CS-BT. Relevant clinical background was present in 2 patients: neurofibromatosis type 1 and high-grade vesico-ureteric reflux (VUR). All presented with localised fusion-negative embryonal BP-RMS (2 botyroid subtype), measuring a median 43mm (23-140mm) in cranio-caudal axis on MRI at diagnosis.

Local control was by PC+BT in three, PEP+BT in four and BT alone in six patients. One patient underwent oophoropexy before brachytherapy. For PC+BT, one third of the bladder was excised in one and one fifth of the bladder in two. The lymph nodes sampled confirmed N0 status.

Follow-up was available for all to a median $3\frac{1}{2}$ years (range $1\frac{3}{4}$-7 years) from diagnosis. No recurrence or relapse occurred. At a median age of 6 years (range 4-9 years), the median (range) bladder capacity was 86% (47%-144%) of that expected for age, including 75% (74-114%) after PC compared to 97% (47%-144%) for other CS-BT patients (p=0.700). Maximum flow rates (Qmax) were 8 to 26ml/sec. There was no significant PVR in all but the VUR-patient with volumes after micturition of 20% the total voided volume.

Invasive video-urodynamic studies were performed in 2 patients who developed complications after treatment. In the patient with pre-existing VUR, this recorded a stable, compliant system with free vesico-ureteric reflux and normal voiding pressures. On extended clamping of the supra-pubic catheter, however, a decompensated picture emerged and a refluxing ureterostomy was created to optimise the safety of the upper tracts. The other patient developed a urethral stricture with a stable compliant bladder but high voiding pressures and low flows on urodynamics; a Mitrofanoff channel was formed for clean intermittent catheterisation. He is dry by day on anticholinergic medication and on free urinary drainage overnight.

The remaining eleven patients are dry by day (Table 1); five with continuous or intermittent assistance of anticholinergic medication for urinary urgency. At night, three patients are enuretic at ages 5, 5 and 9 years; all received BT alone and bladder capacity was assessed at 56%, 120% and 75% of EBCA at last review. Urinary ultrasound scans showed no hydronephrosis in all except one (BT alone) with unilateral mild hydronephrosis (antero-postero-pelvic diameter 12 mm).

No relationship was observed between the radiation dose to the bladder ($2cm^3$ EQD_2) and the assessed bladder capacity (Figure 1), p=0.535. $2cm^3EQD_2$ radiation doses (Table 2) to the bladder were similar for those prescribed anticholinergic medication for urinary urgency (median 191.79Gy, range 61.65-406.17Gy) as compared to those without urgency (median 152.84Gy, range 36.56-217.98Gy), p=0.107. Likewise, no difference in $2cm^3$ $EQD_2$to the bladder was observed between those enuretic (median 154.38Gy, range 61.65-217.98Gy) and those dry at night (median 156.56Gy, range 36.56-406.17Gy), p=1.000. Nor was a patterns observed in the $0.1cm^3$ EQD_2 to the urethra for urgency (median 64.79Gy vs 72.14Gy, ranges 54.59-82.78Gy vs 60.52-222.15Gy), p=0.143; or enuresis (median 64.65Gy vs 71.65Gy, ranges 68.51-72.14Gy vs 54.59-222.15Gy), p=0.540.

Discussion

The clinical management of BP-RMS has changed dramatically over the last decades and improvements in chemotherapy, treatment algorithms including delayed surgery and radiation therapy have made organ preservation feasible for many patients. Published oncological outcomes after CS-BT are good with 84% 5yr EFS and 91% OS survival reported by Chargari et al[7]. Unlike our cohort, their series included 12% with metastatic disease, 4% treated for local relapse and 3% with alveolar histology. At a median follow up $3\frac{1}{2}$ years, all our patients were alive without relapse.

For decades, a radical cystectomy with either an incontinent (ileal conduit) or a continent urinary diversion (ileocecal pouch and catheterizable urinary stoma) was standard treatment. In contrast, our CS-BT approach maintained urethral voiding for 85% of patients. This compares to 75% of those treated by CS and HDR-BT for BP-RMS by Fuchs et al[8].

Fuchs et al[8] also used a HDR-BT technique delivering 30-36 Gy via 4 to 7 cannulae in 12 fractions (3Gy per fraction). However, their surgical approach is much more radical aiming for a “R0” or “R1” resection. While surgery was limited to a partial cystectomy in five of the eight BP-RMS patients in their series, three underwent a partial prostatectomy as well as a partial cystectomy. Only one of the latter group enjoys normal voiding; the others having required urinary diversion surgery. Of those with a partial cystecomy, 60% received anticholinergic medication at 4 to 27 months follow up. In our series, 5 (38%) patients were prescribed anticholinergic medication for urgency with variable uptake.

