POSTRADIATION SARCOMAS

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D E C L A R A T I O N

I, Elizabeth Margaret Murray, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

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27 December 1994

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D E D I C A T I O N

To my mother

Mary Ramsay Murray

1916 - 1994

ABBREVIATIONS

Gy	Gray (unit of absorbed dose)
HVL	Half value layer
MMMT	Malignant Mixed Mullerian Tumor
PRS	Postradiation sarcoma
R	Roentgen (unit of exposure in air)
Rb gene	Retinoblastoma suppressor gene

1. INTRODUCTION

According to international studies, the incidence of post-radiation sarcoma (PRS) is less than 1% (68, 94, 122). This incidence is reported to have increased in recent years (94) and may continue to increase with the incorporation of radiotherapy in the multidisciplinary treatment of an increasing spectrum of malignant disease, and with an increasing number of patients surviving longer than the latent period necessary for the development of a postradiation sarcoma (108). In certain conditions (for example carcinomas of the breast and anus and retinoblastoma) radiotherapy is used so that extensive mutilating surgery may be avoided. It may also be used to improve the chances of local control (for example in some cases of carcinoma of the breast) without having a known effect on long term survival.

It is important that rare but severe complications of radiotherapy are reported and taken into account when weighing up the benefits and disadvantages of various modalities of treatment such as radiotherapy and surgery.

As it is not possible to substantiate a 100% cause and effect relationship between oncogenesis and irradiation (100), the term "postradiation sarcoma" has been used in this report, as has been done in others (121, 122).

Statistical evidence for the relationship between irradiation and oncogenesis does exist (43, 51, 113). The mechanism of induction of postradiation sarcomas remains unclear as there has been difficulty in achieving radiation-induced transformation of human cell lines in vitro (8). Radiotherapy regimens used in patients who have developed postradiation sarcomas have not been well described (27, 49). Dose levels at which these tumors are most likely to occur have not been clearly established. Conflicting reports exist. These tumors either occur in low dose areas on the edge of the field (117) or in high dose areas (14, 114, 47). According to an hypothesis based on experimental work in mice, an increasing incidence of leukemia may be noted after irradiation with increasing dose until cell kill at high doses causes a fall in incidence (38). This hypothesis could possibly be extrapolated to postradiation sarcomas but the peak incidence may not necessarily occur at the same dose level as for leukemia.

This report from Groote Schuur therefore sets out to review cases of postradiation sarcomas, including malignant mixed mullerian tumors (MMMT), presenting to the Radiation Oncology Departments of Groote Schuur Hospital and the affiliated hospitals (Frere Hospital, East London and Provincial Hospital, Port Elizabeth) or known to have occurred in patients initially treated in these hospitals. It aims [1] to establish the features of the initial malignancy as well as the latent period for the development

of postradiation sarcoma, the type of postradiation tumor and the outcome of the disease; [2] to establish as accurately as possible dose levels at which the postradiation tumors have developed; and [3] to briefly describe possible risk factors such as a genetic predisposition to the development of malignancy, repeated courses of radiotherapy, surgery as part of the treatment of the initial tumor, and chemotherapy.

Questions regarding the genesis of postradiation sarcomas cannot be answered by a review of 20 cases, even when combined with an analysis of literature. This review aims to add relevant information to the body of data from which the final answers may come. In view of the late diagnosis often made in cases of postradiation sarcoma (25, 94) the review also aims to heighten awareness of the condition so that it may be more often reported at a curable stage.

2. MATERIALS AND METHODS

2.1. INCLUSION CRITERIA

Possible cases of PRS, including MMMT, in patients treated for malignancy at Groote Schuur or the affiliated hospitals, or presenting to these hospitals with second malignancy, were identified by discussion and correspondence with members of the Radiation Oncology Departments. Cases were included in the study if the patient had developed a sarcoma in a previous radiotherapy field (regardless of the latency period) and if the histology differed from that of the primary tumor. If the postradiation tumor was an aggressive fibromatosis without histological evidence of malignancy and without metastases the case was not included. 20 cases which fulfilled the criteria for inclusion were identified. As the computerised database available did not allow a method of ensuring that all cases have been included in this study, the incidence rate for PRS could not be calculated.

2.2. DOCUMENTS AND SPECIMENS REVIEWED AND METHODS OF REVIEW

The clinical notes and, where available, diagrams, photographs of the postradiation tumors and radiological studies were reviewed. Histological specimens of the postradiation tumors (19 cases) and of the initial tumors (9 cases) were reviewed with a pathologist. Further immunocytochemical studies were obtained where indicated to

elucidate the diagnosis further. The postradiation tumors were graded as low, moderate or high grade according to the criteria of the number of mitoses, the extent to which tissue resembled normal tissue and the presence of necrosis. Clinical notes, x-rays and histological specimens as well as radiological studies were obtained, if this was at all necessary and feasible, from other institutions at which the patients had been treated.

Note was made of other complications of radiotherapy experienced by the patients and where possible of evidence of radiation damage to tissue on x-rays and in pathological specimens. In some cases the entire specimen was of tumor tissue and damage to normal tissue could not be ascertained.

2.3. CALCULATION AND PRESENTATION OF RESULTS

2.3.1. CONVERSION FACTORS

It is indicated in the text or on the tables if a conversion factor has been applied. Where doses were prescribed in Gray for Co-60 or 20MV beams, no conversion was required for tumors in soft tissue or bone. A factor of 0.957 had already been taken into account for C0-60 prescriptions in Gray. Further reduction of this factor to 0.925 for postradiation tumors in bone was not considered necessary for this study. Doses for Tantalum-182 and Radium also required no conversion. For 250kV, HVL 3.5mmCu

irradiation, where it is indicated that f-factor conversion was applied a factor of 1.05 was used for bone and 0.956 for soft tissue. For the 220kV beam a factor of 1.5 was used for bone and 0.948 for muscle. For I-125 in bone a factor of 4.67 was used (52, 102).

The f-factor gives dose in rads and this was subsequently converted to Gray (Gy). (100 rads is equal to 1 Gy.)

It must be noted that the f-factor does not take into account the radiobiological differences of the beams as this is virtually impossible to quantify in such a study. Therefore it has been specified for each case which beam was used. In cases where more than one course of radiotherapy was used, doses have sometimes been added together for the purposes of the study, even when different modalities were used in the same patient.

Prescribed doses have been described as target volume doses (the minimal dose covering the target volume), central doses (the dose on the central axis at the midpoint of the patient in the case of parallel opposed fields) or given (applied) doses. In patients who had had radium insertions for carcinoma of the cervix the dose at Manchester Point A (a point estimated to be 2cm from the vaginal fornix) has been calculated. When necessary "prescribed doses" were actually obtained from the isodose charts. For example in case 19 two courses of radiotherapy were administered, one using a single field with a given dose and one using

parallel opposed fields with a central dose. The isodose charts were used to determine the maximum dose.

Prescribed doses are described in the units used at the time of prescription as far as possible, as conversion factors vary according to the tissue being considered. In the Groote Schuur Radiation Oncology Department orthovoltage radiation is prescribed in Roentgen (R), which indicates exposure in air, and megavoltage and Radium treatment in Gray (absorbed dose).

Field sizes are described in length by breadth.

2.3.2. CASE REPORTS

Results are first presented as case histories.

2.3.3. BODY DIAGRAMS AND ISODOSE CHARTS

The postradiation tumor was drawn onto a body diagram if information about the external beam radiotherapy was available (19 cases). External beam radiation field(s) were reconstructed on the body diagram to indicate the position of the postradiation sarcoma in the field(s).

Where all radiation details were available (18 cases) isodose charts were reconstructed at one to four levels through the postradiation tumor. (In small tumors only one

level was necessary). These included off-axis isodose charts.

If necessary standard anatomical drawings were used in the construction of diagrams (123). Isodose charts with postradiation tumors superimposed have been used previously in our department (69).

Using the clinical notes, diagrams, photographs, and where available radiological studies such as ultrasound scans, angiography and CT scans, drawings of the postradiation tumors were superimposed on the isodose charts. An estimate was made of the dose range in the tissue in which the tumor had developed and the point at which growth was likely to have been initiated. (In most cases this was taken as the centre of the tumor. In patients who developed secondary tumors in the uterus a point at the site of a normal uterus was taken. Where the main bulk of the tumor did not lie at the centre of the tumor a point in the main mass was taken.) A representative diagram was chosen for each patient for inclusion in the report.

In three cases where radiological studies were no longer available, the tumor was reconstructed from descriptions onto the normal scan of another patient and transferred to the isodose charts. In two of these cases, the patient had been less than a year old at the time of radiotherapy and 4 years old at the time of development of the postradiation tumor. The tumor as described in the older child was

reconstructed on the scan of a child of less than a year of age (i.e. involved areas were demarcated) so that it could be seen whether involved structures lay in the radiation field and what dose these structures had received in the infant.

2.3.4. TABULATION OF RESULTS

Results were tabulated with reference to the sex of the patient; age at which the initial radiotherapy was given; the type and site of the initial malignancy (described in this report as the primary tumor); radiotherapy modalities, dose and fractionation regimens; the latent interval (calculated from the start of the first radiation treatment course to the presentation of the second primary, whether or not it was recognized as a postradiation tumor at this time); the age at the presentation with the postradiation tumor; the tissue in which the postradiation tumor developed (bone or soft tissue); site (trunk, head and neck or extremity with a more specific site mentioned); the dose received in the tissue in which the sarcoma or MMMT developed (dose range and point); the pathological type and grade of the postradiation tumor; the treatment of the postradiation condition and outcome of this condition (calculated from the time of presentation with the postradiation tumor). If there was a significant delay in diagnosis of the postradiation tumor after presentation (more than approximately 1 month) the outcome has been

reported in the case history from the time of diagnosis as well as the time of presentation.

2.3.5. STATISTICS

Where indicated in the Results section groups were compared with regard to latency and with regard to the dose point at which the PRS is estimated to have developed. Mean and median ages for certain groups and median survival were also calculated. The package used was Microsoft Excel 4.0 using the Statistical Analysis Toolpak. The test for comparing groups was a two sample t-test assuming unequal variances.

Results are thus presented as brief case reports, with a diagram of the radiation field and PRS on a body outline for each patient, and where available a representative isodose chart. Tables and further description of results are included after the case histories.

3. RESULTS

3.1. CASE REPORTS

Case 1: Primary Tumor: Carcinoma Cervix
Postradiation Tumor: Malignant Mixed Mullerian Tumor Uterus

A 57-year-old patient presented in 1986 with a stage 2A squamous carcinoma of the cervix. A course of C0-60 radiotherapy was commenced in December 1986 utilising 15 by 16cm anterior and posterior fields and 15 by 9cm right and left lateral fields. A target volume dose of 2.00Gy per fraction was achieved 5 times a week in 27 fractions to a total dose of 54.00Gy. The duration of external beam treatment was 43 days. A vaginal cylinder and ovoid containing 55mg of radium were then inserted for 32 hours achieving a dose of 17.6Gy at Manchester point A. The total summated dose at Manchester point A was 71.6Gy. The total duration of treatment was 48 days. At follow-up the patient was noted to have radiation proctitis and vaginal adhesions.

In December 1992, 6 years after the commencement of radiotherapy, the patient was noted to have an enlarged 22-week size uterus. Ultrasound showed a central lower abdominal mass which was solid and cystic. Aspiration biopsy in February 1993 produced cells with features of papillary cystadenocarcinoma. Hysterectomy was performed

in February 1993. The cavity of the uterus was filled by a large tumor mass measuring 6 by 8cms. Omental metastases were present. Histological diagnosis was of an infiltrating malignant mixed mullerian tumor. This was of high grade. Radiation-induced desmoplastic response was present in the myometrium. The patient was not given further active treatment. In June 1993, 4 months after hysterectomy, she was noted to have a local recurrence. She developed intestinal obstruction and probably perforation and died that month, 6 months after presentation with the postradiation tumor and 4 months after cytological diagnosis of malignancy.

As this was a uterine tumor it probably developed in an area between the coccyx and the symphysis pubis (the location of a normal uterus) and not at the central point of the mass at the time of presentation. On isodose curves through the central axis (3cm superior to the symphysis pubis) the tumor lies in an area which received from 60 to 100Gy. On curves taken 1.5cm inferior to the central axis it lies between 58 and 100Gy (fig 1).

The tumor is estimated to have developed in tissue which received between 58 and 100Gy, probably in an area which received approximately 100Gy.

Case 2: Primary Tumor: Carcinoma Cervix
Postradiation Tumor: Malignant Mixed Mullerian Tumor Uterus

A 40-year-old patient presented with a stage 2 squamous carcinoma of the cervix in May 1977. A course of Co-60 radiotherapy to the pelvis was commenced in May 1977 utilising 15 by 15cm anterior and posterior fields and 15 by 9cm left and right lateral fields. A target volume dose of 2.00 Gy was delivered 5 times a week in 27 equal fractions with adjustment of the last fraction achieving a total dose of 54.00Gy. The duration of treatment was 42 days. An intracavitary radium insertion was performed thereafter using a tandem and ovoids containing 75mg of radium and achieving a dose of 19.5Gy at Manchester point A from the radium insertion and a total of 73.5Gy at point A. The total duration of treatment was 47 days. The patient complained of dyspareunia on follow-up and was noted to have vaginal adhesions.

The patient failed to attend appointments after 1979 until June 1993, 16 years and 1 month after the commencement of radiotherapy, when she returned complaing of lower abdominal pain and dysuria. She was noted to have a suprapubic mass the size of an 18 week pregnant uterus. On scan a 12cm cystic mass was noted. She underwent laparotomy, subtotal hysterectomy and bilateral salpingo-oöphorectomy in June 1993. The endometrial cavity was noted to be filled with a polypoid tumor mass. On

microscopic examination this was found to be a malignant mixed mullerian tumor. The tumor infiltrated through the wall of the myometrium into the outer third. It was high grade. Inflammatory cells attributable to prior irradiation have been noted in the specimen. The patient refused chemotherapy and in September 1993, 3 months after presentation with the postradiation sarcoma, returned to her home elsewhere in the country. She was lost to follow-up.

This was a uterine tumor and therefore developed in tissue of the uterus in its position at the time of radiotherapy. On isodose curves through the central axis (2.5cm superior to the symphysis pubis) the tumor at the time of presentation was situated between 45 and 100Gy (fig 2). At a level 1cm superior to the symphysis pubis it was also situated between the 45 and 100Gy curves. It is therefore estimated to have developed in this dose range, probably in tissue which received approximately 60Gy.

Case 3: Primary Tumor: Carcinoma Cervix.
Postradiation Tumor : Malignant Mixed Mullerian Tumor Uterus

A 37-year-old patient presented in October 1972 with a stage 2B squamous carcinoma of the cervix. A course of Co-60 radiotherapy was commenced in October 1972 utilising 8 fields. 15 by 15cm anterior and posterior and 15 by 8cm

left and right antero-lateral fields were used initially. A dose of 1.45Gy was applied to each field 5 times a week for 15 fractions with adjustment of the last fraction achieving a total given dose of 21.50Gy to each field and a total target volume dose of 30.10Gy. Commencing on the day after the fifteenth treatment two radium insertions were performed 1 week apart using a tandem and ovoids containing 75mg of radium in both cases. At each insertion the radium was left in situ for 36 hours achieving a total dose at Manchester point A from both insertions combined of 37.44Gy. Treatment to the pelvic sidewalls commenced the day after the first radium had been removed. Treatment was by means of 15 by 15cm left and right anterior and posterior wedged fields. A dose of 2.00 to 2.11Gy was applied to each field 5 times a week for 11 fractions to the left and 12 to the right fields achieving a total given dose on the right of 22.50Gy and on the left 25.00Gy to each field. The target volume dose from the external beam treatment was 57.50Gy and the maximum dose 67.80Gy. Overall a total dose of approximately 94.94Gy was achieved at point A. The total duration of treatment was 43 days.

The patient later developed radiation cystitis (cystoscopy revealed marked radiation changes) and radiation enteritis. Small bowel enema showed features of radiation enteritis involving the ileum including an area of constant narrowing. Radiation change was noted in both iliac bones.

In June 1986, 13 years and 8 months after commencement of the radiotherapy, the patient was referred back to the radiotherapy department with a solid lower abdominal mass. CT scan revealed a well-defined 9 by 6cm central pelvic mass which could not be separated from the uterus and which appeared to be compressing the bladder inferiorly with some anterior displacement. Aspiration biopsy did not reveal malignant cells and Pap smear was normal. She was assessed as having haemato- or pyometria secondary to cervical stenosis from previous radiotherapy and no further investigations were performed until June 1987. At this time the patient complained of right iliac fossa pain and constipation. Ultrasound showed an 11cm mass resembling fibroids with possible calcification. IVP showed a large soft tissue density pelvic mass and mild obstructive changes. A presumptive diagnosis of pyo- or haematometria was again made and the patient was taken to theatre for this to be drained. The cervix could not be located and the Pouch of Douglas was inadvertantly opened. A laparotomy was performed and a "multifibroid" uterus with multiple thick fibrotic adhesions was found. Through a combined vaginal and abdominal procedure the cervix was located and dilated and the uterus drained. Necrotic material and blood were obtained. Necrotic tissue and curettings were examined and she was diagnosed as having a malignant mixed mullerian tumor of the uterus. This was a high grade tumor. Palliative subtotal hysterectomy and bilateral salpingo-oöphorectomy were performed in July 1987. The tumor was thought to infiltrate the bladder at

surgery. On macroscopic examination it was noted to extrude through ruptured areas which appeared surgical in origin. Histologically it was noted to invade almost to the serosa. Post-operatively the patient received chemotherapy (Cisplatinum, Epirubicin and Cyclophosphamide 4 weekly). After the fifth cycle a pelvic mass was noted. Chemotherapy was given for 8 cycles. It was discontinued in January 1988 when she was noted to have vaginal bleeding and tumor at the vault. A course of 20MV radiotherapy was commenced in February 1988 utilising 10 by 12cm anterior and posterior fields to the lower pelvis and vagina. A central dose of 28Gy was achieved in 8 fractions 3 times a week. The disease continued to progress locally and the patient died in June 1988, 2 years after presentation with the postradiotherapy tumor and one year after the diagnosis was made.

This is a uterine tumor and probably developed in tissue lying between the symphysis pubis and coccyx. At the level of the central axis, 2cm above the symphysis pubis, tumor at the time of diagnosis was situated between the 50 and 60Gy dose levels. Tumor from the larger bulk lying more superiorly has also been superimposed on central axis isodose curves. It lies between 60 and 100Gy (fig 3). Therefore it is estimated that this tumor developed in tissue which received from 50 to 100Gy, probably in an area which received 100Gy.

Case 4: Primary Tumor: Carcinoma Cervix
Postradiation Tumor: Malignant Mixed Mullerian Tumor Uterus

A 55-year-old patient presented with a stage 3B poorly differentiated squamous carcinoma of the cervix in 1957. She underwent two intracavity radium insertions of which the details have been lost. A course of of 220kV, HVL 1.5mmCu radiotherapy was then commenced in November 1957 utilising four fields (right and left anterior oblique and right and left posterior oblique). A dose of 200R was applied to each field 5 times a week. The anterior fields received 18 fractions to a total of 3600R and the posterior 19 fractions to a total of 3800R, the two final fractions to the posterior field being given on the same day. The total target volume dose was approximately 3783R. The duration of external beam treatment was 28 days.

At a routine visit in March 1974, approximately 16 years and 4 months after the commencement of radiotherapy, the patient complained of abdominal pain and swelling. She was noted to have a mass the size of a 14 to 16 week pregnant uterus arising from the pelvis. Ultrasound showed a large cystic mass in the midline. Barium enema showed the colon to be displaced in the sigmoid area by a large soft-tissue density pelvic mass. Liver scan showed patchy uptake throughout the liver. Chest X-ray showed no metastases. The tumor increased rapidly in size over two weeks and the patient was subjected to laparotomy in April 1974. An

irresectable tumor arising from the pelvis was found. The uterus was 20 weeks size. Tumor tissue was bursting through the myometrium. There was parametrial involvement to the pelvic sidewalls. Adhesions were noted around the liver. Biopsy only was performed. On histological examination this was diagnosed as a malignant mixed mullerian tumor. This diagnosis has been confirmed on review. Only stromal sarcoma is noted in the uterine specimen, probably because insufficient material is available. The diagnosis is as noted on the basis of malignant glands in the broad ligament. The differential diagnosis would be stromal sarcoma of the uterus with an adenocarcinomatous component in the broad ligament. Chest x-ray showed a large rounded opacity with fluid levels in the retro-cardiac region. This may have been due to a hiatus hernia which was evident on Barium swallow but lung metastases were not excluded. Therefore the patient was assessed as possibly having spread to lung and liver.

It was decided that the patient should commence chemotherapy with Actinomycin D and Vincristine. After the first injection of Actinomycin D she developed confusion and vomiting. She died in May 1974, 2 months after presentation with the postradiation tumor, before she was due for re-assessment for further chemotherapy.

As details of the doses achieved by the radium insertions have been lost an estimate of the dose at which this tumor developed is not possible. Fig 4 shows the situation of

the tumor at presentation in relation to the external beam fields.

Case 5: Primary Tumor: Carcinoma Cervix
Postradiation Tumor: Rhabdomyosarcoma of the Uterus

This 35-year-old patient presented in March 1983 with a Stage 3B carcinoma of the cervix. A course of 20MV radiotherapy was commenced in May 1983 utilising 17 by 16cm anterior and posterior and 17 by 11cm right and left lateral fields to the pelvis. A target volume dose (minimum tumor dose) of 2.88Gy was delivered 3 times a week for 16 fractions and a final fraction of 2.50Gy to achieve a total target volume dose from external beam therapy of 48.45Gy. The duration of external beam radiotherapy was 57 days. Two days after the completion of external beam treatment the patient underwent a radium insertion. A tandem and two ovoids containing 75mg of radium were inserted for 35.5 hours achieving a dose of 23.08Gy at Manchester point A from the radium insertion and a total summated dose at point A of 71.53Gy. The total duration of treatment was 60 days.

In May 1988 the patient complained of post-coital bleeding and dyspareunia and was noted to have a frozen pelvis. In March 1988 she complained of lower backache. CT scan showed no evidence of lymphadenopathy or definite tumor

recurrence. Loops of small bowel appeared closely applied to the region of the uterus. In March 1993, 9 years and 10 months after commencement of the course of radiotherapy, the patient was admitted to hospital with a rectal stricture. Rectal biosy showed radiation changes. CT scan showed a large midline cystic structure with a soft tissue rim in the pelvis which was thought to represent a fluid-filled uterus. Bilateral hydronephrosis was noted.

In September 1993 the patient was referred back to the Radiotherapy Department with a smooth hard pelvic mass. CT scan was compared to one done in March 1993. This showed an enlargement of the mass previously noted but no hydronephrosis. The patient did not attend clinic again until October when she was seen again complaining of lower abdominal pain and the passing of fresh blood per rectum. Sigmoidoscopy showed a bleeding rectal stricture. Laparotomy was advised to establish the nature of the mass. The patient was reluctant to consent to this. In December 1993 the vaginal vault, previously described as a fibrosed tube, was noted to have broken down. Biopsy of a vault mass showed features of a rhabdomyosarcoma. The differential diagnosis included the rhabdomyosarcomatous component of a carcinosarcoma. On review this has been confirmed to be a high grade rhabdomyosarcoma. In January 1994 the patient complained of haematuria, dysuria and difficulty in passing urine as well as incontinence and suprapubic pain. Cystoscopy revealed slough, possibly due to tumor. Vaginal examination revealed an extensive mass

invading the vagina. The patient was treated symptomatically. She died in August 1994, 17 months after a mass was noted on CT scan and 8 months after histological diagnosis of the postradiation sarcoma. Permission for autopsy was refused by the family.

On isodose curves 5.5cm above the central axis, approximately 2cm below the superior tumor, the tumor is situated between 47 and 48Gy. On isodose curves at a level through the central axis, 1.5cm above the symphysis pubis, it lies between 40 and 62Gy (fig 5). This is a uterine tumor and therefore developed in tissue of the uterus in its position at the time of radiotherapy. It is estimated to have developed in tissue receiving between 40 and 62Gy, at a point receiving approximately 50Gy.

Case 6: Primary Tumor: Carcinoma Cervix
Postradiation Tumor: Leiomyosarcoma of the Abdominal Wall

A 40-year-old woman presented in September 1985 with a Stage 2B squamous carcinoma of the cervix. A course of Co-60 radiotherapy was commenced in September 1985 utilising 16 by 14.5cm anterior and posterior fields to the pelvis. A central dose of 2.85Gy was achieved 4 times a week for 17 fractions to a total central dose of 48.45Gy. The duration of external beam treatment was 33 days. After 5 external beam treatments a vaginal cylinder containing 95mg of

radium was inserted for 10 hours due to bleeding achieving a dose from the cylinder of 4Gy at Manchester point A. A tandem and single ovoid containing 55mg of radium were inserted for 6 hours after the completion of external beam treatment achieving a dose of 3.3Gy at point A from this insertion. Overall a summated dose of 55.75Gy was achieved at Manchester point A in a total of 37 days.

In May 1989 thickening of the skin and superficial muscle thickening were noted in the irradiated area. In December 1993, 8 years and 3 months after the commencement of radiotherapy, the patient complained of a mass in the left lower quadrant which had been present for 5 months and was painful. Fibrosis and a small area of darkening with skin tethering were noted in the irradiated area. There was no obvious mass palpable but CT scan showed a mass lesion just above the level of the acetabula. There was no plane of cleavage between this lesion and the rectus femoris muscle. Aspiration biopsy failed to reveal a diagnosis and further investigations were not undertaken until the patient returned in January 1994. At this time an 8 by 8cm irregular mass was noted in the abdominal wall with a 2cm area of skin infiltration. Biopsy showed this to be a leiomyosarcoma. The tumor was high grade. No surgery was possible and the patient was treated symptomatically with analgesics. She is alive with disease at the time of reporting, 9 months after the presentation with sarcoma in December 1993.

On isodose curves the tumor lies in an area which received between 20 and 52Gy (fig 6). It is thought to have grown at a moderate dose point of 50Gy.

Case 7: Primary Tumor: Low Grade Stromal Sarcoma of the Uterus
Postradiation Tumor: Fibrosarcoma of the Soft Tissues of the Pelvis

A 19-year-old patient underwent dilatation and curettage in 1958 for menorrhagia. Curettings showed features of possible endometrial sarcoma but stromal endometriosis could not be excluded. On review there was found to be malignancy in this specimen which was suspicious of stromal sarcoma. The patient subsequently underwent myomectomy and further dilatation and curettage. Specimens showed no malignancy. The patient presented to our Radiotherapy Department in July 1959 with a pelvic mass. Biopsy of tumor protruding through the cervix showed features of probable endometrial sarcoma. On review a diagnosis of low grade stromal sarcoma has been made.

In July 1959, when the patient was 20 years old, a course of 250kV, HVL 3,5mmCu radiotherapy was commenced to the lower abdomen utilising four 25 by 12,5cm fields (left and right anterior oblique and left and right posterior oblique). An applied dose of 50R was given initially and was increased daily in increments of 10R until 110R was

achieved. The maximum tumor dose was increased from 65R to 143R and the target volume dose from 55R to 121R. After 16 fractions the patient's separation changed. The same applied dose was used achieving a daily maximum tumor dose of 165R and a target volume dose of 148.5R. After a further 5 fractions fields were reduced to 15 by 10cms. A further 6 fractions were given of applied dose 200R achieving maximum tumor dose 220R and target volume dose 200R. Treatment was given 5 times a week for a total duration of treatment of 40 days. The total applied dose was 3300R, the total maximum tumor dose 4160R and the target volume dose 3647R. The size of the mass decreased.

The patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy in November 1959 and a diagnosis of stromal endometriosis was made. On review this has been noted to be the same tumor as in the previous specimen (stromal sarcoma) but of modified appearance. The patient remained well on follow-up and was discharged from the clinic in December 1986.

In November 1989, 30 years and 4 months after the commencement of radiotherapy, the patient presented to a private clinic with a history of lower abdominal pain, urinary frequency and dyspareunia. She was found to have a tender fixed pelvic mass of about 15 by 20cm. Ultrasound showed a solid mass and confirmed the clinical measurements. CT scan showed a central solid mass between the bladder and rectum. On intravenous pyelogram the right

kidney and ureter were non-functioning. Cystoscopy showed a possible area of bladder infiltration. Laparotomy revealed an inoperable tumor arising from the pelvis with the appearance of seedlings on the anterior surface of the rectus muscle. Histology showed an undifferentiated sarcoma with metastasis to muscle.

In June 1990 treatment with a neutron beam was commenced at another institution for a 7 by 7cm tumor with pelvic spread. It is uncertain whether chemotherapy had been given prior to this. 3 angled wedged fields were utilised. A target volume dose of 7.8Gy was achieved in 6 fractions treating 3 times a week. The course was repeated to reduced fields 8 weeks later as there was minimal response and the tumor had remained inoperable. At follow-up the patient appeared well. She had occasional diarrhoea and a cystic mass was palpable fixed to the pelvic sidewall. CT scan showed virtually no change and surgery was not recommended.

The patient subsequently presented to a surgeon in another city with a large pelvic mass. A complete resection was performed in June 1991. There was infiltration of the peritoneum, vault of the vagina, bladder base and small bowel with obstruction of the latter and the right ureter. Histology showed a moderate grade fibrosarcoma. On review the histological appearance of the postradiation tumor (fibrosarcoma) is different from that of the initial tumor (low grade stromal sarcoma).

The patient was subsequently noted to have metastases in the abdominal wall and para-aortic nodes as well as increased tumor in the pelvis. She died in November 1991, 2 years after the presentation with the postradiation sarcoma.

On isodose curves at the level of the central axis (through superior tumor) the tumor is situated in an area which received between 30 and 40.3Gy. 4cm below the central axis (mid-tumor) it lies between 30 and 40Gy (fig 7). 6.2cm below the central axis it lies between 32 and 39.10Gy. The tumor appears to have developed in tissue which received between 30 and 40Gy, probably in tissue receiving approximately 38Gy.

Case 8: Primary Tumor: Carcinoma Breast
Postradiation Tumor: Pleomorphic Sarcoma of the Chest Wall

A 27-year-old woman who had in 1985 been treated with conservation surgery and radiotherapy and subsequently mastectomy for a carcinoma of the right breast, underwent wide local excision and axillary clearance for a T1 node negative ductal carcinoma of the upper outer quadrant of the left breast in July 1987. A course of Co-60 radiotherapy was commenced in August 1987 utilising 17 by 8cm planned tangential fields to the left breast. A target

volume dose of 2.4Gy was achieved 4 times a week in 16 equal fractions to a total dose of 38.4Gy. A 10MeV electron boost was then commenced to the scar utilising a 6 by 10cm field. A dose of 4.5Gy four times a week was applied for five fractions to achieve a total dose of 11.25 Gy at the 90% isodose from the booster field. The total duration of treatment was 40 days.

In July 1989, 1 year and 11 months after commencement of radiotherapy to the left breast, a 2 by 1cm mass was excised from under the breast. Pathologic diagnosis was that this was a malignant fibrous histiocytoma but on review it has been described as a high grade pleomorphic sarcoma. At the time of the last report, in September 1994, 5 years and 2 months after her presentation with the postradiation tumor, the patient was well and free of sarcoma recurrence. A recurrent carcinoma in the left breast had however been recently excised and she had commenced Tamoxifen.

On an isodose curve the tumor lies in a moderate dose area which received 38Gy (fig 8).

Case 9: Primary Tumor: Carcinoma Breast
Postradiation Tumor: Sarcoma of the Axilla

A 52-year-old woman underwent radical mastectomy for a T1 node positive carcinoma of the left breast in February

1976. A course of Co-60 radiotherapy was commenced in March 1976 to the left supraclavicular and superior internal mammary nodes utilising an 18 by 15cm anterior "inverted L" field and a 5 by 12cm posterior supraclavicular field. A dose of 2.25Gy for 16 fractions, followed by 2.65Gy for 8 fractions and then 1.50Gy for 1 fraction was applied five times a week to the anterior field to a total applied dose of 58.7Gy. A dose of 0.95Gy was applied 5 times a week to the posterior field for 8 fractions with adjustment of the last fraction to a total dose of 7.5Gy. A dose of 52.85 Gy was achieved at the apical node. The duration of treatment was 37 days.

In 1983 the patient developed pain in the left shoulder and chest wall. X-ray in September showed increased density in the clavicle and ribs compatible with radiation change. CT scan showed an increase in left axillary soft tissue. In January 1984, 7 years and 10 months after commencement of radiotherapy, a 3 by 3cm left axillary mass was noted. Aspiration cytology showed malignant cells and the patient was treated with Tamoxifen for presumed recurrence of the breast carcinoma. The disease progressed on this treatment and on subsequent chemotherapy (Cyclophosphamide, Methotrexate and 5-Fluorouracil). Biopsy in May 1984 showed features of a sarcoma. The tumor is of moderate grade but there is insufficient material for a more specific diagnosis to be made on review. A course of Co-60 radiotherapy in hyperbaric oxygen was commenced to the axillary mass utilising anterior and posterior opposing

fields. A total central dose of 36Gy was given in 9 fractions with treatment twice a week. The duration of treatment was 29 days. There was initial regression on irradiation but three months after completion of treatment the lesion was noted to have recurred. It continued to progress. Lymphoedema of the left arm, fungation of the tumor and bleeding were noted. The patient died in July 1985, 18 months after presentation with the axillary mass and 14 months after diagnosis of a sarcoma.

The tumor appears to have developed on the edge of the area protected by lead, in tissue which received between 20 and 35Gy, probably in an area which received approximately 30Gy (fig 9).

Case 10: Primary Tumor: Carcinoma of the Breast
Postradiation Tumor: Leiomyosarcoma of the Clavicular Area

A 68-year-old woman with a history of surgery for an ovarian tumor (details unknown) underwent modified radical mastectomy in September 1972 for a Stage 2 carcinoma of the right breast. This was followed two weeks later by excision of slough and skin graft. A course of C0-60 radiotherapy was commenced in October 1972 to the internal mammary and supraclavicular areas utilising a 16 by 21cm "inverted L" anterior field and a 6 by 10cm supraclavicular posterior field. A dose of 2Gy for 2 fractions and then

2.5Gy for 23 fractions with adjustment of the last fraction was applied five times a week to the anterior field to a total applied dose of 60Gy. A dose of 1.15Gy was applied five times a week for 15 fractions to the posterior field with adjustment of the last dose to a total applied dose of 18Gy. A dose of 55Gy was achieved at the apical node. The duration of treatment was 33 days.

In 1984 the patient was noted to have dermatomyositis secondary to liver metastases diagnosed on ultrasound. She was treated with hormonal agents until April 1985 when these were discontinued due to disease progression.

In September 1985, 12 years and 11 months after commencement of radiotherapy, the patient was noted to have a swelling in the right clavicular area. A tumor was incompletely resected in November 1985 and shown on microscopic examination to be a spindle cell sarcoma. On review this has been diagnosed as a leiomyosarcoma in spite of a negative desmin stain. (The tumor contains cigar-shaped cells running in sheets interspersed with striated muscle. Fibrillar cytoplasm is noted). Radiation change with fibrosis and muscle lysis as well as vascular changes in surrounding normal tissue have also been noted in this tumor. It was a high grade tumor.

Six months after resection the tumor recurred in the region of the scar. Treatment was symptomatic. The patient died in June 1986, 9 months after presentation with the

postradiation tumor. The cause of death is not noted and is uncertain in view of the possible presence of metastases from the breast carcinoma.

4cm above the central axis the superior tumor lies between 55 and 64.54Gy. At a level 1cm above the central axis (approximately through mid-tumor) the tumor lies between the 55 and 64.39Gy dose levels (fig 10). 2cm below the central axis the inferior tumor lies between 10 and 58Gy. The tumor is estimated to have grown in tissue which received from 10 to 64Gy, and probably in tissue which received approximately 60Gy.

Case 11: Primary Tumor: Bilateral Retinoblastoma
Postradiation Tumor: Osteosarcoma of the Maxilla

An 8-month-old child was referred to Groote Schuur Hospital in January 1969 having undergone enucleation of the right eye for retinoblastoma in October 1968. Multiple tumors were noted in the left eye. X-ray of the skull and orbits did not show any bony abnormality.

A course of 250kV, HVL 3.5mmCu photon radiotherapy was commenced in February 1969 to both orbits utilizing 5 fields: 1) 5 by 4cm left lateral posterior - 100% 2) 5 by 3cm left lateral anterior -25% 3) 5 by 3cm left anterior - 25% 4) 5 by 5cm right lateral - 100% and 5) 5 by 3cm right lateral oblique - 100%. A maximum tumor dose of 3686R was

achieved in 21 equal fractions of 175.5R. The target volume dose (minimum tumor dose) of 3119R was achieved in 21 equal fractions of 148.5R. Treatment was given five times a week. The duration of treatment was 29 days. 0.6mg of triethanomelamine was administered intravenously on the days of the fifth and 12th fractions and 4 days after treatment had been completed. The lesions did not regress and the patient subsequently received two injections of intravenous Endoxan.

In June 1969 two Tantalum-182 wire ophthalmic applicators were applied to the left eye. 1) One with two ellipses of tantulum, one weak and one strong, of mean diameter 6 and 5mm, was applied to the upper temporal quadrant. The dose rate at 2mm (inclusive of 5R/hr from the other applicator) was 126R/hr. 2) One with an outer rectangle of one weak, one strong wire about 13 by 10mm and an inner circle of 4mm diameter with one weak and one weaker wire was applied to the lower nasal quadrant. The dose rate for the lower nasal applicator (inclusive of 2R/hr from the other applicator) was 138R/hr. The duration of application was 146,5 hours and the dose at the surface of the upper temporal applicator was 18459R. The dose at the surface of the lower nasal applicator was 20217R.

In April 1970 left enucleation was performed as there was thrombotic glaucoma with secondary vitreous haemorrhage and no useful vision in the eye. The lens was cataractous. Histological assessment of the eyeball showed no evidence

of viable tumor. There was focal calcification and degeneration of collagen.

In September 1972, 3 years and 7 months after the commencement of the initial course of radiotherapy, the child presented with a swelling of the left palate. X-ray of the facial bones showed opacification of the left maxillary antrum with apparent erosion of the lateral wall. The floor of the orbit was eroded. Biopsy of the gingiva showed features of osteosarcoma. This was a high grade tumor. Necrosis is evident in the specimen. Examination under anaesthaesia revealed swelling and elevation of the floor of the left orbit, medial displacement of the lateral wall of the nose and ulceration and tumor of the left upper gingiva in the region of the absent left molar. There was a hard swelling of the left half of the hard palate not crossing the midline and of the anterior maxillary wall.

A course of Co-60 radiotherapy was commenced. Initially a single 5 by 5cm anterior field to the left maxilla was utilised. A dose of 2.00Gy was given per fraction 5 times a week. After 5 fractions, when planning had been completed, a 5 by 6cm left anterior field and a 5 by 7cm left lateral oblique field were utilised. A tumor dose of 44Gy was given in 22 equal fractions of 2.00Gy each 5 times a week. There was a rest period of 17 days after 10 fractions due to an acute reaction. The duration of the entire course of radiotherapy (3 fields) was 52 days. The total maximum tumor dose was 62.00Gy and the target volume

dose (minimum tumor dose) 52.00Gy. Five intravenous injections of 125µg Actinomycin D were given during the course of radiotherapy. When treatment was recommenced after the rest period, weekly Vincristine was administered until the end of treatment (3 injections) and 3 times thereafter.A week after the last Vincristine injection 5 daily injections of 185ug Actinomycin were administered.

Maxillectomy was performed in January 1973. The mass had been noted to have decreased in size. At surgery the surgeon's opinion was that the tumor was extending up and over the orbital floor. No residual tumor was seen on histological examination of the surgical specimen. Fibrosis from previous radiotherapy has been noted in this specimen.

In March 1973 extension of tumor in the left orbit was noted. X-ray showed opacification of the orbit. No further active treatment was possible. The child died in June 1973, 9 months after he presented with the osteosarcoma.

