EVIDENCE BASED MANAGEMENT FOR
Ewing’s Sarcoma / PNET

A – Documentation of exact extent of primary tumor
Clinical examination, X-ray, MRI (MRI has become the premier imaging modality for the evaluation of musculoskeletal tumors because of its excellent soft tissue contrast, its sensitivity to bone marrow and soft tissue edema, and its multiple imaging planes).

B – Pathological confirmation of diagnosis by biopsy
A needle biopsy can often confirm the diagnosis. If tissue is inadequate or diagnosis uncertain an open biopsy is indicated. The closed needle biopsy technique has proven to be an extremely effective means of procuring representative tissue, is associated with low morbidity, and avoids many of the potential complications of biopsy. If limb-sparing surgery is contemplated, the biopsy should be performed by the surgeon who will do the definitive operation, since incision placement is crucial.

Traditionally a major distinction has been made between classical Ewing’s sarcoma (which shows minimal evidence of differentiation) and PNET (which shows evidence of neural differentiation). The degree of neural differentiation does not influence outcome.

C- Staging and biochemical investigations
CT chest, bone scan, bone marrow studies, Serum LDH.

Localized : For Ewing’s tumor of bone, the tumor is defined as localized when, by clinical and imaging techniques, it has not spread beyond the primary site or regional lymph nodes. There may be contiguous extension into adjacent soft tissue. Extraosseous Ewing’s has been grouped using the rhabdomyosarcoma staging system shown below:
- Group I : Completely excised.
- Group II : Microscopic residual.
- Group III : Gross residual.

Metastatic : These tumors have spread to distant sites, most commonly lung, bone, and/or bone marrow. Lymph node and, in particular, central nervous system metastases are less common. By other staging systems in common use, this is stage 4 or group IV.

D – Chemotherapy
Induction chemotherapy Ô Local control (Surgery and/ Radiotherapy)
- Maintenance chemotherapy is the usual sequence.

Chemotherapy is multiagent and drugs used include: Vincristine (given weekly), Ifosfamide, Etoposide, Cyclophosphamide, Adriamycin and Actinomycin-D.

After induction chemotherapy (generally between 9-12 weeks) patient is evaluated for local treatment.

E – Local control
Local control can be achieved by surgery and/or radiation. Surgery is generally the preferred approach if the lesion is resectable. (Level III, Grade A)
Adequate surgical margins significantly affect the outcome & hence whenever it is feasible wide/radical resection is indicated. (Level III, Grade A)

Radiation therapy should be employed for patients who do not have a surgical option that preserves function and should be used for patients whose tumors have been excised but with inadequate margins. (Level III, Grade A)

The radiation dose is adjusted depending upon the extent of residual disease after the initial surgical procedure. No radiation therapy is recommended for those who have no evidence of microscopic residual disease following surgical resection. (Level III, Grade B)

**Radiotherapy details**

1) Tailored portals for every patient
2) Entire Medullary cavity need not be included in the RT portal
3) Target volumes (GTV) mentioned are MRI based. Includes bone + soft tissue component.
4) Try and spare a strip of normal tissue for lymph drainage.
5) If disease involves non-infiltrating extension into pre-formed body cavities e.g. lung & pelvis, radiotherapy volume includes post induction volume with 2cm margin in order to reduce treatment related toxicity
6) 3D-CRT / IMRT wherever necessary

**A) Post Operative**

<table>
<thead>
<tr>
<th>Surgical Margins</th>
<th>Radiotherapy Dose If Necrosis 100%</th>
<th>Radiotherapy Dose If Necrosis &lt;100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>No Radiotherapy</td>
<td>45 GY</td>
</tr>
<tr>
<td>Marginal resection/Close</td>
<td>45 Gy</td>
<td>50 GY</td>
</tr>
<tr>
<td>Microscopic Positive (R1)</td>
<td>45 Gy</td>
<td>50 GY</td>
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</table>
Gross + Positive 50 Gy 50 GY (R2)

PTV:
   Phase I: Pre-chemotherapy volume + 2cm. margin
   Phase II: Post-surgery site of residual disease + 2cm. margin

TOTAL DOSE
   Phase I: 45Gy / 25# / 5wks (@1.8Gy / fr.)
   Phase II: 1) If R0:
      <100% necrosis – no further boosts
   2) If Marginal resection/ close margins:
      100% necrosis – no further boost
      <100% necrosis – 5.4Gy / 3# / 0.5wk (@1.8Gy / fr.)
   3) If R1:
      100% necrosis – no further boost
      <100% necrosis – 5.4Gy / 3# / 0.5wk (@1.8Gy / fr.)
   4) If R2:
      100% necrosis – 5.4Gy / 3# / 0.5wk (@1.8Gy / fr.)
      <100% necrosis – 10.8Gy / 6# / 1 wk (@1.8Gy / fr.)

B) Borderline Resectable (As evaluated by multidisciplinary Joint Clinic)
   All patients to receive radical RT doses
   Patients to be evaluated for surgery at 6th week after completion of RT

PTV:
   Phase I: Pre-chemotherapy volume + 3cm. margin
   Phase II: Post-chemotherapy volume + 2cm. margin
   (There is no field reduction for bony component).

TOTAL DOSE:
   Phase I: 45Gy / 25# / 5wks (@1.8Gy / fr.)
   Phase II: 1) If complete response after induction
      No further boost
   2) If >50% regression after induction
      10.8Gy / 6# / 1wk (@1.8Gy / fr.)
   3) If <50% regression after induction
      14.4Gy / 8# /1.5wks (@1.8Gy / fr.)

C) Unresectable
   Same as borderline resectable lesions

D) Hyperfractionation
   Unresectable lesions of the extremity. Although there is no evidence of significant
   improvement in disease free & overall survival, there is evidence to show that it is
   possible to do concurrent Chemo + RT using hyperfractionated RT with equivalent or
   marginally superior local control.

