PART 1
Solid Tumors

Ross Pinkerton

CHAPTER 1
Rhabdomyosarcoma

Commentary by Michael Stevens and Meriel Jenney

Background

Soft tissue sarcoma (STS) accounts for about 8% of all childhood malignancies. As a diagnostic category this represents a rather heterogeneous group of tumor types, some of which are more frequently found in adult life and many of which are very rare in childhood. Rhabdomyosarcoma (RMS) is the single most common diagnosis (accounting for approximately 60% of all STS), and in view of its rarity in adults it is characteristically viewed as a pediatric malignancy. It is consequently the tumor which is best defined, and although there are important differences in behavior between RMS and some of the non-RMS STS (e.g. in their metastatic potential, chemosensitivity, etc.), most of the experience of treatment for non-RMS STS in childhood is derived either from experience of managing the same diagnoses in adult practice or is based on the principles derived from the management of RMS.

Potential difficulties in reviewing clinical trials in RMS

Attempts to compare the results of clinical trials involving RMS in childhood are confused by the lack of use of standard terminology for staging and treatment stratification. Although there is now good communication between the major international collaborative groups, and a convergence toward standard criteria for staging and pathological classification, the experience of reviewing the literature can be confusing. Furthermore, as there have been important differences in the philosophy of treatment, careful consideration is required of the optimal measure by which outcome is defined.

Most of the important differences relate to the method and timing of local treatment, and, more specifically, to the place of radiotherapy (RT) in guaranteeing local control for patients who appear to achieve complete remission (CR) with chemotherapy, with or without significant surgery. This represents an important philosophical difference between the International Society of Paediatric Oncology (SIOP MMT) studies and those of the Intergroup Rhabdomyosarcoma Study Group (IRSG) and, to some extent, those of the German (CWS) and Italian (ICG) Cooperative Groups. Local relapse rates are generally higher in the SIOP studies than those experienced elsewhere although the SIOP experience has also made it clear that a significant number of patients who relapse may be cured with alternative treatment. In the context of such differences, *overall* survival rather than *disease-free* or *progression-free* survival becomes the most important criterion for measuring outcome and, ultimately, there should be some measure of the "cost" of survival which takes into account the total burden of therapy experienced by an individual patient and the predicted late sequelae that may result.

Treatment: the general approach

Experience in all studies has confirmed that a surgical–pathological classification which groups patients according to the extent of residual tumor after the initial surgical procedure predicts outcome. The great majority of patients (approximately 75%) will have macroscopic residual disease (IRS Clinical Group III) at the primary site at the start of chemotherapy (this is equivalent to pT3b in the SIOP post-surgical staging system). The variability with which RMS presents at different anatomical sites has a particularly strong influence on strategies for treatment. The additional prognostic influence of tumor size, histological subtype (embryonal versus alveolar) and patient age adds to the complexities

of treatment stratification. More recently, tumor site and size have also been recognized as independent factors that provide further refinement to the assignment of risk-based chemotherapy. All current clinical trials utilize some combination of the best-known prognostic factors to stratify treatment intensity for patients with good or poor predicted outcomes and the impetus for this approach comes as much to avoid overtreatment of patients with a good prospect for cure, as to improve cure rates for patients with less favorable disease.

The importance of multi-agent chemotherapy, as part of coordinated multi-modality treatment, has been clearly demonstrated for RMS. Cure rates have improved from approximately 25% in the early 1970s when combination chemotherapy was first implemented, and now overall 5-year survival rates of more than 70% are generally achieved. Nevertheless, it is interesting to see how relatively little the results of randomized-controlled trials have actually contributed to decision-making in the selection of chemotherapy and to the development of the design of the sequential studies which have shown this improvement in survival over those years.

Lessons from studies of RMS

IRSG was formed in 1972 as a collaboration between the two former pediatric oncology groups in North America (Children's Cancer Group and Pediatric Oncology Group) with the intention of investigating the biology and treatment of RMS (and undifferentiated sarcoma) in the first two decades of life. This group, whose work and publications have been pre-eminent in the field, now forms the Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG). Results of treatment have improved significantly over time. The percentage of patients alive at 5 years has increased from 55% on the IRS-I protocol (Study 1) to over 70% on the IRS-III and IRS-IV protocols (Studies 3 and 6).

Combinations of vincristine, actinomycin D and cyclophosphamide (VAC) have been the mainstay of chemotherapy in all IRS studies. Actinomycin D was originally given in a fractionated schedule but subsequent experience, including a randomized study from Italy (Study 5), showed no advantage in terms of outcome and has suggested that fractionation may increase toxicity; single dose scheduling is now standard across all studies. There have never been any results that challenge the use of these drugs as first-line therapy and the results of all randomized studies which compare other drugs with, or against, VA or VAC have failed to show significant advantage.

Alternative agents of particular interest include doxorubicin (Adriamycin), which has been evaluated in a number of IRSG studies. A total of 1431 patients with Group III and IV disease were randomized to receive or not receive doxorubicin in addition to VAC during studies in IRS-I to IRS-III. The results did not indicate any significant advantage for those who received doxorubicin. Furthermore, also in IRS-III, patients with Group II (microscopic residual) tumors were randomized between VA alone and VA with doxorubicin without any significant difference in survival. Despite these results, many pediatric oncologists continue to ponder the value of anthracyclines in the treatment of RMS. Both the SIOP MMT and the German–Italian cooperative studies have continued to treat some patients with chemotherapy combinations that include anthracycline drugs. Recent European studies (MMT 95 and CWS–ICG 96) both included randomizations between their ifosfamide-based standard chemotherapy options and an intensified six-drug combination which also included epirubicin (with carboplatin and etoposide). However in both these studies (for which definitive results are not yet available) and in the previous IRS studies, the dose intensity of the anthracyclines used was low which may have underpowered the evaluation. A recent SIOP "window" study in chemotherapy naïve patients with metastatic RMS has provided good new phase II data for the efficacy of doxorubicin with response rates greater than 65%. This justifies further evaluation of the role of doxorubicin in the treatment of RMS and this is now under investigation in a randomized study being undertaken by the European paediatric Soft tissue Sarcoma Group (EpSSG).

One of the most significant differences between IRSG and the European studies has been in the choice of alkylating agent which provides the backbone of first-line chemotherapy. Ifosfamide was introduced into clinical practice earlier in Europe than in the United States and phase II data are available which supports its efficacy in RMS. IRS-IV (Studies 6 and 11) attempted to answer the question of comparative efficacy by randomizing VAC (using an intensified cyclophosphamide dose of 2.2 g/m^2) against VAI which incorporated ifosfamide at a dose of 9 g/m^2. A third arm in this

randomization included ifosfamide in combination with etoposide (VIE). No difference was identified between the higher-dose VAC and the ifosfamide-containing schedules, and VAC remains the combination of choice for future IRSG (now COG) studies. The rationale for this is explained by the lesser cost and easier (shorter) duration of administration required for cyclophosphamide, and concern about the nephrotoxicity of ifosfamide. Nevertheless, the EpSSG has chosen to retain ifosfamide as their standard combination as the experience of significant renal toxicity at cumulative ifosfamide doses less than 60 g/m^2 is now very small and there are preliminary data suggesting that the gonadal toxicity of ifosfamide may be significantly less than that of cyclophosphamide.

Experience of the value of other drugs in IRSG studies has been relatively slim. IRS-III included the addition of cisplatin and etoposide in a three-way randomization between VAC, VAC with doxorubicin and cisplatin, and VAC with doxorubicin, cisplatin and etoposide. No advantage was seen in selected Group III and all Group IV patients and there were concerns about additive toxicity. IRS-IV (and an earlier IRS-IV pilot) explored the value of melphalan in patients with metastatic RMS or undifferentiated sarcoma. Patients were randomized to receive three courses of vincristine and melphalan (VM) or four of ifosfamide and etoposide (IE) (Study 9). There was no significant difference in initial CR and PR (complete and partial remission, respectively) rates. However patients receiving VM had a lower 3-year event-free and overall survival. Patients receiving this combination had greater hematological toxicity and therefore a lower tolerance of subsequent therapy. Other agents that have shown activity in RMS include irinotecan (CPT11) which in combination with vincristine in a recent COG window study had excellent PR and CR rates. The current COG IRS-V study has now included this combination in their latest randomized study. Vinorelbine is well tolerated and has been evaluated in combination with daily oral cyclophosphamide in previously heavily treated patients with relapsed RMS with encouraging results. This combination is now under investigation in the current EpSSG study in which patients who achieve CR with conventional chemotherapy and local treatment are randomized to stop therapy or to continue to receive a further 6 months "maintenance" therapy with this combination.

RT has been a standard component of therapy for the majority of patients in the IRSG studies from the outset. Randomized studies within IRS-I to IRS-III have established that RT is unnecessary for Group I (completely resected) patients with embryonal histology. Analyses from the same studies suggest that RT does offer an improved failure-free survival in patients with completely resected alveolar RMS or with undifferentiated sarcoma. Studies from the European groups have attempted to relate the use of RT to response to initial chemotherapy, the most radical approach being used by the SIOP group who has tried to withhold RT in patients with Group III (pT3b) disease if CR is achieved with initial chemotherapy ± conservative second surgery. This approach has produced evidence that it is possible to avoid local therapy in some children who would otherwise receive RT but there is a need to try to define such favorable patients at the outset so as to reduce the risk of relapse requiring second treatment within the whole group. Doses of RT have, somewhat pragmatically, been tailored to age, with reduced doses in younger children, although there is no defined threshold below which late effects can be avoided and yet tumor control is still achieved. The place for hyperfractionated RT was explored in IRS-IV when randomized against conventional fractionation (Study 10). Although there was a higher incidence of severe skin reaction and nausea and vomiting in patients receiving hyperfractionated RT, it was generally well tolerated. However there was no advantage in failure-free survival, and conventional RT continues to be used as standard therapy.

Although considerable progress has been made in improving overall survival, progress has been incremental and intuitive, based on careful treatment planning, the coordination of chemotherapy with surgery and RT, and better prognostic treatment stratification. Relatively little has been learned about improving treatment from randomized studies but previous conclusions about the role of doxorubicin are being revisited. The challenge for the future requires the development of a greater ability to selectively reduce treatment for some groups of patients with a high chance of cure and to identify better forms of therapy for those with a very poor prognosis. Patients with metastatic disease, for example, continue to have a very poor survival rate. Successful randomized studies in this group of patients will probably require transatlantic collaboration in order to achieve the power

necessary to draw any conclusion; the idea has been mooted and needs to be pursued. It is also gratifying that the new EpSSG studies will harness resources of wide European collaborations with the potential that this may produce a study base of similar size to that currently enjoyed by IRSG/COG.