Of note, Rodeberg et al found the amount of radiotherapy administered for BP-RMS impacted on the functional sequelae for the bladder with 17% of patients receiving <40Gy having dysfunction versus 61% receiving >40Gy. Correcting for differences in fractionation and dose-rate between Chagari et al[7], Fuchs et al[8] and this study, the EQD2 doses used for BT are in fact very similar and lie above the 40Gy threshold identified by Rodeberg et al[19]. We specifically examined the radiation burden on the bladder and urethra as organs at risk, but could not find a relation between the radiation exposure of the bladder or urethra and urinary urgency, enuresis or bladder capacity. Schmidt et al[20] compared the urinary tract function between patients receiving CS with HDR-BT and after bladder-preserving surgery without BT. At 3-111months follow up, no difference in normal voiding behaviour (61% (14/23) vs 60% (6/10)) was observed, based on parental reports, voiding frequency charts, uroflow examination with sonographic bladder emptying, but with improved EFS for those managed with HDR-BT.

While an impact on bladder capacity after partial cystectomy would be expected[6], we found no difference in bladder capacity after resection of one third to one fifth of the bladder compared to those having no resection or minimally-invasive polypectomy alone. Longer follow-up will be required to understand whether this will hold true into adulthood. The median percentage of bladder capacity as expected for age across the study population was 86%, which should be adequate for daytime continence. Indeed, 92% of all our patients were dry by day and 62% dry by night. Day- and night-time continence seems lower than the 72% reported by Chargari et al[7]. However, only children, who had not required cystectomy for bladder failure after completing treatment for BP-RMS, for whom data was available and who were aged over 6 years, were included in their continence analysis.

Not only do techniques of conservative surgery and brachytherapy vary between centres, but the selection criteria also differ. Martelli et alconsider tumour extent >1 cm above the trigone on the posterior bladder wall as unsuitable. In contrast, we consider only localised disease, with a tumour diameter less than 5 cm and/or involvement upto a maximum 1/3 of the bladder after a minimum three cycles of chemotherapy as candiates for CS-BT. In our experience, placement of multiple percutanous brachytherapy cannulae affords reliable coverage of the prostate and bladder neck, meaning that only the bladder above the level of the trigone as well as polyps that remain partially mobile in the bladder are at risk of falling outside the radiation field. Unlike Chargari et al[7] and Fuchs et al[8], resection of the prostate is not needed, and almost half the patients required no surgerical resection.

One patient suffered a urethral stricture and another suffered decompensation on a background of high-grade VUR on clamping the suprapubic catheter. Despite this, and contrary to others' experience[7,8], none of our patients have developed a poorly-compliant small capacity bladder, so far. Whether this is a matter of time or the result of less surgery at the bladder neck remains to be seen. We whole-heartedly agree with previous authors that in- and out-of theatre collaboration by the multi-disciplinary team is essential for optimal tailoring of surgery and brachytherapy to each patient.

Systematic bladder function assessment in children with BP-RMS at a median $3\frac{1}{2}$ years after CS-HDR-BT revealed day-time dryness in 92%, with 85% voiding urethrally, and 62% achieving day-and-night continence at age 4 to 9 years. Bladder capacity remained adequate despite resection of up to one third of the bladder. In comparison to other CS-BT approaches, we report reduced open surgery, with minimally-invasive percutaneous surgery and HDR-BT or brachytherapy alone being suitable for many. So far, all are alive without relapse.

Conflict of Interest statement

The authors have no conflict of interest to declare.

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Data available on request due to privacy/ethical restrictions.

Legends

Table 1. Continence status at last follow-up.

Table 2. Conservative surgery and HDR brachytherapy treatment, including radiation dose and continence outcome.

Radiation dose is presented in Gy to target volume as the D90 EQD_2, the bladder as the $2cm^3EQD_2$ and the urethra using the $0.1cm^3EQD_{2..}$ Male (M), Female (F); DD- dry day, DN- dry night, WN - wet night, CIC – clean intermittent catheterisation. See methods for further details.

Figure 1. Bladder $2cm^3$ EQD_2radiation dose and observed bladder capacity as a percentage of that expected for age.

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