At a level 1.5cm inferior to the central axis of the field the superior tumor lies between 10 and 40Gy. 1cm inferior to this at the inferior field margin, at a level between superior and mid-tumor, the tumor lies between 20 and 33Gy. 1cm inferior to this level, below the inferior field margin, the mid-tumor lies between 5 and 7.7Gy (fig 11). The tumor lies in tissue which extends from that even

further inferior to the external beam field margin, where a minimal dose will have been received, to tissue which received 40Gy. It is estimated to be likely to have developed in tissue which received 8Gy.

Case 12: Primary Tumor: Bilateral Retinoblastoma
Postradiation Tumor: Osteosarcoma Orbital Bones

A 5-month-old girl was referred in May 1976 with the diagnosis of bilateral retinoblastoma. Skull x-ray and tomograms of the orbits and optic canals were normal. She had undergone enucleation on the right. Two nodules were present on the left retina. A course of 250kV, HVL 3 5mmCu photon radiotherapy was commenced in May 1976 utilising 4 by 4cm fields to the right and left head. Three fractions of 140R achieving a central dose of 150R per fraction were applied. The dose was then increased to 190R (central dose 230R) for 2 fractions to compensate for a public holiday. A further 14 fractions of 140R and a final fraction of 70R were then applied. Treatment was given 5 times a week. The total applied dose to each field was 2830R. A total central dose of 3000R was achieved. The duration of treatment was 39 days.

4 days after the completion of radiotherapy the patient was commenced on chemotherapy with CCNU and Vincristine.

In January 1977, 2 months after completing chemotherapy, progression was noted in the left eye and chemotherapy was changed to Dibromodulcitol and Procarbazine. This chemotherapy was continued with interruptions until April 1978. In May 1977 progression was noted on the left and in June an Iodine-125 applicator with four 1.80mCi sources and one 0.95mCi source was applied to the posterior aspect of the left globe. A dose of 45Gy over 150.5 hours was given. The tumor did not respond. In October 1977 a course of Co-60 radiotherapy was commenced utilising a 3 by 2.5cm field to the left lateral orbit. A dose of 14.60Gy was given in two fractions over five days with the sensitizer Ro-07-0582 orally before each treatment. In February 1978 gross recurrence was noted and the patient was again treated with Co-60 radiotherapy utilising a 3 by 3cm field to the left eye. A dose of 14.00Gy was given in 2 equal fractions over 4 days with the sensitizer Ro-07-0582 before each treatment. In April 1978 left enucleation was performed due to progression.

In December 1980, 4 years and 7 months after commencement of the first course of radiotherapy, a mass was noted in the left zygoma. X-rays of the skull and facial bones showed left retro-orbital sclerosis and a possible sphenoid edge mass. The left zygomatic arch was expanded and sclerotic. A bone biopsy in January 1981 showed this to be an osteogenic sarcoma. The tumor is high grade. No active treatment could be offered. The disease progressed and the

patient died in May 1981, 5 months after presentation with the postradiation tumor.

At the level of the central axis, approximately midway between superior and mid-tumor, the tumor lies between 35 and 60Gy. 1cm inferior to this, at approximately the level of mid-tumor, it lies between 20 and 50.3Gy (fig 12). 2cm inferior to the central axis the tumor lies between 20 and 27.1Gy. It is estimated to have developed in tissue receiving between 20 and 60Gy, probably in approximately a 50Gy dose area.

Case 13: Primary Tumor: Bilateral Retinoblastoma
Postradiation Tumor: Pleomorphic Sarcoma of the Orbital Soft Tissues

A 28-month-old female underwent left enucleation for a retinoblastoma involving the optic nerve in September 1972. Multiple lesions were present in the right eye. X-ray of the skull and orbits showed no abnormality except enlargement of the left optic foramen with possible erosion of the cortical margin inferiorly.

A course of 250kV, HVL 3.5mmCu photon radiotherapy was commenced in October 1972 utilising five fields to the orbits and the right retina: 1) 4 by 2cm left lateral; 2) 4 by 6cm left anterior oblique; 3) 4 by 4cm left anterior; 4) 4 by 2cm right anterior; 5) 4 by 5cm right

lateral. A maximum tumor dose of 3630R in 19 fractions of 182R and a final fraction of 172R was achieved and a target volume dose (minimum tumor dose) of 3300R. Treatment was given 5 times a week. The duration of treatment was 30 days. Cyclophosphamide was commenced during radiotherapy and continued each 2 weeks for 6 weeks.

By October 1973 the disease on the right had progressed and in May 1974 right enucleation was performed for retinoblastoma.

In 1974 the patient was commenced on treatment for pulmonary tuberculosis.

In August 1977, 4 years and 10 months after commencement of radiotherapy, the patient was noted to have a mass in the left orbit and zygoma. Tomograms showed a soft tissue mass in the left orbit and destruction of bone. CT scan showed a retro-orbital mass on the left eroding through the postero-lateral aspect of the wall of the orbit. There was a small portion of tumor in the left middle cranial fossa. This has been assessed by a radiologist as being primarily a soft tissue tumor. The patient was initially treated with chemotherapy (Cyclophosphamide and Vincristine) on the assumption that the retinoblastoma had recurred. The initial biopsy was inadequate for a definite diagnosis. Overall features of repeat biopsy were of pleomorphic sarcoma. In view of the radiological evidence of bone destruction by the tumor it was decided to treat it as an

osteogenic sarcoma. Treatment was changed to Vincristine, high dose Methotrexate and Adriamycin and given for two 28-day cycles. Response was noted but there was subsequent progression clinically and on CT scan. Chemotherapy was discontinued. The patient died in February 1978, 6 months after presentation with the postradiation tumor. At autopsy pleomorphic sarcoma was found to have destroyed the left temporal lobe of the brain. It had extended through the greater wing of the sphenoid, and into the pharynx and left maxillary sinus.

CT scans showing the postradiation tumor have been superimposed on the contours taken at the time of radiotherapy. At the level of the central axis mid-tumor lies between 10 and 37Gy (fig 13). 1cm inferior to the central axis it lies between 10 and 37Gy. The inferior part of the tumor is in the region of the inferior field. At the inferior field level the tumor lies between 10 and 28 Gy. The tumor is estimated to have grown between less than 10Gy and 37Gy at a point which received approximately 35Gy.

Case 14: Primary Tumor: Wilms' Tumor
Postradiation Tumor: Osteosarcoma of the Iliac bone

In March 1975 a 4-year-old child presented with a 9 by 15cm mass in the right abdomen. Intravenous pyelogram showed a non-functioning right kidney. A course of 250kV, HVL3.5mm

Cu photon radiotherapy was commenced in March 1975 to the right abdomen utilising 20 by 12.5cm anterior and posterior parallel opposed fields. The fields extended from the superior margin of the tenth thoracic vertebral body to the superior iliac crests and 2cms to the left of the midline. A dose of 130R was applied to each field for 9 fractions and 80R for 1 fraction 5 times a week to acheive a total applied dose of 1250R to each field and a total central dose of 1200R. The duration of treatment was 15 days. Incomplete resection of a Wilms' tumor was performed 6 days later. On the 13th postoperative day 250kV, HVL 3,5mmCu photon radiotherapy was recommenced utilising 14 by 13cm anterior and posterior parallel opposed abdominal fields. The field centres were the same as for the preoperative fields. A dose of 114R was applied to each field for 13 fractions and 154R for 1 fraction to achieve a total applied dose of 1636R to each field and a total central dose of 1800R. Treatment was given 5 times a week. The duration of this course was 18 days.

Chemotherapy with Vincristine, Actinomycin D and Adriamycin was commenced preoperatively and continued for a 68-week course.

In February 1992, 16 years and 11 months after the commencement of radiotherapy, the patient presented with a 2-month history of a mass in the right iliac fossa. The mass measured 10 by 10cm. The right leg was moderately swollen. Ultrasound showed an inhomogeneous mass with a

suggestion of necrosis in it. It measured 9.7 by 4.2 by 6.6cm and appeared fixed to the ileum. X-rays showed a large mass which appeared to arise from the right ileum and had the appearance of a large osteosarcoma. A number of slightly flattened and deformed lumbar and thoracic vertebrae were noted to probably be due to radiotherapy in childhood. A biopsy specimen from the ileum showed features of osteosarcoma. This is a high grade tumor.

The patient was commenced on chemotherapy with Cisplatinum and Adriamycin for 2 cycles 4 weeks apart. There was no response to this chemotherapy and treatment was changed to chemotherapy with Cyclophosphamide, Vincristine, Adriamycin and Dacarbazine for 2 cycles 1 month apart. There was no response to treatment. The patient died in August 1992, 6 months after presentation with the sarcoma.

Isodose curves through the superior iliac crest at the inferior border of the field show the iliac bone to have been in an area which received approximately 10 to 13Gy (fig 14). The tumor is estimated to have grown in bone which received approximately 12Gy.

Case 15: Primary Tumor: Carcinoma Parotid

Postradiation Tumor: Osteosarcoma of the Mandible

A 17-year-old female underwent excision of a tumor at the left angle of the jaw in December 1967. (She had also had

surgery for the swelling 10 years previously.) Histological examination showed a mucoepidermoid carcinoma of salivary gland origin with involvement of a lymph gland. The specimen shows low-grade tumor. A course of Co-60 radiotherapy was commenced in March 1968, when the patient was 18 years old, to the left parotid area utilising a 10 by 7cm left lateral and a 10 by 5cm left anterior field. A dose of 2.50Gy was given to each field 3 times a week for 16 fractions achieving a maximum tumor dose of 3.25Gy and a minimum (target volume dose) of 3.00Gy per fraction. The total maximum tumor dose was 60.00Gy and the target volume dose 48.00Gy. The duration of treatment was 37 days.

In February 1975, 6 years and 11 months after the commencement of radiotherapy, the patient was admitted to the radiotherapy ward with massive swelling of the right face. The history was of 2 months duration. The lesion extended from the right temporal fossa 5cm above the right zygomatic arch to the left lower third molar and from the right external auditory meatus posteriorly. It was assessed as being a T4 tumor. It crossed the midline in the floor of mouth. It was deep to the masseter and bulging into the mouth. Small nodes were noted in the right and left neck. Pigmentation from previous radiotherapy was noted. On the basal view of skull x-rays a large soft tissue tumor was noted in the region of the mandible on the right. Panorex showed a moth-eaten appearance to the right mandible and a poorly-defined periosteal reaction. There was a large soft tissue mass

apparently in the region of the angle of the mandible and extending mainly into the oral cavity. Biopsy showed this to be an osteosarcoma. The tumor is high grade. Methotrexate and Vincristine were administered once. The tumor continued to grow and fungated externally. The patient bled from the mouth. She was sent home in March 1975 and subsequently died. The date of death is uncertain.

At the superior edge of the field the bone containing superior tumor lies at 12Gy. At the central axis, through mid-tumor, the bone lies at 16Gy. The tumor in the body of the mandible lies between less than 8Gy and 16Gy if isodose curves of the field edge are superimposed on this area (fig 15). The tumor appears to have developed in bone which received from less than 8Gy to 16Gy. It is thought to have developed initially in the body of the mandible. Therefore it probably developed from a point which received approximately 12Gy.

Case 16: Primary Tumor: Synovial Sarcoma the Thigh
Postradiation Tumor: Osteosarcoma of the Femur

This 21-year-old patient was referred to our institution in March 1976 after excision of a mass in the left thigh. The histology report was that it was a soft part sarcoma. Review of the specimen led to the report that it was an undifferentiated malignant tumor, probably a sarcoma. At a

later review with immunocytochemical tests a diagnosis of synovial sarcoma has been made.

A course of Co-60 radiotherapy in hyperbaric oxygen was commenced to the left thigh in April 1976 utilising 30 by 11cm anterior and posterior fields to the left thigh. A central dose of 4.5Gy was given twice a week for 10 fractions to a total central dose of 45.00Gy. After 7 fractions the patient refused hyperbaric oxygen and was treated in air. The total duration of treatment was 33 days.

2 weeks after completion of radiotherapy the patient received chemotherapy with Vincristine and Methotrexate.

The patient failed to return to clinic until November 1976 when he presented with an ulcer on the right leg which was not malignant. At that time he received further chemotherapy (Vincristine, Methotrexate and Adriamycin). He was subsequently unable to attend further appointments as his employer would not release him from his duties. At follow-up appointments in April 1977 and April 1978 he was noted to be clinically free of recurrence. In April 1984 the patient was referred back to our institution with a lesion which clinically appeared to be a local recurrence with sepsis and bleeding. Biopsy specimens did not reveal malignancy but pseudoepitheliomatous hyperplasia, fibrous tissue with degenerative cells and radiation changes in vessels.

In 1987 the patient presented to another institution with an adenocarcinoma of the upper lobe of the right lung which was treated by means of lobectomy. He also received treatment for tuberculosis. In November 1992 he presented with symptoms due to recurrence of the bronchial carcimoma. Bronchoscopy revealed a fungating mass of the right bronchus intermedius which on histological examination was again found to be a poorly differentiated adenocarcinoma. Symptoms were controlled by means of palliative radiotherapy.

In July 1993, 17 years and 3 months after commencement of the course of radiotherapy to the left thigh, the patient returned to the same institution with a history of approximately 2 months of swelling of the left thigh, pain and stiffness of the left knee. X-ray of the left femur and knee showed a large osteosarcomatous lesion of the shaft of the femur and underlying osteoporosis of the bones. Biopsy showed a poorly differentiated osteosarcoma which on review of the report appears to have been high grade although grade is not specifically mentioned. The specimens could not be obtained for review. The patient was assessed for palliative amputation. Bone scan in September revealed intense uptake in the left femur and diffuse metastases in the spine, pelvis and skull. The features were those of an osteogenic sarcoma of the left femur and widespread metastases. Chest x-ray showed diffuse metastases in the right lung and CT scan multiple

pulmonary metastases and mediastinal lymphadenopathy. The patient died on 23 October 1993, 3 months after presentation with the postradiation tumor. Amputation had not been performed. The cause of death is ucertain in view of the presence of incurable bronchus carcinoma.

The bone at the level of the superior field border, through the superior tumor, lies between 38 and 39Gy. At a level 7.5cm above the central axis, through the main tumor bulk, the bone lies between 42 and 47Gy (fig 16). At the level of the central axis (mid tumor extent in bone) the bone lies between 45 and 47Gy. The tumor is estimated to have grown between 38 and 47Gy in an area which received approximately 45Gy.

Case 17: Primary Tumor: Giant Cell Tumor of the Pelvic bones

Postradiation Tumor: Postradiation Sarcoma in the Site of a Previously Irradiated Giant Cell Tumor.

A 37-year-old male presented in 1977 with an extensive osteolytic bone lesion involving the right ileum and extending into the right superior pubic ramus. Open biopsy at the junction of the right superior pubic ramus with the ileum had shown tumor totally within the periosteum of the pelvis. Provisional histological diagnosis was of a grade 2 giant cell tumor of bone but the final diagnosis was of possible aneurysmal bone cyst - diagnosis uncertain. On

review the most likely diagnosis is thought to be grade 2 giant cell tumor.

A course of Co-60 radiotherapy was commenced in December 1977 utilising 13 by 9cm anterior and posterior parallel opposed fields to the right pelvis. 24 fractions of 2.20Gy and a single fraction of 3.25Gy were applied to each field 5 times a week. A total applied dose of 56.05Gy and a total central dose of 50.00Gy were achieved. The duration of treatment was 38 days.

Subsequent x-rays showed some ossification in the lesion. In October 1980 the patient complained of pain in the right hip. X-rays were unchanged.

In February 1981, 3 years and 2 months after commencement of radiotherapy, x-rays showed evidence of radiological recurrence. Angiography showed features of a malignant vascular tumor of the right ileum and superior and inferior pubic rami with extension into the obturator foramen and further extension into the pelvis adjacent to the ileopectineal line. CT scan showed the lesion to involve the acetabulum and extend into the right superior pubic ramus. There was extension into the ischium with loss of cortex on the medial aspect and extension of soft tissue into the right obturator muscle which was displaced medially.

In March 1981 the vascular supply to the tumor was removed by embolisation.

In March 1984 the lesion was still unchanged. In July 1984 the patient complained of sciatic pain on the right and increased disablilty. X-rays and CT scan showed an increase in the size of the lesion. Biopsy of the lesion in October 1984 showed malignant fibrous histiocytoma. On review this has been diagnosed as a postradiation sarcoma in the site of a previously irradiated giant cell tumor. A more specific diagnosis could not be made. In view of the absence of non-osteoclastic giant cells the diagnosis of malignant fibrous histiocytoma cannot be confirmed. The specimen is very desmoplastic with fibrosis in response to the initial radiotherapy. Lung tomograms showed multiple metastases. The patient was treated with 2 cycles of chemotherapy with DTIC, Vincristine, Adriamycin and Endoxan one month apart. His condition deteriorated rapidly. Tumor was palpable over the right iliac spine and there was a palpable mass on the chest. He received radiotherapy to a painful area. A single fraction of Co-60 radiotherapy was given to a 15 by 22cm posterior pelvic field. He received a dose of 6.00 Gy. He died in January 1985, 3 years and 11 months after presentation with the postradiation sarcoma.

1cm from the superior border of the initial radiation field, at the level of the superior tumor, the bone in which the tumor grew lies between 30Gy and 54.50Gy. At the level of the central axis (approximately mid-tumor) the

tumor lies between 45 and 55Gy (fig 17). The tumor appears to have developed in bone which received between 30 and 55Gy, probably in an area which received approximately 48Gy.

Case 18: Primary Tumor: Giant Cell Tumor of the Humerus
Postradiation Tumor: Osteosarcoma of the Humerus

A 19-year-old patient was referred to our institution in June 1949 with an osteoclastoma of the right humerus adjacent to the elbow (diagnosed on the basis of clinical and radiological features). A course of 220kV, HVL 1.5mm Cu radiotherapy was commenced in June 1949, when the patient was 20 years of age, utilising 15 by 7.5cm right and left lateral fields to the right humerus. A dose of 100R was applied to each field. For the first and last fractions the dose was 50R. Treatment was given 5 times a week for 21 fractions achieving a total applied dose of 2000R. The duration of treatment was 30 days.

On x-ray in January 1950 extension of the lesion was suspected. A second course of 220kV, HVL 1.5mmCu radiotherapy was commenced in February 1950 utilising 15 by 7.5cm right and left lateral fields. 100R was applied to each field 5 days a week for 20 fractions achieving a total dose of 2000R applied to each field. The total duration of this course of treatment was 28 days. The total central dose in this patient (from both courses of treatment) was

5000R. The patient appears to have been followed up at another hospital. An x-ray in April 1950 showed increased rarefaction. An x-ray in March 1951 apparently showed some improvement. In February 1986 the patient was referred back to the orthopaedic surgeons with symptoms of lateral scar entrapment. An x-ray showed cystic and sclerotic change with osteoarthritis of the elbow joint.

In January 1992, 42 years and 7 months after commencement of radiotherapy, the patient presented with a pathological fracture of the distal right humerus. She had fallen and injured her arm in December 1991. An x-ray showed a supracondylar fracture and a lytic bone tumor. Needle biopsy in April 1992 revealed a sarcoma of bone, thought to probably be an osteosarcoma. On review this has been confirmed as a high grade osteosarcoma. Aspiration revealed malignant cells consistent with a sarcoma. Bone scan in April 1992 showed features in keeping with a primary bony tumor of the distal humeral epiphysis and metaphysis with encroachment on the most distal diaphysis. There was no convincing evidence of metastatic bone involvement. In April 1992 the patient underwent a right above elbow amputation. At that time her symptoms were of increasing swelling of the right elbow, increasing pain of the elbow and stiffness. The arm was flexed at 90 degrees. There was minimal function of the right hand. Chest x-ray, CT scan and marrow biopsy did not show metastases. The patient did not wish to have adjuvant chemotherapy.

At follow-up in November 1993 an x-ray of the right arm stump showed generalised osteopaenia of the right shoulder girdle and right arm stump. She was well and clear of recurrence at her last visit in April 1994, 2 years and 3 months after presentation with the postradiation tumor.

Isodose curves through the central axis are representative of those through the superior tumor. Superior tumor has been superimposed on these curves and show the bone in which the tumor grew to lie between the 75 and 79Gy dose levels. Curves through the inferior border of the field are representative of the area of the main tumor bulk. The bone here lies between the 60 and 61.98Gy dose levels (fig 18). The tumor is estimated to have grown between 60 and 79Gy at a point which received approximately 62Gy.

Case 19: Primary Tumor: Fibromatosis of the Buttock
Postradiation Tumor: Osteosarcoma of the Pelvis and Left Femur

A 10-year-old girl underwent incomplete excision of a tumor in the left buttock in November 1972. Histological features were of an extra-abdominal desmoid tumor or a low-grade fibrosarcoma. On review a diagnosis of fibromatosis has been made due to low cellularity, the absence of the herring-bone pattern of fibrosarcoma, a pushing rather than an infiltrating border, the abscence of muscle invasion and mitotic figures and the presence of myxoid change. X-ray

had shown no bony erosion but a mass in the region of the left buttock and hip. The left ileum was narrowed in the vertical dimension and grooved laterally. It was thought that this might be due to a pressure defect caused by the mass.

A course of Co-60 radiotherapy was commenced in November 1972 utilising first a 10 by 10cm field to the posterior left sacro-iliac region. A dose of 2.00Gy was applied for 8 fractions 5 times a week. The field size was then reduced to 10 by 8cm and a dose of 2.25Gy was applied for a further 8 fractions. The total applied dose was 33.75Gy. The duration of treatment was 22 days.

In May 1973 early erosion of the right greater trochanter was noted. In September 1973 there was noted to be no evidence of disease locally and x-ray was reported to be normal.

In February 1975 a 17 by 15cm mass was noted in the buttock. X-ray showed a defect in the medial aspect of the left ileum, which was not thought to be malignant. There was a relative decrease in the size of the left ileum attributable to previous radiotherapy. The tumor was assessed as being inoperable because of attachment to the underlying iliac bone. Drill biopsy was performed. All slides were reviewed and the final diagnosis was that this patient had a desmoid tumor or fibromatosis. A course of Co-60 radiotherapy was commenced in March 1975 utilising 26

by 18cm parallel opposed fields to the left pelvis. A dose of 3.20Gy was given to each field twice a week for 10 fractions with adjustment of the last fraction to acheive a total applied dose of 31.90Gy. A total central dose of 45.00Gy was achieved. There was complete overlap of the previous field. Treatment was given in hyperbaric oxygen. The total duration of treatment was 34 days. The maximum significant posterior dose from both courses of radiotherapy was 80Gy. 6 days after the completion of radiotherapy the patient was commenced on chemotherapy with Vincristine, Cyclophosphamide and Actinomycin. This was a 50-week course of chemotherapy.

In July 1975 x-ray showed osteoporotic changes in the left hemipelvis and the acetabulum pushed inward by the head of the femur. In September 1975 the patient was noted to have had haemorrhagic cystitis following Cyclophosphamide but no measurable tumor mass. Intravenous pyelogram performed in June 1976 because of haematuria showed radiation necrosis of the head of the left femur, bladder calcification on the left and a hydronephrotic left kidney. Irregularity on the left side of the bladder due to radiation damage was noted. In September 1976 the patient underwent osteotomy and application of a pin and plate to the left femur because of a slipped femoral epiphysis. Marked fibrosis was noted in the irradiated area. This pin was later removed.

In June 1980, 7 years and 7 months after the commencement of radiotherapy, a routine follow-up x-ray showed a large

lytic area in the left iliac bone adjacent to the acetabulum with a break in the cortex medially. Bone scan showed a photopaenic area in the left pelvis in keeping with previous radiotherapy. A focus of increased activity was noted in relation to the left side of the pelvis. Open bone biopsy was performed. The patient was diagnosed as having a sarcoma. The histological appearances were highly suggestive of a malignant fibrous histiocytoma. CT scan showed a large left-sided hydronephrosis associated with a large mass of suspected glands extending downwards and paravertebrally into the pelvis. There was also involvement of the left transverse process of the fifth lumbar verterbra, the proximal sacrum and the left ileum. Caudally there was obvious bone destruction of the left half of the sacrum, and of the left inominate bone. The overlying mass in that area formed a part of the huge paravertebral mass which displaced the kidney. The lesion was too extensive for surgery and further radiotherapy could not be given.

In July 1981 the patient was noted to have a 7 by 8cm mass posteriorly above the iliac crest. CT scan showed a large left loin tumor mass which incorporated the psoas muscle and extended inferiorly to involve the iliacus muscle. The left ischium showed extensive lesions in keeping with tumor or previous radiotherapy. There was also involvement of the left erector spinae muscles and obstruction of the left ureter. Excision biopsy of the mass in the posterior

lumbar area showed a well-differentiated fibrous reaction with no evidence of malignancy.

In December 1981 there was noted to be further lysis of the head and neck of the femur with a previously placed pin protruding beyond the femoral head. There was also a pathological subcapsular fracture on the left. There was deep induration in the left iliac fossa attributable to radiotherapy. Hip replacement surgery was not feasible due to extensive tumor involving the head of femur. The patient was admitted to hospital for traction. Rebiopsy in December 1981 showed osteosarcoma. In January 1982 the patient underwent a Girdlestone procedure to the left hip.

The patient developed septicaemia and died in July 1982 with pulmonary metastases, gross fungation of the local tumor, gangrene of the left foot and anaemia. This was 2 years and 1 month after presentation with postradiation malignancy.

At autopsy features of septicaemia were noted with left-sided hydroureter, hydronephrosis, pyonephrosis and pyelonephritis; constriction of left ureter distal end by fibromatosis/tumor; fibromatosis/malignant fibrous histiocytoma/osteosarcoma involving the left femur and left hemipelvis with erosive destruction; bilateral lung metastases; atrophic breasts, ovaries and uterus; and resolving haemorrhagic cystitis. At this time previous biopsies were reviewed and it was thought that the tumor

was originally an aggressive fibromatosis but after recurrence and radiotherapy the appearance was that of a malignant fibrous histiocytoma. At autopsy as mentioned there were sections containing malignant cartilage and osteoid production indicative of a chondroblastic osteosarcoma. On further review a single diagnosis of osteosarcoma has been made. The diagnosis of malignant fibrous histiocytoma was presumably made initially as osteoid could not be seen in the earlier specimens.

As this was an osteosarcoma with bone involvement it is assessed as being a bone tumor. However there was extensive soft tissue involvement and assessment of the area in which the tumor developed has not been limited to bone. At the superior border of the second (longer) radiotherapy fields the tumor (superior tumor) lies between 30 and 38.14Gy. Isodose curves through the superior border of the initial fields (mid-tumor) show the tumor lying between 40 and 75Gy (fig 19). Curves through the central axis (inferior tumor) show a small amount of tumor between 40 and 70Gy. It is estimated to have grown between 30 and 75Gy, in tissue which received approximately 60Gy.

Case 20: Primary Tumor: Benign Tumor Alveolus
Postradiation Tumor: Osteosarcoma of the Maxilla

A 5-year-old child underwent surgery in 1934 or 1935 at another institution for a lesion of the right upper

alveolus initially thought to be malignant. Radium pellets or needles were inserted. A diagnosis of a benign condition (possibly fibroma or angioma) was then made and the radium was removed. Details are not available. At the age of 13 the patient underwent extensive plastic surgery to correct a mid-facial deformity.

In December 1987, approximately 53 years after the irradiation, the patient presented to our hospital with a locally advanced tumor of the right maxilla. She gave a history of retro-orbital pain, proptosis and a nasal discharge, infra-orbital and right nasal paraesthesia and some diplopia as well as some nasal obstruction. The symptoms dated from October 1987. The right nasal cavity was obliterated by a bony hard mass covered with mucosa and the mass covered the fenestration in the mouth. Full eye movements were present. X-rays showed new bone formation in the sphenoid and ethmoid bones, an opaque left antrum and extensive anterior middle cranial fossa new bone formation. CT scan showed proptosis of the right eye. There was marked new bone formation involving the right ethmoidal sinus and the spheniodal sinus and projecting into the right orbit. There was also some new bone formation projecting from the right frontal bone into the right frontal lobe. There was in addition some soft tissue attenuation in the right antrum and an opaque left antrum. These latter changes had the appearance of mucosal thickening.

Biopsy (right palate/antrum and right lateral nasal wall) showed features of fibrous dysplasia with osteosarcomatous changes. Palliative right total maxillectomy was performed. Bone-like tumor was present in the pterygopalatine-fissure region, especially the orbital apex, and across the roof of the ethmoids in the nasal cavity. Macroscopically tumor was noted within areas of necrosis. Histological features were in keeping with the diagnosis of osteosarcoma. On review osteosarcoma in fibrous dysplasia has been noted and also fibrosis without features of fibrous dysplasia i.e. radiation-induced fibrosis. The osteosarcoma is moderate grade. The patient returned to Harare for further treatment. She received 2 cycles of chemotherapy (Methotrexate, Vincristine and Adriamycin). She elected to discontinue chemotherapy after an episode of neutropaenia, thrombocytopaenia and septicaemia although she did feel the tumor had diminished in size. In June 1988 she attended a hospital in the United Kingdom. CT scan showed increase in the size of the tumor. There was extensive bony destruction with a retro-orbital and maxillary mass. She received further chemotherapy (5 Fluorouracil, Adriamycin and Cyclophosphamide) and was referred for packing of the fungating tumor within the maxilla. A course of radiotherapy was commenced in July 1988 utilising anterior and lateral fields to the right face. A dose of 40Gy was achieved to the right side of the face in 20 fractions over 30 days. She returned to Southern Africa where further

debulking surgery was done. She died in December 1988, a year after presentation with the postradiation tumor.

Fig 20 shows the position of the postradiation sarcoma. The radiation dose in the area of postradiation tumor development cannot be assessed as no radiotherapy details are available.

3.2. TABULATION AND FURTHER ANALYSIS OF RESULTS

Results are tabulated on Tables 1 and 2 (Addendum 2). On Table 1 cases are listed according to primary tumor type, and on Table 2 according to radiation modality.

20 cases were reviewed of patients who developed postradiation sarcomas or MMMT. Patients presented with the sarcoma from September 1972 to June 1993.

3.2.1. AGE AT PRESENTATION WITH PRIMARY TUMOR AND SEX

Ages are described in years except for the subgroup of retinoblastoma patients.

Sixteen patients were female and four male. The age at the time of the radiotherapy commencement was a mean of 28 years with a range of 0 years (5 months) to 68 years. The median was 24 years. In the paediatric group of six cases (patients under the age of 15 at the time of initial presentation) the mean age was 4 years and the range 0 (5 months) to 10 years. The median age was 3 years. In the adult group (fourteen cases) the mean age was 38 with a range of 18 to 68. The median was 37. In the retinoblastoma group (three patients) the mean age at presentation with retinoblastoma was 14 months and the range 5-29 months. The median was 9 months.

3.2.2.PRIMARY TUMOR

In seven cases the initial tumor was of the female reproductive tract (six carcinoma cervix, one low grade stromal sarcoma of the uterus). Three patients had carcinoma of the breast, three bilateral retinoblastoma, one a unilateral Wilms' tumor, one a parotid carcinoma and one a soft tissue sarcoma. In four patients the condition for which the original radiotherapy had been given was a benign one (two giant cell tumors, one fibromatosis, and one unknown, possibly angioma or fibroma).

3.2.3. TREATMENT OF PRIMARY TUMOR

Twelve patients had been treated with cobalt radiotherapy. One of these had also received treatment with a 250 kV beam and I-125 seeds. Four of the patients treated with cobalt therapy had also had radium insertions and one had received an electron boost as part of the initial radiotherapy, but this was not at the site in the field at which the postradiation sarcoma developed. Four other patients had received treatment with a 250 kV beam. One of these also underwent a Tantalum-182 insertion. Two had received treatment with a 220 kV beam and one of these had two radium insertions. One patient had been treated on the linear accelerator with a 20 MV beam and with a radium insertion and one had been treated with radium pellets or needles at another institution.

In thirteen cases the treatment of the initial condition included surgery (including case 17 who underwent open biopsy). The surgery did not necessarily affect the site of postradiation tumor development. Two patients (cases 10 and 19) had more than one operation which may have affected the site of tumor development. The six patients who received chemotherapy for the primary tumor were in the group who had surgery. Three received Cyclophosphamide.

If one or more implants were inserted during or at the end of a course of external beam therapy the radiotherapy is considered as one course. Five patients (cases 11, 12, 14, 18 and 19) received more than one course of radiotherapy and a further case (8) could possibly be considered in this group as the site of tumor development was exposed to direct treatment and also received scatter from a course of radiotherapy to the opposite breast.

3.2.4. LATENCY

The mean latent period was 14 years and 2 months with a range of 1 year 11 months to 53 years. The median was 9 years.

In paediatric cases (6 cases), the mean latency was 15 years 1 month and the range 3 years 7 months to 53 years. The median was 6 years 2 months. In adults (14 cases) the

mean was 13 years 10 months with a range of 1 year 11 months to 42 years 7 months. The median was 11 years 5 months. In the retinoblastoma patients (3 cases), the mean latency was 4 years 4 months (with latent periods of 3 years 7 months, 4 years 7 months and 4 years 10 months) and the median 4 years 7 months. In the non-retinoblastoma patients the mean latency was 15 years 11 months with a range of 1 year 11 months to 42 years 7 months. The median was 11 years. The difference in latency between the adult and paediatric groups was not significant ($p > 0.05$) but the latency of the retinoblastoma patients was significantly shorter than that of the non-retinoblastoma patients ($p < 0.05$).

In patients treated with megavoltage beams alone (Co-60 and 20MV) (seven cases) the mean latency was 8 years 3 months with a range of 1 year 11 months to 17 years 3 months. The median was 7 years 7 months. In patients who received orthovoltage (250 or 220kV) treatment alone (four cases) the mean latency was 23 years 8 months with a range of 4 years 10 months to 42 years 7 months. The median was also 23 years 8 months. The difference was not significant ($p > 0.05$).

In patients who received megavoltage therapy with or without brachytherapy (twelve cases), the average latency was 9 years 3 months and the range 1 year 11 months to 17 years 3 months. The median was 8 years 1 month. In those who received orthovoltage treatment with or without

brachytherapy (six cases) the average was 19 years 1 month and the range 3 years 7 months to 42 years 7 months. The median was 16 years 8 months. Again this difference was not statistically significant ($p > 0.05$).

In patients who received brachytherapy with or without external beam therapy (nine cases), the mean latency was 14 years and 7 months with a range of 3 years 7 months to 53 years. The median was 9 years 10 months. In patients who received no brachytherapy (11 cases) the mean latency was 13 years 10 months with a range of 1 year 11 months to 42 years 7 months. The median was 7 years 10 months. This difference was not statistically significant ($p > 0.05$).

In patients in whom the prescribed dose was more than 60Gy (six cases) the mean latency was 15 years 11 months with a range of 6 years to 42 years 7 months. The median was 11 years 9 months. In patients prescribed for less than 60Gy (twelve cases) the mean was 9 years 11 months with a range of 1 year 11 months to 30 years 4 months. The median was 7 years 5 months. The difference was not statistically significant ($p > 0.05$).

In the MMMT group (four cases) the mean latency was 13 years 4 months and the range 6 years to 16 years 1 months. The median was 14 years 11 months. In the pure sarcoma group (sixteen cases) the mean was 14 years 6 months with a range of 1 year 11 months to 53 years. The median was 8 years 1 month. In the two patients with abnormal bone

prior to irradiation (two giant cell tumors) the latency periods were 3 years 2 months and 42 years 7 months.

Postradiation tumors developing in bone (nine cases) had a mean latency of 17 years 3 months (range 3 years 7 months to 53 years) and a median of 7 years 7 months, and those in soft tissue (eleven cases) 11 years 8 months (range 1 year 11 months to 30 years 4 months). The median was 9 years 10 months. This difference was not statistically significant ($p > 0.05$).

3.2.5. AGE AT PRESENTATION WITH SECONDARY TUMOR

The age of the patients in years at the presentation with the sarcomas was a mean of 42 years with a range 4-81 years. The median was 46.5 years.

3.2.6. TISSUE AND SITE OF SECONDARY TUMOR

The tissue in which the sarcoma developed was soft tissue (including uterus) in eleven patients and bone in nine patients.

In eight of the patients who had received megavoltage therapy (CO-60 or 20MV beam) with or without brachytherapy the postradiation malignancy developed in soft tissue and in four it developed in bone. (One of these patients

developed a sarcoma in an irradiated giant cell tumor). In three patients who received orthovoltage treatment (250kV or 220kV) with or without brachytherapy the postradiation malignancy developed in soft tissue and in three in bone (one in an irradiated giant cell tumor). One patient developed a tumor in bone after treatment with orthovoltage and megavoltage beams and an I-125 implant and one in bone after brachytherapy only.

Thirteen patients developed tumors in the trunk, five in the head and neck region and two in the extremities.

3.2.7. PRESCRIBED DOSES AND DOSES AT SITE OF SECONDARY TUMOR DEVELOPMENT

The initially prescribed doses and the dose ranges and points at which the postradiation tumors are estimated to have developed can be seen on Tables 1 and 2. Table 1 includes prescribed doses, and the dose range and point at which the tumor is estimated to have grown in Gray. Table 2 shows the prescribed doses and the prescribed doses in Gray (using f-factor conversion). Table 2 also indicates the doses in Gray at which the sarcomas developed, as shown on Table 1.

The prescribed doses ranged from 3000R orthovoltage treatment (case 14) to 94.94Gy at Manchester Point A

(case 3) in a patient who received megavoltage treatment and an intracavitary radium insertion.

If R/rad corrections are calculated for prescribed doses and courses of radiotherapy are added together, no patients were prescribed for less than 30Gy, twelve were prescribed for 30 to 60Gy and six for more than 60Gy.

The lowest dose point at which a tumor was estimated to have developed was 8Gy (case 11). Excluding the patients with retinoblastoma the lowest dose point was 12Gy (Cases 14 and 15).

For details of fractionation and duration of treatment see Table 1 and case reports.

The range of estimated dose points at which tumors developed was from 8Gy (case 11) to 100Gy (cases 1 and 3). The mean estimated dose point was 48Gy (eighteen cases). The median was 49. The dose point was less than 30Gy in three cases, from 30 to less than 60Gy in nine cases and 60Gy or more in six cases.

Three of the MMMT developed at estimated dose points of 60, 100 and 100Gy. In the fourth all radiotherapy details are not available.

In patients who received <u>megavoltage therapy only</u> (seven cases) the mean dose point was 42Gy with a range of 12 to

60Gy. The median was 45Gy. In the group who received orthovoltage therapy only (four cases) the mean dose point was 37Gy with a range of 12 to 62Gy. The median was 36.5 Gy. The difference is not significant ($p > 0.05$). In patients who received orthovoltage with or without brachytherapy (five cases) the mean dose point at which the PRS is estimated to have developed was 31Gy with a range of 8 to 62Gy. The median was 35Gy. In the megavoltage group (twelve cases) the mean was 54Gy with a range of 12 to 100Gy. The median was 50Gy. The difference was not significant ($p > 0.05$). In all patients who received brachytherapy (seven cases) the mean was 60Gy and the range 8 to 100Gy. The median was 50Gy. In those who did not receive brachtherapy (eleven cases) the mean was 40Gy with a range of 12 to 62Gy. The median was 38Gy. This difference was not significant ($p > 0.05$).

3.2.8. POSSIBLE PREDISPOSITION TO SECOND MALIGNANCIES

There is no indication in the case notes that the patient with Wilms' tumor had features of the genetic form of the disease. In the patients with bilateral retinoblastoma the mean dose point at which the PRS was estimated to have developed was 31Gy. The median was 35Gy. The points were 8, 35 and 50Gy. In the non-retinoblastoma patients (15 cases with information on dose) the mean was 51Gy and the range 12 to 100Gy. The median was 50Gy. The difference was not significant ($p > 0.05$).

Three other patients (cases 8, 10 and 16) developed three malignancies altogether (i.e.triple primary). A fourth patient (19) may have had a third primary but the final opinion was that the specimens characteristic of malignant fibrous histiocytoma and osteosarcoma should be regarded as coming from the same tumor.

3.2.9. PRESENTATION WITH SECONDARY TUMOR

Sixteen patients presented with clinical features of swelling or a mass. In five pain was also present. Three presented with x-ray changes and one with a pathological fracture.

