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Title page

Brachytherapy for pediatric patients at Gustave Roussy Cancer Campus: A model of international cooperation for highly specialized treatments

Cyrus Chargari, MD, PhD¹, Christine Haie-Meder, MD¹, Sophie Espenel, MD¹, Max-Adrien Garcia, MD², Myriam Ben-Arush, MD³, Stéphanie Bolle, MD¹, Anna Borjesson, MD⁴, Maja Cesen, MD⁵, Rita Costa Lago, MD⁶, Anne-Sophie Defachelles, MD⁷, Barbara De Moerloose, MD⁸, Christine Devalck, MD⁹, Pernille Edslev, MD¹⁰, Nuno Jorge Farinha, MD¹¹, Nadine Francotte, MD¹², Heidi Glosli, MD¹³, Sebastien Gouy, MD, PhD¹⁴, Gabriela Guillen Burrieza, MD¹⁵, Sylvie Helfre¹⁶, Sabine Irtan, MD, PhD¹⁷, Antonis Kattamis, MD¹⁸, Ana Lacerda, MD¹⁹, Antonin Levy, MD, PhD¹, Lisa Lyngsie Hjalgrim, MD²⁰, Ludovic Mansuy, MD²¹, Eric Mascard, MD²², Salma Moalla, MD²³, Daniel Orbach, MD, PhD²⁴, Cormac Owens, MD, ²⁵, Pascale Philippe-Chomette, MD, PhD²⁶, Barry Pizer, MD²⁷, Claire Pluchart, MD²⁸, Marleen Renard, MD²⁹, Anne Gro Wesenberg Rognlien, MD¹³, Angélique Rome, MD³⁰, Sabine Sarnacki, MD, PhD²², Akmal Safwat, MD³¹, Amalia Schiavetti, MD³², Jill Serre, MD³³, Cécile Verite, MD³⁴, Nicolas Von Der Weid, MD³⁵, Mariusz Wysocki, MD³⁶, Dominique Valteay-Couanet³⁷, Eric Deutsch, MD, PhD¹, Véronique Minard-Colin, MD, PhD³⁷, Hélène Martelli, MD, PhD³⁸, Florent Guérin, MD, PhD³⁸

1. Radiation Oncology, Gustave Roussy Cancer Campus, Villejuif, France
2. Centre Hygiène, Saint Etienne, France
3. Ruth Rappaport children's hospital, Haifa, Israel
4. Department of Pediatric Surgery, Lund University Hospital, SE-22185 Lund, Sweden
5. University Childrens Hospital Ljubljana, Slovenia
6. Radiation Oncology Department, Centro Hospitalar Universitário de São João, Porto, Portugal
7. Pediatric oncology, Centre Oscar Lambret, Lille, France
8. Department of Pediatric Hemato-Oncology, Ghent University Hospital, Ghent, Belgium
9. Hôpital Universitaire des Enfants Reine Fabiola, Brussels (HUDERF), Belgium
10. Child and Adolescent Health, Division for Hematology and Oncology, Aarhus University Hospital, Aarhus, Denmark
11. Pediatric Oncology Department, Centro Hospitalar Universitário de São João, Porto, Portugal
12. SUHOPL Service Interhospitalier Universitaire d'Hématologie et d'Oncologie Pédiatrique Liégeois, Liège, Belgium
13. Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway
14. Gynecological surgery, Gustave Roussy Cancer Campus, Villejuif, France
15. Hospital Infantil Universitari Vall d'Hebron, Spain
16. Radiation Oncology, Institut Curie, Paris, France
17. Sorbonne Université, Visceral and Neonatal Pediatric Surgery, Centre Hospitalier Universitaire Armand Trousseau, Assistance Publique-Hôpitaux de Paris, Paris, France
18. Division of Pediatric Hematology-Oncology, First Department of Pediatrics, National and Kapodistrian University of Athens, Greece
19. Pediatric Oncology, Instituto Portugues de Oncologia de Lisboa Francisco gentil, Lisboa, Portugal
20. Department of Pediatrics and Adolescent Medicine, University Hospital Rigshospitalet, Copenhagen, Denmark
21. Pediatric Oncology, Centre Hospitalier Universitaire de Nancy, Nancy, France
22. Pediatric Surgery, Centre Hospitalier Universitaire Necker, Paris, France
23. Department of Radiology, Gustave Roussy Cancer Campus, Villejuif, France
24. SIREDO Oncology Center (Care, Innovation and Research for Children, Adolescents and Young Adults with Cancer), PSL University, Institut Curie, Paris, France
25. National Pediatric Oncology Unit, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland.
26. Pediatric surgery, Hôpital universitaire Robert-Debré, Assistance Publique de Hôpitaux de Paris, Paris, France
27. Department of Paediatric Oncology, Alder Hey Children's Hospital, Liverpool, UK
28. Service d'oncologie pédiatrique, Centre Hospitalier Universitaire de Reims, Reims, France
29. Kinderhemato-oncologie, University hospital, Leuven Belgium
30. Pediatric Oncology, Hôpital La Timone, Marseille, France
31. Oncology Department and Danish Center for Particle Therapy, Aarhus University hospital, Aarhus, Denmark
32. Pediatric Oncology Unit, "Sapienza" University of Rome
33. Centre Hospitalier regional et Universitaire Clocheville, Tours, France
34. Pediatric Oncology, Groupe Hospitalier Pellegrin Hôpital des Enfants, Bordeaux, France
35. Pediatric Oncology, Universitäts-Kinderspital beider Basel (UKBB), University of Basel, Basel, Switzerland
36. Department of Pediatric Hematology and Oncology, University Hospital in Bydgoszcz, Poland
37. Department of Pediatric and Adolescent Oncology, Gustave Roussy, Université Paris-Saclay, Villejuif, France

Corresponding author:

Prof. Cyrus Chargari
Department of Radiation Oncology
Gustave Roussy Cancer Campus
114 rue Edouard Vaillant
94800 VILLEJUIF France
Email : cyrus.chargari@gustaveroussy.fr

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Authors email addresses:

cyrus.chargari@gustaveroussy.fr; sophie.espenel@gustaveroussy.fr; Antonin.levy@gustaveroussy.fr;
stephanie.bolle@gustaveroussy.fr; christine.haiemededer@gustaveroussy.fr;
marleen.renard@uzleuven.be; nuno.reis.farinha@gmail.com; rogann@ous-hf.no;
wojciech.mlynarski@umed.lodz.pl; k.anna.borjesson@gmail.com; amalia.schiavetti@uniroma1.it;
nadine.francotte@chc.be; pern.edsl@rm.dk; christine.devalck@huderf.be; m.wysocki@cm.umk.pl;
majacesen78@gmail.com; alacerda@ipolisboa.min-saude.pt; lisa.lyngsie.hjalgrim@regionh.dk;
gguillenburrieza@gmail.com; m_benarush@rambam.health.gov.il; Barbara.DeMoerloose@uzgent.be;
hglosli@ous-hf.no; cormac.owens@olchc.ie; ritalago_88@hotmail.com; ankatt@med.uoa.gr;
Nicolas.VonderWeid@ukbb.ch; a.m.l.peek@prinsesmaximacentrum.nl; Barry.Pizer@alderhey.nhs.uk;
akmal.safwat@auh.rm.dk; lu.mansuy@chru-nancy.fr; eric.mascard@aphp.fr; sabine.irtan@aphp.fr;
sylvie.helfre@curie.fr; Angelique.rome@ap-hm.fr; sabine.sarnacki@aphp.fr; AS-Defachelles@o-
lambret.fr; pascale.philippe-chomette@aphp.fr; daniel.orbach@curie.fr;
salma.moalla@gustaveroussy.fr; j.serre@chu-tours.fr; cecile.verite@chu-bordeaux.fr; cpluchart@chu-
reims.fr; florent.guerin@aphp.fr; Veronique.minard@gustaveroussy.fr; eric.deutsch@gustaveroussy.fr;
Dominique.valteau@gustaveroussy.fr; Sebastien.gouy@gustaveroussy.fr ; Helene.martelli@aphp.fr

ABSTRACT

Purpose: Childhood cancer is rare, and treatment is frequently associated with long-term morbidity. Disparities in survival and long-term side-effects encourage the establishment of networks to increase access to complex organ conservative strategies, such as brachytherapy (BT). We report our experience of an international cooperation model in childhood cancers.

