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Analysis of radiation dose/volume effect relationship for anorectal morbidity in children treated for pelvic malignancies

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Running Title: Rectal morbidity in pediatric brachytherapy

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ABSTRACT

PURPOSE: To examine dose-volume effect relationships for anorectal morbidity in children treated with image-guided brachytherapy for pelvic tumors.

METHODS AND MATERIALS: Medical records of all consecutive children with pelvic tumors treated in our center and receiving image-guided pulsed-dose-rate (PDR) brachytherapy with or without external beam radiation therapy (EBRT) between 2005 and 2019 were reviewed. The impact of the minimal doses to the most exposed 0.5 cm³, 1 cm³ and 2 cm³ of the anorectum (respectively: D_{0.5cm³}, D_{1cm³} and D_{2cm³}), total reference air kerma (TRAK) and volume of 100% isodose was examined for anorectal toxicities.

RESULTS: 78 consecutive children were included. Median age was 2.9 years (range: 0.8-14.9 years). Most of the tumors were bladder/prostate (67%) or vaginal (22%) rhabdomyosarcoma. Six patients received EBRT in addition to brachytherapy. Median follow-up was 21.3 months. At last follow-up, 30 children (38%) had experienced CTCAEv5 grade \geq 1 acute or late anorectal events: 24% had grade 1 events, 7.7% had grade 2 and 6.4% had grade 3. No grade $>$ 3 toxicity was observed (e.g. fistula or stricture). In univariate analysis, the D_{0.5cm³} and D_{1cm³} were significant for probability of grade 1-3 (p=0.009 and p=0.017, respectively) and grade 2-3 anorectal morbidity (p=0.007 and p=0.049, respectively). There was no significant correlation for D_{2cm³} (p=0.057 for grade 1-3 and p=0.407 for grade 2-3). A 10% probability (95% CI: 4-20%) for grade \geq 2 anorectal toxicity was reached for a D_{0.5cm³} = 52 Gy. The age, EBRT use, TRAK, and treated volume were not significant.

CONCLUSIONS: This is the first study showing significant dose/volume effect relationships for anorectal morbidity in children treated with brachytherapy. Integrating these data into

brachytherapy treatment planning may help to optimize the therapeutic index in these very young patients.

Keywords: brachytherapy; rhabdomyosarcoma; children, rectal dose; morbidity; proctitis.

INTRODUCTION

Pelvic pediatric tumors are rare and consist primarily of urogenital tract rhabdomyosarcomas (RMS), including bladder/prostate RMS (BP-RMS) and vaginal RMS (1–4). The mortality rate of these cancers has been decreasing for several years (5) and five years overall survival is now close to 80% for genital and bladder prostate RMS (6). A therapeutic challenge in these very young patients (median age < 3 years) is not only to achieve cure but also to minimize long-term toxicity (7–9). This approach is made possible with multimodal conservative strategies combining chemotherapy, conservative surgery and radiation therapy (10–15). Radiation therapy carries a potential for acute and late toxicities, especially at anorectal level (16,17). Although usually transient, rectal radiation-induced side effects may include rectal bleeding, proctitis, transit disorder, encopresis, abdomino-pelvic pain, fistula, stricture and subsequent malignant neoplasm. These effects may be disabling and definitively impact on quality of life and, in rare cases, might require invasive procedures and mutilating surgery (16–20). It is therefore important to better examine those toxicities in the global management of pediatric cancers. By contrast to the adult patient population (21), there is to our knowledge no published data on dose/effect relationships for rectal morbidity in children.

Compared to EBRT, brachytherapy allows for decreasing the volume of normal tissues irradiated. Because of very sharp dose gradients allowing focal dose escalation and optimal organs at risk (OARs) sparing, brachytherapy is an appropriate alternative to external radiotherapy in order to optimize the efficacy/toxicity ratio. Brachytherapy can be used to minimize the long-term effects of EBRT, especially in terms of bowel morbidity and impact on bone growth. Brachytherapy reduces the long-term effects of EBRT, especially in terms of bowel morbidity, urogenital side effects, and impact on bone growth. It is therefore proposed as part of the treatment of pelvic pediatric tumors in highly specialized centers (11–13,15). In

the past years, there has been a systematic implementation of 3D imaging for brachytherapy planning in an attempt to improve target coverage, but also to better spare the OARs, including the rectum. So far, treatment optimization has primarily been based on the principle of achieving as low as reasonably acceptable doses and translation of adult tolerance data. Despite this, the clinical goal for cure frequently requires doses and/or volumes that unavoidably expose the rectum to potential morbidity. In adults, relationships have been clearly shown between dose/volume parameters and the probability of anorectal toxicities (21). However, the particular radiosensitivity and pelvic anatomy in children suggest results difficult to transpose (22,23).

Based on the amount of dosimetric parameters collected in these children, we examined radiation dose/volume parameters and potential correlations with the occurrence of anorectal events after image-guided brachytherapy, in order to establish dose/volume relationships.

MATERIAL AND METHODS

Study population

Medical records of all consecutive children with histologically proven pelvic malignant tumors treated at our center and receiving brachytherapy for pelvic malignancy between November 2005 and January 2019 were retrospectively reviewed. All pediatric malignant pelvic tumors treated during this time interval were included, regardless of histological type, with the exception of anorectal tumors that were excluded to limit biases in interpreting treatment-related symptoms. Patients addressed for re-irradiation and those for whom rectal

dose/volume parameters were not available (2D treatments) were also excluded. Patient flowchart is shown in **FIGURE 1S**.