3.2.10. PATHOLOGY OF SECONDARY TUMOR

Four patients developed MMMT. Eight developed osteosarcoma of the bone, one after radiotherapy for a giant cell tumor. Two developed leiomyosarcomas, one a rhabdomyosarcoma, two pleomorphic sarcomas, one a fibrosarcoma and one a sarcoma not otherwise specified. A second patient developed a radiation induced sarcoma in the site of a previously irradiated giant cell tumor and this tumor could not be classified further. Four of the sarcomas were of moderate grade and sixteen tumors were high grade. The moderate grade tumors were [1] a fibrosarcoma of the pelvis, occurring more than 30 years after radiotherapy for a low

grade stromal sarcoma of the uterus; [2] a sarcoma of the axilla which cannot be classified further and which occurred at 7 years and 10 months after radiotherapy for carcinoma of the breast; [3] a sarcoma of the bone which presented 3 years and 2 months after radiation of a Grade 2 giant cell tumor of the pelvis; and [4] an osteosarcoma in fibrous dysplasia, with radiation induced fibrosis noted in the specimen, occurring 53 years after irradiation for a benign condition of the alveolus.

3.2.11. TREATMENT OF SECONDARY TUMOR

In the majority of patients treatment with a curative aim could not be carried out for the postradiation tumor due to the advanced nature of the disease at the time of presentation.

Four patients received no active therapy. One of these declined surgery to establish the nature of a pelvic mass. In three no active treatment could be offered.

In ten patients the initial treatment was surgical. In only three of these was a radical resection possible. Case 8 underwent an excision of a chest wall sarcoma. No further therapy was recommended and she was alive with no evidence of sarcoma recurrence at the time of the last report, 5 years and 2 months after surgery. One patient (case 18) underwent amputation of the upper extremity and

refused chemotherapy. She is alive with no evidence of recurrence at 2 years and 3 months. One (case 2) underwent subtotal hysterectomy and bilateral salpingo-oöphorectomy for a MMMT of the uterus. She refused chemotherapy and was lost to follow up. Cure is unlikely as this was a MMMT which infiltrated into the outer third of the myometrium. A fourth patient (case 3) underwent a subtotal hysterectomy and bilateral salpingo-oophorectomy for a MMMT of the uterus which invaded almost to the serosa. Macroscopically there were ruptured areas which appeared surgical in origin. The surgery was described as palliative in nature. The patient received postoperative chemotherapy but developed a pelvic mass during treatment. She subsequently received palliative radiotherapy.

In two patients the initial surgical procedure was a laparotomy and at operation it was found that the tumor was inoperable. Case 7 went on to receive neutron radiotherapy at a later date and further resection. Case 4 received chemotherapy but died early in the course, 2 months after presentation with the postradiation tumor.

Case 1 underwent a hysterectomy but metastases were noted at operation. Case 20 had a palliative maxillectomy which was followed by two courses of chemotherapy, further chemotherapy, packing, radiotherapy and palliative surgery. Case 10 had an incomplete resection of a sarcoma in the clavicular area which was not followed by further

treatment. Case 19 underwent a variety of palliative surgical procedures.

Two patients received radiotherapy as initial treatment of the postradiation tumor. Case 9 received a total dose of 36Gy in 9 fractions after hormonal and chemotherapy had been administered for presumed recurrence of breast cancer. Although there was an initial regression after irradiation the lesion had recurred 3 months after completion of treatment. Case 11 underwent a course of radical radiotherapy followed by chemotherapy and maxillectomy at which time it was thought that the tumor was extending over the orbital floor. Extension of tumor had occurred by 2 months postoperatively.

Three patients received chemotherapy as initial treatment of the postradiation tumor. In only one was there any response but this was followed by disease progression and chemotherapy was discontinued (Case 13).

In one patient an initial embolization was performed (Case 17). Approximately 3 years later the patient received two cycles of chemotherapy but his condition deteriorated. He received palliative radiotherapy.

3.2.12. OUTCOME OF TREATMENT OF SECONDARY TUMOR

The outcome of treatment of the postradiation tumors was poor. Two patients are alive and clear of recurrence of postradiation sarcoma at 5 years 2 months and 2 years 3 months after presentation. One is alive with disease 9 months after presentation. One has been lost to follow-up and is presumed dead. One patient died with disease and the date of death is unknown. Fifteen patients died with disease at an average of 14 months (range 2 months to 3 years 11 months) after presentation, but in two the cause of death may have been metastases from another primary. The median survival of the thirteen patients who died with sarcoma, in whom the date of death is known, and excluding the two patients who may have died from another malignant disease, was 12 months and the mean 15 months. The range was 2 to 47 months.

4. DISCUSSION

Table 3 (Addendum 3) shows features of some clinical studies reported in the English literature.

4.1. INCIDENCE

4.1.1. DIFFICULTIES IN DETERMINING INCIDENCE

Postradiation sarcoma is a rare condition. Of malignant lesions reported in irradiated tissue (carcinoma, leukemia and sarcoma) sarcoma is the least common (104). In a report published in 1963 Phillips noted that a review of the literature produced only thirty cases of bone sarcoma occurring in normal bone after radiotherapy. Fifty cases had been reported after irradiation of benign bone lesions (87). Castro reported in 1967 that a literature survey revealed only ninety-three cases of radiation-induced bone sarcoma. Including his own cases, only thirty-five cases of radiation-induced sarcoma in normal bone had been reported (15). In 1970 Hatfield reported that approximately 150 cases of PRS had been reported (46). Including five of his own cases eleven cases had been reported after radiotherapy for carcinoma of the breast. In 1972 Sim mentioned 150 recorded cases of sarcoma in bone following irradiation (104).

Because of the rarity of the condition and the potentially long latent period between irradiation and the development of the sarcoma, accurate estimates of the incidence are not easily made (94). The number of patients receiving radiotherapy is often not reported and the risk in any given radiotherapy patient is difficult to establish (94, 49).

The paucity of relevant statistics and possibly the failure to recognise and report sarcomas occurring in radiation fields also renders estimation of risk and incidence difficult (46). Most reports do not provide a denominator (i.e. the number of patients receiving radiotherapy) for assessing risk (122). In our own department patient data is entered on a computer database but it is not possible to determine from the database which patients have developed a postradiation malignancy. The denominator (5- or 10-year survivors of radiotherapy) can also not be determined except for certain specific primary conditions and treatments.

Some reported incidence rates have not been calculated over a long enough period to cover the average latency period for postradiation tumors (27).

4.1.2. PROPORTION OF SARCOMAS ATTRIBUTABLE TO RADIOTHERAPY

The proportion of sarcomas which can be attributed to previous irradiation varies considerably among different institutions.

At the Roswell Park Memorial Hospital in Buffalo 0.17% of sarcomas could be defined as PRS (75).

Huvos from the Memorial Sloan-Kettering Cancer Centre reported that 5.5% of osteosarcomas seen there since 1921 were PRS (49).

It was reported from the Mayo Clinic that 1.5% of primary malignant bone tumors (including myeloma), 17.6% of fibrosarcomas, 3.4% of osteosarcomas and 0,7% of chondrosarcomas were PRS (121).

At the University of California, Los Angeles Medical Center 6% of 229 head and neck sarcomas were identified as PRS (67).

In a comparison of second and single primary sarcomas reported from 1973 to 1986 by the Surveillance, Epidemiology and End Results (SEER) Program of the U.S. National Cancer Institute (93), 8815 patients were found to be registered with sarcoma as a first and 240 with sarcoma as a second primary tumor. 74 patients (31% of patients with sarcoma as the second primary and 0.8% of all the

patients with sarcomas) had undergone radiotherapy for the first tumor and these patients were assumed to have postradiation sarcomas although actually there is no record of whether the sarcoma developed in the radiation field or not.

As already discussed I am unable to comment on the proportion of sarcomas presenting to Groote Schuur which are attributable to radiotherapy.

Overall the proportion attributable to radiotherapy varies according to the type of sarcoma. It also appears to vary among different institutions which may in part reflect referral patterns to certain clinics.

4.1.3. EVIDENCE FOR NO INCREASE IN RISK OF SARCOMA AFTER RADIOTHERAPY

Because of the difficulty in determining the denominator, the risk of development of a PRS in a 5- or 10-year survivor of radiotherapy is probably more difficult to establish than the proportion of sarcomas which occur in radiation fields. Not all clinical studies support radiotherapy as a risk factor for sarcoma development.

Lavey et al (60) reported that among breast cancer patients at Duke University Medical Center the relative risk (RR) for solid tumors other than breast cancer was not significantly different from unity in any treatment group.

(Patients were treated with surgery alone, surgery and adjuvant chemotherapy, surgery and adjuvant radiotherapy, or all three modalities.) 95.3% of the patients in all treatment arms in this study had been followed up for a minimum of 5 years or until death. Only 16% were observed for more than 10 years.

Bagshaw (6) observed no increase in second cancers after radiotherapy in 914 patients treated for carcinoma of the prostate.

Parker and Enstrom (83) found no difference in the incidence of second primary cancers in Head and neck cancer patients whether they received radiotherapy or not.

4.1.4. EVIDENCE FOR INCREASE IN RISK OF SARCOMA AFTER RADIOTHERAPY

In spite of evidence from studies such as the ones mentioned above, Mark (68) notes in a recent extensive literature review that the weight of the evidence suggests that radiotherapy does increase the relative risk of subsequent sarcomas and second cancers, but that the risk appears small.

Hankey et al (40), reviewing 25 724 cases of breast cancer in the Connecticut Tumor Registry, found no difference in incidence of second cancers between those who had surgery

alone and those who had postoperative radiotherapy. However in an update of this analysis it was found that the relative risk of soft tissue sarcoma was higher in patients who had received radiotherapy (43, 68).

Mark et al (68) reported a series of patients with PRS from the Unversity of California Medical Centre with a review of the literature and estimated the risk of PRS with long-term follow-up to be 0.03 to 0.8%. Even in this study the denominator could not be reliably assessed.

Phillips (87) reported that at the University of California 0.03% of irradiated patients and 0.1% of 5-year survivors developed bone sarcomas.

Tountas (114) from the Princess Margaret Hospital in Toronto reported that PRS of the bone occurred in 0.02% of irradiated patients, and in 0.035% of 5-year survivors.

A recent report comes from data in the Danish Cancer Registry. In a review of second primary malignancies in 6187 men with testicular carcinoma registered in the Danish Cancer Registry from 1943 to 1987 (51) seven patients were found who had developed sarcomas within the field of radiotherapy and three at the periphery. Eight patients had had seminomas. The incidence of sarcoma was four times higher than expected. Eight sarcomas occurred in the 2241 patients who survived 10 years, yielding an absolute risk of 0.4%.

4.1.4.1) Risk of Postradiation Sarcoma in Irradiated Breast Cancer Patients

Some reports of PRS refer only to patients with specific primary tumors such as carcinoma of the breast or gynaecologic malignancy, or evaluate risk separately for these patients. In 1948 Cahan (14) reported that of an estimated 3 000 to 4 000 patients receiving postoperative radiotherapy for breast cancer, of whom approximately forty percent survive 5 years, only one developed a radiation-induced osteogenic sarcoma (i.e.0.07% of an estimated 1400 5-year-survivors).

Kurtz reported an incidence of PRS of 0.07% (two cases in 2850 patients) or 21.9 cases per 10^5 patient years for survivors beyond the fifth year in breast cancer patients treated with radiotherapy alone or following breast-conserving surgery (57).

At the Princess Margaret Hospital in Toronto the incidence of PRS in 5-year-survivors treated for cancer of the breast was 0.05% (114).

Taghian et al (113) found the cumulative incidence of PRS at the Gustave Roussy was 0.2% at 10 years for patients who received radiotherapy after mastectomy or breast-conserving surgery. It was 0.43% at 20 years and 0.78% at 30 years. However two of the eleven sarcomas were attributed to the

Stewart Treves syndrome. The relative risk (number of observed/expected cases in an age-matched control population) was 1.81.

At the Massachussetts General Hospital an overall incidence of PRS of 0.22% was estimated in breast cancer patients who received radiotherapy and survived 10 years (46). Hatfield estimates that the incidence of naturally-occurring osteosarcoma is only 0.0005%. Irradiated patients do appear to be at risk for this condition (75, 46).

The percentage risk of radiation-induced sarcoma in breast cancer patients treated at the Western General Hospital in Edinburgh with post-mastectomy radiotherapy or radical radiotherapy was 0.26% over 16 years (27).

Hatlinghus et al (47) reported three cases of postradiation sarcoma following radiotherapy for breast cancer in a total of 2 764 patients who received radiotherapy for breast cancer. Approximately 40% of these patients survived 10 years so it is estimated that one sarcoma developed per 365 patients surviving 10 years giving an estimated incidence of 0.27% in 10-year survivors. These authors felt that some cases are not recognized so this estimate is probably a minimum figure.

0.22 of irradiated survivors of carcinoma of the breast at the University of California developed bone sarcomas (87).

Pierce (88) observed three (0.18%) cases of breast sarcoma in 1624 women undergoing lumpectomy and radiotherapy at the Joint Centre for Radiation Therapy in Boston. The 10-year actuarial risk was 0.8%.

Incidence figures are not available from Groote Schuur.

Overall the incidence of postradiation sarcoma in irradiated breast cancer patients is well below 1%. Variation in incidence figures from different institutions may be partly due to the difficulties in diagnosing this condition and to the difficulties in determining incidence figures which will be affected, for example, by the duration of follow-up.

4.1.4.2) Risk of Postradiation Sarcoma in Patients Irradiated for Gynaecological Malignancies

The risk of PRS following radiotherapy for a gynaecological malignancy has also been reported by several authors.

The incidence among 5-year-survivors treated for cancer of the cervix at the Princess Margaret Hospital in Toronto was reported to be 0.06% (114).

Boice et al (10) reported a relative risk for bone sarcomas of 1.3 among 150 000 patients who had received radiotherapy for carcinoma of the cervix. 56% arose in the pelvis in

contrast to an expected 15%. The risk of connective tissue tumors (not including soft tissue sarcomas arising in specific organs) was not increased (RR 0.7) although the risk was increased among 10-year survivors receiving greater than 10Gy and those exposed after age 45. The anatomical distribution of soft tissue sarcomas (28% in the pelvic and 11% in the abdominal area) did offer some support for a radiation aetiology.

0.20% of irradiated 5-year-survivors of carcinoma of the cervix at the University of California developed bone sarcomas (87).

At the Roswell Park Memorial Hospital 0.14% of patients with carcinoma of the cervix treated with radiotherapy developed sarcoma of the pelvic bones (15, 75).

0.64% of patients with squamous carcinoma of the cervix who were treated with radiotherapy at the University of Minnesota Hospital and who survived 9 years developed a sarcoma of the irradiated bone. Using previous reports an estimation was made that an adult woman has a chance of less than 1 in 4 000 000 of developing a spontaneous osteosarcoma of the pelvic girdle. In this series one PRS arose in 6 000 patient years (31).

Ruka et al (96) reported that the expected incidence of lower trunk soft tissue sarcoma was 0.23/100 000. In patients treated for cervical cancer the observed incidence

was 10.84/100 000 and the RR 47.13. The incidence in 5-year survivors who received radiotherapy for endometrial cancer was 73.9/100 000, the expected incidence being 0.23/100 000 and the relative risk 321.3.

Eleven of Ruka's patients developed soft tissue PRS after treatment with radium and orthovoltage external beam therapy. This was considered a negligibly small fraction - 0.12% of all the patients treated with orthovoltage therapy for cancer of the cervix and 0.25% of the 5-year survivors. Two cases occurred among patients irradiated for endometrial cancer and this constituted 0.8% of the whole group irradiated for endometrial cancer and 1.5% of 5-year survivors. These authors point out that if risk is calculated for the whole group of patients who received radiotherapy, without assuming the minimum latency and excluding the patients who died within the first 5 years after treatment, the relative risk would be lowered by about 10%. However patients who did not survive 5 years would represent a small proportion of the person-years observed and whether or not minimum latency time is used the RR of developing a soft tissue sarcoma in the radiation field is markedly increased for cervical as well as endometrial cancer patients (96).

Again there is variation among figures from different institutions but overall the incidence appears to be less than 1%.

4.1.4.3) Risk of Postradiation Sarcoma in Survivors of Paediatric Malignancy

In a series from 10 paediatric oncology centres children who developed one malignancy were reported to have an approximately tenfold increase in risk of a second malignancy in comparison to age-matched populations 5 to 15 years after the diagnosis of the first malignancy. (This report excluded retinoblastoma patients as referrals of retinoblastoma patients at high risk of second malignancy were particularly likely at these institutions.) (73) In another report by the Late Effects Study Group (70) bone sarcomas were the most common second malignancies and soft tissue sarcomas also occurred frequently. 68% of second tumors, and 75% of the sarcomas, were reported to be associated with radiotherapy. The most common initial primary in this study was retinoblastoma. 81% of the retinoblastoma patients had bilateral disease. One third of the patients with Wilms' tumor had features associated with the genetic form of the Wilms' tumor (70).

Li (61) from the Sidney Farber Cancer Institute reported that fifteen patients who had been followed up at that institution due to an initial primary, subsequently developed another cancer, in contrast to 0.7 expected cases. All these patients had had prior irradiation and in thirteen with solid malignancies twelve arose in the radiation field. Five of the twelve were sarcomas. The

cumulative probability of a new malignancy was 12% and for patients who had received radiotherapy it was 17%.

The incidence of PRS in retinoblastoma patients and their predispositon to malignancy is discussed in section 4.4.

4.1.5. PRESENT TRENDS IN INCIDENCE

The change from orthovoltage to megavoltage radiotherapy was expected to lead to a decrease in the incidence of PRS, particularly those occurring in bone (44). However this decrease has not been seen (121, 116). The analysis of the Finnish Cancer Registry did not show a decrease in incidence and bone tumors were actually more frequent in those treated with megavoltage irradiation. However there were fewer cutaneous and subcutaneous tumors in this group, perhaps because of the skin-sparing effect of megavoltage radiotherapy (122).

Boice (10) found no evidence to support the supposition that the incidence of bone tumors may be lower in patients treated with megavoltage than with orthovoltage radiotherapy.

Not only has no decrease in incidence been noted with the use of megavoltage equipment, but it has also been predicted (49) that the incidence of PRS will increase as the survival of cancer patients improves. However undue

fear that this is a frequent complication of radiotherapy is unnecessary (49).

Robinson, in a review of the subject in 1988, noted that PRS had been increasing in frequency but were still rare (94). Other authors (5, 109) have also been of the opinion that the incidence is increasing.

Souba noted in 1986 that PRS of the chest wall were being reported with increasing frequency and predicted that the incidence of PRS would increase as radiotherapy is used more frequently in the multidisciplinary treatment of malignant disease and as patients survive longer than the latency period necessary for a PRS to arise (109).

With improved survival of cancer patients a higher overall incidence of postradiation malignancy should be expected.

4.2. CRITERIA FOR DIAGNOSIS. LATENCY PERIOD

4.2.1. CRITERIA FOR DIAGNOSIS

In 1948, in the first edition of Cancer, Cahan (14) published a report of PRS which has been much quoted ever since. He reported eleven cases arising in irradiated bone. The criteria for case selection were as follows:

"1. There must have been microscopic or roentgenographic evidence of the nonmalignant nature of the initial bone condition.
2. Irradiation must have been given and the sarcoma that subsequently developed must have arisen in the area included within the radiotherapeutic beam.
3. A relatively long, asymptomatic period must have elapsed after irradiation before the clinical appearance of the bone sarcoma. In these cases, this has been longer than the so-called five-year-cure period.
4. All sarcomas must have been proved histologically."

The latent period was calculated from the date of the last radiotherapy treatment and appears to have been defined as lasting until the onset of clinical change due to the sarcoma, although this is not clear from the paper.

Other authors have thought shorter latency periods acceptable. Arlen (5) suggested in 1971 that a five-year

period was not necessary to ensure that a histologically independent lesion had developed and proposed an interval of 3 to 4 years. According to Robinson (94) these amended criteria have been generally accepted. Arlen also suggested that the first criterion should be modified so that initial bone lesions may have been malignant provided they did not have osteoblastic activity. He described two cases where an osteogenic sarcoma arose in a radiotherapy field used in the treatment of an unrelated sarcoma (Ewing's sarcoma and reticulum cell sarcoma of bone). He also mentioned a possible fifth criterion of radiation osteitis, but noted that in many cases adequate radiologic examination of the bone prior to the development of the tumor was not available (5).

Senyszyn et al (100) recommended that in the case of a radiation-induced bone sarcoma there should have been x-ray evidence of osteodysplasia more than a year before the onset of obvious tumor formation as this would in most cases prevent a spontaneous tumor being diagnosed as a radiation-induced tumor. In the case of a radiation-induced malignancy of the soft tissues or skin there may be clinical evidence of severe skin atrophy, telangiectasia and/or "radiation dermatitis". As is suggested in their paper, it is impossible to be sure that a tumor is radiation-induced whatever the criteria employed.

A report from the Mayo Clinic in 1971 (104) criticised Cahan's first criterion as roentgenographic criteria of

malignancy are not specific and the second as it referred only to external therapy.

Hatlinghhus et al (47) suggested that it seems reasonable to apply similar criteria to Cahan's in the diagnosis of postradiation soft tissue sarcoma. Obviously the first criterion, which refers to bone sarcomas developing in previously benign bone lesions, is an exception.

In the Groote Schuur study all patients with a sarcoma or MMMT in a radiation field have been included provided the histology differed from the initial histology. In one case (case 18) the initial diagnosis of a giant cell tumor was made on the basis of radiological features and a tissue specimen was not taken. However in view of the initial radiological diagnosis and the long latent period of 42 years and 7 months before the development of osteosarcoma, this has been accepted as being of a different histology. (The spontaneous development of sarcomas in giant cell tumors is discussed elsewhere.) Latent period was not used as an inclusion or exclusion criterion in the Groote Schuur study as any such specification is arbitrary and anyway does not exclude spontaneously occurring tumors or those developing on a genetic basis being classified as radiation-induced tumors. In one patient (case 20) no radiation details are available. The patient had given a history of being irradiated at another institution and this was confirmed by her family at the time of this study.

Evidence of radiation fibrosis (as well as fibrous dysplasia) was present in tissue from the sarcoma.

4.2.2. REPORTED LATENCIES FOR POSTRADIATION SARCOMAS INCLUDING SEPARATE REPORTS FOR BONE AND SOFT TISSUE

Latency periods reported in various clinical studies can be seen on Table 3.

Latency periods for groups of bone and soft tissue sarcomas combined are reported in the following studies:

1) Hatfield et al from the Massachusetts General Hospital (46) reported a range of latency from 3 to 24 years with a mean of 12 years in eleven cases of postradiation sarcoma.

2) In an analysis of thirty-three postradiation sarcomas from the Finnish Cancer Registry Wiklund et al (122) reported a latency of 3.2 to 22.8 years (median 13.2) (from start of radiotherapy to the second tumor diagnosis, including retrospective diagnoses). No interval of more than 35 years could be recorded.

3) Mindell (75) suggests that some of the reported early postradiation sarcomas could be second primaries unrelated to the previous radiotherapy. In a review of twenty patients with PRS presenting to the Roswell

Park Memorial Hospital he recorded a latency range of 1 to 29 years with a mean of 12.5 years. Three occurred before 5 years.

4) Mark, (67) in a report of thirteen PRS of the head and neck area, found a latency which ranged from 3 months to 50 years with a median of 12 years. All except one patient had a latency of more than 4 years. The patient with the short latency period had received radiotherapy for bony fibrous dysplasia which had more than one recurrence.

5) In nine cases of sarcoma arising in the radiotherapy field (excluding Stewart Treves Syndrome) in patients who had had treatment for breast carcinoma at the Institut Gustave Roussy, the latency ranged from 5 to 24 years with a mean of 10 years (113). In the accompanying literature review it was noted that most second solid tumors occurred after a mean of not less than 10 years. This included bone and soft tissue sarcomas, with a relative risk slightly increasing in relation to the latent period. Only leukemia occurred after a latency less than 10 years and had a RR inversely related to the latency.

6) In Souba's series of sixteen patients with radiation-induced sarcomas of the chest wall (109) the latency ranged from 5 to 28 years with a mean of 13 years and a median of 10 years.

7) Robinson et al (94), in a literature review and analysis of 344 cases of PRS, found the mean time interval between first and second neoplasms to be 11 years with a range of 1.2 to 33 years.

In the Groote Schuur study the average latency was 14 years 2 months and the median 9 years. The patient with a latency of 53 years is unusual, presumably because most studies have not included patients followed for such a long period.

More series exist of reports of PRS of bone only than reports for soft tissue only. This may be because earlier reports included a higher proportion of sarcomas occurring after irradiation of benign bone lesions.

The following studies refer to postradiation bone sarcomas:

1) In Cahan's eleven cases of PRS of bone the latency ranged from five to twenty-two years and averaged eleven and two-tenths years (14).

2) In the reported series of thirty-four postradiation sarcomas of bone of Sim et al (104) the latent period (from the date of commencement of radiotherapy to the time of diagnosis of sarcoma) ranged from 5 to 42 years and the mean was 16 years.

3) Doherty et al found the latency of forty reported cases of sarcoma of the bone following radiotherapy for breast cancer to have a range of 4.5 to 20 years. The average was 10.9 years (27).

4) In 10 cases of PRS of bone reported from the Princess Margaret Hospital the latent period ranged from 5 to 23 years and the mean was 15 years (114).

5) Huvos (49) from the Memorial Hospital for Cancer and Allied Diseases reported sixty-three patients who developed postradiation osteogenic sarcoma. Overall the range of the latent period was 3.5 to 33 years, the mean 12.8 years and the median 10 years. Latent periods were expressed as the time between the start of radiation exposure and the diagnosis of osteogenic sarcoma. In sixty-three patients who developed postradiation osteogenic sarcoma Huvos reported a range of latency from 4 to 30 years for patients whose bones were normal at the time of irradiation and 3 to 33 years in those whose bones were diseased. The median in both groups was 10.5 years. The mean in the first group was 12.5 years and in the second 13.3 years. There was no significant difference in the mean latency periods in the two groups.

The following reports refer to postradiation soft tissue tumors:

1) In a report by the Armed Forces Institute in 1988 (59), in which fifty-three cases of postradiation soft tissue sarcoma were reviewed, Cahan's original criteria were modified so that the first was omitted (it is not relevant to soft tissue sarcomas), a latency period of 2 years was accepted, and the fourth was modified so that proof was necessary that the sarcoma was histologically different from the irradiated primary lesion. (This means that a radiation-induced sarcoma can be diagnosed when the initial treatment was for a histologically different sarcoma.) If it was not specified that the postradiation tumor arose within the radiation field these investigators searched for radiation effects in surrounding nonneoplastic tissue. In these cases it was not possible to prove that the area had been irradiated previously if the sarcoma had effaced the radiation field. The latency period ranged from 2 to 40 years with a mean of 10 years and a median of 8 years.

2) In a report of seven cases of postradiation soft tissue sarcoma in breast cancer patients Kuten found the latency ranged from 4 to 26 years with a mean of 13 years (58).

3) Ruka (96) reported a study of thirteen cases of soft tissue PRS in patients treated for uterine cancer (mainly cancer of the cervix) at a Warsaw institute.

The latent period ranged from 7 to 31 years with a mean of 18 years.

In the Groote Schuur study sarcomas in bone developed after a mean latency of 17 years 3 months (and a median of 7 years 7 months) and those in soft tissue after a mean of 11 years 8 months (and a median of 9 years 10 months). The difference between the groups was not statistically signigicant.

Two patients in the Groote Schuur study had abnormal bone at the time of irradiation. (They were irradiated for giant cell tumors.) The latent periods were relatively long at 17 years 3 months and 42 years 4 months.

Overall mean or median latencies appear to usually lie between 10 and 20 years and no conclusion can be drawn as to whether there is a significant difference in latency between groups with soft tissue and bone sarcomas.

4.2.3. LATENCY AND AGE

Some authors have indicated that that there may be a different sensitivity of the immature tissues in prepubertal children (104, 20, 105). Huvos (49) from the Memorial Hospital for Cancer and Allied Diseases found a significantly shorter latency for postradiation osteogenic sarcomas in patients irradiated under the age of 16 years.

Weatherby (121), in a report of 78 cases of PRS of bone, noted that patients irradiated before the age of 18 tended to have longer latent periods than those irradiated after 18.

Conversely, in the following series, age at irradiation has not been found to affect the latency period:

1) In Sim's series from the Mayo clinic (104) it was found that it made no significant difference whether radiotherapy was given in infancy or adulthood - eleven of the patients in this series were 21 years or younger at the time of radiotherapy and a shorter latency period in this group was not noted.

2) In a study of 25 patients with postradiation malignancy after treatment of retinoblastoma the average latency was more than 10 years among patients with sarcoma in whom the latent period was known. In a comparison with series of tumors induced by irradiation in adults, the author found that the latent period was not appreciably different whether irradiation occurred in childhood or infancy (108). In a comment on this paper Hatfield noted that the average latency was overall greater than 10 years in spite of a threefold increase in average dose and the fact that treatment was given to young, actively proliferating bone and cartilage. Therefore Hatfield commented that one cannot assume that radiation-

induced malignancy develops sooner in young than in adult bone (46).

3) Other authors have also found no definite relationship between age at the time of the first radiotherapy and latency (59, 122).

In the Groote Schuur study the difference in latency between children (mean 15 years 1 month and median 6 years 2 months) and adults (mean 13 years 10 months and median 11 years 5 months) was not statistically significant. The latency of 53 years in one paediatric case has of course affected the mean which is calculated for a total of only 6 cases.

Overall there is no convincing evidence that latent periods are significantly different between paediatric and adult patients.

4.2.4. LATENCY IN RELATION TO PRIMARY MALIGNANCY, SEX AND GENETIC PREDISPOSITION TO CANCER

Souba (109) in a report of PRS of the chest wall found no difference in latency if patients were stratified according to histology of the primary malignancy or sex and Wiklund (122) reported that patients considered to have a genetic predisposition to malignancy had a median latency of 13.9 years and those not having such a predisposition one of

12.5 years. This difference was not statistically significant. Histologic subtype and treatment with chemotherapy were also not associated with a significant difference in latency.

In the Groote Schuur series the retinoblastoma group did have a significantly shorter mean latency (4 years 4 months) than the patients with other primary malignancies (15 years 11 months). The median in the former group was 4 years 7 months and in the latter 11 years.

4.2.5. LATENCY AND MODALITY

Some authors have attempted to determine whether the latency period is affected by the radiotherapy modality.

In Wiklund's analysis of thirty-three cases of PRS from the Finnish Cancer Registry (122) the median latency was longer for patients who had received orthovoltage radiotherapy than for those who had received megavoltage treatment (15.9 versus 7.4 years). In Wilkund's study this difference was not significant when patients who had been followed up for a short period only were excluded from the analysis, but a threshold latency of 11.3 years after orthovoltage and one of 3.4 years after megavoltage radiotherapy were noted.

Two other large studies have found a longer latency after orthovoltage than megavoltage therapy. In Robinson's

literature review and analysis of 344 cases of PRS (94) the difference in latency between those treated with orthovoltage therapy (mean 127,84 months) and supervoltage (mean 103.63 months) was statistically significant. The longest interval was actually found in those treated with brachytherapy (mean 162,21 months) or a combination of external beam therapy and brachytherapy (mean 165,43 months). The interval for the combination was significantly longer than for the orthovoltage and supervoltage groups.

In the Armed Forces Institute study (59) most of the patients (5/7) who had received orthovoltage radiotherapy had latency periods of more than 13 years but those who had received megavoltage radiotherapy had latencies less than the mean.

The differences between the orthovoltage and megavoltage groups in the Groote Schuur study appear to be consistent with those in these other reports with a longer mean and median latency after orthovoltage therapy than megavoltage therapy, whether or not brachytherapy was given. However the differences were not significant and follow-up periods had not been taken into account. The group which received brachytherapy (with or without external beam therapy) had a longer mean latency than the group without brachytherapy, but this difference was not statistically significant. In view of the combinations of various modalities of external

beam treatment with brachytherapy and differences in dose it is difficult to assess the relevance of these findings.

Overall it appears that orthovoltage therapy may be associated with a longer latency period than megavoltage therapy, but this has not been definitely shown. The duration of follow-up should be taken into account when differences such as this are analysed, particularly as orthovoltage therapy has been in use longer than megavoltage therapy.

4.2.6. LATENCY AND DOSE

Hatfield et al (46) could not correlate the length of the latent period with the initial radiation dose and found the same in other reported series. The latency period did not appear to be shortened by higher doses.

In the analysis based on the Finnish Cancer Registry (122) concerning possible influences on the latency period it was found that in patients who had received a total dose of more than 36Gy the median latency was 7.4 years with a range of 3.4 to 16.1 years. In those who had received less than 36Gy the median was 14.4 years with a range of 8.3 to 22.8 ($p=0.09$ Kolmogorov-Smirnov test). Other reports on the association of latency and dose, as discussed by Wiklund, have shown conflicting results (122). The maximum

single dose per fraction in the Finnish study was not associated with a significant difference in latency.

The quality of radiotherapy, total dose, year of treatment and duration of follow-up were closely linked. The number of patients and time interval studied was limited. For these reasons the authors of the Finnish analysis did not feel they could draw definite conclusions on the relationship between latency and dose.

In the Armed Forces Institute study (59), in the patients with malignant fibrous histiocytoma the latency again tended to be inversely related to the dose of radiation. 71% of these patients who had received 3000 rads or more had latencies less than the mean. 67% of those who died of their sarcoma had latencies less than the mean. These authors reported that the mean and median latencies in their series correlated with those in other recent reports.

In the Groote Schuur group the latency was longer in the group in whom more than 60Gy was prescribed but the difference in latency between this group and the group in which less than 60Gy was prescribed was not significant. Due to the problems of comparing total doses no comment can really be made about association between latency and dose from this study.

Overall no conclusions can be drawn on the relationship between dose and latency.

In conclusion, there is no definite evidence to show that tissue type, age, modality, dose, sex, type of primary malignancy or a genetic predisposition to malignancy affect the latency period. There is some evidence to suggest that megavoltage radiotherapy and higher doses may be associated with shorter latency periods.

4.3. CAUSES OF SARCOMA DEVELOPMENT IN RADIATION FIELDS

Radiation should be considered carcinogenic for all tissues of the body in appropriate conditions of dose and host responsiveness. A tumor may appear in a specific tissue in a particular population group because that tissue was preferentially irradiated (for example bone tumors in radium dial painters). If radiation is more generalised some tissues such as thyroid, breast and lung seem to be more susceptible than others. It is estimated that the ratio of solid tumors to leukemias will be in the range of 4 to 6 even though the incidence of leukemia is higher earlier after exposure (38).

Some investigators have reported that doses between 40 to 60Gy to limited areas in radiotherapy patients do not lead to a significantly increased cancer incidence. Others report an increase. Assessment of risk is difficult because cancer patients are often at increased risk of a second cancer because of their lifestyle. Chemotherapy may add to the cancer risk. It appears that radiation does increase the risk of second malignancy, both in heavily irradiated areas and in more distant organs that received a few gray. However according to Hall at most approximately 5% of second cancers can be convincingly associated with radiation (38). It will probably remain impossible to be certain that a particular malignancy is radiation-induced (100).

Sarcomas are among the malignancies that may be induced by ionizing radiation (15, 14, 38). In the earliest recorded cases in man these tumors developed after irradiation for benign bone lesions but later were noted to have occurred in normal bone and soft tissues in the irradiated areas (47).

4.3.1. MALIGNANT TRANSFORMATION AT A MOLECULAR LEVEL

Malignant transformation induced by radiation is thought to be related to DNA damage (18) but the actual molecular mechanisms are not clearly understood (39). In 1980 Borek (11) reported for the first time the neoplastic transformation *in vitro* of human diploid cells by x-ray irradiation into cells which could progress *in vitro* into advanced stages of neoplastic development, i.e. to form colonies in agar and give rise to tumors when injected into nude mice. The transformation of human cells has been very difficult (8).

Malignant transformation induced by radiation or chemicals appears to be a progressive, multistage process (39, 5, 113, 38). At least two steps, which have been described as initiation and promotion, are involved. These two stages may be followed by another period which is less well-defined and which itself may be made up of different components (38). Carcinogenesis extends over many years or decades (113). (This may partly explain why tumors as

malignant and rapidly progressive as PRS have a relatively long latent period). According to Hallahan ionizing radiation, like most other known carcinogens, can act as both initiator and promoter and is therefore termed a complete carcinogen (39).

Malignant transformation may be due to activation of an oncogene, loss of a suppressor gene (as in retinoblastoma or Wilms' tumor) or possibly sometimes both (38).

In radiation carcinogenesis a normal indigenous proto-oncogene may be changed and activated by the radiation. As oncogenes act dominantly, a single copy of the gene in the cell is enough to lead to a transformed phenotype, even if normal copies of the same oncogene are present. Proto-oncogenes may be activated to produce malignant cells by point mutations, chromosomal rearrangement, translocation (which often places the proto-oncogene next to a strong promotor sequence), or gene amplification. Some known oncogenes are associated with certain cancers and chromosomal changes (38).

In an analysis of tumor cells derived from seven radiation-induced tumors, six out of seven of the radation-induced human tumors had abnormalities of one or both of the suppressor genes Rb and p53 (13). Rb and p53 have been implicated in the causation of a variety of tumors, including spontaneous sarcomas (77, 91, 38).

The development of retinoblastomas is discussed in section 4.4.

Recent studies have supported the concept that multiple genetic changes are necessary for tumorigenesis. According to Nowell's clonal-evolution model of tumor progression, a cell which acquires a specific genetic change may develop a proliferative advantage and clonal expansion of the cell, driven by successive mutations, could lead to tumor progression (78, 92). According to a basic model of tumorigenesis reviewed by Renan (92), the age-specific incidence rate is proportional to an integral power of age. According to this model malignancy only appears as a clinical entity after the necessary set of m sequential changes has occurred. The number of alterations in a particular tumor can be deduced. On double logarithmic coordinates, a plot of incidence against age will give a straight line of which the slope is (m-1). Renan has taken twenty-eight different malignancies and plotted the log of the age-specific mortality rate against the log of age in years and then determined the best-fit linear regression coefficients for each tumor. He thus lists the number of mutations calculated to be necessary after birth for the development of the tumor. The mortality rates of commonly occurring solid tumors such as stomach and pancreatic cancer allowed straight lines in a log-log plot, sometimes with a deviation in early childhood or old age. Seven or eight mutations appeared to be necessary in this group. For prostate cancer twelve mutations appeared necessary,

which may explain why it is primarily a disease of old age. This may also explain the incidence of "partially transformed" lesions of the prostate found at autopsy. It may be that the premalignant cells have not undergone the full number of alterations necessary for overt neoplasia (92).

Relatively high incidences at younger ages for certain tumors are thus presumed to be due to inherited defects. The final shape of a curve may depend on data from two separate groups: patients who develop the tumor in early childhood and those who develop it in adulthood. For bone cancer there is a peak in the late teenage years and another increase after approximately age 35. The high rate in teenage years could result from a population group susceptible to bone cancer early in life (92), for example those with a lesion in the retinoblastoma suppressor locus (38, 28). For bone cancers in the younger age group three alterations appeared to be necessary, and over 35 years of age six. If this is a single disease, these data imply that patients with a familial prediposition are born with three genetic changes, rather than only one, in the precursor tumor cell. It is suggested that one of these, the Rb gene lesion, is a germline mutation, and two lesions follow rapidly in utero. Renan thus explains why in certain tumor types there are early and late onset patient groups. The early onset cases may be a result of inherited susceptibility, necessitating less genetic alterations before malignancy develops (92).

If this model is correct, postradiation desmoid tumors or aggressive fibromatosis may be due to the same phenomenon as suggested for carcinoma of the prostate, with the final mutations which would have given rise to definite histological evidence of malignancy or to metastasis being absent.

4.3.2. THRESHOLD FOR TUMOR INDUCTION

Radiation damage may occur according to a deterministic or stochastic (random) effect. In general, loss of a large number of cells will lead to observable harm. The probability of such harm will be nil at small radiation doses but above a threshold dose it will increase rapidly with dose to 100%. This is called a deterministic effect. There is a threshold level and the severity of the effect is dose-related. This first outcome could result in, for example, a radiation-induced cataract (38).

Whether or not there is a threshold for radiation carcinogenesis has been the subject of controversy.

According to a report of the United Nations Scientific Committee on the Effects of Atomic Radiation reviewed by Tountas (114), for external radiation there is a negligible probability of radiation induced sarcomas of bone below 10Gy. In a report on bone sarcomas linked to radiotherapy

and chemotherapy in children Tucker noted no increased risk associated with doses of less than 10Gy (116).

