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● *Original Contribution*

IMPROVING THE THERAPEUTIC RATIO OF CRANIOSPINAL IRRADIATION IN MEDULLOBLASTOMA

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Radiation therapy delivered to the entire cerebrospinal axis is indicated for a number of pediatric brain tumors, especially medulloblastoma. Improved radiotherapy techniques have changed the near fatal prognosis for children with medulloblastoma to a 50%, 5-year survival. Nevertheless, the treatment results in substantial acute toxicity, and many survivors have serious sequelae. Further improvement in survival with optimal surgery and radiotherapy is not expected unless chemotherapy is added. Refinements in radiotherapy technique, however, can improve the therapeutic ratio of the treatment by lowering its side effects. In the last year children who required craniospinal irradiation at M. D. Anderson Hospital were treated with 6 MV photons to the brain and primary tumor and with 15–17 MeV electrons to the spinal canal. The elective dose to the whole brain was 30 Gy in 17 fractions and 30 Gy in 20 fractions to the spine. The primary tumor received an additional 20–25 Gy. An electron-beam dose distribution was drawn on a computerized tomography (CT) reconstructed sagittal plane. The electron energy was selected so that the 90% isodose line was at least 3 mm anterior to the cord after correction for bone heterogeneity. The treatment was well tolerated in the first five patients. It is projected that the current technique will cause fewer late effects and improve the tolerance to chemotherapy.

Craniospinal irradiation, Medulloblastoma, Electron beam, Dosimetry, Computerized tomography.

INTRODUCTION

A significant number of pediatric brain tumors have a tendency to seed along the pathways of the cerebrospinal fluid (CSF). These include medulloblastoma, malignant ependymoma, germinoma, and infratentorial glioblastoma. Medulloblastoma alone accounts for 20% of all pediatric brain tumors. Better survival for medulloblastoma is reported when the spinal cord down to S_2 and the whole brain are irradiated.[16] Surgery alone, with no radiation, has resulted in only one survivor in 40 patients,[18] confirming Cushing's experience of more than 50 years ago. Improved survival is achieved as the dose to the primary tumor is increased to 50 Gy. The optimal dose to be given electively (prophylactically) to the supratentorial brain and the spine is not known.

Ideally, treatment to the primary tumor and the elective areas should be given at the same time to prevent floating tumor cells in the CSF from escaping the radiation therapy. In practice, however, this ideal is very difficult to accomplish because of acute gastrointestinal and bone marrow toxicity. Of necessity, treatment is given sequentially or with only partial temporal overlap.[15]

Brain irradiation

Brain irradiation, as administered in the past, has serious consequences. The treatment is well tolerated at the time of delivery with transitory epilation as the only consistent acute side effect. However, mental retardation and learning disabilities in survivors of medulloblastoma are reported from many institutions.[9,12,20,24] The radiation dose, which is higher than that given to the brain in acute leukemia, plays a major role. Hydrocephalus, brain surgery, and the presence of tumor may add to the mental deterioration. Another late effect related to cranial irradiation is the suppression of the pituitary, with reduction of growth hormone and gonadotropin.[12,21]

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Although primary medulloblastoma shows dose-response characteristics, the minimal elective dose required to eradicate truly occult metastases in the remaining CNS is unknown. The recommended dose for elective brain irradiation is usually higher by 5–10 Gy than for the spinal cord just because the brain has a higher threshold for radiation damage. But this recommendation is not logical. In the compiled series of MacFarland *et al.*,[17] spinal metastases composed 94% and brain only 6% of metastatic medulloblastoma within the CNS. Comprehensive irradiation lowers the number of recurrences in the spinal cord but not in the brain. In a large pooled series of 159 documented failures of treatment, 75% failed in the posterior fossa alone, 6% in the posterior fossa and spinal cord, 8% in the spinal cord, 6% in the cerebrum, and 5% had distant metastases outside the CNS.[5] The seeming ineffectiveness of the elective brain irradiation can be explained by inadequate coverage of the floor of the temporal fossa and the cribriform plate.[6,11,14] Recurrences in the mid brain may be the result of direct extension of the tumor through the brain stem.

These considerations led us to conclude that the elective dose to the brain could safely be lowered and should not exceed the dose delivered to the spinal cord. Improved technique rather than higher dose should be the logical treatment for the relatively infrequent cerebral metastases. Of interest is the report by Landberg *et al.*,[16] where 30 Gy in 20 fractions were delivered to the entire subdural space. No mental retardation was detected in any of the survivors.

Spinal cord irradiation

Megavoltage irradiation to the spine causes rapid and serious reduction in the number of peripheral lymphocytes, granulocytes, and platelets.[7,19] Since major parts of the upper aerodigestive and lower gastrointestinal tract are located just anterior to the irradiated vertebral column, related symptoms are the rule. These include sore throat, dysphagia, peptic pain, nausea and vomiting, hoarseness, and cough. Marrow and gastrointestinal toxicity are often serious enough to cause an interruption, or even cessation, of the planned treatment.

Irradiation of the growing vertebral column decreases sitting height and causes kyphoscoliosis.[10,20] The mandible can also be affected by undergrowth.[4] The treated volume also contains most of the lymph nodes, so that decreased immunity results.[7]

In one study, compensated hypothyroidism was found in 58.6% of children examined after treatment for medulloblastoma.[12] More alarming are reports of thyroid cancer developing 8–18 years after craniospinal irradiation.[22,23] This complication of treatment is expected to rise as more children survive beyond 10 years after treatment.

