Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a multicentre, open-label, randomised controlled, phase 3 trial

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Summary

Background Rhabdomyosarcoma is an aggressive tumour that can develop in almost any part of the body. Doxorubicin is an effective drug against rhabdomyosarcoma, but its role in combination with an established multidrug regimen remains controversial. Therefore, we aimed to evaluate the possible benefit of early dose intensification with doxorubicin in patients with non-metastatic rhabdomyosarcoma.

Methods We did a multicentre, open-label, randomised controlled, phase 3 trial involving 108 hospitals from 14 countries. We included patients older than 6 months but younger than 21 years with a pathologically proven diagnosis of rhabdomyosarcoma. We assigned each patient to a specific subgroup according to the EpSSG stratification system. Those with embryonal rhabdomyosarcoma incompletely resected and localised at unfavourable sites with or without nodal involvement, or those with alveolar rhabdomyosarcoma without nodal involvement were considered at high risk of relapse. These high-risk patients were randomly assigned (1:1) to receive either nine cycles of IVA (ifosfamide 3 g/m² given as a 3-h intravenous infusion on days 1 and 2, vincristine 1·5 mg/m² weekly during the first 7 weeks then only on day 1 of each cycle [given as a single intravenous injection], and dactinomycin 1·5 mg/m² on day 1 given as a single intravenous injection) or four cycles of IVA with doxorubicin 30 mg/m² given as a 4-h intravenous infusion on days 1 and 2 followed by five cycles of IVA. The interval between cycles was 3 weeks. Randomisation was done using a web-based system and was stratified (block sizes of four) by enrolling country and risk subgroup. Neither investigators nor patients were masked to treatment allocation. The primary endpoint was 3-year event-free survival assessed by the investigator at each centre in the intention-to-treat population. Patients who received at least one dose of study treatment were considered in the safety analysis. In agreement with the independent data monitoring committee, the study was closed to patient entry on Dec 16, 2013, after futility analysis. This trial is registered with EudraCT, number 2005-000217-35, and is currently in follow-up.

Findings Between Oct 1, 2005, and Dec 16, 2013, 484 patients were randomly assigned to receive each chemotherapy regimen (242 in the IVA group and 242 in the IVA plus doxorubicin group). Median follow-up was 63·9 months (IQR 44·6–78·9). The 3-year event-free survival was 67·5% (95% CI 61·2–73·1) in the IVA plus doxorubicin group and 63·3% (56·8–69·0) in the IVA group (hazard ratio 0·87, 95% CI 0·65–1·16; p=0·33). Grade 3–4 leucopenia (232 [93%] of 249 patients in the IVA plus doxorubicin group *vs* 194 [85%] of 227 in the IVA group; p=0·0061), anaemia (195 [78%] *vs* 111 [49%]; p<0·0001), thrombocytopenia (168 [67%] *vs* 59 [26%]; p<0.0001), and gastrointestinal adverse events (78 [31%] *vs* 19 [8%]; p<0·0001) were significantly more common in the IVA plus doxorubicin group than in the IVA group. Grade 3–5 infections (198 [79%] *vs* 128 [56%]; p<0·0001) were also significantly more common in the IVA plus doxorubicin group than in the IVA group, in which one patient had grade 5 infection. Two treatment-related deaths were reported (one patient developed septic shock and one affected by Goldenhar syndrome developed intractable seizures) in the IVA plus doxorubicin group, both occurring after the first cycle of treatment, and none were reported in the IVA group.

Interpretations The addition of dose-intensified doxorubicin to standard IVA chemotherapy did not show a significant improvement in the outcome of patients with high-risk non-metastatic rhabdomyosarcoma. Therefore, the IVA chemotherapy regimen should remain the standard of care for patients with localised rhabdomyosarcoma in Europe.

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Introduction

Rhabdomyosarcoma is an aggressive tumour that can develop in almost any part of the body and is thought to arise from primitive mesenchymal cells. It is the most common form of soft tissue sarcoma in children and young adults, and accounts for approximately 4–5% of all childhood malignancy with an annual incidence of 4·5 cases per million children younger than 20 years.

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Research in context

Evidence before this study

We searched PubMed between Jan 1, 1980, and Dec 1, 2017, for all randomised trials of patients with rhabdomyosarcoma. We also searched for published papers with the following search terms: "rhabdomyosarcoma", "randomiz(s)ed trial", and "doxorubicin". We found four randomised trials investigating the role of anthracycline-containing regimens (four doxorubicin and one epirubicin) and one meta-analysis. Regimens containing doxorubicin have been shown to improve survival in selected subgroups of patients with rhabdomyosarcoma in a trial, but overall no convincing evidence for doxorubicin benefit was found as most studies were underpowered.

Added value of this study

In our trial, doxorubicin was added to the standard IVA (ifosfamide, vincristine, and dactinomycin) chemotherapy regimen in the initial part of the treatment and administered in a more intensive way in comparison with previous studies. However, we did not find any survival benefit, and adverse events were more severe in the IVA plus doxorubicin group.

Implications of all the available evidence

Doxorubicin should be omitted from the first-line chemotherapy of patients with localised rhabdomyosarcoma, sparing them from significant acute toxic effects and late morbidity.

The peak incidence is seen early in childhood with a median age at diagnosis of about 5 years.[1] Two main forms of rhabdomyosarcoma have been identified on the basis of histological appearance: the embryonal subtype, which accounts for approximately 80% of all cases and has a better prognosis; and the alveolar subtype, which accounts for 15–20% of cases, characterised by the fusion of the *FOXO* transcription factor gene to either the *PAX3* or *PAX7* transcription factor genes, and is associated with poorer outcomes.

