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Original Article

A National Referral Service for Paediatric Brachytherapy: An Evolving Practice and Outcomes Over 13 Years

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Abstract

Aims: Most children requiring radiotherapy receive external beam treatment and few have tumours suitable for brachytherapy. No paediatric radiotherapy centre will treat enough patients from its own normal catchment population for expertise in brachytherapy to be developed and sustained. Following discussion and agreement in the national paediatric radiotherapy group, a service for paediatric brachytherapy in the UK has been developed. We report the process that has evolved over more than 10 years, with survival and functional outcome results.

Materials and methods: Since 2009, potential patients have been referred to the central paediatric oncology multidisciplinary team meeting, where imaging, pathology and treatment options are discussed. Since 2013, the National Soft Tissue Sarcoma Advisory Panel has also reviewed most patients, with the principal aim of advising on the most suitable primary tumour management for complex patients. Clinical assessment and examination under anaesthetic with biopsies may be undertaken to confirm the appropriateness of brachytherapy, either alone or following conservative surgery. Fractionated high dose rate brachytherapy was delivered to a computed tomography planned volume after implantation of catheters under ultrasound imaging guidance. Since 2019, follow-up has been in a dedicated multidisciplinary clinic.

Results: From 2009 to 2021 inclusive, 35 patients (16 female, 19 male, aged 8 months to 17 years 6 months) have been treated. Histology was soft-tissue sarcoma in 33 patients and carcinoma in two. The treated site was pelvic in 31 patients and head and neck in four. With a median follow-up of 5 years, the local control and overall survival rates are 100%. Complications have been few, and functional outcome is good.

Conclusion: Brachytherapy is effective for selected paediatric patients, resulting in excellent tumour control and good functional results. It is feasible to deliver paediatric brachytherapy at a single centre within a national referral service.

Key words: Bladder prostate rhabdomyosarcoma; brachytherapy; paediatric radiotherapy; service provision

Introduction

Most childhood cancers requiring radiotherapy receive external beam treatment with either photon or proton techniques. Brachytherapy offers advantages for some localised primary tumours, typically sarcomas in this age group as carcinomas are relatively rare. Unlike radical surgery, it facilitates organ preservation and, because of highly conformal dosimetry, it causes fewer late effects than external beam radiotherapy. Few paediatric tumours are suitable for brachytherapy. Treatment of a range of anatomical sites is technically complex, requiring a skilled, experienced team. No single paediatric centre is likely to treat enough patients from its normal catchment population for this expertise to be developed and sustained. Historically, in the UK, as in Europe, treatment practices varied [1]. A few patients amenable to brachytherapy may have been treated locally, others were referred abroad to experienced centres, but many for whom brachytherapy might have been advantageous were not offered this option.

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The Radiotherapy Group of the Children's Cancer and Leukaemia Group (CCLG), the professional association for paediatric oncology in the UK and Ireland, agreed in 2008 that a national referral service should be set up. It aimed to bring together a team with all the necessary skills to select patients appropriately, deliver the treatment competently and safely, and evaluate results over time; providing equity of access for all suitable children, regardless of where they lived. This decision was in line with national guidance [2].

This article describes: first, how the service was initially established and has subsequently evolved; second, the treatment pathway used; third, the patient and disease characteristics and treatment delivered; and, finally, outcome in terms of local control, survival and morbidity in patients treated.

Materials and Methods

Establishment and Evolution of the Service

Following the decision to create a national service, it was established at University College London Hospitals (UCLH). Approval to deliver new procedures was granted by the UCLH governance group. An experienced brachytherapist and a paediatric radiotherapy specialist came together to lead the service jointly and integrated other essential specialties to form a holistic multi-professional team, including clinical radiology, paediatric oncology, paediatric urological surgery and paediatric anaesthesia, together with therapy radiographers and clinical scientists (radiotherapy physics) with knowledge and experience of brachytherapy. Inpatients were accommodated on a paediatric oncology ward to provide support from the multi-professional team, including experienced paediatric oncology doctors, nurses and play specialists.

