F1000Prime REPORTS

Published: 12 May 2015

Recent advances in understanding and managing rhabdomyosarcoma

Susan M. Hiniker and Sarah S. Donaldson*

Address: Stanford University Medical Center, Stanford, CA 94305

* Corresponding author: Sarah S. Donaldson (sarah2@stanford.edu)

F1000Prime Reports 2015, **7**:59 (doi:10.12703/P7-59)

Abstract

Rhabdomyosarcoma is the most common childhood soft tissue sarcoma and the fourth most common pediatric solid tumor. For most patients, treatment consists of a multimodality approach, including chemotherapy, surgery, and/or radiotherapy. To guide treatment, patients with rhabdomyosarcoma are risk stratified based on a number of factors. These factors include clinical group, which depends largely on the extent of resection and nodal involvement, and stage, which takes into account tumor size, invasion, nodal involvement, and disease site. Histology of the tumor and age at diagnosis are also factored into risk stratification. Recent advances in understanding the biology of the disease have allowed for the further sub-classification of rhabdomyosarcoma. In addition, elucidation of additional clinical features associated with poor prognosis has allowed for better understanding of risk and provides more clarity regarding those patients who require more intensive therapy. Many areas of active investigation are ongoing, including the following: further delineation of the biological underpinnings of the various disease subtypes with the possibility of molecularly targeted therapy; a better understanding of clinical risk factors, including the evaluation and management of potentially involved lymph nodes; determination of the appropriate role of post-treatment imaging and assessment of response to therapy; and incorporation of advanced radiotherapeutic techniques, including conformal intensity-modulated photon and proton therapy.

Introduction

Rhabdomyosarcoma is the most common childhood soft tissue sarcoma and the fourth most common pediatric solid tumor [1]. Since the development of the Intergroup Rhabdomyosarcoma Study Group (IRSG) in the early 1970s, survival outcomes for patients with rhabdomyosarcoma have continued to improve, due to advances in therapy and a better understanding of which patients require more aggressive treatment. Therapy for most patients consists of a multimodality approach, including chemotherapy as well as local treatment with surgery and/or radiotherapy. To guide treatment decision-making, patients with rhabdomyosarcoma are risk stratified based on a number of factors, including clinical group, which depends largely on the extent of resection and nodal involvement; stage, which takes into account tumor size, invasion, nodal involvement, and disease site; histology of the tumor, and age at diagnosis. Recent advances in understanding the biology of the disease have allowed for the further sub-classification of rhabdomyosarcoma, including distinction by molecular fusion product status, with fusion-positive alveolar rhabdomyosarcoma a more aggressive disease, and alveolar rhabdomyosarcoma without fusion and embryonal rhabdomyosarcoma having a similar, better prognosis. In addition, elucidation of additional clinical features associated with poor prognosis has allowed for better understanding of risk and provides more clarity regarding those patients who require more intensive therapy, as well as the timeframe in which it is necessary to introduce local therapy in high-risk patients. We examine here the many ongoing areas of active investigation, including the following: further delineation of the biological underpinnings of the various disease subtypes with the

possibility of molecularly targeted therapy; a better understanding of clinical risk factors, including the evaluation and management of potentially involved lymph nodes; determination of the appropriate role of post-treatment imaging and assessment of response to therapy, as well as the prognostic importance of pre-treatment imaging including positron emission tomography-computed tomography (PET-CT); and incorporation of advanced radiotherapeutic techniques, including conformal intensity-modulated photon and proton therapy. Here we discuss recent advances in the understanding and management of rhabdomyosarcoma.

Advances in biology

Investigation of the biologic underpinnings of rhabdomyosarcoma has been an area of extensive research, with promising results. The distinction between embryonal rhabdomyosarcoma and alveolar rhabdomyosarcoma has been understood for many years, with stage-matched and group-matched alveolar rhabdomyosarcoma generally behaving more aggressively than embryonal rhabdomyosarcoma and, indeed, classification of alveolar histology precludes stratification in the low-risk group in current trials. Further biologic features are now being identified, with distinct differences being confirmed. Studies have indicated that most alveolar rhabdomyosarcomas express one of two oncogenic gene fusions: PAX3 or PAX7 with FOXO1, known as P3F and P7F, respectively. P3F is the protein produced by the chromosomal translocation t(2;13)(q35;q14), which is present in approximately 60% of cases of alveolar rhabdomyosarcoma [2]. P7F is present in 20% of cases and is produced by the translocation t(1:13)(p36;q14). Approximately 20% of alveolar rhabdomyosarcoma cases are fusion-negative [2].