Bloom and co-workers made phantom measurements and found scatter radiation doses of 1.2 Gy to the ovary and 0.75 Gy to the testis throughout the treatment.[3] The long-term effects of such doses on the gonads are not known.

In order to reduce the immediate and late effects of spinal irradiation, we abandoned the use of megavoltage X ray therapy in favor of high-energy electrons, 15 MeV and above. The disadvantage of cobalt-60 compared to electrons is that it is too penetrating, delivering substantial doses to all midline structures. With electrons, there is a rapid reduction of the dose beyond the region of the spinal cord. Van Dyk *et al.*[25] have shown that the depth of the cord in children less than 12 years old varies between 3.1 and 4.0 cm, well within the reach of energetic electrons. Even though electrons are clearly superior, megavoltage X ray therapy is still widely used

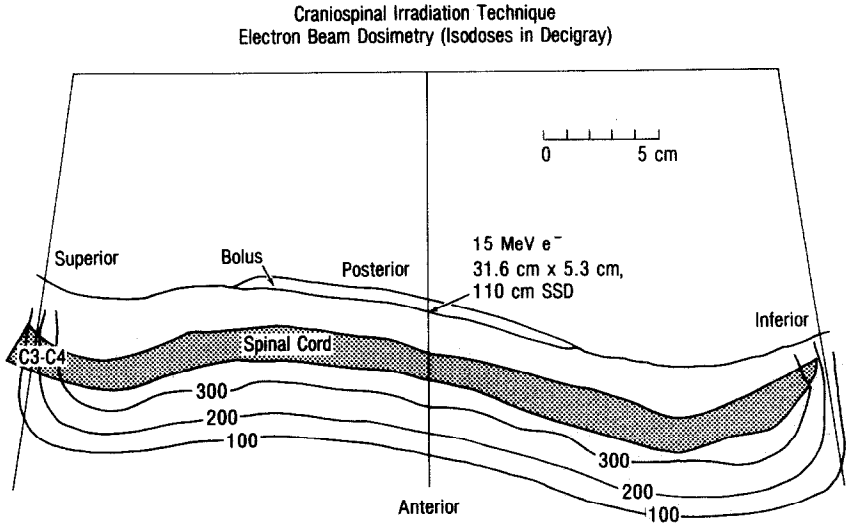
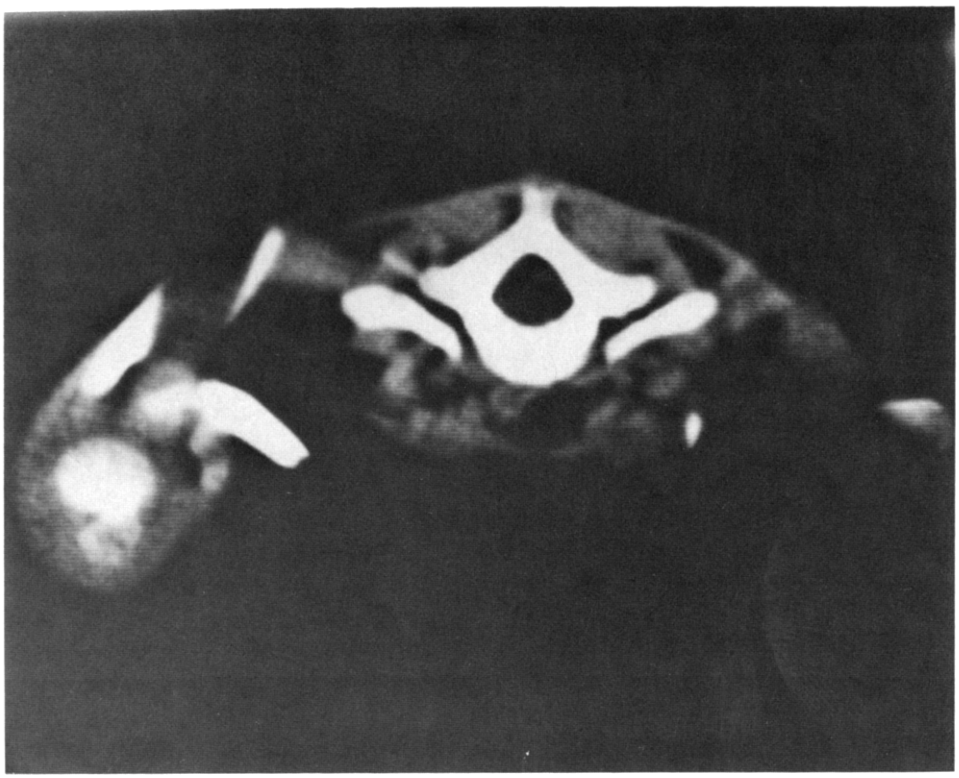


Fig. 1. Dose distribution of spinal field of a 3 year-old boy. The 15 MeV electron distribution is uncorrected for bone.