Lessons from studies of non-RMS STS

Although this chapter refers to two studies that include patients with non-RMS STS (Studies 7 and 8), Study 7 is the only published study which was specifically designed to answer a randomized question about the value of chemotherapy in this difficult and heterogeneous group of patients. Unfortunately, the power of this study was limited and further work needs to be undertaken to better understand optimal therapy. Perhaps the most important immediate question is to ascertain whether the treatment of children with non-RMS STS, particularly with the diagnoses more frequently seen in adults, should be assessed any differently than for adults with the same condition. If not, combined studies, particularly of new agents, could be productive. An important recent development in Europe has been the development of a new EpSSG study specifically for children with non-RMS STS. This will facilitate the systematic collection of data from the consistent treatment of children with these rare tumors. Separate approaches are offered for synovial sarcoma, for "adult"-type non-RMS STS and for unique pediatric histiotypes. None of these studies yet include a randomized element and the numbers of patients in some of these rare diagnostic groups, even when collected at European level, still make this a logistical and statistical challenge.

Conclusion

Despite progress made, many children with STS continue to have an outcome that is unsatisfactory in terms of overall cure. Wider international collaboration is the key to providing a patient base that will allow timely and valid randomized studies.

Studies

Study 1

Maurer HM, Beltangady M, Gehan EA, Crist W, Hammond D, Hays DM, Heyn R, Lawrence W, Newton W, Ortega J. The Intergroup Rhabdomyosarcoma Study-I. A final report. *Cancer* 1988;**61**: 209–20.

This study was carried out between 1972 and 1978 by the US Intergroup Rhabdomyosarcoma Study Group.

Objectives

The aims of the study were:

- To evaluate the role of local radiotherapy in IRS Group I patients who received vincristine, actinomycin D (dactinomycin) and cyclophosphamide (VAC) chemotherapy.
- To determine whether the addition of cyclophosphamide to vincristine and actinomycin (VA) was of benefit in Group II patients who received local irradiation.
- To document the complete remission rate achieved by pulsed VAC with local irradiation in patients with Group III and IV disease.
- To evaluate the role of adding doxorubicin (Adriamycin) to VAC in Group III and IV patients.

Details of the study

Patients eligible were under 21 years with rhabdomyosarcoma or undifferentiated sarcoma.

The treatment regimens were as shown in Figure 1.1. Local irradiation was given at the start of treatment in Group I/II patients and after 6 weeks of chemotherapy for all other patients. Radiation dose was 50–60 Gy, reduced to 40 Gy for those under 3 years of age. Patients with lung metastases received 18-Gy bilateral lung irradiation.

The randomization method is not described in detail. The study was designed to detect a doubling of the median disease-free survival (DFS) time for both Group I and II patients, with 90% power at the 5% level, requiring 87 patients in each arm in both of these studies.

For Groups III and IV it was predicted that there would need to be 100 patients in each arm to detect a 20% improvement in response rate, with 90% power at the 5% level. A response rate of 50% was assumed for the control group.

Outcome measures were disease-free, overall survival (DFS, OS, respectively), and local and distant response.

Outcome

A total of 799 patients were registered, of whom 686 were eligible for inclusion. After review of all pathology, radiology and treatment flow sheets 575 were deemed evaluable, but all 686 eligible patients are included in the outcome analysis on an intention-to-treat basis.

Group I

Regimen A: 43 patients, 5-year DFS 81%, OS 93%.
Regimen B: 43 patients, 5-year DFS 79%, OS 81%.

No significant difference between the two arms. No difference was noted in the site of relapse in the two groups with regard to local or distant metastases.

Group II

Regimen C: 87 patients, 5-year DFS 72%, OS 72%.
Regimen D: 98 patients, 5-year DFS 66%, OS 72%.

No significant difference between the two arms.

Group III

Regimen E: 146 patients, complete response rate 67%, median time to achieve complete remission (CR) 12 weeks, event-free survival (EFS) at 5 years 49%, OS 69%.
Regimen F: 134 patients, complete response rate 72%, median time to CR 13 weeks, DFS 50%, OS 68%.

No significant difference between the two arms.

Group IV

Regimen E: 61 patients, complete response rate 51%, median time to CR 15 weeks, EFS 19%, OS 14%.
Regimen F: 68 patients, complete response rate 50%, median time to CR 10 weeks, EFS 41%, OS 26%.

No significant difference between the two arms.

Figure 1.2 shows EFS for Group IV patients.

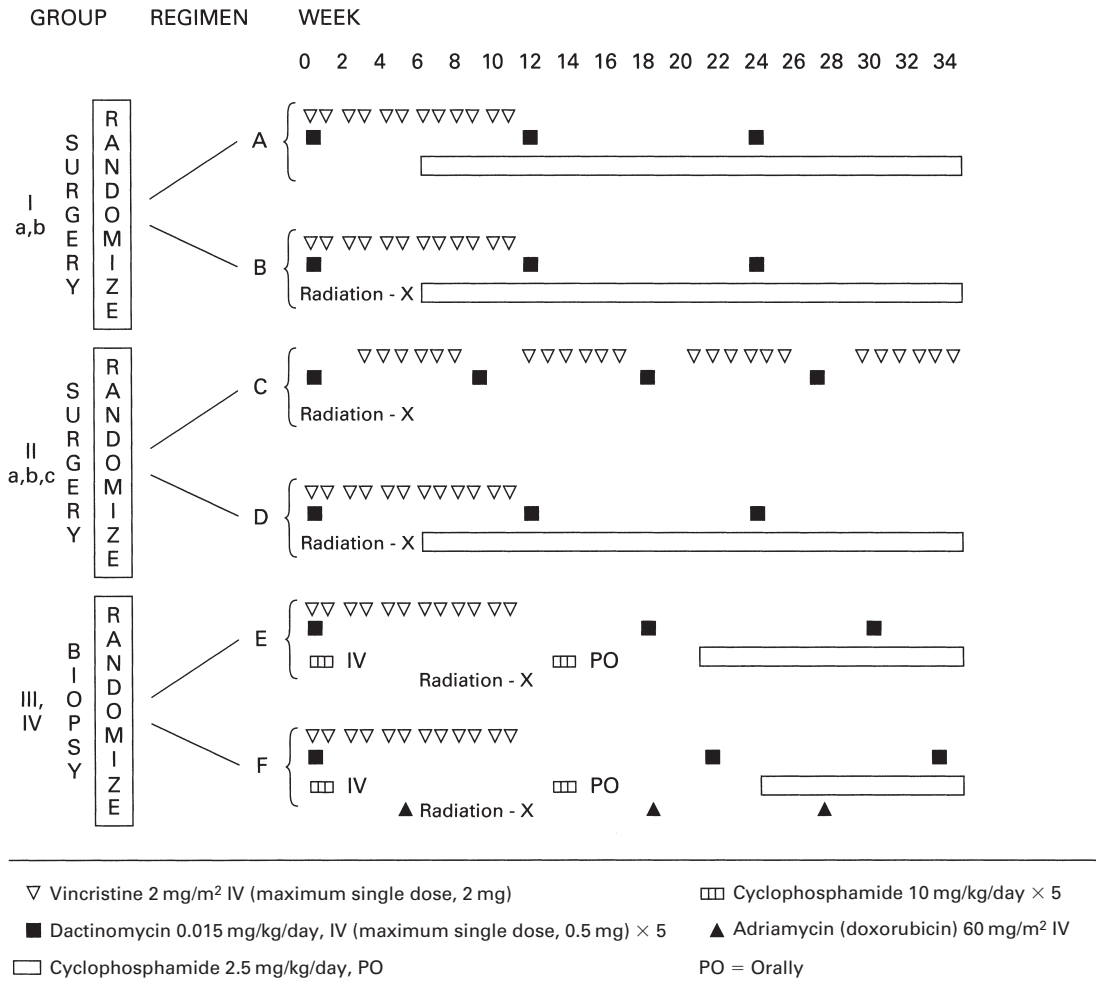

Figure 1.1 Treatment regimens. Copyright © 1988 American Cancer Society. Reprinted and adapted from Maurer *et al.* (full reference on p. 7) with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Toxicity

There was a 2% treatment-related death rate, all occurring on regimen E or F. There were three severe cardiac toxicities in patients receiving anthracyclines.

Conclusions

- Group I patients achieved no benefit from local irradiation.
- The addition of cyclophosphamide did not add to the efficacy of VA in Group II patients who received local irradiation.
- Doxorubicin did not add to VAC in Group III patients who received local irradiation.
- Although there was a trend to benefit from doxorubicin in Group IV with regard to a more rapid complete response rate and a lower relapse rate in those achieving a complete response, there was no significant difference overall in EFS or OS.

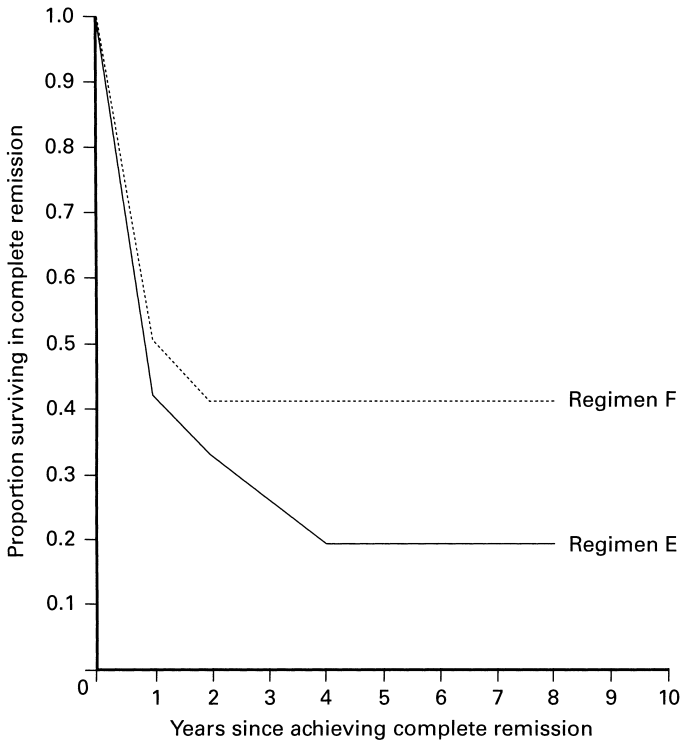

Figure 1.2 Event-free survival for Group IV patients. Duration of complete remission curves among complete responders in Group IV by randomized treatments: "pulse" VAC + radiation (regimen E) and "pulse" VAC + Adriamycin (doxorubicin) + radiation (regimen F). Copyright © 1988 American Cancer Society. Reprinted and adapted from Maurer *et al.* (full reference on p. 7) with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Study 2

Maurer HM, Gehan EA, Beltangady M, Crist W, Dickman PS, Donaldson SS, Fryer C, Hammond D, Hays DM, Herrmann J. The Intergroup Rhabdomyosarcoma Study-II. *Cancer* 1993;**71**:1904–22.