Methods and materials: We examined the outcome of all children referred to our center from national or international networks to be treated according to a multimodal organ-conservative approach including BT.

Results: 305 patients were identified; median age at diagnosis was 2.2 years (1.4 months-17.2 years). Ninety-nine (32.4%) were treated within 2015-2020. One hundred seventy-two (56.4%) were referred from national centers and 133 (43.6%) were international patients, from 31 countries (mainly Europe). Two hundred sixty three patients were referred for primary treatment and 42 for salvage treatment. Genito-urinary tumors were the most frequent sites, with 56.4% bladder/prostate rhabdomyosarcoma (RMS) and 28.5% gynecological tumors. In addition to BT, local treatment comprised partial tumor resection in 207 (67.9%) and 39 (13%) had additional external radiotherapy. Median follow-up was 58 months (range: 1 month-48 years), 93 months for national patients and 37 months for international patients ($p < .0001$). Five-year local control (LC), disease-free survival (DFS) and overall survival rates were 90.8% (CI95%: 87.3–94.4%), 84.4% (CI95%:80.1-89.0) and 93.3% (CI95%:90.1-96.5), respectively. Patients referred for salvage treatment had poorer DFS ($p < 0.01$). Implementation of image-guided pulse-dose rate BT was associated with better LC among RMS patients referred for primary treatment (HR: 9.72; CI95%:1.24-71.0). At last follow-up, 16.7% patients had long-term severe treatment-related complications and two (0.7%) had developed second malignancy.

Conclusion: This retrospective series shows the feasibility of a multinational referral network for brachytherapy allowing high patient number in rare pediatric cancers. High local control probability and acceptable late severe complication probability could be achieved despite very challenging situations. This cooperation model could serve as a basis for generating international reference networks for high-tech radiation such as brachytherapy to increase treatment care opportunities and cure probability.

Keywords: cancer ; brachytherapy; radiation oncology ; bladder-prostate rhabdomyosarcoma ; rhabdomyosarcoma ; vaginal cancer ; pediatrics; malignant germ-cell tumors; conservative treatment; referral networks

INTRODUCTION

Childhood cancers account for only 1% of all human cancers but are the second leading cause of death in children in the United States or in Europe.¹⁻⁴ Radiotherapy has a major role in the treatment of pediatric soft tissue tumors, especially when a complete surgery is not possible without major mutilation. It is however associated with significant late morbidities, potentially leading to definitive functional impairment.⁵ In order to optimize the therapeutic index in children, the most appropriate radiotherapy technique for each specific situation should be used.^{6;7}

Brachytherapy (BT) is a highly conformational modality of interventional radiotherapy without equal in terms of organs at risk (OARs) sparing capability. It was developed in expert centers as part of a multimodal conservative treatment. By placing directly radioactive sources into or next to the tumor, it is possible to escalate the dose focally and to minimize volumes of normal tissue being irradiated as compared to external beam radiotherapy (EBRT) techniques.⁸ Such organ-conservative procedure however requires a high expertise and a close collaboration with pediatric surgeons to take into account perioperative findings in the target volume definition and a dedicated paramedical and medical team for the therapeutic process.⁹⁻¹³ Few centers have experience of this multimodal approach in pediatric cancer. Given the low number of patients treated each year, such treatments require expertise in adult BT to maintain and develop technical skills. Disparities in survival and long-term side-effects from pediatric cancer observed across countries encourage the establishment of appropriate networks for all complex radiotherapy procedures to reduce disparities in patient care and improve outcome.^{14;15}

We report our experience of pediatric BT, based on a national and international cooperation in the treatment of childhood cancer.

PATIENTS AND METHODS

Inclusion criteria

The outcome of children referred to Gustave Roussy Cancer Campus, brachytherapy department, between 1971 and 2020 and treated for a histologically confirmed tumor according to a multimodal approach involving BT was examined. All consecutive cases treated after 2000 were included. Patients treated prior to 2000 represented only a small but unselected subset of those treated at this time, due to lack of prospective registration. All histologies and primary tumor sites were included. Patients referred for re-irradiation of the primary tumor site were excluded from analysis. This study was conducted in accordance with ethical standards and approved by local ethic committee (reference **2021-28**).

Therapeutic indication

The decision of performing BT was taken on an individual basis. Patients could be referred from other national centers or from international centers for their local treatment. Each time, the indication was discussed at a dedicated multidisciplinary meeting and weighted against all other possibilities,

including surgery alone and/or EBRT. The decision was made in order to be as conservative as possible and to minimize normal tissue irradiation, without compromising oncological outcome. The definitive possibility to perform BT depended mainly on the tumor site accessibility as well as organs at risk proximity. Tumors involving nervous or bone structures were contra-indications. BT was schematically indicated for: 1/ tumors that would require mutilating surgery to be completely removed with negative margins; 2/ locally recurrent or persistent tumors after primary surgery and/or systemic treatment.

Associated treatments

Prior to BT, children with sarcoma or malignant germ cell tumor (MGCT) received chemotherapy (CT) according to current pediatric protocols. For patients with RMS, BT timing depended on tumor response but the procedure was usually planned after 4 to 6 cycles. For patients with MGCT, BT was planned after patients had completed CT protocol.

Patients without lymph node extension received BT as sole irradiation modality. In case of lymph node extension, or for patients with locally advanced carcinoma (including clear cell carcinoma), BT was delivered as a boost modality, in association with EBRT treating the tumor bed and lymph nodes. BT was also associated with EBRT in tumors involving the anal canal or margin (to minimize the risk of necrosis).

According to tumor extent, BT could be associated with tumor resection, aimed at being conservative and therefore accepting a microscopic or macroscopic residuum, considering that BT would irradiate the residual disease. Therapeutic indications and strategies are previously detailed.^{9;10;16-20} Schematically, patients with bladder/prostate rhabdomyosarcoma (BP RMS) were treated with primary chemotherapy then they received BT as part of a multimodal local treatment at time of a delayed primary partial conservative surgery to treat the tumor residuum. For patients with gynecological RMS, a partial debulking surgery may be performed at time of diagnosis or at time of brachytherapy, always conservative. For patients with RMS of the trunk or limbs, BT could be performed either at time of primary excision (for alveolar histologies) or at time of second look surgery (for alveolar histology and positive/close margins), usually as a perioperative approach. For head and neck RMS, brachytherapy was proposed as exclusive local treatment (without surgery) or as an adjuvant, in the context of alveolar histology or close/positive margins.

Prior to BT, girls with genito-urinary (GU) tumors had a temporary ovarian transposition. From 2015, a temporary unilateral testicular transposition was performed in young male patients requiring perineal irradiation (+/- bilateral in case of very close proximity of the implanted area).¹⁷

Target volume definition

For patients with RMS and MGCT, clinical target volume (CTV) was defined as the residual disease following CT, with the exception of vaginal rhabdomyosarcoma (RMS) treated prior to 1990 (for which the CTV was the initial tumor extent). This definition took into account all clinical, radiological, and

histopathological findings. For vaginal tumors, a gynecological examination was performed under general anesthesia (GA). Permanent radiopaque seeds could be used to identify tumor extents and a vaginal impression was performed.¹⁷ Bladder/prostate RMS (BP-RMS) patients underwent a cystotomy and/or cystoscopy to guide target volume definition. For operated patients, the CTV was defined as the tumor bed, taking into account histological findings.