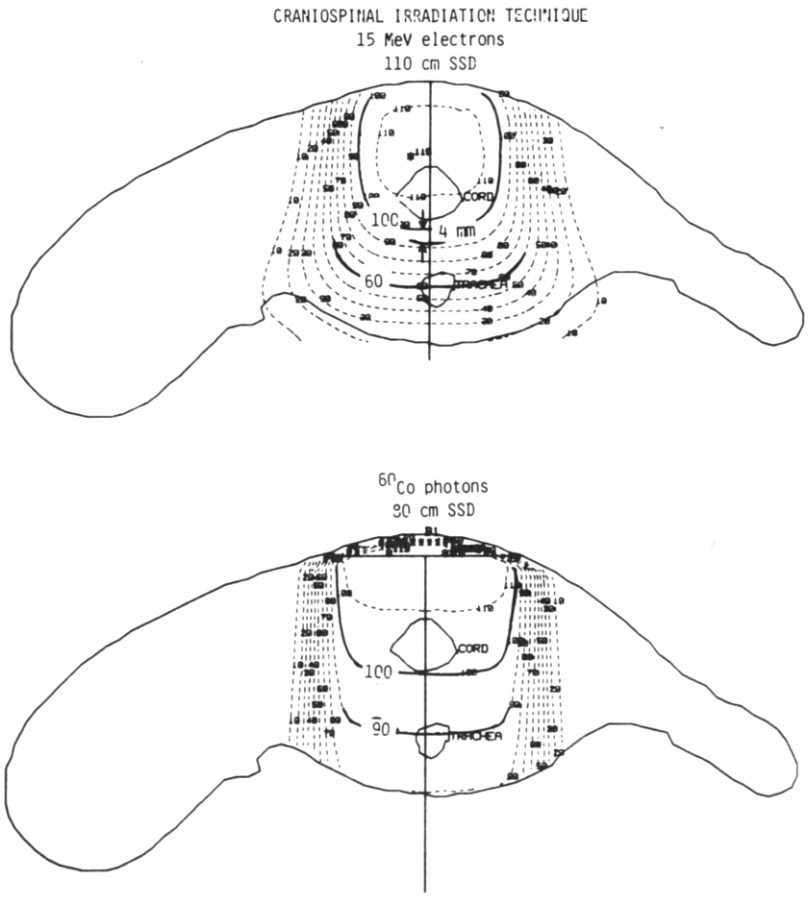


Fig. 2. (A) Transverse CAT scan through neck and (B) corresponding dose distribution of spinal field using electrons (corrected for heterogeneity) compared to that using cobalt-60 (uncorrected). The position of the 100% isodose line of the uncorrected electron distribution is marked for comparison. (Note: dose is prescribed to the 90% depth dose for electrons; therefore, that isodose has been normalized to 100%).

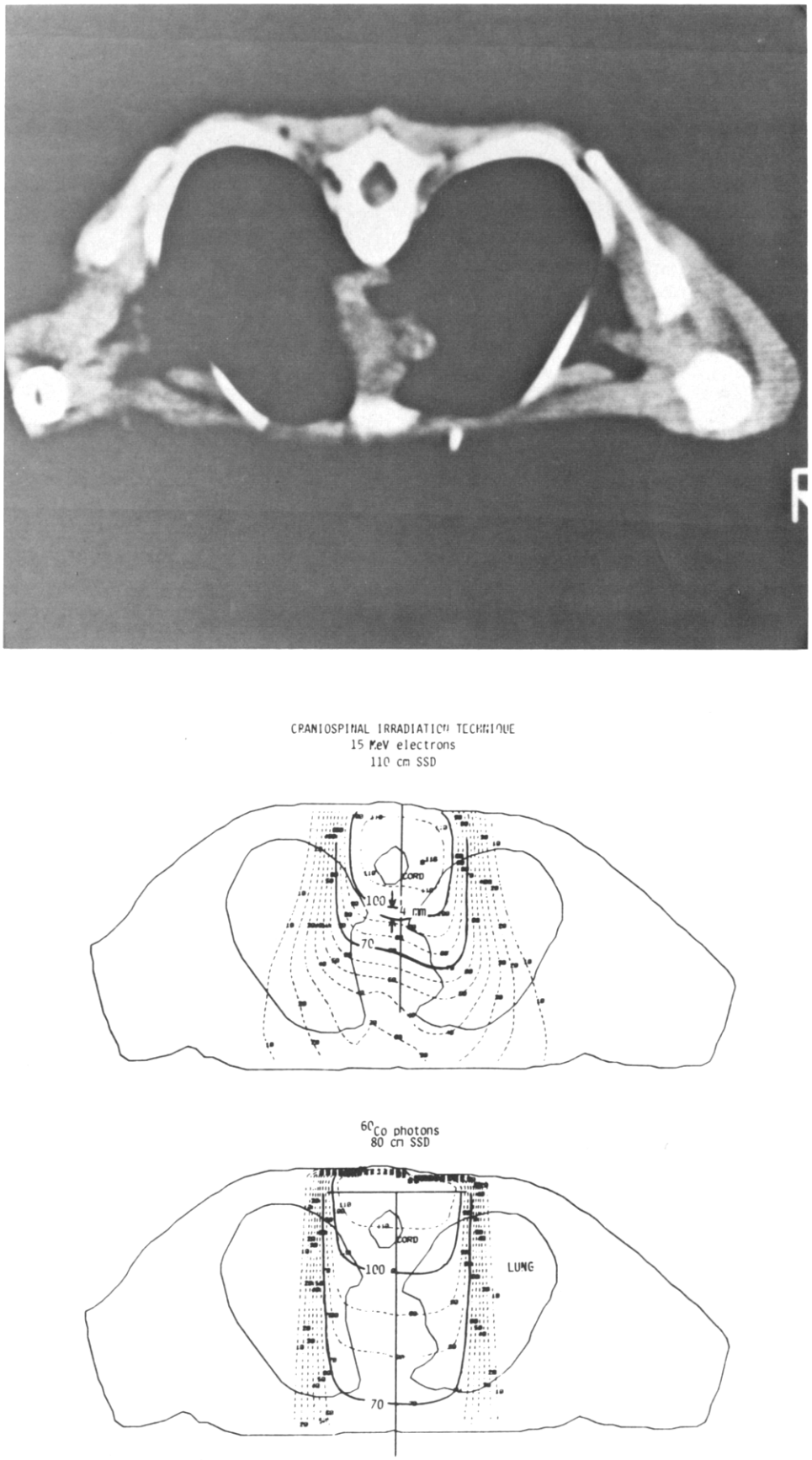
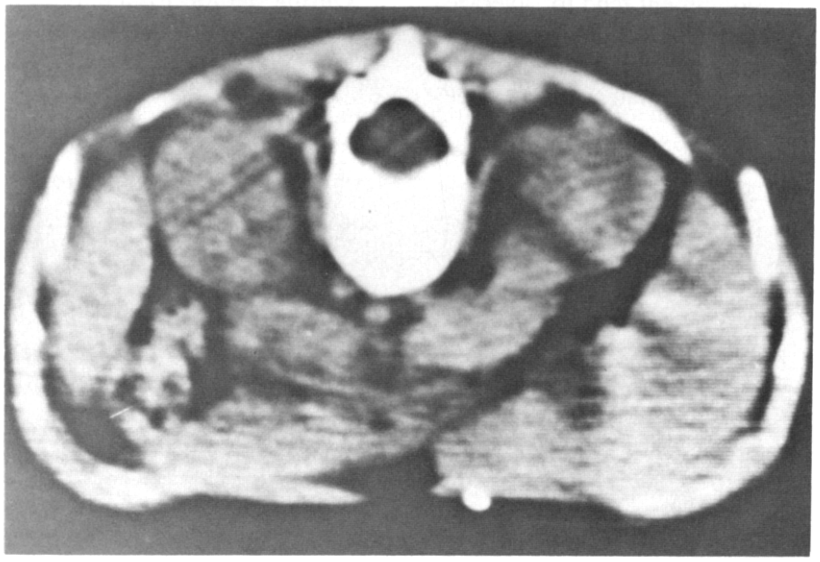