The prognostic implication of this fusion is critically important. In a subset analysis from D9803, an intermediate-risk rhabdomyosarcoma trial, patients were evaluated for the prognostic value of PAX-FOXO1 fusion status. Patients with embryonal rhabdomyosarcoma and alveolar rhabdomyosarcoma with no detectable fusion (alveolar rhabdomyosarcoma fusion-negative) had a similar prognosis after therapy. Patients with alveolar rhabdomyosarcoma P3F had statistically worse event-free survival (EFS) than patients with embryonal rhabdomyosarcoma, and those with P3F had poorer survival than those with P7F. Interestingly, there is a trend toward improved EFS in alveolar rhabdomyosarcoma fusion-negative patients vs. those with embryonal rhabdomyosarcoma (90% vs. 77%, P=0.15). The results indicate that it is the fusion status driving outcome for rhabdomyosarcoma, as opposed to the histopathologic subtype [3]. In fact, outcomes in alveolar rhabdomyosarcoma fusion-negative patients compare favorably with those in embryonal rhabdomyosarcoma patients, although this was not statistically significant. Other reports have also noted that alveolar rhabdomyosarcoma fusion-negative and embryonal rhabdomyosarcoma patients have very similar gene expression patterns, clinical features, and outcomes [4]. Indeed, even histologic distinction between alveolar rhabdomyosarcoma fusion-negative and embryonal rhabdomyosarcoma can be challenging. Rudzinski *et al.* re-reviewed 255 cases originally classified as alveolar rhabdomyosarcoma and compared these cases with a control group of 38 embryonal rhabdomyosarcoma cases [5]. On review, many cases classified as alveolar rhabdomyosarcoma had a densely cellular pattern with cytological features and myogenin expression more typical of embryonal rhabdomyosarcoma. After this re-review, 33% of cases initially classified as alveolar rhabdomyosarcoma were reclassified as embryonal rhabdomyosarcoma. All reclassified embryonal rhabdomyosarcomas were fusion-negative, while 82% of confirmed alveolar rhabdomyosarcomas were fusion-positive. The total number of cases of alveolar rhabdomyosarcoma returned to historic rates of 25-30%, and alveolar rhabdomyosarcoma fusion-negative decreased to 18% of alveolar rhabdomyosarcoma cases, down from 37% [5]. Given the similar prognosis of alveolar rhabdomyosarcoma fusion-negative to embryonal rhabdomyosarcoma, this group of patients may be more appropriately stratified and treated as if they were histologically embryonal rhabdomyosarcoma cases rather than as part of the alveolar rhabdomyosarcoma positive group. Fusion status and risk stratification are currently being investigated for patients with rhabdomyosarcoma enrolled on Children's Oncology Group (COG) clinical trials.

Analyses of gene expression microarray data have shown that several techniques help distinguish fusion status in rhabdomyosarcoma. Reverse-transcription polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH) are able to detect fusion-gene positive rhabdomyosarcoma, but notably both techniques require a significant quantity of high-quality material for analysis. Recently, Rudzinski *et al.* reported that a panel of four immunohistochemical markers can be used as surrogate markers of fusion-positive status in rhabdomyosarcoma: myogenin, AP2B, NOS-1, and HMGA-2, of particular importance when the available pathologic material is minimal or of poor quality. The use of a panel of four immunohistochemical markers also has the advantage of not missing a rare fusion variant [6].

With the new information regarding the molecular underpinnings of alveolar rhabdomyosarcoma have come new opportunities for targeted therapy, although these have not yet reached the clinic. Recent preclinical

data have shown that FANCD2 is a potential therapeutic target in fusion-positive alveolar rhabdomyosarcoma. In mouse models, FANCD2 may have a significant role in the radiation resistance of alveolar rhabdomyosarcoma, and offers a possibility for targeting this DNA repair protein through mTOR inhibition [7]. Targeting of the fusion protein is an area of active research from multiple directions; Jothi *et al*. reported a small molecule inhibitor of the sarco/endoplasmic reticulum as an effective inhibitor of the fusion protein binding to target genes and promoting its degradation in the proteasome [8].