In Wiklund's (122) series of thirty-three cases of PRS from the Finnish Cancer Registry, all the patients had received doses of more than 15Gy. A higher threshold dose has also been suggested (53). Wiklund (122) pointed out that these differences probably reflect, in part, the difficulty of finding out the dose previously given at the sarcoma site.

Senyszyn (100) suggested that 30Gy was probably the critical dose for tumor induction in bone as doses less than this had not been reported to cause bone tumors.

In the Groote Schuur group the lowest prescribed dose was 3 000R (case 14). Three patients were estimated to have developed tumors for which the dose at the estimated tumor development point was less than 30Gy (Cases 11, 14 and 15).

According to Hall (38) carcinogenesis is the result of a stochastic effect and there is probably no threshold. The probability of cancer is dose-related. The severity of the cancer is of course not dose-related but a higher dose gives a higher probability of cancer (38).

A relationship between incidence and dose and the rarity of the condition overall would account for the fact that it is

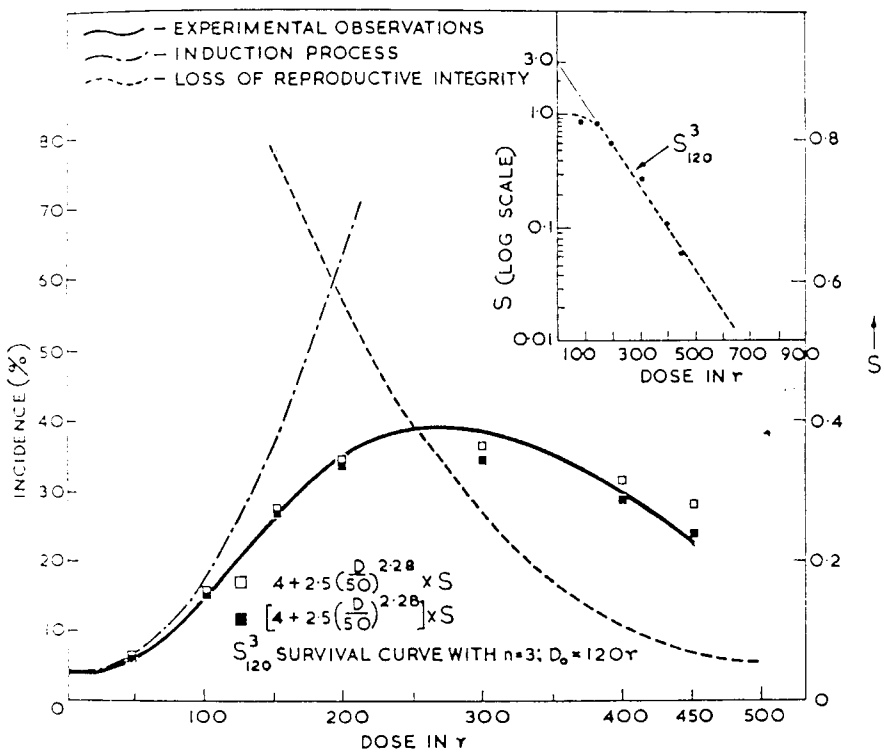
difficult to detect an increase in incidence at very low doses as found in the studies discussed.

4.3.3. GRAY'S HYPOTHESIS AND THE EFFECT OF DOSE

In small experimental animals a variety of dose-response relationships in carcinogenesis have been reported. In the characteristic type of curve obtained, if incidence of leukemia is plotted against dose, the incidence of malignancy increases with dose up to a maximum (usually between 3 and 10Gy) and this is followed by a decrease in incidence with further increases in dose. It is thought that the shape of the curve is due to a dose-related increase in the proportion of transformed cells and at higher doses a dose-related decrease of the probability that such cells survive the radiation. The fraction of transformed cells is therefore reduced at high doses. It is thought that the same effect might well be found in humans if enough data were available for a specific tumor type (38). This hypothesis has become known as Gray's hypothesis. The curves drawn by Gray (37) are reproduced on Graph 1. The significance of this effect for most cancers other than leukemia remains unclear (63).

GRAPH 1

Dose response relations for the induction of myeloid leukemia. From Gray (37)



It appears that there is not a single model for the description of dose-response curves for tumor induction in different tissues (118). For some tumors the mechanism of transformation may be mainly a result of direct effects on the target cell, perhaps involving one or more mutations. A variety of host factors such as endocrine status, immune competence and cell population kinetics of the target and interacting cells can influence the eventual expression of the tumor. In other tumors indirect effects may play a major role in the tumor initiation or expression (118).

Two different types of model can be used to explain radiation carcinogenesis. In the absolute risk model it is assumed that the radiation induces a mumber of malignancies over and above the natural incidence and unrelated to it. This model was favoured in the past. In the relative risk model it is assumed that the radiation increases the natural incidence of cancer at all ages subsequent to exposure. As the spontaneous cancer incidence rises in old age, this model predicts a larger number of radiation-induced cancers in old age, too. In the time-dependent relative risk model, used in the most recent assessments of cancer risks in A-bomb survivors, the excess incidence was assumed to be a function of dose, (dose)-squared, age at radiation exposure, and time since exposure (38).

4.3.4. EVIDENCE FROM CLINICAL STUDIES FOR SARCOMA INDUCTION AT LOW DOSES

Some authors have suggested that PRS develop in low-dose areas within radiation fields.

1) According to Brachman et al (13) it is known that second malignancies, usually sarcomas, arise at or within the edge of radiation fields several years after the radiation.

2) Turner and Greenall from the John Radcliffe Hospital in Oxford described two cases of sarcoma after breast conservation surgery and radiotherapy. They mentioned that a distinguishing feature of PRS, as demonstrated by their cases, is that the sarcomatous change tends to occur at the periphery of the field, whereas a recurrence of the breast cancer would often be more central (117).

3) Arlen et al (5) pointed out that in nineteen cases reported or reviewed by Senyszyn (100), six of the PRS developed in the scapula although the "apparent" dose to this bone appeared to be the least to all sites treated.

4) In children who generally received an exposure of only 350-400R for tinea capitis the RR for bone and connective tissue cancer was 9. Most of these occurred in the head and neck area. (9.4% received more than one treatment but it was not specified if the children who developed bone sarcomas were in this group.) (95)

5) Among patients treated for ankylosing spodylitis an excess of deaths due to bone cancer has been reported (23) but this report was based on only five deaths. Among patients who received a skeletal dose of the order of 3Gy for ankylosing spondylitis a RR of 2.96 after 25 years of follow up was calculated (23).

> However among atomic bomb survivors, and in a study combining results of atomic bomb survivors and irradiated spondylitics, there were no excess deaths from bone cancers (24).

Postradiation sarcomas may be found in relatively low dose areas in radiation fields but this does not preclude a dose effect with higher incidences in higher dose areas.

It has been speculated that sarcomas appear at the periphery of the radiation fields where the radiation levels have not been great enough to destroy all viable cells (5) or that sarcomatous change occurs in areas of intermediate damage, while the more heavily damaged areas lack even neoplastic recuperative ability (21).

4.3.5. EVIDENCE FOR SARCOMA INDUCTION AT HIGHER DOSES AND A DOSE-RESPONSE EFFECT

The frequency of PRS reported in bone as compared to soft tissue has been attributed to the greater absorption of irradiation by bone, particularly when orthovoltage treatment is used (114). This supports the theory that the sarcomas occur at higher doses.

In a review of the literature more studies are found which report the development of PRS in conventional or high rather than low dose areas:

1) In a study of postradiation soft tissue sarcomas at the Royal Marsden Hospital in London (25) it was found, in patients in whom complete radiotherapy details were available, that the mean total dose was 37.3Gy with a range from 8.8 to 79Gy. Most patients had received 20 to 50Gy. Both ortho- and megavoltage therapy had been used with conventional and large-fraction schedules. There was no evidence that the sarcomas arose at the edge of the treatment field. It had been hoped that full tumoricidal doses of radiotherapy might limit the induction of malignancy. However in this series it was shown that PRS may occur following radical doses and regardless of voltage (25).

2) In a study of thirteen patients with postirradiation sarcoma of the head and neck from the University of California, Los Angeles Medical Center, doses were known in ten patients and ranged from 30 to 124.4Gy with a mean of 60.03Gy (67). According to this author most series report doses in the range of 16-112 Gy with most of the sarcomas occurring at doses of about 55Gy.

3) In a series of seven postradiation soft tissue sarcomas in breast cancer patients from the Northern Israel Oncology Centre, the mean dose was 39.14Gy and the range from 22 to 54Gy (58).

4) Evans and Hughes from the Middlesex Hospital (30) reported two cases of PRS of the clavicle. They pointed out that, as in most cases previously reported, it was not possible for them to calculate accurately the dose actually absorbed by the clavicle because of insufficient documentation at the time of treatment. They estimated the dose to have been in excess of 4500rad. Both patients were treated by means of an orthodox kilovoltage source.

5) Meredith and co-workers (72), in their review from the Ohio State University, noted that 17% of patients developing uterine malignancy after pelvic radiotherapy had mixed mesodermal sarcomas. The proportion of sarcomas was higher in those patients who developed the malignancy after radiotherapy for a malignant condition. Patients who had been irradiated for malignant conditions also tended to develop more aggressive tumors.

6) Souba (109) from the M.D. Anderson has reported sarcoma development after doses in the range 42 to 55 Gy, Doherty (27) after 18 to 100 Gy, and Tountas (114) from the Princess Margaret Hospital after 30 to 63 Gy. Wiklund (122), in an analysis from the Finnish Cancer Registry, reported a range of 16 to 112 Gy with a median of 36 Gy. In the latter study only two of the

thirty-three patients had received larger doses than is usual.

Referring to a report from the National Research Council Committee on the Biological Effects of Ionizing Radiations, from the National Academy of Science in Washington, DC, Coleman (18) noted that sarcomas require higher doses than thyroid or breast cancer with none occurring in the atomic bomb population in which the maximum dose was 6Gy.

There are also many reports of sarcomas occurring in particularly heavily irradiated tissue:

1) Boice et al (10), in a study of dose and second cancer risk in patients treated for cancer of the cervix (which has been discussed in section 4.1.4.2) found that several cancers seem to be related to doses of radiation of the order of hundreds of gray. Suggestive, but not conclusive, results were obtained for cancers of the bone and connective tissue. (High doses did not seem to increase the risk of cancers of certain organs such as the small intestine and colon. Lower radiation doses have been associated with an increased risk of colon cancer among atomic bomb survivors and these authors suggested that the high doses received during the radiotherapy for cervical cancer cause cell killing rather than transformation. They pointed out that many colon cells proliferate at a relatively high rate. Very high doses have also

been associated with decreased risk of cancer at other sites with a high proliferation rate.)

High radiotherapy doses appeared to increase the risk of cancers of the female genital tract in the order of 6% per 10Gy. 332 cancers of the uterine corpus developed. 77% were adenocarcinomas and 17% sarcomas (including 6% carcinosarcomas). The others were either carcinoma not otherwise specified or unknown type. The RR was 6 at 15 or more years after the radiation exposure and it appeared that the risk increased with increasing dose. The authors (10) suggested that for their patients with cervical carcinoma the very high doses in the pelvic area are likely to have caused severe tissue damage which may have contributed to the development of a second cancer in a different way from lower doses. The risk may have been influenced by the nature of the exposure circumstances. Intracavitary radiums were used as well as external beam treatments. The authors pointed out that the effects of fractionation, protraction and nonhomogeneous organ exposures are not easily predictable.

2) According to a review by In Sook Seo from the Indiana University School of Medicine (101) most radiation-induced tumors in patients treated for benign conditions are carcinomas and sarcomas are more common after treatment for malignancy. (This would agree

with the theory that sarcomas develop after high doses as doses for malignant conditions are generally higher than for benign ones.) According to In Sook Seo's review most sarcomas occurred in heavily irradiated tissues.

3) Two soft tissue sarcomas in the radiation field following breast conservation therapy were reported from the Cancer Institute and associated clinics in Marseilles. Both occurred in the high dose irradiated area, in the region of supplementary electron beam irradiation, which had received doses of 70 and 80 Gy respectively (57).

4) Other authors (96, 104, 47, 14, 45) have reported sarcoma development in heavily irradiated tissue.

It has been pointed out (113) that out it is difficult to differentiate between the direct role of radiotherapy in the induction of sarcomatous changes and its indirect role via a chronic post-irradiation ulcer.

In most studies of PRS where details of radiotherapy are available, a prescribed dose is reported rather than the dose at the site of tumor development. Corrections for dose in bone are not always made. In the Groote Schuur study an attempt has been made to estimate the dose level at which the tumor developed. This is not very precise due to lack of information about the exact situation of the

radiation field with respect to the postradiation tumor. Corrections have been made for the various modalities according to whether bone or soft tissue was affected by the postradiation malignancy. The range of dose points at which tumor is estimated to have developed is from 8 to 100Gy with a mean of 48Gy and a median of 49 Gy. Only three patients were estimated to have developed PRS in tissue which received less than 30Gy. The tumor developed between 30 and 60Gy in 9 cases and at 60Gy or more in 6 cases.

The data from Groote Schuur appear to support the other evidence available that sarcomas are more likely to develop in higher dose areas. However conclusive evidence is lacking.

Boice's results (10) supported the concept of a dose-response relationship as does work done on children.

In children with bone sarcomas related to cancer treatment a dose response has been reported such that the risk reached 40-fold after doses of more than 60Gy to bone. For doses less than 10Gy the RR was 0.6, for doses of 30-40Gy it was 17 and for doses of more than 60Gy it was 38. The risk did appear to decrease when the dose was more than 80Gy (116).

Experimental work on animals has supported the concept of a dose-response relationship (48, 103, 35):

1) In an abstract from the Russian literature (102), the development of strontium-90 induced osteosarcomas in rats is discussed. The highest dose (9.5μCi) yielded 2-22% osteosarcomas and the incidence was not dependent on duration of exposure. 1 and 2μCi yielded 36 and 60% respectively after 6 months and further extension of exposure did not change the process of carcinogenesis. In the 4μCi group the yield increased from 20% after 1 month to 52% after 3 months and further prolongation resulted in inhibition of carcinogenesis.

2) In Gillette's study (59) of intra-operative radiotherapy in dogs the incidence of tumor induction increased with increasing dose between 47.5 and 90 Gy and decreased at 97.5Gy total dose. Two of the dogs which did not develop tumors had received 47.5Gy intra-operative therapy and 50Gy external beam radiotherapy and developed septic osteoradionecrosis with very few viable bone cells present (89, 35).

It is possible that the curve for sarcoma induction would be similar to that described by Gray for leukemia induction but that the dose levels at which maximum malignant transformation and decreased transformation occur would fall at higher dose levels. This could be due to slower turnover of connective tissue and bone cells allowing cells to survive and be transformed at higher dose levels.

Another possible explanation for sarcoma development at high doses is that malignant cells grow in from the periphery of the field (where lower doses have been received) (5) to produce tumors more centrally in higher dose areas. The tissue damage in these areas may promote tumor growth but this is controversial as will be discussed later (82, 74). Some connective tissue and bone cells must survive in high dose areas and it seems more likely, considering the differences in dose reported in patients developing leukemia, breast and thyroid cancer and sarcomas, that sarcomas develop in higher dose areas than these other tumors, but perhaps with a fall-off in induction at doses at which cell kill overtakes malignant transformation.

4.3.6. THE EFFECT OF TISSUE DAMAGE

Sarcomas may arise in surgical sites where no radiotherapy has been given. Several authors have reported such sarcomas (50, 29). These and other reports support a role for mechanical damage in tumor development (66, 15). According to one hypothesis reviewed by Gillette in Cancer Research in 1990 (35), radiation has a direct and indirect effect on tumor induction. The direct effect is the malignant change in the regenerating cells and the indirect the creation of an environment for expression of malignant change. Stromal damage, more severe with large single doses, may have contributd to the incidence of tumor induction after intra-operative radiotherapy. Repetitive irradiation has been

reported to be more effective at tumor induction in a study on radiation-induced osteosarcomas in mice (80).

Thus even where there is no other reason, such as previous surgery, for mechanical damage, it is possible that radiation alone may have a mechanical effect which influences tumor development. It has been suggested that the reason for the development of PRS in the scapula after radiotherapy for breast carcinoma may be radiation damage to vessels which have their origin in the radiation fields. The scapula may be more radiosensitive because of a relatively better oxygen supply due to the rich blood supply (100).

Papaioannou presents evidence from the literature that breast cancer recurrence may be facilitated by the injury caused by mastectomy or radiotherapy through local, regional and systemic mechanisms which promote tumor growth. Both local and systemic relapse may be affected and the effect appears to be proportional to the degree of injury (82). Similar factors may have a role in sarcoma development, with prior tissue irradiation promoting tumor growth.

According to the theory of the tumor bed effect, tumor cells transplanted into pre-irradiated subcutaneous tissue need more time to establish tumors than those transplanted into non-irradiated tissue, and further tumor growth in the irradiated tissue is reduced. The phenomenon is thought to

be due to the reduced blood supply to tumor in irradiated tissue as the tissue has a decreased ability to provide blood vessels to tumors. The effect is dose-dependent. The tumor type is an important factor in the tumor bed effect with carcinomas showing a more pronounced effect than fibrosarcomas. Experimental work using murine tumors has shown that pre-irradiation of the tumor bed can influence the therapeutic response to Cyclophosphamide in a deleterious or advantageous way, depending on whether the endpoint for assessing anti-tumor activity is tumor cure (which was reduced) or regrowth delay (which was increased). It is explained that the reduced blood supply may account for the reduced curability but the same effect accounts for the delayed regrowth (74).

There has been much speculation as to whether bone injury and reparative proliferation are necessary as an initiating factor in tumor development. In a report from the Memorial and James Ewing Hospitals many patients did have evidence of radiation osteonecrosis before signs of sarcoma development but the authors did not feel there was clinical evidence at the time of their report to support the concept described. There had been relatively few reports of the phenomenon (5).

Several patients in the Groote Schuur study had undergone surgery as well as radiotherapy in the treatment of the initial tumor and had received more than one course of

radiotherapy to the relevant area before the development of a postradiation tumor.

In general it appears that mechanical factors may affect sarcoma development. It is impossible to assess the magnitude of this effect in the clinical setting.

4.3.7. THE EFFECT OF AGE

It has already been noted (section 4.2.3.) that tissues in children may respond differently to radiation from those in adults.

Age at the time of radiation exposure is thought to be important in the development of bone cancer. It is suggested by Hall that in exposure to a fetus or young person the rapid deposition of the bone-seeking radioisotopes during active bone growth might confer a higher risk of cancer induction than in adults (38). Other authors (124, 5) have noted that doses greater than 50Gy are likely to cause complete devitalization of adult bone, but the bones of children survive higher doses. A greater likelihood of cell survival would increase the risk of malignant transformation. It is difficult to estimate the effect of age in view of the large numers of paediatric cases with a genetic predisposition to malignancy.

4.3.8. THE EFFECT OF MODALITY

4.3.8.1) THE EFFECT OF MODALITY ON THE DEVELOPMENT OF POSTRADIATION SARCOMAS

The effect of radiation modality on the development of malignancy should be related to radiobiological effects as well as the dose absorbed by different tissues with different modalities. In 1970 Hatfield (46) stated that the issue of the incidence of sarcomas as a function of the energy of the external beam has not been resolved. This statement still holds true today. The absence of the expected decrease in incidence of PRS with the increasing use of megavoltage therapy has already been mentioned (section 4.1.5.). Boice's survey also supported this finding (10).

Laskin (59) suggested that a possible increase in PRS may be due to the profound mutagenic effect of megavoltage treatment on deep mesenchymal soft tissue. The transformation may be due to the effect on undifferentiated mesenchymal stem cells and result in malignant transformation along primitive fibrohistiocytic lines. Transformation into osteoid-producing cells may occur under the influence of increased oxygen tension in congested tissue (7).

In the Groote Schuur study thirteen patients had received megavoltage therapy. One of these had also received

orthovoltage therapy and brachytherapy. One had received electron beam treatment (not at the site of sarcoma development) and five had received radium insertions. Six had been treated with orthovoltage and no megavoltage therapy. Of these, two were also treated by means of brachytherapy.

The evidence from the literature and our study suggests that PRS have not become less common with the introduction of megavoltage therapy.

4.3.8.2) THE EFFECT OF MODALITY ON THE DOSE AT WHICH POSTRADIATION SARCOMAS DEVELOP

A further question relating to modality is whether the dose at which a PRS develops is related to the type of radiotherapy employed. In Wiklund's analysis of thirty-three cases of PRS the median total dose for megavoltage therapy was 36Gy (range 31 to 112Gy) and orthovoltage 24Gy (range 16 to 90Gy, p0.02). Whether or not the patients received intracavitary treatment was also not significant (122).

In the Groote Schuur study, if f-factor corrections are made, the patients who received orthovoltage treatment developed tumors at a lower mean dose point (31Gy) and range of dose point (8 to 62Gy) than in the megavoltage group (mean 54Gy and range 12 to 100Gy). This difference was however not statistically significant and there is

insufficient data in the literature to draw conclusions regarding this point.

4.3.9. GENETIC FACTORS AND THEIR RELATIONSHIP TO THE DOSE AT WHICH POSTRADIATION SARCOMAS DEVELOP

Several authors have discussed the relationship between genetic factors and the development of second malignancies.

Even in the absence of a family history of malignancy there may be a genetic factor which increases the susceptibility to malignancy in the radiation field (110).

There are hereditary or familial disorders with an increased risk of cancer development and an association between hereditary retinoblastoma and osteogenic sarcoma in children has been shown (28). This will be discussed in more detail in section 4.4.

Coleman (18) notes that between 25 and 50% of second tumors in a paediatric population may be due to a genetic syndrome or some other hereditary predisposition and thus may not be truly treatment-related.

Approximately 5% of the second malignant neoplasms in a report from the Late Effects Study Group were not associated with radiotherapy, chemotherapy or genetic disease. If, as previously suggested, the incidence of

second malignancies in children is tenfold greater than that of cancer in the age-matched general population, this fraction of cases would be expected to occur by chance alone (70).

It has been suggested that a fraction of patients with Wilms' tumor also carry a genetic predisposition to the disease (55). In a report by Meadows on second malignant neoplasms in survivors of paediatric cancer (70), almost 30% of the Wilms' group had characteristics of the genetic form of that embryonal tumor although the age at diagnosis of Wilms' was not earlier than expected. This suggests that, as in retinoblastoma, second malignancies occurred excessively in patients with the genetic form of Wilms' tumor. Ionising radiation was associated with the majority of second malignancies reported in this study.

In Wiklund's study the mean and median total dose was lower for patients with a genetic predisposition to malignant disease than for those without such a predisposition (30).

In the Groote Schuur study the retinoblastoma patients developed PRS at an average of 31Gy. In the non-retinoblastoma group the mean was 51Gy. This result was not statistically significant but the trend is in keeping with Wiklund's finding. It is impossible to determine whether the PRS in retinoblastoma patients developed due to genetic factors alone and what role the radiotherapy played.

In conclusion, genetic factors may increase the risk of a second malignancy but the relationship between genetic factors and dose is not clear.

4.3.10. CHEMOTHERAPY AND CHEMICALS

Various chemicals have also been associated with sarcoma development (67).

An association between the use of chemotherapy and sarcoma development has been shown in the following studies:

(1) A higher incidence of bone sarcomas has been noted in survivors of paediatric malignancies who received chemotherapy as well as radiotherapy, than in patients who received radiotherapy alone (116).

(2) Cyclophosphamide may play a role in the induction of second tumors in retinoblastoma patients (28). Of the eight patients with sarcomas occurring within the radiation field in Draper's study of second primary neoplasms in retinoblastoma patients, three patients had been given Cyclophosphamide. Of the thirteen who developed tumors out of the field, five had received Cyclophosphamide. Of the two who developed soft tissue sarcomas within the field one patient had received Cyclophosphamide, and one of the four who

developed a soft tissue sarcoma outside the field. The incidence of second primary tumors overall was greater among patients given chemotherapy than among those not given it (28).

In the Groote Schuur study six patients had received chemotherapy as well as radiotherapy before the development of the PRS. In this report no comment can be made on the effect of chemotherapy on the incidence of PRS. It appears from reports in the literature that chemotherapy may further increase the risk of a sarcoma developing in a radiation field.

4.3.11. OTHER FACTORS IN THE DEVELOPMENT OF SARCOMAS IN RADIATION FIELDS

4.3.11.1) "SPONTANEOUS" SARCOMAS AND UNKNOWN PREDISPOSITIONS TO SARCOMA DEVELOPMENT

A sarcoma may occur by chance in the irradiated area (34, 84). It should be remembered that patients with primary malignant tumors are statistically more at risk of second unrelated tumors than the general population. If the risk of a double primary has been outlived, patients who have been irradiated are at risk from "spontaneous" sarcomas just as the rest of the population is (46).

292 patients with 308 second malignancies were reported by the Late Effects Study Group in 1985 (70). It was noted

that although most cases of second malignancy in survivors of childhood cancer can be attributed to radiation, genetic disease, chemotherapy or combinations of these, unrecognized predisposition or chance may also play a role. 25% of the patients in this series had a known cancer-prone condition.

It has been suggested that there is an "unknown predisposing factor" implicated in the rare development of sarcomas in breast cancer patients (115).

Reports of third neoplasms in patients with PRS are rare. Hatlinghus and co-workers (47), in a report of three PRS, noted that two had multiple primaries and others have been noted (3, 34). Hatlinghus (47) pointed out that the presence of multiple primaries might suggest that the sarcomas were actually spontaneous tumors but he and his co-authors felt there was good reason to regard them as radiation-induced tumors in patients with an increased disposition to develop cancer.

4.3.11.2) UNDERLYING BONE DISEASE

Benign conditions including fibrous dysplasia and giant cell tumor of bone have been associated with later sarcoma development, even in the absence of radiotherapy (121). It is possible that the development of sarcoma in these cases may be associated with the tissue damage effect as discussed earlier (5).

In patients with diseased bone at the time of irradiation in Huvos' series the median dose was 59Gy with a range of 16.60 to 115.00 Gy and in those with normal bone the median was 45Gy with a range of 25 to 110Gy (49).

In the Groote Schuur study the two sarcomas which developed in diseased bone were estimated to have developed in tissue which had received 48 and 62Gy. No conclusions can be drawn regarding these patients due to the small number.

4.3.11.3) THE CAUSE OF TUMOR DEVELOPMENT CANNOT BE ASCERTAINED IN INDIVIDUAL LESIONS

Hatfield (46) pointed out that postirradiation sarcomas occur later than unrelated second primaries and should be considered as a separate group of lesions. He also noted that sarcomas do occur spontaneously and absolute proof of radiation as a cause is lacking in man. Statistical evidence is available. Hatfield stated that it is prudent to assume that tumors which have been called PRS are causally related to the previous radiation and are not spontaneously-occurring second primaries.

As can be seen from the preceding discussion, although sarcomas developing in postradiation fields may be termed radiation-induced sarcomas in some reports, they may have developed spontaneously. Genetic, chemical or mechanical

factors, or disease in the underlying bone, may also have played a part in their development.

4.4. POSTRADIATION SARCOMAS IN RETINOBLASTOMA PATIENTS

4.4.1. HISTORICAL BACKGROUND AND CLINICAL STUDIES

In 1969 Sagerman from the Columbia-Presbyterian Medical Centre of New York wrote a report (97) on radiation-induced tumors following external beam treatment for retinoblastoma. It was not the first report of tumors following radiotherapy for this condition but it is an interesting paper and particularly interesting in retrospect. Among 243 retinoblastoma patients followed up for 5 or more years, second malignant neoplasms occurred in twenty-three. Two were osteosarcomas outside the field. Therefore twenty-one postradiation tumors were available for analysis. Sixteen were sarcomas and nine of these osteosarcomas. The incidence figures for second malignancies in patients surviving 5 or more years ranged from 2.5 to 32% and appeared to depend on the dose of radiotherapy the patients had received.

Sagerman noted that in other large series of radiation-induced tumors the incidence had only been about 0.1% and he referred to reports by Castro and Phillips. These are actually both reports of postradiation sarcomas (15, 87), and do not include other postradiation malignancies. However Sagerman's patients had an incidence of 6.6% for sarcomas, so even if only sarcomas are considered the incidence in Sagerman's series was higher than in other series. Sagerman suggested several factors to explain the

discrepancy. He pointed out that a high proportion of patients at his unit were cured of retinoblastoma and therefore at risk of a second tumor for many years. He also pointed out that generally higher doses of radiation were used in his patients than in most patients in other series and that patients in his series were young and therefore the effect of the radiation might be more pronounced. Sagerman did note that the two cases of osteosarcoma of the femur, one in a patient who had not been irradiated, raised the possibility of an increased susceptibility to neoplasia in retinoblastoma patients which was being investigated.

No mention was made in the paper of whether Sagerman's patients had a family history of retinoblastoma.

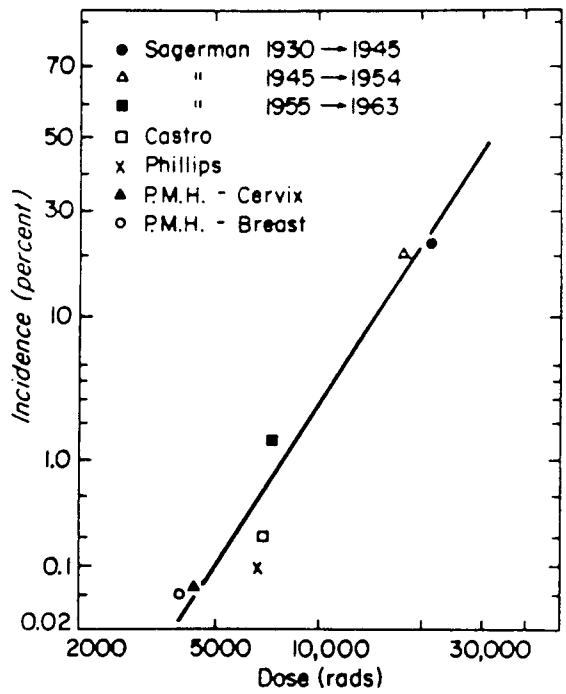
An interesting aspect of Sagerman's work was that he found a significant reduction in the risk of developing a radiation tumor with lower doses. He noted a gradual decrease in the tumor dose which had been used to control retinoblastoma from about 14 000R before 1945 to 3 500 - 4 500R at the time of reporting. The risk of damage to irradiated bone decreased by a factor of approximately 2 when megavoltage equipment was introduced, and the incidence of all tumors and of osteosarcoma alone appeared to be significantly decreased. It was not possible to determine what the true incidence of radiation-induced tumors would eventually be in

Sagerman's patients with the schedule in use at the time of reporting as of course new cases were expected to develop.

10 years after Sagerman's report, Tountas from the Princess Margaret Hospital used the results in a further analysis (114). Tountas calculated the absorbed bone dose in rad in the cases of PRS of bone and compared this with the incidence of bone sarcomas produced, expressed as a percentage of 5-year survivors. He produced a graph (Graph 2) with on the X-axis the log% incidence of radiation-induced sarcomas among 5-year survivors and on the Y-axis the absorbed bone dose in rad which produced these sarcomas. It appears from the graph that Sagerman's patients had a higher incidence of sarcoma with higher dose. Tountas included on the graph figures for PRS of bone in patients treated for cancer of the breast and cervix at his own institution and figures from the series of Castro and Phillips. These were the only series he could use, as in general techniques are not well reported for these patients. Tountas thus produced convincing evidence for an increased incidence of sarcoma with increasing dose. However he did not take into account the effect of duration of follow-up (1).

GRAPH 2

Graph showing the relationship of log % incidence of irradiation induced sarcomas (X-axis) amongst five year survivors vs the absorbed bone dose in rads. From Tountas et al (114)



It had already been recognised that there was a 15 to 20% incidence of second, non-ocular tumors, most commonly osteosarcoma in long bones, in patients with bilateral retinoblastoma. A mean latency of 13 years was reported from Columbia University. These tumors were reported to appear on average 10 years after the treatment of the original tumor and occured almost exclusively in patients with bilateral disease. Second primaries were rare in patients with unilateral disease (54, 9, 90). A review of over 2 000 cases of retinoblastoma indicated that survivors of bilateral disease are about 300 times more likely than the rest of the population to develop osteosarcoma of the

femur and over 1000 times more likely to develop osteosarcoma of the skull (90).

Patients with genetic retinoblastoma are at substantial risk of developing oseosarcoma and other tumors (28). Meadows reported 65% of the second tumors to have occurred within the irradiated field and 64% of these to be osteosarcomas (71). Other tumors including soft tissue sarcomas were much less common than osteosarcoma (71).

The question arose whether the genetic predisposition did not account for all the so-called radiation-induced tumors in these patients as well as the tumors outside the field. Abramson (2) like Sagerman wrote from the Columbia-Presbyterian Medical Centre in New York. He described twenty-two patients who survived and were followed up after bilateral enucleation alone for retinoblastoma. Three of the twenty-two developed second tumors and this was at a mean of 15 years after bilateral enucleation. The incidence of second tumors in patients who survived bilateral retinoblastoma treated without radiation was 14% which was noted to be comparable to figures reported for patients treated with enucleation and radiotherapy.

Because of the long latent period involved, Abramsom estimated that the incidence of second neoplasms would probably be between 15 and 20% in patients with bilateral retinoblastoma who survived treatment. The role of

radiation in inducing any of the tumors was not certain (2).

Draper from Oxford University (28) reported a series of 882 retinoblastoma patients in 1986. 384 had genetic disease and 498 sporadic. Thirty developed second malignancies. The incidence was 2% at 12 years and 4.2% at 18 years. Most of the second tumors (26/30) occurred among patients with the genetic type of disease. For patients with genetic disease the cumulative incidence rate after 18 years was 8.4% for all second neoplasms and 6% for osteosarcoma alone.

For patients with genetic disease the cumulative incidence of all second neoplasms within the radiation field after 18 years was 6.6% and for osteosarcoma alone 3.7%. 46% of second primaries among the cases of genetic retinoblastoma developed outside the radiation field. Nine of twelve were osteosarcomas, two soft tissue sarcomas and one an epithelial tumor. The estimated cumulative incidence rate of second malignancies outside the field for genetic cases 18 years after the diagnosis of retinoblastoma was 3%, all the second tumors observed within this time period being osteosarcomas. The estimate of risk for patients with the genetic form of retinoblastoma developing osteosarcoma, excluding any risk from treatment, was about 200 times that for the general population.

Osteosarcomas of the orbit are rare and probably less than 10% of all osteosarcomas usually occur at any site in the skull and jaw bones in this age-group. It would be expected that less than one person in 100 000 would develop such a tumor in the first 20 years of life. The observed rate in this study was of the order of 4 000 times as great as this.

Among the 498 patients with non-genetic retinoblastoma only four second primaries were recorded. The incidence rate for second malignancies outside the field at 18 years was therefore 0.4% or 0% (as the one patient in this category may have actually had the genetic form of the disease). The corresponding rate for the genetic cases as we have seen was 3%. For tumors inside the field the contrast between the rates for genetic and non-genetic disease was also striking. Among 100 patients with non-genetic disease only one developed a tumor in the field. This was a meningioma of the brain at 31 yrs. The corresponding estimated rates for the patients with genetic disease were 3.4% at 12 and 6.6% at 18 years.

Draper's results suggested that patients with genetic retinoblastoma may be more susceptible to the induction of second tumors by radiation and, as has been discussed in section 4.3.10, that Cyclophosphamide may be implicated in the induction of second primary cancers in these patients (28).

It is difficult to test the hypothesis that patients with the genetic form of retinoblastoma may have an increased susceptibility to the induction of second tumors by radiation since other individuals exposed to radiation differ from retinoblastoma patients in respect of the doses received, the area irradiated and the type of tissue exposed. The most direct test of the hypothesis is to compare patients with the genetic and non-genetic forms of retinoblastoma treated by irradiation. In Draper's series the rate of second tumors among the eyes of patients with the genetic form is greater than the rate among the eyes of patients with the non-genetic form of the disease. (28)

Abramson (1) used actuarial methods of analysis and calculated the incidence of second tumors in patients with genetic retinoblastoma to be 20% after 10 and 90% after 30 years survival. In patients treated without radiation or where tumors developed outside the field the incidence was 10% at 10 years and 68% at 32 years.

A further study providing evidence for the genetic origin of second malignancies, and particularly sarcomas, in retinoblastoma patients was reported by Meadows et al of the Late Effects Study Group (70). 292 patients had had cancer in childhood and developed second malignancies. (Altogether there were 308 second malignant neoplasms.) The most common primary was retinoblastoma (52 patients), followed by Hodgkin's disease, soft tissue sarcoma and Wilms' tumor. 68% of second malignancies in retinoblastoma

patients were bone or soft tissue sarcomas. 67% of these sarcomas arose in an irradiated site and 33% were not associated with radiation (70).

Smith (106) from the Stanford University Medical Centre reported the actuarial incidence of second non-ocular malignancies among patients with heritable retinoblastoma to be 6% at 10 years, 19% at 20 years and 38% at 30 years. The latent period from treatment of retinoblastoma to the diagnosis of second malignancy ranged from 5 to 36 years with a median of 16 years.

The cumulative risk in Smith's study lies between that reported by Abramson in 1984 of 20, 50 and 90% and the risk reported by Draper of 4.3% at 12 years and 8.4% at 18 years (1, 28, 106).

Abramson (1) concluded that radiation increased the total risk of second malignancies above the already high incidence in patients with the genetic form of retinoblastoma as more second malignancies developed within than outside the irradiated field.

4.4.2. GENETIC ALTERATIONS AND THEIR EFFECTS IN RETINOBLASTOMA PATIENTS

Retinoblastoma appears to occur because of two separate mutations in all the tumor cells. It has been proposed

that in sporadic cases both mutations occur in the same retinal precursor cell during in utero life or early childhood. In the absence of a functioning retinoblastoma (Rb) gene a tumor develops. In the inherited form it is proposed that one of the mutations is inherited and is therefore present in all the cells. The second occurs spontaneously (38).

The retinoblastoma gene was located on the short arm of chromosome 13 in the early 1980's and has been cloned and sequenced. It appears to be associated with several other human cancers such as osteosarcoma, small cell lung cancer and breast cancer, but other changes in addition to the loss of the Rb gene are necessary for these tumors to develop. The Rb gene therefore may have a role in growth suppression in various tissues (38).

In the sporadic form of retinoblastoma there may be two independent mutations in the two alleles, but actually homozygosity is more likely. In this process a single deletion occurs in one chromosome and the second is lost completely. The chromosome with the deletion replicates so the cell has both alleles from one parent with the piece containing the suppressor gene missing. (38)

The observation that children with hereditary retinoblastoma frequently develop second malignancies, principally sarcomas, led to the detection of similar Rb gene deletions in some osteosarcomas. Reissman (91)

studied forty-four unselected sarcomas from patients with no antecedent retinoblastoma to determine the prevalence and nature of Rb gene alterations. In total eight of thirty-eight sarcomas were found to have alterations of the Rb gene. These data indicate that the Rb gene is inactivated in a number of sarcomas unrelated to retinoblastoma, and that the potential role of the gene in the pathogenesis of human malignancy may not be limited to retinoblastoma.

Draper's data suggested that the mutation predisposing patients so predictably to retinoblastoma might predispose patients in a less predictable manner to osteosarcoma and that the development of osteosarcoma was influenced further by environmental factors such as radiotherapy (111). The frequent onset of osteosarcoma during adolescence, with a latent period of 10 to 20 years after radiotherapy, and the much-reduced penetrance for osteosarcoma, suggested that additional events might be necessary for tumor development (111). Current molecular genetic data on sporadic osteosarcoma suggest the development may be considered a "two-hit" phenomenon, requiring mutations at both allelles of the Rb locus and at the tumor suppressor p53 gene locus (41). Inheritance of a mutation at Rb predisposes a person to osteosarcoma, but several additional mutational events must occur. The same genetic loci, Rb and p53, appear to be mutated in the more common sporadic osteosarcoma.

Strong (111) notes in a review that the Rb gene is involved in the development of many different tumor types, but for most tumor types it is only one of several genetic alterations necessary for tumor development. Therefore, although germline mutations in this gene predictably give rise to heritable retinoblastoma, they less predictably increase the risk of at least some of these other tumors.