Fig. 3. (A) Transverse CAT scan through the mediastinum and (B) corresponding dose distribution of spinal field using electrons (corrected for heterogeneity) compared to that using cobalt-60 (uncorrected). The position of the 100% isodose line of the uncorrected electron distribution is marked for comparison.



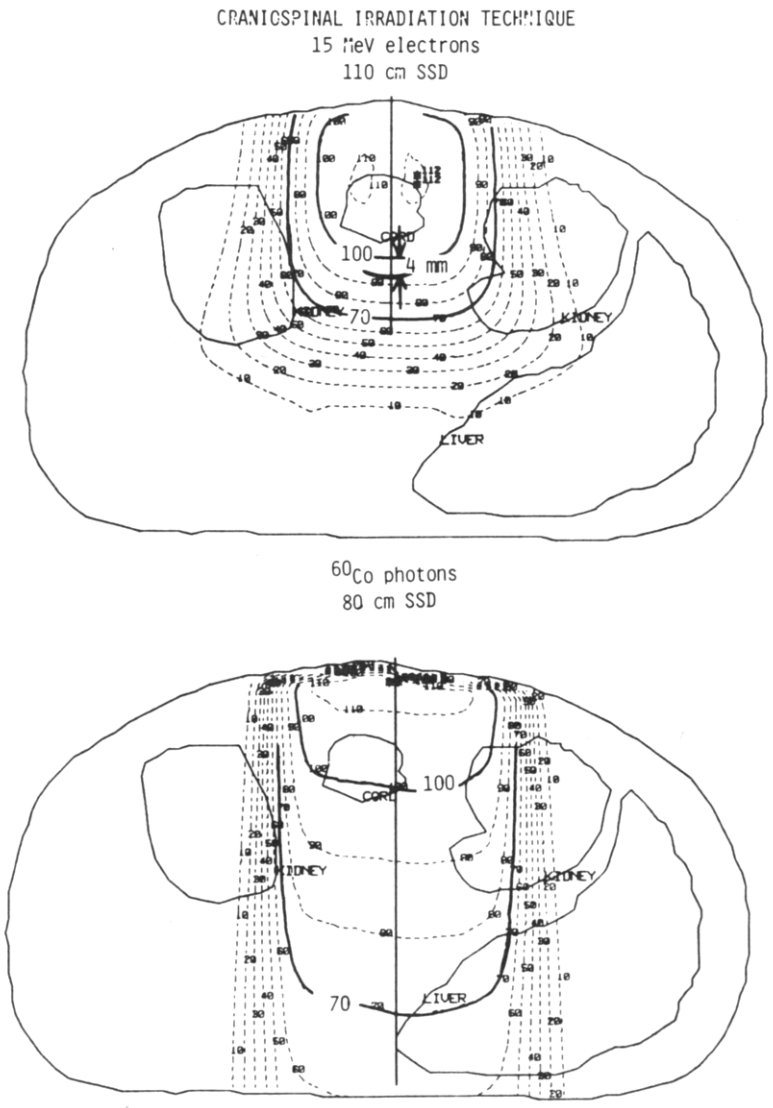


Fig. 4. (A) Transverse CAT scan through the abdomen and (B) corresponding dose distribution of spinal field using electrons (corrected for heterogeneity) compared to that using cobalt-60 (uncorrected). The position of the 100% isodose line of the uncorrected electron distribution is marked for comparison.