Anorectal morbidities were collected from medical data files in January 2020. Children were followed by the radiation oncologist, pediatrician and surgeon, in turn, every 3-4 months during the first 3 years, then every 6 months during the next 2 years and yearly thereafter. An MRI was performed at least twice a year for the first 2 years and annually thereafter. In addition to routine clinical evaluation, a gynecological examination was performed under general anesthesia (according to the age) in case of gynecological RMS. The indication for endoscopic examination was left to the discretion of the physician, depending on the importance and duration of the complaint. If patients were followed in other institutions (e.g. for international patients), follow-up data were regularly provided by the referring onco-pediatrician about the patient's clinical condition. If no update was received, the referring physician was contacted. All patients were included in the statistical analysis. This retrospective study was conducted in accordance with ethical standards and with the 1964 Helsinki declaration and its later amendments.

Brachytherapy treatment

After a multidisciplinary discussion, brachytherapy was deemed an essential part of multimodal management for all patients subsequently analyzed in this study. Therapeutic strategy was decided on an individual basis after validation by multidisciplinary tumor board, depending mainly on tumor location, histological type and disease extent. Treatment indications and modalities have been reported elsewhere, and are therefore not described (10,14,24). In all cases, the strategy included a thorough analysis of the risk/benefit balance and brachytherapy was preferred to external irradiation where possible. However, EBRT was

still used in the case of lymph node involvement and in this situation brachytherapy was used as a boost technique. Systemic treatments depended on the clinical situation and on current protocols.

Patients were referred for local treatment after having received first line chemotherapy, depending on their risk group of treatment and according to international pediatric current protocols. No patient received chemotherapy concurrently with brachytherapy.

In BP-RMS, implantation of plastic tubes was conducted peri-operatively, during the same procedure as conservative surgery, through a transperineal approach. The surgery consisted of a partial cystectomy and/or partial prostatectomy +/- bilateral ureteral reimplantation. Four single leader plastic tubes encompassing the prostate and bladder neck were implanted. To avoid topographical modification, plastic tubes were sutured to bladder wall. A temporary ovarian transposition was done. Unilateral testicular transposition was performed in boys from 2016. Irradiation began 5-6 days later to manage perioperative complications.

For gynecological tumors, brachytherapy was the only local treatment performed whenever possible. Ovarian transposition was still performed before brachytherapy. Gynecological tumors were treated using a personalized vaginal mold applicator built from a vaginal impression and inserted under general anesthesia. An intrauterine tube was added for tumors extending into the cervix. Interstitial brachytherapy using a plastic tube technique was used if the vulva was affected or if the vagina was invaded more than 5 millimeters thick. For the three cervix cancers treated in this cohort, only endocavitary cervico-vaginal application was used. The personalized vaginal mold applicator was sutured to the vaginal wall to avoid movements or expulsion. Irradiation for gynecological cancers began the day after implantation.

All patients were treated with three-dimensional image-guided pulse-dose rate (PDR) brachytherapy, using Iridium-192 as radionuclide. Computed tomography (CT) scans and MRI scans were acquired in the supine position, without contrast media or radiopaque marker. Slice thickness was 1.5mm. After acquisition, axial images were transferred to the Plato BPS treatment planning system (Nucletron, Veenendaal, The Netherlands). A three-dimensional set was reconstructed and the application was digitized. Target volumes and OARs, including the anorectum, were delineated. Treatment was planned on the CT scan. An additional MRI (T2 sequence) then merged with the dosimetric CT scan, to improve target definition. Brachytherapy target volume was defined as the residual tumor following chemotherapy. No additional margin was applied. The dose was prescribed according to the Paris system rules (85% of the minimal dose rate between the planes) for interstitial brachytherapy, or to peripheral envelope for endocavitary implants. In both cases, we first performed normalization to prescription points then we completed a manual optimization based on manual modification of dwell times and positions to achieve good target coverage (at least 90% of the prescription dose delivered to at least 90% of the clinical target volume) while minimizing OARs' doses. For BP-RMS, we used the possibility of adjusting dwell times to slightly decrease the doses to the anterior rectal wall or to increase coverage of the bladder wall in the cranial direction, if necessary, to achieve proper target coverage. For each patient, the anorectum was contoured as an anatomical unit according to the criteria proposed by the Radiation Therapy Oncology Group (25), as a single organ, from the anal verge to the rectosigmoid flexure. The whole organ was contoured, not only wall contours. No dose constraint was applied to the anorectum, but optimization aimed at minimizing as much as possible overlaps between the anorectum and the 100% isodose. Two examples of dose distribution are presented in **FIGURE 2S** and **FIGURE 3S**.

For brachytherapy alone treatments, prescription dose was 50 to 60 Gy, regardless of the patient's age. In the situation of pelvic nodal metastases, brachytherapy dose was kept at 15-20 Gy, and the treatment was completed by EBRT with a 3D conformal or Volumetric Modulated Arc Therapy (VMAT) technique, delivering a total dose of 40-45 Gy to treat initial sites of disease, including initially involved lymph nodes. Brachytherapy dose was delivered through continuous hourly pulses of 0.42 Gy per pulse, 24 hours per day (in order to deliver 10 Gy per day), resulting in a total brachytherapy duration ranging from 1.5 to 6 days of treatment (depending on the prescribed dose).

The position of the brachytherapy tubes was checked daily by measuring of the external length of each catheter. X-rays with dummy sources were performed in order to ensure integrity and proper localization of the tubes every two days. A control CT scan was performed during the brachytherapy if the external length of a catheter was abnormal, if an irregularity was detected on the X-rays or if an event that could be responsible for a topographical modification of the tubes occurred. After treatment completion, brachytherapy catheters and/or vaginal mold applicators were pulled out under brief general anesthesia. Chemotherapy was resumed thereafter to complete the protocol (up to a total of 9 cycles in most of RMS), without actinomycin D during the 6 weeks following brachytherapy to avoid increasing radiation-induced side effects.