Although rhabdomyosarcoma is an aggressive tumour, survival of patients with non-metastatic disease has improved in the past 30 years owing to the application of a multimodality approach that includes chemotherapy coordinated with surgery and, in most cases, radiotherapy. This strategy has been promoted by several cooperative Groups, the largest being the Children Oncology Group (COG) in the USA and the more recently founded European paediatric Soft tissue sarcoma Study Group (EpSSG) in Europe. A series of studies have established that a chemotherapy regimen including an alkylating agent, such as cyclophosphamide or ifosfamide, combined with vincristine and dactinomycin (VAC [vincristine, dactinomycin, and cyclophosphamide] or IVA [ifosfamide, vincristine, and dactinomycin]) represents the standard combination for patients with rhabdomyosarcoma.[2,3] Over the years, different attempts to improve cure rates by adding other drugs to this combination have been made for patients with unfavourable prognostic factors, such as alveolar histology or a primary tumour arising in unfavourable sites, but progression-free survival remained around 55–70%.[4,5] To date, however, no randomised controlled trial has shown a survival advantage for other drugs combined with VAC or IVA compared with standard VAC or IVA chemotherapy regimens.[3]

Doxorubicin has often been used in the treatment of patients at high risk of relapse or those with metastatic disease because the response to doxorubicin, used as a single drug in the up-front window setting, is one of the highest among chemotherapeutic agents. However, its contribution when combined with an established multidrug regimen remains controversial.[6,7] Therefore, we did the EpSSG RMS 2005 trial, which incorporated a trial with two consecutive independent randomisations, to investigate the benefit of early dose intensification with doxorubicin and the value of a maintenance treatment after standard therapy in patients with high-risk localised rhabdomyosarcoma. In this study, we report the results of the first randomisation of doxorubicin dose intensification.

Methods

Study design and participants

We did a multicentre, open-label, randomised controlled, phase 3 trial involving 108 hospitals from 14 countries (Belgium, Brazil, Czech Republic, France, Israel, Italy, Norway, Slovakia, Slovenia, Spain, Switzerland, Netherlands, UK, and Ireland).

We included participants who were older than 6 months but younger than 21 years. Patients also had to have had pathologically proven diagnosis of rhabdomyosarcoma, no evidence of distant metastatic lesions, previously untreated except for primary surgery, no pre-existing illness preventing treatment, no previous malignant tumours, and an interval between diagnostic surgery and systemic treatment of 8 weeks or less. Histopathological material had to be available for central diagnostic review although risk group and randomisation were assigned on the basis of the local assessment. Molecular confirmation of the presence of *FOXO1* was not mandatory to classify a tumour as alveolar.

Each patient was assigned to a specific risk group according to six prognostic factors identified in a common retrospective analysis of European protocols: pathology (embryonal *vs* alveolar), the Intergroup Rhabdomyosarcoma Study (IRS) grouping, tumour primary site, nodal involvement, tumour size, and patient age (appendix p 1). The high-risk group included patients categorised in subgroup E (defined as those with embryonal histology, tumour incompletely resected at diagnosis [IRS group II or III], primary tumour site unfavourable [parameningeal, extremities, genitourinary

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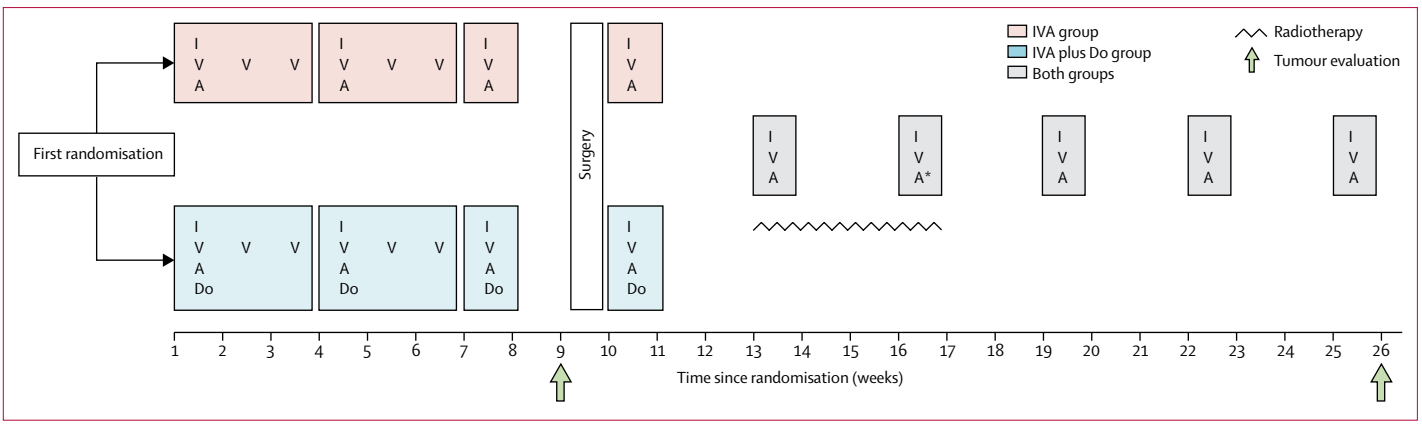

Figure 1: **Treatment plan for patients with high-risk rhabdomyosarcoma**
IVA=ifosfamide, vincristine, and dactinomycin. Do=doxorubicin. *Dactinomycin might be given at the very beginning of radiotherapy (week 13) but is omitted during radiotherapy (week 16).

bladder-prostate, and other sites] and tumour size >5 cm or patient aged ≥10 years), subgroup F (defined as those with embryonal histology, tumour incompletely resected at diagnosis [IRS group II or III], and involvement of regional nodes), and subgroup G (defined as those with alveolar histology without nodal involvement). Patients with alveolar paratesticular rhabdomyosarcoma were excluded in recognition of the better prognosis of this group of patients.

All participating centres were required to obtain written approval from their local authorities and ethics committees, and written informed consent from the patient or from their parents or legal guardians, or both. This study was done in accordance to the Declaration of Helsinki and the Good Clinical Practice guidelines.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either the standard chemotherapy regimen or the investigational chemotherapy regimen. We did the randomisation using a web-based system based on the Advanced Multicenter Research methodology created by CINECA (Bologna; an Italian academic non-profit consortium), and stratified patients in block sizes of four by enrolling country and high-risk subgroup (ie, E, F, and G). Neither investigators nor patients were masked to treatment allocation.

Procedures

We did a diagnostic work-up that comprised CT or MRI scans or both of the primary tumour, chest CT scan, radionuclide bone scan, and bone marrow aspirate and biopsy. ^{18}F-fluorodeoxyglucose PET was optional and a baseline echocardiogram was also required. Primary tumour resection was recommended only for those in which a complete resection was considered feasible without harming the patient, otherwise a biopsy was requested to establish the diagnosis.