For patients with clear cell carcinoma, CTV was the macroscopic disease plus a 5-10 mm margin, encompassing microscopic extension (in case of exclusive BT) or the residual disease following EBRT (for patients with locally advanced disease treated with combination of EBRT and BT). In case of carcinoma of the uterine cervix, the whole cervix was always included as part of the CTV.

Implant modalities

BT procedures were performed in an operating room under GA. Implant geometry (number and position of catheters) was selected in order to properly cover the CTV while avoiding OARs.

Vaginal tumors were treated with intracavitary BT (ICBT), using personalized vaginal mold applicator +/- intrauterine tube (if cervix was involved). For deeply seated tumors, percutaneous interstitial catheters were implanted equidistant and parallel possibly through a perioperative approach (illustrated in **supplementary FIGURES S1 and S2**).

Treatment planning

Prior to 2005, treatment was delivered through low dose rate (LDR) with manually after-loaded 192-Iridium wires or exceptionally with 137-Cesium sources delivering <0.5 Gy/hour. Treatment planning was mainly based on radiographs and active lengths were decided according to clinical and radiological findings. From 2005, the 3D concepts of image guidance were progressively introduced into treatment strategy and patients were treated with 3D image-guided BT and a stepping Iridium-192 source from remote pulse-dose rate (PDR) after-loader. Dose optimization could be used to improve implant geometry and target coverage while minimizing OARs doses. No firm dose constraint was applied. PDR irradiation was delivered through continuous hourly pulses of 0.42 Gy, keeping the total daily dose <10Gy.

Statistics and follow-up

During BT, a manual control of catheters was systematically done every day and X-rays were performed twice a week to ensure that there was no displacement of catheters. Patients were seen by the pediatrician and by the BT team on a daily basis. After catheter removal (usually under GA), gonads were repositioned and patients could receive additional CT courses (without dactinomycin during the six weeks following BT) +/- maintenance, depending on histology, tumor stage, and protocols. Patients were followed as per usual pediatric protocols. International patients were followed by their referring physician and regular contacts were provided by mails or emails to update on tumor control and toxicities. First sites of relapse were examined and classified into local (primary tumor site), regional (proximity lymph nodes) or distant (metastases). Survival rates were calculated from the

date of diagnosis to the occurrence of the studied event. The Kaplan Meier method was used to obtain curves of disease-free survival (DFS), overall survival (OS), pelvic and local control (LC). Five-year DFS, OS, and LC were estimated with 95% confidence interval (95% CI). Multivariate analyses (Cox model) for prognostic factors were performed for variables with p value < 0.2 in univariate analysis (log rank test). The multivariate model was refined using Akaike Information Criterion (AIC). Only severe locoregional toxicities grade ≥ 3 (Common Terminology Criteria for Adverse Events v-5) were examined. Data inclusion was performed from March 1971 to September 2020, with cut off analysis in February 2021. Significance was defined by p value < 0.05. Statistical analyses were performed using R-4.0.4 (R Core Team. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients and tumors

Patients and tumors characteristics are detailed in **Table 1**. A total of 305 patients were identified, with a median age of 2.2 years (range: 1.4 months–17.2 years) at diagnosis. One hundred seventy-two children (56.4%) were referred from national networks and 133 (43.6%) were international patients, with a continuous increase in the number of patients referred for BT procedure from international networks over the past 20 years (**Figure S3 and S4**). Ninety-nine patients (32.4%) were treated since 2015. At time of diagnosis, 270 (88.5%) patients had a localized disease, 16 (5.2%) had regional lymph node involvement, and 19 (6.3%) had distant lymph node or visceral metastases. 263 patients (86.2%) were referred for primary treatment and 42 (13.8%) for local relapse/progression. These latter accounted for 27/133 (20.3%) international patients ($p < 0.01$), *versus* 15/172 (8.7%) patients referred from national centers. Primary tumor sites were mainly represented by GU tumors, with 172 (56.4%) patients treated for a BP-RMS and 87 (28.5%) having a gynecological cancer. Predominant tumor histologies were embryonal RMS (ERMS; 80%) and alveolar RMS (ARMS; 10.2%). A total of 280 patients had sarcoma histology, including 275 patients with RMS. Among RMS patients, 125/275 (45.6%) had tumor size > 5 cm, 31/275 (11.3%) had alveolar histology, 12/275 (4.4%) had regional lymph node involvement and 15/175 (5.5%) had distant lymph node or visceral metastatic sites.

Treatments delivered

Treatment characteristics are detailed in **Table 2**. Prior to BT, all patients with RMS and MGCT had received primary CT, median number of 6 cycles (range: 3–18 cycles). The most frequently used protocol therapy was EpSSG RMS-2005 ($n=165$, 58.9% of all RMS patients). After BT, 36 (12.9%) patients with RMS received a maintenance CT.

In addition to BT, local treatment comprised a partial resection of the primary tumor in 207 (67.9%) patients. BT catheters placement was performed as a perioperative procedure in 180 (59.0%) patients. Median prescribed BT dose was 60 Gy (range: 10–80 Gy). Thirty-nine patients had additional EBRT, with a median dose 41.4 Gy (range: 25–50.6 Gy). Adding contribution of both BT and EBRT,

median total primary tumor dose was 60 Gy (range: 40–80 Gy). BT was planned on 2D radiographs in 180 (59.0%) patients and on 3D imaging in 125 patients (41.0%), including all 99 patients treated since 2015.

Tumor control

Median follow-up was 58 months (range: 1 month – 48 years), 93 months for national patients, *versus* 37 months for international patients ($p < .0001$). A total of 222 (73%) patients had a follow-up time \geq 24 months; 141/172 (82%) for national patients *versus* 81/133 (61%) for international patients ($p < 0.001$). Seventy-nine patients (26%) had a follow-up longer than 10 years. Forty-four (14.4%) patients had tumor relapse, including local failure in 27 (8.9%). At five years, LC, regional control, DFS, and OS probabilities in the whole cohort were 90.8% (CI95%: 87.3–94.4%), 94.9% (CI95%: 92.3-97.7%), 84.4% (CI95%:80.1-89.0) and 93.3% (CI95%:90.1-96.5), respectively. Survival curves are shown in **Figure 1**.

Among patients with RMS, median follow-up was 55 months (range: 1 month – 48 years). In this subgroup of patients, 39/275 (14.2%) had tumor relapse, including 24 (8.7%) local failures as first event. At five years, LC probability was 92.4% (95% CI = 88.1-96.9) for BP RMS and 94.2% (95% CI = 88.1-100) for gynecological RMS. Five years LC, regional control, DFS, and OS probabilities per tumor site for patients with RMS are detailed in **Table 3**.

Prognostic factors for disease control

The following factors were tested for DFS, OS and LC among patients with RMS ($n = 275$): 1/ age at diagnosis (<1 year or >10 years, *versus* 1-10 years), histology (alveolar RMS *versus* others), 2/ tumor stage (localized *versus* regional/metastatic extension), 3/ BT modality (LDR *versus* PDR), 4/ tumor size (≥ 5 *versus* <5 cm), 5/ referral modality (primary *versus* salvage treatment).