Progress has also been made in understanding the biology of embryonal rhabdomyosarcoma. Genomic analysis has shown that embryonal rhabdomyosarcoma has more structural and copy number variations than alveolar rhabdomyosarcoma, and mutations in RAS/NF1 pathway are significantly associated with intermediate- and high-risk embryonal rhabdomyosarcoma. In intermediate- and high-risk embryonal rhabdomyosarcoma, orthotopic xenografts were recently developed, characterized, and whole genome sequencing performed. High-throughput screening of primary cultures derived from these xenografts identified recurrent p53 and RAS pathway mutations in embryonal rhabdomyosarcoma, and pointed to oxidative stress as a potential pathway of therapeutic relevance for embryonal rhabdomyosarcoma. The thioredoxin reductase inhibitor auranofin was found to have activity against the embryonal rhabdomyosarcoma xenografts [9]. In addition, fibroblast growth factor receptor 4 (FGFR4) has been found to be upregulated in embryonal and alveolar rhabdomyosarcoma, with higher protein expression in alveolar rhabdomyosarcoma. Crose *et al*. reported that stable expression of P3F induced elevated FGFR4. FGFR4 blockade was found to have differential effects in alveolar and embryonal rhabdomyosarcoma, inducing cell death in alveolar rhabdomyosarcoma, while inhibiting proliferation and tumorigenesis in embryonal rhabdomyosarcoma, highlighting a potential target for therapy in alveolar rhabdomyosarcoma [10]. Additionally, new molecular and genetic insight into anaplastic rhabdomyosarcoma has been reported based on a recent analysis of children with anaplastic rhabdomyosarcoma. Hettmer *et al*. found that 11 of 15 children with anaplastic rhabdomyosarcoma had TP53 germline mutations, and further found that in children with anaplastic rhabdomyosarcoma with a family cancer history consistent with Li-Fraumeni syndrome, 5 of 5 had a TP53 germline mutation, and 4 of 5 patients without this family history had TP53 germline mutation [11]. The most comprehensive genomic analysis of rhabdomyosarcoma thus far was recently reported by Shern *et al.*, in which they reported a relatively low rate of somatic mutations, particularly in P3F and P7F cases. However, the receptor tyrosine kinase/RAS/PIK3CA axis was altered in 93% of cases, highlighting a potential opportunity for intervention [12]. The key to better treatment and outcome for patients with rhabdomyosarcoma is likely to lie in a better understanding of the biological basis of disease.

Defining clinical risk

Risk stratification

Combining the understanding of histologic findings along with clinical presentation has allowed for the ability to estimate the risk of metastatic disease at presentation, and thereby potentially avoid unnecessary staging studies in very low-risk patients. In an analysis of patients from the Intergroup Rhabdomyosarcoma Study (IRS) and COG studies treated from 1991 to 1997 and from 1999 to 2004, specific features of disease associated with metastasis were evaluated. Rhabdomyosarcoma without local invasion was found to have a low rate of metastasis, particularly embryonal rhabdomyosarcoma (0%). Alveolar rhabdomyosarcoma with invasion had a high rate of distant metastases [13]. The authors argue that bone marrow aspirate and biopsy can be safely omitted in a very low-risk subgroup of patients, and note that those patients with node-positive disease are also at high risk of hematogenous metastases. From these data, a staging algorithm was developed to guide the use of staging studies in newly diagnosed rhabdomyosarcoma.

Other efforts to risk stratify patients have resulted in the development of a nomogram from Surveillance, Epidemiology, and End Results (SEER) data to predict overall survival (OS). In a cohort of 1679 pediatric rhabdomyosarcoma patients treated between 1990 and 2010, 5 year OS was 64.5%. In multivariate analysis, age at diagnosis, tumor size, histological type, surgery, and radiotherapy were all significantly associated with survival [14].

Based on improved understanding from clinical risk, efforts are now focused to further tailor therapy among subsets of patients. In an effort to shorten the total duration of treatment for a subset of low-risk patients, in an analysis of COG ARST 0331 patients with subset 1 low-risk embryonal rhabdomyosarcoma (stage 1–2, group I/II embryonal rhabdomyosarcoma, or stage 1 group III orbit embryonal rhabdomyosarcoma), it was found that giving lower-dose cyclophosphamide and radiotherapy did not compromise survival. Patients with microscopic or gross residual disease at entry received radiotherapy. These findings built upon IRSG III and IV which showed improved failure-free survival (FFS) with vincristine-actinomycin D-cyclophosphamide vs. vincristine-actinomycin D for patients with subset 1 low-risk embryonal rhabdomyosarcoma [15].

