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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

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Abstract ***Background:*** The prognostic significance of response to induction therapy for rhabdomyosarcoma (RMS) by anatomic imaging [computerised tomographic (CT) or magnetic resonance imaging (MRI) scan] is controversial. We previously reported no relationship between early response and failure-free survival (FFS) on Intergroup Rhabdomyosarcoma Study (IRS)-IV. We repeated the same analysis using a more recent clinical trial as an independent cohort of patients with non-metastatic, initially unresected RMS.
Methods: A total of 338 patients enrolled in Children's Oncology Group (COG) study D9803 met the inclusion criteria for this analysis: (1) non-metastatic, initially unresected (Group III); (2) embryonal (ERMS) or alveolar (ARMS) histology; (3) documented protocol week 12 response to induction chemotherapy (excluding progressive disease) based on anatomic imaging (CT/MRI) and (4) documented protocol therapy beyond week 12. Response at week 12 was determined by the treating institution as complete response (CR), partial response (PR)

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or no response (NR). FFS was estimated using the Kaplan–Meier method and comparisons between patient subsets were made using the log-rank test.

Results: Overall objective response rate (CR + PR) at week 12 of therapy was 85% and was similar between ERMS and ARMS. FFS was similar among all patients with CR, PR or NR ($p = 0.49$). Restricting the analysis to either ERMS or ARMS, there was no difference in FFS by response within either histology subset ($p = 0.89$ and $p = 0.08$, respectively).

Conclusions: These findings provide additional evidence that anatomic imaging to assess early response to therapy among patients with RMS does not predict outcome and has questionable use in tailoring subsequent therapy.

1. Introduction

Collaborative research has enabled dramatic improvements in outcomes for patients with rhabdomyosarcoma (RMS), and current, risk-based treatment strategies aim to optimise survival while minimising acute and long-term toxicities [1]. Pre-treatment risk stratification for RMS is based on stage (including tumour size, site, invasiveness and regional nodal status) [2] and clinical grouping (the extent of surgical resection prior to systemic chemotherapy) [3]. Other known prognostic factors include age and tumour histology, with embryonal RMS (ERMS) associated with superior outcomes compared to alveolar RMS (ARMS) [4]. Combining stage, Group, and histology, an intermediate risk category includes all non-metastatic ARMS patients and incompletely resected (Group III) ERMS patients with an unfavorable primary site [1]. Overall, intermediate-risk RMS is associated with failure-free survival (FFS) rates of 65–73% [5–7].

Response to initial chemotherapy is related to outcome in several paediatric cancers and provides potential for further risk-stratification and/or early treatment modification. For example, microscopic measurement of residual disease is related to outcome among patients with acute lymphoblastic leukaemia [8], Ewing sarcoma [9] and osteosarcoma [10,11]. Functional imaging modalities such as fluorodeoxyglucose positron emission tomography (FDG PET) and metaiodobenzylguanidine (MIBG) predict outcome among patients with Hodgkin Lymphoma [12–14] and neuroblastoma [15,16], respectively. Among patients with RMS, response assessments have historically been determined by anatomic imaging assessments such as computed tomography (CT) or magnetic resonance imaging (MRI), despite evidence that the predictive power of these assessments may be limited in patients with soft tissue sarcomas [17], and other cancer-types [12,18]. The relationship between early anatomic imaging response and outcome among patients with RMS is unclear. On Intergroup Rhabdomyosarcoma Study (IRS)-IV, anatomic imaging response at week 8 of therapy was unrelated to FFS [19], leading to the conclusion that anatomic assessment could not reliably distinguish viable from necrotic tumour or scar tissue. However, other RMS clinical trials, including the Cooperative Soft Tissue Sarcoma (CWS) [20–22] and the Société Internationale d' Oncologie Pédiatrique (SIOP) Malignant Mesenchymal Tumour (MMT) [23,24] studies, have used early anatomic response to tailor subsequent therapy, based upon observations in CWS trials that change in tumour volume is associated with outcome [20,21].

To assess the relationship between anatomic imaging response and FFS among patients with Group III RMS, we used the same methodology we applied to IRS-IV in an independent data-set from the more recent Children's Oncology Group (COG) clinical trial for intermediate risk RMS, D9803 [6].

2. Patients and methods

The methods of COG D9803 have been described previously [6]. Briefly, patients with newly diagnosed, intermediate risk RMS were enrolled between 1999 and 2005. All patients were randomly assigned to treatment with either vincristine, dactinomycin and cyclophosphamide (VAC) or VAC alternating with vincristine, topotecan and cyclophosphamide (VAC/VTC, Table 1). Response assessments were conducted at weeks 12, 24, and at the end of therapy. No changes in chemotherapy were made based upon radiographic response. Patients with primary parameningeal tumours with intracranial extension (ICE) were non-randomly assigned to treatment with VAC and up-front radiation therapy (RT). For all other patients, RT was delayed until after the week 12 assessment. Delayed primary excision was encouraged when feasible after the week 12 assessment for selected primary sites, including the extremity, dome of the bladder and trunk. Patients whose tumour was completely resected with negative margins at week 12 received 36 Gy of RT; those with microscopic residual tumour following resection or those with clinical complete remission by imaging and biopsy confirmation received 41.4 Gy. All other Group III patients received 50.4 Gy. Depending on whether delayed primary excision was or was not performed,