The first patients treated had relapsed disease having not received prior radiotherapy. Subsequently, brachytherapy was considered as part of primary treatment for newly diagnosed children. Initially, patients were selected following discussion at the weekly solid tumour multidisciplinary meeting in the local principal treatment centre for children and young people (teenagers and young adults). In 2011, the CCLG established a National Advisory Panel to discuss the management of children with rhabdomyosarcoma and other soft-tissue sarcomas, with a focus on challenging local control issues. The panel meets monthly by videoconference and offers advice on treatment options to the clinicians who present cases. It is then the local team's responsibility to select the most appropriate course of action, but usually, when brachytherapy with or without conservative surgery has been suggested, the child is referred for multidisciplinary clinical assessment.

Typically, patients with a bladder, prostate or other pelvic rhabdomyosarcoma are invited for a cystoscopy and examination under anaesthetic after three courses of chemotherapy, to map the extent of disease. At the time of this procedure, exophytic or polypoid extensions of the tumour from the prostate may be excised endoscopically, leaving intrinsic tumour in the prostate for brachytherapy. If tumour infiltrates the bladder wall beyond what can be encompassed with brachytherapy, a partial cystectomy may be undertaken. Biopsies of any suspicious lymph nodes may be undertaken at that time. Multiple biopsies are taken both of visible tumour and of macroscopically apparently normal tissue beyond its margins, to assess whether the tumour is more widespread than clinically recognised.

Consideration is given to potential adverse effects of treatment on future fertility and appropriate measures to reduce this risk may be offered, including gonadal transposition or cryopreservation.

Operative findings are then reviewed in conjunction with the histopathology and serial imaging assessment to decide whether brachytherapy is the most appropriate next step.

Selection criteria for brachytherapy are: a localised embryonal (fusion negative) rhabdomyosarcoma with no evidence of lymph node or distant metastases; tumour at an anatomically accessible site measuring less than about 3 cm in maximum diameter following cytoreductive chemotherapy and surgery. Patients with lesions that do not quite meet these criteria may be accepted, following further careful discussion.

To ensure robustness of the service, the team has been expanded to widen experience and allow continuity of care in the event of extended leave and to facilitate succession planning.

Follow-up is undertaken on a shared care basis between the brachytherapy team and the referring centre. Since 2019, patients have been assessed in a designated combined clinic with paediatric oncology, paediatric urological surgery and clinical oncology staff. This has focused on late effects, functional outcomes and child development as well as tumour control.

The Treatment Pathway

Following patient selection, a consultation is held between the child and family members, and the responsible clinical oncologist, often supported by the surgeon and radiographers, to explain the planned procedure, the likely and possible but unexpected short-term side-effects and complications, and possible late effects. This is supported by written patient information sheets, in line with good practice recommendations [3].

The child is usually admitted to the paediatric ward 3 days ahead of the planned procedure. This allows time to ensure medical fitness, correct anaemia, undergo anaesthetic assessment, administer bowel preparation so the colon and rectum are empty for pelvic procedures, receive play specialist support, check parental understanding and, if necessary, to reiterate information, and receive written informed consent.

As many patients travel long distances, family accommodation is provided nearby, in addition to parental stay facilities in the inpatient ward.

The implant procedure is carried out under general anaesthetic, with a caudal block for pelvic procedures to

ensure durable pain control. Prophylactic antibiotics are usually administered. Imaging will be reviewed with a radiologist. Bladder, prostate and vaginal implants are undertaken in the lithotomy position, with a urethral catheter *in situ*. This is used, even if a suprapubic catheter is in place, for accurate definition on cross-sectional imaging of the urethra and bladder base. Fiducial markers are placed within the implant volume to enable verification of the implant prior to treatment. A transperineal, transrectal ultrasound-guided, technique is used to place flexible high dose rate afterloading catheters (Elekta, Stockholm, Sweden) in the region to be treated. Skin fixation is provided by a flexible plastic template (Mount Vernon template CE marked, MHRA reference number 9142) glued and sutured to the perineum. For superficial vaginal and cervical tumours, an intracavitary applicator is inserted, together with interstitial catheters if appropriate. For labial or perineal tumours, and for most head and neck tumours including the cheek or lip, flexible high dose rate afterloading catheters fixed with beads (Elekta) are used.