The standard chemotherapy regimen (the IVA group) was a combination of ifosfamide 3 g/m² given as a 3-h intravenous infusion with mesna (3 g/m²) and hydration on days 1 and 2, vincristine 1·5 mg/m² (weekly during the first 7 weeks then only on day 1 of each cycle, given as a single intravenous injection) and dactinomycin 1·5 mg/m² on day 1 given as a single intravenous injection. This same regimen with the addition of doxorubicin 30 mg/m² given as a 4-h intravenous infusion on days 1 and 2 comprised the investigational chemotherapy regimen (the IVA plus doxorubicin group). Four cycles of standard or investigational chemotherapy had to be administered in the initial part of treatment before local control measures were implemented, such as surgery or radiotherapy. Subsequently both groups received five cycles of IVA, the interval between cycles was 3 weeks (figure 1). Conditions to start each chemotherapy cycle were white blood cell counts of 2×10^9/L or neutrophil counts of 1×10^9 cells per L and platelet counts of 80×10^9 cells per L, and absence of any relevant organ dysfunction. In children aged 6–12 months or those with a bodyweight of less than 10 kg, drug doses were calculated according to bodyweight: vincristine 0·05 mg/kg per dose, dactinomycin 0·05 mg/kg per dose, ifosfamide 100 mg/kg per dose, and doxorubicin 1 mg/kg per dose.

We measured tumour dimensions at diagnosis using the three maximum diameters (ie, length, width, and thickness) and tumour volume estimated with the following formula:

$$\frac{\pi}{6}\times\text{length}\times\text{width}\times\text{thickness}$$

Tumour response assessment in patients with macroscopic residual disease after initial surgery (IRS group III) was evaluated at week 9—choosing, as far as possible, the diameters selected at diagnosis—and at the end of the treatment (with further assessments at the clinicians' discretion). Tumour response was defined as complete response (clinically or histologically confirmed complete disappearance of disease), very good partial response (tumour volume reduction >90%),

partial response (tumour volume reduction >66%, but <90%), minor response (tumour volume reduction >33%, but <66%), no response or stable disease (tumour volume reduction <33%), and progressive disease (any increase in tumour size of any measurable lesion or appearance of new lesions). When all the three diameters were not available, two dimensions (2D) were used to establish the tumour response with corresponding 2D cutoffs. All responses had to last at least 4 weeks without evidence of tumour progression or relapse.

After the initial three cycles of chemotherapy (week 9), a full clinical and radiological assessment of the tumour was done. Patients in complete remission or with evidence of tumour volume reduction of more than 33% continued the allocated treatment. In case of stable disease or progressive disease, patients were considered to be taken off the study and the protocol recommended to switch to different chemotherapy regimens, including doxorubicin if initially allocated to the IVA group, in the attempt to obtain a better tumour response.

The local treatment of the tumour was planned after the tumour response assessment and implemented at week 13. Where a residual mass was present, surgical resection was encouraged if free margins without organ or function impairment were anticipated. Marginal resection in sites where complete resection was not deemed possible was accepted, provided that it was always followed by radiotherapy.

Radiotherapy represented the only local treatment possible for patients who could not undergo secondary surgery because of the tumour location (eg, parameningeal rhabdomyosarcoma). Radiotherapy doses were delivered according to histology, chemotherapy response, and surgical results: 41·4 Gy were given to patients with alveolar rhabdomyosarcoma in IRS group I or II, those in IRS group III who achieved a complete remission after secondary surgery, and patients with embryonal rhabdomyosarcoma who achieved a complete remission with initial chemotherapy; and 50·4 Gy for cases of incomplete or unfeasible secondary resection. A boost of 5·4 Gy in three fractions to the residual tumour was allowed for large tumours with poor response to chemotherapy. Radiotherapy to the involved lymph node sites was recommended at a dose of 41·4 Gy independent of histology and surgical resection. Treatment was delivered with megavoltage photons, one fraction per day, 5 days per week, with conventional fraction sizes of 1·8 Gy per day. In patients with large abdominal or craniospinal fields, or in patients younger than 3 years, smaller fractions were allowed (eg, 1·5 Gy).

The clinical target volume was defined as the initial gross tumour volume plus 1 cm in all directions, except for limb tumours in which the longitudinal gross tumour volume to clinical target volume expansion was 2 cm. The clinical target volume to planning target volume margin was typically 1 cm. In patients receiving 50·4 Gy of radiotherapy, the planning target volume was reduced by 1 cm after 41·4 Gy. In patients with orbital tumours, the initial radiation of the whole orbit was reduced to a planning target volume of the gross tumour volume plus 1 cm after 36 Gy. At the start of the trial in 2005, three-dimensional conformal radiotherapy plans were most commonly used, but because the trial covered a period of increasing availability of more sophisticated radiotherapy planning and treatment delivery, advanced photon techniques such as intensity modulated radiotherapy became more commonly used. Alternative techniques, such as brachytherapy, electrons, and proton beam therapy, were permitted when clinically appropriate. The protocol mandated doxorubicin therapy to be completed before starting radiotherapy. Dactinomycin was omitted during radiotherapy.

Further assessment of the tumour was done after the ninth chemotherapy cycle. Patients with high-risk rhabdomyosarcoma, who were either included in the first randomisation or excluded for whatever reason, and were in complete remission were eligible for the second randomisation to stop treatment or to continue with the administration of weekly vinorelbine and low-dose continuous oral cyclophosphamide for 6 months. This second randomisation was closed on Dec 31, 2016, and the results will be reported separately.

Supportive care was provided to patients according to the respective institutional guidelines. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was not mandated, however, it was recommended during IVA plus doxorubicin chemotherapy treatment for life-threatening neutropenic infection, or treatment delay of more than 1 week due to neutropenia in a previous cycle.

Outcomes

The primary endpoint was event-free survival assessed by the investigator at each centre and defined as the time from first random assignment to the time of the first event defined as death from any cause, progression of disease (in cases for which complete tumour remission was never achieved), relapse after previous complete remission, appearance of a new tumour and switch to second-line chemotherapy in patients with unsatisfactory chemotherapy response (stable disease or progressive disease), or time of the latest follow-up. Secondary endpoints were overall survival, measured as time from date of first randomisation up to death from any cause or time of the latest follow-up; progression-free survival, measured as time from date of first randomisation to tumour progression, relapse, or time of the latest follow-up; response to initial treatment, evaluated at the ninth week; and toxicity, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).

