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# EFFECT OF LOW DOSE IRRADIATION ON RENAL ENLARGEMENT IN CHILDREN FOLLOWING NEPHRECTOMY FOR WILMS' TUMOR

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Radiation nephropathy is a well-recognized potential consequence of irradiation with high doses (KUNKLER et coll. 1952) and has been recognized as occurring with lower doses when radiation therapy has been augmented with Actinomycin D and Vincristine (ARNEIL et coll. 1974). However, little has been published regarding the effect of renal irradiation with 15 Gy or less on subsequent renal hyperplasia and hypertrophy of the remaining kidney following nephrectomy for Wilms' tumor. VAETH (1964), EKLÖF & RINGERTZ (1976) and LUTENEGGER et coll. (1975) reported continued enlargement of the remaining kidney after operation for Wilms' tumor. However, the dose delivered to the remaining kidney was either uncertain or quite heterogeneous in these reports and the role of adjuvant chemotherapy unclear, and no attempt was made to compare renal growth in irradiated versus non-irradiated kidneys. SAGERMAN et coll. (1969) were able to show cessation of growth or decrease in renal size without other clinical sequelae in children with neuroblastoma following irradiation. Most recently, MOSKOWITZ & DONALDSON (1979) have described two patients whose remaining kidney failed to hypertrophy after renal irradiation and chemotherapy comprising Actinomycin D, Vincristine, and Adriamycin.

The purpose of this report is to compare growth of the remaining kidney in 3 groups of patients following nephrectomy for Wilms' tumor.

## Material and Methods

In group I (direct irradiation), the remaining kidney received 12 Gy in 1.50 Gy daily fractions immediately following nephrectomy because of gross peritoneal contamination by tumor cells or implants occurring before or at the time of nephrectomy.

Children in group II, with more limited tumors, received only irradiation of the ipsilateral renal fossa without direct irradiation of the remaining normal kidney. The relative dose distribution outside the irradiated field was calculated using the Artonix PC12 irregular field calculation. This is a Clarkson integration of scattered dose. The average scattered dose of 1.25 Gy was obtained assuming a midplane dose of 25 Gy using fields measuring 10 cm×14 cm and 4 MV roentgen rays delivered at 80 cm distance and assuming an average patient thickness of 16 cm. Scattered dose across the non-irradiated kidney ranged from approximately 2 Gy to 0.6 Gy from the medial renal limit to the lateral edge. Scatter irradiation to the remaining kidney from the irradiation of the contralateral renal fossa was estimated to average 5 per cent or approximately 1.25 Gy. Two patients, with limited Stage I tumors, were not irradiated. They are included in group II but identified separately in the Figure.

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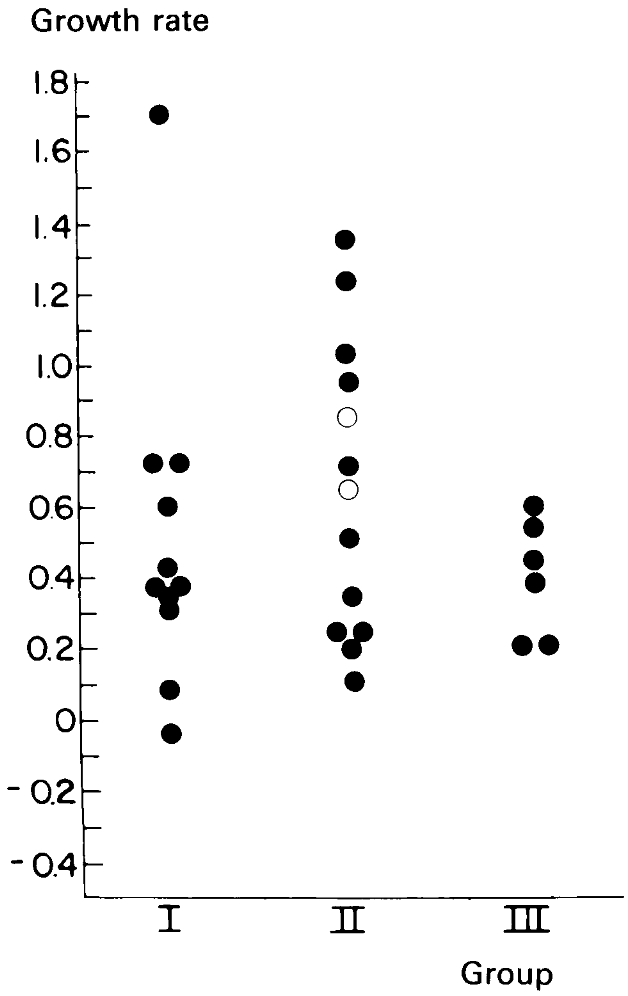