This study was carried out between 1978 and 1984 by the US Intergroup Rhabdomyosarcoma Study Group, with participation of the United Kingdom Children's Cancer Study Group (UKCCSG).

Objectives

The aims of the study were:

- To determine the value of cyclophosphamide in favorable site/pathology IRS Group I patients.
- To evaluate the role of pulsed VAC (vincristine, actinomycin D and cyclophosphamide), compared to VA in favorable Group II patients.
- To evaluate the role of doxorubicin (Adriamycin) in Group III and IV patients, excluding special pelvic sites.

In addition, in the non-randomized component of the trial, to evaluate the value of local meningeal irradiation in parameningeal tumors, the potential reduction in cystectomy rates using primary chemotherapy and the value of pulsed VAC in extremity alveolar tumors using comparisons with IRS-I data.

Details of the study

Patients below the age of 21 years with rhabdomyosarcoma, soft tissue Ewing's sarcoma and undifferentiated sarcoma were eligible.

All IRS Group I and II patients were included, except those with extremity alveolar tumors.

The dose of local irradiation in Group II patients was 40–45 Gy. For Group III patients under 6 years of age with tumors less than 5 cm, the dose was 40–45 Gy; over 5 cm, 45–50 Gy; for those over 6 years of age with tumors less than 5 cm, 45–50 Gy and over 5 cm, 50–55 Gy.

Group IV patients with lung disease received 18-Gy bilateral lung irradiation and those with other soft tissue deposits received 50–55 Gy.

For details of the treatment regimens see Figure 1.3.

Primary outcome measures were disease-free survival (DFS) and survival with documentation of response rates.

The method of randomization was not described.

For Group I and II patients there was a 1:2 stratification standard:study regimen. It was estimated that for the Group I patients 25 and 50 patients, respectively, were required. For Group II, 38 and 75, respectively, and for Groups III and IV, a total of 186 patients. The difference between the curves was analyzed using log-rank tests and generalized Wilcoxon tests. The p-values obtained from statistical tests were used as a measure of the strength of the evidence against the null

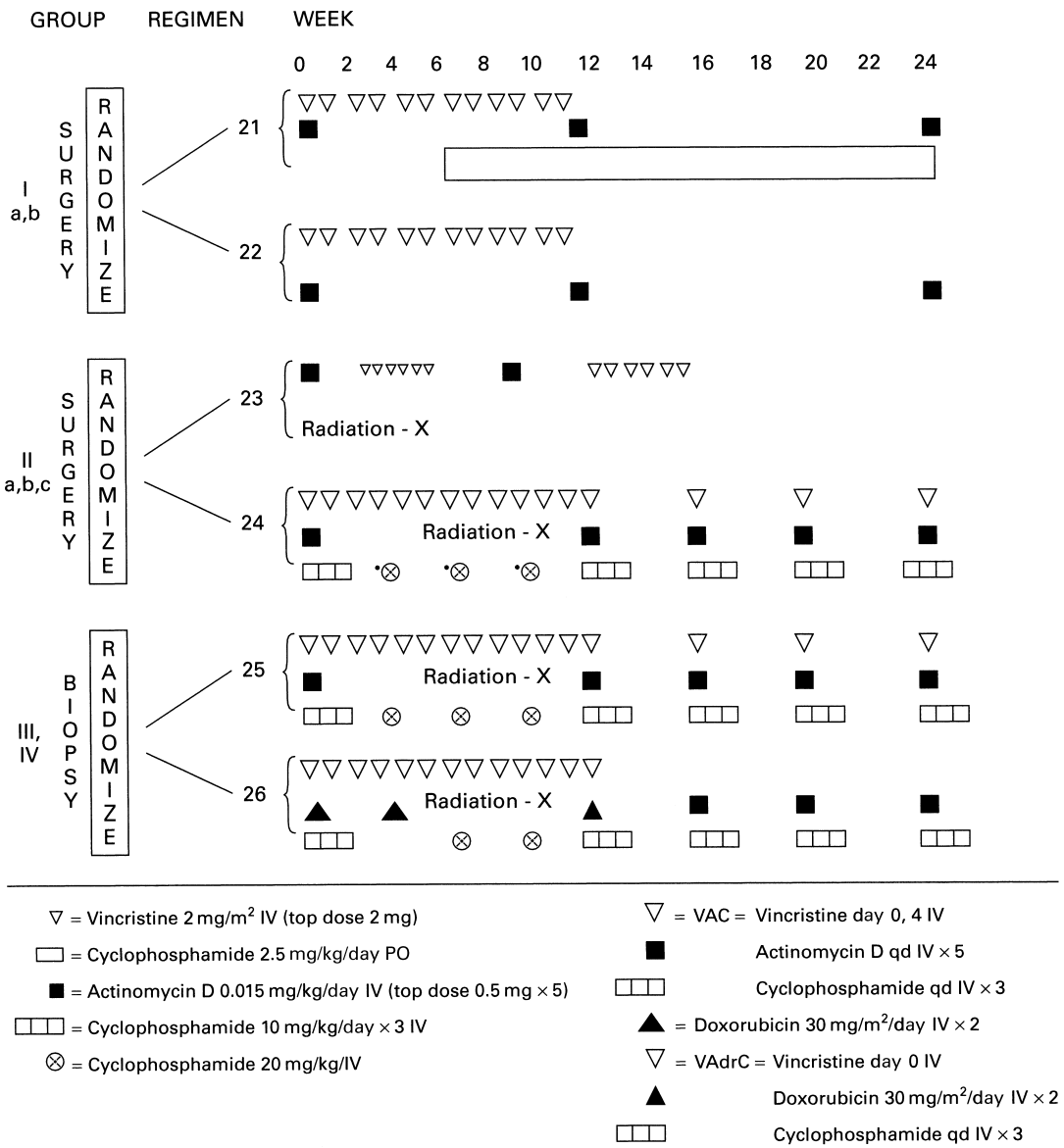

Figure 1.3 Intergroup Rhabdomyosarcoma Study II treatment regimen. Copyright © 1993 American Cancer Society. Adapted and reprinted from Maurer *et al.* (full reference on p. 9) with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

hypothesis being tested, $p < 0.05$ indicating a statistically significant result with moderate evidence against the null hypothesis, and $p < 0.01$ indicating a highly significant result with strong evidence against the null hypothesis.

Outcome

A total of 1115 patients were registered, of whom 116 were excluded, 100 due to unconfirmed eligible pathology on review. The allocation to treatment group by local center was confirmed on review in 92% of cases. Of the 999 patients, 776 were regarded as evaluable. Reasons to be non-evaluable included wrong treatment assignments, protocol violation or inadequate data collection. All 999 patients were included in the analysis on an intention-to-treat basis.

Group I

Regimen 21: 37 patients, 5-year DFS 80%, OS 85%.
Regimen 22: 64 patients, 5-year DFS 70%, OS 84%.

There appeared to be more local recurrences in the arm not receiving cyclophosphamide (14% versus 5%), but this was not statistically significant.

Group II

Regimen 23: 45 patients, DFS 69%, OS 88%.
Regimen 24: 85 patients, DFS 74%, OS 79%.

No significant difference between the treatment arms.

Group III

Regimen 25: 211 patients, complete remission (CR) rate 74%, continued clinical remission (CCR) at 5 years 75%, OS in CR patients 66%.
Regimen 26: 197 patients, CR rate 78%, CCR at 5 years 70%, OS 65%.

No significant difference between the treatment arms, but significantly better than in IRS-I.

Group IV

Regimen 25: 83 patients, CR rate 52%, median time to CR 13 weeks, CCR of CR patients at 5 years 38%.
Regimen 26: 88 patients, CR rate 53%, median time to CR 15 weeks, CCR at 5 years 38%.

Overall progression-free survival of all patients at 5 years 21% for Regimen 25 and 25% for Regimen 26.

No significant difference.

Toxicity

There were 21 fatalities associated with treatment, overall 1–4% by regimen. There were five severe cardiac toxicities. The precise details by regimen were not specified.

Conclusions

- Vincristine and actinomycin given for 1 year is equivalent to 2 years of VAC in Group I patients not given local irradiation.
- Cyclophosphamide does not add benefit to VA in Group II patients who receive local irradiation.
- The addition of doxorubicin to a VAC-based combination does not significantly improve either complete response rate or ultimate outcome in patients with Group III or IV disease.

Comments

Womer has noted some reservations about the comparability of the regimens (Womer RB. The Intergroup Rhabdomyoma studies come of age. *Cancer* 1993;**71**: 1719–21). For Group II patients, Regimen 23 had three times the vincristine and half the actinomycin dose, compared to Regimen 24 which contained cyclophosphamide. Moreover, it is possible that the addition of doxorubicin could have had an impact on the different pathological subgroups within Groups III and IV, but insufficient patient numbers were recruited to determine whether there was a difference between embryonal or alveolar rhabdomyosarcoma.

Study 3

Crist W, Gehan EA, Ragab AH, Dickman PS, Donaldson SS, Fryer C, Hammond D, Hays DM, Herrmann J, Heyn R. The Third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol* 1995;**13**:610–30.

This study was carried out between 1984 and 1991 by the US Intergroup Rhabdomyosarcoma Study Group.