To reduce the risk of catheter displacement by the child in between treatment fractions, an immobilisation device is made for pelvic implants while the child is still anaesthetised. This holds the legs adducted, and a rigid thermoplastic skirt is custom made to prevent the child's hands from accessing the treated site.

While still anaesthetised, the child undergoes a planning computed tomography scan. The clinical target volume (CTV) is delineated, based on prior imaging, the results of clinical assessment under anaesthesia and pathology results. The aim is to cover the known disease location and any areas of expected microscopic extension, while keeping the volume as small as possible. Organs at risk (OARs) are contoured, including in pelvic cases, the bladder, urethra, rectum, gonads, femoral heads, triradial cartilages and pubic symphysis. Volumes are peer reviewed in real time by more than one clinical oncologist. The radiotherapy physicists reconstruct the position of the treatment catheters on the computed tomography scan, and prepare a treatment plan using the Oncentra® Brachytherapy planning system (Elekta), aiming to give as homogeneous dose to the CTV as possible, keeping close OARs (such as the urethra) within tolerance levels, and ensuring that the dose to more distant OARs is as low as reasonably achievable.

Following plan approval, treatment is given with a high dose rate 192-iridium source using remote afterloading equipment. Initially this was a Nucletron (Utrecht, the Netherlands) microSelectron® and since 2018 with an Elekta Flexitron®.

The prescribed dose in most cases is 27.5 Gy in five fractions delivered over 3 days, with one fraction on the first day and two fractions on the second and third days, and a minimum 6-h inter-fraction interval. Patients are almost always anaesthetised for all treatment fractions and computed tomography scans.

Positioning of the treatment catheters is checked before each fraction by measurement of the protruding lengths and by a C-arm image intensifier image, and on days 2 and 3 by a repeat computed tomography scan. In the event of minor movement of one or two catheters, repositioning alone may be sufficient, but if major movement has occurred, repositioning is followed by a further computed tomography scan and re-delineation of volumes and replanning, to ensure the greatest possible accuracy of treatment.

Holistic care of the patient on the children's ward in between fractions of treatment includes attention to nutrition, while ensuring appropriate starvation before each general anaesthetic, pain control, which may require an infusion pump for patient- or parent/nurse-controlled analgesia, observation for signs of complications such as infection, and constipating drug administration, following bowel preparation, to reduce the likelihood of the need to defaecate while perineal treatment catheters are in place.

After the final treatment, the treatment catheters are removed. The child is then observed overnight. The next day, if the urine is clear and it is no longer necessary, the urinary catheter is removed, and if there are no other problems the child is discharged home. Further chemotherapy can restart immediately, but to prevent a radiation recall reaction, radiosensitising drugs are avoided for 3 weeks.

Patient and Disease Characteristics

The age and sex of the patients, the anatomical site and histological type of the tumour, prior treatments and referral centre were noted. Details of treatment, including doses to the CTV and OARs, the type of implant, the number of catheters placed and used, and the volumes treated were recorded.

Outcome

Following brachytherapy, patients completed systemic therapy and were followed up clinically and with imaging, as per protocol for signs of local recurrence or distant metastasis. Toxicity is reported according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [4]. Surveillance has continued in all patients for late complications, and assessment of bladder and other function carried out as appropriate for the tumour site treated.

Statistical Analysis

The data presented are descriptive, as there is no comparator group. Observational data, such as age and follow-up duration, are reported as the median and range, as they are not normally distributed.