In conclusion, patients with heritable retinoblastoma have a genetic predispostion to second malignancies, particularly sarcomas. They appear to be particularly susceptible to the carcinogenic effects of radiotherapy, but a dose-response relationship has not been definitely proved.

The three retinoblastoma patients in the Groote Schuur series of patients with PRS all had bilateral disease and had received chemotherapy. Two had received Cyclophosphamide. The latency in the three cases was relatively short at 3 years 7 months, 4 years 7 months and 4 years 10 months. Schwarz (98) reported an average latency for head and neck sarcomas following radiotherapy for retinoblastoma of 10 years. Therefore the role of radiotherapy in the development of these tumors must be more in doubt than in other cases of PRS with longer latency periods. The latent period was significantly shorter than the period for non-retinoblastoma patients.

4.5. PATHOLOGY OF POSTRADIATION SARCOMAS

4.5.1. HISTOLOGICAL TYPES OF POSTRADIATION SARCOMA

Osteosarcoma has probably been the most commonly reported PRS (94, 47, 115, 100, 112, 42, 79, 114, 121, 14, 21, 27, 36, 65, 101). The Groote Schuur study is therefore not unusual with eight (40%) cases of osteosarcoma. Extraskeletal osteosarcomas have also been reported (47, 122, 59) but all our cases included involvement of bone.

In a report published in 1945 Hatcher (45) reviewed the world literature on PRS of bone and found nine of twenty-four to be chondrosarcomas. However Fitzwater (32) noted in 1976 that only 9% of reported cases since 1948 were chondrosarcoma and of the remainder 62% were osteosarcoma, 27% fibrosarcoma and 2% not readily classifiable. Histological description of several of the osteosarcomas included chondroid elements as a prominent feature. Even allowing for differences in classification Fitzwater noted that chondrosarcoma is a relatively infrequent type of PRS of bone.

Fibrosarcoma has also been relatively frequently reported (47, 75, 115, 42, 36). Some early studies reported a high percentage of fibrosarcomas and extraskeletal osteosarcomas, probably reflecting earlier diagnostic criteria and nomenclature (59). Only one case in our study was a fibrosarcoma. This occurred in soft tissue.

Nomenclature of sarcomas has changed periodically (57, 59). For example cases earlier diagnosed as fibrosarcoma would later have been classified as malignant fibrous histiocytomas (57, 113). In a recent report of PRS from the Finnish Cancer Registry there were ten osteosarcomas, ten malignant fibrous histiocytomas and six fibrosarcomas (122). Malignant fibrous histiocytoma was the most common tumor (68%) in a review of fifty-three postradiation soft tissue sarcomas submitted to the Armed Forces Institute of Pathology from 1954 to 1986 (59).

A literature review reveals a host of sarcoma types to have occurred in radiation fields. These include rhabdomyosarcoma (47), malignant mesenchymoma (115, 47), spindle cell sarcoma (65, 67, 112, 15, 27), angiosarcoma (67, 58, 117, 122, 26, 59), malignant schwannoma (67, 112, 122, 59), chondrosarcoma (104, 114, 15, 27, 65), extraskeletal chondrosarcoma (59), undifferentiated sarcoma (100, 122, 114, 58), osteochondrosarcoma (113, 14), leiomyosarcoma (122), pleomorphic sarcoma (4), meningeal fibrosarcoma (34), cutaneous angiosarcoma (81), hemangiosarcoma (64, 96), malignant chondroblastoma (65), neurofibrosarcoma (96), neurosarcoma (96), alveolar soft part sarcoma (following radiotherapy for a spinal hemangioma) (120), lymphangiosarcoma (25), sarcoma not otherwise specified (25), gastric leiomyosarcoma (62, 120) and cutaneous sarcoma (101). The tumors in our series were not of particularly unusual histological type for tumors occurring in radiation fields.

It is not possible to determine from histological examination whether a sarcoma occurring in a radiation field has been induced by radiation or not (5, 35, 36, 59) although the proportion of different types may differ from that found among spontaneously occurring tumors (122) and there may be some variation in morphology (5, 59).

4.5.2. HISTOLOGICAL CHANGES IN IRRADIATED TISSUE AND HISTOGENESIS OF POSTRADIATION SARCOMAS

There may be evidence of radiation damage in soft tissue or bone adjacent to a tumor occurring in a radiation field (5, 59, 96, 36) and this may be used to confirm the origin of the sarcoma within the field if radiation details are lacking (59). The field may however be completely effaced by the sarcoma (59).

The location and extent of radiation changes in adjacent tissue have been noted to depend on the radiation source and the latency period (96).

PRS may simply represent one end of a spectrum of changes which may occur in a radiation field. Pettit noted in 1954 (86) that fibromatosis following radiation was more frequent than fibrosarcoma and that the two entities had often been confused. He stated that irradiation fibromatosis may blend into fibrosarcoma, which is usually

a low-grade lesion and is peculiar in that it kills by local infiltration rather than by distant metastases.

In 1986 Gössner (36) reviewed data on the pathology of radiation-induced bone tumors. Fibro-osseous lesions may represent early or transitional stages between the radiation reaction and radiation sarcoma. As well as hyperplastic processes the lesions can show different degrees of osteodysplasia. Intraosseous osteosarcomas (the earliest malignant lesions) were found less frequently than overt osteosarcomas, indicating rapid progression of osteosarcoma.

In our series case 6 is of interest in that thickening in the irradiated area was noted more than 3 years before the patient presented with a mass. She was diagnosed as having a leiomyosarcoma of the abdominal wall. Biopsy of the postradiation tumor in case 20 revealed osteosarcoma in fibrous dysplasia and also fibrosis without fibrous dysplasia. The fibrous dysplasia may have been a premalignant event in this patient.

4.5.3. GRADE OF POSTRADIATION SARCOMAS

Many postradiation tumors are described as poorly differentiated or high grade (59, 94). Only four (5%) tumors in the Groote schuur study were of moderate grade and the rest were high grade.

4.5.4. GIANT CELL TUMOR AND POSTRADIATION SARCOMA

Sarcoma complicates the course of 10% of giant cell tumors, particularly if radiation has been used in treatment. Malignant change usually occurs 10 to 15 years after primary treatment but has been known to occur after 40 years. (22)

In Cahan's report in 1948 (16), in two cases giant cell tumor had been the initial diagnosis. In one the sarcoma was seen adjacent to a fibrosed area, presumably old giant-cell tumor. In the other the osteogenic sarcoma merged with residual giant-cell tumor but was still a distinct new entity.

In the Mayo clinic series (22) twenty-three of twenty-eight malignancies in giant cell tumors occurred after treatment of typical giant cell tumors. In twenty-one the treatment of the benign giant cell tumor had included radiotherapy. The average interval from treatment to the appearance of sarcoma was 13.5 years. In only one case was residual giant cell tumor present when the sarcoma was diagnosed. In two cases sarcoma developed without previous radiotherapy - one 1.5 years after curettage and one 15 years after second curettage. Overall in seven cases no radiation had been used and in five both giant cell tumor and sarcoma were present at the time of the first operation. In this series seventeen of the secondary

tumors were fibrosarcomas, five osteosarcomas and one a malignant fibrous histiocytoma.

Histologically one cannot determine the precise site of origin of the sarcoma, that is, whether it arises within a pre-existing lesion or in the surrounding normal bone (104). In a report from the Mayo Clinic in 1971 Sim (104) accepted long latency as evidence of benignness and the indolent course of the initial lesion. Four of eight verified initial benign lesions in his series of thirty-four PRS of bone were giant cell tumors. There is no doubt that spontaneous malignant transfromation can occur, but there is evidence to support the importance of previous radiotherapy in this complication (121).

Boriani (12) from the University of Bologna reported that in patients who received more than 40Gy for giant cell tumors the incidence of malignancy was 29%. No malignancies developed in patients who received less than 30Gy.

Mirra (76) reported that three forms of radiation-induced sarcomas in the site of a previously irradiated conventional giant cell tumor may be identified histologically. These are osteogenic sarcomas and fibrosarcomas, both of which are related to radiation induced anaplastic transformation of host bone mesenchyme, and osteoclastic sarcoma, which is related to radiation induced anaplastic transformation of residual conventional

giant cell tumor. In the Groote Schuur series two PRS developed in the site of irradiated giant cell tumors. In neither case was the initial diagnosis of giant cell tumor absolutely certain as one (case 18) was diagnosed radiologically, and in the other a diagnosis of possible aneurysmal bone cyst was made initially. Case 18 developed an osteogenic sarcoma. In case 17 a more specific diagnosis than sarcoma could not be made on review. Both patients had received a total of more than 40Gy. In the patient treated with a 220kV beam (case 18) the total prescribed dose was 5 000R, but the Roentgens to rad conversion factor of 1.5 for the 220kV beam in bone indicates that the dose in bone was actually 75Gy.

4.5.5. PELVIC SARCOMA AFTER RADIOTHERAPY FOR LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

In 1989 Chumas et al (17) reported a case of high-grade heterologous pelvic sarcoma in a 60-year-old woman 15 years after she received whole-pelvic radiation for a low-grade endometrial stromal sarcoma. Approximately 50% of patients with low grade stromal sarcoma will develop recurrence although it is a relatively indolent sarcoma.

Smith (107) noted that late recurrence and spread are the rule in endolymphatic stromal myosis (another term for low grade stromal sarcoma) (56) with survival at 10 years being close to 100%, often after multiple excisions, but a death

rate of 20% at 20 years (107). Smith reports a case of frank sarcoma developing from endolymphatic stromal myosis. He notes that this is an unusal occurrence. In the Groote Schuur series one patient (case 7) with PRS developed a sarcoma of the pelvis 30 years after radiotherapy and surgery for a low grade stromal sarcoma of the uterus. Initial histology of the recurrence was undifferentiated sarcoma. Subsequent resection almost 2 years later revealed a moderate grade fibrosarcoma. We have therefore considered this to be a separate tumor of different histology rather than a progression of the low grade stromal sarcoma, although the possibility of the latter diagnosis must be borne in mind.

4.5.6. MALIGNANT MIXED MULLERIAN TUMOR AFTER PELVIC RADIOTHERAPY

MMMT's have generally been classified with the sarcomas in publications concerning uterine neoplasms (19) and have been included in studies of PRS (17, 72). Therefore in this dissertation they have been included under the general heading of postradiation sarcomas. However it must be noted that in discussions of poorly differentiated ovarian tumors MMMT's are grouped with carcinomas and it has recently been suggested that MMMT's probably represent "metaplastic" (sarcomatoid) carcinomas rather than true carcinosarcomas (19).

In a report of thirty cases of uterine corpus malignancies after pelvic radiotherapy from the Ohio State University Hospitals (72), five sarcomas were noted. These were mixed mesodermal sarcomas and four were stage 3 or 4 at diagnosis. Four occurred in patients initially treated for malignancy while most of the adenocarcinomas occurred in patients initially treated with radiotherapy for benign conditions. Most of the patients with adenocarcinomas had stage 1 disease.

In the Groote Schuur series four out of six patients who developed PRS after radiotherapy for carcinoma of the cervix developed MMMT. The four cases were all advanced at presentation, one having omental metastases (case 1) and one being irresectable with possible metastases (case 4). All the tumors were high grade. In case 2 the tumor infiltrated into the outer third of the myometrium and in case 3 almost to the serosa. Three patients died within a year of surgery and one has been lost to follow-up.

In conclusion, the Groote Schuur series does not appear to differ markedly from other reported series with respect to histological types of PRS, grade or extent of tumor at presentation.

4.6. CLINICAL CHARACTERISTICS OF POSTRADIATION SARCOMA

Clinical characteristics of patients in some series reported in the English literature are summarised on Table 3.

4.6.1. PRIMARY TUMOR

Some authors have included all PRS in their reports (94), as has been done in our study. In others the report has been limited to PRS after a specific primary tumor such as breast cancer (27, 58, 113) or uterine cancer (96). In these and other reports a certain tissue (bone or soft tissue) may have been specified. In Wiklund's report (122), for example, visceral sarcomas were excluded. These specifications affect the apparent incidence of certain primary tumors preceding PRS. Sundaresan (112) chose spinal involvement as the common denominator in his series. Up to 30% of PRS arise in or around the axial skeleton.

Common primary tumors after which PRS have occurred can be seen on Table 3. In Wiklund's report from the Finnish Cancer Registry (122) most of the first primary tumors were of breast and female genital origin. According to Wiklund this agreed with previous reports and was probably a reflection of the frequency of these tumors, the use of radiotherapy in treatment and the long survival of many of the patients. These factors also explained the predominance of females in the series (122). Robinson et

al (93) noted that in a review of sarcomas in the SEER (Surveillance, Epidemiology and End Results) Program of the United States National Cancer Institute there was a higher proportion of females in the PRS group than in the group with sarcomas as a single primary, as more females receive radiotherapy for their first primary tumors, probably reflecting a large fraction of breast and gynaecological tumors.

In his extensive literature review of PRS Robinson (94) noted that the sarcoma site depended on the location of the first primary and the treatment portals. The most common first primary was breast cancer (30.8%) and the second most common cancer arising in the female genital organs (22%). The third most common was retinoblastoma (19.5%) with 76% of retinoblastoma patients having bilateral retinoblastoma. The multiple other sites included the head and neck, thyroid, spine, abdomen and limbs.

Gössner (36) noted in a review on the pathology of PRS of bone that when these had been reported after radiotherapy for extraskeletal tumors they most commonly followed treatment for retinoblastoma. After retinoblastoma, carcinomas of the breast or uterus were the most common primary conditions.

Wiklund (122) explained the comparative rarity of lymphomas in his report as probably reflecting the poor prognosis of lymphomas during the first decades of the study period.

However this study included patients whose first primary was diagnosed after January 1, 1953 and in two reports which included patients from earlier years Hodgkin's disease was a common primary (59, 49). A previous poor prognosis of lymphomas therefore may not account for the disparity in the frequency of this primary in different reports but comment is difficult due to the rarity of PRS overall and problems in obtaining true incidence figures. If the incidence of PRS is dose-related this would also affect the relative incidence of primaries such as Hodgkin's disease.

Reports of the site and type of the primary tumor become very important when radiotherapy is not the only treatment option available. An example is early stage breast cancer, a condition in which the trend is to treat greater numbers of relatively young women with potentially curable cancers with conservation treatment including radiotherapy (25). Turner et al (117) from the John Radcliffe Hospital in Oxford reported two cases of sarcoma complicating breast conservation radiotherapy. These authors were not aware of sarcoma having previously been reported as a complication of radiotherapy in breast conservation. However reports of this complication had previously appeared (57, 109). This complication must be considered in patients developing abnormalities within the radiation fields after breast conservation treatment. The sarcoma tends to occur after a longer period than is generally the case for local recurrence (117). In the Groote Schuur patients the only

PRS after breast conservation treatment (Case 8) appears to have developed below the breast rather than in irradiated breast tissue. The latency of less than 2 years is not in accordance with Cahan's criteria (14) and would have excluded this patient from many studies of PRS.

The most common primary in our series was carcinoma of the cervix followed by carcinoma of the breast. Three patients in our series were retinoblastoma patients. They all had bilateral disease. We are not aware of any PRS in patients treated with lymphoma at Groote Schuur since 1964.

Therefore it appears that overall tumors of the female genital tract and breast may relatively frequently precede PRS. Retinoblastoma is another common primary. Some authors report lymphoma as a relatively common primary.

4.6.2. PRESENTATION AND DIAGNOSIS OF POSTRADIATION SARCOMAS

In the Groote Schuur series sixteen patients presented with clinical features of swelling or a mass. In five pain was also a presenting symptom. Three patients presented with x-ray changes and one with a pathological fracture. In other studies swelling or a mass has also been the most common symptom (109, 122, 96, 49). Pain is a common symptom (122, 49). In Sundaresan's series of thirteen PRS involving the spine all the patients complained of pain and in four a mass was present (112).

In Huvos' series (49) of osteogenic sarcomas, lesions which were predominantly sclerotic, mostly lytic, and mixed were equally represented radiologically among bone sarcomas. Permeative osseous changes were rarely seen on x-rays. Sundaresan (112) noted that in PRS involving the spine plain radiographic findings included nonspecific lytic destruction of the spine with little reactive sclerosis. The distinction between a radiation osteitis or malignancy could not be made. Calcification was noted in one patient with a paraspinal soft tissue mass. CT scan was the most useful test and often revealed extensive soft tissue tumor as well as osseous destruction of the spine.

Mindell (75) noted that PRS should be suspected whenever a patient who has previously received radiotherapy presents with increasing pain or swelling in the irradiated area. On examination oedema, tenderness and a palpable mass may be evident. The skin in the irradiated area may show changes due to the previous irradiation and often the differential diagnosis may rest between radiation osteitis and PRS. Increasing pain, the clinical presence of a mass and a radiographic mass may suggest the presence of sarcoma.

Many of the tumors in the Groote Schuur study were advanced at presentation. Robinson et al (94) noted in a literature review that PRS are generally of advanced stage at diagnosis. These authors noted that PRS tend to be diagnosed in a more advanced stage than other sarcomas.

Possible explanations put forward are that the second tumor may be more aggressive leading to a more advanced stage at diagnosis, and that there may be a delay in the diagnosis of a PRS (94).

Wiklund (122) noted that in his series in many cases there was delay from the date of first discovery of a second primary to the date of the final histological diagnosis or start of treatment (median 0.2 years but in 8 the delay exceeded 1 year). In some cases the tumor was at first regarded as benign clinically or histologically and in some as a recurrence of the first primary. In many cases the therapy was adversely affected by an incorrect original diagnosis and this may have had an impact on treatment outcome. Souba (109) also noted that delay in diagnosis may be caused by the attending doctor. These tumors are grossly often difficult to differentiate from radiation changes. Biopsy in an irradiated field carries the risk of poor healing (109). O'Neill (79) pointed out that time is lost while the patient undergoes further radiotherapy to control a PRS misdiagnosed as a local recurrence and that biopsy may further delay initiation of treatment as radiation-induced changes may lead to an erroneous diagnosis of radiation-induced fibrosis.

Cahan (14) stated that when a patient had pain with or without swelling in an area previouly irradiated for a benign bone lesion 5 or more years previously, suspicion of malignant change should be aroused. X-rays and biopsy

should be immediately performed, the latter preferably by aspiration to avoid incision of irradiated tissues.

A high index of suspicion is necessary to pursue the finding of a new swelling or pain that develops in an irradiated field at least 5 years after radiation treatment. It has been recommended that any new pain or swelling that occurs in an irradiated field 5 years after radiation should be promptly evaluated (109). As there is a risk of second malignancies before 5 years, and in any case differentiation must be made as to whether the lesion is benign or malignant and appropriate treatment instituted, the specification as to 5 years seems unwise.

For clinically suspicious lesions repeat biopsy is necessary despite a benign pathological diagnosis. In some patients multiple recurrent excisions have been necessary to make the diagnosis (79).

4.6.3. TREATMENT OF POSTRADIATION SARCOMAS

4.6.3.1) Surgery

Several authors have stressed the importance of early diagnosis in PRS (113, 112, 79). Sundaresan (112) noted that prompt recognition and early surgery for postradiation bone sarcomas are important because these tumors grow quickly and respond poorly to conventional radiation and chemotherapy. In a report of soft tissue postradiation

fibrosarcomas of the chest wall, O'Neil noted that adequate palliation and potential cure depend on awareness of these lesions, early diagnosis, persistent repeat biopsies in suspicious cases, early aggressive radical excision without fear of the resultant defect and adequate reconstruction (79).

Surgery, when feasible, is the basis of treatment (109, 75, 58, 79). In fact in cases of fibrous proliferation following postmastectomay radiotherapy, aggressive surgical resection may have to be considered even if the microscopic appearance of the biopsied tissue does not appear malignant (34).

In a review of 344 cases of PRS in the English literature (94) Robinson et al noted that only 46% were reported to be operable. It appeared that in 28% the disease was too advanced for surgery to be used. In 27% no information regarding treatment was available. Most of the tumors were located in areas where radical surgery could not be performed. Other authors have also found that the extent of surgery may be limited by the site of the tumor and the proximity of vital structures (109, 104, 75).

In the Groote Schuur series ten (50%) of patients underwent surgery as initial treatment but in only three could it be described as radical. A further patient underwent maxillectomy after radiotherapy and chemotherapy.

It appears that surgery is employed whenever possible in the treatment of postradiation sarcomas but frequently the disease is too advanced for radical resection to be possible.

4.6.3.2) Radiotherapy

Both radiotherapy and chemotherapy have been used as adjuncts to surgery in the treatment of PRS.

In a case of prostatic PRS isolated pelvic perfusion with Cisplatin and pelvic exenteration was used (99). Outcome is not reported, presumably because it was too early for this to be relevant.

Several patients in Wiklund's report from the Finnish Cancer Registry received radiotherapy as part of the treatment of PRS although many tumors were in previously heavily irradiated tissues. In general this appears to have been postoperative radiotherapy and presumably that is the reason reponse is not mentioned. One of these patients later developed severe chronic radiation sequelae leading to death (122).

In a series of PRS involving the spine, brachytherapy was used after resection as most patients had already received radiation dosages approaching spinal cord tolerance. The three patients who survived more than 2 years had all

undergone extensive resection as well as brachytherapy. None were cured and completely disease-free. Five of six who underwent extensive resecton and brachytherapy were thought to have adequate local control but eventually distant metastases were noted (112).

The role of radiotherapy in the treatment of PRS is limited, as apart from the problem of exceeding tissue tolerance in related structures it has been noted that PRS of bone responds poorly to conventional radiation and chemotherapy (112).

In the Groote Schuur series radiotherapy was used in six patients. Data on reponse were available in four cases. One progressed in spite of palliative radiotherapy (case 3), one responded initially to treatment but was noted to have progressed at 3 months (case 9) and in one there was a response to a combination of chemotherapy and radiotherapy (case 11). In the fourth patient (case 7) there was virtually no response to two courses of neutron radiotherapy.

Thus radiotherapy is used in the treatment of PRS, in spite of previous irradiation to the tissues, but no promising results have been noted.

4.6.3.3) Chemotherapy

Several other authors have noted that results using chemotherapy are poor (49, 94, 109, 58, 5). Poor results in soft tissue sarcomas have been attributed to the fibrotic changes due to previous radiotherapy resulting in an inadequate blood supply for the chemotherapy to produce significant concentrations in the target organ (58).

Robinson (94) recommended that more aggressive and investigative chemotherapy regimens are warranted because of the poor prognosis of PRS.

Souba suggested that more modern chemotherapy regimens might be more effective. In patients with primary sarcomas, preoperative chemotherapy has been helpful in determining which patients will benefit from continued adjuvant therapy as well as allowing good disease-free survival. However chemotherapy cannot take the place of good surgery with wide resection (109).

In the Groote Schuur series nine patients with PRS received chemotherapy. One patients was treated for a presumed breast recurrence and the disease progressed (case 9). In case 11, as has been mentioned, there was a repsonse to a combination of chemotherapy and radiotherapy. In case 13 there was an initial response but subsequent progression of disease. In cases 3, 14 and 17 there was either no

response or deterioration. Cases 4 and 15 did not receive more than one cycle. In case 20 the response is unknown.

Thus, as in the case of radiotherapy, chemotherapy is used in the treament of PRS, but results have been disappointing.

4.6.4. PROGNOSIS OF POSTRADIATION SARCOMAS

4.6.4.1) Comparison of Prognosis of Postradiation and Spontaneously-occurring Sarcomas

It is controversial whether the prognosis of postradiation sarcomas is poorer than that of spontaneously-appearing lesions.

Some authors, including Robinson (94) and Laskin (59) (who analysed fifty-three cases of soft tissue PRS and reported a 32% 2-year survival), state that the prognosis of PRS is worse than that of primary sarcomas. Robinson noted that this applied to primary sarcomas of similar stage to the PRS. (94, 59, 75)

Meredith (72) noted that survival in irradiation-induced MMMT is poorer than that reported for the same tumors not necessarily occurring post radiation. However in Meredith's series the patients with radiation-induced tumors tended to present with late stage disease and received less aggressive therapy.

Others have not found there to be a worse prognosis for a sarcoma which develops in a radiation field.

In a University of Minnesota study comparing uterine sarcomas developing in previously irradiated women with those among unirradiated controls, a significant difference in survival was not shown (119). However the patients who had been previously irradiated presented at a younger age with symptoms of more advanced disease.

Arlen (5) reported a relatively good disease-free survival rate in that nine out of twenty-eight (32%) of the patients in his series of PRS of bone were alive and disease-free over 5 years. He assessed the results as being "surprisingly good considering the poor overall survival rate for osteogenic sarcoma". All the patients in whom the PRS was apparently cured had developed these tumors in the long bones. Among four patients with sarcomas of the head and neck region only one survived. Arlen reported a more favourable prognosis for postradiation osteosarcomas than for the spontaneously appearing lesions (5).

Wiklund, in his series of PRS from the Finnish Cancer Registry (122), reported overall 2- and 5-year survival rates of 45 and 29%. Wiklund noted that in his study the prognosis was "fairly good" in the radically treated group and also that four patients achieved long-term remission

and perhaps cure after salvage therapy for local recurrence.

In 1992 Robinson reported a population-based study comparing the clinical characteristics of second primary and single primary sarcomas and noted there was no difference in survival time between the PRS group and the non-PRS group (single primary and second primary in non-radiation-exposed area) overall nor for any stage (93).

Thus there is not agreement as to whether postradiation sarcomas have a poorer outlook than sarcomas arising in unirradiated tissue.

4.6.4.2) Assessment of potential prognostic factors

Various factors have been analysed to determine whether they affect the prognosis of PRS. In two studies there were reported to be no significant survival differences between males and females (109, 49).

It is controversial whether the outcome is affected by the site of the saroma (68, 121). It has been reported that central lesions have a worse prognosis than those of the extremities (121).

Robinson found that for PRS occurring after orthovoltage treatment the mean survival was 19.98 months, after

external beam treatment combined with brachytherapy it was 17.34 months, after supervoltage 10.13 months and after brachytherapy 11.28 months (94). According to his review patients with fibrosarcoma, angiosarcoma and carcinosarcoma had a better survival than those with osteosarcoma or chondrosarcoma. Patients with lymphangiosarcoma had a better survival than those in the other histologic groups (94).

Overall there is inadequate data to assess the impact of these factors on the prognosis of PRS.

4.6.4.3) Poor Prognosis of Postradiation Sarcomas and Reasons for Poor Prognosis

The poor prognosis of PRS has been confirmed by many reports (25, 94, 104, 114,59). Meredith (72) reported that four out of five patients with postradiation MMMT in her study died within 7 months.

In Robinson's extensive literature review (94) the median survival of the 266 PRS patients for whom survival information was available was 12 months, with a 2-year survival of 22% and a 5-year survival of 11%. 73.5% of patients died of disease and 12.8% were alive at the time of reporting. In 9.6% follow-up data were not available. 4.1% were alive with disease at the time of reporting. Death was almost always due to recurrent or metastatic

sarcoma. An indication of the poor survival generally reported can be obtained from Table 3.

The dismal outlook for this condition has been attributed to a variety of factors, some of which have already been discussed. Factors may include delay in presentation, difficulty in diagnosis when a soft tissue sarcoma arises in an indurated irradiated field (25) and unfavourable site (trunk and limb girdle) (25). The anatomical site of the primary, such as in retinoblastoma or pelvic tumors, may make adequate radical surgery for the PRS impossible. According to Robinson's review however it seems that the prognosis of sarcomas in retinoblastoma patients is also poor for sarcomas outside the radiation field. Therefore the site cannot be the sole reason for the poor prognosis (94). Another adverse factor may be the preclusion of further radiotherapy in patients already treated to tissue tolerance (25).

Delay in diagnosis because symptoms are considered related to the original disease or radiation necrosis may contribute to a poorer outlook for PRS as opposed to primary sarcomas (75). Tumors in areas with prior chronic irradiation changes may behave in a more malignant way due to local factors and therefore progress more rapidly, similarly to the manner in which chest wall recurrences of breast cancer in irradiated areas progress rapidly and are more resistant to therapy (94). Lymphatic obstruction,

vascular compromise and fibrosis from radiation may shield potentially malignant cells from immune surveillance (33).

The immunosuppressive effect of the initial tumor or chemotherapy (85, 59) as well as the aggressive nature of the tumor, grade (94, 109) and stage may all contribute to the poor prognosis. Where data were available in Robinson's review (94) (which was not often) many tumors were noted to be high grade. In Souba's study of PRS of the chest wall all the sarcomas were of high grade (109). In 39% of cases in Robinson's review stage was mentioned and most of these were diagnosed at an advanced stage.

Robinson (94) states that all PRS, regardless of the histologic appearance, should be considered as poor prognosis. Because of the poor prognosis and malignant behaviour of these tumors a more aggressive approach to their treatment is warranted. More radical surgery should be done where possible, together with innovative radiotherapy and systemic therapy. Currently a radical surgical approach offers the best means of palliation and the only chance for cure (94). The planned combined approach advocated for secondary sarcomas in the head and neck region (106) should probably be used when it is feasible for all postradiation sarcomas.

4.7. CONCLUSIONS AND RECOMMENDATIONS

4.7.1. SUMMARY

Overall it appears that the incidence of PRS is certainly less than 1% (68, 94, 122), except in certain groups where a genetic predisposition to sarcoma development also exists (28). The latency period which must have passed between radiotherapy and presentation with the tumor for it to be classifiable as a postradiation sarcoma is controversial, but in general a shorter latency period than the 5 years initially proposed by Cahan has been accepted (14, 5, 94). The median latency in our study was 9 years.

It is impossible to determine in an individual case of sarcoma arising in an irradiated field whether or not the irradiation was completely or even partly responsible for the development of the tumor (100). A very wide variety of sarcomas have been reported to arise in radiation fields as described in section 4.5.1. Histological features cannot be used to differentiate between a primary sarcoma and one occurring due to irradiation (50, 35, 36, 59). Factors such as the previous use of chemotherapy (116, 28) and genetic factors (28, 110) may also contribute to the development of sarcomas as second malignancies. The dose-relationship in the development of PRS is not clear. It is possible that the tumor is more likely to arise at relatively high therapeutic doses but that the incidence falls when cell kill exceeds the transforming effect of the

irradiation (38). The median dose at which tumors were estimated to have developed in our study was 49Gy.

The treatment of PRS includes surgery if this is feasible (109, 75, 58, 79). The response to radiotherapy and chemotherapy has generally been poor but this does not preclude their use in the treatment of the condition (122, 109). The prognosis of PRS is poor (94) but there is not agreement as to whether it is poorer than for spontaneous sarcomas (72, 93, 94, 59).

4.7.2. RECOMMENDATIONS

4.7.2.1) Awareness and Record-keeping

Heightened awareness of the condition is essential so that unnecessary radiation is avoided and an early diagnosis is made when a sarcoma does arise in a previously irradiated field. Careful records must be kept so that true incidence figures can be assessed. Record-keeping systems should allow the numerator (number of cases) and the denominator (in this case possibly 5-year-survivors of radiotherapy) to be determined.

In view of the rarity of the condition a multicentre study should be performed. In the absence of this, literature reviews such as that by Robinson et al (94) form a very useful part of our database on this condition.

The reporting of radiotherapy treatment regimens in patents in whom PRS has arisen is also important if further clarity about the cause of this condition is to be obtained. The risk of tumor induction must be included in the evaluation of new therapeutic modalities such as intraoperative radiotherapy (35).

For such a review as Robinson's (94) to be feasible, each report of a series must include details of previous treatment. Further understanding of this condition should contribute to our understanding of carcinogenesis (51, 70).

4.7.2.2) Primary Malignancies: Treatment Decisions

An awareness of the likelihood of the condition arising in different circumstances is important if balanced decisions regarding the use of different treatment modalities are to be made.

Every effort should be made to avoid the occurrence of PRS by avoiding unnecessary radiation, such as radiotherapy for benign conditions when it is not strictly necessary (75, 14, 112), particularly if surgery without severe morbibity is an option (87). This warning also applies to the use of postoperative radiotherapy for low grade endometrial stromal sarcoma. In this condition an option is to use progesterone therapy (17). As PRS is generally a rare

complication of radiotherapy it should not be considered a contraindication to the use of radiotherapy for treating malignant tumors (15). Coleman (18) has stated that all possible efforts should be made to avoid second tumors if cures will *not* be compromised.

In a literature review that compared mortality risks of chemotherapy, general surgery and anesthesia, Mark et al (68) noted that the risk of PRS and second cancers after radiotherapy in general did not appear worse than risks of other treatments. Thus they felt that, given the large number of patients cured or palliated by radiotherapy, this potential complication should not be a major factor influencing treatment decisions in cancer patients.

This still leaves unanswered the question of the use of radiotherapy for conditions such as early breast cancer when other modalities of therapy are available. Davidson (25) has noted that induced malignancy may be considered an acceptable complication when radiotherapy is the only, or most appropriate, treatment for a patient with a life-threatening cancer; and that an induced tumor would be unlikely in a radiotherapy failure. However where the choice between radiotherapy and other treatments is more finely balanced, such as in early breast carcinoma, the morbidity and mortality of radiation-induced malignancies must be borne in mind (25). Choy (16) has suggested that it is unlikely that radiation-induced secondary tumors will

emerge as a significant complication of the breast-conserving treatment of breast cancer.

Further evidence in favour of radiotherapy in early breast cancer is 1) the possibility of sarcoma development complicating mastectomy (29) and 2) the extreme rarity of reports of PRS after breast conservation radiotherapy.

The use of radiotherapy is not as problematic in paediatric cancers, where its application may be essential to improve the cure rate, as in early breast cancer. However as more children survive cancer potential complications of treatment such as second tumor development do become more important in initial treatment decisions (44).

With improvement in methods of delivering radiation and protecting tissues as well as improved case selection it has been hoped that the incidence of PRS will decrease (75).

A further question is the problem of explaining this possible complication to a patient without arousing unnecessary anxiety. It has been suggested in relation to the treatment of uterine malignancies that only the absolute risk should be discussed with the patient, making her aware of the problem but avoiding unnecessary fears (96).

4.7.2.3) The Importance of Follow-up after Radiotherapy

It has been recommended that if patients are irradiated for benign uterine disorders, they should be indefinitely followed up and educated as to the signs and symptoms of uterine cancer (72). Permanent follow-up has also been recommended after radiotherapy for benign bone lesions (104). This recommendation should be applied to all patients who have received radical radiotherapy (109, 99).

4.7.2.4) The Development of Postradiation Sarcoma in relation to Dose

It should be clarified as urgently as possible whether or not there is a dose-relationship between radiotherapy and sarcoma development. The relative tissue dose and bone absorption with different modalities should be considered when deciding upon treatment. It has been suggested in the case of uterine malignancy that if only selected patients can receive Co-60 radiotherapy rather than orthovoltage therapy, young women with longer life expectancy, more sensitive to postirradiation effects, and patients with greater antero-postero diameter, should be selected for the higher energy treatment (96). High energy radiation has been recommended if radiotherapy is to be used in the case of giant cell tumor of bone (76). The relative absorption in bone from, for example, I-125, should be borne in mind when this isotope is used in the treatment of

retinoblastoma patients who appear to be particulary susceptible to postradiation sarcomas.

4.7.2.5) Treatment Approach to Postradiation Sarcomas

It has been seen in the previous chapter that the poor prognosis of PRS should lead to a more aggressive approach rather than a less aggressive one (106). The dismal outlook for the condition overall does not always preclude cure and careful investigation and staging should be performed, followed by an aggressive radical planned combined modality treatment approach where feasible (106).

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ADDENDUM 1

Figures 1-20

KEY TO FIGS 1-20

 Tumor

◊ Maximum dose point

 Field centre

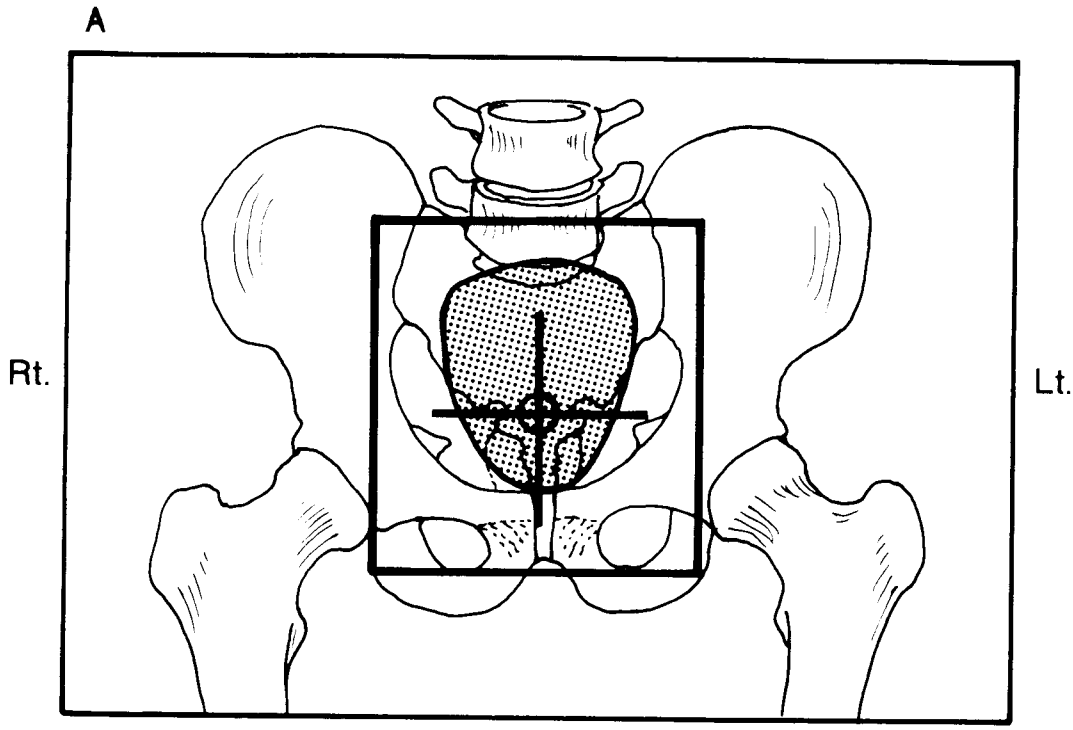
* ✕ Centre of field entrance

* ↓ Centre of field entrance

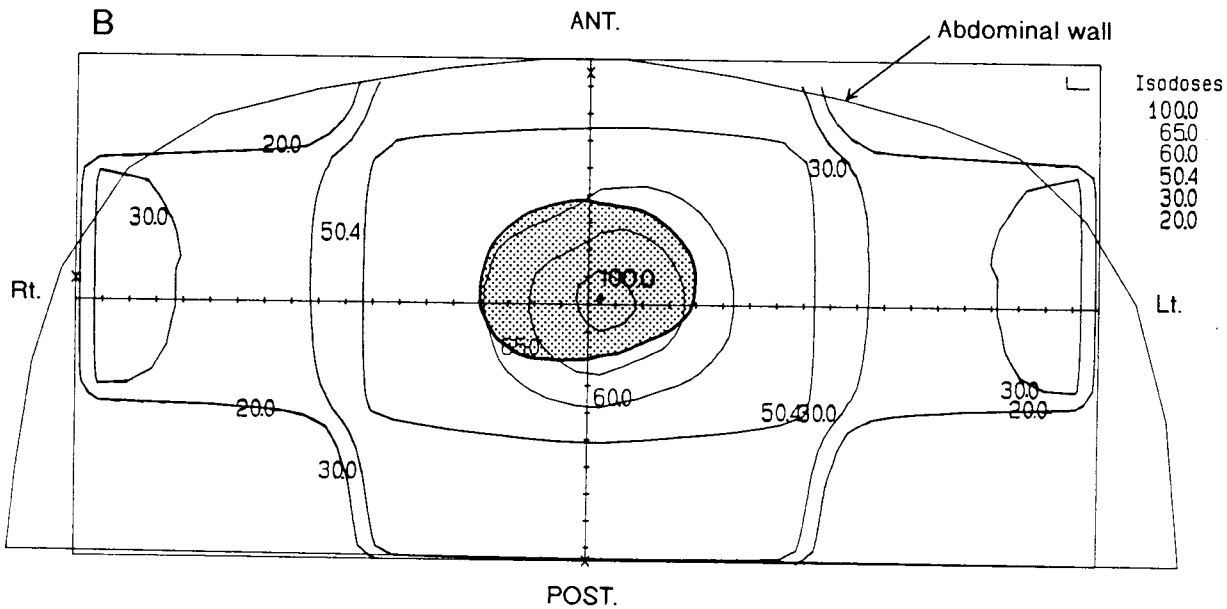
* ↑ Centre of field exit

* not included for all radiation fields

FIGURE 1

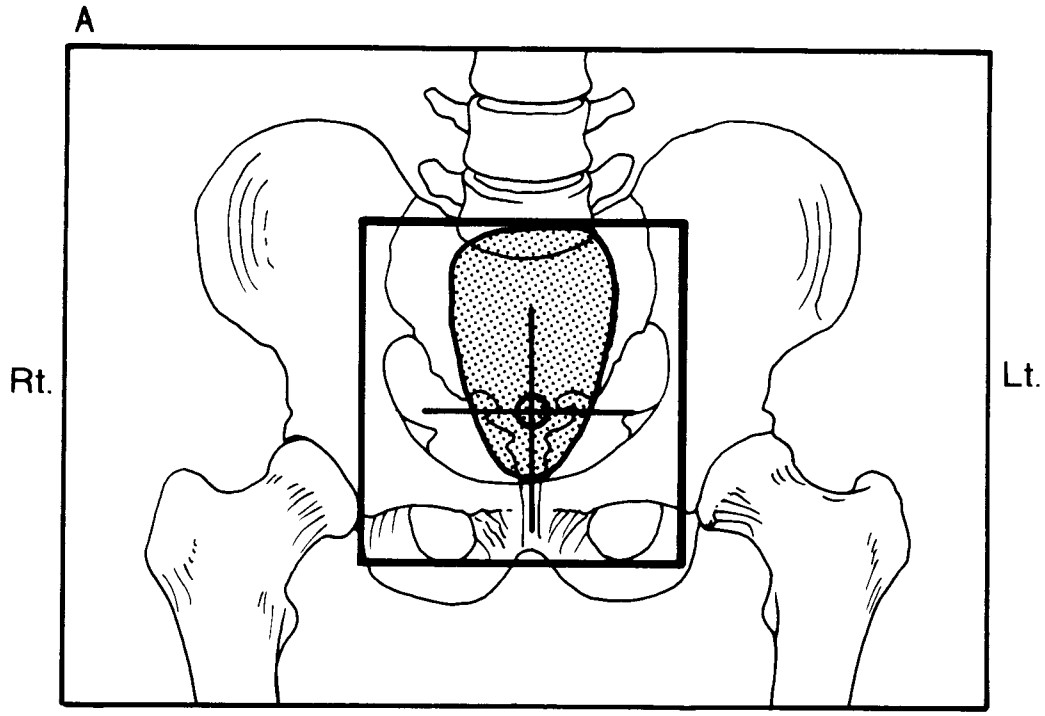


PRIMARY TUMOR: Ca cervix
RADIOTHERAPY: 4 planned fields and radium insertion
Secondary tumor in anterior field.