Objectives

The aims of the study were:

- To determine the role of doxorubicin (Adriamycin) in addition to VAC (vincristine, actinomycin D and cyclophosphamide) chemotherapy in Group II patients.
- To determine the role of the addition of either cisplatin/doxorubicin or cisplatin/doxorubicin and etoposide in Group III and IV patients.
- To make non-randomized comparisons with IRS-II for all other patient groups.

Details of the study

Eligible patients were under the age of 21 years with rhabdomyosarcoma, undifferentiated sarcoma, extraosseous sarcoma and extraosseous Ewing's sarcoma. Treatment had to be started within 42 days of tumor biopsy and 21 days of definitive primary surgery.

Outcome measures were progression-free survival (PFS) and overall survival (OS), in addition to local and metastatic response.

It was estimated that for Group II patients, to demonstrate a 15% increase in end point from 80% to 95% with 73% power at the 5% level would require 92 patients. It was planned to include comparable non-randomized patients from IRS-II who received the identical standard comparator regimen.

For Group III patients, in order to detect an increase from 70% to 80%, with 76% power at the 5% level, would require a total of 472 patients. Again, it was planned to include comparable patients from the IRS-II who required the identical standard regimen.

The precise methods of randomization were not detailed.

Details of the chemotherapy and radiotherapy regimens are given in Figure 1.4.

Group II favorable histology patients received either VA with radiotherapy or VA/doxorubicin with radiotherapy for a total of 1 year. Patients with testicular, orbit or head and neck non-parameningeal primaries were excluded from the randomized study.

Group III patients, with the exception of special pelvic sites and parameningeal tumors, either received the standard regimen of pulsed VAC with radiotherapy or a regimen including doxorubicin and cisplatin or doxorubicin/cisplatin/etoposide. All three regimens incorporated second-line chemotherapy for patients who achieved partial response. For the standard VAC

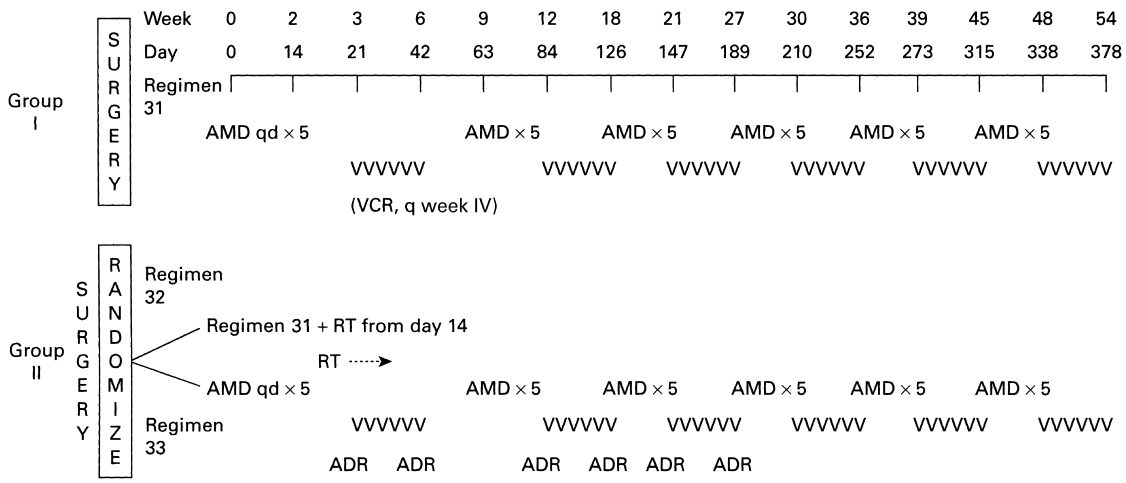

Figure 1.4a Intergroup Rhabdomyosarcoma Study III treatment regimen for Groups I and II (ADR: doxorubicin; AMD: actinomycin D; RT: radiotherapy and VCR: vincristine). © American Society of Clinical Oncology (full reference above).

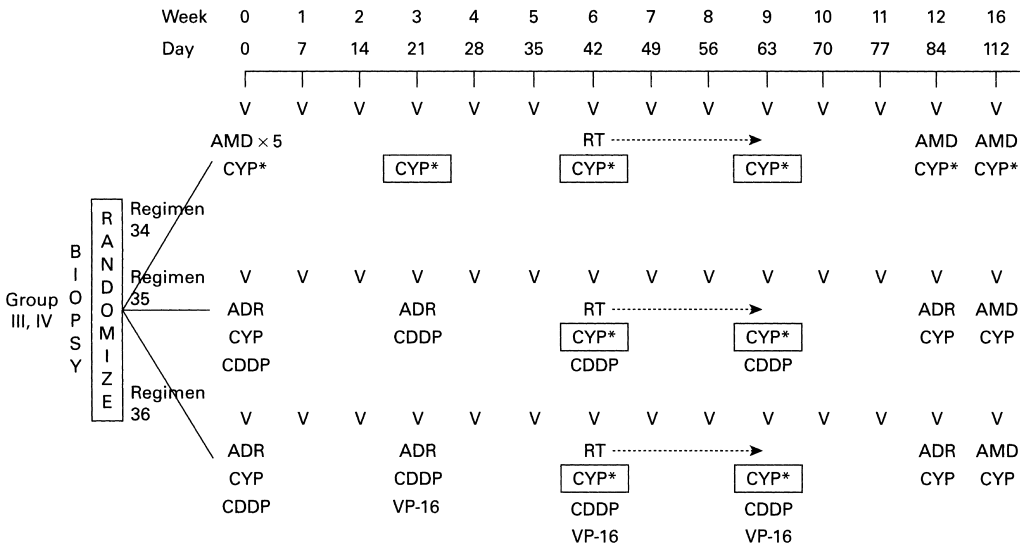

Figure 1.4b Intergroup Rhabdomyosarcoma Study III treatment regimen for Groups I and II (CDDP: cisplatin; CYP: cyclophosphamide; VP-16: etoposide and other abbreviations as in Figure 1.4a). © American Society of Clinical Oncology (full reference on p. 12).

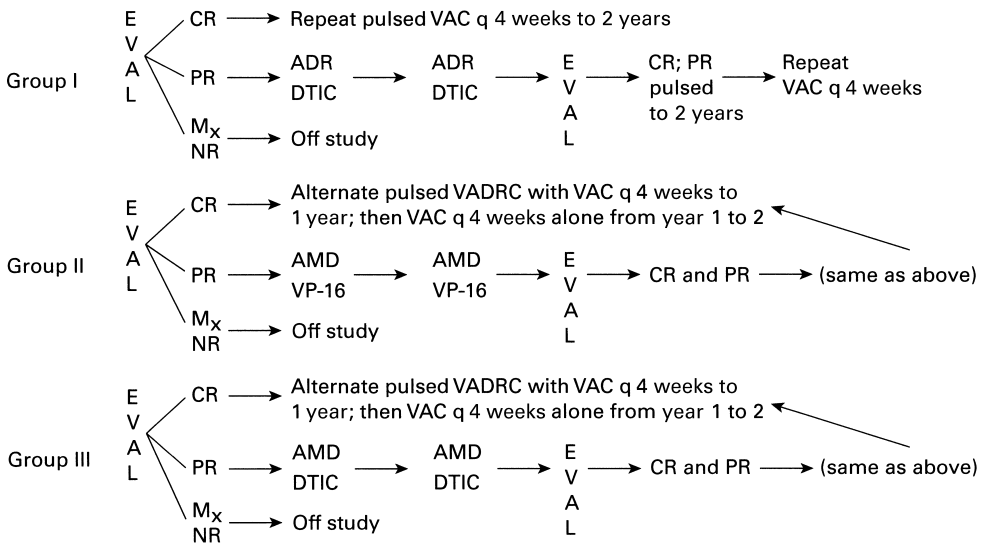

Figure 1.4c Intergroup Rhabdomyosarcoma Study III treatment regimen (NR: no remission; PR: partial remission and other abbreviations as in Figure 1.4a). © American Society of Clinical Oncology (full reference on p. 12).

regimen this comprised doxorubicin and DTIC; for the doxorubicin/cisplatin regimen, actinomycin D/etoposide; and for the four-drug regimen, actinomycin D and DTIC.

Outcome

A total of 1194 patients were enrolled, of whom 132 were excluded, 79 due to incorrect pathology. Of the 1062 eligible patients, 235 were regarded as

non-assessable for a variety of reasons on central review of grouping, radiotherapy, chemotherapy and surgical details. All patients eligible and randomized were included in the subsequent analyses on an intention-to-treat basis. Overall, there was pathological agreement with the Central Review Panel in 79% of alveolar cases and 77% of embryonal cases.

Group II

Regimen 32: 23 patients, 5-year PFS 56%, OS 54%.
Regimen 33: 51 patients, 5-year PFS 77% and OS 89%. With the addition of the identical IRS-II Regimen 23 patients, PFS in the control arm was 63% and OS 73%.

No statistical difference between the two treatment arms.

Group III

Regimen 34: 58 patients, at week 20 complete remission (CR) rate 39%, with an eventual CR rate of 79%, 5-year PFS 70% and OS 70%.
Regimen 35: 113 patients, week 20 CR rate 45%, final CR 78%, PFS 62%, OS 63%.
Regimen 36: 118 patients, week 20 CR rate 48%, final CR 84%, PFS 56%, OS 64%.

No statistical significant difference in the initial response, final CR rate or ultimate outcome.

Group IV

Regimen 34: 29 patients, week 20 CR rate 42%, final CR rate 50%, PFS 27%, OS 27%.
Regimen 35: 65 patients, week 20 CR rate 30%, final CR rate 57%, PFS 27%, OS 31%.
Regimen 36: 56 patients, week 20 CR rate 38%, final CR rate 62%, PFS 30%, OS 29%.

Comparing with IRS-II, the Group III patients did significantly better, $p < 0.01$, with 61% versus 52% PFS. This was concluded to be due to the value of second-line chemotherapy achieving complete response.

Toxicity

Overall 5% fatalities. Morbidity of individual regimens was not detailed. Overall, there were 9% cardiac toxicities, of which 5% were severe. There were five cases of secondary acute myeloid leukemia – four on Regimen 36.