Results

Patient Population

All patients aged younger than 18 years treated with brachytherapy at UCLH over a 13-year period between January 2009 and December 2021 are reported (Figure 1). The number of patients treated each year has fluctuated (Figure 2), but gradually increased over time, with 12

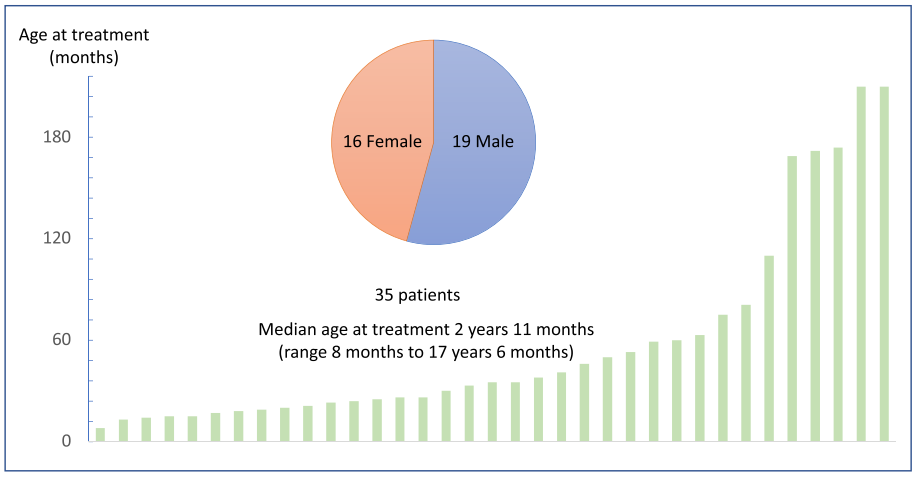

Fig 1. Age and sex distribution of the patient population.

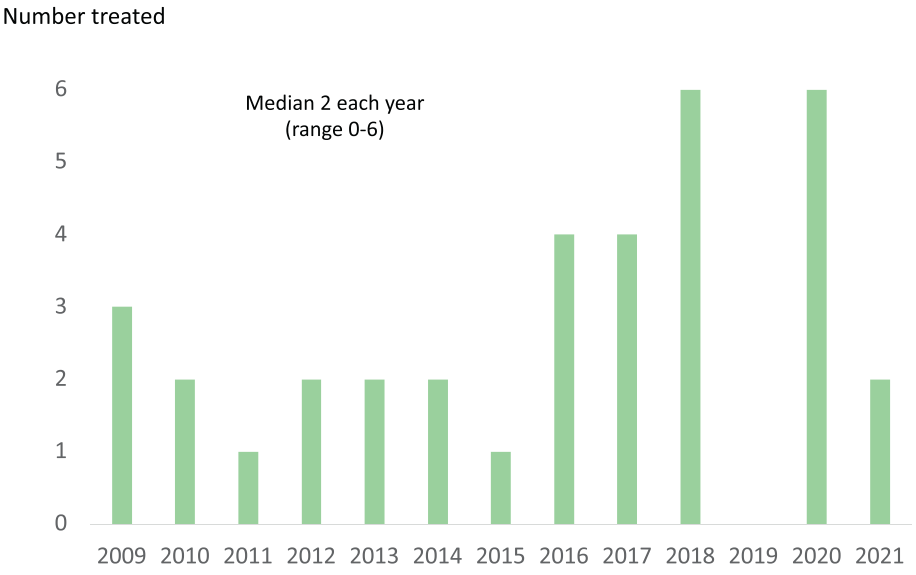

Fig 2. Fluctuating number of patients treated in each calendar year, with a trend to increasing numbers over time.

patients treated in the first half of the time period and 23 in the second. Referrals came from all countries of the UK (Figure 3).

Nine patients were treated before the introduction of the CCLG National Sarcoma Advisory Panel. Of the 26 treated since then, most (16) were discussed by the panel and brachytherapy was recommended as an option to consider.

The histological diagnosis was sarcoma in 33 patients: embryonal rhabdomyosarcoma in 31 and alveolar rhabdomyosarcoma and undifferentiated sarcoma in one patient each.

The primary site for the sarcoma cases was bladder or prostate in 15 boys (six prostate alone and both prostate and bladder in nine cases), bladder in six girls (in two cases also involving the urethra), vagina in three young girls (in one case involving the urethra), cervix in three teenagers, lip in two boys, face in one boy, perineum in one boy and one girl and one vulva. All had localised tumours with no lymph node or distant metastases. In four of these patients, brachytherapy was part of salvage treatment for relapse following prior chemotherapy and surgery without radiotherapy. In the remaining 29, brachytherapy was part of the initial treatment protocol.