PTV:
   Phase I: Pre-chemotherapy volume + 3cm. margin
Phase II: Post-chemotherapy volume + 2cm. margin  
(There is no field reduction for bony component).

**TOTAL DOSE:**
- Phase I: 45.6 Gy / 38# / 4wks (@1.2 Gy/ fr. X 2 # / day)
- Phase II: 20.4 Gy / 17# / 1.5wks (@1.2 Gy/ fr. X 2 # / day)
- 24.0 Gy / 20 # / 2wks (@1.2 Gy/ fr. X 2 # / day)
- Total Dose: 66 Gy / 55# / 5.5wks (@1.2 Gy/ fr. X 2 # / day)
- 69.6Gy / 37# / 7wks (@1.2 Gy/ fr. X 2 # / day)

**E) Lung Bath** (Whole Lung Irradiation)

All patients with metastatic disease to the lungs at presentation receive whole lung irradiation ("Lung Bath"), even if complete remission of pulmonary metastatic disease has been achieved after chemotherapy.

Rt Target Volume: Bilateral Lung  
No Cardiac Shield  
Shield Bilateral Shoulder

Dose: 12.6Gy/ 7#/ 1week

**F – Histopathology report and its importance**

The specimen is evaluated for margins of surgical resection. Response to chemotherapy is noted based on percentage necrosis of tumor cells. This is an important prognostic factor. (Level III, Grade A)

The radiation dose is adjusted depending upon the percentage necrosis of tumor and margins of resection. (Level III, Grade B)

Grading of response in Ewing’s sarcoma is based on percentage of viable tumor.

Grade I: Tumor specimen contains at least one macroscopic nodule of viable tumor mass which is larger than one 10 X magnification field.

Grade II – Isolated small nodules of tumor are found, the total area of these nodules not exceeding 10 X field.

Grade III – No viable tumor nodules are identified within the surgical specimen.

An ideal pathology report should include
- Type of specimen received with entire gross description
- A numerical list of the various sections submitted for histological examination
- Histological diagnosis with grade of tumor where applicable
- The exact anatomical location of the soft tissue or bone tumor
- The extent of the tumor with respect to the various cut margins and also with respect to skin and bone including involvement of cortex, periosteum, muscle, subcutaneous fat, joint capsule and articular cartilage
- Evidence of angiolymphatic invasion, perineural invasion, lymph node invasion
- Status of cut margins of bone, skin, soft tissue, neurovascular cut margins
- Comments on response to chemotherapy with percentage of necrosis

**G – Follow up schedule**
Patient is followed up at 3 monthly interval for the first 2 years, 6 monthly intervals for next 3 years and annually thereafter.

At every follow up, an X ray of the local part & chest radiograph is done. A CT scan of the chest and a bone scan is done at 6 monthly intervals for the first 2 years and annually for the next 3 years.

(Currently there is inadequate evidence to suggest that intensive follow up with early detection of recurrent disease would significantly impact on survival).

**Ewing’s Sarcoma - Investigations**

**Neuroectodermal differentiation in Ewing's sarcoma family of tumors does not predict tumor behavior.**
Parham DM, Hijazi Y, Steinberg SM et al.

Abstract: The observation that neuroectodermal differentiation imparts a worse prognosis to the Ewing family of tumors has been suggested by some studies and refuted by others. To assess whether the diagnosis of Ewing’s sarcoma versus peripheral primitive neuroectodermal tumor (PNET) affects prognosis, we analyzed tumors from 63 analogously treated pediatric and young adult patients from the National Cancer Institute and St Jude Children’s Research Hospital and retrospectively compared the results with clinical outcomes. The tumors were assessed using standard light microscopy and immunohistochemical stains for neuron-specific enolase, CD57, S100 protein, neurofilament protein, and synaptophysin with or without antigen retrieval. Ultrastructural evaluation was also performed in 39 tumors. Classification was performed using Kiel criteria as well as a modified classification. Kaplan-Meier analyses, with Mantel-Haenzel evaluation of the significance of the differences, were performed separately for localized or metastatic tumors. Using the Kiel classification on a subset of 60 cases, 39 tumors qualified as PNET and 21 as Ewing’s sarcoma. Using the modified classification on a subset of 61 cases, 14 were classified as PNET, 21 as atypical Ewing’s sarcoma, and 26 as Ewing’s sarcoma. The addition of electron microscopy to the diagnostic armamentarium significantly increased the likelihood of identifying PNET. No significant differences in event-free or overall survival were seen using either the modified or Kiel classification, regardless of the ancillary diagnostic techniques employed. In this exploratory analysis, **neuroectodermal differentiation did not play a role in clinical outcome**. Confirmation of this finding will require a larger, separate study of similarly treated patients, and it may not apply to older patients.

**SERUM LDH IN EWING’S SARCOMA OF BONE - A PROGNOSTIC INDICATOR**

**Prognostic significance of serum LDH in Ewing’s sarcoma of bone.**
Bacci G, Ferrari S, Longhi A et al.

Abstract: The pretreatment serum lactic dehydrogenase (SLDH) levels of 618 patients with Ewing’s sarcoma of the extremities (136 metastatic at presentation and 482 localized) were analyzed to evaluate whether the enzyme level had a clinical value in predicting the course of the disease. The percentage of patients with increased SLDH
was significantly higher in the metastatic group than in the group of patients with localized disease (68% vs 32%; P<0.0001). In the latter group treated with neoadjuvant chemotherapy the 5-year disease-free survival rate was significantly higher in patients with normal pretreatment SLDH than in those with high levels (65% vs 41%; P<0.0001). The time to relapse was significantly shorter for patients with elevated SLDH than in patients with normal values of the enzyme. The site of the tumor was significantly related with the stage of the disease, and for patients with localized disease, with the disease survival rate, at the multivariate analyses site of the tumor and SLDH levels were independently related with the stage of disease and with prognosis. These data demonstrate that in Ewing’s sarcoma of bone pretreatment SLDH have a prognostic value and should be considered in the comparison of the results achieved with different therapies and in planning new randomized clinical therapeutic trials.