Disease site

Specific considerations for individual disease sites are also becoming more clearly defined. The parameningeal site carries a known adverse prognosis in children with localized rhabdomyosarcoma and, in a pooled analysis from North American and European cooperative groups, 1105 patients with parameningeal disease in 10 studies treated between 1984 and 2004 were analyzed. There was a significant difference in OS between patients who did and did not receive radiotherapy (68.5% vs. 40.8%, respectively). The analysis also differentiated those with a good prognosis from those with a poor prognosis, and confirmed unfavorable prognostic factors to be: age <3 or >10, signs of meningeal involvement, unfavorable site, and tumor size [16]. In a separate study on the effect of radiation timing on outcome in patients with parameningeal disease, Spalding *et al.* analyzed two recent clinical trials for intermediate-risk rhabdomyosarcoma (IRS-IV and COG D9803). In IRS-IV, patients with any high-risk features (cranial nerve palsy, cranial base bony erosion, or intracranial extension) began treatment on day 0. On D9803, only those patients with intracranial extension received day 0 radiotherapy; those with cranial nerve palsy or cranial base bony erosion had radiotherapy at week 12. The 198 patients with parameningeal disease in IRS-IV and 192 patients with parameningeal disease in D9803 had no difference in 5 year local failure (19% vs. 19%), FFS (70% vs. 67%), or OS (75% vs. 73%). Of note, patients in D9803 were more likely to have been staged by magnetic resonance imaging (MRI) (71% vs. 53%) [17].

Lymph nodes

The question of whether, and how, to address lymph node involvement remains a matter of investigation. Surgery is most useful to confirm lymph node involvement, as in IRS-IV, boys with paratesticular tumors over 10 years of age who were classified as Group I after orchiectomy and retroperitoneal nodal assessment by CT scan had inferior outcome [18]. However, this surgical sampling is most useful to confirm lymph node involvement. Patients with lymph node involvement require radiation. In a recent SEER analysis of lymph node management in 255 patients with paratesticular rhabdomyosarcoma, authors found that among 173 boys 10 years or older, lymph node dissection was associated with an improved 5 year OS rate (64% vs. 86%). Patients younger than 10 had excellent outcomes with or without lymph node dissection (5 year OS 100% vs. 97%). Radiotherapy was found to be beneficial in those with node-positive disease [19]. There is increasing interest in sentinel node biopsy, but this remains investigational, and not all sites are amenable. Still, it is important to know lymph node status for radiation planning purposes, as lymph nodes are not irradiated electively, but require radiotherapy if involved with disease. 18-fluorodeoxyglucose (FDG)-PET appears to be useful in the detection of in transit and regional nodal disease [20].

Assessing response to treatment

In an analysis of response-related treatment and outcome in the German Cooperative Weichteilsarkom Studiengruppe (CWS) group studies, patients with IRSG-III rhabdomyosarcoma who were non-responders after induction chemotherapy (<33% volume reduction) were compared with partial responders (at least 33% reduction). Of note, the non-responder group contained more patients having an unfavorable primary site. Response to induction chemotherapy was an important surrogate marker of poor outcome in patients with stable or progressive disease, primarily due to ineffective local control [21]. This indicates that a lack of significant tumor volume reduction following neoadjuvant chemotherapy is a marker for poor outcome.

However, response by anatomic imaging does not predict FFS in patients with Group III rhabdomyosarcoma. On IRS-IV, there was no relationship between early response and FFS. In a more recent analysis of COG D9803 with non-metastatic, initially unresected embryonal or alveolar rhabdomyosarcoma, which excluded those with progressive disease, patients were categorized as follows: complete response (CR), partial response (PR), or no response (NR). The overall objective response rate (CR+PR) assessed at week 12 was 85%, similar between embryonal rhabdomyosarcoma and alveolar rhabdomyosarcoma. Anatomic imaging including CT and MRI did not predict outcome, and was felt to have questionable use in tailoring subsequent therapy [22]. Still, a lack in change of the size of the tumor does not necessarily reflect viability of the tumor and, as such, there has been considerable interest in PET as a tool to assess functional response to treatment. Data on PET are still scarce, though it has shown benefit in prospective studies of sarcoma in pediatric patients [23]. PET scans improve during and after chemotherapy, but rarely normalize. A recent report of the Memorial Sloan Kettering Cancer Center (MSKCC) experience with PET in 107 patients with rhabdomyosarcoma showed that initial standardized uptake value (SUV) was predictive of progression-free survival (PFS) and OS, but not local control, with higher SUV associated with poor outcomes. SUV after 12 weeks of chemotherapy was predictive of PFS and local control. A positive PET scan after local therapy was predictive of worse PFS, local control, and OS [24]. The current open ARST 0531 and ARST 08P1

trials are assessing the value of PET prospectively by performing PET at baseline and during treatment.