The other two patients had brachytherapy as treatment for cervical adenocarcinoma following external beam pelvic radiotherapy and for recurrent nasopharyngeal carcinoma following prior chemoradiotherapy.

Procedural Details

The dose and fractionation schedule used for all patients with sarcoma was 27.5 Gy in five fractions of 5.5 Gy over

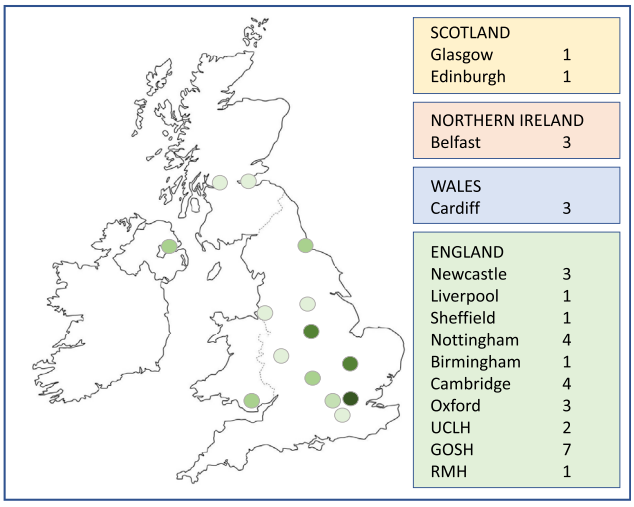

Fig 3. Number of patients referred from different principal treatment centres for children and young people in the UK. GOSH, Great Ormond Street Hospital for Children; RMH, The Royal Marsden Hospital; UCLH, University College London Hospitals.

three consecutive days with a minimum inter-fraction interval of 6 h. This schedule was broadly equivalent in terms of tumour control to the external beam dose of 41.4 Gy in 23 fractions of 1.8 Gy over 4.5 weeks often used for more favourable rhabdomyosarcoma cases, assuming an alpha/beta ratio of 10, but clearly delivered over a much shorter timescale.

The patient with recurrent nasopharyngeal cancer received 10 Gy in five fractions over the same time course. The patient with cervical adenocarcinoma received a brachytherapy boost of 24 Gy in four fractions.

Implants and treatments were personalised according to the anatomy of each individual tumour. For the 21 bladder and prostate patients, a median of 12 (range 5–18) treatment catheters was used to deliver treatment to a median CTV of 17.5 ml (range 8.1–43.2 ml).

The median maximum dose to 0.1 ml of the urethra was 7.41 Gy per fraction (range 0.26–13.48 Gy) in this bladder/prostate patient group. The median rectal dose (D2cc) was 2.44 Gy per fraction (range 0.21–6.27 Gy). In male bladder/prostate patients, the median mean testis dose was 0.47 Gy per fraction (range 0.26–0.61 Gy).

In all patients receiving brachytherapy to pelvic sites, the median mean tri-radial cartilage of the acetabulum dose was 1.40 Gy per fraction (range 0.97–3.45 Gy); the median mean femoral head dose was 0.5 Gy per fraction (range 0.17–1.24 Gy); and the median mean pubic symphysis dose was 2.90 Gy (range 0.42–4.65 Gy).

Follow-up and Outcome

No patients were lost to follow-up. The follow-up period has been at least 5 years for 18 patients and at least 2 years for a further 13 patients. Only four patients have been followed up for less than 2 years, and so are still at some risk of recurrence. The median follow-up duration is 5 years 0 months (range 8 months–13 years 3 months). No patients have died and all have maintained local control without the development of metastatic disease.

Acute morbidity of the procedure has been very limited. One patient developed sepsis following removal of the implant (CTCAE v5.0 grade 4), but this resolved quickly with prompt treatment. There were no other severe complications. For patients with bladder or prostate implants, genital oedema (CTCAE v5.0 grade 1), localised bruising (CTCAE v5.0 grade 1) and haematuria (CTCAE v5.0 grade 1 or 2) were not uncommon, but all settled rapidly after the end of the procedure.