**Efficacy of MRI as a Diagnostic and Staging Modality**

*Radiographic imaging of musculoskeletal neoplasia.*

Sanders TG, Parsons TW 3rd.,


BACKGROUND: Imaging is an integral part of the diagnosis, staging and evaluation of outcomes for bone and soft-tissue neoplasms. Each of the available imaging tools has a different role. METHODS: The authors reviewed the efficacy of the current imaging modalities in the diagnosis, staging, and follow-up of patients with musculoskeletal neoplasia. RESULTS: Plain-film radiography remains the gold standard in the differential diagnosis of bone lesions. Bone scintigraphy is an excellent screening modality, and computed tomography is especially useful in evaluating lesions of the axial skeleton. The superior soft-tissue resolution and multiplanar capabilities achieved with magnetic resonance imaging, however, has replaced the need for CT scans in many cases. CONCLUSIONS: The technological advances seen in recent years in all areas of imaging have improved the capabilities of these modalities to assist in the diagnosis, definition of tumor extent, and accurate staging of musculoskeletal tumors.

**Addition of ifosfamide and etoposide to standard chemotherapy for Ewing’s sarcoma and primitive neuroectodermal tumor of bone.**

Grier HE, Krailo MD, Tarbell NJ et al.


BACKGROUND: Ewing’s sarcoma and primitive neuroectodermal tumor of bone are closely related, highly malignant tumors of children, adolescents, and young adults. A new drug combination, ifosfamide and etoposide, was highly effective in patients with Ewing’s sarcoma or primitive neuroectodermal tumor of bone who had a relapse after standard therapy. We designed a study to test whether the addition of these drugs to a standard regimen would improve the survival of patients with newly diagnosed disease. METHODS: Patients 30 years old or younger with Ewing’s sarcoma, primitive neuroectodermal tumor of bone, or primitive sarcoma of bone were eligible. The patients were randomly assigned to receive 49 weeks of standard chemotherapy with doxorubicin, vincristine, cyclophosphamide, and dactinomycin or experimental therapy with these four drugs alternating with courses of ifosfamide and etoposide. RESULTS: A total of 518 patients met the eligibility requirements. Of 120 patients with metastatic
disease, 62 were randomly assigned to the standard-therapy group and 58 to the experimental-therapy group. There was no significant difference in five-year event-free survival between the treatment groups (P=0.81). Among the 398 patients with nonmetastatic disease, the mean (+/-SE) five-year event-free survival among the 198 patients in the experimental-therapy group was 69+/-3 percent, as compared with 54+/-4 percent among the 200 patients in the standard-therapy group (P=0.005). Overall survival was also significantly better among patients in the experimental-therapy group (72+/-3.4 percent vs. 61+/-3.6 percent in the standard-therapy group, P=0.01). CONCLUSIONS: The addition of ifosfamide and etoposide to a standard regimen does not affect the outcome for patients with metastatic disease, but it significantly improves the outcome for patients with nonmetastatic Ewing’s sarcoma, primitive neuroectodermal tumor of bone, or primitive sarcoma of bone.

Italian Cooperative Study for the treatment of children and young adults with localized Ewing sarcoma of bone: a preliminary report of 6 years of experience.
Rosito P, Mancini AF, Rondelli R et al.

BACKGROUND: In 1991, the Italian Association for Pediatric Hematology-Oncology and the National Council of Research (CNR) initiated an Italian Cooperative Study (SE 91-CNR Protocol) with the main objective of improving the overall survival (SUR) and the event free survival (EFS) of children and young adults with localized Ewing sarcoma and primitive neuroectodermal tumors of bone compared with a previous study (IOR/Ew2 Protocol). METHODS: Between November 1991 and November 1997, 165 patients were enrolled in this study, 160 of whom were evaluable. The patients were treated with a multimodal approach characterized by intensified chemotherapy, hyperfractionated and accelerated radiation therapy, and the addition of ifosfamide and etoposide to standard chemotherapy with vincristine, actinomycin-D, doxorubicin, and cyclophosphamide. RESULTS: After a median follow-up of 37 months, 126 of the 160 evaluable patients remained free of disease recurrence. Thirty-one patients developed a disease recurrence (20 with disseminated disease). CONCLUSIONS: The 3-year SUR and EFS rates found in the current study (83.6% and 77.8%, respectively) may be considered satisfactory. Only age at diagnosis < or =14 years and a good histologic response appeared to affect the outcome of patients with localized Ewing sarcoma positively. These results appear to demonstrate the efficacy of the addition of ifosfamide in induction chemotherapy to four-drug standard combination chemotherapy, as confirmed by the improved outcome in terms of 3-year EFS reported in the SE 91-CNR Protocol compared with the IOR/Ew2 Protocol (77.8% vs. 60.7%). In addition, the better outcome also could be explained by the change in treatment strategy with a trend toward the use of more surgery than radiation therapy compared with the authors’ previous protocol.