Dose/volume parameters analysis

$D_{0.5\text{cm}^3}$, $D_{1\text{cm}^3}$ and $D_{2\text{cm}^3}$ were retrospectively reported and converted into equivalent doses per 2 Gy fractions (EQD2) according to the linear quadratic model with $\alpha/\beta = 3$ Gy and a half-time repair of 1.5 hour (26). The volume of 100% isodose was also examined, as well as the Total Reference Air Kerma ($\text{TRAK} = \sum t_i \times S_i$ with S_i as the reference air kerma rate for each

source and t_i as the irradiation time for each source) expressed in cGy at 1 meter reference distance. In case of external radiotherapy, the EBRT dose (converted into EQD2 according to the same model) was added to the brachytherapy dose, on the assumption that anorectal small volumes studied ($D_{0.5\text{cm}^3}$, $D_{1\text{cm}^3}$ and $D_{2\text{cm}^3}$) were located in the prescription isodose of EBRT.

Definition of morbidity

Acute morbidity was defined as the occurrence or worsening of symptoms during brachytherapy or in the following three months. Late morbidity was defined as any toxicity event occurring or lasting over three months after the first day of brachytherapy. Acute and late morbidity were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. If the symptoms were pre-existing, they had to be increased in grade to be recorded. Anorectal morbidity endpoints examined followed morbidity analysis data from adults treated with image-guided brachytherapy and included rectal bleeding, proctitis, stenosis and fistula (21). Based on radiation proctitis-specific quality of life analyses from the European Organization for Research and Treatment of Cancer (EORTC), the following endpoints were also included: encopresis, transit disorders (diarrhea and/or constipation) and, if associated with other anorectal symptoms, abdomino-pelvic pain (27). Anorectal events were analyzed independently and together as overall anorectal morbidity.

Statistical analysis

The data processing and analysis was done using R v3.6.1 (The R Core Team 2019). Because doses for each volume of interest were not normally distributed, mean doses were compared through the Kruskal-Wallis test. For the toxicity threshold analysis, a logistic regression was performed with a probit link function on the continuous dose variable (21,28–30). Alpha value was set at 5%. Before reporting on the models, potentially confounding variables were

investigated. The addition of other independent variables such as age and gender to the models did not impact the outcome thus it was decided to report on the simplest models for more clarity. Descriptive survival plots using Kaplan and Meier curves with toxicity for events and a time window of two years were reported. Secondary endpoint with failure for events (reporting the failure-free survival (FFS)) was briefly evaluated.

RESULTS

Study population and previous treatments

Patients and treatments characteristics are shown in **TABLE 1**. A total of 78 patients were included for analysis. Among them, 72 (92%) were treated between 2014 and 2019 (prior to 2014, children were mainly treated with low dose rate (LDR) brachytherapy). Thirty-two (41%) patients had been previously treated with chemotherapy in France and 46 patients (59%) were referred from international centers only for brachytherapy. Median age at the time of brachytherapy was 2.9 years (range: 0.8-14.9 years) and the male/female ratio was 1.3. The predominant histology was embryonal rhabdomyosarcoma (88%). Most of the tumors were bladder/prostate (67%) or vaginal rhabdomyosarcoma (22%). Five children (6%) were treated for a vaginal malignant germ cell tumor and one (1%) was treated for an alveolar rhabdomyosarcoma involving the urethra and the vagina. Three girls (4%) were treated for a cervical cancer: two for a clear cell adenocarcinoma and one for an undifferentiated carcinoma.

Fifty-eight patients (74%) were treated according to the “RMS protocol 2005” depending on their group and risk subgroup. The remaining 30 patients (including those with non-RMS histology) were treated with other protocols. The most frequently used chemotherapy regimen was IVA (ifosfamide, vincristine and actinomycin D) +/- doxorubicine in 56 patients (72%).

At the time of brachytherapy, a median number of seven chemotherapy cycles (range: 3-15) had been delivered. After brachytherapy, chemotherapy was resumed to complete the protocol.

Mean follow-up time in our study population was 31 months (range: 3 months–13.5 years). Median follow-up was 21.3 months. A total of three patients experienced tumor relapse. One patient with vaginal germ cell tumor experienced local failure associated with lung metastases three months after brachytherapy. She had been heavily pretreated in her local center and was addressed at time of relapse. One patient treated for a vaginal RMS experienced 10 months later a bladder RMS, distant from the primary gynecological tumor site. In the whole cohort studied for rectal morbidity, 4-year estimated median FFS was 95.4% (95% CI: 86.3-98.5%).

Brachytherapy characteristics

Median physical dose of brachytherapy was 60 Gy (range: 15-60 Gy) in 143 pulses (range: 40-150 pulses). Median number of catheters used was four (range: 2-9 catheters). Six patients (7.7%) received EBRT before or after brachytherapy in order to deliver a total median physical dose of 60 Gy (range: 48.73-65 Gy), including both contribution of brachytherapy and EBRT. After converting doses into EQD2, median $D_{0.5\text{cm}^3}$, $D_{1\text{cm}^3}$ and $D_{2\text{cm}^3}$ doses were 53.4 $\text{Gy}_{\alpha\beta 3}$ (range: 10.4-97.6 $\text{Gy}_{\alpha\beta 3}$), 45.7 $\text{Gy}_{\alpha\beta 3}$ (range: 8.2-74.8 $\text{Gy}_{\alpha\beta 3}$) and 35.4 $\text{Gy}_{\alpha\beta 3}$ (range: 6.4-69.4 $\text{Gy}_{\alpha\beta 3}$), respectively. Median TRAK was 1.89 cGy (range: 0.44-3.6 cGy) and median volume of the prescription isodose was 35.63 cm^3 (range: 3.39-235.09 cm^3). The median absolute rectal volume receiving a physical dose of 60 Gy was 0.2 cm^3 (range: 0-2.07 cm^3). The median relative rectal volume receiving 60 Gy was 0.69 % (range: 0-11.2%). Median $D_{2\text{cm}^3}$ dose to the sigmoid was 9 Gy_{EQD2} (when delineated).