for spinal irradiation because equipment capable of delivering high energy electrons to extended fields became available only in the last decade. Also, the dosimetry of electrons is more complex than that of photons, with greater dependency on the geometry and composition of the irradiated volume. The spinal cord poses a particular challenge for electron therapy because of its varying depth and the overlying spinous processes, with their increased absorption and scatter of electrons. These difficulties have recently been overcome in our institution by using an algorithm that calculates electron-beam isodose curves in a particular plane, accounting for tissue inhomogeneities as disclosed by computerized axial tomography (CAT).[13]

The dose required to eradicate occult disease in the spinal theca has yet to be confirmed. Many spinal recurrences occur in association with failure at the site of the primary tumor. Nonetheless, isolated spinal metastases happen at various dose levels.[5] New light was shed on this issue with the discovery that many patients harbor unsuspected gross metastatic disease in the spinal cord. Myelography performed on newly diagnosed patients with medulloblastoma revealed asymptomatic spinal cord involvement in 8/22 (33%)[8] and 9/30 (30%).[1] Thus, recurrences in the spine may result from reseeding from a recurrent primary tumor or may be a manifestation of further growth of an undiagnosed preexisting tumor. It follows that after gross metastatic disease has been ruled out by a CAT scan of the brain and a myelogram of the spine, a moderate radiation dose should suffice for possible microscopic foci. We believe that an elective dose of 30 Gy, as recommended by Landberg *et al.*,[16] is optimal as it combines maximal tumor control with minimal long-term stigmata.

METHODS AND MATERIALS

Our technique calls for immobilization of the patient's head in the prone position using a customized face

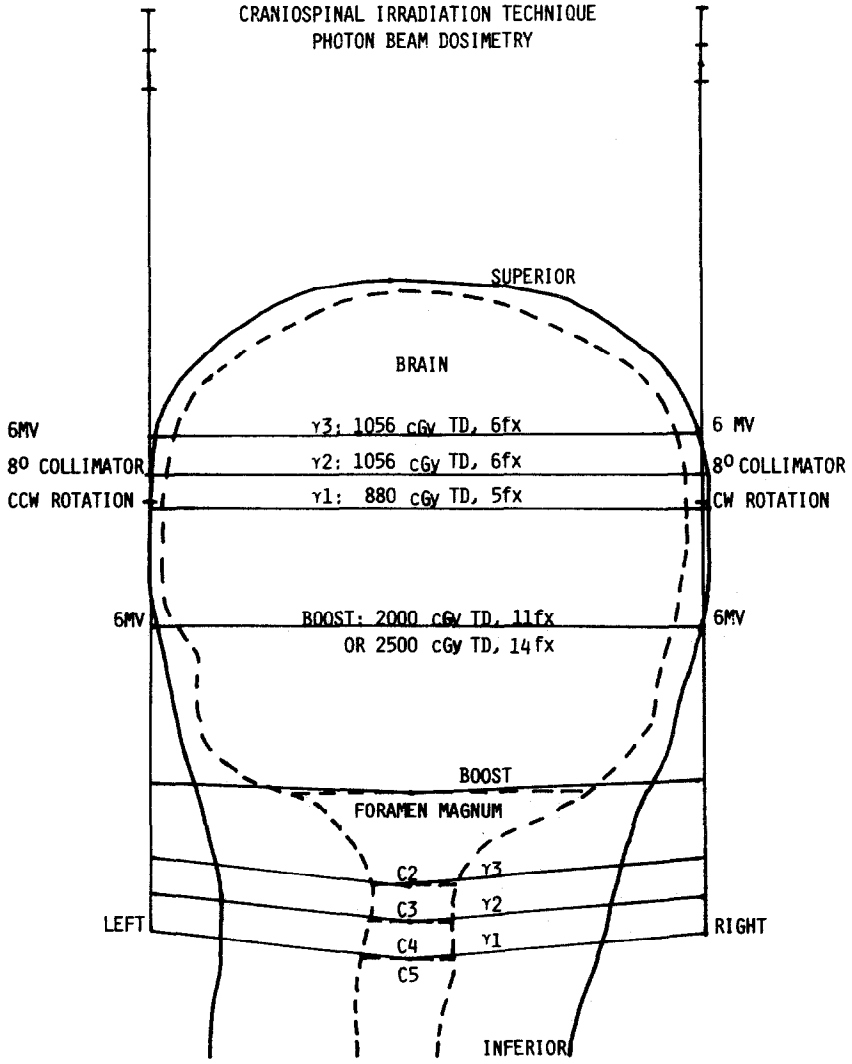


Fig. 5. Position of 6 MV brain fields in a coronal plane passing through the spinal cord.

mask. Whole-brain irradiation is delivered through lateral portals with 6 MV X rays. This energy is ideal, as it gives full dosage to the superficial meninges but has more skin sparing and a better depth-dose distribution than cobalt-60. A dose of 30 Gy in 17 fractions is delivered to the entire brain. An added dose ("boost") of 20–25 Gy is delivered to the primary tumor. The dose chosen depends upon the type of tumor, completeness of surgery, and age of the patient.