At univariate analysis, alveolar histology (*versus* non-alveolar histology) was associated with poorer OS ($p < 0.01$) and poorer DFS ($p < 0.01$). A localized tumor stage was associated with better DFS ($p = 0.03$) and better OS ($p = 0.01$). Referral at time of relapse was associated with poorer DFS ($p = 0.04$) and poorer LC probability ($p = 0.02$). Image-guided BT was associated with a better LC ($p = 0.04$). Tumor size and patient age were not significant.

At multivariate analysis, alveolar histology was significantly associated with poorer OS (adjusted hazard ratio [HR]: 5.54; 95%CI: 2.09-14.69; $p < 0.01$) and poorer DFS (adjusted HR: 5.66; 95%CI: 2.66-12.04; $p < 0.01$). Image-guided PDR BT was associated with a better LC (adjusted HR: 3.33; 95%CI: 0.98-11.32, $p = 0.05$). Among RMS patients referred for primary treatment ($n = 241$), LC probability was 96.5% (CI95%: 90.1-100) for 3D treatments, *versus* 88.7% (CI95%: 83.5-95.3) for 2D ($p = 0.02$) (**Figure 2**).

Severe late toxicities

At last follow-up, a total of 51/305 (16.7%) patients had long-term severe complications, including only one grade 4 complication (**Table 4**). Five and 10-year probability of survival without late side effect were 84.6% (95%CI: 80.1 – 89.3%) and 74.4% (CI95%: 68.0 – 81.1%) (**Figure 1**).

Among BP-RMS patients, 27/172 (15.7%) had late severe complications, including five patients requiring total cystectomy because of a non-functioning bladder and two requiring enterocystoplasty for bladder enlargement. Among the BP-RMS patients treated with conservative intent (excluding the three patients with upfront cystectomy), 159/169 (94.1%) kept their bladder at last follow-up (10 required a cystectomy: five because of isolated local failure and five because of toxicity).

Among patients with gynecological tumor, 19/87 (23%) had late severe morbidity, mainly represented by vaginal stenosis (13 patients) requiring dilatation and/or vaginoplasty. Among these, 10/13 had been treated with LDR-BT, prior to 3D-guided optimization capabilities.

Second malignancies

Two patients (0.7%) developed second malignancy: one had osteosarcoma (occurring in the iliac bone 13 years after exclusive BT for a vaginal RMS treated at the age of 1.1 years) and one developed uterine leiomyosarcoma (37 years after exclusive BT for a vaginal RMS treated at the age of 20 months). Information on potentially predisposing syndromes was not available.

DISCUSSION

Brachytherapy is an optimal technique to minimize organs at risk doses and there is an appealing technique to reduce late side effects of irradiation in children. It may be indicated for various histologies and for treatment of various tumor sites. RMS is the most frequent pediatric soft tissue tumor, accounting for 4-6 % of all pediatric cancers. One common RMS site is genitourinary tract.²¹ Therapeutic strategies take into account the histological and molecular subtype, patient age and risk group classification, based on the combination of tumor characteristics (location, size, stage). Locoregional relapses represent > 70% of failures in patients with localized RMS.²²⁻²⁵ In combination with CT, treatment of the primary tumor is of first importance in the accomplishment of a curative plan. Local treatment modalities, mainly based on surgery and/or radiotherapy, should take into account potential treatment sequelae, but also the dismal prognosis in case of relapse.^{26;27}

Organ conservative surgical procedures without additional irradiation are rarely feasible, especially in pelvic sites. In case of unresected residual microscopic or macroscopic tumor, omission of radiation therapy is not an option. Indeed, probability of cure without local treatment is <10% in BP-RMS. Even in the subset of patients with the best prognosis (vaginal RMS), only 30% can avoid local treatment after careful multimodal (clinical, radiological, histological) evaluation confirming complete remission following chemotherapy, at the cost of an increased risk of local relapse.^{22;23;26-32}

EBRT is the most frequently proposed radiation technique.³³ In RMS protocols, the target volume should include the initial sites of disease (sites involved at diagnosis, taking into account anatomical modifications) with boost to residual disease. The standard conventional fractionated radiotherapy

dose ranges from 36 Gy for microscopic disease to 50.4 Gy for macroscopic residuum. However, tumors larger than 5 cm have a high local failure rate, encouraging dose escalation.²⁹ One limitation is the major impact of EBRT in children, especially for pelvic irradiation, leading to impaired growth capabilities and organs development.^{26;27} EBRT contributes to the excess mortality persisting long after a cancer diagnosis.³ In addition, the risk of radiation-induced cancer is significant (around 2-3%), and correlated to the irradiated volume. It could be higher in younger patients.^{34;35}

Pediatric BT was indicated to increase the dose focally while minimizing OARs doses in order to increase the therapeutic index in these children. Dosimetric comparisons demonstrated that BT remains the best irradiation modality in terms of dose escalation and OARs sparing capability.³⁶⁻³⁸ BT minimizes integral dose delivered to the patient body by better conformality and by targeting only the tumor residuum without additional set-up margins, which is relevant for late morbidity as well as for the risk of second cancer.^{34;39} In the present series, including very young patients, 84% did not develop severe complications. Although low grade complications were not examined here, morbidity was lower than expected with EBRT at this very young age (retrospective data showing that up to 54% of patients receiving EBRT for pelvic cancer in childhood needed surgery for late complications).²⁷ In an international report, 21% of BP-RMS patients undergoing EBRT required total cystectomy, either because of relapse or complication (versus 3.6% in our cohort).²⁶ Furthermore, no statural delay was reported among patients treated with exclusive BT, contrary to a recent publication where 2/19 BP-RMS patients had skeletal deformity following proton therapy.⁴⁰ We observed two cases (0.6%) of subsequent cancer, which seems particularly low as compared to patients treated with EBRT, especially at this very young age. This is however in line with larger studies of adult patients, showing no increase in secondary cancer incidence after BT, contrary to EBRT techniques.³⁴ Longer follow-up is necessary to better analyze the secondary cancer risk in this cohort and to confirm that this rate is not lowered by underreporting.

Our results also compare favorably to the literature in terms of morbidity and LC. In the analysis of the SIOP-MMT84, 89 and 95 studies, including 77 patients with IRS-III pelvic RMS, the local relapse rate was 26% after RT (*versus* 8.9% in our cohort).⁴¹ This strategy of irradiating only the tumor residuum did not jeopardize outcome, with high to excellent LC probability, according to primary tumor site (**Table 3**). In parallel with the potential benefit of dose escalation, the importance of a close radio-surgical collaboration to guide catheter placement in peroperative procedures should be emphasized. In the subgroup of patients with BP-RMS, 157/172 (91.3%) had their peroperative procedure performed with the same surgical team. In addition, long term sequelae of a multimodal approach are multifactorial. In our cohort of patients with BP RMS, there has been a trend, in parallel with the development of image guided brachytherapy, to progressively decrease the extent of resection in these patients, particularly avoiding bladder neck resection, to minimize long-term urinary morbidity. More recently, we examined the outcome of 86 patients with BP RMS treated with partial surgery and brachytherapy. With median follow-up of 6.3 years, posterior bladder wall dissection used in large prostatic tumors, operation at age less than 2 years and partial prostatectomy were identified as risk factors for late urinary complications.⁴²