Morbidity analysis

No patient had anorectal morbidity prior to brachytherapy except for one child who had clostridium difficile diarrhea. This patient had no acute or chronic toxicity after brachytherapy. At the time of analysis, thirty children had developed acute and/or late anorectal toxicities of any grade (38.5%). Eleven patients (14.1%) had grade ≥ 2 and five (6.4%) patients experienced grade 3 toxicity, resulting in a cumulative incidence at 1 year of grade ≥ 2 acute and/or late anorectal toxicities of 16.4% (95% CI: 6.9-24.9%). No grade > 3 rectal toxicity was observed. No patient required transfusion for rectal bleeding. No fistula or stricture occurred during follow-up. Cumulative incidence of overall anorectal morbidity (all grades) is shown in **FIGURE 1**. Most frequent anorectal events were as follows: rectal bleeding, proctitis and transit disorders. Anorectal morbidities and grades are detailed in **TABLE 2**.

Eleven patients developed acute toxicity. Median time to symptom onset was 6.5 days (range: 1-28 days). Median duration of symptoms was 5.5 months (range: 0.2-36 months). The only grade 3 acute toxicity observed was abdomino-pelvic pain that required introduction of morphine and lasted seven months. This complication occurred in a patient treated with combination of surgery and postoperative brachytherapy (without EBRT) for a bladder prostate RMS and was associated with acute grade 2 rectal bleeding. Among patients with acute toxicity, 6/11 (54.5%) had symptoms which continued beyond 3 months; for 2/11 their symptoms resolved within 3 months but they then experienced sequential late toxicity.

With mean follow-up time of 31 months, a total of 27 patients had late morbidity. Median time to onset of late morbidity was 7.7 months (range: 3-35 months) and median duration of symptoms was 7 months (range: 1-96 months). Five patients (6.4%) had late grade 3

toxicities, consisting primarily of rectal bleeding and proctitis. These toxicities were treated with morphine, local steroids or non-steroidal anti-inflammatory drugs. A more invasive procedure was required in only one patient, treated by endoscopic catheterization of vascular ectasias and after one failure, with hemostatic powder with excellent efficacy. Another patient underwent two cycles of argon plasma electrocoagulation with partial improvement of symptoms and one child was treated with hyperbaric oxygen therapy. Radiation proctitis was confirmed in six patients undergoing endoscopic examination (rectoscopy or colonoscopy) because of symptoms.

Dose–volume effect analysis

There was a significant correlation between the $D_{0.5\text{cm}^3}$, $D_{1\text{cm}^3}$ ($\text{EQD2}_{\alpha/\beta=3}$) and the probability of grade 1-3 toxicity ($p=0.009$ and 0.017 , respectively). The impact of $D_{0.5\text{cm}^3}$ and $D_{1\text{cm}^3}$ doses were also significant for grade 2-3 anorectal morbidity ($p=0.007$ and $p = 0.049$, respectively) (**FIGURE 2**). The risk of grade 2-3 anorectal morbidity was 8.9% (95% CI: 4-19%) for a $D_{0.5\text{cm}^3}$ of 50 $\text{Gy}_{\alpha\beta 3}$, 16.5% (95% CI: 9-28%) for a $D_{0.5\text{cm}^3}$ of 60 $\text{Gy}_{\alpha\beta 3}$ and 27.4% (95% CI: 14-44%) for a $D_{0.5\text{cm}^3}$ of 70 $\text{Gy}_{\alpha\beta 3}$. The 10% probability (95% CI: 4-20%) for grade ≥ 2 anorectal toxicity was reached for a $D_{0.5\text{cm}^3} = 52 \text{ Gy}_{\alpha\beta 3}$. $D_{2\text{cm}^3}$ did not show significant correlation with anorectal toxicities ($p=0.057$ for grade 1-3 and $p=0.407$ for grade 2-3). Mean rectal $D_{0.5\text{cm}^3}$, $D_{1\text{cm}^3}$ and $D_{2\text{cm}^3}$ doses and p values for comparisons according to the occurrence of rectal symptoms are shown in **TABLE 3**. Other factors tested for rectal morbidity (age, EBRT use, TRAK, the volume of 100% isodose) were not significant. Logistic regression analyses with a probit link function testing the rectal dose as a continuous variable are shown in **FIGURE 3**.

Due to missing data, we could not thoroughly examine the potentially deleterious interactions between chemotherapy delays and brachytherapy in terms of anorectal morbidity. Based on

available data (40 patients with complete data on pre-BT and post-BT chemotherapy dates), the time interval between brachytherapy and chemotherapy (delivered before or after brachytherapy) was not significant for anorectal morbidity probability.

DISCUSSION

Very scarce data exist on the tolerance doses for rectal morbidity in children. In our institute, brachytherapy is preferred to any other irradiation modality for treatment of children with genitourinary malignancies, in order to avoid the long-term sequelae of abdomino-pelvic irradiation. Rectal side effects are frequent, usually mild and spontaneously resolving. More rarely, anorectal symptoms associated with brachytherapy may lead to significant morbidity and require specific management. With the advent of image-guidance as part of the dosimetric process, it has become possible to accurately register OARs' doses. Our objective was to identify potential dose/volume relationships that could be used as optimization objectives at the time of treatment planning.

An analysis from the Childhood Cancer Survivor Study (16) has examined the probability of anorectal complication among patients treated with external beam radiotherapy. It was reported that exposure to external irradiation doses was associated with late-onset of anorectal morbidity, with an adjusted rate ratio (RR) of 1.6 (95% CI: 1.1-2.3) for doses ranging from 30 to 49.9 Gy and of 5.4 (95% CI: 3.1-9.2) for doses \geq 50 Gy. There was no significant deleterious effect for doses less than 30 Gy (adjusted RR: 1.1; 95% CI: 0.7-1.8). However, this study with very long-term follow-up lacks dose/volume parameters and therefore does not provide accurate information to guide treatment optimization.