Advances in radiotherapy

Radiotherapy has proven to be critical in most settings in rhabdomyosarcoma and, indeed, when radiotherapy is omitted, studies have shown higher recurrence rates, as reflected in the SIOP MMT 89 study, and the female genitourinary (GU) primary site arm of ARST0331 [25]. There may, however, be ways to reduce dose and still retain the local-regional benefit from radiotherapy. One such method of doing so comes via delayed primary excision. As most intermediate-risk rhabdomyosarcoma patients have gross residual disease after the first operative procedure, Rodeberg *et al*. analyzed whether, following induction chemotherapy, resection might allow radiotherapy dose reduction in select patients enrolled on COG D9803 (1999–2005). They found that delayed primary excision could be performed in only 45% of eligible Group III rhabdomyosarcoma patients with select anatomic sites (bladder dome, extremity, and trunk). Of those with delayed primary excision, 84% were eligible to receive a radiotherapy dose reduction to 36–41.4 Gy, with local control outcomes unchanged from historical rates [26].

Many pediatric patients are now treated with intensity-modulated radiotherapy (IMRT). In an intermediate-risk group of patients with rhabdomyosarcoma enrolled in the soft tissue sarcoma protocol D9803, IMRT improved the target dose coverage compared with three dimensional-conformal radiation therapy (3D-CRT), although an improvement in locoregional control or FFS could not be demonstrated in this population [27]. There has also been considerable interest in proton therapy with the goal of minimizing dose to adjacent normal tissue in these pediatric patients. A multicenter prospective phase II study undertaken at Massachusetts General Hospital (MGH) and MD Anderson was performed to assess disease control and assess acute and late effects of treatment with proton therapy. Ladra *et al*. analyzed results from 57 patients with localized rhabdomyosarcoma or metastatic embryonal rhabdomyosarcoma. Mean follow-up was 47 months for survivors, and 5 year EFS, OS, and local control were 69%, 78%, and 81%, respectively. There were 13 patients with grade 3 acute toxicity and 3 patients with grade 3 late toxicity but no acute or late toxicities greater than grade 3 [28]. While the early proton results appear promising, long-term follow-up is essential to analyze outcome, late effects, and quality of life issues. Determining who may benefit from protons will also be important to consider. As is often true for particle therapy, dosimetric plans may appear superior, but whether this translates to a meaningful clinical benefit, particularly in the era of skyrocketing health care costs and issues with access to care, is unclear.

Summary

What have we learned about rhabdomyosarcoma in recent years? We now know that rhabdomyosarcoma is likely a collection of subtypes of disease with differing biological underpinnings and prognoses, warranting tailored treatment. Each of these subtypes continues to be further delineated through careful and rigorous study. Fusion-positive alveolar rhabdomyosarcoma is a more aggressive disease, while alveolar rhabdomyosarcoma without fusion and embryonal rhabdomyosarcoma appear to have a similar, better prognosis. While the presence of the fusion product is a negative prognostic indicator, it also provides a potential target for therapy and, indeed, a number of exciting therapies are under study, including small molecule inhibitors and other targeted therapies. Importantly, clinical trials that include stratification based on molecular findings incorporate therapies that have been shown preclinically to benefit that patient population. We also continue to learn more about the biology of embryonal rhabdomyosarcoma and anaplastic rhabdomyosarcoma. The biological advances in understanding subtypes of rhabdomyosarcoma are exciting and hold promise for future therapy. The Childhood Solid Tumor Network (CSTN) is an important new, freely available resource that is likely to facilitate these advances [29].

We are now better able to clinically differentiate patients into risk categories based on other factors, even potentially avoiding some staging studies in select patients. The timing of radiotherapy in patients with parameningeal disease is becoming better clarified, and it appears that in patients with cranial nerve palsy or cranial bone erosion, radiotherapy can be delayed to week 12 without adversely impacting local control. No data yet show that patients with intracranial extension can avoid immediate (day 0) radiotherapy. Treatment paradigms will continue to evolve and be better defined by patient and disease characteristics.

What do we not yet know? The optimal way of assessing lymph node status has not yet been defined, and will likely differ for various cases and disease sites. We know that boys under age 10 with paratesticular rhabdomyosarcoma have an excellent survival whether or not the lymph nodes are addressed, but older boys benefit from pathologic confirmation of nodal involvement so radiotherapy can be reserved for those with positive nodes.