Most patients have not experienced significant (CTCAE v5.0 grade 3 or worse) late side-effects – there were three CTCAE v5.0 late complications noted. Two patients experienced urethral stricture formation: one male developed a stricture (CTCAE v5.0 grade 3) following treatment of a prostatic rhabdomyosarcoma, which was treated by urinary diversion with a Mitrofanoff appendico-vesicostomy for intermittent self-catheterisation, and one female developed a stricture (CTCAE v5.0 grade 3) following treatment of a bladder rhabdomyosarcoma, which was treated by surgical incision, resulting in normal urinary voiding. One female developed a vaginal stricture (CTCAE v5.0 grade 3) that will require reconstructive surgery when she is older. One post-pubertal teenager developed secondary amenorrhoea due to ovarian failure following treatment of a cervical rhabdomyosarcoma (CTCAE v5.0 grade 2). No rectal toxicity has been observed. A detailed analysis of bladder function and urinary outcome in a subset of 13 patients with bladder and/or prostate rhabdomyosarcoma reported here has been published separately [5]. In this subset, daytime dryness at a median of 3.5 years after treatment was achieved in 92%. Cosmesis at visible sites has been good (Figure 4).

No second malignancies have occurred. Most of our patients are still too young for us to have a detailed understanding of sexual function and reproductive ability, and we continue to follow these patients.

Discussion

The acceptability of a national paediatric brachytherapy referral service to both families and clinicians is shown by the wide referral base of our patients and the increasing numbers treated. Confidence will be enhanced by the very good local control and survival outcomes achieved, resulting from careful patient selection and meticulous technique delivered by an increasingly experienced team.

Since the 1980s, paediatric genitourinary rhabdomyosarcoma brachytherapy has predominantly been undertaken in Paris [6–8]. The experience and good outcomes have encouraged others to create a similar service [9,10]. The patients we report have been treated with a similar philosophy, but with appreciably different details: we use

an image-guided percutaneous approach for the insertion of treatment catheters, conservative surgery is carried out as a separate procedure prior to brachytherapy and we use a lower total dose administered as a fractionated high dose rate regimen over a shorter overall time.

The absolute dose is not the only parameter that needs to be considered. Dose rate and fractionation and overall time need to be taken into account. For example, the Paris team, which has the longest and largest experience world-wide, switched from low dose rate to pulsed dose rate in 2014, and a median dose of 60 Gy is used at a dose rate less than or equal to 10 Gy per day for patients receiving brachytherapy with or without surgery and without external beam radiotherapy [11].

Table 1 shows the relative doses for two different fractionation schedules and the corresponding dose if delivered in 2 Gy fractions (EQD2) and the biological effective dose.

The radiobiology of rhabdomyosarcoma has not been widely studied and there are differences in the interpretation of available data. One randomised study of dose escalation with hyperfractionation [12] was predicated on an assumption of an alpha/beta ratio of 10 Gy for tumour control, which would be considered standard for many tumour tissues, and 3 Gy for late normal tissue toxicity. However, others calculated an alpha/beta ratio of 2.8 based on the data reported from that trial [13], but this was challenged [14]. If we assume that an alpha/beta ratio of 10 is correct, then our schedule gives a significantly lower dose than the Paris regimen as judged by EQD2.

It is not clear whether any one system is appreciably better than any other, but our schedule in terms of local control and survival and toxicity is at least as good, and the shorter overall duration, 3 days rather than 6 days, is advantageous.