The spinal cord is treated with a single posterior electron beam portal with the patient in the same prone position (two abutted fields may be required in teenagers or adults). The selection of a particular electron energy depends on the depth of the cord in the patient. The aim is to cover the cord with the 90% isodose line and to treat that line to 30 Gy.

Treatment planning of the posterior electron field proceeds as follows. The patient undergoes CAT scanning in the treatment position with transverse slices 1 cm thick taken every 2–3 cm extending from above C_{3-4} to below S_3. From the resulting series of transverse cuts, a sagittal contour is constructed, showing the relationship between the skin surface and the posterior and anterior border of the spinal cord. Energy is selected and bolus designed so that the depth of the 90% dose falls approximately 7 mm anterior to the anterior cord. The 7 mm margin accounts for an approximately 4 mm posterior shift of the 90% isodose because of bone, leaving a 3 mm treatment margin. A typical electron-beam dose plan for a 3 year-old boy using 15 MeV electrons with bolus is illustrated in Fig. 1.

The shifting of the 90% isodose line because of the increased density of bone has been evaluated by performing dose calculations in transverse planes with and without a CAT-based heterogeneity correction. These calculations were performed in the transverse rather

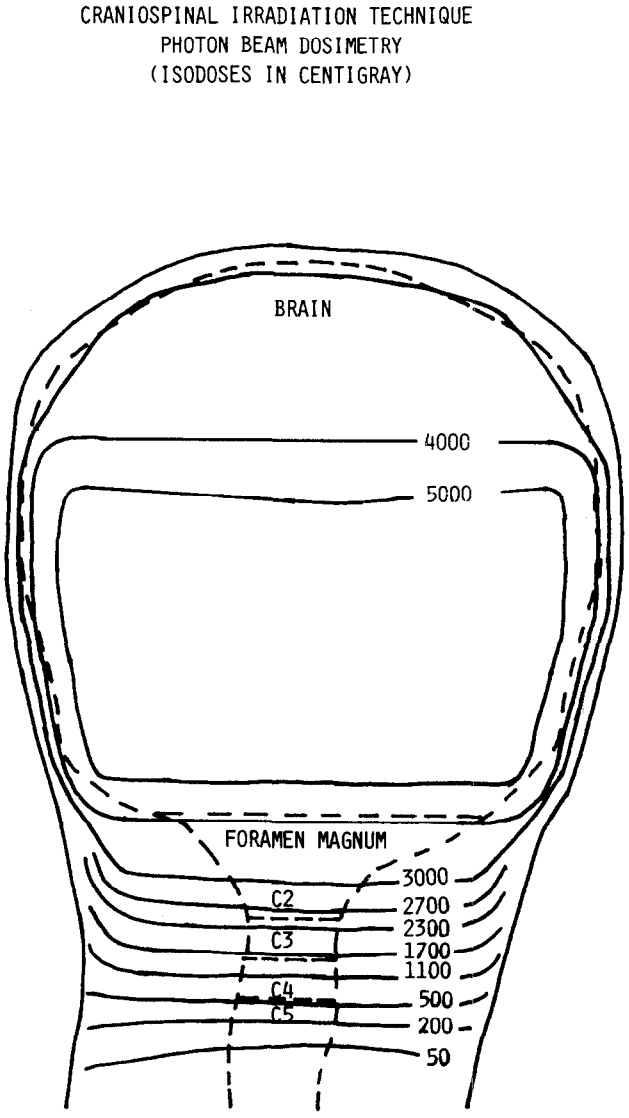


Fig. 6. Dose distribution from 6 MV fields of Fig. 5. Note the broad penumbra from C_2 and C_5 generated by the moving border.

than the sagittal plane because the cross section of the bone in the transverse plane gives a more accurate scatter calculation. The shift was found to be approximately 4 mm for children 3–4 years-old, but is currently being determined for each patient using the CAT data as illustrated for the three transverse slices in Figs. 2–4.

An extended treatment distance of 110 cm is typically used to produce a broadened penumbra for abutting to the photon dose distribution. The resulting penumbra width must be considered to ensure that an adequate field margin exists around the spinal cord, particularly when scoliosis is present. The penumbra width at the level of the cord is obtained from the dose distribution in the transverse slices (Fig. 2–4), and the R-L field width is opened accordingly to encompass the cord in the PA simulation film. Skin collimation to restore the penumbra has not been pursued at this time. A second advantage of the extended treatment distance is to maximize the length of the field. By opening the collimators to their maximum square field size for electrons, and then adding a blocking insert with the rectangular field placed diagonally, maximum field lengths of 34 and 41 cm at 110 cm SSD are obtained for square field sizes of 25 and 30 cm at 100 cm SSD, respectively.