Presentation of linear growth (cm/year). Group I children are those 11 receiving abdominal irradiation including the contralateral 'normal' kidney. Group II children include 12 who never received direct radiation to the remaining kidney and one who received lung (and partial renal) irradiation just before death. Group III children are those 6 in whom the normal kidney was not irradiated at the time of flank treatment but later required successful lung (and partial renal) irradiation because of the development of lung relapse. Two children who received no irradiation are shown in Group II with open circles.

Finally, children in group III (intermediate) are those who required irradiation of the ipsilateral renal fossa only (and therefore received only scatter irradiation to the remaining kidney) who subsequently developed pulmonary metastases. The treatment of these metastases included irradiation of both lungs to approximately 15 Gy in 10 fractions in 2 weeks. During the course of this treatment, a significant portion of the upper pole of the remaining kidney was irradiated. Because of this delayed, direct irradiation, these children represent an intermediate group.

The records and films, including urograms, of all children with Wilms' tumor treated at these departments from 1971 to December 1976 were reviewed. Patients with bilateral Wilms' tumor and those whose original examinations could not be found or in whom follow-up was unavailable, were excluded. Patients treated elsewhere and seen only in consultation were also excluded. Group I consisted of 11 children, group II of 13 (one patient received pulmonary irradiation just before death) and group III of 6 whole lung irradiated and long-term surviving children.

The radiation therapy was delivered using a 4 or 8 MV linear accelerator for all but one patient, who was treated with $^{60}Co$. In the 11 patients with tumor spread or peritoneal implants, 11.25 to 13 Gy were delivered in 1.5 Gy fractions to the entire abdomen and pelvis (including the remaining kidney). Anterior and posterior 6 HVL blocks (approximately 1.5% transmission) were then constructed using a simulator with concurrent urography. These blocks were utilized while the abdominal field was given an additional 8 Gy (total 20 Gy). An additonal 4 to 8 Gy was then delivered to the affected (post-nephrectomy) renal fossa. All other children received only irradiation of the renal fossa totalling 22 to 31 Gy.

Maintenance Actinomycin D was given to all children (70 $\mu$g/kg intravenously in 7 daily doses every 6 weeks for 2 years). In addition, 13 were given Vincristine (2 mg/m$^2$ intravenously weekly $\times 12$). The variables known to change the length of the kidney (HERNANDEZ et coll. 1979) were considered. All measurements were made by two of the authors (A. H. and R. L. L.), without knowledge of the mode of therapy, on a film exposed 3 min after the injection of a constant dose, per unit weight, of contrast medium. The film was exposed with the child supine, and the table top—Bucky tray distance remained constant. The renal growth rate per unit time was calculated by dividing net change in renal length (cm) by time elapsed (years) following the initial examination. Slopes were calculated for all patients in each group and averaged, and the standard error of the mean calculated.

### Results

The range in growth rates (cm/years) for the children in group I varied from –0.04 to +1.7 (Figure). Seven of 11 patients had a slope of less than 0.50, and all but one were less than 0.80. The mean slope for this group was 0.50 with a SE of 0.138.

Slopes for the 13 children in group II ranged from

+0.10 to +1.33, 5 of 13 having slopes less than 0.50. The mean growth rate for this group was 0.65 (SE 0.11).