In adult locally advanced cervical cancer patients treated with image-guided brachytherapy, strong correlations have been shown between dose/volume parameters and the probability of

rectal complications (21,31,32). To our best knowledge, our study is the first one to show such a correlation in children. Indeed, due to potential differences in radiosensitivity and anatomic specificities, it was important and necessary to more thoroughly examine how rectal dose may impact on functional outcome in pediatric cancer (22,23). We observed that a 10% probability for grade ≥ 2 anorectal toxicity was reached for a $D_{0.5\text{cm}^3} = 52$ Gy, while Mazon et al. reported a 10% probability for a $D_{2\text{cm}^3} = 69.5$ Gy in adults (21). Such a difference should be analyzed in the light of the considerably smaller rectal volumes of interest we were dealing with in this population of very young patients (median age at time of brachytherapy: 2.9 years). The rectal volume varies according to the age and repletion. Taking into account this variability, the mean rectal volume is around 25-30 cm^3 in 3-year old children, versus 55–60 cm^3 in adults. Based on this ratio of 1:2 in terms of rectal absolute volumes, it would be expected that the same probability of complication would be achieved if the most irradiated 2 cm^3 of the rectum in adults receive the same minimal dose as the most irradiated 1 cm^3 of a rectum in children. Analysis of probit curves suggests however that the difference between adults and children is not only because of smaller volumes of the organ, but also of an increased intrinsic radiosensitivity. Indeed, the probability of grade ≥ 2 complication was 30% for a $D_{1\text{cm}^3} = 70$ Gy (vs 10% expected from adult data) (21). The delivery of chemotherapy prior to and after brachytherapy, as per pediatric protocols, may also have favored radiation-induced side effects (e.g.: Actinomycin D). This is a significant concern, especially if chemotherapy is reintroduced after brachytherapy at time of acute rectal symptoms. Due to missing data, we were unable to thoroughly examine the potentially deleterious interactions between chemotherapy timing and brachytherapy in terms of anorectal morbidity.

We observed a significant correlation between the $D_{0.5\text{cm}^3}$, $D_{1\text{cm}^3}$ and the probability of grade 1-3 ($p=0.009$ and 0.017 , respectively) and grade 2-3 anorectal morbidity ($p=0.007$ and 0.049 , respectively). In adults, most clinical evidence has been collected for $D_{2\text{cm}^3}$ (10,31,33,34) and

therefore, brachytherapy treatment planning aims for rectal dose volume constraints are usually presented in terms of $D_{2\text{cm}^3}$. It is however clinically relevant to report on smaller volumes. Indeed, the anorectum has a serial architecture. Limited volumes irradiated at high doses might be associated with local effects such as local inflammation, telangiectasia, ulceration or necrosis. High value of $D_{0.5\text{cm}^3}$ may be regarded as a rectal wall hot spot which may indicate an increased risk of a clinically relevant effect (21,35). In other publications reporting on the outcome of BP-RMS patients and focusing on bladder preservation probability, no significant dose/effect correlation could be shown for rectal morbidity, probably because of a low number of events, insufficient follow-up and lack of dosimetric parameters (10,11). In the current series, in which BP-RMS and gynecological cancers were merged, significant dose/volume parameters were identified.

These results, based on a relatively small number of patients, should however be interpreted with caution, and the retrospective design of the study does not allow definitive conclusions to be drawn on normal tissue response following radiotherapy. Pelvic pediatric tumors are rare and our cohort is the largest one with image-guided brachytherapy but nevertheless, the number of anorectal events was low, especially for grade 2-3 (11 events). Secondly, the follow-up remains relatively short, with >90% of patients treated within the past 5 years. Although most of the late effects occurred within a median of 8 months, we cannot rule out that very late toxicities may occur in these very young children for whom the risk may be even higher (22). Dose/volume parameters may also not fully reflect the true rectal exposure in the context of PDR treatment, as there may be changes in rectal repletion during brachytherapy duration. A limitation common to most series examining rectal morbidity in adult patients treated with brachytherapy, is that some of the observed toxicities, such as abdomino-pelvic pain or transit disorder, might have been caused (or increased) by sigmoid or bowel irradiation (21,32). As small intestine and sigmoid were systematically given low doses

(because of the irradiated sites and techniques), we hypothesized that most events were caused by anorectal irradiation. In order to limit the biases related to EBRT (used in a minority of patients), abdomino-pelvic pain was considered in the statistical analysis only if associated with rectal symptoms of similar or higher grade.

Anorectal morbidity may have a strong impact on children's quality of life. Treatment and prevention of radiation-induced rectal side effects are therefore essential. In our experience, symptomatic and dietetic treatment was often sufficient to control symptoms. For grade 3 rectal bleeding and proctitis, semi-invasive procedures were necessary. These approaches have demonstrated their effectiveness, though recurrence of symptoms is frequent (36,37). Prevention of rectal complications may be achieved by decreasing doses to the rectum and our data may be seen as a first step to integrate dose/volume constraints into brachytherapy treatment planning in order to reduce long-term morbidity. In the era of stepping source technology, it is possible to adjust dwell times to decrease the doses to the anterior rectal wall and minimize the probability of rectal complications. Use of tissue expanders may also be adequate to minimize rectal doses, though such a strategy may be difficult to implement in children given anatomical constraints (34,35,36). Brachytherapy use itself appears to reduce the rectal dose compared to IMRT, as shown in the Heinzelmann et al. study (38). Authors showed that rectal doses could be reduced by 1/3 using brachytherapy, compared to IMRT. This ability to deliver very conformal dose distribution around target volumes while sparing organs at risk, such as the rectum, is particularly relevant in these very young children. In this series, we observed only 6.4% of patients developing grade 3 and no grade 4-5, stricture or fistulas were reported. This is a satisfactory toxicity profile given the very young age at time of treatment, confirming that brachytherapy is an adequate tool to maximize the therapeutic index for the treatment of pelvic malignancies in children (39,40).