Statistical analysis

The trial was originally projected to enrol 600 patients with high-risk rhabdomyosarcoma to detect an increase

of 10% in the 3-year event-free survival with IVA plus doxorubicin chemotherapy treatment, assuming a baseline 3-year event-free survival of 50% in the IVA group, equivalent to a hazard ratio (HR) of 0·74. Overall, 343 events were needed to ensure a power of 80%, with a two-sided α level of 5%. Two interim analyses were planned after a third and two-thirds of the events, using an O'Brien-Fleming boundary for the efficacy boundary and the Harrington-Fleming-O'Brien process of repeated testing of the alternative hypothesis at an α level of 0·005 for futility monitoring. An independent data monitoring committee (IDMC) periodically monitored safety and efficacy during the study. The recruitment of patients was slower than expected, therefore, in Dec 1, 2011, the IDMC recommended a sample size re-estimation with a reduction in the HR to 0·65, maintaining the power of the study and extending the enrolment period. With these assumptions, a new sample size of 500 patients and 169 events as well as one interim analysis after observing 50% of events was planned. At the time of the planned interim analysis, the IDMC recommended to continue the randomisation as planned, asking for a second interim analysis in December, 2013. This analysis was done when 79% of the expected information was available. The estimate of the HR was 1·024 between the IVA plus doxorubicin group and IVA group (p=0·89). Repeated testing of the alternative hypothesis has been done to assess futility. The randomisation of IVA plus doxorubicin versus IVA was closed on Dec 16, 2013.

We estimated survival probabilities according to the intention-to-treat principle (ie, inclusion of patients in the group to which they were assigned, whether or not they received the allocated treatment) using the Kaplan-Meier method, and we assessed heterogeneity among strata of selected variables (ie, by the country of enrolment and risk subgroup) using the log-rank test. We did a post-hoc exploratory sensitivity efficacy analysis for the per-protocol population (ie, eligible patients who received the allocated treatment). The 3-year event-free survival, 3-year overall survival, and 3-year progression-free survival were reported with 95% CIs, calculated according to the Greenwood method. HRs with 95% CIs, calculated according to the Wald method, and p values for the interaction between treatment effect and any subgroup variable were estimated from the Cox regression model for event-free survival and overall survival in relevant clinical subgroups of patients. For the primary endpoint analysis, HR was adjusted for the stratification factors at randomisation.

We summarised the description of treatment exposure using descriptive statistics (medians and IQRs). Because the dose intensity of doxorubicin was an important factor in our study, we compared the time interval between the start of treatment and the administration of the fourth cycle in the two groups, and the cumulative dose of doxorubicin administered with a target of 240 mg/m². We included in this intention-to-treat analysis those that did not complete the four cycles of chemotherapy or did not receive the complete dose of doxorubicin. Patients who received at least one dose of treatment during the study were considered in the safety analysis. We analysed adverse events according to the actual treatment received as per protocol. Comparison of distribution was done with the χ^2.

Data collected as of June 16, 2017, were analysed with SAS (version 9.4). This trial is registered with EudraCT, number 2005-000217-35.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. GB, ADP, and GLDS had full access to the raw data. The corresponding author had final responsibility for the decision to submit for publication on behalf of the EpSSG board members.

Results

The randomisation of IVA plus doxorubicin versus IVA was closed on Dec 16, 2013, after repeated testing of the alternative hypothesis had been done to assess futility (log relative risk estimate 0·024, SE 0·173, log relative risk β −0·431; p=0·004), suggesting the study could be stopped for futility; between Oct 1, 2005, and Dec 16, 2013, 645 patients with high-risk rhabdomyosarcoma were assessed for eligibility, of which 161 were excluded. Overall, 484 patients were randomly assigned to a chemotherapy regimen (242 in the IVA group and 242 in the IVA plus doxorubicin group; figure 2). 33 patients were found not to fulfil the eligibility criteria after randomisation, mainly because of incorrect staging or change of histological diagnosis. One patient, who was randomly assigned to the IVA group, rapidly progressed and was treated according to the IVA plus doxorubicin regimen. All randomly assigned patients were included in the analysis according to the intention-to-treat principle.

Incorrect staging for metastatic lesions was found in ten patients and for nodal involvement in five patients, and the size of tumour was incorrectly recorded in two patients. One patient was affected by a genetic syndrome with cardiovascular anomalies preventing the administration of anthracyclines. The diagnosis of rhabdomyosarcoma was not confirmed in eight patients and the subtype was changed in seven (five embryonal to alveolar and two alveolar to embryonal). Six patients received a rapid review soon after the diagnosis and did not start the treatment; whereas in nine patients, the diagnosis was changed after they had already received the treatment. Overall, 410 (85%) of 484 cases were submitted for central pathology review at the national or international level, or both. 14 patients allocated to the IVA group did not start the allocated treatment after randomisation compared with none in the IVA plus doxorubicin group. This difference is explained by the EpSSG protocols,