Ewing’s Sarcoma - Surgery

IMPROVED RESULTS WITH SURGERY AND IMPORTANCE OF MARGINS

Role of surgery in local treatment of Ewing’s sarcoma of the extremities in patients undergoing adjuvant and neoadjuvant chemotherapy
Bacci G, Ferrari S, Longhi A et al.
Abstract: Although more and more patients with Ewing’s sarcoma of bone (ESB) are being treated by surgery, the relative role of surgery and radiotherapy in the local treatment of this tumor has yet to be determined. Because the outcome of ESB may differ according to the anatomical site of the tumor, results reported in the literature, which generally refer to series with tumors located in all sites, may be selection biased. Therefore, we have retrospectively evaluated patients with ESB exclusively in the extremity and locally treated by surgery or radiotherapy. Two hundred and sixty-eight patients treated at Rizzoli 1979-1996 for non-metastatic ES of the extremities were assessed. Chemotherapy was administered according to four sequentially activated protocols. One hundred and thirty-six patients were treated by surgery, 70 by surgery and radiotherapy, and 60 patients by radiotherapy. Two patients underwent only chemotherapy. The follow-up range was 5-23 years (mean 13 years). One hundred and fifty-two patients remained continuously free of disease, 108 relapsed, 2 died of chemotherapy toxicity and 6 developed a second malignancy. The 5-year event-free survival (EFS) and overall survival (OS) were respectively 62 and 69%. Although patients of all groups were matched for possible risk factors, the rates of 5-year EFS and local control were significantly lower in patients treated with radiotherapy compared to patients treated by surgery or surgery and radiotherapy (48% vs 66%, p=0.002; 80% vs 94%, p=0.0001). Furthermore, in group 3 there were 6 secondary malignancies. Our results indicate that surgery should always be considered in the local treatment of ES of the extremities. Postoperative radiation therapy must be added in case of inadequate surgical margins.

Local therapy in localized Ewing tumors: results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials.
Schuck A, Ahrens S, Paulussen M et al.

PURPOSE: The impact of different local therapy approaches on local control, event-free survival, and secondary malignancies in the CESS 81, CESS 86, and EICESS 92 trials was investigated. METHODS AND MATERIALS: The data of 1058 patients with localized Ewing tumors were analyzed. Wherever feasible, a surgical local therapy approach was used. In patients with a poor histologic response or with intralesional and marginal resections, this was to be followed by radiotherapy (RT). In EICESS 92, preoperative RT was introduced for patients with expected close resection margins. Definitive RT was used in cases in which surgical resection seemed impossible. In CESS 81, vincristine, adriamycin, cyclophosphamide, and actinomycin D was used. In CESS 86, vincristine, adriamycin, ifosfamide, and actinomycin D was introduced for patients with central tumors or primaries >100 cm(3). In CESS 92, etoposide, vincristine, adriamycin, ifosfamide, and actinomycin D was randomized against vincristine, adriamycin, ifosfamide, and actinomycin D in patients with primaries >100 cm(3). RESULTS: The rate of local failure was 7.5% after surgery with or without postoperative RT, and was 5.3% after preoperative and 26.3% after definitive RT (p=0.001). Event-free survival was reduced after definitive RT (p=0.0001). Irradiated patients represented a negatively selected population with unfavorable tumor sites. Definitive RT showed comparable local control to that of postoperative RT after intralesional resections. Patients with postoperative RT had improved local control after intralesional resections and in tumors with wide resection and poor histologic response compared with patients receiving surgery alone. Patients with marginal resections with or without postoperative radiotherapy showed comparable local control, yet the number of patients with good histologic response was higher in the latter treatment group (72.2% vs. 38.5%).
CONCLUSION: Patients with resectable tumors after initial chemotherapy had a low local failure rate. With preoperative RT, local control was comparable. RT is indicated to avoid intralesional resections. After intralesional or marginal resections and after a poor histologic response and wide resection, postoperative RT may improve local control.

Local and systemic control in Ewing’s sarcoma of the femur treated with chemotherapy, and locally by radiotherapy and/or surgery.
Bacci G, Ferrari S, Longhi A et al.

Abstract: The role of radiotherapy and/or surgery in the local treatment of Ewing’s sarcoma has still to be determined. The outcome of Ewing’s sarcoma may differ according to its location and a selection bias towards surgery limits the ability to compare methods of local treatment. We have carried out a retrospective review of 91 consecutive patients treated for non-metastatic Ewing’s sarcoma of the femur. They received chemotherapy according to four different protocols. The primary lesion was treated by surgery alone (54 patients), surgery and radiotherapy (13) and radiotherapy alone (23). One was treated by chemotherapy alone. At a median follow-up of ten years, 48 patients (53%) remain free from disease, 39 (43%) have relapsed, two (2%) have died from chemotherapeutic toxicity and two (2%) have developed a radio-induced second tumour. The probability of survival without local recurrence was significantly (p=0.01) higher in patients who were treated by surgery with or without radiotherapy (88%) than for patients who received radiotherapy alone (59%). The five- and ten-year overall survival rates were 64% and 57%, respectively. Patients who were treated by surgery, with or without radiotherapy, had a five- and ten-year overall survival of 64%. Patients who received only radiotherapy had a five and ten-year survival of 57% and 44%, respectively. Our results indicate that in patients with Ewing’s sarcoma of the femur, better local control is achieved by surgical treatment (with or without radiotherapy) compared with the use of radiotherapy alone. Further studies are needed to verify the impact of this strategy on overall survival.

Role of Surgery and Resection Margins in the Treatment of Ewing’s Sarcoma.
Maria Sluga, Reinhard Windhager, Susanna Lang et al.

Because of the enormous progress in surgery in the treatment of patients with tumors, the current study analyzed the influence of wide surgical resection margins on the outcome of patients with Ewing’s sarcoma. Between 1980 and 1994, 86 patients were treated with systemic therapy and surgery (biopsy in six patients, tumor resection in 80 patients). Forty-four patients also had radiation therapy. The 5-year overall survival was 56.8% (5-year disease-free survival, 59.4%). The 5-year overall survival after radical or wide resection was 60.2% (5-year disease-free survival, 58.2%), in comparison with 40.1% (46.7%) after marginal or intralesional resection. Two patients with inadequate resection margins had local recurrences. In addition to the influence of neoadjuvant chemotherapy for higher survival rates (5-year overall survival with a good response was 80.2% versus 41.7% with a poor response), adequate surgical margins significantly affect the outcome for patients with Ewing’s sarcoma.