Conclusion

It was concluded that although the overall results were superior to IRS-II, no particular subgroups benefited directly from the intensification of chemotherapy within the randomized comparison.

Study 4

Flamant F, Rodary C, Voute PA, Otten J. Primary chemotherapy in the treatment of rhabdomyosarcoma in children. Trial of the International Society of Pediatric Oncology (SIOP) preliminary results. *Radiother Oncol* 1985;**3**:227–36.

The study was run from 1975 to 1983 by the European collaboration group SIOP.

Objectives

The aim of the study was:

- To determine whether the use of chemotherapy with radiotherapy prior to surgery could minimize treatment sequelae without jeopardizing survival rate.

Details of the study

Eligible patients included those aged 1–15 years with embryonal or alveolar rhabdomyosarcoma, deemed initially unresectable, with either incomplete removal or biopsy only. Patients had to have had equal or greater than 25% reduction in tumor volume after one course of VAC (vincristine, actinomycin D and cyclophosphamide) chemotherapy. Patients were also excluded if there was a major intolerance to this initial course of chemotherapy.

The method of randomization is not specified. Randomization was performed on day 28, with pairing according to the localization. Ear, nose and throat primaries were also paired according to age and bone involvement of the base of the skull.

Patients received regimen A or B (see Figure 1.5). Regimen A was continuation of VAC, followed by vincristine doxorubicin (VAD) chemotherapy, alternating for an 18-month period. If a complete clinical response was achieved, no other treatment was given.

If a partial response was achieved, chemotherapy was given to maximum effect, followed by surgery and/or radiotherapy. If there was no response after two VAC/VAD, surgery and/or radiotherapy was given. With regimen B systematic radiotherapy was given to the initial tumor volume, even if the tumor had regressed after pre-trial chemotherapy. A dose of 45 Gy was used accompanied by daily actinomycin on each of the first seven radiotherapy sessions and vincristine every 2 weeks during radiotherapy. Following radiotherapy, VAC/VAD was given for 18 months, as in regimen A. In the case of bladder and prostate tumors, anterior exenteration was done followed by radiotherapy if the surgery was not microscopically complete.

Outcome at 3 years was analyzed in paired cases. Using a closed pragmatic design the probability of preferring one treatment when in reality the other was better in 65% of the untied pairs was 5%. Under these conditions the number of pairs required was estimated to be 37, i.e. 74 patients. If the accrual rate was 25 patients per year, 3 years would have been needed, and the results of the last pair treated would have been available 6 years after the study started.

In the analysis the best result of the pair was chosen. If both patients died, neither treatment was preferable and this pair resulted in a tie. When only one of the pair was dead, the treatment given to the living patient was counted as preferable, even if the patient was living with a relapse. If both were living, the treatment which had given the best results, taking into consideration the existing and expected therapeutic sequelae, was preferred. When the results were equal, the less heavy treatment was chosen.

Outcome

Eighty-one patients were entered. Fifteen failed to show a sufficient response to course 1 and three were excluded due to protocol violation or pathological error. Local complete response was achieved in 21 of 32 in arm A and 21 of 31 in arm B.

The final assessment at 3 years was estimated for 22 pairs of patients. No difference was seen between the arms; the overall survival rate was 40% at 3 years. Of 56 patients with more than 2 years follow-up, 41% in arm A were in complete clinical remission compared with 48% of arm B. It was noted that in all children

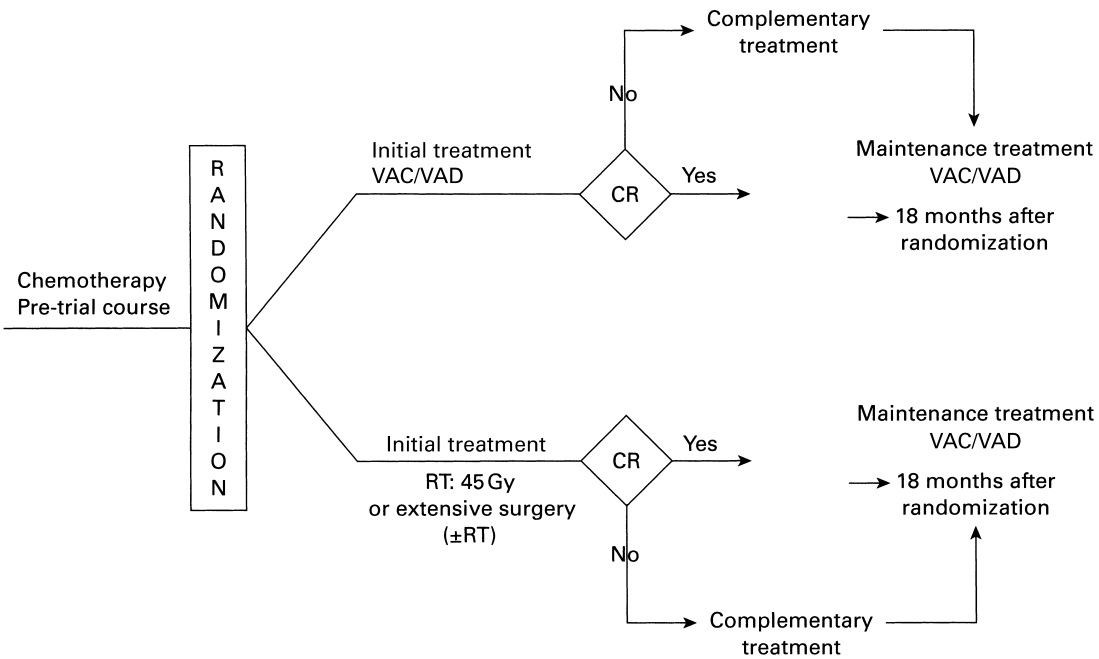

Figure 1.5 Design of the trial. Reprinted from Flamant *et al.* (full reference on p. 14) with permission from Elsevier.

with bladder primaries cystectomy was eventually performed in both treatment arms.

Conclusion

It was concluded that primary chemotherapy could avoid many late sequelae with no adverse effect on outcome, although overall disease-free survival was poor in both the arms. The numbers were too small to conclude unequivocally whether disease-free survival differed between the two arms. This study was stopped prematurely due to poor results in those with parameningeal localization, and the refusal by doctors and the families to allow patients with bladder and prostate primaries to undergo anterior pelvectomy.

Study 5

Carli M, Pastore G, Perilongo G, Grotto P, De Bernardi B, Ceci A, Di Tullio M, Madon E, Pianca C, Paolucci G. Tumor response and toxicity after single high-dose versus standard five-day divided-dose dactinomycin in childhood rhabdomyosarcoma. *J Clin Oncol* 1988; **6**:654–8.

The study was run from 1979 to 1985 by the Italian Multicentre Collaborative Group.

Objectives

The study was aimed:

- To compare two methods of administration of actinomycin, as part of VAC.

Details of the study

Eligible patients with a rhabdomyosarcoma included those under 15 years of age with one of the following: a tumor greater than 5 cm in size, primary of bladder, prostate, vagina, uterus and orbit, and included those with distant metastases.

Randomization was carried out centrally using a closed envelope method. It was balanced for primary site, clinical group and center size. A projected accrual rate of 15–20 patients per year was planned to achieve around 50 patients in each arm to show a 30% difference in response or toxicity, α 0.05, β 0.2.

Actinomycin, as part of vincristine, actinomycin D and cyclophosphamide (VAC), was given at 0.45 mg/m^2 daily for 5 days, the combination repeated every 28 days for three courses. This schedule was compared with 1.7 mg/m^2 on day 8 only and the regimen was repeated every 21 days for four courses.

The major outcome measure was response to treatment prior to course 4, 3 weeks after the second course.

Outcome

Thirty-six patients received split dose VAC and 42 single dose VAC. Eight patients were excluded, due to early death in four, two refused after randomization and two had prior chemotherapy.

Complete or partial remission was 67% on the split dose VAC and 70% for the single dose VAC. Overall survival at 3 and 5 years with split dose was 48% and 38% and single dose 43% and 43%, respectively.

Toxicity

The split dose VAC was more myelosuppressive, although not statistically significant. There was significantly more stomatitis with split dose VAC ($p < 0.01$). There were two severe episodes of sepsis, both in the split dose arms.

Conclusion

It was concluded that the fractionated regimen was somewhat more toxic and no more effective in achieving an initial response than the simpler single dose regimen. In particular, there was no evidence of any increase in liver toxicity associated with the single dose regimen.

Study 6

Baker KS, Anderson JR, Link MP, Grier HE, Qualman SJ, Maurer HM, Breneman JC, Wiener ES, Crist WM. Benefit of intensified therapy for patients with local or regional embryonal rhabdomyosarcoma: results from the Intergroup Rhabdomyosarcoma Study-IV. *J Clin Oncol* 2000;**18**:2427–34.

The study was carried out by the US Intergroup Rhabdomyosarcoma Study between 1991 and 1997 (IRS-IV).

Objectives

The study was designed:

- To compare three induction and continuation chemotherapies based on the VAC regimen, with the substitution of ifosfamide for cyclophosphamide or the replacement of actinomycin and cyclophosphamide with ifosfamide and etoposide.

Details of the study

Eligible patients were under 21 years of age with either rhabdomyosarcoma or undifferentiated sarcoma. Chemotherapy was to start within 42 days of initial surgery.

No details of randomization method are given, nor the predicted number of patients required to address the issue of differences in efficacy of the respective chemotherapies.

The regimens are shown in Figure 1.6. The cyclophosphamide dose of 2.2 g/m^2 is higher than in previous IRS regimens and this was compared with 9 g of ifosfamide infused over 5 days and the same dose combined with etoposide 500 mg/m^2 over 5 days.

Excluded from the study were patients felt to be at risk of renal problems, namely those with raised creatinine, single kidneys or pre-existing hydronephrosis. Also excluded were the good risk Group I patients with testis, orbit or eyelid primaries who received only vincristine and actinomycin D.

The primary outcome measure was failure-free survival.