BT is a challenging treatment with potential barriers to implementation. Technological equipment is inexpensive, as compared to protons, but it requires a dedicated medical and paramedical team. Individual expertise and the need for a specific BT workflow should be acknowledged, in the context of very rare tumors.⁴³⁻⁴⁶ Almost all national pediatric BT procedures are performed in our center, but this represents approximately 15 procedures per year, accounting for 3-4% out of 500 patients treated in our BT department per year. To develop pediatric BT, previous and concomitant experience in adult treatments is necessary and patient outcome could be impacted by the skills of the center, the experience of the clinician and the number of patients treated each year (as for surgical treatments). In addition, innovation in pediatric BT derives from adult data, such as the implementation of 3D treatment planning. The integration of image-guidance into the treatment planning process has yielded to benefits in adult patients receiving BT, through a better definition of target volume and better OARs sparing.⁸ We observed a better LC with PDR BT, suggesting that integration of modern BT tools such as 3D-guided treatment planning and stepping source technology may increase the therapeutic index, together with an increasing use of complex interstitial implants.⁴⁷ The improved outcome associated with 3D treatments adds to the rationale for increasing delivery by specialized and experienced centers, with access to MRI-guided PDR treatments. Although compliance to PDR BT in pediatric patients was previously reported, the logistic aspects should also be appraised, as well as treatment constraints.⁹ Prerequisites for a safe and high-quality treatment include: permanent availability of specialized brachytherapists and radiotherapy technicians (24h/day, 7days/week) for emergencies (e.g. radioactive source blockade), daily visits of pediatrician to prescribe analgesics or soft conscious sedation, access to specialized pediatric surgeons and anesthesiologists to replace catheters without delay in case of displacement, presence of nurses familiar with the management of these very young patients.

Although this series is the largest published on pediatric BT, it has some limitations. First, we do not know the number of patients for whom an opinion was sought but who were not considered eligible for brachytherapy. In addition, patients were treated over a period of 50 years, with progressive changes and improvements in systemic treatment, surgery, and BT techniques. Furthermore, 254/305 (83.3%) patients included in this series were treated between 2000 and 2020. This was not a prospective database and patients treated prior to 2000 represented only a small but unselected subset of those treated at this time. In addition, there has been an increase in the referral of international patients over the past 10 years, leading to relatively short follow-up time in this subgroup, compounded by the difficulty to receive regular follow-up updates (**Figure S4**). While tumor control data are usually provided, analysis of toxicity data based on reports from treating physicians may also not be exhaustive and more focused toxicity analyses should be performed per tumor site (e.g. low grade impotence in BP RMS). This highlights one difficulty of international referral networks, and there is still room for substantial improvement in this setting to generate long-term data on patients outcomes. This is especially crucial for pediatric cancer, as late morbidities still occur decades following treatment without plateauing, even if highly conformal irradiation modalities such as BT are used.

Patients receiving salvage BT, more likely to be international patients, had poorer outcomes than those treated with upfront treatment. This highlights the need to promote BT use at an international level, from cancer diagnosis. Involvement of academic societies of pediatric oncology and radiation oncology is required to reinforce education, training, companion-training programs and treatment cooperation with identification of a dedicated referral team from the early steps of treatment. New European Union (EU) rules allow trans-border crossing and patient mobility for very rare techniques for pediatric cancers.⁴⁸ The S2 (« Entitlement to scheduled treatment ») certificate authorizes patients to travel to France from another EU or European Economic Area member state to receive medical care that will be covered as provided by local law and according to local rates. Therefore, patients may receive the same care as members of the French social security system, meaning that treatment for cancer is free. Parents need to apply for this document along with a detailed medical certificate specifying the need for brachytherapy. There remains at the charge of families a financial participation for hospitalization (20 euros per day) and costs for transportation. As parents need to stay in Paris for approximately two weeks, there are accommodation facilities located 100 meters from Institute and dedicated to parents of children hospitalized in Gustave Roussy (cost : 10 euros per family per day). Private insurance policies may cover these expenses. Interpreters are available in our Institute for foreign patients from any country, in interaction with embassies. These administrative steps must be anticipated and contact must be made with the referral center from the first stages of care.

International support for pediatric cancer treatment may contribute to avoid inappropriate upfront treatments that impair quality of life and compromise oncological outcome. In the COVID-19 crisis context, transition to virtual multidisciplinary tumor board discussions may help homogenize treatment indications through presentation of all cases to a dedicated referral center, but also to update patients functional outcome on a more regular basis. To facilitate the specific care of international patients, referral centers with high patient volumes and expertise should be signposted at an international level, with development of online tools for expedient second opinion requests and data sharing.¹⁴

CONCLUSION

Though limited by its retrospective design, our study suggests that brachytherapy has potentially a major role in selected pediatric patients to achieve high local control probability and minimize late severe complication probability. Integration of image guidance was associated with a better LC probability. A multicenter and multinational collaboration is needed in rare cancers to achieve high patient volume and offer access to highly specialized treatments such as 3D-guided brachytherapy to an increasing number of children. There are still difficulties (especially for the very long-term follow-up) but this cooperation model could serve as a basis for generating international reference networks for high-tech radiation to increase treatment care opportunities.

REFERENCES

1. Kaatsch P. Epidemiology of childhood cancer. *Cancer Treat Rev* 2010;277-285.
2. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J Clin*. 2020;70:443-459.
3. Mertens AC, Liu Q, Neglia JP et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2008;100:1368–1379
4. Alexander S, Pole JD, Gibson P, et al. Classification of treatment-related mortality in children with cancer: a systematic assessment. *Lancet Oncol*. 2015 Dec;16(16):e604-10.
5. Palmer JD, Hall MD, Mahajan A, Paulino AC, Wolden S, Constine LS. Radiotherapy and Late Effects. *Pediatr Clin North Am*. 2020 Dec;67(6):1051-1067.
6. Kortmann RD, Freeman C, Marcus K, et al. Paediatric radiation oncology in the care of childhood cancer: A position paper by the International Paediatric Radiation Oncology Society (PROS). *Radiother Oncol*. 2016;119:357-60.
7. Mandeville HC. Radiotherapy in the Management of Childhood Rhabdomyosarcoma. *Clin Oncol (R Coll Radiol)* 2019 Jul;31(7):462-470.
8. Chargari C, Deutsch E, Blanchard P, et al. Brachytherapy: An overview for clinicians. *CA Cancer J Clin*. 2019;69:386-401.
9. Chargari C, Martelli H, Guérin F, et al. Pulsed-dose rate brachytherapy for pediatric bladder prostate rhabdomyosarcoma: Compliance and early clinical results. *Radiother Oncol*. 2017;124:285-290.
10. Chargari C, Haie-Meder C, Guérin F, et al. Brachytherapy Combined With Surgery for Conservative Treatment of Children With Bladder Neck and/or Prostate Rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys*. 2017;98:352-359.
11. Fuchs J, Paulsen F, Bleif M, et al. Conservative surgery with combined high dose rate brachytherapy for patients suffering from genitourinary and perianal rhabdomyosarcoma. *Radiother Oncol*. 2016;121:262-267.
12. Lautz TB, Martelli H, Fuchs J, et al. Local treatment of rhabdomyosarcoma of the female genital tract: Expert consensus from the Children's Oncology Group, the European Soft-Tissue Sarcoma Group, and the Cooperative Weichteilsarkom Studiengruppe. *Pediatr Blood Cancer*. 2020 Aug 6:e28601. doi: 10.1002/pbc.28601.
13. Sütterlin AL, Demmert M, Kovács G, Claviez A, Schulz C, Lauten M. Interventional radiotherapy (brachytherapy) achieves very good long-term quality of life in children and adolescents with soft-tissue sarcoma. *Pediatr Blood Cancer*. 2020;67:e28464.
14. Janssens GO, Timmermann B, Laprie A, et al. Recommendations for the organisation of care in paediatric radiation oncology across Europe: a SIOPE-ESTRO-PROS-CCI-Europe collaborative project in the framework of the JARC. *Eur J Cancer*. 2019 Jun;114:47-54.
15. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCORE-5--a population-based study. *Lancet Oncol*. 2014 Jan;15(1):35-47. doi: 10.1016/S1470-2045(13)70548-5. Epub 2013 Dec 5.
16. de Lambert G, Chargari C, Minard-Colin V, Haie-Meder C, Guérin F, Martelli H. Testicular transposition in children undergoing brachytherapy for bladder and/or prostate rhabdomyosarcoma. *J Pediatr Surg*. 2018;53:1428-1431.
17. Magné N, Chargari C, Levy A, et al. Clear cell adenocarcinoma of the female genital tract: long-term outcome and fertility aspects after brachytherapy aimed at a conservative treatment. *Int J Gynecol Cancer*. 2012;22:1378-82.
18. Magné N, Haie-Meder C. Brachytherapy for genital-tract rhabdomyosarcomas in girls: technical aspects, reports, and perspectives. *Lancet Oncol*. 2007;8:725-9.
19. Magné N, Oberlin O, Martelli H, Gerbaulet A, Chassagne D, Haie-Meder C. Vulval and vaginal rhabdomyosarcoma in children: update and reappraisal of Institut Gustave Roussy brachytherapy experience. *Int J Radiat Oncol Biol Phys*. 2008;72:878-83.
20. Magné N, Chargari C, SanFilippo N, Messai T, Gerbaulet A, Haie-Meder C. Technical aspects and perspectives of the vaginal mold applicator for brachytherapy of gynecologic malignancies. *Brachytherapy*. 2010 Jul-Sep;9(3):274-7.
21. Howlader N, Noone AM, Krapcho M et al (eds) (2012) SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD (based on November 2011 SEER data submission, posted to the SEER web site, April 2012). Available from: http://seer.cancer.gov/csr/1975_2009_pops09/.
22. Rodeberg DA, Anderson JR, Arndt CA, et al. Comparison of outcomes based on treatment algorithms for rhabdomyosarcoma of the bladder/prostate: Combined results from the Children's Oncology Group, German Cooperative Soft Tissue Sarcoma Study, Italian Cooperative Group, and