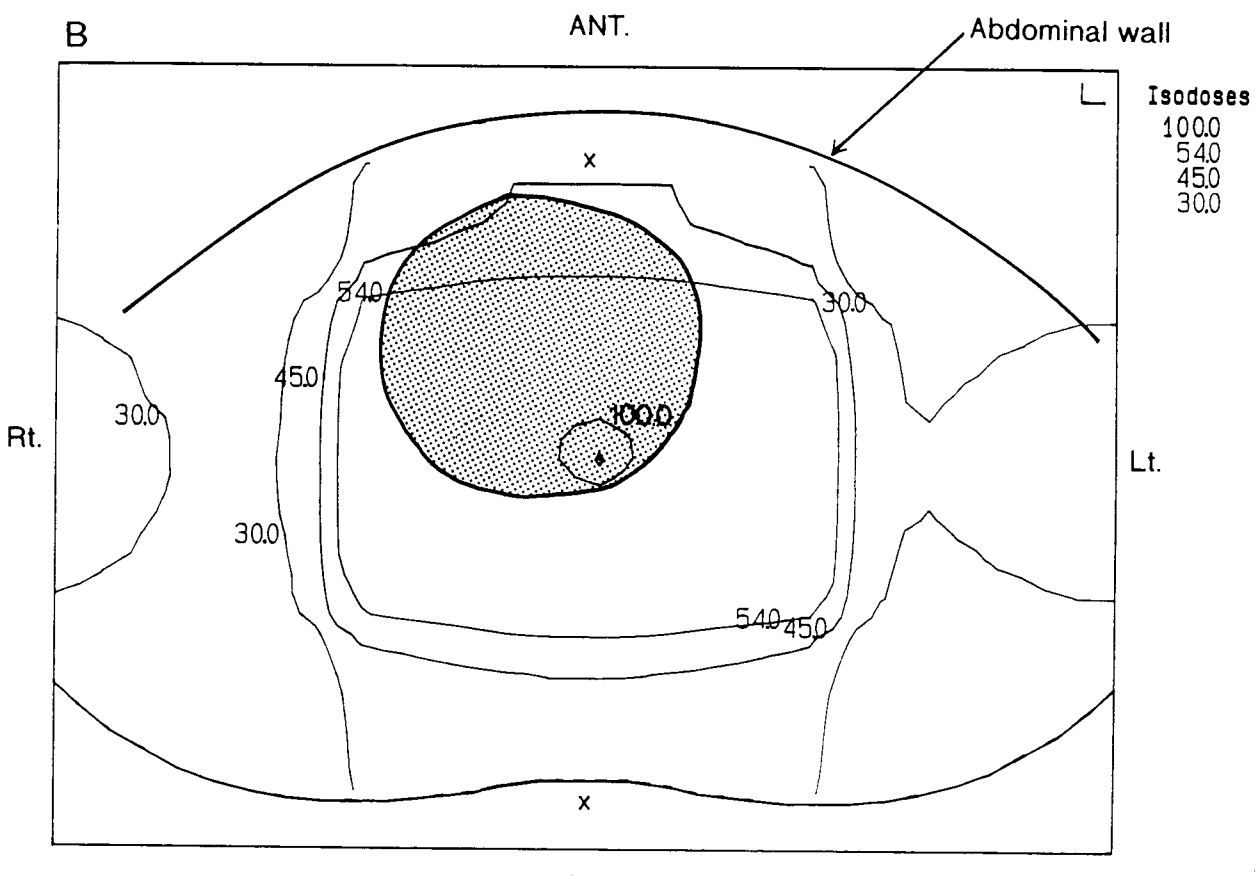


Total Gray Distribution 1.5 cm inferior to central axis. Secondary tumor at this level at presentation (representative of main mass of tumor)

FIGURE 2



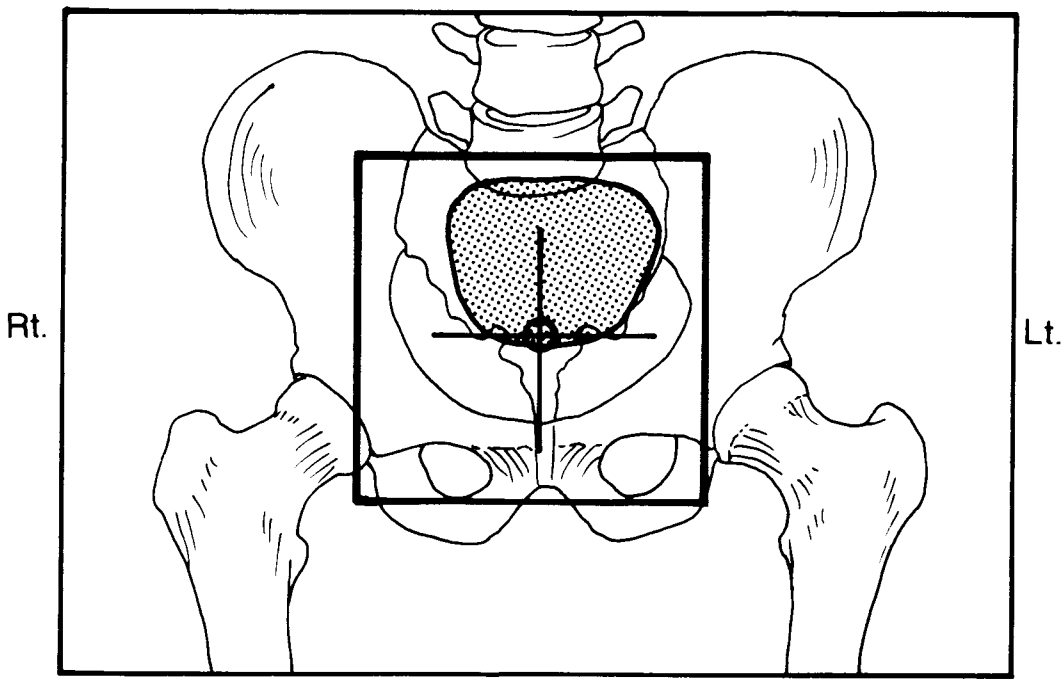
PRIMARY TUMOR: Ca cervix
RADIOTHERAPY: 4 planned fields and radium insertion.
Secondary tumor in anterior field.



Total Gray Distribution central axis. Secondary tumor at this level at presentation.

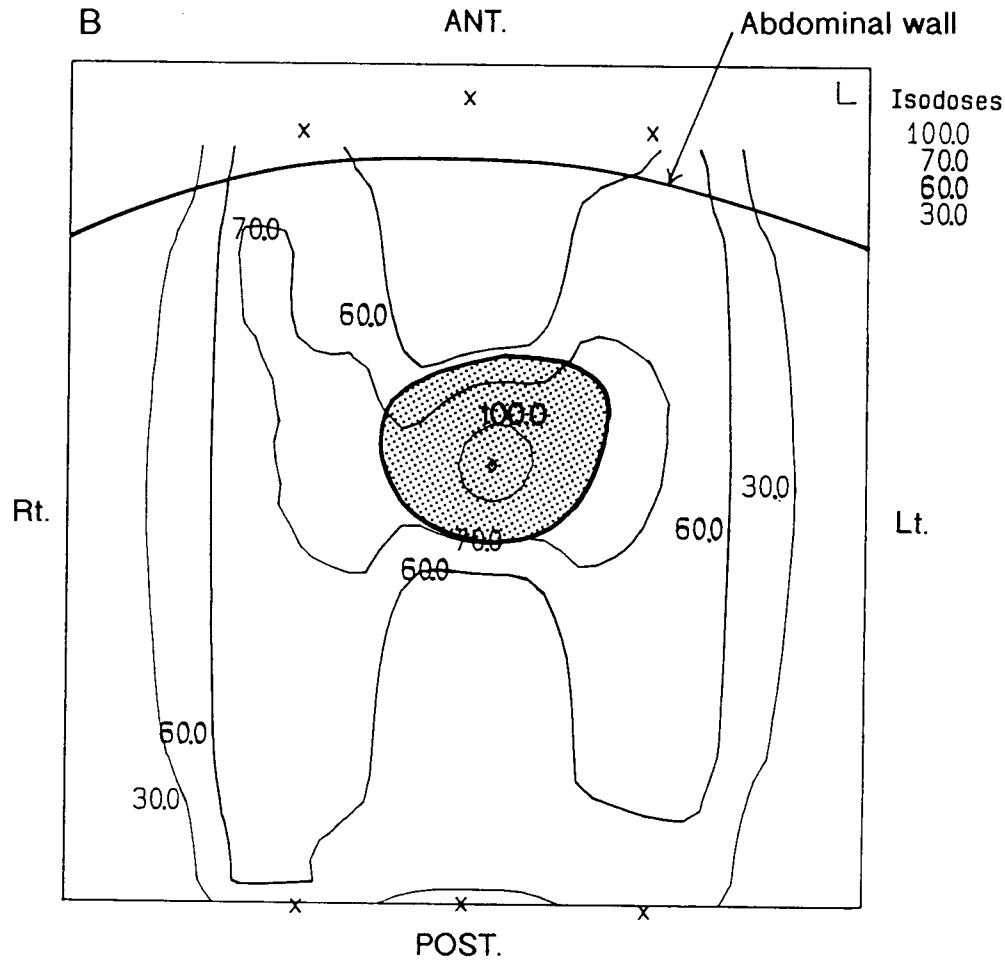
FIGURE 3

A



PRIMARY TUMOR: Ca cervix
RADIOTHERAPY: 8 planned fields and 2 radium insertions.
Secondary tumor in anterior field.

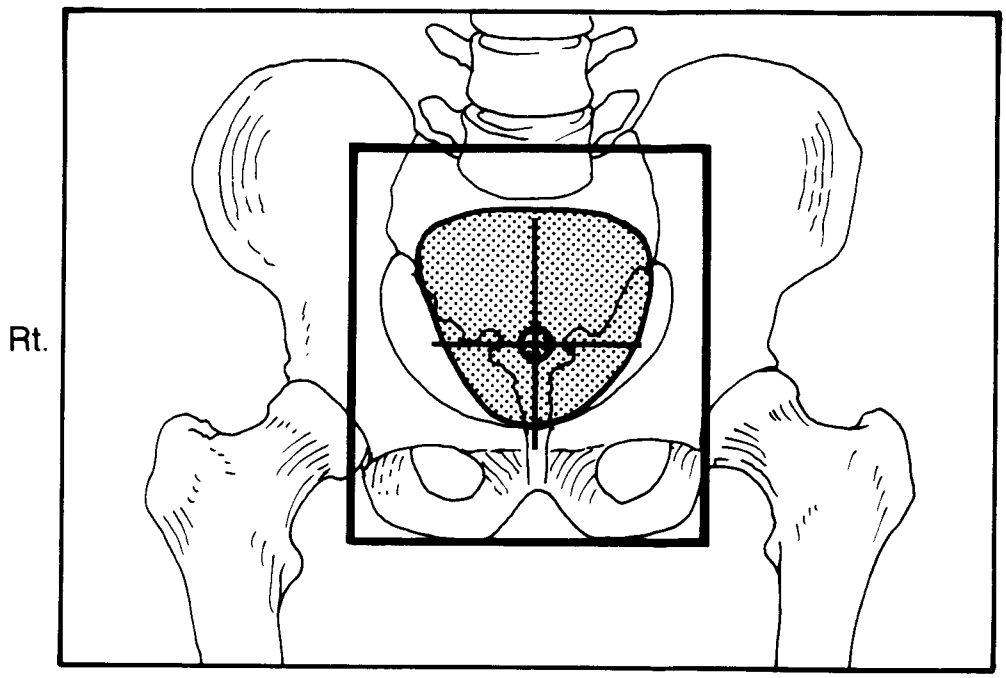
B



Total Gray Distribution central axis. Secondary tumor 4 cm above the central axis at presentation (approx. mid-secondary tumor) superimposed.

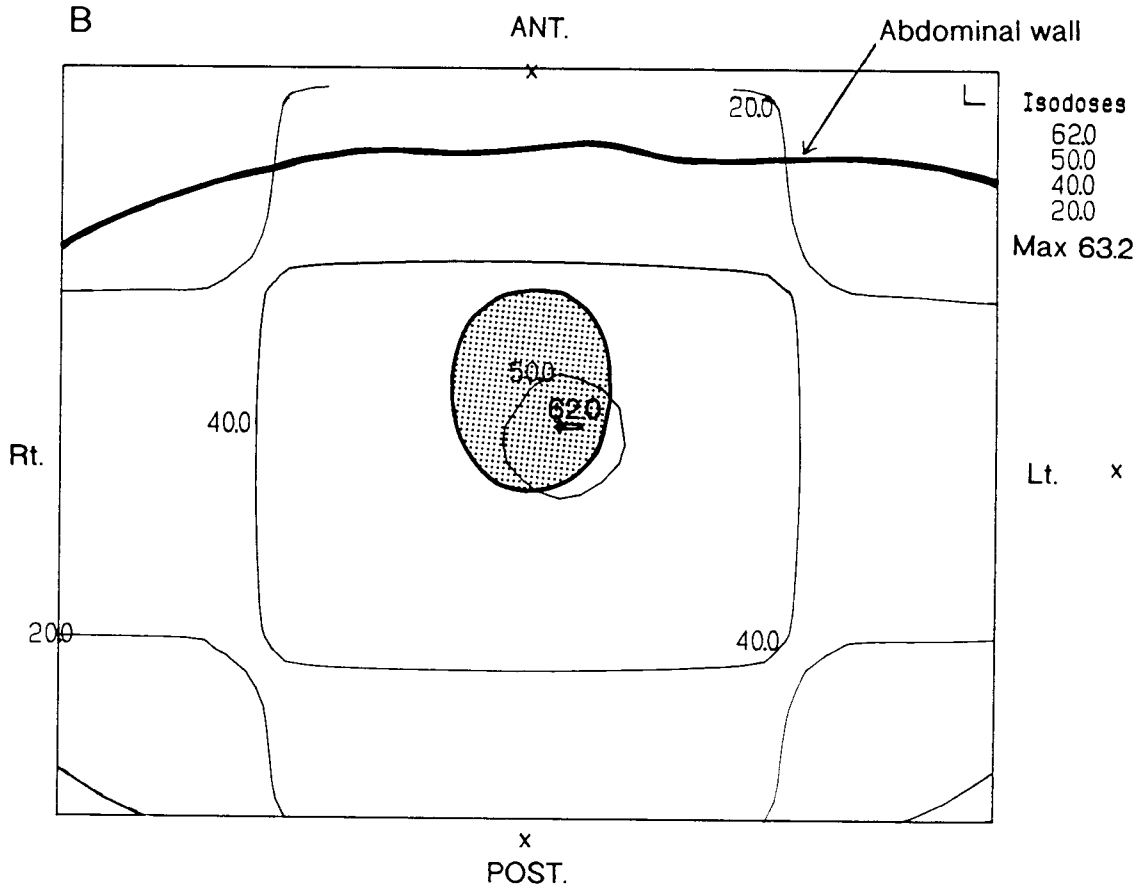
FIGURE 5

A



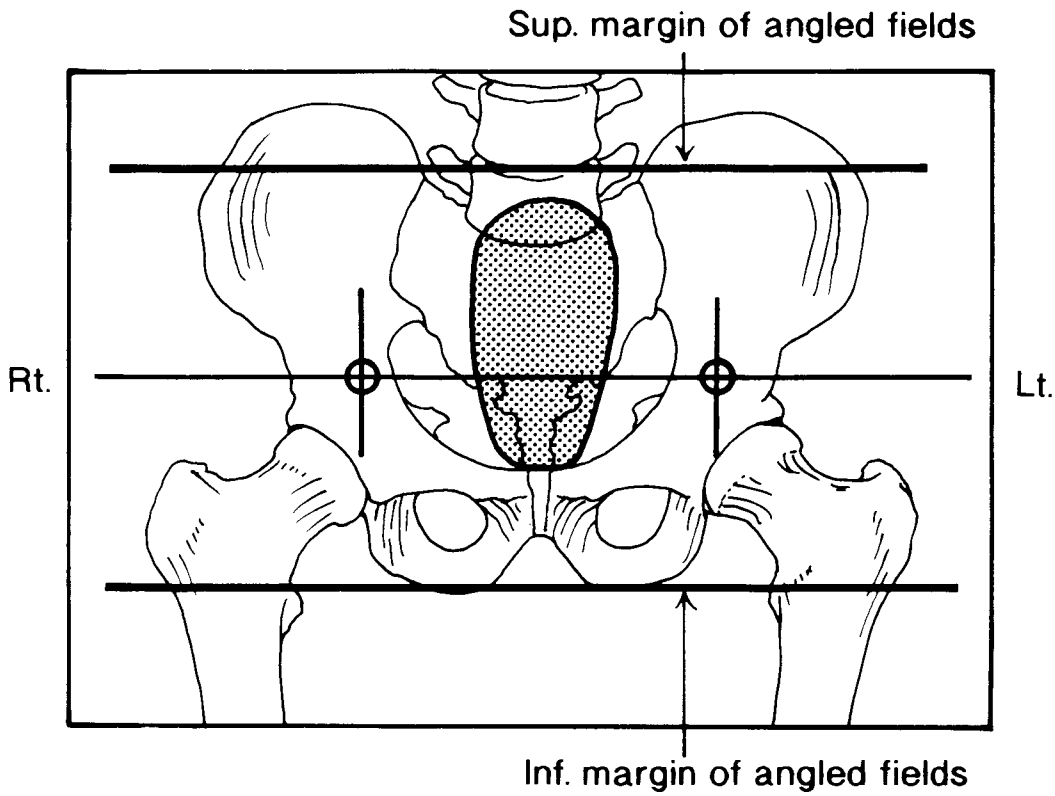
PRIMARY TUMOR: Ca cervix
RADIOTHERAPY: 4 planned fields and radium insertion. Secondary tumor in relation to anterior field.

B



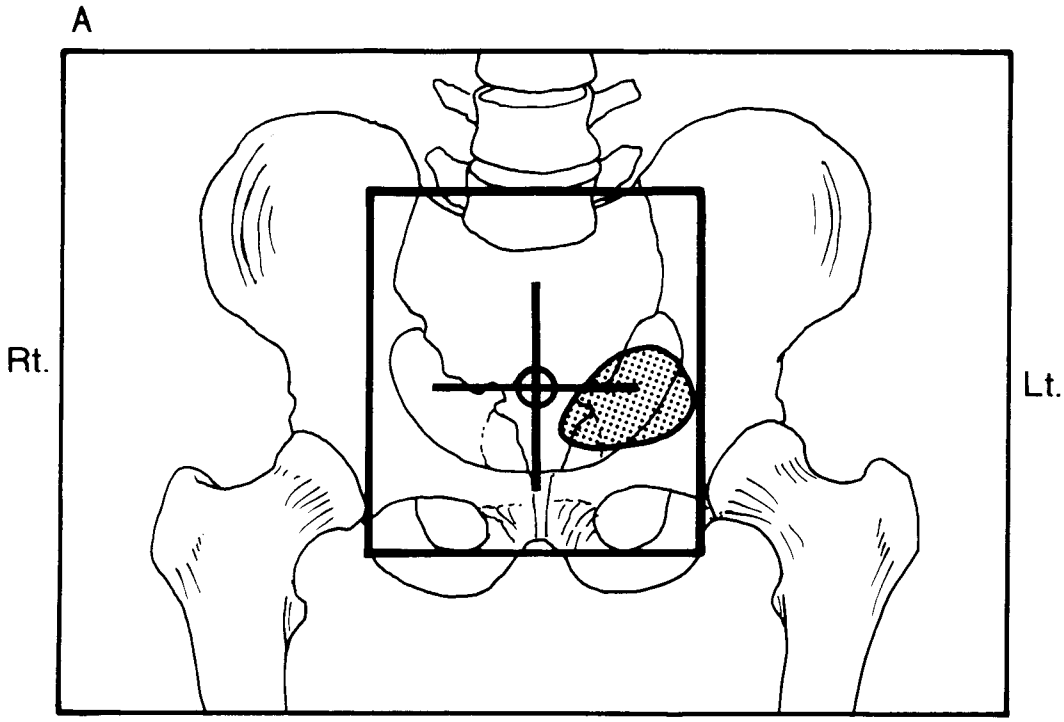
Total Gray Distribution central axis. Secondary tumor at this level at time of presentation.

FIGURE 4

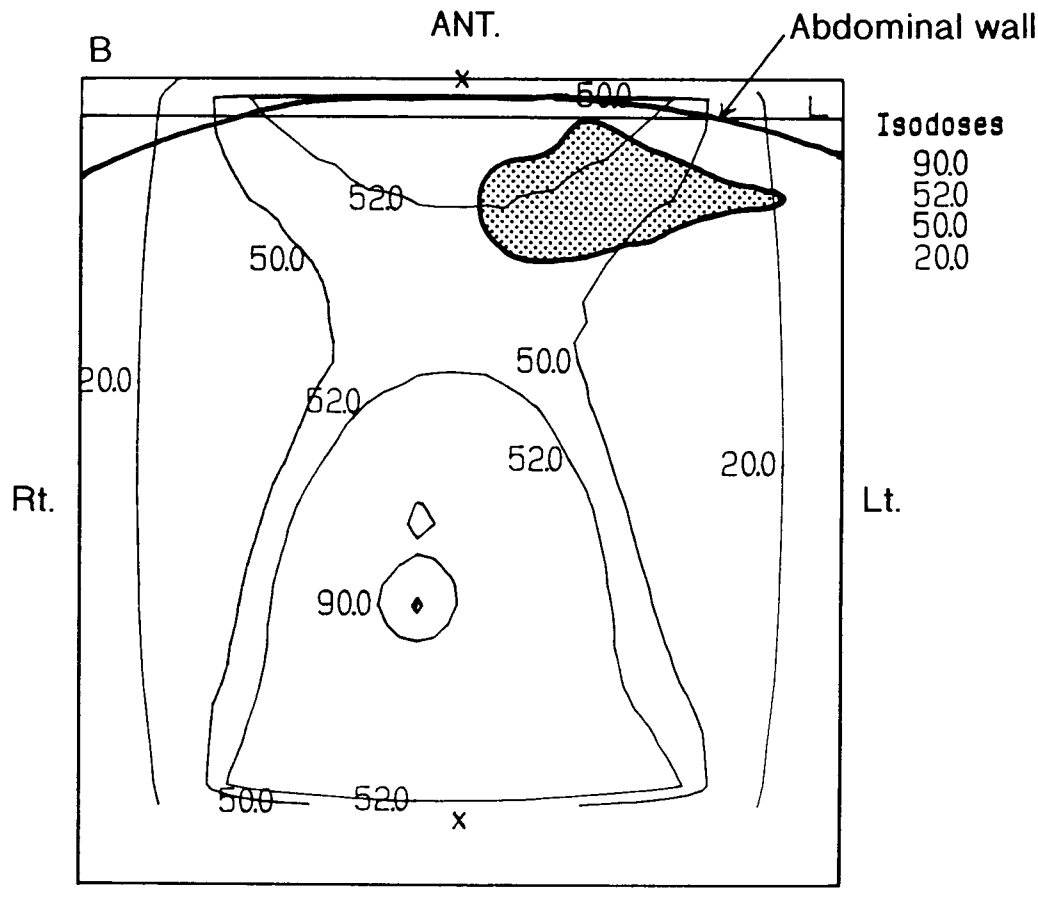


PRIMARY TUMOR: Ca cervix
RADIOTHERAPY: 2 radium insertions and 4 planned fields. Secondary tumor in relation to anterior fields.

FIGURE 6

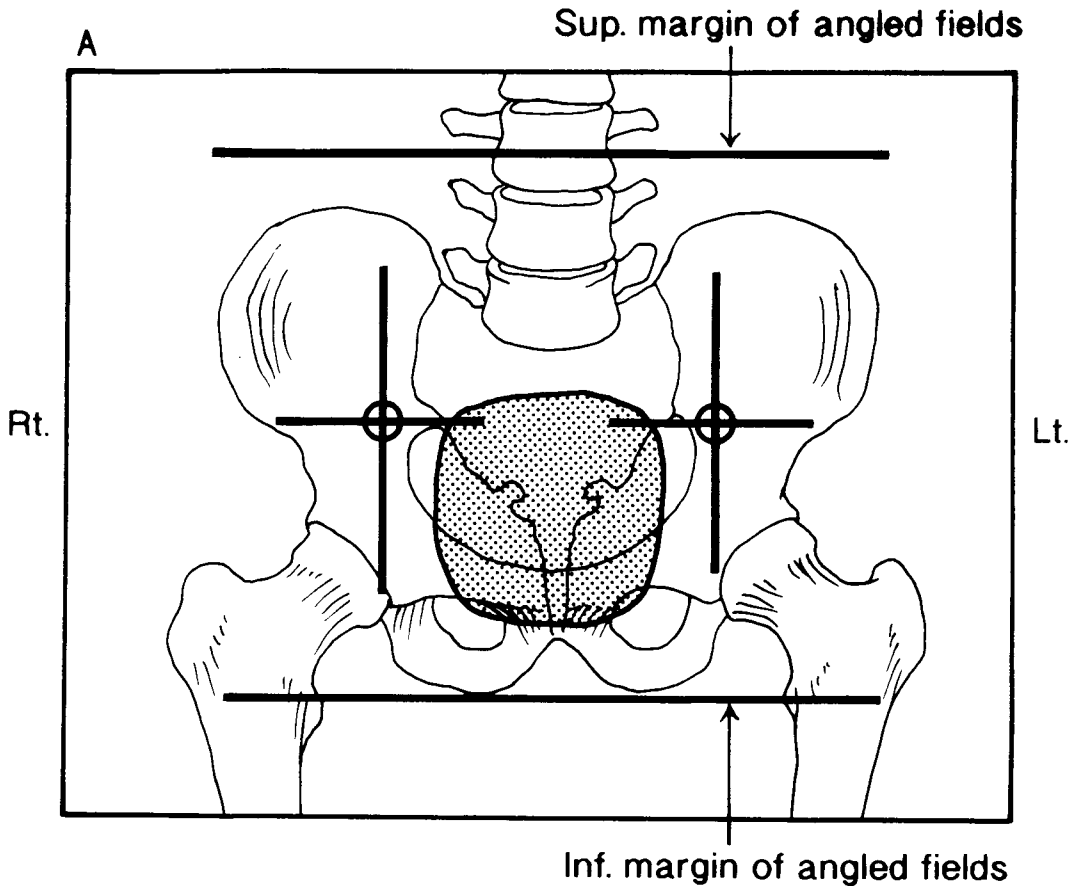


PRIMARY TUMOR: Ca cervix
RADIOTHERAPY: Anterior and posterior fields and 2 radium insertions. Secondary tumor in anterior field.

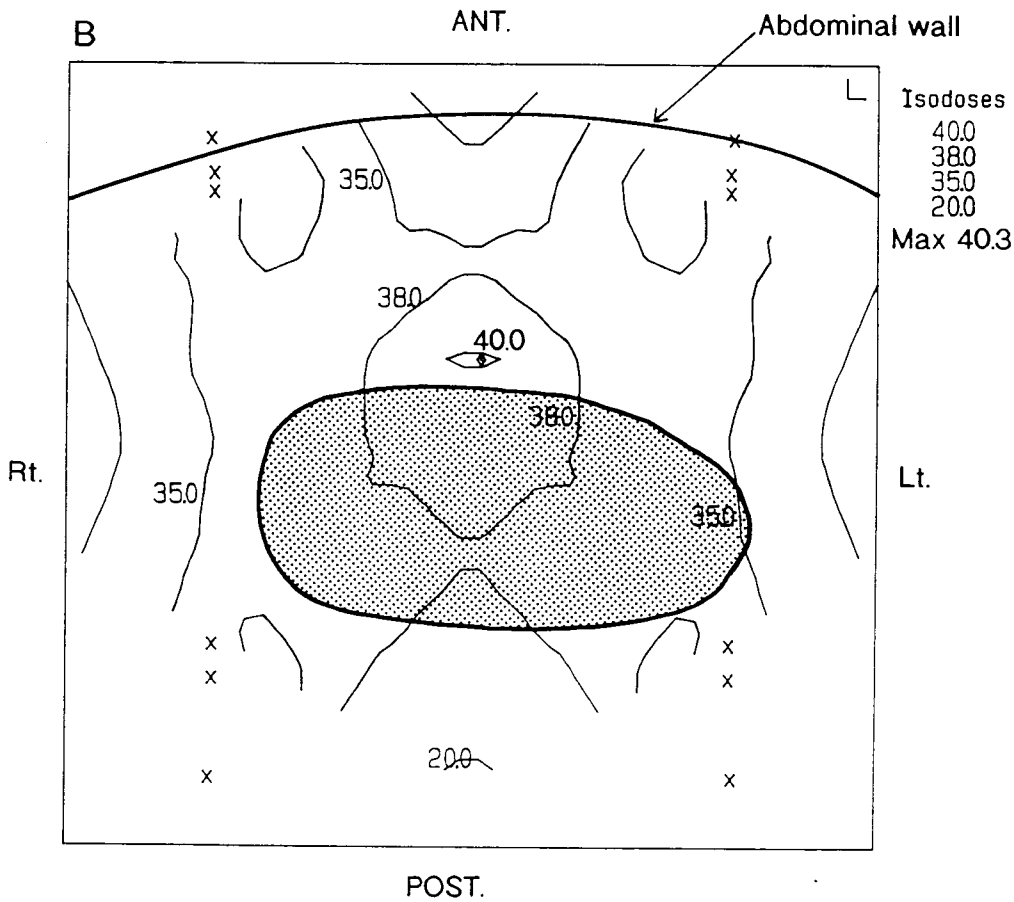


Total Gray Distribution 1 cm inferior to central axis. Level through secondary tumor.

FIGURE 7

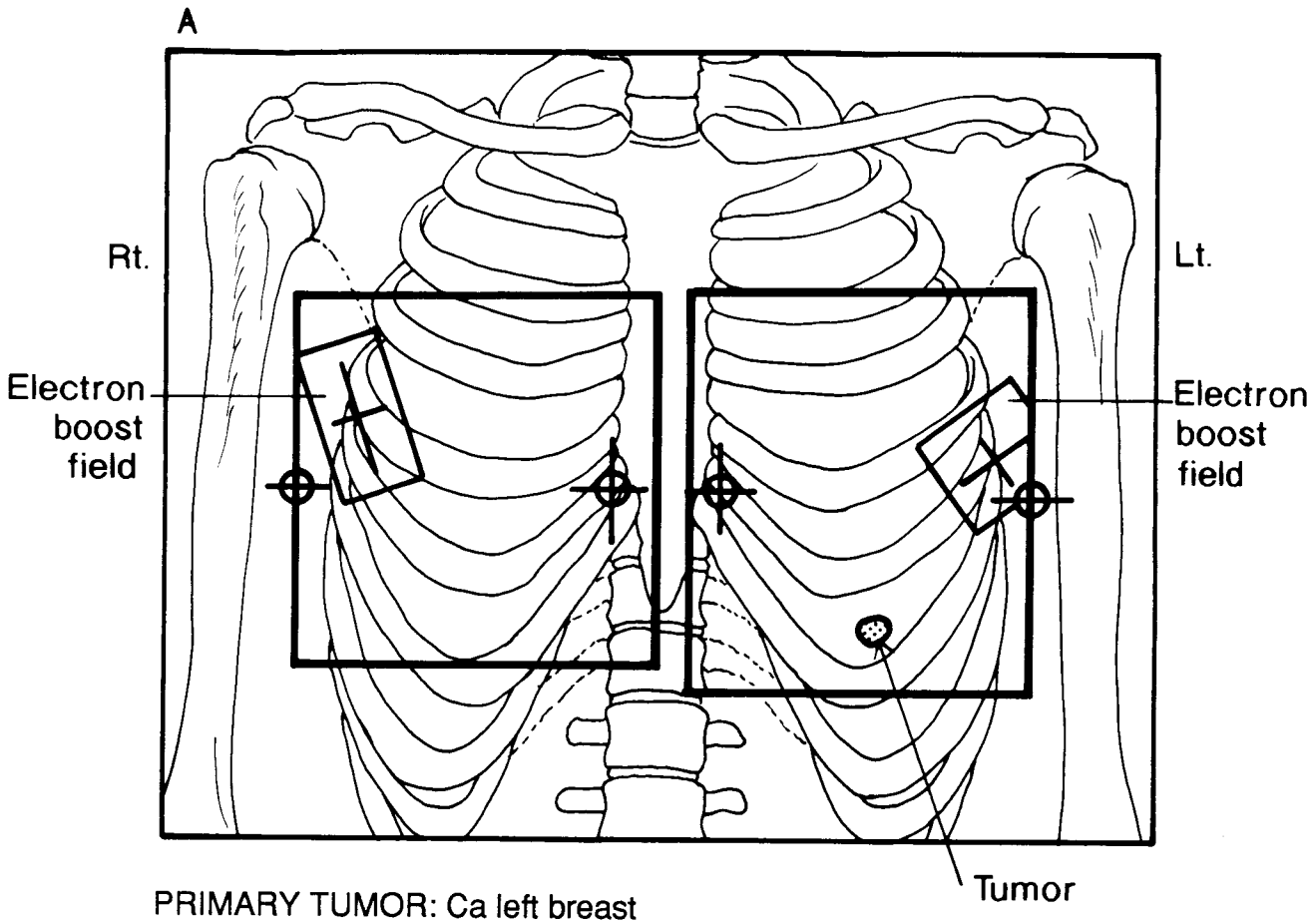


PRIMARY TUMOR: Low grade stromal sarcoma uterus
RADIOTHERAPY: 8 planned fields. Secondary tumor in anterior fields.

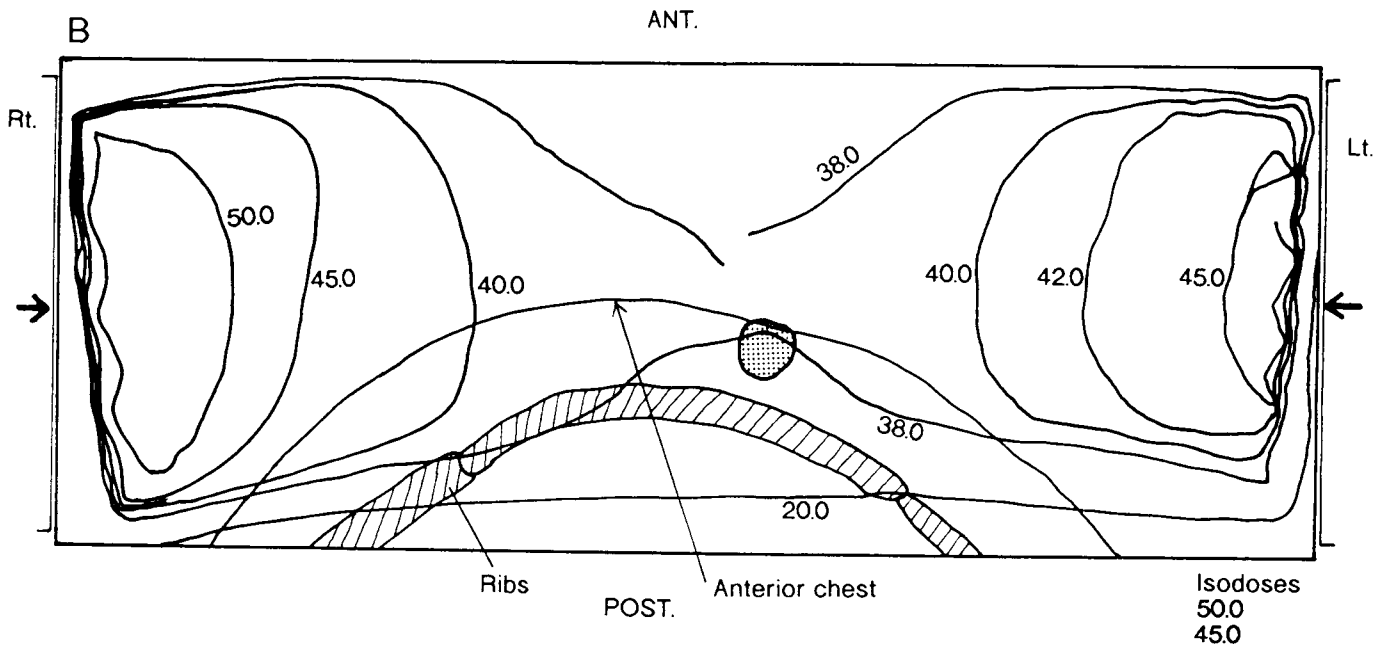


Total Gray Distribution 4 cm inferior to central axis. Level through mid-secondary tumor.