For carefully selected patients, brachytherapy offers an advantage over external beam therapy with photons and

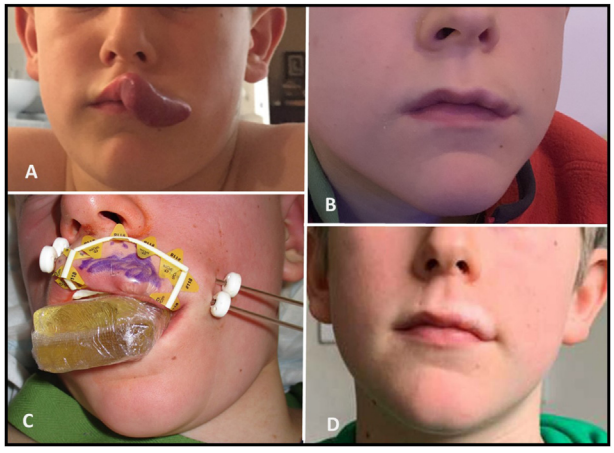

Fig 4. A 9-year-old boy with a fusion-negative rhabdomyosarcoma of the upper lip: (A) at presentation; (B) after chemotherapy; (C) with two brachytherapy catheters in place, and bolus in the mouth to displace the lip away from the maxilla and dentition; (D) 2 years after treatment to show the satisfactory cosmetic appearance of the treated lip.

Table 1
Biological effective dose (BED) and the equivalent dose in 2 Gy fractions (EQD2) of the fractionation schedule used in this series, compared with that typically used in Paris, taking into account two potential values for the alpha/beta ratio

	Paris schedule Dose 60 Gy in 144 fractions		London schedule Dose 27.5 Gy in 5 fractions	
Alpha/beta ratio	3	10	3	10
EQD2	41 Gy	52.08 Gy	46.75 Gy	35.52 Gy
BED	68.33 Gy	62.5 Gy	77.92 Gy	42.63 Gy

even protons, in terms of a lower integral normal tissue dose, which should translate into a lower risk of radiation-induced second malignancy [15–17]. However, it will take much larger patient numbers, and significantly longer follow-up, to demonstrate that this theoretical benefit is actually true in practice. There is also better sparing of OARs, as a result of no beam pathway through normal tissue into the tumour, and the more rapid dose fall off outside the target volume as a result of the inverse square law. There are, therefore, fewer late effects and an improved quality of survival [18]. The short overall treatment time of 3 days compares favourably with an external beam schedule of 45 Gy in 25 fractions over 5 weeks, requiring many fewer anaesthetic episodes for a young child.

Other centres have developed brachytherapy expertise in areas we have not yet explored, for example brachytherapy combined with ablative surgery for head and neck tumours (AMORE) and limb sarcomas [19,20].

There are data to suggest that in some countries, paediatric brachytherapy is an underutilised treatment modality [21]. Given the good results presented here, we would like to ensure that this option is considered in all appropriate cases. No doubt our service will continue to evolve over time, and new indications and techniques may be introduced. We are committed to ensuring the quality of what we do is optimal, for example by the implementation of external peer review through the QUARTET system for patients in clinical trials [22].

Conclusions

A UK-wide national service has been created to select children and young people suitable for brachytherapy (with or without conservative surgery) and to deliver treatment and provide careful follow-up.

Over 13 years, 35 children have been treated; with a median follow-up period of 5 years, local control, disease-free and overall survival rates are 100% with only one case of CTCAE v5.0 grade 4 acute toxicity and three CTCAE v5.0 grade 3 late complications.

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

MNG is the guarantor of integrity of the entire study. MNG, NS and PJH were responsible for study concepts and design. MWF and MNG carried out the literature research. MNG, NS, RA, CA, NB, MB, AC, GE, EG, MWF, PDH, PL, IM, TN, CP, DP, SP, HR, GS, AS, OS, TS and PJH were responsible for clinical studies and data collection and interpretation. GS, MB, TS and MNG were responsible for data analysis. MNG carried out the statistical analysis. MNG, NS and PJH prepared the manuscript. MNG, NS, RA, CA, NB, MB, AC, GE, EG, MWF, PDH, PL, IM, TN, CP, DP, SP, HR, GS, AS, OS, TS and PJH were responsible for manuscript review, critical revision for important intellectual content and editing. MNG, NS, RA, CA, NB, MB, AC, GE, EG, MWF, PDH, PL, IM, TN, CP, DP, SP, HR, GS, AS, OS, TS and PJH gave final approval of the submitted version.

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