- International Society of Pediatric Oncology Malignant Mesenchymal Tumors Committee. *Int J Cancer* 2011;128:1232-1239.
23. Raney RB, Maurer HM, Anderson JR, Andrassy RJ, Donaldson SS, Qualman SJ, et al. The Intergroup Rhabdomyosarcoma Study Group (IRSG): Major Lessons From the IRS-I Through IRS-IV Studies as Background for the Current IRS-V Treatment Protocols. *Sarcoma*. 2001;5:9-15. doi: 10.1080/13577140120048890.
 24. Sadak KT, Ritchey ML, Dome JS. Paediatric genitourinary cancers and late effects of treatment. *Nat Rev Urol*. 2013;10:15-25.
 25. Bisogno G, Jenney M, Bergeron C, Gallego Melcón S, Ferrari A, Oberlin P, et al. Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a multicentre, open-label, randomised controlled, phase 3 trial. *Lancet Oncol*. 2018 Aug;19(8):1061-1071. doi: 10.1016/S1470-2045(18)30337-1. Epub 2018 Jun 22.
 26. Raney B Jr., Heyn R, Hays DM, et al. Sequelae of treatment in 109 patients followed for 5 to 15 years after diagnosis of sarcoma of the bladder and prostate. A report from the Intergroup Rhabdomyosarcoma Study Committee. *Cancer* 1993;71:2387-2394.
 27. Spunt SL, Sweeney TA, Hudson MM, Billups CA, Krasin ML, Hester AL. Late effects of pelvic rhabdomyosarcoma and its treatment in female survivors. *J Clin Oncol*. 2005;23:7143-51.
 28. Breneman J, Meza J, Donaldson SS, et al. Local control with reduced-dose radiotherapy for low-risk rhabdomyosarcoma: a report from the Children's Oncology Group D9602 study. *Int J Radiat Oncol Biol Phys*. 2012;83:720-6.
 29. Steinmeier T, Schulze Schleithoff S, Timmermann B. Evolving Radiotherapy Techniques in Paediatric Oncology. *Clin Oncol (R Coll Radiol)*. 2019;3:142-150.
 30. Shah C, Verma V, Takiar R, et al. Radiation Therapy in the Management of Soft Tissue Sarcoma: A Clinician's Guide to Timing, Techniques, and Targets. *Am J Clin Oncol*. 2016;39:630-635.
 31. Minard-Colin V, Waterhouse D, Bisogno G, et al. Localized vaginal/uterine rhabdomyosarcoma-results of a pooled analysis from four international cooperative groups. *Pediatr Blood Cancer*. 2018 Sep;65(9):e27096.
 32. Breneman JC, Donaldson SS, Constine L, et al. The Children's Oncology Group Radiation Oncology Discipline: 15 Years of Contributions to the Treatment of Childhood Cancer. *Int J Radiat Oncol Biol Phys*. 2018 Jul 15;101(4):860-874. doi: 10.1016/j.ijrobp.2018.03.002.
 33. Glosli H, Bisogno G, Kelsey A, Chisholm JC, Gaze M, Kolb F, McHugh K, Shipley J, Gallego S, Merks JHM, Smeele LE, Mandeville H, Ferrari A, Minard-Colin V, Corradini N, Jenney M, Zanetti I, De Salvo GL, Orbach D; EpSSG members. Non-parameningeal head and neck rhabdomyosarcoma in children, adolescents, and young adults: Experience of the European paediatric Soft tissue sarcoma Study Group (EpSSG) - RMS2005 study. *Eur J Cancer*. 2021 May 7;151:84-93.
 34. Chargari C, Goodman KA, Diallo I, et al. Risk of second cancers in the era of modern radiation therapy: does the risk/benefit analysis overcome theoretical models? *Cancer Metastasis Rev*. 2016;35:277-88.
 35. Archer NM, Amorim RP, Naves R, et al. An Increased Risk of Second Malignant Neoplasms After Rhabdomyosarcoma: Population-Based Evidence for a Cancer Predisposition Syndrome? *Pediatr Blood Cancer*. 2016;63:196-201.
 36. Georg D, Kirisits C, Hillbrand M, Dimopoulos J, Pötter R. Image-guided radiotherapy for cervix cancer: high-tech external beam therapy versus high-tech brachytherapy. *Int J Radiat Oncol Biol Phys*. 2008;71:1272-8.
 37. Yanez L, Ciudad AM, Mehta MP, et al. What is the evidence for the clinical value of SBRT in cancer of the cervix? *Rep Pract Oncol Radiother*. 2018;23:574-579.
 38. Otahal B, Dolezel M, Cvek J, et al. Dosimetric comparison of MRI-based HDR brachytherapy and stereotactic radiotherapy in patients with advanced cervical cancer: A virtual brachytherapy study. *Rep Pract Oncol Radiother*. 2014;19:399-404.
 39. Meadows AT, Friedman DL, Neglia JP et al (2009) Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. *J Clin Oncol* 27:2356–2362.
 40. Buszek SM, Ludmir EB, Grosshans DR, et al. Patterns of failure and toxicity profile following proton beam therapy for pediatric bladder and prostate rhabdomyosarcoma. *Pediatr Blood Cancer*. 2019;66:e27952.
 41. Réguerre Y, Martelli H, Rey A, Rogers T, Gaze M, Ben Arush MW, et al. Local therapy is critical in localised pelvic rhabdomyosarcoma: experience of the International Society of Pediatric Oncology Malignant Mesenchymal Tumor (SIOP-MMT) committee. *Eur J Cancer*. 2012;48:2020-7.
 42. Akkary R, Chargari C, Guérin F, Jochault L, Audry G, Pio L, Minard-Colin V, Haie-Meder C, Martelli H. Long-term urological complications after conservative local treatment (surgery and

brachytherapy) in children with bladder-prostate rhabdomyosarcoma. A single team experience. *Pediatr Blood Cancer* in press

43. Nag S, Tippin D, Ruymann FB. Intraoperative high-dose-rate brachytherapy for the treatment of pediatric tumors: The Ohio State University experience. *Int J Radiat Oncol Biol Phys* 2001;51:729-735.