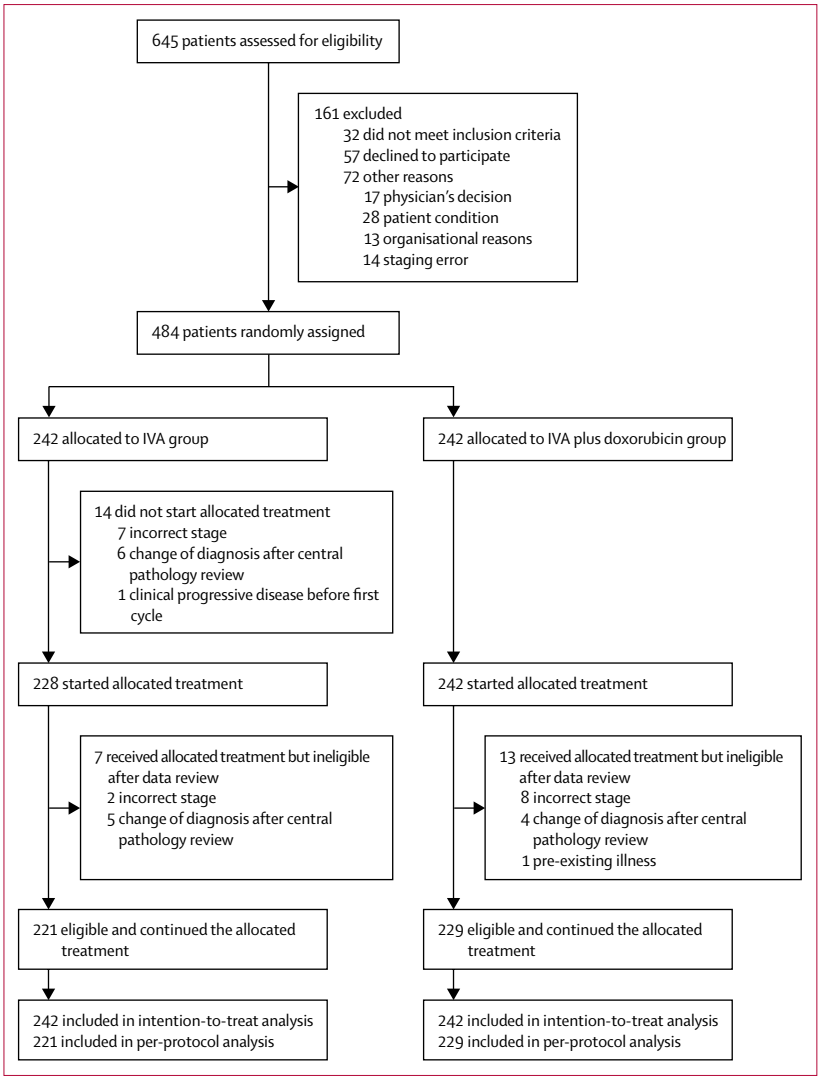

Figure 2: **Trial profile**

which recommended IVA plus doxorubicin chemotherapy treatment for patients in the very high-risk group or metastatic group, so patients in the IVA plus doxorubicin group that were upstaged after diagnosis or staging review simply continued the treatment as allocated whereas those in the IVA group changed to IVA plus doxorubicin chemotherapy treatment.

Patient and disease characteristics were well balanced between the two groups (table 1). The number of patients was also balanced in terms of the treatment received after the ninth cycle of chemotherapy: 87 (36%) of 242 patients in the IVA group and 89 (37%) of 242 in the IVA plus doxorubicin group received maintenance therapy because they were included in the second randomisation of the trial or because of physician choice.

The median time between the start of treatment and the administration of the fourth cycle was 9·3 weeks (IQR 9·0–9·9) for the IVA group and 9·4 weeks (9·0–10·0) for the IVA plus doxorubicin group. The median cumulative dose of doxorubicin administered was 237·2 mg/m² (IQR 228·9–240·0). Tumour response (ie, complete response, very good partial response, partial response, and minor response) evaluated after initial chemotherapy was 88·9% for the IVA group versus 92·3% for the IVA plus doxorubicin group (p=0·24). Radiotherapy treatment was administered in 210 (87%) patients in the IVA group and 202 (83%) in the IVA plus doxorubicin group. 234 patients had at least one secondary surgery (118 in the IVA group and 116 in the IVA plus doxorubicin group) and complete tumour resection was achieved in 149 patients (71 in the IVA group and 78 in the IVA plus doxorubicin group).

Median follow-up for patients was 63·9 months (IQR 44·6–78·9): 63·2 months (45·2–77·7) in the IVA group and 64·3 months (41·4–79·4) in the IVA plus doxorubicin group. The 3-year event-free survival was 67·5% (95% CI 61·2–73·1) in the IVA plus doxorubicin group and 63·3% (56·8–69·0) in the IVA group (HR 0·87, 95% CI 0·65–1·16; p=0·33; figure 3A). 3-year overall survival was 78·3% (95% CI 72·4–83·0) in the IVA plus doxorubicin group versus 80·6% (74·9–85·1) in the IVA group (HR 1·17, 95% CI 0·82–1·67; p=0·37; figure 3B).

Overall, 181 (37%) of 484 patients had an event. The type of event distribution was similar between the two groups; however, 19 patients in the IVA group switched to second-line treatment for insufficient tumour response (table 2). This switch was considered an event for the event-free survival calculation, but not for the 3-year progression-free survival, which was 67·6% (95% CI 61·1–73·3) in the IVA group and 68·1% (61·7–73·6; p=0·97) in the IVA plus doxorubicin group, demonstrating that this outcome did not affect significantly on the overall trial results.

450 (93%) of 484 patients met the criteria for the per-protocol post-hoc exploratory analysis. 3-year event-free survival was 68·8% (95% CI 62·3–74·4) in the IVA plus doxorubicin group compared with 63·1% (56·4–69·1) in the IVA group (0·82, 0·60–1·10; p=0·19). 3-year overall survival was 79·2% (73·3–84·0) in the IVA plus doxorubicin group versus 81·1% (75·2–85·7) in the IVA group (1·13, 0·78–1·65; p=0·51).

A post-hoc exploratory analysis taking into account the most relevant clinical variables (age at diagnosis, gender, histological subtype, nodal involvement [IRS group], primary tumour invasiveness, tumour size, and site) did not show any difference among the two groups in any subgroup of patients (appendix p 2).

Dose reduction occurred in 160 (8%) of 1889 cycles (with information available) in the IVA group and 180 (9%) of 2072 cycles in the IVA plus doxorubicin group. Grade 1–5 adverse event data for the initial chemotherapy phase (cycles 1–4) were available for 476 patients (table 3). Two treatment-related deaths were reported, both

	IVA group (n=242)	IVA plus doxorubicin group (n=242)
Country		
Belgium	13 (5%)	11 (5%)
Brazil	5 (2%)	6 (2%)
Czech Republic	7 (3%)	8 (3%)
France	66 (27%)	65 (27%)
Israel	6 (2%)	4 (2%)
Italy	64 (26%)	64 (26%)
Norway	5 (2%)	2 (1%)
Slovakia	1 (<1%)	0
Slovenia	0	1 (<1%)
Spain	16 (7%)	18 (7%)
Switzerland	0	3 (1%)
Netherlands	10 (4%)	10 (4%)
UK	48 (20%)	49 (20%)
Ireland	1 (<1%)	1 (<1%)
Age at diagnosis (years)		
≤1	14 (6%)	4 (2%)
>1 to <10	175 (72%)	171 (71%)
≥10 to <18	48 (20%)	60 (25%)
≥18	5 (2%)	7 (3%)
Sex		
Female	94 (39%)	95 (39%)
Male	148 (61%)	147 (61%)
Histology		
Alveolar rhabdomyosarcoma	76 (31%)	71 (29%)
Botryoid rhabdomyosarcoma	11 (5%)	11 (5%)
Embryonal rhabdomyosarcoma	153 (63%)	149 (62%)
Rhabdomyosarcoma not otherwise specified	1 (<1%)	6 (2%)
Spindle cells or leiomyomatous rhabdomyosarcoma	1 (<1%)	5 (2%)
Pathology		
Favourable	165 (68%)	165 (68%)
Unfavourable	77 (32%)	77 (32%)
Post-surgical tumour staging (IRS grouping)		
I	2 (1%)	9 (4%)
II	24 (10%)	22 (9%)
III	216 (89%)	211 (87%)
(Table 1 continues in next column)		