Significance of surgical margin on the prognosis of patients with Ewing’s sarcoma. A report from the Cooperative Ewing’s Sarcoma Study.

BACKGROUND : There is little information regarding an adequate surgical margin for local control of Ewing's sarcoma. METHODS : Two hundred and forty-four patients (PTS) with Ewing's sarcoma who were registered in the Cooperative Ewing's Sarcoma Studies underwent surgical treatment. Ninety-four PTS underwent definitive surgery (surgery alone), 131 PTS received postoperative irradiation, and 19 PTS received preoperative irradiation. The surgical margins were distributed as follows: radical, 29 PTS; wide, 148 PTS; marginal, 39 PTS; and intralesional, 28 PTS. The impact of the surgical margin on the treatment outcome of PTS was analyzed statistically. RESULTS : The local or combined (local recurrence and systemic metastasis) relapse rate after surgery with or without irradiation was significantly lower compared with that after definitive irradiation (irradiation alone) (7% vs. 31%, P<0.0001). The local or combined relapse rate after complete resection (radical or wide margin) with or without irradiation was less compared with that after incomplete resection (marginal or intralesional margin) with or without irradiation (5% vs. 12% P=0.0455). The local or combined relapse rate did not greatly decreased after irradiation after incomplete surgery (from 14% to 12%). In both groups of good (viable tumor cells < 10%) and poor (viable cells > or = 10%) histologic response, the difference in systemic or combined relapse rate between patients undergoing complete and incomplete surgery was not significant. The 10-year overall survival of the PTS for each of the margins was distributed as follows: radical, 58%; wide, 65%; marginal, 61%; and intralesional, 71% (P = not significant). CONCLUSIONS : Surgery in patients with Ewing’s sarcoma adds to the safety of local control. Under the current treatment regimen with intensive chemotherapy and irradiation, complete resection of the tumor appears capable of decreasing the risk of local recurrence.

HISTOPATHOLOGY RESPONSE TO CHEMOTHERAPY – A PROGNOSTIC INDICATOR
The histological response to chemotherapy as a predictor of the oncological outcome of operative treatment of Ewing sarcoma.

Abstract : Seventy-four patients who had a Ewing sarcoma of bone were managed with preoperative and postoperative chemotherapy and operative resection, with or without postoperative irradiation. The primary objectives of the study were to determine the histological response to preoperative chemotherapy in terms of the percentage of tumor necrosis and to assess the relationship between the histological response and the oncological outcome. The minimum duration of follow-up of the surviving patients who were continuously free of disease was five years. Sections of each operative specimen were examined, and the histological response to chemotherapy was graded semiquantitatively. Grade I indicated necrosis of 50 per cent of the tumor or less; grade II, necrosis of more than 50 per cent but less than 90 per cent; grade III, necrosis of 90 to 99 per cent; and grade IV, necrosis of 100 per cent of the tumor. Of the seventy-four tumors, forty-four (59 per cent) were exquisitely sensitive to chemotherapy and had complete (grade-IV) or nearly complete (grade-III) necrosis. In contrast, fourteen tumors (19 per cent) had little or no response to chemotherapy (grade I) and sixteen (22 per cent) had a moderate degree of necrosis (grade II). The histological response to preoperative chemotherapy (p=0.0001), followed by the size of the tumor (p=0.001), were the most important predictors of event-free
survival. At five years, the rate of event-free survival was zero of fourteen patients who had had a grade-I response, six of sixteen who had had a grade-II response, and thirty-seven (84 per cent) of forty-four who had had a grade-III or IV response. The risk of local recurrence was most strongly associated with the operative margins; there were only four local recurrences (6 per cent) after sixty-seven resections with negative margins. Local recurrence may also have been influenced by the histological response and the use of local radiation. There were no local recurrences after operative treatment of six tumors that had been associated with pathological fracture. The histological response to preoperative chemotherapy and the size of the primary tumor are the most important clinical predictors of the outcome of operative treatment of non-metastatic Ewing sarcoma. These indicators should be used to identify patients who are at high risk for metastasis as such patients may be candidates for more intensive or novel therapies.

Predictive factors of histological response to primary chemotherapy in Ewing’s sarcoma.
Bacci G, Picci P, Mercuri M et al.

Abstract : Clinicopathologic variables associated with a good histological response to primary chemotherapy in Ewing’s sarcoma are identified. The histological response to preoperative chemotherapy in 243 cases of Ewing’s sarcoma treated with neoadjuvant chemotherapy was analyzed in relation to different clinicopathological features (sex and age of the patients, tumor size, serum lactate dehydrogenase (LDH) levels, tumor site) and to the type and schedule of anticancer drugs delivered preoperatively according to three consecutive chemotherapy regimens. A higher rate of good responses was achieved with the use of ifosfamide and dactinomycin in addition to a conventional three-drug VAC regimen, suggesting that these drugs should be included from the beginning in neoadjuvant regimens for the treatment of Ewing’s sarcoma. The analysis of event-free survival in 158 patients with a 4-year minimum follow-up confirmed that histological response to preoperative chemotherapy is a reliable predictor of outcome in Ewing’s sarcoma.

Ewing’s Sarcoma - Radiotherapy

RADIOTHERAPY TARGET VOLUME

A multidisciplinary study investigating radiotherapy in Ewing’s sarcoma: end results of POG #8346. Pediatric Oncology Group.
Donaldson SS, Torrey M, Link MP et al.