The superior border of the electron field is placed at the C_{3-4} vertebral interspace; the inferior border is typically just below S_3. If the length of the spinal field exceeds the maximum available insert dimension, then a second electron field of the same energy is abutted at the inferior border. The gantry is rotated caudally for this field so that the source position relative to the patient is the same for both fields; therefore, the diverging inferior edge of the superior field exactly coincides with the diverging superior edge of the inferior field. This theoretically produces a nearly uniform dose distribution in the abuttment region. However, a 2 mm gap (overlap)

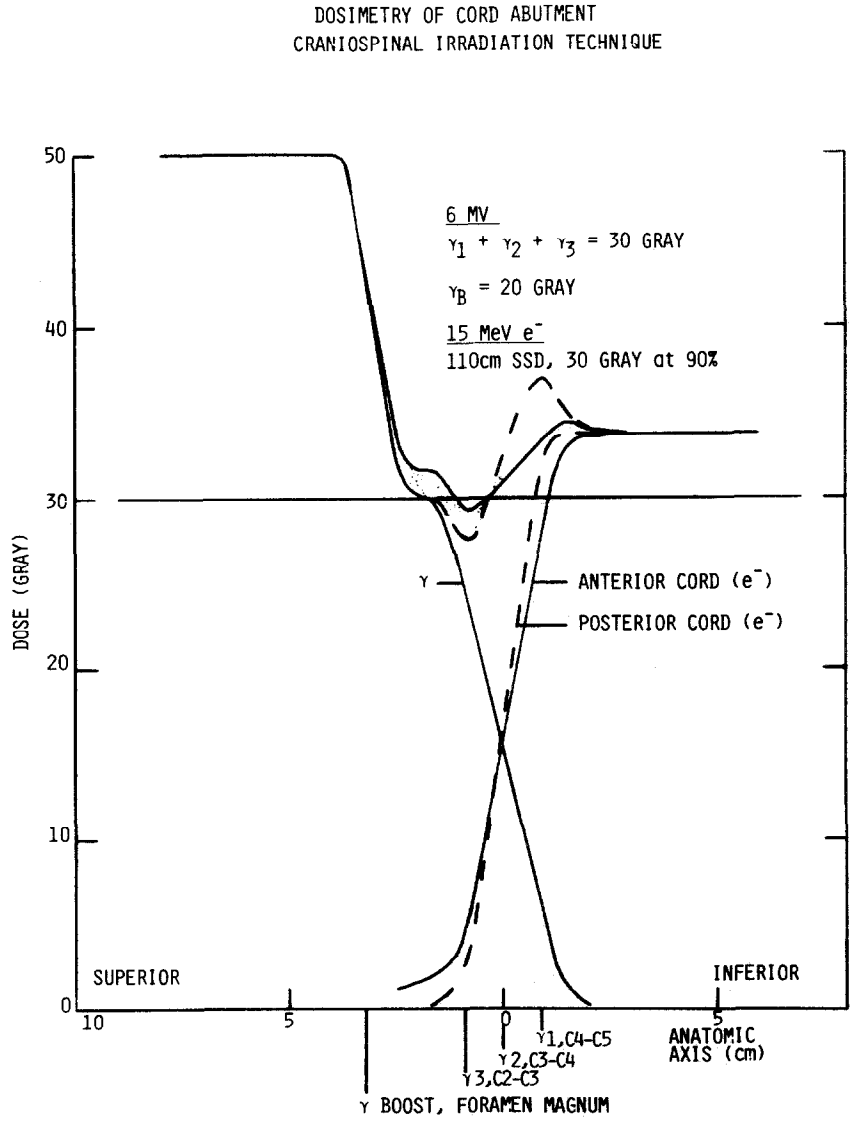


Fig. 7. Composite distribution from abutting the electron and photon fields at anterior and posterior aspects of spinal cord in the vicinity of C_{3-4}.

in field placement could result in a 10% underdose (overdose) in the resulting distribution. We believe that such discrepancies due to misalignment tend to "average out" over a course of therapy. If one is concerned with a potential underdose or overdose, then the abuttment border could be shifted by one centimeter two or three times during treatment.

The first step in simulating the photon field is to determine the necessary collimator rotation. Once the dimension of the superior electron field has been set, the angle between its superior border and central axis is determined. The photon jaws are then rotated by that amount so that the inferior border of the photon field is parallel with the superior border of the electron field. As stated above, a dose of 30 Gy in 17 fractions is delivered to the entire brain. For the middle six fractions the inferior border of the photon field exactly coincides with the C_{3-4} interspace. For the first five fractions the border lies approximately 9 mm below C_{3-4}, and for the last six fractions the border lies approximately 9 mm above C_{3-4}. These 9 mm shifts produce a photon penumbra that matches the electron penumbra, allowing a uniform dose where the fields abutt. Figure 5 shows the relative locations of the photon fields in a coronal plane; the resulting dose distribution is shown in Fig. 6. The spinal cord lies at the intersection of this plane with the sagittal plane of Fig. 6. The dose distribution along the cord resulting from adding the photon and electron dose components is plotted in Fig. 7.

During photon irradiation the viscerocranium is protected by a lead block individually designed from the lateral skull X ray to clear the meninges by 1 cm (Fig. 8). A frequent benefit in simulation, particularly in 3- to 4-year old children, is that the 9 mm shifts of the inferior photon field border correspond to the length of approximately one vertebral body. Therefore, the inferior border for the first five fractions falls at C_{4-5}, that of the next six fractions at C_{3-4} and that of the final six fractions at C_{2-3}. If the separation of the interspaces is in the range of 8–10 mm, then the borders are still placed at these interspaces. Note on the simulation film of Fig. 8 that the border is placed at the C_{3-4} interspace.