FIGURE 8

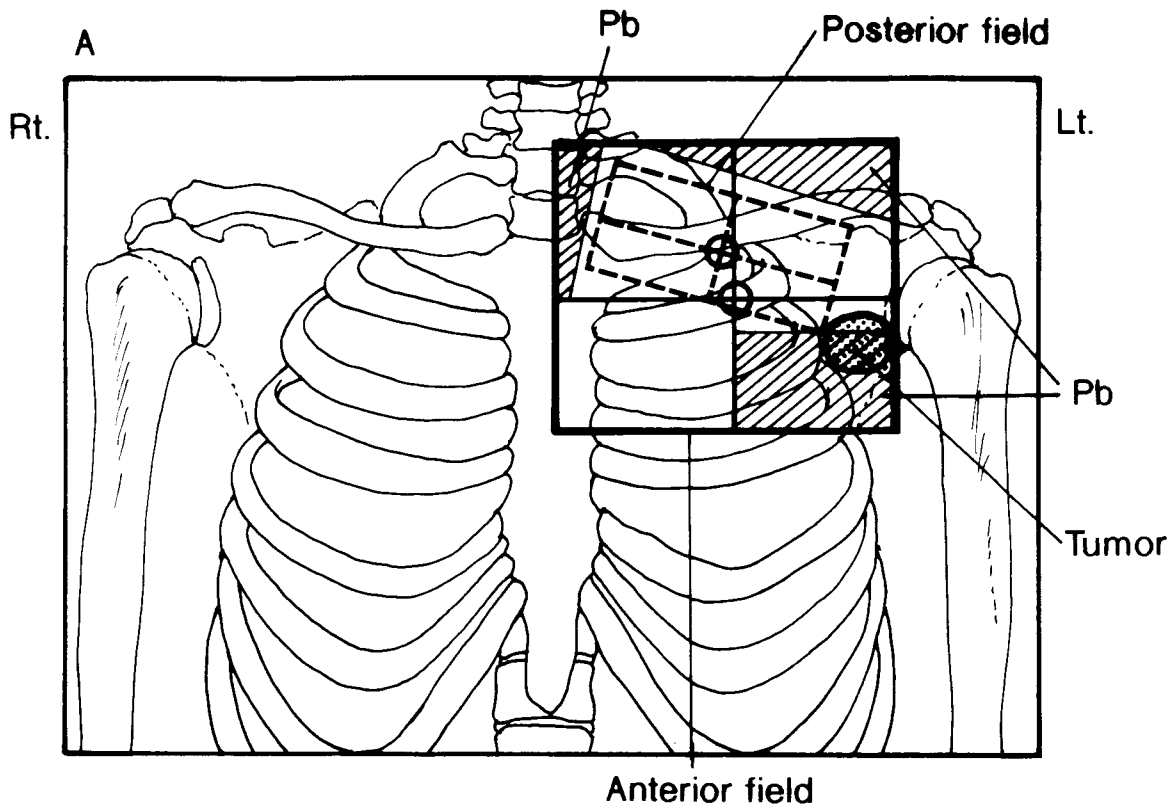


PRIMARY TUMOR: Ca left breast
RADIOTHERAPY: 2 tangential fields and electron boost left (previous treatment right breast) Secondary tumor in relation to fields.

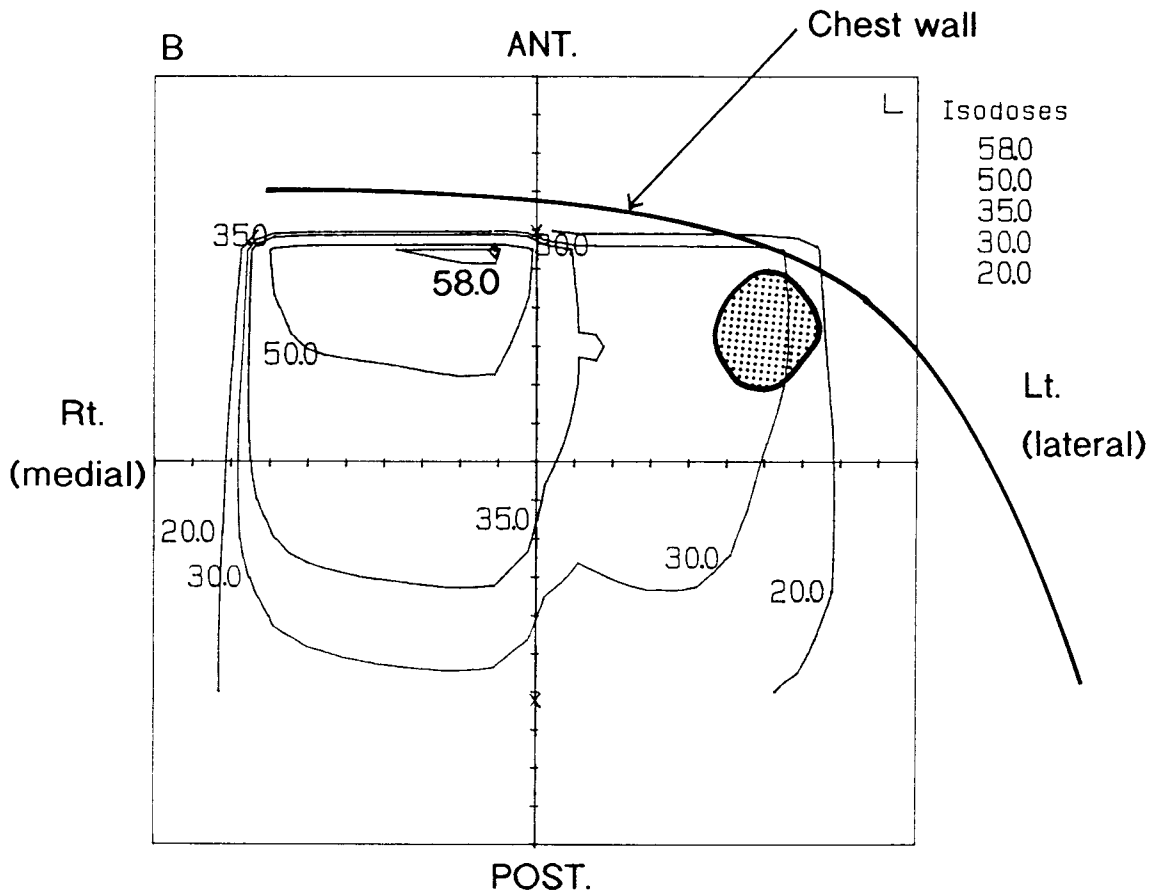


Total Gray Distribution 6.5 cm inferior to central axis. Level through secondary tumor (scatter from fields to right breast included)

FIGURE 9

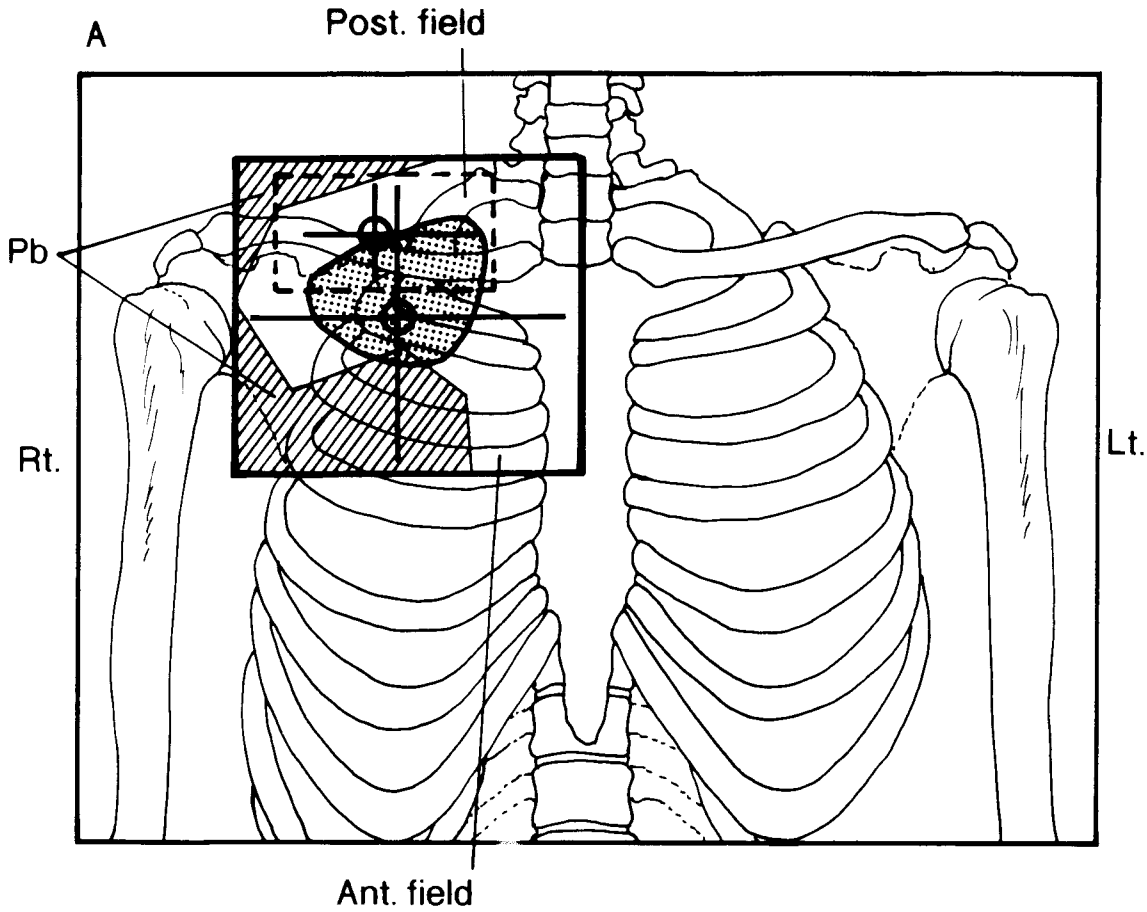


PRIMARY TUMOR: Ca left breast
RADIOTHERAPY: Anterior and posterior planned fields. Secondary tumor in relation to fields.

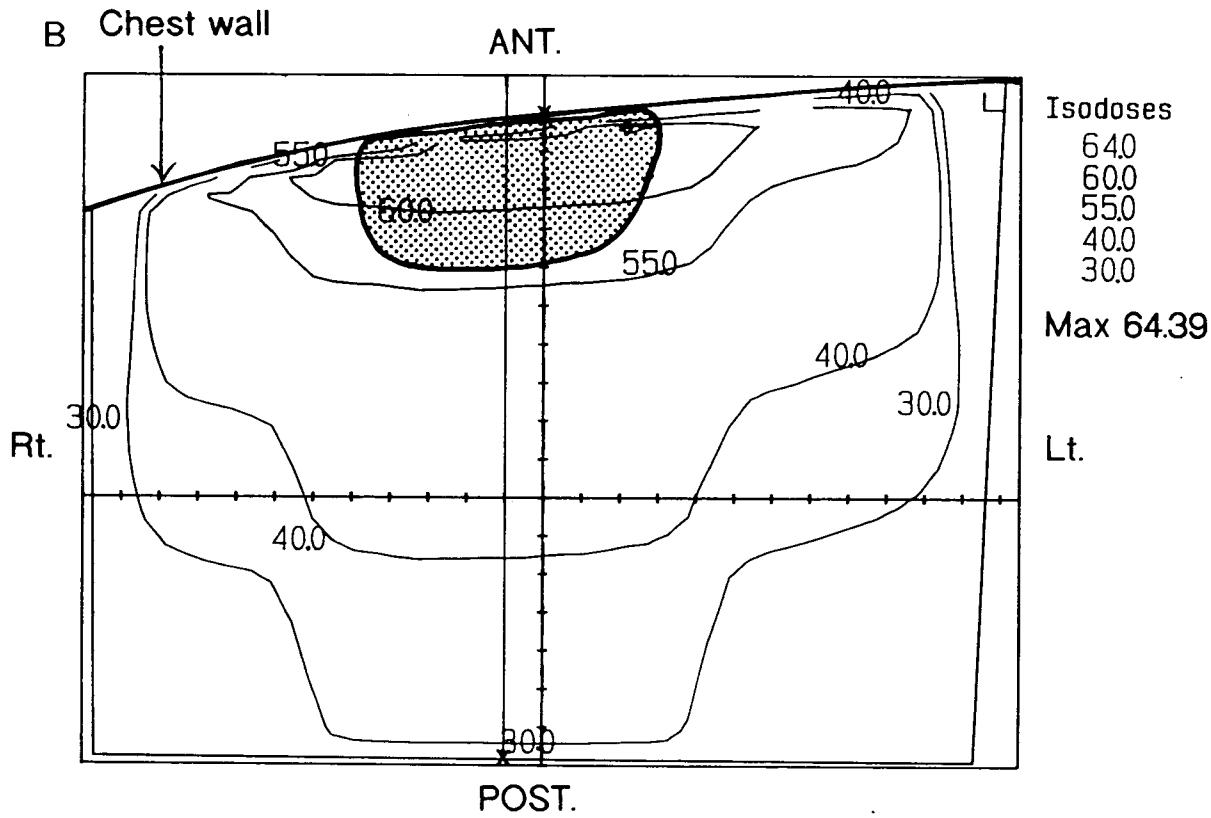


Total Gray Distribution 2 cm inferior to central axis (edge of Pb.)
Level through secondary tumor.

FIGURE 10

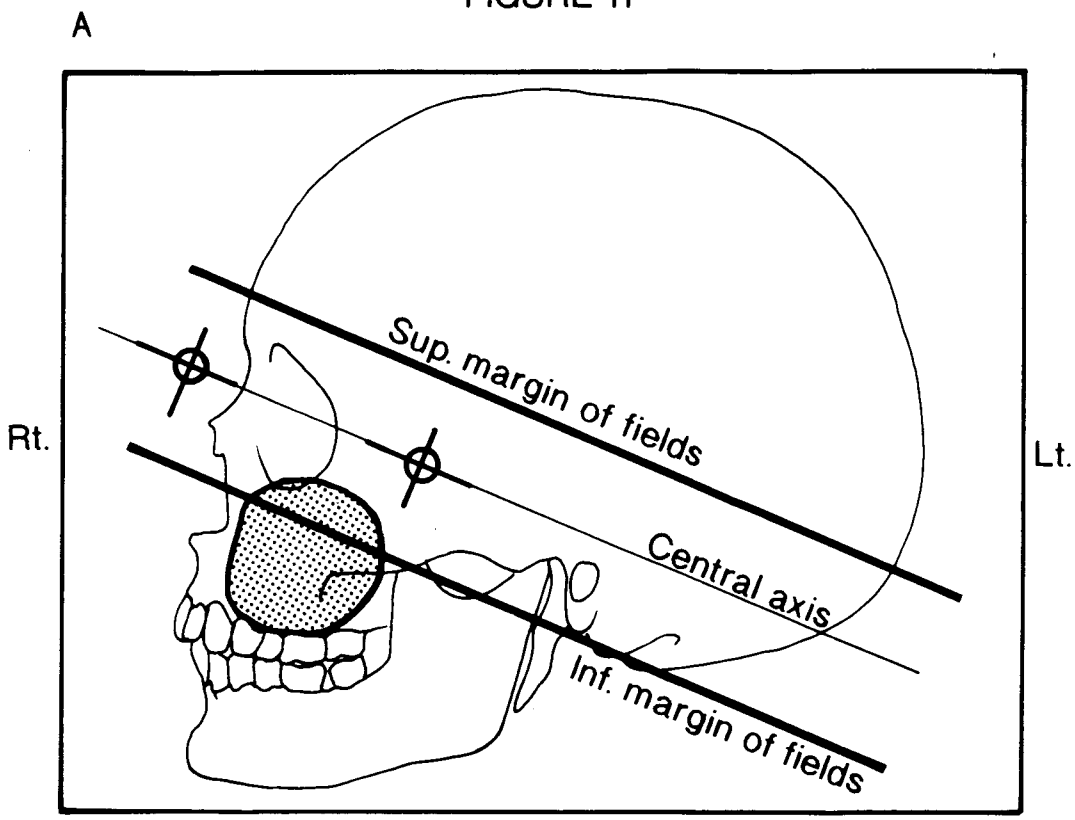


PRIMARY TUMOR: Ca right breast
RADIOTHERAPY: Anterior and posterior planned fields.
Secondary tumor in relation to fields.

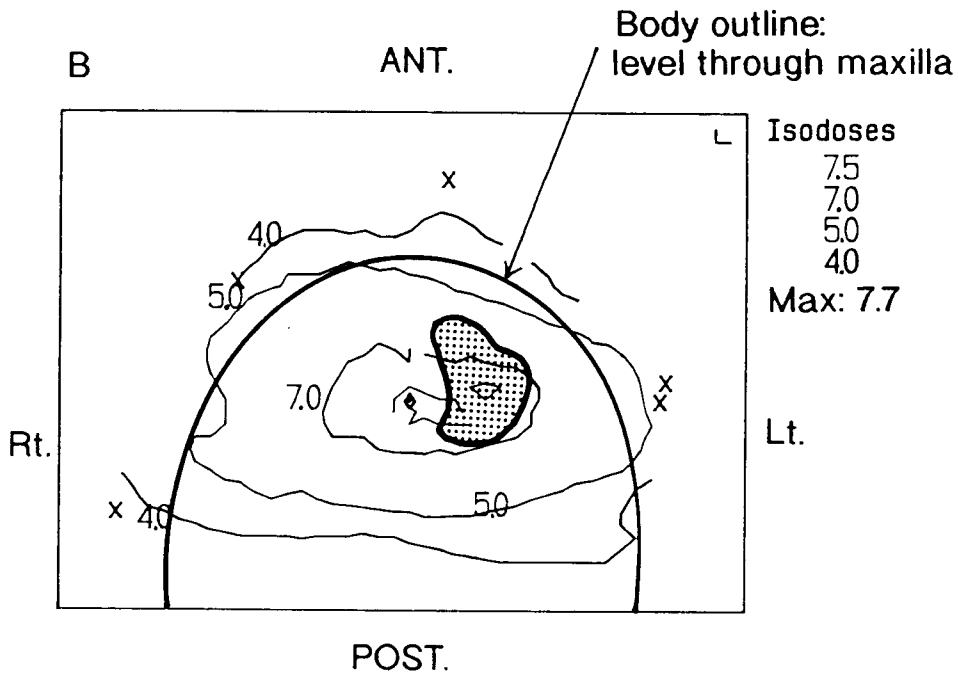


Total Gray Distribution 1 cm superior to central axis. Level through mid-secondary tumor.

FIGURE 11

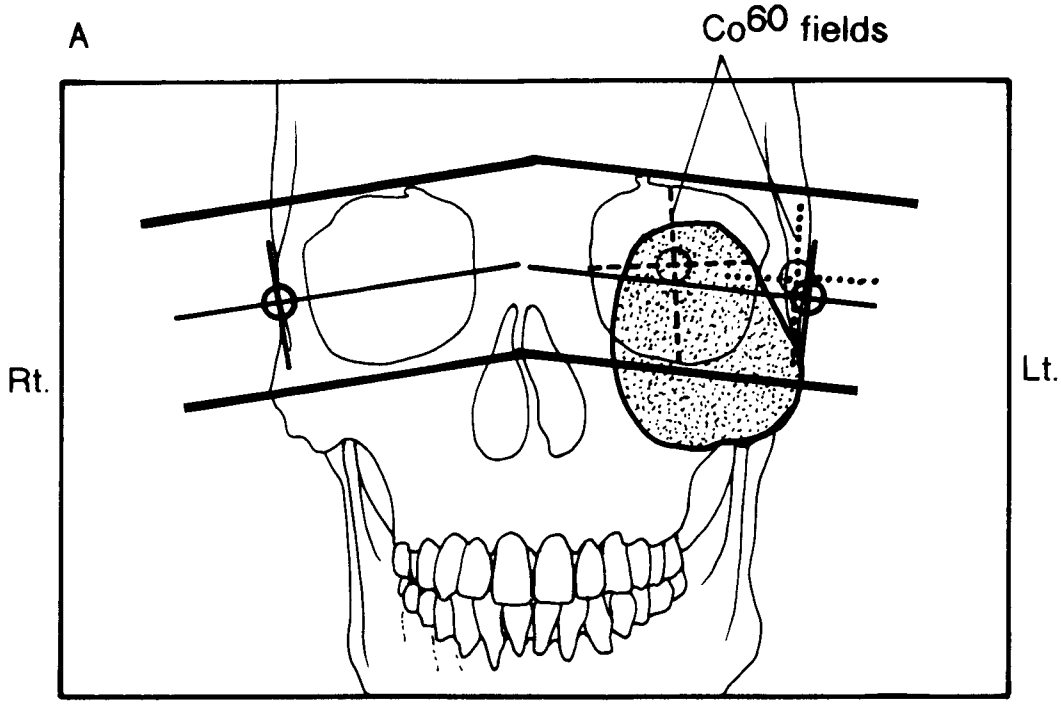


PRIMARY TUMOR: Bilateral retinoblastoma
RADIOTHERAPY: 5 planned fields, 2 Tantalum-182 applicators. Secondary tumor in relation to left lateral fields.

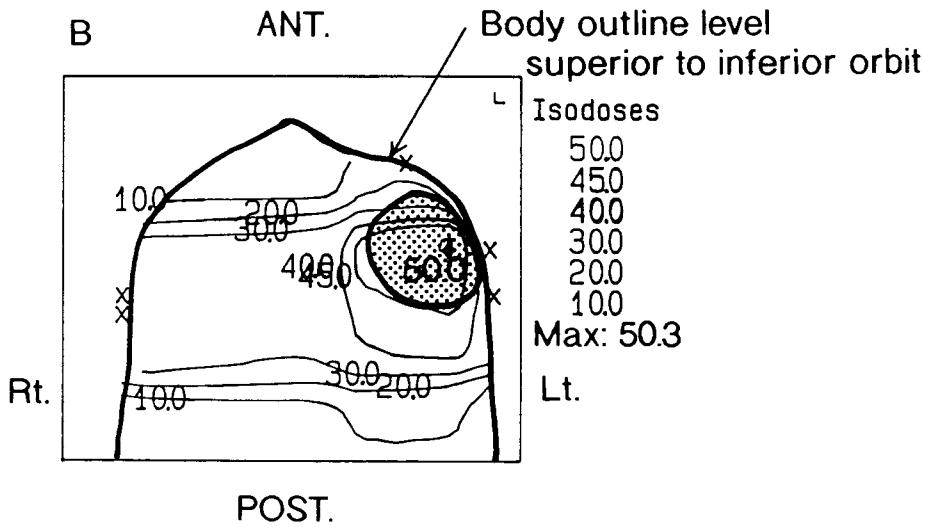


Total Gray Distribution 3.5 cm inferior to central axis. Level through mid-secondary tumor.

FIGURE 12



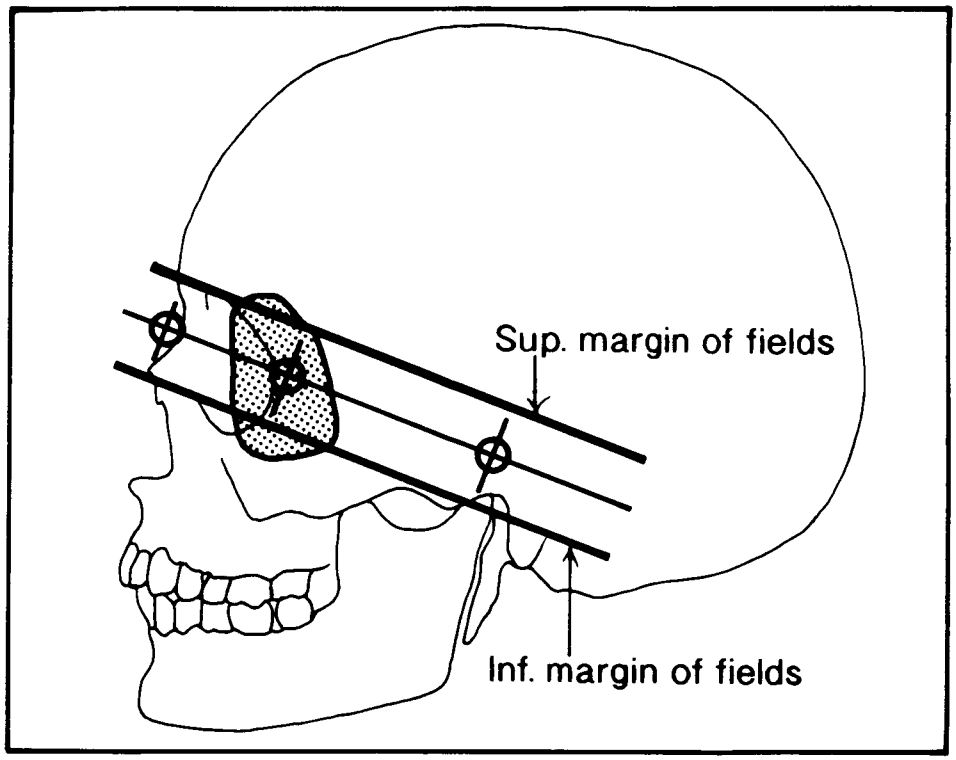
PRIMARY TUMOR: Bilateral retinoblastoma.
RADIOTHERAPY: Two 250 kV fields, I-125 implant, 2 courses of Co-60. Secondary tumor in the 250 kV fields. Centres of Co-60 fields are shown.



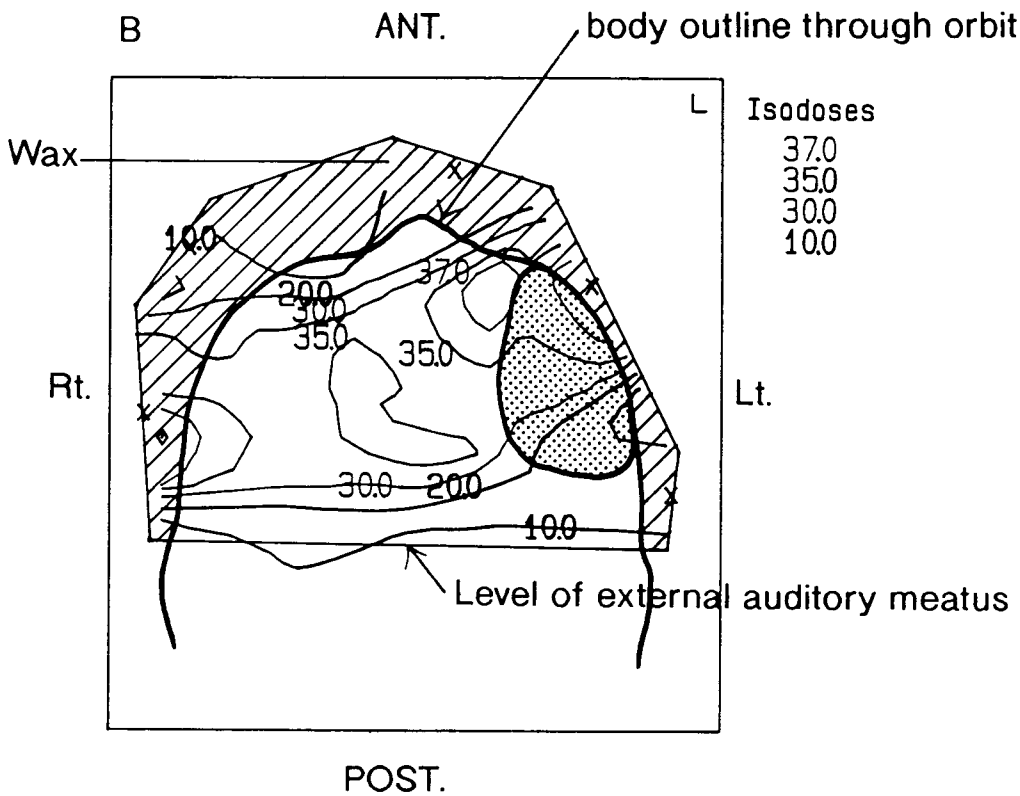
Total Gray Distribution 1 cm inferior to central axis of 250 kV fields. Level through mid-secondary tumor.

FIGURE 13

A

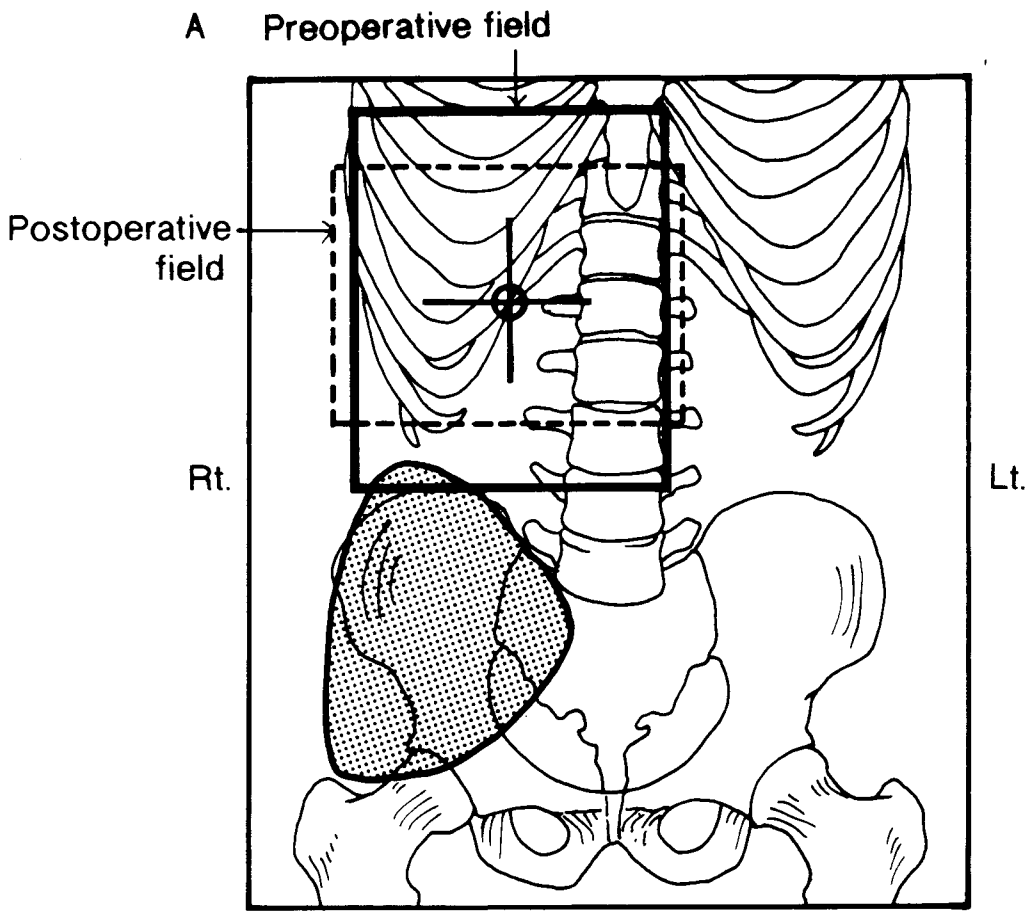


PRIMARY TUMOR: Bilateral retinoblastoma
RADIOTHERAPY: 5 planned fields. Secondary tumor in relation to left fields.

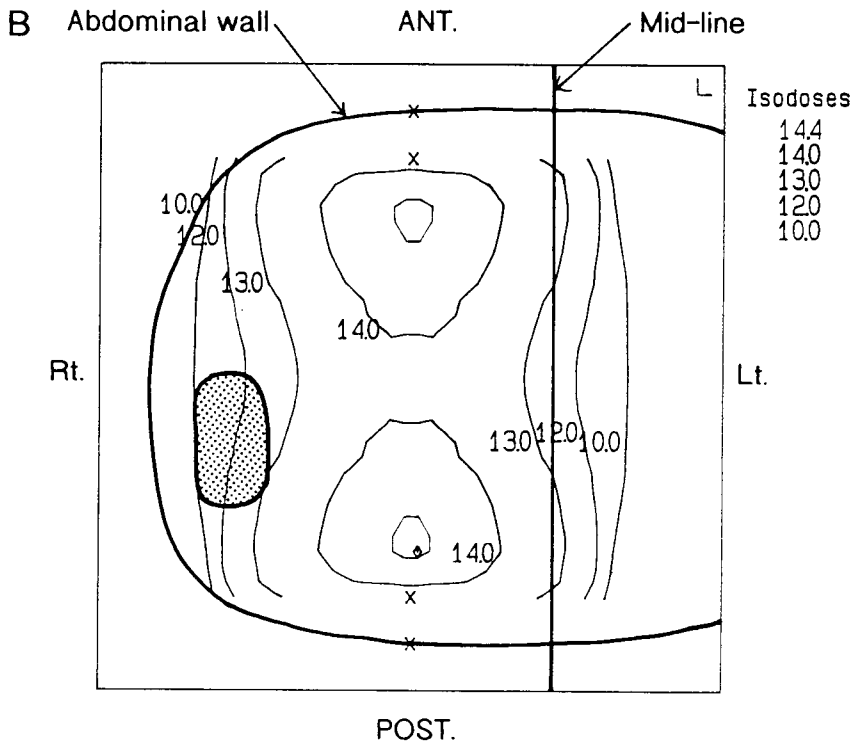


Total Gray Distribution central axis. Level through mid-secondary tumor.

FIGURE 14



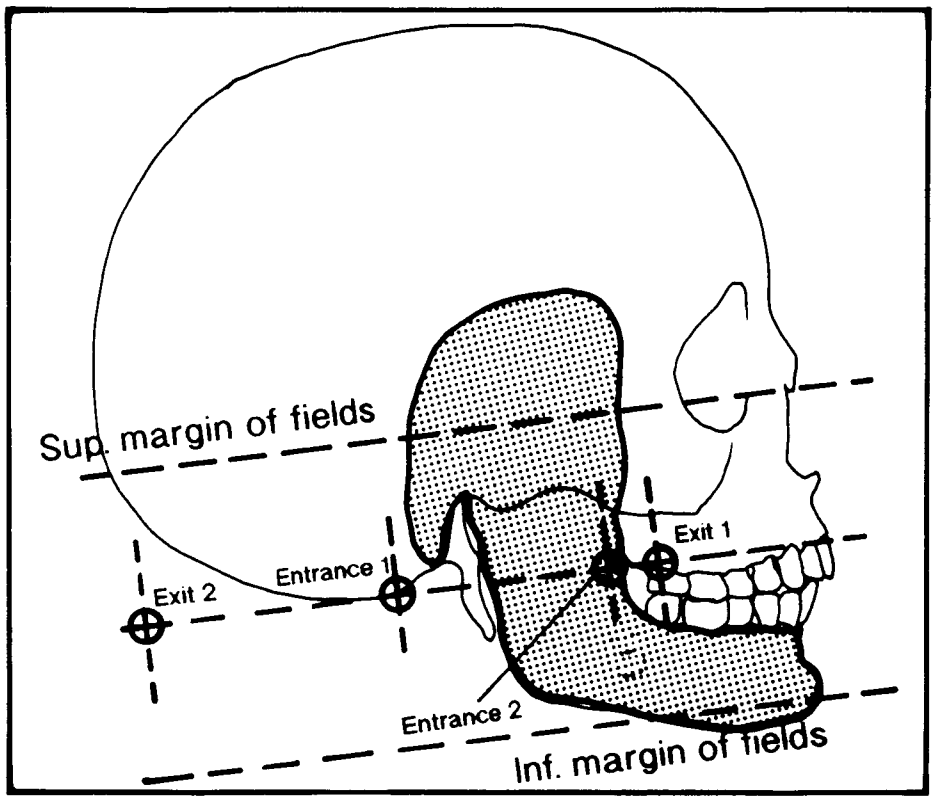
PRIMARY TUMOR: Wilms' tumor right kidney
RADIOTHERAPY: Anterior and posterior fields pre- and post-operatively.
Secondary tumor in relation to anterior fields.



Total Gray Distribution inferior border of pre-operative fields. Level through superior iliac crest.

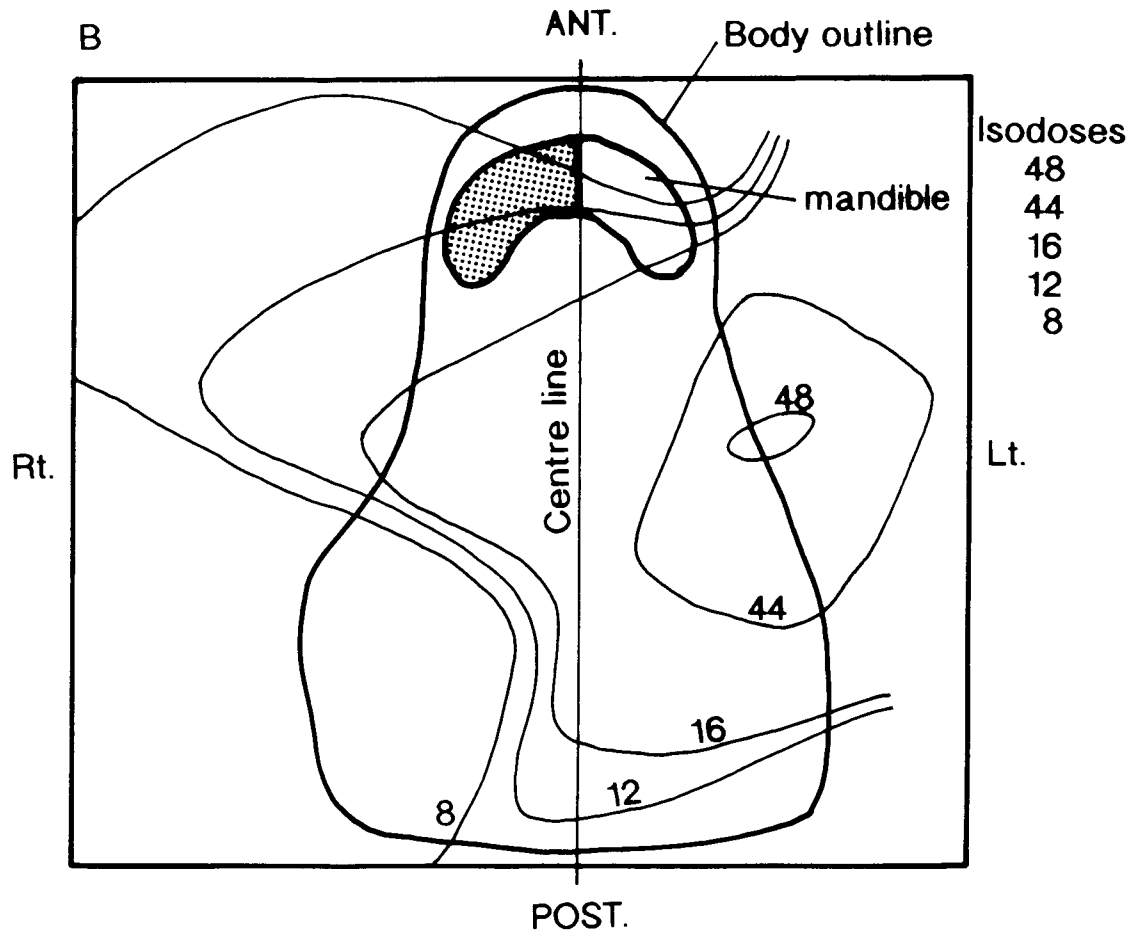
FIGURE 15

A



PRIMARY TUMOR:Ca left parotid.
RADIOTHERAPY: 2 planned fields left parotid area. Secondary tumor on RIGHT in relation to exit of fields.

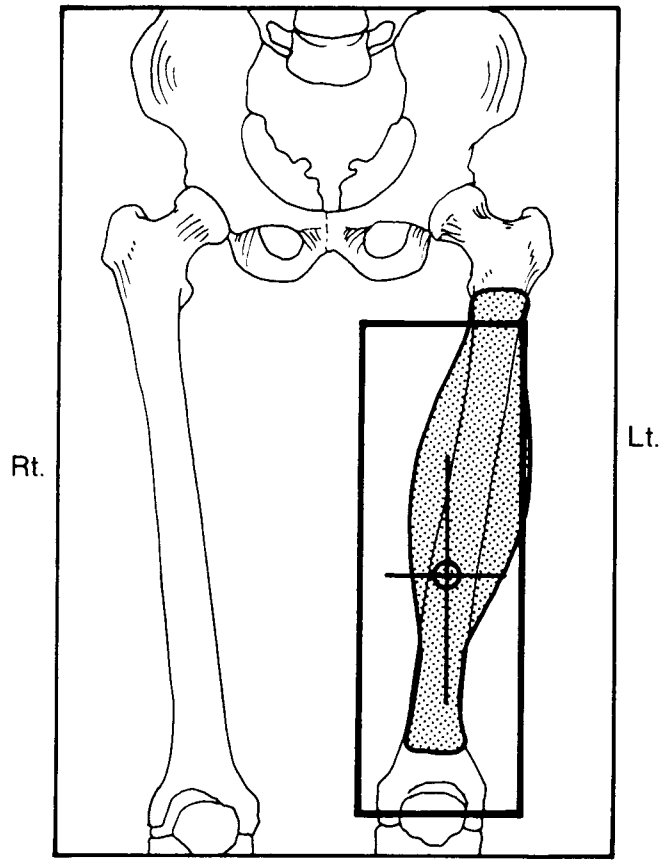
B



Total Gray Distribution through inferior margin of fields. Body of mandible superimposed.