Seven children required whole lung irradiation by which direct irradiation (15 Gy/10 fractions/2 weeks) was delivered to the upper portion of the remaining kidney. (One boy was given lung irradiation shortly before death and he is considered with the patients in group II. Growth rates for the remaining 6 patients in group III ranged from +0.20 to 0.57 (mean 0.39). Three of 11 patients in group I receiving whole abdomen irradiation subsequently developed pulmonary metastases which required lung irradiation. Because of their previous renal irradiation, shielding of the upper portion of the kidney was performed throughout the pulmonary irradiation.

Although the timing of post-nephrectomy urography varied slightly among the children, timing did not vary significantly from group to group. Post nephrectomy follow-up periods averaged 25 months, 28 months, and 45.5 months for groups I, II, and III, respectively.

### Discussion

High radiation doses have been shown to significantly reduce or eliminate renal growth (SAGERMAN et coll.). The current retrospective analysis was undertaken in an attempt to determine if a dose of approximately 12 Gy could be shown to have an intermediate effect.

Analysis of mean growth rates between the three groups of patients fails to show a difference which achieves statistical significance. However, differences between mean growth rates of irradiated patients in group I (0.50 cm/year) and non-irradiated (excluding scatter) patients in group II (0.65 cm/year) suggest that analysis of a larger group of patients might achieve significance should this trend continue.

HODSON et coll. (1962) analysed normal renal growth from birth to 15 years of age. Using these compiled data, a relatively constant growth rate is evident from 16 months to 11 years of age. Increase in renal length during this period approximates one centimeter for every 2.4 years of life, a growth rate of 0.41 cm per year.

LAUFER & GRISCOM (1971) have demonstrated significant acceleration in growth of the remaining kidney in children with unilateral multicystic dysplasia, an excellent model for fetal unilateral nephrectomy.

An increase in the rate of renal growth has also been demonstrated in children with unilateral renal agenesis (EKLÖF & RINGERTZ). A comparison of renal and lumbar spine growth has been used in assessing this latter condition and a slope increase of 1.4 compared with normal has been obtained. This represents a growth rate of 0.56 using as units, centimeters of increase in renal length per year. This technique must be questioned for children with Wilms' tumor, however, as growth retardation of the lumbar spine following irradiation could make the apparent renal growth rate spuriously high, especially in the absence of direct renal irradiation.

Although hypertrophy rather than hyperplasia is usually felt to account for the compensatory enlargement following nephrectomy or functional loss of renal tissue, the intrarenal structural changes accounting for this enlargement are not well-documented. The mechanism whereby irradiation apparently inhibits the rate of renal growth is uncertain and requires further investigation. It seems unlikely that irradiation affects the ability of the individual cell to enlarge, and it would appear more likely that change occurs either because of death of a small fraction of cells in the irradiated kidney (making the total renal mass and hyperplasia less despite equivalent individual cell enlargement) or through changes in the renal blood supply. The report of BURY et coll. (1965) lends support to the importance of hyperplasia in compensatory growth.

Analysis of a larger group of children, both irradiated (i.e. given direct renal irradiation to the remaining kidney) and non-irradiated will be required to establish if a significant difference in these 2 groups of patients exists.

Finally, it must be emphasized that slight changes in renal growth have not produced clinically recognizable impairment of the renal function, whereas abdominal irradiation for gross peritoneal contamination is of critical importance in minimizing subsequent local recurrence, thereby permitting optimum survival for the child with Wilms' tumor (CASSADY et coll. 1977). However, longer follow-up will be necessary to confirm complete absence of renal toxicity.

## SUMMARY

The effect of low dose irradiation on subsequent compensatory renal enlargement in a group of children operated upon with unilateral nephrectomy for Wilms' tumor is reported. Comparison groups were children whose re-

maining kidney received either no direct irradiation or irradiation to only the upper portion of the kidney. The rate of growth of the kidney in the irradiated group was slightly less but this was not statistically significant. Thus, radiation therapy in children with Wilms' tumor, so crucial to optimum survival, does not seem to cause significant renal toxicity.

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