RESULTS AND DISCUSSION

At present, five patients have completed craniospinal irradiation as described. Their clinical features are shown in Table 1. Treatment was very well tolerated. No patient complained of sore throat, dysphagia, nausea or vomiting. There was no dietary problem and all patients gained weight under treatment. There was a moderate reduction in the blood counts (Table 1). The lowest count was registered in a patient whose bone marrow was compromised by seven previous cycles of mechlor-

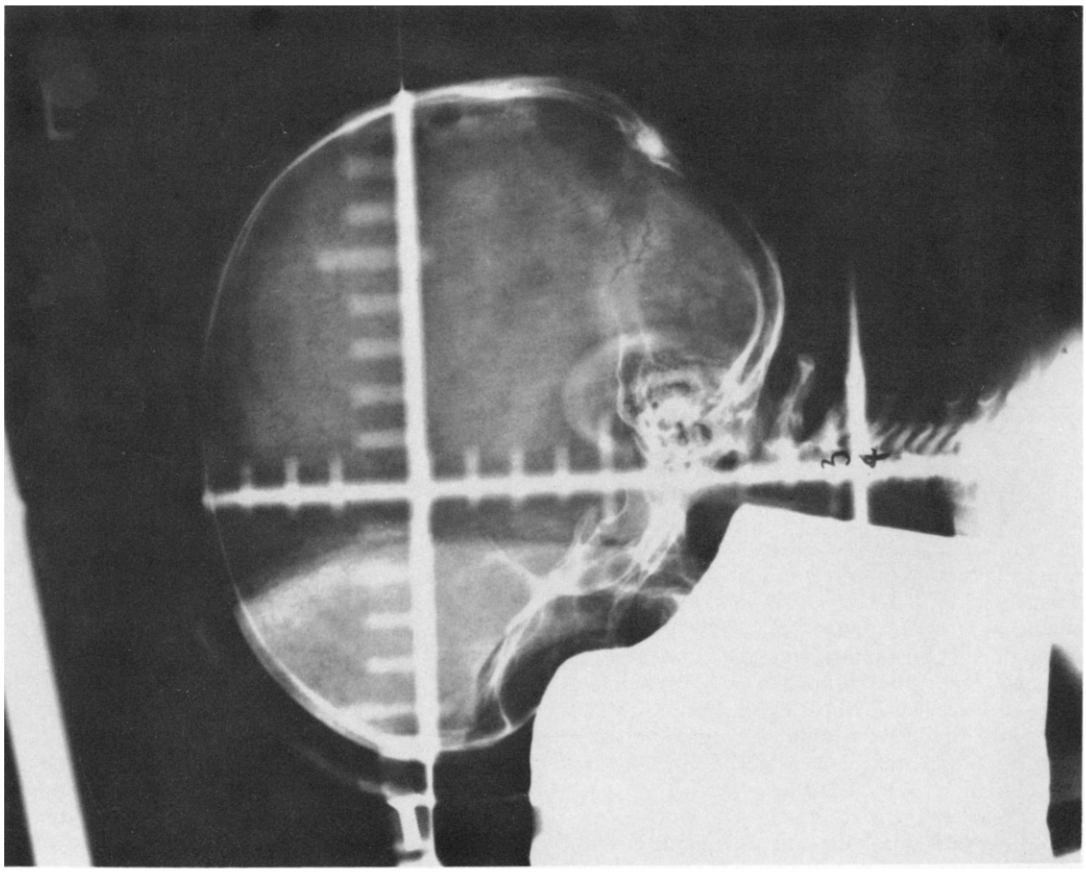


Fig. 8. Lateral simulation film of 6 MV fields for inferior border at C_{3-4}.

Table 1. Patients receiving spinal irradiation with electrons

Diagnosis	Age	XRT started	Lowest counts WBC/platelets (×1000)	Symptomatic side effects
Glioblastoma of cerebellum	9	5/2/83	2.4/106	None
Medulloblastoma recurrent post MOPP × 7	3 + 8/12	6/6/83	1.6/63	None
Ependymoma IV ventricle	3 + 8/12	7/13/83	3.2/146	None
Medulloblastoma	4 + 8/12	8/24/83	2.1/437	None
Choriocarcinoma of pineal	8	11/17/83	3.2/178	None

ethamine hydrochloride, vincristine, procarbazine, and prednisone (MOPP). In no instance was treatment interrupted because of radiation toxicity.

Insufficient time has elapsed for us to evaluate late effects, in particular the effect of the inhomogenous electron-beam dose on the growth of the vertebral column. We are hopeful, however, that their incidence will be much lower. The incidence of dementia and thyroid cancer should be decreased because of the lower doses to the brain and thyroid.

At present, it seems that the maximum survival benefit for medulloblastoma with surgery and radiation therapy has already been reached and is approximately 50% at 5 years. Improvement can still be achieved if the marked side effects, both acute and late, of the treatment are reduced. Reduced toxicity, especially to the bone marrow, may make the administration of adjuvant chemotherapy more plausible. Significant improvement in the survival of children receiving adjuvant chemotherapy was shown in the International Society of Radiation Oncology (SIOP) study.[2]

CONCLUSIONS

1. Our current technique for craniospinal irradiation, using electrons for the spine, is much better tolerated than techniques using only photons.
2. The lesser dose to the whole brain is expected to cause less mental retardation and pituitary hormone deficiency.
3. The incidence of thyroid cancer should be markedly reduced.
4. The lesser overall dose and volume will improve the tolerance to chemotherapy.

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