PURPOSE : To determine if involved field radiation (IF) is equivalent to standard whole bone radiation (SF) in local tumor control; to establish patterns of failure following treatment; and to determine response, event-free survival (EFS), and overall survival rates from multidisciplinary therapy in Ewing’s sarcoma. METHODS AND MATERIALS : Between 1983 and 1988, 184 children with Ewing’s sarcoma were enrolled onto Pediatric Oncology Group 8346 (POG 8346). A total of 178 (97%) met eligibility criteria; 6 had pathology other than Ewing’s sarcoma. Induction chemotherapy of cyclophosphamide/doxorubicin (adriamycin) (C/A) x 12 weeks was followed by local treatment either surgery or radiation therapy and C/A, dactinomycin, and vincristine for
50 weeks. Resection was advised for patients with small primary tumors if accomplished without functional loss. Forty patients were randomized to receive SF, whole bone radiation to 39.6 Gy plus a 16.2 Gy boost (total 55.8 Gy) or IF to 55.8 Gy, and the remainder were assigned to IF radiation. RESULTS: Of 178 eligible patients, 141 (79%) had localized disease and 37 (21%) had metastases at presentation. Their 5-year EFS was 51% (SE 5%) and 23% (SE 7%) respectively. The response rate to induction chemotherapy was 88% (28% complete, 60% partial), but after radiotherapy the response rate increased to 98%. Thirty-seven of the localized patients underwent resection, of whom 16 (43%) required postoperative radiotherapy; the 5-year EFS of these surgical patients was 80% (SE 7%). The remaining 104 localized patients were eligible for randomization or assignment to receive radiotherapy; the 5-year EFS of these patients was 41% (SE 5%), with no significant difference in EFS between those randomized to SF vs. IF. Site of primary tumor correlated with 5-year EFS: distal extremity 65% (SE 8%), central 63% (SE 10%), proximal extremity 46% (SE 8%), and pelvic-sacral 24% (SE 10%) (p=0.004). Initial tumor size did not correlate significantly with EFS. Patterns of failure among the 141 localized patients revealed 23% of patients experienced a local failure, while 40% had a systemic failure. The 5-year local control rate for the surgical patients +/- postoperative radiotherapy was 88% (SE 6%), while for the patients undergoing radiotherapy alone it was 65% (SE 7%). There was no difference in local control between those randomized to SF vs. IF. The 5-year local control rate for the patients with pelvic-sacral tumors was 44% (SE 15%), significantly worse than the local control rates for those with central tumors 82% (SE 8%), distal extremity 80% (SE 8%), or proximal extremity 69% (SE 9%) (p=0.023). However, quality of radiotherapy correlated with outcome. Patients who had appropriate radiotherapy had a 5-year local control of 80% (SE 7%), while those with minor deviations had 5-year local control of 48% (SE 14%), and those with major deviations had a local control of only 16% (SE 15%) (p=0.005). The local failure was within an irradiated volume in 62% of patients, outside the irradiated volume in 24% of cases, while the precise location could not be determined in the remaining 14%. CONCLUSIONS: As most failures in Ewing’s sarcoma are systemic, improved EFS requires more effective systemic chemotherapy. Adequate IF radiotherapy requires treatment to appropriate volumes as defined by MRI imaging and full radiation doses. Pretreatment review of radiologic images with a musculoskeletal radiologist to determine appropriate tumor volumes, as well as use of conformal radiotherapy techniques are important for improved outcome.

Ewing’s sarcoma: local tumor control and patterns of failure following limited-volume radiation therapy.

Arai Y, Kun LE, Brooks MT et al.

Abstract: Sixty children with localized osseous Ewing’s sarcoma were treated between 1978 and 1988 with induction chemotherapy (cyclophosphamide, Adriamycin), irradiation and/or surgery, and 10 months of maintenance chemotherapy (cyclophosphamide, Adriamycin, Dactinomycin, Vincristine). Following induction chemotherapy, 43 patients received primary radiation therapy to limited radiation volumes defined by post-chemotherapy residual soft tissue tumor extension and initial osseous tumor extent. Irradiation was defined as low dose at 30-36 Gy (median 35 Gy) for 31 cases with objective response to induction chemotherapy and high dose at 50-60 Gy (median 50.4 Gy) for 12 patients with poor response to induction chemotherapy or with tumors greater than or equal to 8 cm. Overall event-free survival at 5 years is 59% and local tumor control is 68%. Initial failures have been local (12), simultaneous
local and distant failures (7), and distant (6). In the surgical resection group, 14 patients had complete resection without radiation therapy, and 3 patients had microscopic residual plus 35-41 Gy; 100% local control has been maintained. In 43 patients with primary radiation therapy group, local tumor control is 58% (p=.004). Despite limited radiation volume, 18/19 local failures occurred centrally within the bone, well within the radiation volume. Imaging response to induction chemotherapy predicted local tumor control in the radiation therapy group: 62% with complete response/partial response versus 17% with no response/progressive disease (p less than 0.01). Local tumor control related strongly to primary tumor size in the radiation therapy group; among 31 cases receiving 35 Gy, local tumor control is 90% for lesions less than 8 cm versus 52% for tumors greater than or equal to 8 cm (p=.054). The central pattern of local failure in this experience suggests the effectiveness of limited radiation volume. The overall local tumor control rate following the tested dose level of 35 Gy appears to be inadequate, although results in selected cases with tumors less than 8 cm in greatest tumor dimension indicate potential efficacy in a yet limited experience.

Radiation therapy in Ewing’s sarcoma: an update of the CESS 86 trial.
Dunst J, Jurgens H, Sauer R et al.