	IVA group (n=242)	IVA plus doxorubicin group (n=242)
(Continued from previous column)		
Primary tumour invasiveness		
Localised to the organ or tissue of origin	84 (35%)	95 (39%)
Extending beyond the tissue or organ of origin	149 (62%)	143 (59%)
Insufficient information about the primary tumour	9 (4%)	4 (2%)
Tumour size		
≤5 cm	54 (22%)	66 (27%)
>5 cm	187 (77%)	170 (70%)
Not evaluable	1 (<1%)	6 (2%)
Regional lymph node involvement		
No evidence of lymph node involvement	191 (79%)	194 (80%)
Evidence of regional lymph node involvement	42 (17%)	39 (16%)
No information about lymph node involvement	9 (4%)	9 (4%)
Site of origin of primary tumour		
Orbit	8 (3%)	8 (3%)
Head neck	21 (9%)	13 (5%)
Parameningeal	80 (33%)	81 (33%)
Bladder prostate	47 (19%)	39 (16%)
Genitourinary non-bladder prostate	5 (2%)	14 (6%)
Extremities	35 (14%)	36 (15%)
Other sites	46 (19%)	51 (21%)
Subgroup risk		
High risk (subgroup E)	123 (51%)	126 (52%)
High risk (subgroup F)	42 (17%)	39 (16%)
High risk (subgroup G)	77 (32%)	77 (32%)

IVA=ifosfamide, vincristine, and dactinomycin. IRS=Intergroup Rhabdomyosarcoma Study.

Table 1: **Patient and clinical characteristics of the intention-to-treat population**

occurring after the first cycle of IVA plus doxorubicin treatment: one patient developed septic shock and one affected by Goldenhar syndrome developed intractable seizures (appendix p 4). Considering grade 3–4 adverse events together, patients treated in the IVA plus doxorubicin group had significantly more myelotoxicity with leucopenia than those in the IVA group (232 [93%] of 249 *vs* 194 [85%] of 227; p=0·0061), anaemia (195 [78%] *vs* 111 [49%]; p<0·0001), and thrombocytopenia (168 [67%] *vs* 59 [26%]; p<0·0001). The higher proportion of myelotoxicity in the IVA plus doxorubicin group caused the investigators to more frequently use G-CSF, which was administered in 37·7% of the cycles in the IVA plus doxorubicin group versus 22·5% in the IVA group. For non-haematological grade 3–5 adverse events, patients included in the IVA plus doxorubicin group had a higher number of infections than those in the IVA group (198 [79%] *vs* 128 [56%]; p<0·0001), in which one patient had grade 5 infection. Approximately a third of children in the IVA plus doxorubicin group had grade 3–4 gastrointestinal adverse events compared with the IVA group (78 [31%] *vs* 19 [8%]; p<0·0001), and this difference was mainly due to mucositis probably caused by the concomitant administration of doxorubicin and dactinomycin. This same combination was expected to increase the risk of veno-occlusive disease but only three patients in the IVA plus doxorubicin group had this type of adverse event compared with five patients in the IVA group. No difference in cardiotoxicity was noted (three

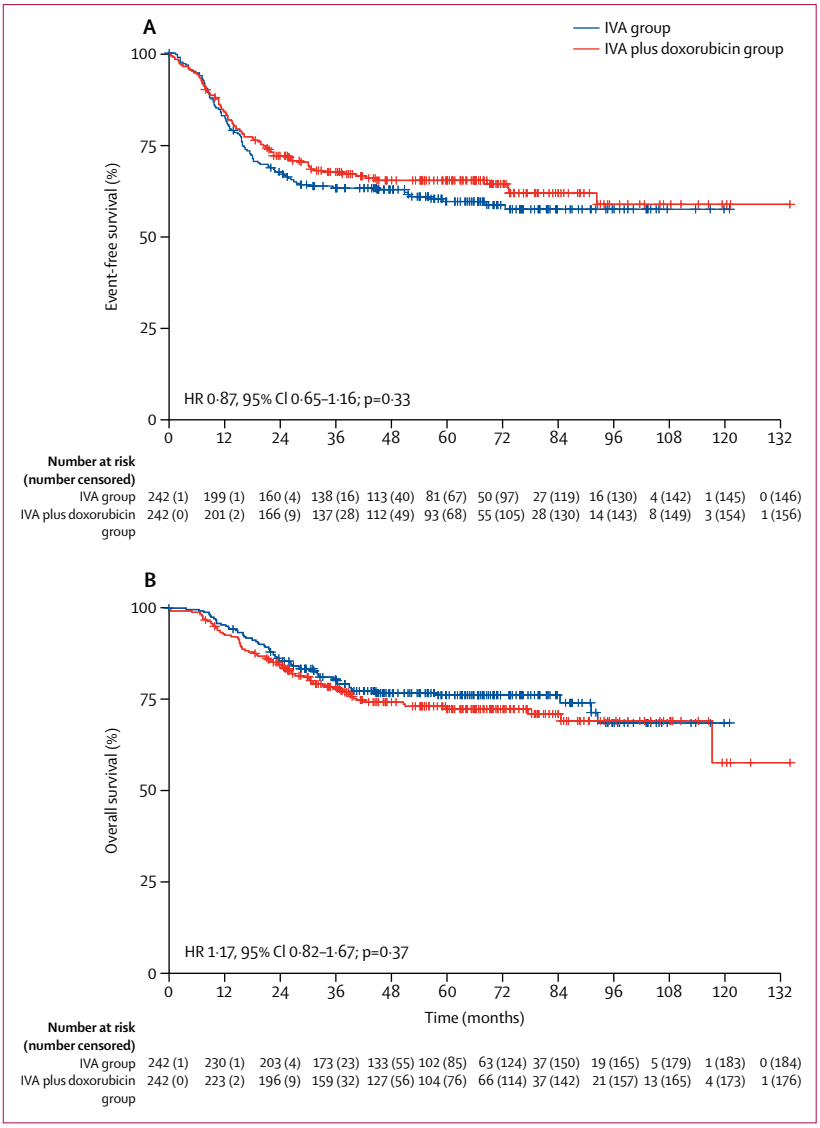

Figure 3: **Kaplan-Meier plots for event-free survival (A) and overall survival (B) in the intention-to-treat population**
IVA=ifosfamide, vincristine, and dactinomycin. HR=hazard ratio.