44. Blank LE et al (2010) Brachytherapy as part of the multidisciplinary treatment of childhood rhabdomyosarcomas of the orbit. *Int J Radiat Oncol Biol Phys* 2010;77:1463–1469.

45. Folkert MR, Tong WY, LaQuaglia MP, et al. 20-year experience with intraoperative high-dose-rate brachytherapy for pediatric sarcoma: Outcomes, toxicity, and practice recommendations. *Int J Radiat Oncol Biol Phys* 2014;90:362-368.

46. Levy A, Martelli H, Fayeck C, et al. Late toxicity of brachytherapy after female genital tract tumors treated during childhood: Prospective evaluation with a long-term follow-up. *Radiother Oncol*. 2015;117:206-12

47. Romano E, Simon R, Minard-Colin V, et al. Analysis of Radiation Dose/Volume Effect Relationship for Anorectal Morbidity in Children Treated for Pelvic Malignancies. *Int J Radiat Oncol Biol Phys*. 2021;109:231-241.

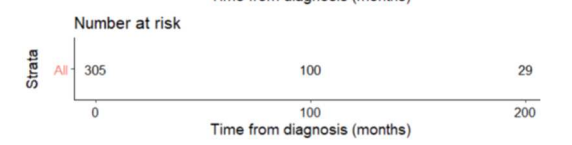
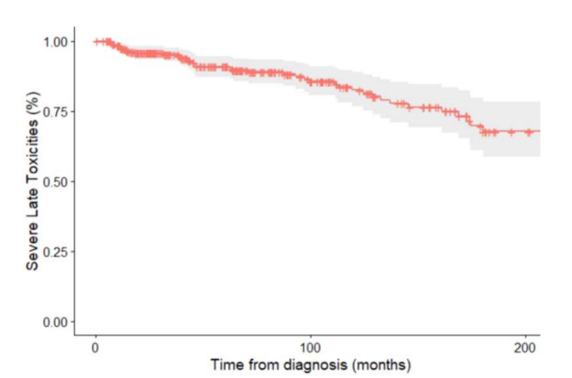
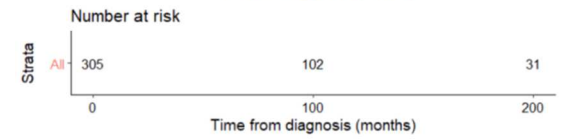
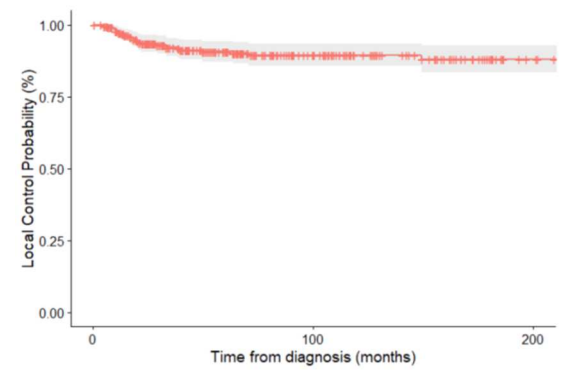
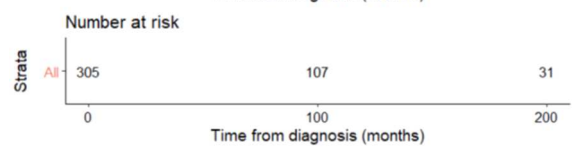
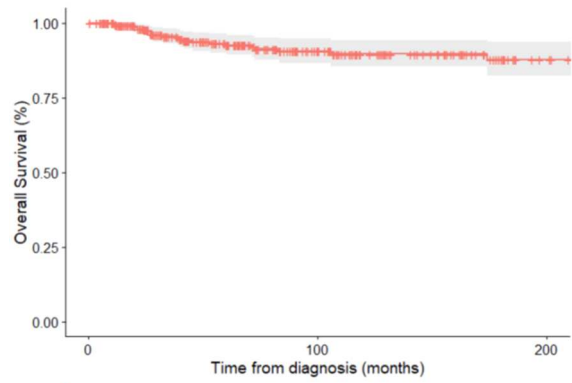
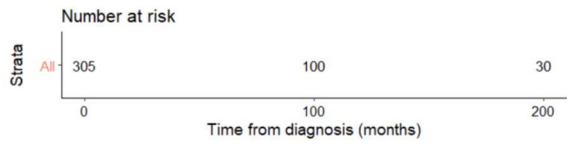
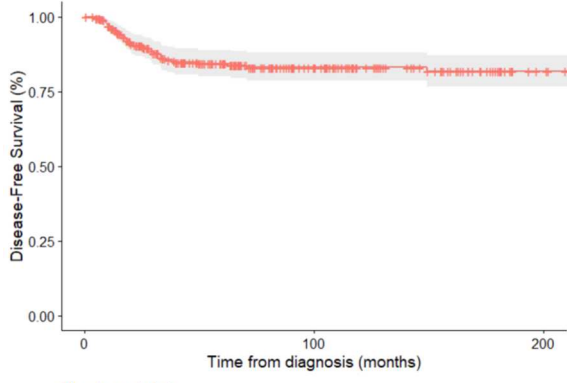
48. Berns A, Ringborg U, Celis JE, et al. Towards a cancer mission in Horizon Europe: recommendations. *Mol Oncol*. 2020 Aug;14(8):1589-1615. doi: 10.1002/1878-0261.12763. PMID: 32749074; PMCID: PMC7400777.

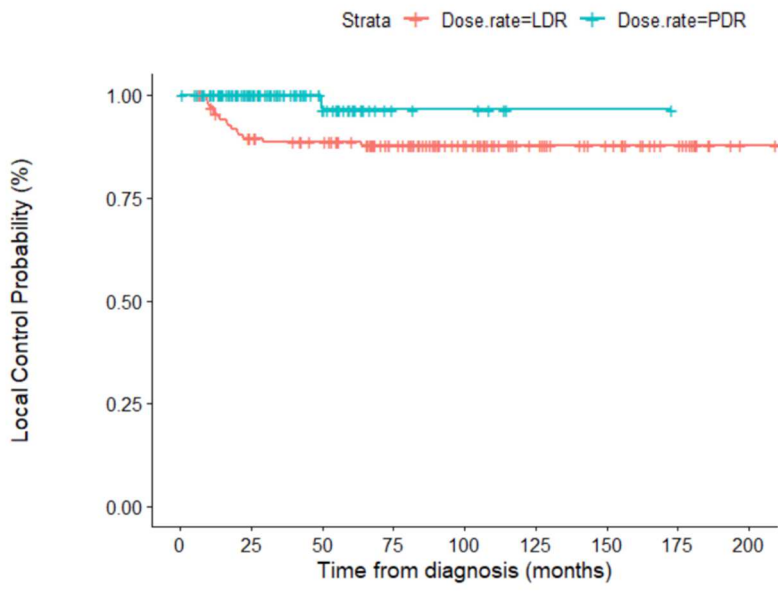
FIGURES LEGENDS

FIGURE 1. Kaplan-Meier estimated survival curves showing disease-free survival, overall survival, survival without local relapse, and survival without late severe morbidity probabilities

FIGURE 2. Local control probability according to brachytherapy modality: low dose rate treatments (LDR) or image-guided pulse dose rate treatments (PDR).