PURPOSE : We present an update analysis of the multiinstitutional Ewing’s sarcoma study CESS 86. METHODS AND MATERIALS: From January 1986 through June 1991, 177 patients with localized Ewing’s sarcoma of bone, aged 25 years or less, were recruited. Chemotherapy consisted of four 9-week courses of vincristine, actinomycin D, cyclophosphamide, and Adriamycin (VACA) in low-risk (extremity tumors < 100 cm³), or vincristine, actinomycin D, ifosfamide, and Adriamycin (VAIA) in high-risk tumors (central tumors and extremity tumors > or = 100 cm³). Local therapy was an individual decision in each patient and was either radical surgery (amputation, wide resection) or resection plus postoperative irradiation with 45 Gy or definitive radiotherapy with 60 Gy (45 Gy plus boost). Irradiated patients were randomized concerning the type of fractionation in either conventional fractionation (once daily 1.8-2.0 Gy, break of chemotherapy) or hyperfractionated split-course irradiation simultaneously with the VACA/VAIA chemotherapy (twice daily 1.6 Gy, break of 12 days after 22.4 Gy and 44.8 Gy, total dose and treatment time as for conventional fractionation). For quality assurance in radiotherapy, a central treatment planning program was part of the protocol. RESULTS : Forty-four patients (25%) received definitive radiotherapy; 39 (22%) had surgery, and 93 (53%) had resection plus postoperative irradiation. The overall 5-year survival was 69%. Thirty-one percent of the patients relapsed, 30% after radiotherapy, 26% after radical surgery, and 34% after combined local treatment. The better local control after radical surgery (100%) and resection plus radiotherapy (95%) as compared to definitive radiotherapy (86%) was not associated with an improvement in relapse-free or overall survival because of a higher frequency of distant metastases after surgery (26% vs. 29% vs. 16%). In irradiated patients, hyperfractionated split-course irradiation and conventional fractionation yielded the same results (5-year overall survival of definitively irradiated patients 63% after conventional fractionation and 65% after hyperfractionation; relapse-free survival 53% vs. 58%; local control 76% vs. 86%, not significant). The six local failures after radiotherapy did not correlate with tumor size or response to chemotherapy. Radiation treatment quality (target volume, technique, dosage) was evaluated retrospectively and was scored as unacceptable in only 1 out of 44 patients (2%) with definitive radiotherapy. Grade 3-4 complications developed in 4 out of 44 (9%) patients after definitive radiotherapy.
CONCLUSIONS: Under the given selection criteria for local therapy, radiation therapy yielded relapse-free and overall survival figures comparable to radical surgery. Hyperfractionated split-course irradiation simultaneously with multidrug chemotherapy did not significantly improve local control or survival.

INDICATIONS & DOSE MODULATION FOR POST OPERATIVE RADIOTHERAPY

Prognostic Factors in Localized Ewing’s tumours and peripheral neuroectodermal tumours: the third study of the French Society of Paediatric Oncology (EW88 study).

PURPOSE: (1) To improve survival rates in patients with Ewing’s sarcoma (ES) or peripheral neuroectodermal tumours (PNET) using semi-continuous chemotherapy and aiming to perform surgery in all; (2) To identify early prognostic factors to tailor therapy for future studies. PATIENTS AND METHODS: One hundred and forty-one patients were entered onto the trial between January 1988 and December 1991. Induction therapy consisted of five courses of Cytoxan, 150 mg/m² x 7 days, followed by Doxorubicin, 35 mg/m² i.v on day 8 given at short intervals. Surgery was recommended whenever possible. The delivery of radiation therapy was based on the quality of resection and the histological response to CT. Maintenance chemotherapy consisted of vincristine + actinomycin and cytoxan + doxorubicin. The total duration of therapy was 10 months. RESULTS: After a median follow-up of 8.5 years, the projected overall survival at 5 years was 66% and disease-free survival (DFS) was 58%. In patients treated by surgery, only the histological response to CT had an influence on survival: 75% DFS for patients with a good histological response (less than 5% of cells), 48% for intermediate responders and only 20% for poor responders (> or = 30% of cells), P < 0.0001. The initial tumor volume by itself had no influence on DFS in these patients. In contrast, the tumour volume had a strong impact on DFS in patients treated by radiation therapy alone. Age had no impact on outcome. CONCLUSION: Therapeutic trials for localized Ewing’s sarcoma should be based on the histological response to chemotherapy or on the tumour volume according to the modality used for local therapy.

Local therapy in localized Ewing tumors: results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials.
Schuck A, Ahrens S, Paulussen M et al.

PURPOSE: The impact of different local therapy approaches on local control, event-free survival, and secondary malignancies in the CESS 81, CESS 86, and EICESS 92 trials was investigated. METHODS AND MATERIALS: The data of 1058 patients with localized Ewing tumors were analyzed. Wherever feasible, a surgical local therapy approach was used. In patients with a poor histologic response or with intralesional and marginal resections, this was to be followed by radiotherapy (RT). In EICESS 92, preoperative RT was introduced for patients with expected close resection margins. Definitive RT was used in cases in which surgical resection seemed impossible. In CESS 81, vincristine, adriamycin, cyclophosphamide, and actinomycin D was used. In CESS 86, vincristine, adriamycin, ifosfamide, and actinomycin D was introduced for patients with central tumors or primaries >100 cm³. In CESS 92, etoposide, vincristine, adriamycin, ifosfamide, and actinomycin D was randomized against vincristine, adriamycin,
ifosfamide, and actinomycin D in patients with primaries >100 cm(3). RESULTS: The rate of local failure was 7.5% after surgery with or without postoperative RT, and was 5.3% after preoperative and 26.3% after definitive RT (p=0.001). Event-free survival was reduced after definitive RT (p=0.0001). Irradiated patients represented a negatively selected population with unfavorable tumor sites. **Definitive RT showed comparable local control to that of postoperative RT after intralesional resections.** Patients with postoperative RT had improved local control after intralesional resections and in tumors with wide resection and poor histologic response compared with patients receiving surgery alone. Patients with marginal resections with or without postoperative radiotherapy showed comparable local control, yet the number of patients with good histologic response was higher in the latter treatment group (72.2% vs. 38.5%). CONCLUSION: Patients with resectable tumors after initial chemotherapy had a low local failure rate. With preoperative RT, local control was comparable. RT is indicated to avoid intralesional resections. After intralesional or marginal resections and after a poor histologic response and wide resection, postoperative RT may improve local control.