	IVA group (n=242)	IVA plus doxorubicin group (n=242)
Local relapse	30 (31%)	29 (34%)
Regional lymph node relapse	2 (2%)	6 (7%)
Regional lymph node relapse and metastases relapse	1 (1%)	0
Local and regional lymph node relapse	7 (7%)	2 (2%)
Local and regional lymph node and metastases relapse	1 (1%)	2 (2%)
Local relapse and metastases	3 (3%)	2 (2%)
Metastases	15 (16%)	17 (20%)
Progressive disease	13 (14%)	17 (20%)
Progressive disease and regional lymph node relapse	1 (1%)	0
Treatment-related death	0	2 (2%)
Switch to second-line therapy (not due to progressive disease)	19 (20%)	5 (6%)
Second tumour	2 (2%)	3 (4%)
Death	2* (2%)	0

Data are number of events (%). IVA=ifosfamide, vincristine, and dactinomycin. *Cause of death was recorded as suicide (n=1), and meningitis after end of treatment (n=1).

Table 2: **Type of events in the intention-to-treat population**

grade 3–4 adverse events occurred in each group). The number of patients with grade 3–4 thrombocytopenia was higher in the IVA plus doxorubicin group than in the IVA group in the subsequent phase of treatment (ie, five cycles of IVA treatment in both groups; p=0·037), whereas no differences were observed for the other grade 3–4 adverse events apart from a higher frequency of nausea or vomiting in the IVA group with no clear reason (appendix p 3).

Overall, 123 patients died: 114 due to the disease (53 in the IVA group and 61 in the IVA plus doxorubicin group) and nine for other reasons (five in the IVA group and four in the IVA plus doxorubicin group; appendix p 4).

Discussion

The role of doxorubicin in the treatment for children with rhabdomyosarcoma has long been debated. This randomised controlled trial shows that there is no benefit from the addition of doxorubicin to the standard IVA chemotherapy regimen in event-free survival, overall survival, or progression-free survival. Doxorubicin is a very active drug against rhabdomyosarcoma as shown by early studies done initially in relapsed rhabdomyosarcoma[8] and more recently in patients with newly diagnosed metastatic rhabdomyosarcoma.[6] A phase 2 window study[9] in children with newly diagnosed metastatic rhabdomyosarcoma showed the activity of ifosfamide and doxorubicin, with a 63% response rate after 12 weeks of treatment. This finding is very similar to the 65% response rate obtained by the administration and initial treatment of two cycles of single-agent doxorubicin 60 mg/m² over 2 days.[6] However, the role of doxorubicin as part of a multidrug regimen is controversial. It is not clear whether its addition to an established regimen such as VAC or IVA chemotherapy improves the survival of patients with rhabdomyosarcoma. A possible benefit of doxorubicin addition must be carefully considered, because the toxicity profile of the drug might worsen immunosuppression and gastrointestinal adverse events in the short term and cause cardiotoxicity in the long term.

Different randomised trials[10–12] done by the IRS group have not shown a substantial difference in survival and progression-free survival for patients with rhabdomyosarcoma treated with VAC chemotherapy or VAC plus anthracyclines. In the IRS-I protocol,[10] the addition of five VAdrC (vincristine, doxorubicin, and cyclophosphamide) courses to VAC chemotherapy treatment did not improve

	IVA group (n=227)			IVA plus doxorubicin group (n=249)				p value for events grade ≥3
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4	Grade 5	
Haematological								
Haemoglobin	20 (9%)	99 (44%)	12 (5%)	6 (2%)	149 (60%)	46 (18%)	0	<0·0001
Leucocytes	15 (7%)	65 (29%)	129 (57%)	7 (3%)	17 (7%)	215 (86%)	0	0·0061
Neutrophils	14 (6%)	31 (14%)	177 (78%)	8 (3%)	8 (3%)	228 (92%)	0	0·17
Platelets	93 (41%)	39 (17%)	20 (9%)	30 (12%)	97 (39%)	71 (29%)	0	<0·0001
Non-haematological								
Cardiac	221 (97%)	3 (1%)	0	230 (92%)	2 (1%)	1 (<1%)	0	0·56
Hepatobiliary or pancreas	217 (96%)	4 (12%)	0	235 (94%)	1 (<1%)	0	0	0·14
Infection	81 (36%)	126 (56%)	2 (1%)	43 (17%)	190 (76%)	7 (3%)	1 (<1%)	<0·0001
Nephrotoxicity	206 (91%)	2 (1%)	1 (<1%)	232 (93%)	0	0	0	0·06
Neurology	182 (80%)	15 (7%)	3 (1%)	194 (78%)	10 (4%)	5 (2%)	1 (<1%)	0·41
Nausea or vomiting	64 (28%)	33 (15%)	0	51 (20%)	47 (19%)	4 (2%)	0	0·089
Gastrointestinal	107 (47%)	19 (8%)	0	59 (24%)	55 (22%)	23 (9%)	0	<0·0001
Allergy	223 (98%)	0	0	239 (96%)	1 (<1%)	0	0	0·33
Dermatological	221 (97%)	0	0	237 (95%)	0	1 (<1%)	0	0·33
Other	156 (69%)	19 (8%)	4 (2%)	154 (62%)	30 (12%)	7 (3%)	0	0·12

Data are n (%). There were no grade 5 events in the IVA group. Differences in adverse events were analysed using χ^2 test. For adverse events that did not meet the requirement for χ^2 analysis (absolute count was <5), Fisher's exact test was used. IVA=ifosfamide, vincristine, and dactinomycin.