Analysis was performed in the sub-cohort of 241 patients referred for primary treatment of a rhabdomyosarcoma





Number at risk

Strata	0	25	50	75	100	125	150	175	200
PDR.BDD=0	139	116	109	88	67	49	40	30	18
PDR.BDD=1	102	66	28	6	5	1	1	0	0

TABLE 1. Patients and tumors

Patients and tumors characteristics		N	% (range)
Patients characteristics			
Number of patients		305	100
Males / Female		170/135	55.7/44.3
Median age at time of diagnosis		2.2 y	(1.4 mo – 17.2 y)
	Age < 1 year	46	15.1
	Age ≥ 1 and < 2 years	92	30.2
	Age ≥ 2 and < 5 years	113	37.0
	Age ≥ 5 and < 10 years	33	10.8
	Age ≥ 10 years	21	10.1
Median age at time of brachytherapy		2.9 y	(5.8 mo – 17.6 y)
Primary tumor site			
	Bladder-prostate	172	56.4
	Vagina	73	28.5
	Cervix	6	2.0
	Vulva	8	2.6
	Perineum	15	4.9
	Limbs/trunk	10	3.2
	Naso-labial fold	14	4.6
	Cheek	3	1.0
	Tongue	1	0.3
	Mouth floor	1	0.3
	Parotid	1	0.3
	Para-labial area	1	0.3
Tumors characteristics			
Histology			
	Non-alveolar RMS	244	80.0
	ARMS	31	10.2
	MGCT	14	4.6
	CCA	10	3.3
	US	3	1.0
	UC	1	0.3
	Synovialosarcoma	1	0.3
	Dermatofibrosarcoma*	1	0.3
Tumor stage			
	Localized	270	88.5
	Regional LN metastases	16	5.2
	Metastatic disease	19	6.3
Tumor size			
	≥ 5 cm	141	46.2
	< 5 cm	152	49.3
	NR	12	4.5
IRS group for RMS patients (n = 275)			
	IRS II	17	6.2
	IRS III	202	73.5
	IRS IV	25	9.1
	NA (relapse)	31	11.3

ARMS: alveolar rhabdomyosarcoma; CCA: clear cell adenocarcinoma; ERMS: embryonal rhabdomyosarcoma; IRS: international rhabdomyosarcoma; LN: lymph nodes; MGCT: malignant germ cell tumor; NA: not available; NR: not reported; UC: undifferentiated carcinoma; US: undifferentiated sarcoma

*patient treated in 1988

TABLE 2. Treatments delivered

Treatments delivered		N	% (range)
Chemotherapy			
Number of chemotherapy cycles prior to BT		6	(3 – 18)
Chemotherapy Backbone Protocols			
Sarcoma patients (n = 280)	RMS-2005	165	58.9
	MMT-95	36	12.9
	CWS-2006	11	3.9
	Other containing IVA	31	11.0
	Other containing VAC	12	4.3
	Maintenance chemotherapy	36	12.9
MGCT patients (n = 14)	VBP/VIP	8	57
	Other protocol	6	43
Carcinoma (n = 11)	Concurrent cisplatin	4	36
Surgical treatment			
Partial (R1 or R2) primary tumor resection		207	67.9
No primary tumor surgery		98	32.1
Brachytherapy			
Radioelement			
	Iridium-192 wire	176	57.7
	Iridium-192 stepping source	125	41.0
	Cesium-137	4	0.01
Implant modality			
Perioperative		180	59.0
Postoperative or exclusive		125	41.0
Technique			
Interstitial BT only		225	73.8
Intracavitary BT only		68	22.3
Combination of interstitial and intracavitary BT		12	3.9
Radiation dose and BT indication			
Exclusive treatment		266	87.2
Boost in combination with EBRT		39	12.8
Median EBRT dose (Gy)		41.4	(25 – 50.6)
Median BT dose (Gy)		60	(10 – 80)
Median total primary tumor dose (Gy)		60	(40 – 80)
Treatment planning – irradiation modality			
LDR		180	59
PDR		125	41

BT: brachytherapy; CWS: Cooperative Weichteilsarkom-Studie CWS; EBRT: external beam radiotherapy; Gy Gray; IVA: ifosfamide, vincristine and actinomycin D; LDR: low-dose rate; MGCT: malignant germ cell tumor; MMT: Malignant Mesenchymal Tumors studies; PDR: pulse dose rate; RMS: rhabdomyosarcoma; VAC: vincristine, actinomycin,D, cyclophosphamide; VAC: vincristine, actinomycin D and cyclophosphamide; VBP: vinblastine, bleomycin, and cisplatin; VIP: etoposide, ifosfamide, cisplatin;

TABLE 3 Patient outcome at 5 years according to primary tumor site among RMS patients (n = 275)

Patients with head and neck or perineal tumors seemed to have poorer outcome than others though difference not statistically significant (low number of patients in these groups).

Tumor site	Nb. of pts (*)	Local control (95%CI)	Regional control	DFS	OS
Bladder prostate	172 (8)	92.4% (95% CI = 88.1-96.9)	97.8% (95% CI = 95.3-100)	87.9% (95% CI = 82.7-93.6)	95.1% (95% CI = 91.4-99.0)
Gynecological**	61 (12)	94.2% (95% CI = 88.1-100)	100 % (no event)	94.2% (95% CI = 88.1-100)	100% (no event)
Head and neck	19 (9)	75.8% (95% CI = 57.3-100)	64.3% (95% CI = 45.7-90.4)	45.0% (95% CI = 28.8-75.6)	65.5% (95% CI = 44.7-96.2)
Perineum	15 (4)	62.5.% (95% CI = 38.2-100)	70.7 % (95% CI = 47.6-100)	50.0% (95% CI = 27.9-89.5)	83.6% (95% CI = 64.9-100)
Limbs and trunk	8 (1)	100% (no event)	100 % (no event)	87.5% (95% CI = 67.3-100)	87.5% (95% CI = 67.3-100)

DFS: disease free survival; Nb: number; OS: overall survival; pts: patients

*numbers in parentheses indicate the patients referred for salvage treatment

**including vagina, cervix, vulva

TABLE 4. Late grade ≥ 3 complications in the cohort and according to tumor site (number of patients with severe events and details of events).

Late grade ≥ 3 complications		Number of patients (%)	Number of events
Total number		51/305 (16.7)	
Bladder prostate site		27/172 (14.5)	
	Nonfunctional bladder requiring cystectomy		5
	Anterior fistula requiring reoperation		1
	Poor capacity requiring bladder enlargement		2
	Detrusor hyperactivity requiring botulinum toxic therapy		1
	Urethritis requiring hyperbaric oxygen therapy		1
	Urethral stenosis		6
	Neurogenic bladder and urethral stenosis		1
	Ureteral stenosis		7
	Neurogenic bladder requiring suprapubic catheterisation		1
	Proctitis		7
	Vaginal stenosis		3
Gynecological site		19/87 (23)	
	Vaginal stenosis		13
	Fistula		2
	Osteitis		2
	Proctitis		2
	Urinary incontinence requiring artificial sphincter		1
Perineal site		1/15 (14)	
	Growth delay ⁽²⁾		1
	Lymphedema ⁽¹⁾		1
Head and neck site (number of patients)		4/21 (19)	
	Esthetic sequels requiring reconstructive surgery ⁽³⁾		3
	Osteoradionecrosis ⁽⁴⁾		1
Limbs / trunk site (number of patients)		0/10 (0)	

(1) patients treated with lymph node dissection and external radiotherapy

(2) patient treated with bevacizumab and external radiotherapy

(3) patients treated with BT + surgery

(4) patient treated with BT + external radiotherapy