	INDUCTION Treatment weeks 0–16																		CONTINUATION Treatment weeks 20–46								
Regimen	0	1	2	3	4	5	6	7	8	EVALUATION	9	10	11	12	13	14	15	16	EVALUATION	20	21	22	23	24	25	26	27	28
VAC	V	V	V	V	V	V	V	V	V		V	V	V	V	–	–	–	V		V	V	V	V	V	V	–	–	–
	A			A			A				C			C				A		A			A					
	C			C			C				Radiation therapy							C		C			C					
VAI	V	V	V	V	V	V	V	V	V		V	V	V	V	–	–	–	V		V	V	V	V	V	V	–	–	–
	A			A			A				I			I				A		A			A					
	I			I			I				Radiation therapy							I		I			I					
VIE	V	V	V	V	V	V	V	V	V		V	V	V	V	–	–	–	V		V	V	V	V	V	V	–	–	–
	I			I			I				I			I				I		I			I					
	E			E			E				Radiation therapy							E		E			E					

V, vincristine 1.5 mg/m^2 (2 mg maximum)

A, actinomycin D 0.015 mg/kg/day (0.5 mg maximum daily dose), days 0–4

C, cyclophosphamide 2.2 mg/m^2, day 0

I, ifosfamide 1.8 mg/m^2/day, days 0–4

E, etoposide 100 mg/m^2/day, days 0–4

Figure 1.6 Treatment plans for IRS-IV patients at intermediate risk of failure. © American Society of Clinical Oncology (full reference above).

Outcome

A total of 894 patients were registered with locoregional disease. For the chemotherapy comparisons no details of patient numbers or disease group are provided in this report, just the outcome. The 3-year failure-free survivals for VAC, VAI and VAE were 74%, 74% and 76%, respectively, with overall survivals of 81%, 83% and 87%, respectively; i.e. no significant difference between the three arms.

No details of toxicity between the three treatments are provided.

Conclusion

Overall, the results in IRS-IV were no different from IRS-III, except for the subgroup of patients with intermediate risk embryonal histology, where there was a significant improvement in event-free and overall survival. This was claimed to be due to the increase in the dose of alkylating agent in IRS-IV, compared to IRS-III.

It was concluded that none of the novel regimens had any advantage over the VAC protocol containing a higher dose of cyclophosphamide.

Study 7

Pratt CB, Pappo AS, Gieser P, Jenkins JJ, Salzberg A, Neff J, Rao B, Green D, Thomas P, Marcus R, Parham D, Maurer H. Role of adjuvant chemotherapy in the treatment of surgically resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: a Pediatric Oncology Group Study. *J Clin Oncol* 1999;**17**:1219–26.

This study was carried out by the Pediatric Oncology Group (POG 8653) between 1986 and 1992.

Objectives

The study was designed:

- To evaluate whether administration of chemotherapy following surgical resection of nonrhabdomyosarcomatous soft tissue sarcomas improved local or systemic control.

Details of the study

Patients were under 21 years of age, previously untreated and pathologies that were excluded comprised rhabdomyosarcoma, extraosseous Ewing's sarcoma, fibromatosis, undifferentiated sarcoma, angiofibroma, dermatofibrosarcoma protuberans and mesothelioma.

The randomization method is not given, but it was balanced for clinical group status. The initial design specified a sample size of 112 patients would be required to detect a 20% improvement in 2-year event-free survival (EFS) (70% versus 50%) with an 80% power. A 5%, one-sided significance level was assumed. Overall survival and EFS were the primary outcome measures. All pathology was centrally reviewed.

The treatment schema is given in Figure 1.7. Children with Group I disease received no postoperative irradiation and were randomly assigned to be observed or receive adjuvant chemotherapy with vincristine 1.5 mg/m^2, doxorubicin (Adriamycin) 60 mg/m^2 and cyclophosphamide 750 mg/m^2 (VAdrC), alternating every 3 weeks with vincristine 1.5 mg/m^2, cyclophosphamide 750 mg/m^2 and actinomycin D 1.25 mg/m^2 (VAC) for a total of 31 weeks. Children with clinical Group II disease, i.e. microscopic residual tumor, received age-adjusted postoperative radiotherapy to the tumor bed at a dose between 35 and 45 Gy. After completion of irradiation, patients were randomly assigned to receive or not receive chemotherapy. Patients with clinical Group III disease underwent second-look surgery 6–12 weeks after completing radiation therapy. If complete tumor regression was documented, these patients were also randomly assigned to receive or not receive adjuvant chemotherapy.

Outcome

Ninety-nine patients were enrolled, 18 were excluded due to ineligible pathology; 30 of the 81 remaining were randomized. Reasons for the high non-randomization rate are not given, but 19 were electively treated with chemotherapy and 32 with observation alone. Overall, most patients in Group I had extremity primaries – synovial sarcoma was the commonest pathology (36%) followed by malignant fibrous histiocytoma (12%), malignant peripheral nerve sheath tumor (10%) and fibrosarcoma (10%); 47% had grade 3 tumors.

For the randomized cases, the 5-year EFS was 87% for those observed, versus 41% for those receiving

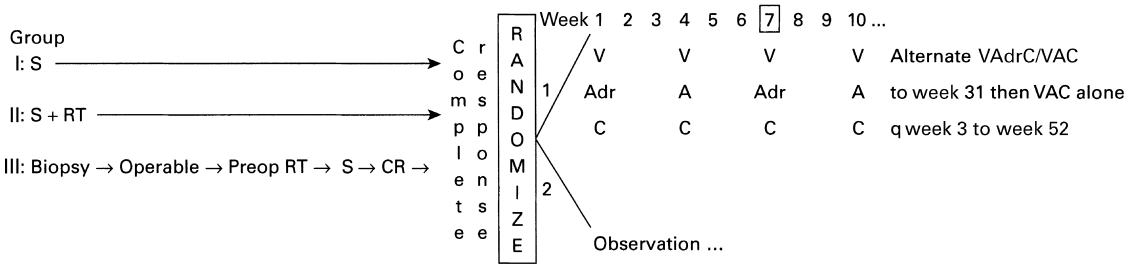

Figure 1.7 Treatment schedule for POG 8653 (A: actinomycin; Adr: Adriamycin; C: cyclophosphamide; Preop: preoperative; S: surgery; RT: radiotherapy and V: vincristine). © American Society of Clinical Oncology (full reference on p. 18).

chemotherapy ($p = 0.01$) and overall survival was 93% and 69%, respectively ($p = 0.016$). These differences were due to an imbalance in histological grade, with 73% of grade 3 in the chemotherapy arm, compared to 40% in the observation arm. Histological grade 3 included the following diagnoses: pleomorphic or round-cell liposarcoma, mesenchymal chondrosarcoma, extraskeletal osteogenic sarcoma, malignant triton tumor, alveolar soft part sarcoma and a group of tumors with a high level of necrosis and mitotic activity.

Conclusion

It was concluded that this study failed to show any significant benefit from chemotherapy but the low randomization rate and ultimately small numbers limit the conclusions that can be drawn.

Study 8

Pratt CB, Maurer HM, Gieser P, Salzberg A, Rao BN, Parham D, Thomas PRM, Marcus RB, Cantor A, Pick T, Green D, Neff J, Jenkins JJ. Treatment of unresectable or metastatic pediatric soft tissue sarcomas with surgery, irradiation and chemotherapy: a Pediatric Oncology Group Study. *Med Ped Oncol* 1998;**30**:201–9.

The study was carried out by the Pediatric Oncology Group (POG 8654) between 1986 and 1994.

Objectives

The objective of the study was:

- To compare two chemotherapy regimens in children with either gross residual disease at presentation following surgery or distant metastases, either at presentation or as recurrent disease after initial treatment with surgery alone.

Details of the study

Details of patient eligibility are not given with regard to age, pathology, etc.

The randomization technique is not reported. It was assumed that there would be a 25% response rate for standard chemotherapy with vincristine, doxorubicin, cyclophosphamide and actinomycin D, and 94 patients would be required to document an increase to 40% with the addition of DTIC, with 80% power using Type I error.

The study outline is shown in Figure 1.8. All patients received VACA – vincristine 1.5 mg/m^2, actinomycin D 1 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin (Adriamycin) 60 mg/m^2 – and were randomized to receive, or not receive, additional DTIC of 500 mg/m^2. All received local radiotherapy at week 6, with an age-adjusted dose with maximal tumor dose of 55–65 Gy. Sites of metastases were also irradiated.

Delayed surgery was performed on Group III patients 6–12 weeks after radiotherapy.

Infants under 12 months received half-dose chemotherapy and the 3-weekly schedule was delayed 1 week if the absolute neutrophil count (ANC) was less than 0.5/μl and platelets was less than 50/μl at any time. If the ANC was less than 0.25×10^9/l and platelets was less than 10×10^9/l, doses were decreased by 25%.

Primary outcome measures were response at 6 weeks and relapse-free survival.

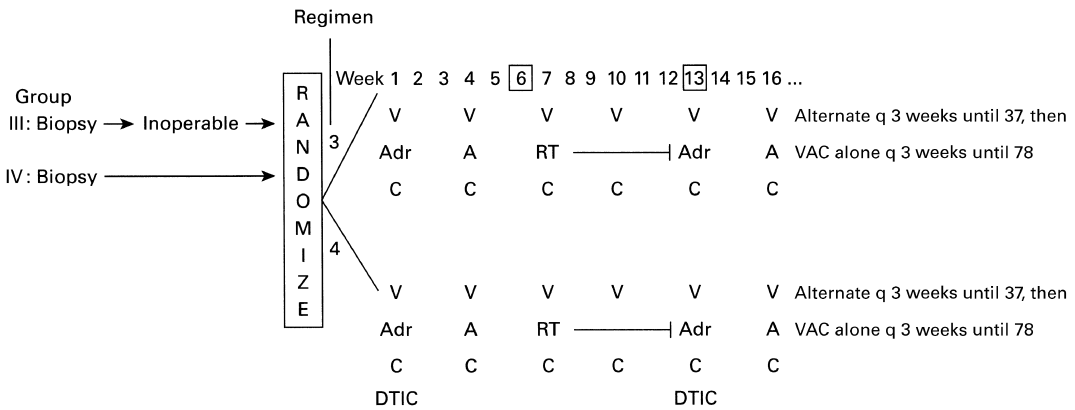

Figure 1.8 Treatment schema for POG 8654 (abbreviations as in Figure 1.7). Reprinted from Pratt *et al.* (full reference on p. 19) with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Outcome

Seventy-five patients were accrued prior to premature closure of the study. This was due to slow accrual, accompanied by investigator bias related to randomization. Among the 75 patients, 14 were ineligible due to problems with pathology on review. These included rhabdomyosarcoma, lymphoma, fibromatosis, osteosarcoma and thymoma. Of the 61 eligible patients there were 13 malignant peripheral nerve sheath tumors, 8 synovial sarcomas, 5 alveolar soft part sarcomas, 5 malignant fibrous histiocytomas and 6 non-specified sarcomas. Twenty-five patients received VACA and 25 patients received VACA with DTIC. Eleven received VACA electively, in part due to a lack of DTIC availability for a 12-month period during the study.