Table 3: **Adverse events reported during the initial four cycles of chemotherapy**

the outcomes in patients with gross residual disease after surgery or metastatic disease at diagnosis (IRS groups III–IV). In the IRS-II study,[11] a similar comparison was done; however, doxorubicin was given continually in pulse combination with vincristine and cyclophosphamide (pulse VAdrC). This VAdrC regimen[11] was given in alternating with VAC cycles and was compared with repeated VAC chemotherapy treatment as the standard group. Additionally, the cumulative dose of doxorubicin (480 mg/m²) was higher in this trial[11] than in the previous IRS-I protocol.[10,11] Despite this intensification, the two groups showed similar results (event-free survival of 75% *vs* 70%; p=0·84), and the investigators concluded that the addition of doxorubicin did not offer any survival advantage and was more toxic than the standard chemotherapy regimens.[11] The role of doxorubicin was further investigated in the IRS-III study,[12] which showed conflicting results. A comparison of randomised groups showed a significant benefit from the addition of doxorubicin in patients in clinical IRS group II (microscopic post-surgical disease). This advantage, however, disappeared when the historical control from the IRS-II protocol[11] were included in the analysis. Other patients' subgroups showed better results in the IRS-III study in comparison with those obtained in the IRS-II study, but doxorubicin was included along with other chemotherapy agents, making its contribution hard to determine. Overall, the investigators of the IRS-II and IRS-III studies concluded that that the precise role of doxorubicin in patients with newly diagnosed rhabdomyosarcoma required further evaluation.[7] It should be noted that in IRS group studies, the treatment schemes were based on the alternating administration cycles of VAC and VAdrC; consequently, the intervals between doxorubicin-containing courses were wide, reducing the anthracycline dose intensity.

In Europe, a trial[5] done by the Malignant Mesenchymal Tumour Group of the International Society of Pediatric Oncology compared the IVA chemotherapy regimen against a six-drug regimen containing an anthracycline (epirubicin). No difference in survival was found between the two groups. Once again, the anthracyclines dose intensity was low because epirubicin was included in only three of a total of nine cycles. The possibility that increasing anthracyline dose intensity might be of benefit is supported by a meta-analysis[13] of several trials done in patients with bone sarcomas. This analysis showed that an induction treatment including doxorubicin in every course was better than a regimen alternating doxorubicin with dactinomycin. To explore this strategy, we added doxorubicin to the IVA chemotherapy regimen avoiding the alternation between courses with and without anthracyclines, which was done in previous studies. We also hypothesised that the use of IVA plus doxorubicin in the initial part of treatment could have induced a higher number of tumour responses, allowing a better local control with surgery and radiotherapy. The IVA plus doxorubicin combination had previously been tested in a pilot study and was shown to be feasible.[14]

The population of patients classified at high risk and included in the RMS 2005 trial largely corresponds with the population classified at intermediate risk in the most recent studies done by COG,[3,15] which also includes patients with alveolar histology and regional nodal involvement as well as patients younger than 10 years with metastatic embryonal rhabdomyosarcoma. Another difference between the EpSSG RMS 2005 and the COG study is the change of chemotherapy in cases of stable disease after initial chemotherapy, because this lack of tumor reduction (ie, stable disease) seems to be an indicator of poor outcome.[16] This study design might have been a limitation for our study because patients with stable disease in the IVA group changed to a different chemotherapy, often doxorubicin based. The number of patients switching to second-line chemotherapy was small, however, and it is unlikely this effect might have affected the results.

The RMS 2005 trial confirms on a large scale that the IVA plus doxorubicin chemotherapy regimen is manageable. The doxorubicin dose intensity was maintained as shown by the median interval between the initial and last IVA plus doxorubicin cycle and the median cumulative dose of doxorubicin administered. As expected, there were significantly more adverse events in patients receiving IVA plus doxorubicin chemotherapy than those receiving IVA chemotherapy, particularly in terms of myelosuppression and mucositis. Despite the feasibility of the IVA plus doxorubicin regimen and the adverse events observed in patients, our study shows that the addition of doxorubicin did not add any meaningful benefit to patients' survival. It is interesting that this result is in line with evidence progressively collected by other studies dedicated to paediatric tumours. Findings from reports[17,18] have shown that doxorubicin can be omitted from the treatment plan of patients with standard hepatoblastoma or favourable histology stage II and III Wilms tumour without jeopardising outcome. Therefore, the role of anthracyclines in the first-line treatment should be reconsidered in a growing number of paediatric tumours.

Since the 1970s, a series of randomised clinical trials have been done with the aim of improving the treatment of children with high-risk rhabdomyosarcoma. None of the trials done so far has been able to identify a chemotherapy regimen more effective than the standard VAC or IVA regimens. Despite these so-called negative results, the duration of survival in children with rhabdomyosarcoma has progressively increased over the years. The same has happened with this trial: we were not able to show that the new IVA plus doxorubicin regimen was more effective than the standard IVA regimen, but the observed 3-year event-free survival for the whole population was substantially better than anticipated. This observation can be explained by a general improvement of care with better imaging, surgery, and radiotherapy planning; but one major reason might be the higher number of patients that received radiotherapy during first-line treatment (85%) in comparison with previous European studies (approximately 60%).[5]

In conclusion, this study provides evidence that the addition of doxorubicin has no benefit in standard first-line chemotherapy for patients with localised rhabdomyosarcoma. This finding could save a substantial number of children and adolescents with localised rhabdomyosarcoma from acute toxic effects due to IVA plus doxorubicin chemotherapy and potential late morbidity. The IVA chemotherapy regimen should remain the standard of care for patients with localised rhabdomyosarcoma in Europe.

Contributors

All authors contributed to the study design, data collection and interpretation, management of the clinical trial, writing and review of the paper, and approval of the final version. GB acted as principal investigator. GB, MJ, CB, SGM, AF, OO, MC, MS, AK, MNG, HM, and GLDS wrote the protocol and organised data collection. AK coordinated the central pathology review. MNG coordinated the radiotherapy. HM coordinated the surgical review. GLDS coordinated the data centre. ADP and GLDS did the statistical analysis.

Declaration of interests

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