Proton therapy is being increasingly used in pediatric cancers because of its ballistic advantages, but its superiority on brachytherapy is not demonstrated and there are still scarce data on proton therapy in pediatric pelvic tumours. Dosimetric data suggested that rectum doses could be reduced by 2/3 using proton therapy compared to IMRT (38). On the contrary, other authors did not find a statistically significant difference between proton therapy and IMRT in terms of median dose received by the rectum (median anterior rectum dose: 41 Gy with proton therapy versus 38 Gy with IMRT) (41). A cohort of 19 BP-RMS patients treated with proton therapy showed an acceptable toxicity profile but still high local failure rates in larger tumors, supporting dose escalation in these patients (42). In this context, brachytherapy is particularly appropriate to increase focally the dose while minimizing doses to the rectum. An adult study on ten patients comparing different irradiation techniques for localized prostate cancer showed that brachytherapy would allow for a better rectal sparing, as compared to proton therapy (median dose to the rectal wall: 19 Gy with proton therapy *versus* 10 Gy with HDR brachytherapy) (43). Dosimetric comparisons in adult gynecological cancers also highlighted the superiority of brachytherapy to any other EBRT modality, including protons, in terms of dose escalation and OARs sparing (44). One important inconvenience of proton therapy in these pelvic locations is the extremely high sensitivity of the dose calculation regarding bladder and rectum movements, which require applying additional margins. Finally, the ability of brachytherapy to minimize integral dose delivered to the patient body is particularly relevant in children for the stochastic risk of second cancer (45). Further studies are therefore needed to explore this subject.

CONCLUSION

To our knowledge, this is the first study showing significant dose/volume effect relationships for anorectal morbidity in children treated with brachytherapy. The $D_{0.5\text{cm}^3}$ appeared to be the most relevant factor with a $D_{0.5\text{cm}^3} > 52$ Gy associated with a $> 10\%$ probability for grade ≥ 2 anorectal toxicities. Comparison with data from adults suggests a higher intrinsic sensitivity to high doses delivered to small volumes. Integrating these data into brachytherapy treatment planning may help to optimize the therapeutic index in these very young patients. Such dosimetric data may be potentially applicable to other irradiation techniques, though validation in specific cohorts of EBRT patients is still lacking. Long-term follow-up is required, in particular to correlate dose/volume parameters with quality of life analyses and ensure that the satisfactory functional outcome of brachytherapy in terms of anorectal morbidity is maintained over time.

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FIGURE LEGENDS

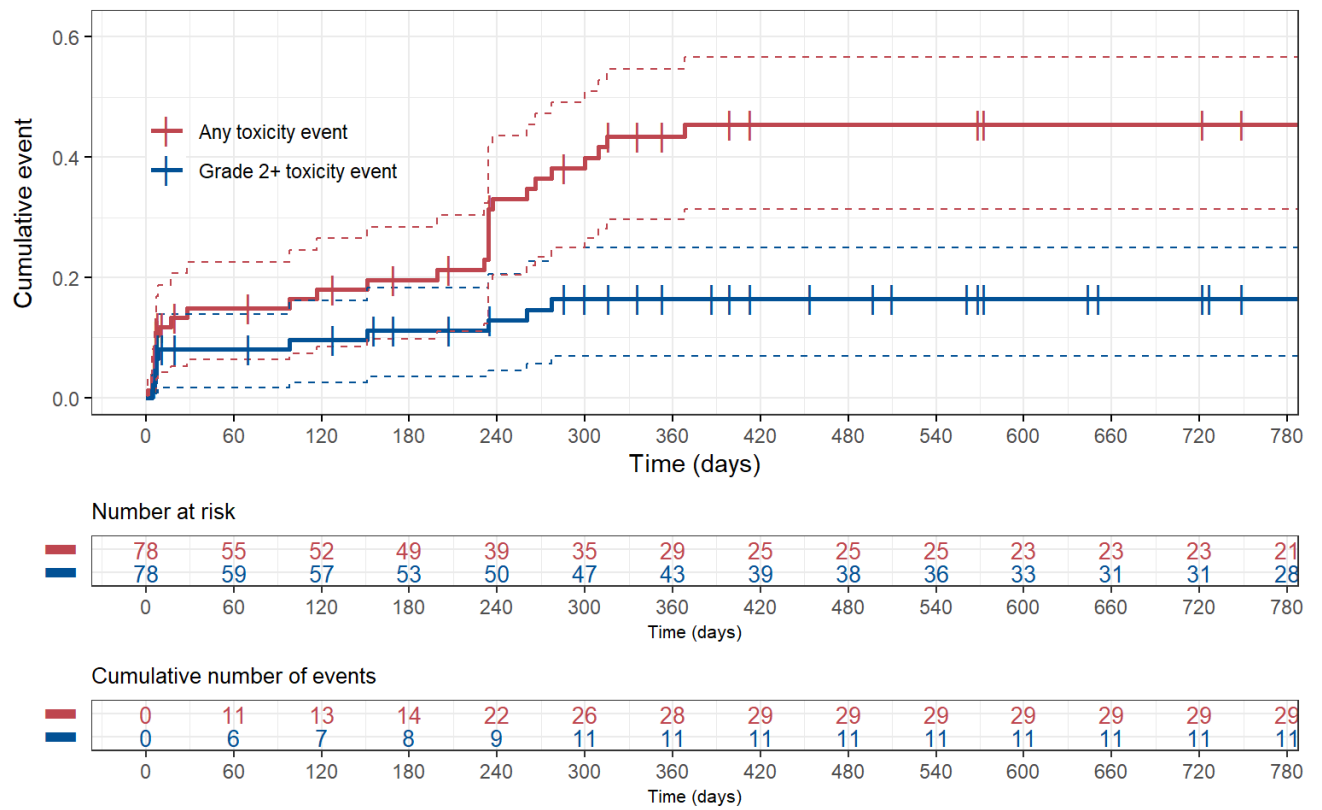
Figure 1 – Cumulative incidence of overall anorectal morbidity in the whole cohort

Number of patients at risk and number of events are reported in tables below the plot

Figure 2 – Cumulative incidence of overall anorectal morbidity according to the $D_{0.5cm^3}$ (EQD $_{2\alpha/\beta=3}$)

Figure 3 – Probability of any grade and grade ≥ 2 anorectal morbidity according to $D_{0.5cm^3}$ and D_{1cm^3} (EQD $_{2\alpha/\beta=3}$)

Figure 1 – Cumulative incidence of overall anorectal morbidity in the whole cohort



Number of patients at risk and number of events are reported in tables below the plot.