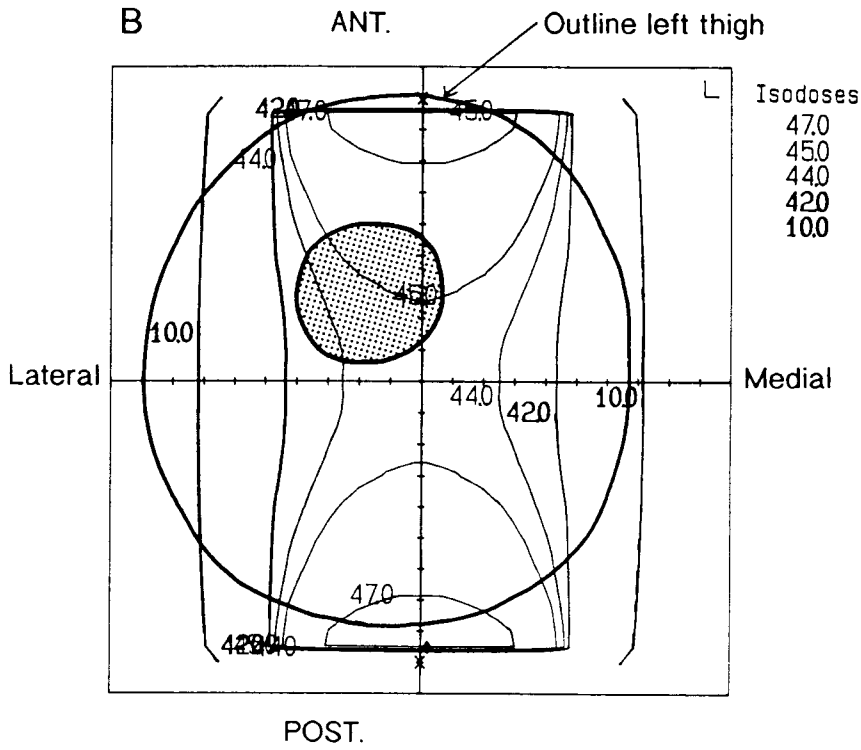
FIGURE 16

A



PRIMARY TUMOR:Synovial sarcoma left thigh
RADIOTHERAPY: Anterior and posterior fields.
Secondary tumor in anterior field.

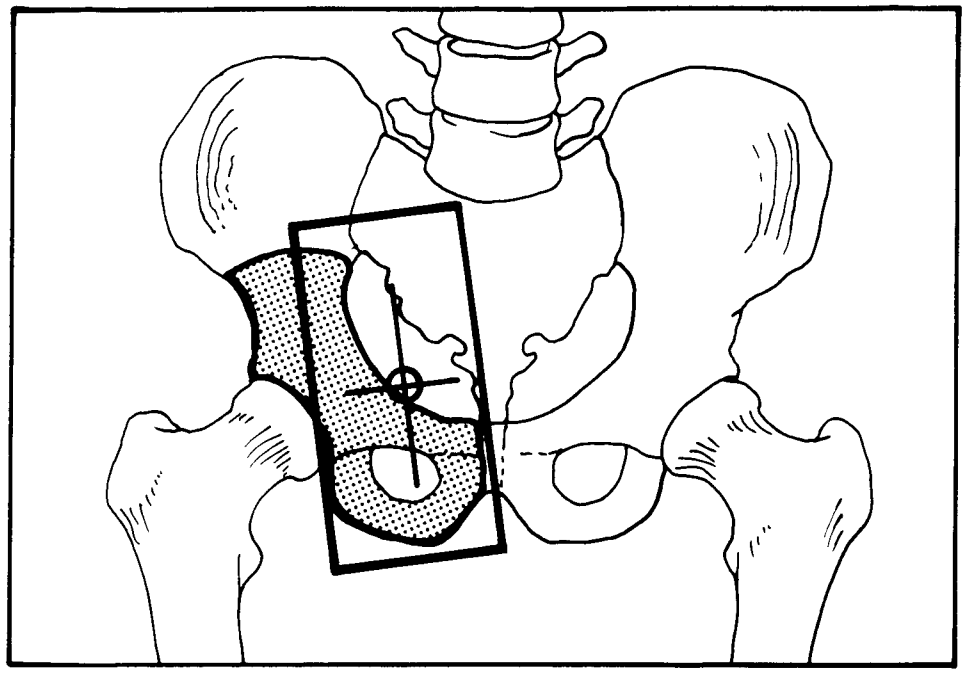
B



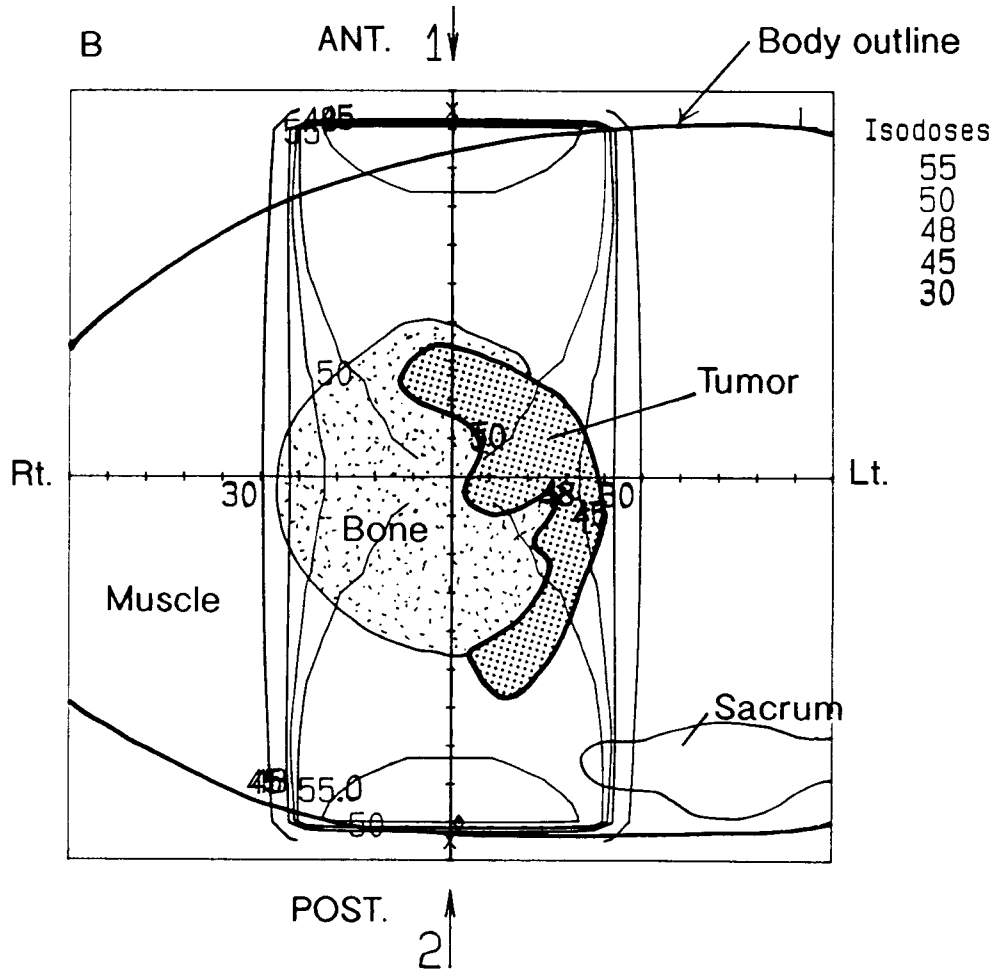
Total Gray Distribution 7.5 cm superior to central axis. Level through centre of main mass of secondary tumor.

FIGURE 17

A



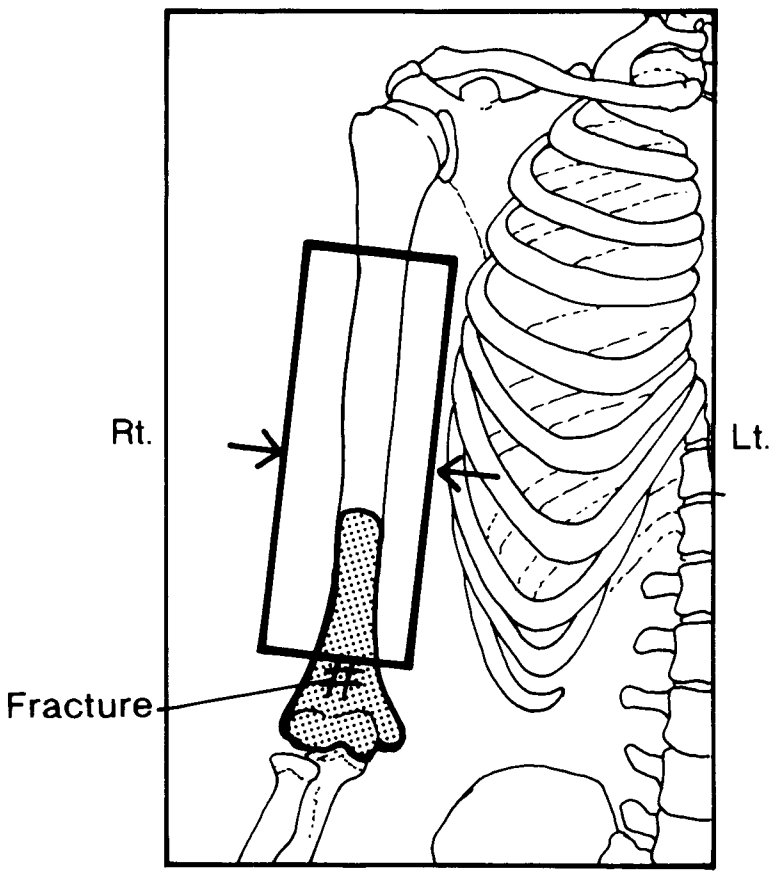
PRIMARY TUMOR: Giant cell tumor right pelvis
RADIOTHERAPY: Anterior and posterior fields .
Secondary tumor in anterior field.



Total Gray Distribution central axis. Level centre of secondary tumor.

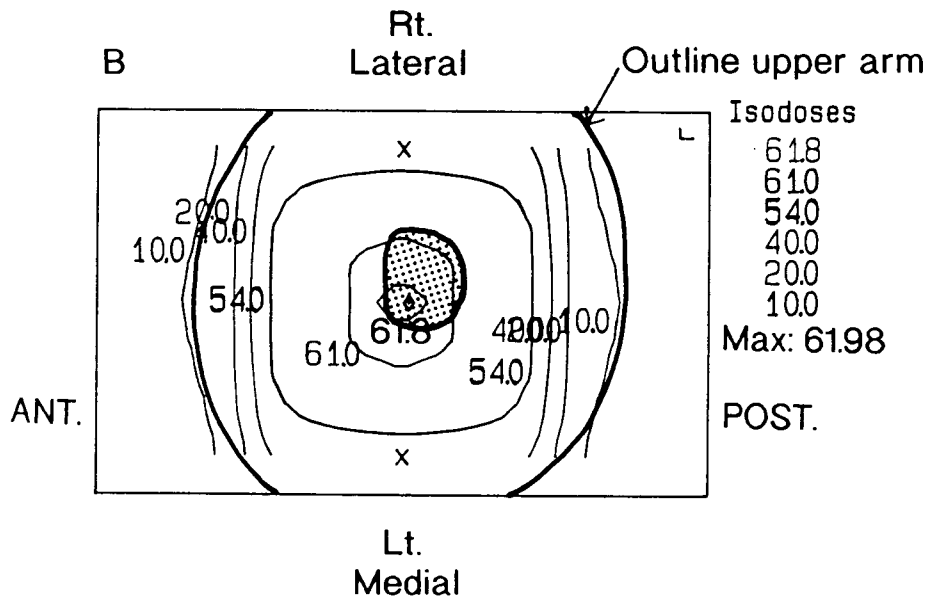
FIGURE 18

A



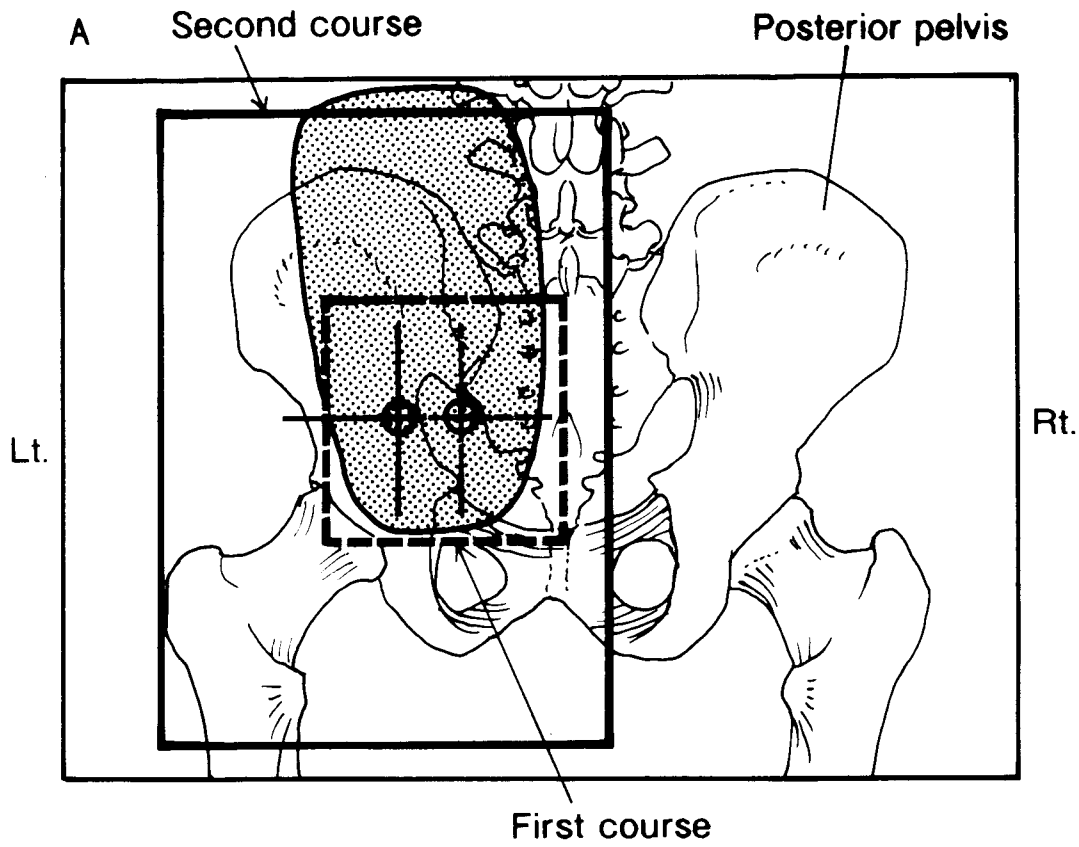
PRIMARY TUMOR: Giant cell tumor right humerus
RADIOTHERAPY: Right and left lateral fields. 2 courses.
Secondary tumor in relation to fields.

B

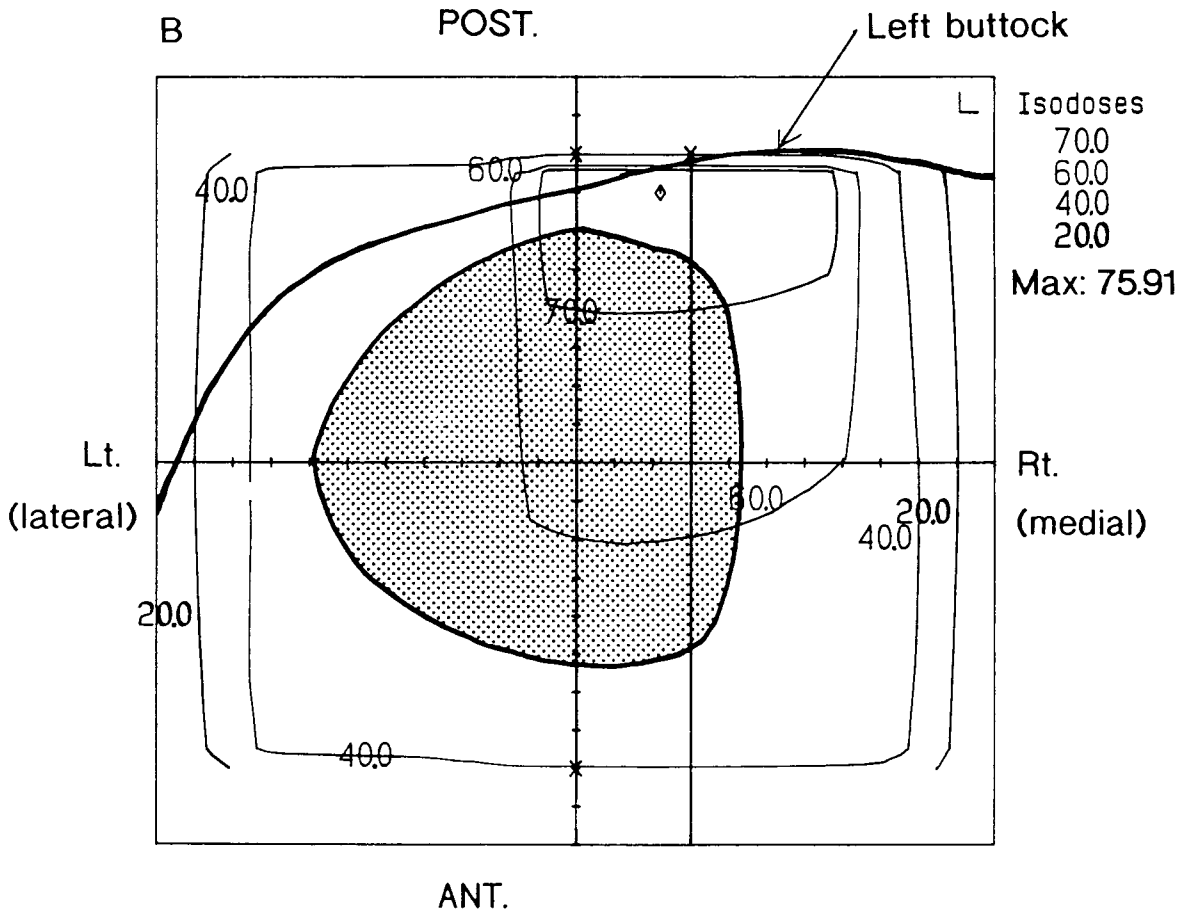


Total Gray Distribution 7.5 cm inferior to central axis. Level through main tumor mass.

FIGURE 19

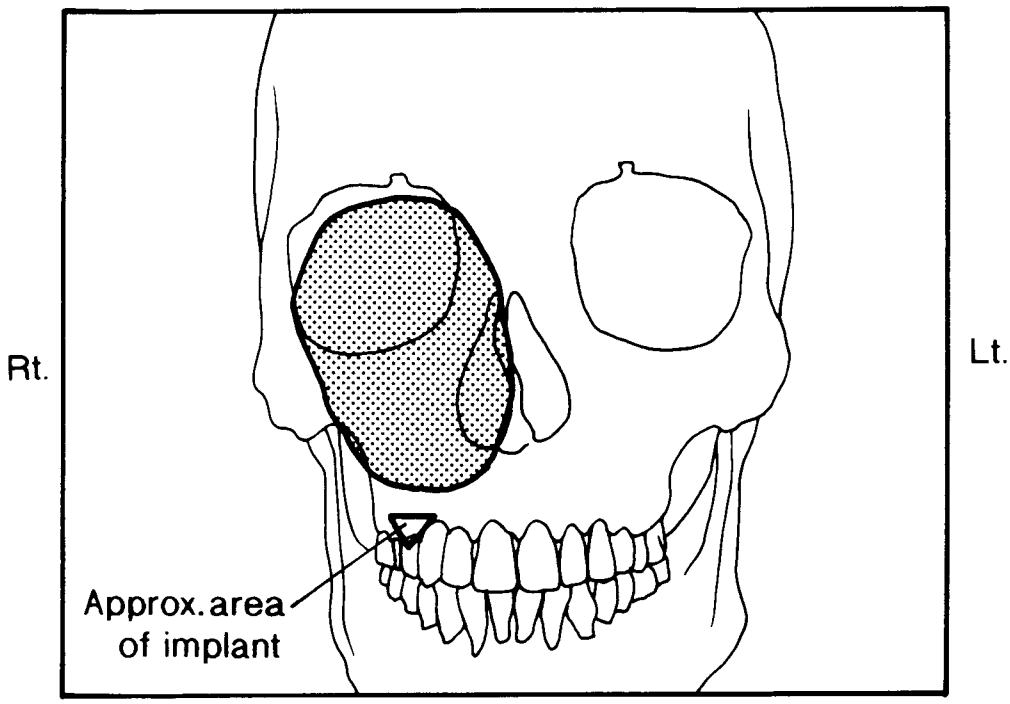


PRIMARY TUMOR: Fibromatosis left buttock
RADIOTHERAPY: 1. Posterior field. 2. Anterior and posterior fields.
Secondary tumor in relation to posterior fields.



Total Gray Distribution 5 cm superior to central axis. Level centre of
econdary tumor.

FIGURE 20



PRIMARY TUMOR: Benign tumor right alveolus
RADIOTHERAPY: Radium implant. Secondary tumor as shown.

ADDENDUM 2

TABLES 1 AND 2

TABLE 1

POSTRADIATION SARCOMAS - 20 CASES FROM THE UNIVERSITY OF CAPE TOWN

CASE NO.	SEX AGE AT RT	PRIMARY	MODAL.	DOSE FRACT.	LATENCY MNTHS	AGE AT SA	TIS	SITE	DOSE RANGE. POINT IN Gy	PATH GRADE	Rx OF SA	OUTCOME FROM PRESENTAT.
1.	F 57	Ca. cervix	Co^{60} Ra	54 Gy 27# 5/wk 17.6 Gy	72	63	So	T Uterus	58-100 100	MMMT High	Su	DWD 6 m
2.	F 40	Ca. cervix	Co^{60} Ra	54 Gy 27# 5/wk 19.5 Gy	193	56	So	T Uterus	45-100 60	MMMT High	Su	Lost
3.	F 37	Ca. cervix	Co^{60} Ra x2	57.5 Gy 26# 5/wk 37.44 Gy	164	51	So	T Uterus	50-100 100	MMMT High	Su CT RT	DWD 24 m
4.	F 55	Ca. cervix	Ra x 2 220 kV	U 3783 R 19# 5/wk	196	72	So	T Uterus	U	MMMT High	Su CT	DWD 2 m
5.	F 35	Ca. cervix	20 MV Ra	48.45 Gy 17# 3/wk 23.08 Gy	118	45	So	T Uterus	40-62 50	RMS High	Nil active Ref	DWD 17 m

CASE NO.	SEX AGE AT RT	PRIMARY	MODAL.	DOSE FRACT.	LATENCY MNTHS	AGE AT SA	TIS	SITE	DOSE RANGE. POINT IN Gy	PATH GRADE	Rx OF SA	OUTCOME FROM PRESENTAT.
6.	F 40	Ca. cervix	Co^{60} Ra x2	48.45 Gy CD 17# 4/wk 7.3 Gy	99	48	So	T Abdominal Wall	20-52 50	LMS High	Nil active	AWD 9 m
7.	F 20	Stromal sa. uterus	250 kV	3647 R 27# 5/wk	364	51	So	T Pelvis	30-40 38	FS Mod	Su RT Su	DWD 24 m
8.	F 27	Ca. Breast	Co^{60} e-	38.4 Gy 16# 4/wk 11.25 Gy at 90% 5# 4/wk	23	29	So	T Chest wall	38	Pleo. Sa. High	Su	NED 62 m
9.	F 52	Ca. Breast	Co^{60}	52.85 Gy 25# 5/wk	94	60	So	T Axilla	20-35 30	Sa. Mod.	H CT RT	DWD 18 m
10.	F 68	Ca. Breast	Co^{60}	55 Gy 25# 5/wk	155	81	So	T Clavicular area	10-64 60	LMS High	Su	DWD 9m ?cause

CASE NO.	SEX AGE AT RT	PRIMARY	MODAL.	DOSE FRACT.	LATENCY MNTHS	AGE AT SA	TIS	SITE	DOSE RANGE. POINT IN Gy	PATH GRADE	Rx OF SA	OUTCOME FROM PRESENTAT.
11.	M 9m	Bilat. Rb	250 kV Ta-182	3119 R 21# 5/wk See text	43	4yr	B	H+N Maxilla	<5-40 8	OS High	RT CT Su	DWD 9 m
12.	F 5m	Bilat. Rb	250 kV I-125 Co^{60} Co^{60}	3000R CD 20# 5/wk 45 Gy in 150.5 hrs 14.6Gy 2# 5 dys 14 Gy 2# 4 dys	55	5	B	H+N Orbit	20-60 50	OS High	Nil active	DWD 5 m
13.	F 29m	Bilat. Rb	250 kV	3300 R 20# 5/wk	58	7	So	H+N Orbit	<10-37 35	Pleo. Sa. High	CT	DWD 6 m
14.	M 4	Wilms'	250 kV 250 kV	1200 R CD 10# 5/wk 1800 R CD 14# 5/wk	203	21	B	T Iliac bone	<10-13 12	OS High	CT	DWD 6 m

CASE NO.	SEX AGE AT RT	PRIMARY	MODAL.	DOSE FRACT.	LATENCY MNTHS	AGE AT SA	TIS	SITE	DOSE RANGE. POINT IN Gy	PATH GRADE	Rx OF SA	OUTCOME FROM PRESENTAT.
15.	F 18	Ca. Parotid	Co^{60}	48 Gy 16# 3/wk	83	25	B	H+N Mandible	<8-16 12	OS High	CT x1 cycle	DWD date U
16.	M 21	Synovial sa. left thigh	Co^{60}	45 Gy CD 10# 2/wk	207	39	B	Ex Femur	38-47 45	OS High	Nil active	DWD 3 m ? cause
17.	M 37	Giant cell tumor pelvis	Co^{60}	50 Gy 25# 5/wk	38	40	B	T Pelvic bones	30-55 48	Sa. Mod	Embol. CT RT	DWD 47 m
18.	F 20	Giant cell tumor humerus	220 kV 220 kV	2000R GD (2500 CD) 21# 5/wk 2000R GD 20# 5/wk	511	62	B	Ex Humerus	60-79 62	OS High	Su	A NED 27 m
19.	F 10	Fibrom. left buttock	Co^{60} Co^{60}	33.75 Gy GD 16# 5/wk 45 Gy CD 10# 2/wk	91	17	B	T Pelvis	30-75 60	OS High	Su	DWD 25m
20.	F 5	Benign tumor alveolus	Ra	U	636	58	B	H+N Maxilla	U	OS Mod N	Sux3 CTx2 RT	DWD 12m

Footnotes

1. Radium doses are described at Manchester Point A
2. Prescribed doses are described as dose at target volume unless otherwise specified.
3. Dose range refers to the dose range received in the tissue in which the postradiation tumor developed.
4. Point refers to the dose point at which the tumor is estimated to have grown
5. Age is in years unless otherwise indicated.

Abbreviations

#	Fractions
A	Alive
AWD	Alive with disease
B	Bone
Bilat Rb	Bilateral Retinoblastoma
Ca	Carcinoma
CD	Central dose
CT	Chemotherapy
DWD	Died with disease
Embol	Embolisation
Ex	Extremity
F	Female
Fibrom	Fibromatosis
Fract	Fractionation
FS	Fibrosarcoma
GD	Given or applied dose
H	Hormonal therapy
H + N	Head and Neck
LMS	Leiomyosarcoma
M	Male
m/mnths	months
Mod	Moderate
Modal	Modality
NED	No evidence of disease
OS	Osteosarcoma
Path	Pathology
Pleo	Pleomorphic
Presentat	Presentation
Ref	Refused
RMS	Rhabdomyosarcoma
RT	Radiotherapy
Rx	Treatment
Sa	Sarcoma
So	Soft
Su	Surgery
T	Trunk
Tis	Tissue
U	Unknown

TABLE 2

POSTRADIATION SARCOMAS (UNIVERSITY OF CAPE TOWN) - MODALITY AND DOSE

CASE NO.	MODALITY	PRESCRIBED DOSE	TOTAL PRESCRIBED DOSE IN GY (f-FACTOR CONVERSION)	SARCOMA DEVELOPMENT DOSE RANGE & POINT IN GY (f-FACTOR CONVERSION)
4.	Ra x 2 220 kV	U 3783 R 19# 5/wk	U	U
18.	220 kV	2000R GD (2500R CD) 21# 5/wk	75 Gy CD	60 - 79 62
	220 kV	2000R GD 20# 5/wk		
7.	250 kV	3647 R 27# 5/wk	34.87	30 - 40 38
11.	250 kV	3119 R 21# 5/wk	50	<5 - 40 8
	Ta-182	See text		
13.	250 kV	3300 R 20# 5/wk	31.55	<10 - 37 35

CASE NO.	MODALITY	PRESCRIBED DOSE	TOTAL PRESCRIBED DOSE IN GY (f-FACTOR CONVERSION)	**SARCOMA DEVELOPMENT** DOSE RANGE & POINT IN GY (f-FACTOR CONVERSION)
14.	250 kV	1200R CD 10# 5/wk	12.60	<10-13 12
	250 kV	1800R CD 14# 5/wk	18.90	
12.	250 kV	3000R CD 20# 5/wk	50 Gy total central axis	20 - 60 50
	I-125	45 Gy in 150.5 hrs		
	Co^{60}	14.60 Gy GD 2# 5 dys		
	Co^{60}	14 Gy GD 2# 4 dys		
1.	Co^{60}	54 Gy 27# 5/wk	71.6 PtA	58-100 100
	Ra	17.6 Gy		
6.	Co^{60}	48.45 Gy CD 17# 5/wk	55.75 PtA	20 - 52 50
	Ra x 2	7.3 Gy		

CASE NO.	MODALITY	PRESCRIBED DOSE	TOTAL PRESCRIBED DOSE IN GY (f-FACTOR CONVERSION)	**SARCOMA DEVELOPMENT** DOSE RANGE & POINT IN GY (f-FACTOR CONVERSION)
2.	Co^{60}	54 Gy 27# 5/wk	73.5 PtA	45 - 100 60
	Ra	19.5 Gy		
3.	Co^{60}	57.50 Gy 26# 5/wk	94.94 PtA	50 - 100 100
	Ra x 2	37.44 Gy		
8.	Co^{60}	38.40 Gy 16# 4/wk 11.25 Gy at 90% 5# 4/wk	49.65	38
9.	Co^{60}	52.85 Gy 25# 5/wk	52.85	20 - 35 30
10.	Co^{60}	55 Gy 25# 5/wk	55	10 - 64 60
15.	Co^{60}	48 Gy 16# 3/wk	48	< 8 - 16 12
16.	Co^{60}	45 Gy CD 10# 2/wk	45	30 - 47 45

CASE NO.	MODALITY	PRESCRIBED DOSE	TOTAL PRESCRIBED DOSE IN GY (f-FACTOR CONVERSION)	**SARCOMA DEVELOPMENT** DOSE RANGE & POINT IN GY (f-FACTOR CONVERSION)
17.	Co^{60}	50 Gy 25# 5/wk	50	30 - 55 48
19.	Co^{60} x 2	33.75 Gy GD 16# 5/wk 45 Gy CD 10# 2/wk	75 Signif. max dose on isodose curves	30 - 75 60
5.	20 MV	48.45 Gy 17# 3/wk	71.53 PtA	40 - 62 50
	Ra	23.08 Gy		

Footnotes:

1. Radium doses are described as Manchester Point A
2. Prescribed doses refer to doses received at target volume unless otherwise specified.
3. f-factor conversion for prescribed doses calculated for the tissue in which the postradiation tumor developed
4. Dose range refers to the dose range received in the tissue in which the postradiation tumor developed
5. Point refers to the dose point at which the tumor is estimated to have grown

U = Unknown
CD = Central dose (mid-point dose)
GD = Given (applied) dose
# = fractions

ADDENDUM 3

TABLE 3

TABLE 3

21 REPORTED SERIES OF POSTRADIATION SARCOMA FROM THE ENGLISH LITERATURE

See footnotes and example below footnotes

AUTHOR YEAR (ref) NO. CASES	PRIMARY TUMOR	DOSE	MODAL.	LAT. (YRS)	TIS.	AGE AT PRS	SEX	Rx	SURV.
1. Pettit 1954 (86) 4 FS*	1 Rb 3 Oth	NR	NR	15 6-29	So	55 6-89	1 M 3 F	All Su 1 RT	2 DWD 2 A (1 AWD)
2. Soloway 1966 (108) 21	Rb*	15719R 2800-26800R	NR	11 4-27	NR	12 5-29	NR	NR	Ave S 21 m
3. Castro 1967 (15) 5	3 G 1 Rb 1 Oth	78.12 R 67.5-107R	4 Or (3 w Ra)	12 3-23	B*	49 10-88	2 M 3 F	NR	NR
4. Sim 1972 (104) 34	16 B 6 G 3 Br 9 Oth	NR	32 Or (6 w Ra)	16 5-42	B*	46 9-77	14 M 20 F	21 Su±CT/RT 8 pall RT±CT	Ave14m
5. Mindell 1977 (75) 20	4 Br 8 G 1 L 7 Oth	57 20-81	8 Or (4 w Ra, 1 w Me) 3 Me (1 w Ra) 1 Ra, 1 Radon	12.5 1-29	NR	56 23-78	3 M 17 F	14 Su±CT/RT/IMM 1 RT 5 nil active	15 DWD 4 D of other 1 ADF

AUTHOR YEAR (ref) NO. CASES	PRIMARY TUMOR	DOSE	MODAL.	LAT. (YRS)	TIS.	AGE AT PRS	SEX	Rx	SURV.
6. Tountas 1979 (114) 10	4 Br 3 G 1 HD 1 U 1 Oth	46 35-60	NR	15 5-29	B*	59 34-79	1 M 9 F	1 Su+RT+CT 6 RT 1 RT+CT	1 AWD 9 DWD 6-15m
7. Weatherby 1981 (121) 78	45 B 12 G 8 Br 1L 13 Oth	1400- 10000R or 30-67Gy	Or Me Me+Ra	14.3 2.8-55	B*	45 9-77	30 M 48 F	44 Su±RT 17 RT±CT 3 nil	Ext/Head: 30% 5 YDFS Central: 0% 5 YDFS
8. Huvos 1985 (49) 66 OS	24 B 6 Br 9 HD 3 G 4 Rb 13 Oth 1 NHL 6 NR	All >20 Gy	60-80kV to 6 MeV Ra-226	12.8 3.5-33	7 So 59 B	38 9-75	31 M 35 F	Su±RT Su±CT	Bone: med S 12m and 5 YS 17%
9. Kuten 1985 (58) 7	Br*	39.14 22-54	4 Or 3 Me	13 4-26	So*	68 53-85	? F	3 Su±CT 4 CT	All D 6-36m
10. Doherty 1986 (27) 4	Br*	4250R 45 Gy Ave	1 Or 3 Me	15.9 12.2-19.4	B*	71 50-91	F	Nil active	Ave S 2.5m
11. Davidson 1986 (25) 20	6 Br 3 G 2 HD 9 Oth	37.3 8.8-70	8 Or 6 Me	16.2 7-45	So*	NR	NR	All Su 2 w CT 7 RT 7 CT+RT	14.5% 5 YS

AUTHOR YEAR (ref) NO. CASES	PRIMARY TUMOR	DOSE	MODAL.	LAT. (YRS)	TIS.	AGE AT PRS	SEX	Rx	SURV.
12. Souba 1986 (109) 16 Chest Wall	10 Br 4 HD 2 Oth	49 OOR 42 OO- 55 OOR	NR	13 5-28	NR	47 18-77	2 M 14 F	11 Su±CT others CT only	13 D 1 long term surviv.
13. Sundaresan 1986 (112) 13 Spine	4 HD 2 Br 3 G 4 Oth	44.75 28-76	3 Or 10 Me (Cs in 1)	10 med 6-30	4 So 9 B	53 28-72	5 M 8 F	Su±CT±RT	med S 8m 3 long term surviv.
14. Hatlinghus 1986 (47) 3	Br*	56.33 at PRS ±55-57	1 Or (w Cs) 2 Me	7.7 8-14	2 So 1 B	47 29-62	F	All Su	1 DWD 1 AWD 1 D Oth
15. Laskin 1988 (59) 53	12 Br 7 G 15 L mainly HD 3 Rb 16 Oth	43.71 19.45-76	7 Or 39 Me	10 2-40	So*	47 5-77	23 M 30 F	NR	2 YS 32%
16. Lorigan 1989 (65)	5 Br 3 G 4 HD 7 Oth	42.8 Ave	Me	17 5-50	B*	52 16-80	8 M 11 F	NR	NR

AUTHOR YEAR (ref) NO. CASES	PRIMARY TUMOR	DOSE	MODAL.	LAT. (YRS)	TIS.	AGE AT PRS	SEX	Rx	SURV.
17. Smith 1989 (106) 7 (6 patients)	Rb*	72.8 55-96 (7 cases)	NR	20.2 5.3-36.2	NR	NR	NR	6 Su w RT in 5, CT in 3 1 RT only	3 DWD 3 ADF Ave 50m
18. Wiklund 1991 (122) 33	7 Br 14 G 1 HD 1 NHL 9 Oth	36 med 16-112	18 Or 15 Me	13.2 med 3.4-22.8	25 So 8 B	55 9-84	6 M 27 F	25 Su w rad aim (±CT,RT) 8 pall.	Med S 22m
19. Taghian 1991 (113) 9	Br*	50.67 45-90/100	All Me (2 Me+Or)	10.1 4-24	6 So 3 B	65 49-78	? F	Su±CT±RT Pall CT	2 ADF. 7D w ave S 2.4Y
20. Ruka 1991 (96) 13	G*	NR	12 Or (11 w Ra) 1 Me w Ra	18 7-31	So*	med 58 36-71	F	12 Su 1 ref	Med S 30 m
21. Mark 1994 (68) 37 (limited primary sites reviewed)	7 Br 13G 3 Rb 2 HD 2 NHL 10 Oth	56.4 30-124.4	NR	12 0.25-50	NR	57 med 5-79	9 M 28 F	Su28±RT/CT 4 CT only 2 RT only	5 YDFS 19%

Footnotes

* Denotes feature specified for case to be included in series

Averages and ranges calculated from figures available. Figures not always available for all cases in series

Dose reported in Gy unless otherwise specified. Usually refers to prescribed dose

Dose, latency and age in average and range unless otherwise indicated.

A	Alive
ADF	Alive disease free
Ave	Average
AWD	Alive with disease
B	Bone
Br	Breast
Cs	Caesium
CT	Chemotherapy
D	Died
DF	Disease free
DFS	Disease free survival
DWD	Died with disease
F	Female
FS	Fibrosarcoma
G	Female reproductive tract
HD	Hodgkin's disease
I	Rad Radical
IMM	Immunotherapy
L	Lymphoma
Lat	Latency
M	Male
m	Months
Me	Megavoltage
Med	Median
Modal	Modality
NHL	Non Hodgkin's Lymphoma
NR	Not reported/not calculated
Or	Orthovoltage
OS	Osteosarcoma
Oth	Other
P	Palliative
Ra	Radium
Rb	Retinoblastoma
ref	Refused
RT	Radiotherapy
Rx	Treatment
S	Survival
So	Soft
Su	Surgery
SURV	Survival
Surviv	Survivor
TIS	Tissue
U	Unknown
w	With
Y	Year
YDFS	Year disease free survival
YS	Year survival

EXAMPLE (CASE 1)

In 1954 Pettit (86) described 4 cases of postradiation fibrosarcoma. 1 occurred after radiotherapy for a retinoblastoma and 3 after treatment for other primaries. Radiotherapy dose and modality were not reported. The postradiation sarcomas developed after a mean latency of 15 years (range 6 to 29). They all occurred in soft tissue. The mean age of the patients at presentation with the PRS was 55 years (range 6 to 89). 1 patient was male and 3 female. All were treated with surgery. 1 also received radiotherapy. 2 died with disease. 2 were alive at the time of reporting (1 with disease).