How could imaging reduce therapy-associated morbidity in rhabdomyosarcoma of the bladder or prostate?

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The treatment of pediatric rhabdomyosarcoma (RMS) of the pelvis has been changing in recent years. Local treatment after chemotherapy is delayed or even avoided completely without effecting overall survival. Imaging is playing a growing role in individualized treatment planning in these patients. In cases of questionable recurrence or residual disease, fusion biopsies may allow a safe and reliable bioptic examination.

Tumors of the urogenital tract comprise approximately 10% of childhood tumors [101] and 7–8% of all solid tumors are sarcomas [1]. RMS are the most common soft tissue sarcoma in children [2]. The two main histological types of RMS are embryonal and alveolar, with a favorable prognosis for the embryonal subtype [2].

To date, it remains unclear which treatment strategy is best for RMS of the small pelvis. The first scientific evaluation of multimodal treatments in patients with RMS was initiated by the Intergroup Rhabdomyosarcoma Study (IRS) with their first study carried out between 1972 and 1978 (IRS I) [3]. During the following trials (IRS II–IV), a 6-year survival rate of 82% with a bladder preservation rate of 62% was reported, but of these patients, less than 40% had a normal bladder function [4]. Thus, when the bladder is preserved, treatment often leads to significant dysfunction of the lower urinary tract, including nocturnal enuresis, abnormal voiding, abnormal bladder capacity and/or continuous dribbling. Unfortunately, only a few small studies tried to objectively evaluate these patients with urodynamic examinations. The largest systematic study examined 11 patients treated for RMS [5]. Only four out of 11 children had a normal

voiding function 6 years after treatment. Various study groups (Children's Oncology Group [COG] Soft Tissue Sarcoma Committee, Italian Cooperative Group [ICG] and German Cooperative Soft Tissue Sarcoma Study [CWS]) are currently investigating treatment strategies for pediatric RMS worldwide. The regimes vary in risk stratification, which is carried out according to stage and disease spread. Most of these therapy regimes consist of chemotherapy and at least one additional local treatment (e.g., radiation therapy or surgery).

Recently, the necessity of aggressive local treatment after chemotherapy has been discussed in order to minimize long-term adverse effects, since both surgery and radiotherapy severely compromise bladder function [6]. In 2011, results of the Intergroup Rhabdomyosarcoma Study Group trial (IRSG) 9602 were reported [7] and 108 out of the 125 study patients with low-risk disease (stage I and II) were treated with chemotherapy alone. Only six out of the 125 patients suffered from recurrent disease. Similarly, Rodeberg *et al.* analyzed the outcome of different therapy regimes in different countries from 379 patients diagnosed between 1979 and 1998. Radical surgical treatment was only performed in 12% of cases [8]. Radiotherapy was performed in some protocols, but owing to the growing perception of side effects, a number of protocols only performed radiation therapy in cases of poor response to chemotherapy. As a result, the local failure-free survival differed between these protocols, but overall survival was not influenced in a negative way.

To reduce side effects and organ dose by radiation therapy, Cotter *et al.* reported on

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the opportunity of dose saving by using proton radiotherapy in children with RMS of the bladder/prostate [9]. They performed proton radiotherapy on seven patients between 2002 and 2008. In this study, they were able to reduce the mean organ dose for the bladder from 33.2 to 25.1 Gy compared with intensity-modulated radiation therapy. The same effect was observed for other pelvic organs, including the testes and pelvic bone.

Stein *et al.* recently reported their long follow-up (median: 132 months) of 25 children treated with urinary diversion for RMS of the bladder/prostate [10]. Eight out of 14 (57%) patients who survived needed future operative revisions due to diversion-related complications such as fistula, stenosis or stones. The surviving patients are continent today. Twelve of the patients have a continent cutaneous urinary diversion and perform catheterization. Only two void through the urethra by performing a valsalva maneuver (orthotopic bladder substitution). These numbers demonstrate the tremendous impact of ablative surgery on the body integrity of children suffering from RMS that needed radical therapy.

Imaging plays a growing role in the concept of individualized treatment planning. Today, in many circumstances, an additional MRI is carried out in soft tissue tumors to gather detailed

information about margins and infiltration. Owing to the side effects of radiation therapy in the small pelvis and radical surgery, it is very important to understand whether these treatments can be delayed or even avoided. Therefore, high-quality staging is required. Appropriate imaging for navigation during such biopsies is essential. Only few reports of computed tomography [11–13] and MRI examinations [14] in prostatic stromal tumors in children have been published in the literature. With regard to soft tissue resolution, MRI is most appropriate for restaging children with RMS [15]. Optimally, RMS patients are followed-up with high-resolution multiparametric MRI so that residual disease can be detected at very early stages. Multiparametric MRI has a long examination time of 45 min. However, the excellent resolution and the significant impact on the following course of treatment outweigh the complexity of performing high-spatial resolution MRI under sedation. Raney *et al.* described the impact of tumor viability at surgical procedures in patients with RMS [16]. They reported a significant correlation between complete response on MRI and nonviable tumor in surgical resection in 93% of patients. Interestingly, 41% of patients without a complete response on imaging had no viable tumor and, therefore, these patients could have been spared from surgery with improved imaging.

Figure 1. Local recurrence of prostate cancer (arrows) after external radiotherapy. (A) A T_2 -weighted transversal magnetic resonance image of the pelvis and **(B)** PET-magnetic resonance image with high accumulation of ^{68}Ga -labeled PSMA tracer [18]. For color images please see online www.futuremedicine.com/doi/pdf/10.2217/FON.13.116.

Figure 2. MRI/transrectal ultrasound scan fusion image during biopsy planning of a 18-month-old boy after combined chemotherapy and radiation therapy for alveolar rhabdomyosarcoma. The orange part shows the transrectal ultrasound scan and the gray part shows multiparametric MRI. Note the non-matching contours of the bladder wall caused by differing bladder fullness [20].

In times of personalized medicine and rapid development of new imaging techniques, such as PET/MRI (FIGURE 1) [17], MRI/ultrasound fusion systems [18] and high-field 7T MRI, the questions arises, can patients further benefit from these advances? Our group recently described the case of a young boy suffering from RMS, who underwent MRI/transrectal ultrasound scan fusion imaging (FIGURE 2) of a residual tumor mass in the pelvis after radiochemotherapy for RMS of the prostate [19]. Since histology showed no active malignancy, the boy was spared exenterative surgery and has been observed without signs of residual disease until now (follow-up: 22 months). The use of PET/MRI systems with novel radiopharmaceutical tracers has already improved the detection rate in other malignant tumors and will probably impact pediatric imaging in the future. Afshar-Oromieh *et al.* reported an improved detection rate of prostate cancer by the use of ^{68}Ga -labeled PSMA compared with fluorodeoxyglucose FECH [17]. In RMS, the use of PET/CT has shown variable results and needs further improvement [20,21].

In conclusion, the success of systemic and local treatment will probably be monitored with enhanced safety using the developing imaging techniques. In cases of suspicious findings in any imaging modality, the use of fusion systems can improve the reliability of bioptic sampling. Thereby, further treatment steps can be planned on a highly individual basis. This concept of personalized treatment regimes may spare more patients from treatment-related morbidity and, thus, improve their quality of life significantly.

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