FDG-PET appears useful in the initial staging of disease, particularly with respect to regional and distant spread. The value of early post-treatment imaging remains unclear, and anatomic imaging does not appear to provide a benefit. Very recent data suggest that PET-CT may help predict outcome, and prospective trials are currently evaluating this possibility. Finally, in the radiotherapy setting, advanced technologies including IMRT photon and proton therapy show increasing dosimetric advantages in coverage and dose distribution over 3D conformal plans. Early studies of proton therapy appear promising, though long-term follow-up and quality of life studies are not yet available to determine whether particle therapy will provide a meaningful clinical benefit. The future of rhabdomyosarcoma therapy will involve individualized, tailored therapy to provide intensive additional treatment to those who need it, and avoid the risk of potential toxicity of excessive treatment in those who do not.

Abbreviations

COG, Children's Oncology Group; CR, complete response; CT, computed tomography; EFS, event-free survival; FDG-PET, 18-fluorodeoxyglucose-positron emission tomography; FFS, failure-free survival; FGFR4, fibroblast growth factor receptor 4; IMRT, intensity-modulated radiotherapy; IRSG, Intergroup Rhabdomyosarcoma Study Group; MRI, magnetic resonance imaging; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; SEER, Surveillance, Epidemiology, and End Results; SUV, standardized uptake value.

Disclosures

The authors declare that they have no disclosures.

References

1. Siegel DA, King J, Tai E, Buchanan N, Ajani UA, Li J: **Cancer incidence rates and trends among children and adolescents in the United States, 2001-2009.** *Pediatrics* 2014, **134:**e945-55.

   F1000Prime RECOMMENDED

2. Barr FG, Smith LM, Lynch JC, Strzelecki D, Parham DM, Qualman SJ, Breitfeld PP: **Examination of gene fusion status in archival samples of alveolar rhabdomyosarcoma entered on the Intergroup Rhabdomyosarcoma Study-III trial: a report from the Children's Oncology Group.** *J Mol Diagn* 2006, **8:**202-8.

   F1000Prime RECOMMENDED

3. Skapek SX, Anderson J, Barr FG, Bridge JA, Gastier-Foster JM, Parham DM, Rudzinski ER, Triche T, Hawkins DS: **PAX-FOXO1 fusion status drives unfavorable outcome for children with rhabdomyosarcoma: a children's oncology group report.** *Pediatr Blood Cancer* 2013, **60:**1411-7.

   F1000Prime RECOMMENDED

4. Williamson D, Missiaglia E, de Reyniès A, Pierron G, Thuille B, Palenzuela G, Thway K, Orbach D, Laè M, Frèneaux P, Pritchard-Jones K, Oberlin O, Shipley J, Delattre O: **Fusion gene-negative alveolar rhabdomyosarcoma is clinically and molecularly indistinguishable from embryonal rhabdomyosarcoma.** *J Clin Oncol* 2010, **28:**2151-8.

   F1000Prime RECOMMENDED

5. Rudzinski ER, Teot LA, Anderson JR, Moore J, Bridge JA, Barr FG, Gastier-Foster JM, Skapek SX, Hawkins DS, Parham DM: **Dense pattern of embryonal rhabdomyosarcoma, a lesion easily confused with alveolar rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group.** *Am J Clin Pathol* 2013, **140:**82-90.

   F1000Prime RECOMMENDED

6. Rudzinski ER, Anderson JR, Lyden ER, Bridge JA, Barr FG, Gastier-Foster JM, Bachmeyer K, Skapek SX, Hawkins DS, Teot LA, Parham DM: **Myogenin, AP2β, NOS-1, and HMGA2 are surrogate markers of fusion status in rhabdomyosarcoma: a report from the soft tissue sarcoma committee of the children's oncology group.** *Am J Surg Pathol* 2014, **38:**654-9.

   F1000Prime RECOMMENDED

7. Singh M, Leasure JM, Chronowski C, Geier B, Bondra K, Duan W, Hensley LA, Villalona-Calero M, Li N, Vergis AM, Kurmasheva RT, Shen C, Woods G, Sebastian N, Fabian D, Kaplon R, Hammond S, Palanichamy K, Chakravarti A, Houghton PJ: **FANCD2 is a potential therapeutic target and biomarker in alveolar rhabdomyosarcoma harboring the PAX3-FOXO1 fusion gene.** *Clin Cancer Res* 2014, **20:**3884-95.