Overall response rate for VACA was 56% (35–76%) and with the addition of DTIC, 44% (24–65%). For Group III patients there were14 complete responses and 5 partial responses out of 36 overall. For Group IV patients, 3 complete responses and 6 partial responses in 25 patients. For the randomized VACA patients, there were 4 complete responses and 6 partial responses out of 25. For the DTIC arm, 7 complete responses and 4 partial responses out of 25. Event-free survival for VACA was 36% at 2 years, with DTIC it was 26%. The difference was not significant.

Conclusion

In conclusion, there appeared to be a high initial response rate but poor overall event-free survival and there appeared to be no benefit from the addition of DTIC.

Study 9

Breitfeld PP, Lyden E, Raney RB, Teot LA, Wharam M, Lobe T, Crist WM, Maurer HM, Donaldson SS, Ruymann FB. Ifosfamide and etoposide are superior to vincristine and melphalan for pediatric metastatic rhabdomyosarcoma when administered with irradiation and combination chemotherapy: a report from the Intergroup Rhabdomyosarcoma Study Group. *J Pediatr Hematol Oncol* 2001;**23**(4):225–33.

Study carried out by the American Intergroup Rhabdomyosarcoma Study Group between 1991 and 1995.

Objectives

The aim of the study was:

- To compare response rates of two novel drug pairs, vincristine and melphalan or ifosfamide and etoposide in untreated metastatic rhabdomyosarcoma.
- To determine whether incorporation of these combinations in patients who had shown a response in proven survival.

Details of the study

Eligible patient included all rhabdomyosarcoma or undifferentiated sarcoma under the age of 21 years.

All pathology and stage allocation were centrally reviewed.

No details of randomization method or site are given.

No details of the anticipated difference between the drug pairs with regard to response or subsequent influence on outcome are given. Plan numbers required are not defined.

Study design

The randomized comparison shown in Figure 1.9 and essentially compared four courses of ifosfamide and etoposide (IE) with three of vincristine and melphalan (VM). This was then followed by a standard vincristine, actinomycin D and cyclophosphamide (VAC) regimen with local radiation therapy and treatment continued up to 39 weeks with VAC to which in the case of responding patients either VM or IE was added. The sport GCSF was given with both initial chemotherapy arms.

Primary tumor excision was recommended if possible and second surgery after local radiation was also recommended. Radiation dose was 50.4 Gy to gross unresected disease, 41.4 Gy to microscopic post-surgical residue. Radiation field was the pre-treatment volume with 2-cm margin including adjacent lymph nodes. With lung metastases a dose of 14.4 Gy was given. Patients with parameningeal primaries were radiated on day 1 to the primary sites.

Outcome

One hundred and fifty-one patients with metastatic disease were recruited, 81 randomized to VM and 70 to IE. In the melphalan group 12 were excluded in the IE 11 excluded. Exclusions were due to non-pathology review, wrong pathological diagnosis or miss staging. Analysis was based on 69 VM and 59 IE. Groups were well balanced with regard to risk factors for VM and IE, respectively, T2 tumors 86% and 91%, bone marrow involvement 67% and 62%, bone involvement 58% and 45%, alveolar pathology 43% and 49%, age over 10 years 37% and 41%.

Toxicity

Hematological toxicity was more marked with melphalan with a significant excess of anemia in weeks 19–24, neutropenia in weeks 12–18 and thrombocytopenia in weeks 12–24. There was no significant difference in documented infection rates. There were three cases of hepatic veno-occlusive disease in the VM arm and one with IE. The incidence rate of electrolyte abnormalities was significantly higher with the ifosfamide-based regimen.

There were two secondary leukemias with VM and one with IE. There were four toxic deaths, one due to sepsis, one due to pneumonitis, one veno-occlusive disease and one bronchiolitis obliterans.

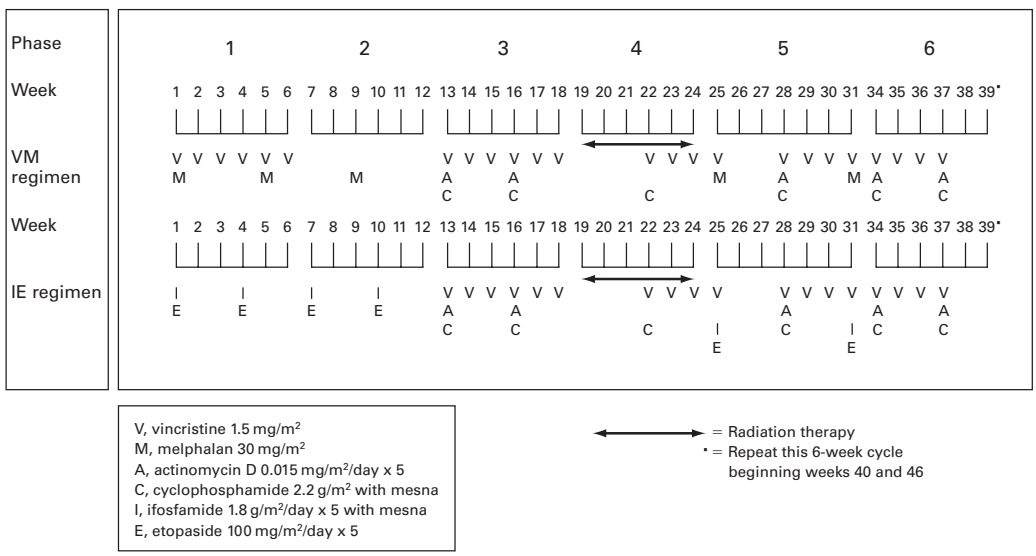

Figure 1.9 Chemotherapy and radiation therapy outline for patients randomized to either IE- or VM-containing regimens, Second-look surgery at the primary site was recommended for consideration at 6 months after completion of RT. Reproduced with permission of Lippincott, Williams & Wilkins (full reference on p. 20).

The initial drug couplets had a significant impact on the tolerance of subsequent VAC chemotherapy. This was significantly worse with the melphalan including regimen. Administration of chemotherapy between weeks 13 and 18 took 63 days versus 54 days, $p < 0.04$. A greater than 10% reduction in chemotherapy was required in the 48% versus 25% between weeks 25 and 33 and 74% versus 45% between weeks 34 and 38.

Complete response rates did not differ at week 12, 13% versus 12%, partial response 61% versus 67% and progressive disease 13% versus 12%. There was a significantly worse 3-year event-free survival with VM 19% versus 33% and overall survival 27% versus 55%, $p = 0.04$ and 0.01, respectively.

With regard to the outcome of patients who progressed during the window phase of the study two of seven who failed VM survived and two of six of IE survived. Outcome following relapse was worse after VM, $p = 0.03$.

Conclusion

The chemotherapy couplets were of comparable initial activity, however there was an adverse impact due to the influence of melphalan on hematopoietic stem cell function; this resulted in later (poor) intolerance to VA chemotherapy and consequent dose reduction. Possibly as a result of this the event-free and overall survival with VM was worse. The outcome after IE appears to be better than with VAC, however numbers are small and this would need to be tested prospectively.

Study 10

Donaldson S, Meza J, Breneman J, Crist W, Laurie F, Qualman S, Wharam M. Results from the IRS-IV randomized trial of hyperfractionated radiotherapy in children with rhabdomyosarcoma – a report from the IRSG. *Int J Radiation Oncology Biol Phys* 2001;**51**: 718–28.

Study carried out between 1991 and 1997 by the American Intergroup Rhabdomyosarcoma Study Group (IRS-IV).

Objectives

The aim of the study was:

- To compare the effectiveness and toxicity of hyperfractionation versus conventionally delivered radiation therapy in children with IRS Group III Rhabdomyosarcoma.

Details of the study

Eligibility included patients under the age of 22 years with a diagnosis of rhabdomyosarcoma or undifferentiated sarcoma. Extraosseous Ewing's sarcoma (EOS) were excluded as were sarcomas of brain, spinal cord or liver. All pathology were centrally reviewed as was documentation regarding group and stage. Group III tumor was defined as localized tumor with gross residual disease following incomplete resection or biopsy. Residual disease could be either primary tumor or nodal disease. Distant metastases were excluded. From early 1995 patients with renal problems who had initially been excluded from the study were included. Patients with localized vulval or vaginal tumors were not randomized but were given conventional radiotherapy electively.

Patients had to commence chemotherapy with 42 days of biopsy or 21 days of initial surgery. The randomization method and site were not stated.

Primary end point was event-free survival; 438 patients were to be randomized providing an 80% power, two-sided test, 5% significance to detect 77% versus 65% increase in failure-free survival. Secondary end point was the local relapse rate where the same numbers would have a 79% power to detect a reduction of 8% in local relapse rate from 16% to 8%.