**Second malignancies after Ewing’s sarcoma: radiation dose-dependency of secondary sarcomas.**
Kuttesch JF Jr, Wexler LH, Marcus RB et al.

BACKGROUND: An excess risk of second malignancies has been reported in survivors of Ewing’s sarcoma. We examined a multiinstitutional data base to reevaluate the risk among survivors of Ewing’s sarcoma and to identify possible causal factors. METHODS: Information was derived from a data base that included 266 survivors of Ewing’s sarcoma. Cumulative incidence rates of second malignancies were calculated. Contributions of clinical features, type and dose of chemotherapy, and cumulative radiation dose to the risk of second malignancies were evaluated. RESULTS: After a median follow-up duration of 9.5 years (range, 3.0 to 30), 16 patients have developed second malignancies, which included 10 sarcomas (five osteosarcomas, three fibrosarcomas, and two malignant fibrous histiocytomas) and six other malignancies (acute myeloblastic leukemia, acute lymphoblastic leukemia, meningioma, bronchioalveolar carcinoma, basal cell carcinoma, and carcinoma-in-situ of the cervix). The median latency to the diagnosis of the second malignancy was 7.6 years (range, 3.5 to 25.7). The estimated cumulative incidence rates at 20 years for any second malignancy and for secondary sarcoma were 9.2% (SD = 2.7%) and 6.5% (SD = 2.4%), respectively. The cumulative incidence rate of secondary sarcoma was radiation dose-dependent (P=.002). No secondary sarcomas developed among patients who had received less than 48 Gy, while the absolute risk of secondary sarcoma was 130 cases per 10,000 person-years of observation among patients who had received > or = 60 Gy. CONCLUSION: The overall risk of second malignancies after Ewing’s sarcomas is similar to that associated with treatment for other childhood cancers. **The radiation dose-dependency of secondary sarcomas justifies modification in therapy to reduce radiation doses.**

**ROLE OF LUNG BATH IN PULMONARY METASTASIS:**

**Primary metastatic (stage IV) Ewing tumor: survival analysis of 171 patients from the EICESS studies.**
Paulussen M, Ahrens S, Burdach S et al.
BACKGROUND: In the multicenter European Intergroup Cooperative Ewing's Sarcoma Studies, localized Ewing tumors of bone were treated by combination chemotherapy with surgery and/or radiotherapy. Patients with primary metastases (pm-pts) were treated in high risk protocols. PATIENTS AND METHODS: One hundred seventy-seven pm-pts were registered from January 1990 to December 1995, 171 were evaluable for survival analyses. Thirty-six pm-pts received myeloablative megatherapy with stem cell rescue following conventional treatment. Bilateral whole lung irradiation (WLI) was administered in 57 pm-pts with pulmonary involvement. Event-free survival (EFS) rates were estimated by Kaplan-Meier analysis. Prognostic factors were identified by log-rank statistics, Cox procedures and logistic regression. RESULTS: Eighty-nine deaths were recorded by 1 February 1997, EFS four years after diagnosis for all 171 pm-pts was 0.27. EFS for isolated lung metastases was 0.34, for bone/bone marrow (BM) metastases, 0.28, and for combined lung plus bone/BM metastases, 0.14 (P<0.005). WLI improved outcome in case of isolated pulmonary involvement (0.40 vs. 0.19, P<0.05). In pm-pts with combined pulmonary/skeletal metastases, intensification by megatherapy and/or WLI improved EFS from 0.00 to 0.27 (P=0.0001). CONCLUSIONS: EFS four years after diagnosis in patients with disseminated Ewing tumors is 0.27. Whole lung irradiation and megatherapy improve outcome in subgroups of patients with disseminated Ewing tumors is 0.27.

Selective use of whole-lung irradiation for patients with Ewing sarcoma family tumors and pulmonary metastases at the time of diagnosis.
Spunt SL, McCarville MB, Kun LE et al.

PURPOSE: The benefit of whole-lung irradiation (WLI) for patients who have pulmonary metastases (PM) of Ewing sarcoma family tumors (ESFT) is unclear. At our institution, WLI is reserved for patients with PM that do not respond completely to induction chemotherapy. We reviewed our experience to assess the impact of WLI on clinical outcome. PATIENTS AND METHODS: Twenty-eight patients with ESFT and PM were treated in three consecutive institutional trials (1979-1996). Extent of pulmonary involvement at diagnosis, response of PM after induction chemotherapy, local treatment of PM thereafter, and clinical outcome were recorded. Treatment included primary tumor surgery and/or radiotherapy and 42 to 58 weeks of multiagent chemotherapy. RESULTS: Only eight patients (29%) received WLI. For the entire study group, the estimated 5-year event-free survival was 22.9% +/- 9.0%; the 5-year survival was 37.3% +/- 9.8%. Complete resolution of PM after induction chemotherapy was not correlated with survival (P=0.53), nor was treatment with WLI (P=0.87). CONCLUSIONS: The comparable survival of patients with poor and good response of PM to induction chemotherapy suggests that WLI may benefit poor responders. The use of WLI in good responders may provide similar benefit and merits further study.