   F1000Prime RECOMMENDED

8. Jothi M, Mal M, Keller C, Mal AK: **Small molecule inhibition of PAX3-FOXO1 through AKT activation suppresses malignant phenotypes of alveolar rhabdomyosarcoma.** *Mol Cancer Ther* 2013, **12:**2663-74.

   F1000Prime RECOMMENDED

9. Chen X, Stewart E, Shelat AA, Qu C, Bahrami A, Hatley M, Wu G, Bradley C, McEvoy J, Pappo A, Spunt S, Valentine MB, Valentine V, Krafcik F, Lang WH, Wierdl M, Tsurkan L, Tolleman V, Federico SM, Morton C, Lu C, Ding L, Easton J, Rusch M, Nagahawatte P, Wang J, Parker M, Wei L, Hedlund E, Finkelstein D *et al.*: **Targeting oxidative stress in embryonal rhabdomyosarcoma.** *Cancer cell* 2013, **24:**710-24.

   F1000Prime RECOMMENDED

10. Crose Lisa ES, Etheridge KT, Chen C, Belyea B, Talbot LJ, Bentley RC, Linardic CM: **FGFR4 blockade exerts distinct antitumorigenic effects in human embryonal versus alveolar rhabdomyosarcoma.** *Clin Cancer Res* 2012, **18:**3780-90.

    F1000Prime RECOMMENDED

11. Hettmer S, Archer NM, Somers GR, Novokmet A, Wagers AJ, Diller L, Rodriguez-Galindo C, Teot LA, Malkin D: **Anaplastic rhabdomyosarcoma in TP53 germline mutation carriers.** *Cancer* 2014, **120:**1068-75.

    F1000Prime RECOMMENDED

12. Shern JF, Chen L, Chmielecki J, Wei JS, Patidar R, Rosenberg M, Ambrogio L, Auclair D, Wang J, Song YK, Tolman C, Hurd L, Liao H, Zhang S, Bogen D, Brohl AS, Sindiri S, Catchpoole D, Badgett T, Getz G, Mora J, Anderson JR, Skapek SX, Barr FG, Meyerson M, Hawkins DS, Khan J: **Comprehensive genomic analysis of rhabdomyosarcoma reveals a landscape of alterations affecting a common genetic axis in fusion-positive and fusion-negative tumors.** *Cancer Discov* 2014, **4:**216-31.

    F1000Prime RECOMMENDED

13. Weiss AR, Lyden ER, Anderson JR, Hawkins DS, Spunt SL, Walterhouse DO, Wolden SL, Parham DM, Rodeberg DA, Kao SC, Womer RB: **Histologic and clinical characteristics can guide staging evaluations for children and adolescents with rhabdomyosarcoma: a report from the Children's Oncology Group Soft Tissue Sarcoma Committee.** *J Clin Oncol* 2013, **31:**3226-32.

F1000Prime RECOMMENDED

14. Yang L, Takimoto T, Fujimoto J: **Prognostic model for predicting overall survival in children and adolescents with rhabdomyosarcoma.** *BMC cancer* 2014, **14:**654.

F1000Prime RECOMMENDED

15. Walterhouse DO, Pappo AS, Meza JL, Breneman JC, Hayes-Jordan AA, Parham DM, Cripe TP, Anderson JR, Meyer WH, Hawkins DS: **Shorter-duration therapy using vincristine, dactinomycin, and lower-dose cyclophosphamide with or without radiotherapy for patients with newly diagnosed low-risk rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group.** *J Clin Oncol* 2014, **32:**3547-52.

F1000Prime RECOMMENDED

16. Merks JHM, De Salvo GL, Bergeron C, Bisogno G, Paoli A de, Ferrari A, Rey A, Oberlin O, Stevens MCG, Kelsey A, Michalski J, Hawkins DS, Anderson JR: **Parameningeal rhabdomyosarcoma in pediatric age: results of a pooled analysis from North American and European cooperative groups.** *Ann Oncol* 2014, **25:**231-6.

F1000Prime RECOMMENDED

17. Spalding AC, Hawkins DS, Donaldson SS, Anderson JR, Lyden E, Laurie F, Wolden SL, Arndt Carola AS, Michalski JM: **The effect of radiation timing on patients with high-risk features of parameningeal rhabdomyosarcoma: an analysis of IRS-IV and D9803.** *Int J Radiat Oncol Biol Phys* 2013, **87:**512-516.