Figure 3 – Probability of any grade and grade ≥ 2 anorectal morbidity according to $D_{0.5cm^3}$ and D_{1cm^3} (EQD2 $_{\alpha/\beta=3}$)

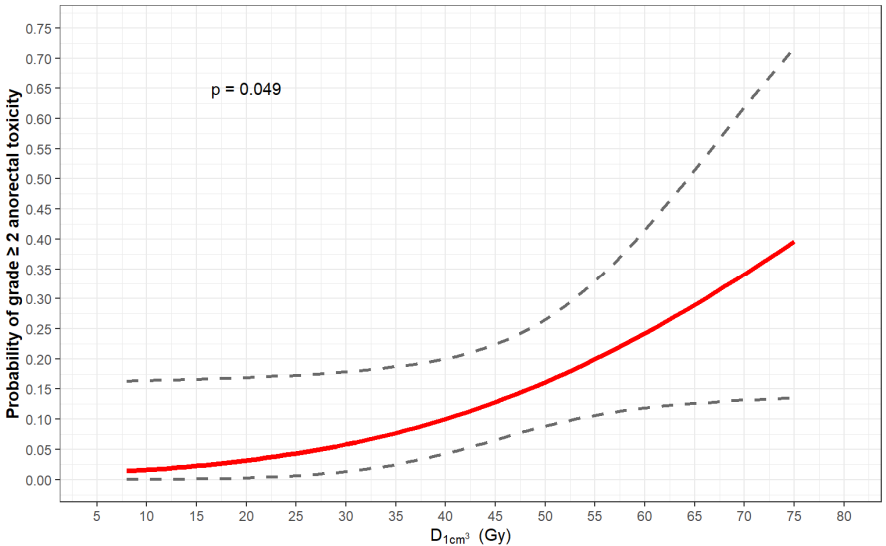
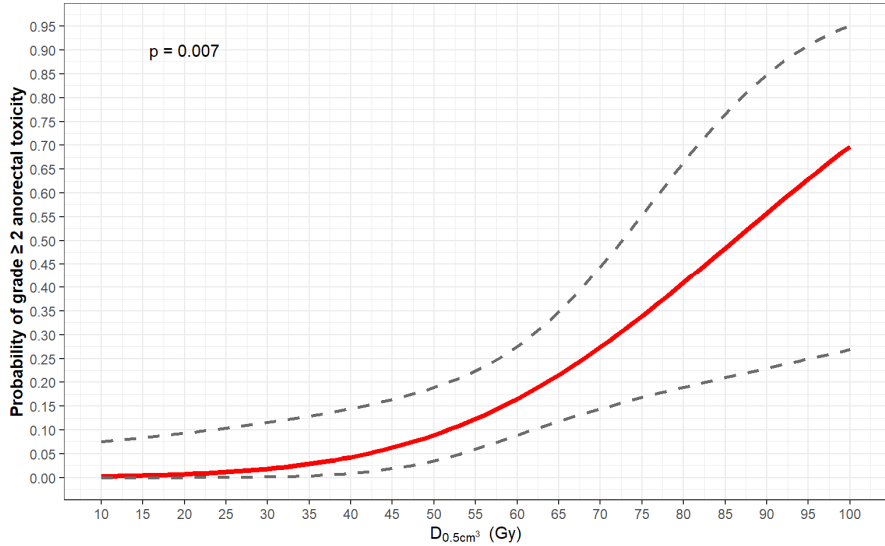
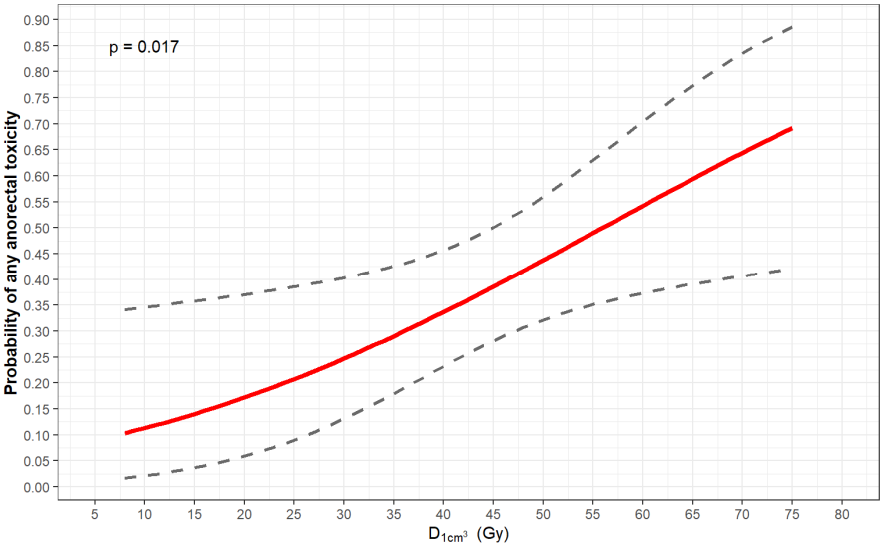
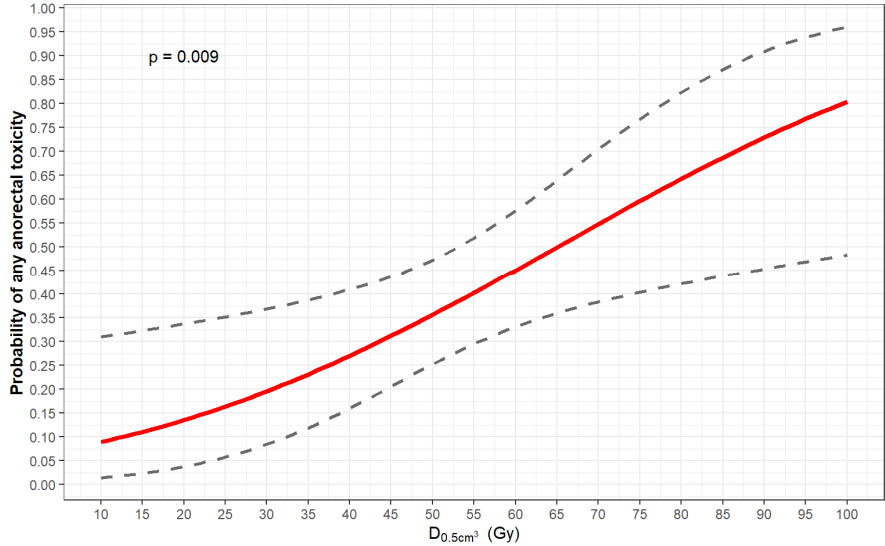