Radiation field was planned on gross tumor volume prior to surgery and prior to chemotherapy with a 2-cm margin. Radiotherapy was commenced at week 9 except in emergencies or high-risk parameningeal primaries (those with direct extension) intracranially or bone erosion or nerve palsy. Conventional fractionated radiation therapy consists of dose of 50.4 Gy and 28 fractions compared with hyperfractionation dose of 59.4 Gy in 1.1 Gy doses twice a day with a 6-hour interval between doses. If there were treatment delays during radiation the doses were topped up after completion up to a total dose of 54 Gy for conventional therapy and up to 63.8 Gy

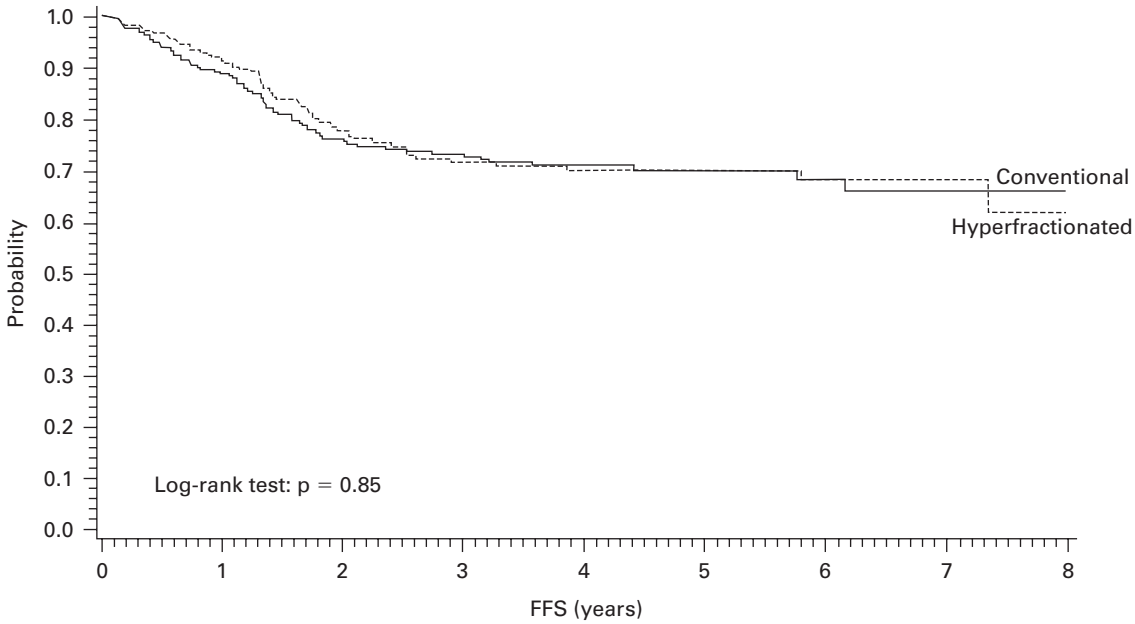

Figure 1.10 Failure-free survival for patients randomized to conventional fractionated or hyperfractionated radiation therapy. Reproduced from Donaldson *et al.* (full reference on p. 22) with permission from Elsevier.

for hyperfractionation. All radiation therapy planning and delivery details were centrally reviewed with regard to the fraction dose delivered, dose to primary site and dose to nodes.

Chemotherapy details are given in Study 11.

Outcome

Five hundred and fifty-nine patients entered IRS-IV, 12% were ineligible due to histology, surgery or other violations. Of the 490, 251 were randomized to conventional fraction radiation therapy and 239 to hyperfractionation.

There was a good balance with regard to risk factors for conventional versus hyperfractionated; T2 primary tumor, 66% versus 66%, alveolar 22% versus 20%, stage III 60% versus 60% and parameningeal 40% versus 46%.

Compliance with planned radiation therapy for hyperfractionation 76% and conventional 83%.

Fifty-four patients received no radiation therapy due to early progressive disease, 10 early deaths, 2 young age, 9 parental decision. Including 34 randomized to hyperfractionation who received conventional fractionation, event-free survival was identical in both arms. Event-free survival 70% and overall survival 75%. There were no differences in any subset or any chemotherapy regimen. When analyzed by actual rather than planned treatment the results were also identical (Figure 1.10).

Overall, local failure rate was 13%, regional 3%, distant 13% with no difference between the two arms.

Hyperfractionation was associated with a significantly higher instance of severe skin reaction 16% versus 7% ($p = 0.03$) and also a higher instance of nausea and vomiting 13% versus 5% ($p = 0.02$). Also the instance of mucositis during initial chemotherapy was higher in the hyperfractionated arm 66% versus 46% ($p = 0$).

Conclusion

Hyperfractionation was well tolerated but showed no advantage with regard to local control or overall outcome.

Study 11

Crist W, Anderson J, Meza J, Fryer C, Raney R, Ruymann F, Brenemen J, Qualman S, Wiener E, Wharam M, Lobe T, Webber B, Maurer H, Donaldson S. Intergroup Rhabdomyosarcoma Study-IV: results for patients with non-metastatic disease. *J Clin Oncol* 2001;**19**:3091–102.

Study carried out between 1991 and 1997 by the American Intergroup Rhabdomyosarcoma Study Group (IRS-IV).

Objectives

The aim was to find out whether:

- The addition of etoposide and ifosfamide to the basic VAC regimen would improve outcome.
- Increasing the radiation dose through hyperfractionation improves local control without increasing late sequelae.

Details of the study

Eligibility included patients less than 21 years of age with rhabdomyosarcoma or undifferentiated sarcoma. It excluded soft tissue Ewing's and primary sarcoma of central nervous system, spinal cord and liver. Chemotherapy was commenced within 42 days of biopsy and 21 days of resection. There was centralized review of all pathology and clinical details for staging and grouping and all surgical data. No details provided of randomization method or site.

No details of the numbers required or power of study.

All patients with IRS Groups I–III were randomized except those with Group I para-testicular tumors who received VA, those with Group I or II orbital tumors who received VA and in the first instance those with pre-existing renal disfunction were given VAC to avoid potential toxicity with ifosfamide. This was subsequently modified and such patients were included.

Patients with stages I and II who achieved surgical complete remission were not given radiation therapy, stage III Group I and all Group II received 41.4 Gy.

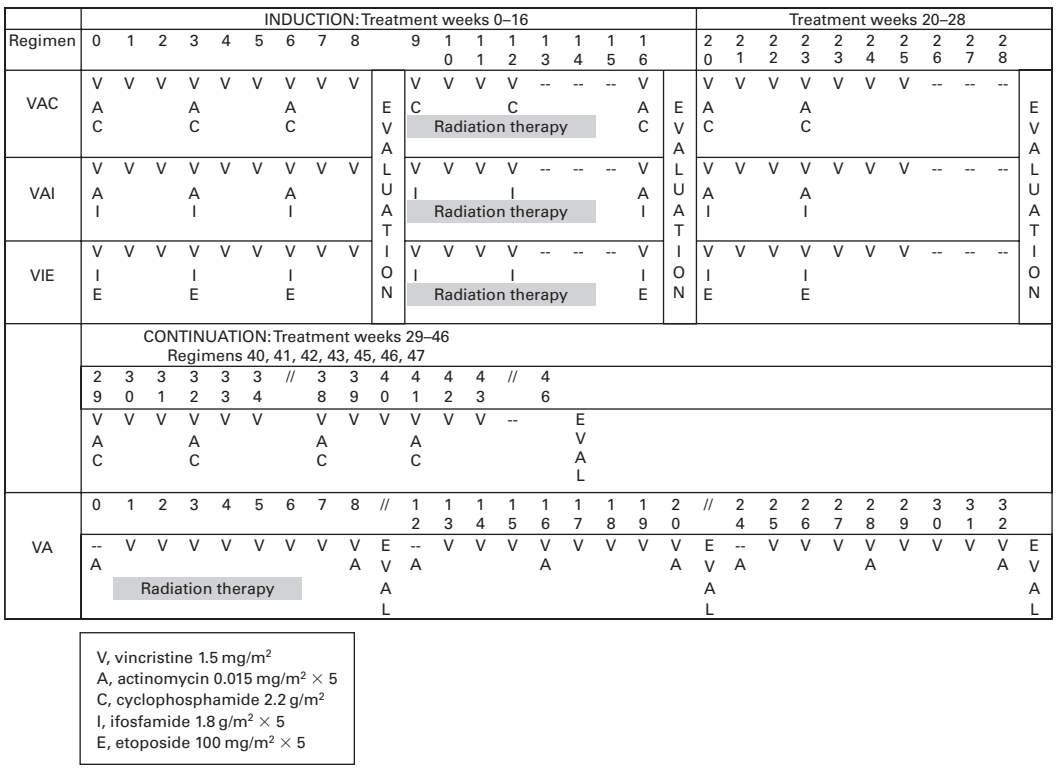

Figure 1.11 Chemotherapy details. © American Society of Clinical Oncology (full reference above).

All the others were randomized to receive 50.4 conventional versus 59.4 hyperfractionation (see Study 10).

The chemotherapy question compared vincristine, actinomycin D and cyclophosphamide (VAC) versus vincristine, actinomycin D and ifosfamide (VAI) versus vincristine, ifosfamide and etoposide (VIE) (Figure 1.11).

A total of 989 patients were enrolled, 106 were excluded, 56 on pathology review, 10 institutional pathology review and 13 due to metastases. Overall sites were extremity 13%, parameningeal 25%, genitourinary 31%, head and neck 7%, orbit 9%, 51% were over 5 cm in diameter and 15% lymph node positive. At pathology review the concordance for alveolar versus embryonal.

Clinical grouping showed good concordance: 96% Group I, 89% Group III and 98% Group III.

Parental directive 134 testicular or vulval primaries, 56 renal dysfunctions; 235 randomized VAC, 236 to VAE and 222 to VAI. With regard to the three arms there was a good balance of risk factors for VAC, VAE, VAI, respectively: age over 10 years 27%, 28% and 31%, alveolar 27%, 24% and 24%, greater than 5-cm tumor 50%, 64% and 51% and extremity tumor 16%, 16% and 17%.

There was no difference in significant toxicity between the chemotherapy arms.

There were ten second cancers and five leukemias. There were eight toxic deaths, six due to sepsis, three of those within initial renal dysfunction.

Outcome

Overall event-free survival in Group I was 89%, with a survival of 100%. In the randomized trial at 3.9 years median follow-up the 3-year failure-free survival for VAC, VAI and VIE, respectively, were 75%, 77% and 77% and survival 84%, 84% and 88%. No difference in any pathological or clinical subgroup. With regard to radiotherapy no significant difference was observed between conventional and hyperfractionation (see study).

Compared the outcome with IRS-III there was a significantly better outcome for patients with embryonal stage II or stage II or III Groups I and II with failure-free survival of 93% versus 76% ($p < 0.001$).

Conclusion

Ifosfamide was not superior to cyclophosphamide at the doses and schedule studied VAC chemotherapy remains the goal standard. Outcome in Groups I and II stages I and II was better than historical control due to increased intensity therapy. In Group I para-testicular tumors failure-free survival was 81% versus 95% in IRS-III; i.e. a worse outcome due to the absence of surgical staging, perhaps missing nodal involvement. As a consequence node sampling is now recommended for those over 10 years of age.