18. Gosiengfiao Y, Reichek J, Walterhouse D: **What is new in rhabdomyosarcoma management in children?** *Paediatr Drugs* 2012, **14:**389-400.

19. Dang ND, Dang P, Samuelian J, Paulino AC: **Lymph node management in patients with paratesticular rhabdomyosarcoma: a population-based analysis.** *Cancer* 2013, **119:**3228-33.

F1000Prime RECOMMENDED

20. La TH, Wolden SL, Rodeberg DA, Hawkins DS, Brown KL, Anderson JR, Donaldson SS: **Regional nodal involvement and patterns of spread along in-transit pathways in children with rhabdomyosarcoma of the extremity: a report from the Children's Oncology Group.** *Int J Radiat Oncol Biol Phys* 2011, **80:**1151-7.

21. Donatello TM, Stark M, Timmermann B, Fuchs J, Selle B, Linderkamp C, Handgretinger R, Hagen R, Feuchtgruber S, Kube S, Kosztyla D, Kazanowska B, Ladenstein R, Niggli F, Liungman G, Bielack SS, Klinebiel T, Koscielniak E, Cooperative Weichteilsarkom Studiengruppe [CWS]: **Tumour volume reduction after neoadjuvant chemotherapy impacts outcome in localised embryonal rhabdomyosarcoma.** *Pediatr Blood Cancer* 2015, **62:**16-23.

F1000Prime RECOMMENDED

22. Rosenberg AR, Anderson JR, Lyden E, Rodeberg DA, Wolden SL, Kao SC, Parham DM, Arndt C, Hawkins DS: **Early response as assessed by anatomic imaging does not predict failure-free survival among patients with Group III rhabdomyosarcoma: a report from the Children's Oncology Group.** *Eur J Cancer* 2014, **50:**816-23.

F1000Prime RECOMMENDED

23. Völker T, Denecke T, Steffen I, Misch D, Schönberger S, Plotkin M, Ruf J, Furth C, Stöver B, Hautzel H, Henze G, Amthauer H: **Positron emission tomography for staging of pediatric sarcoma patients: results of a prospective multicenter trial.** *J Clin Oncol* 2007, **25:**5435-41.

F1000Prime RECOMMENDED

24. Casey DL, Wexler LH, Fox JJ, Dharmarajan KV, Schoder H, Price AN, Wolden SL: **Predicting outcome in patients with rhabdomyosarcoma: role of [(18)f]fluorodeoxyglucose positron emission tomography.** *Int J Radiat Oncol Biol Phys* 2014, **90:**1136-42.

F1000Prime RECOMMENDED

25. Walterhouse DO, Meza JL, Breneman JC, Donaldson SS, Hayes-Jordan A, Pappo AS, Arndt C, Raney RB, Meyer WH, Hawkins DS: **Local control and outcome in children with localized vaginal rhabdomyosarcoma: A report from the soft tissue sarcoma committee of the children's oncology group.** *Pediatr Blood Cancer* 2011, **57:**76-83.

26. Rodeberg DA, Wharam MD, Lyden ER, Stoner JA, Brown K, Wolden SL, Paidas CN, Donaldson SS, Hawkins DS, Spunt SL, Arndt CA: **Delayed primary excision with subsequent modification of radiotherapy dose for intermediate-risk rhabdomyosarcoma: A report from the Children's Oncology Group Soft Tissue Sarcoma Committee.** *Int J Cancer* 2014, [Epub ahead of print].

27. Lin C, Donaldson SS, Meza JL, Anderson JR, Lyden ER, Brown CK, Morano K, Laurie F, Arndt CA, Enke CA, Breneman JC: **Effect of radiotherapy techniques (IMRT vs. 3D-CRT) on outcome in patients with intermediate-risk rhabdomyosarcoma enrolled in COG D9803–a report from the Children's Oncology Group.** *Int J Radiat Oncol Biol Phys* 2012, **82:**1764-70.

28. Ladra MM, Szymonifka JD, Mahajan A, Friedmann AM, Yong Yeap B, Goebel CP, MacDonald SM, Grosshans DR, Rodriguez-Galindo C, Marcus KJ, Tarbell NJ, Yock TI: **Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma.** *J Clin Oncol* 2014, **32:**3762-70.

F1000Prime RECOMMENDED

29. Stewart E, Federico S, Karlstrom A, Shelat A, Sablauer A, Pappo A, Dyer MA: **The childhood solid tumor network: a new resource for the developmenntal biology and oncology research communities.** *Genome Res* 2015, [Epub ahead of print].