Table 1 – Epidemiological characteristics of patients and their treatments

		Number of cases
Patients	Age (years)	
	Median [range]	2.9 [0.8 – 14.9]
	Sex	
	Male	44 (56%)
	Female	34 (44%)
	Tumor histology	
	Embryonal rhabdomyosarcoma	69 (88%)
	Alveolar rhabdomyosarcoma	1 (1%)
	Malignant germ cell tumor	5 (6%)
	Clear-cell adenocarcinoma	2 (3%)
	Undifferentiated carcinoma	1 (1%)
	Tumor location	
	Bladder or bladder/prostate	52 (67%)
Vagina	23 (29%)	
Cervix	3 (4%)	
Tumor size (mm)		
Median [range]	60 [10 – 162]	
Node stage		
Negative	71 (91%)	
Positive	7 (9%)	
Group risk		
IRS III (locally advanced disease diagnosed on biopsy)	68 (87%)	
IRS IV (metastatic disease)	3 (4%)	
Relapsed tumor	7 (9%)	
Treatments	Brachytherapy dose (Gy)	
	Median [range]	60 [15 – 60]
	EBRT before or after brachytherapy	6 (8%)
	EBRT dose (Gy)	
	Median [range]	43.2 [30 – 45]
	Total dose (Gy) (brachytherapy + EBRT)	
	Median [range]	60 [48.73 – 65]
	Surgery before brachytherapy	64 (82%)
	Clinical response before local treatment	
	Progression	0
Stability	1 (1%)	
Partial response	77 (99%)	
Complete response	0	
Chemotherapy before brachytherapy	77 (99%)	

Table 2 – Acute and late anorectal morbidity (number of patients indicated)

		Toxicity grade according to the CTCAE 5.0				
		Grade 1	Grade 2	Grade 3	Grade 1-3	
Morbidity detail (number of cases)	Acute toxicities	Rectal bleeding	5 (6%)	1 (1%)	0	6 (8%)
		Proctitis	1 (1%)	5 (6%)	0	6 (8%)
		Abdominal pain	3 (4%)	0	1 (1%)	4 (5%)
		Encopresis	1 (1%)	0	0	1 (1%)
		Transit disorder	5 (6%)	0	0	5 (6%)
		Overall morbidity	5 (6%)	5 (6%)	1 (1%)	11 (14%)
	Late toxicities	Rectal bleeding	11 (14%)	3 (4%)	3 (4%)	17 (22%)
		Proctitis	6 (8%)	1 (1%)	3 (4%)	10 (13%)
		Abdominal pain	6 (8%)	0	1 (1%)	7 (9%)
		Encopresis	3 (4%)	0	0	3 (4%)
		Transit disorder	10 (13%)	1 (1%)	0	11 (14%)
		Overall morbidity	20 (26%)	2 (3%)	5 (6%)	27 (35%)
	Acute and/or late toxicities	Rectal bleeding	15 (19%)	4 (5%)	3 (4%)	22 (28%)
		Proctitis	6 (8%)	6 (8%)	3 (4%)	15 (19%)
		Abdominal pain	8 (10%)	1 (1%)	0	9 (12%)
		Encopresis	3 (4%)	0	0	3 (4%)
		Transit disorder	14 (18%)	1 (1%)	0	15 (19%)
		Overall morbidity	19 (24%)	6 (8%)	5 (6%)	30 (38%)

The row “overall morbidity” represents the number of children having at least one toxicity. If a child had multiple toxicities, only the highest grade was counted in this row. In the part “acute and/or late toxicities”, if a patient had an acute toxicity that persisted after three months, it was counted for one, using the highest grade. In the row “overall morbidity” in this last part, only the highest grade toxicity was counted, whether acute or late.

Table 3 – Comparison of toxicity grades (acute and late) according to mean $D_{0.5cm^3}$, D_{1cm^3} and D_{2cm^3} (EQD $_{2\alpha/\beta=3}$)

Toxicity grade	$D_{0.5cm^3}$	D_{1cm^3}	D_{2cm^3}
Grade 0	48 +/- 17	41 +/- 15	33 +/- 13
Grade 1	54 +/- 14	47 +/- 13	39 +/- 12
Grade ≥ 2	67 +/- 20	58 +/- 15	39 +/- 13
P value	0.006	0.035	0.238