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CLINICAL SECTION AND PHYSICS SECTION

70-MV X-RAYS FOR CLINICAL USE

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The choice of a 70-million-volt x-ray machine as a tool with which to treat cancer resulted from many factors. In 1949, when a decision had to be made as to what voltage was to be tried and what type of machine was to produce it, the following factors played their parts. One-million-volt machines had been in use for about 20 years – the University of California Hospital, San Francisco, had had one from 1934 to 1949. Radio-cobalt telecurie units were being tried in many places. Four-million-volt linear accelerators were being produced for clinical trials in Great Britain. At least two 24-Mev betatrons were in clinical use and three more institutions were planning to install similar units. In Europe, one 31-Mev betatron was in use for the treatment of patients and two more were on order. In England, two 31-Mev synchrotrons were being completed in hospitals. It seemed as if the field of energies up to 30 Mev was likely to be well investigated.

The possibility of using beams of high-energy electrons was under discussion. Experiments indicated that if electron beams of adequate intensity were to penetrate 10 cm. or more of tissue, an energy of 40 to 50 Mev would be required. A betatron could be adapted to clinical use which could produce x-rays and electrons with such energies – but a synchrotron of the same size and weight could produce 70-Mev radiations and thus allow the investigation of a range so far not examined. The General Electric Company had made a synchrotron of this capacity and said it was willing to make such an instrument for clinical use. The order was given for such a machine and it was installed in 1951. It took from then till July, 1956 to put it in proper shape to treat patients.

The patient-treatment program was initiated just over two years ago. Treatments for patients have been cancelled during one day only by reason of synchrotron inoperability.

Description of Synchrotron

The synchrotron is an electrical device which is designed to accelerate electrons to high energies (in this case to 70 Mev). The main components of the synchrotron are (1) an electromagnet, (2) an evacuated

Treatment Planning

The treatment plan for a typical patient is derived in steps. First, the radiologist determines the locale and extent of the disease, and decides the volume to be treated, the dose to be delivered, and frequently also the relative location of nearby structures which for one reason or another should not receive a large dose of radiation. Second, the physicist composes one or more plans, using appropriate combinations of fields, treatment distances and angulations, and bolus to satisfy these desiderata. He also supplies factors which relate the exposure (number of monitor integration units) required to deliver the prescribed daily absorbed dose to the periphery of the tumor volume. Last, the plans suggested are discussed with the radiologist for approval or revision. Not infrequently it happens that a plan providing a slightly more uniform absorbed dose throughout the tumor volume is discarded in favor of another which is more suitable clinically.

Typical contours representing the skin surface of the patient on an appropriate plane through the center of the diseased region are taken for each patient. On this are superimposed isodose curves for the specific combination of fields comprising the treatment plan for that patient. Typical calculations of dosage to areas of interest are made on the same sheet and the whole becomes part of the permanent record for that patient.

Clinical Approach

By 1956, when all was ready to start treating patients, there was already considerable clinical experience and some biological data available from other laboratories and clinics using multimillion-volt x-rays. However, the comparisons of conventional and supervoltage x-rays with megavolt x-rays at the other laboratories were based mainly on adaptations of the roentgen rather than on direct measurements of the absorbed doses from the beams of the various machines. Hence, it was not easy to take the data from other places and adapt them to the needs of this Laboratory. Through the efforts of one of us (G.D.A.) and of Dr. H. I. Kohn of the Biology Section of this Laboratory, it was determined on the basis of the physical measurements in ergs absorbed per gram that the 70-Mv x-rays were probably between 85 and 90% as effective as the 250-kvcp x-rays.

In the selection of patients for treatment with this previously untried energy, it was decided to utilize patients whose cancers were of such a type or at such a stage of growth that the patient would have less than a 50% chance of five-year survival with standard 250- or 100-kv x-ray therapy. In addition to this, the patients were selected so as to take advantage of the physical characteristics of the radiation from the synchrotron. Any patient whose lesion had to be treated through several centimeters of normal tissue was selected. Stout patients were accepted because the radiation penetrates to relatively great depths

before the region of maximum absorption is reached. Patients with lesions in places where either bone or air was interposed between the surface of the patient and the tumor, such as the pharynx and the lung, were treated because these materials do not vary the depth dose from 70-Mv x-rays as much as they do that from 250-kv x-rays.

It was necessary to start patient treatment at doses that were known to be safe. In the Radiation Therapy Department at the University of California Medical Center, 5000 tissue roentgens were being delivered to many tumors in 5 weeks, using either the 250- or the 1000-kv x-ray machines. Five-thousand tissue roentgens are equivalent to about 4800 rads when measured in soft tissue. It was therefore decided that we should start synchrotron treatments with doses to the tumor of approximately 4800 rads, making no allowance for relative biological effectiveness (RBE). Such a dose was given to the first 6 patients and then an interval of three months was allowed to pass during which these patients were observed. The mucosal and skin reactions that were seen were noted to be quite mild. No unexpected reactions occurred in the patients, and, in general, the clinical observations confirmed the predictions based on the physical factors. It was felt that the dose delivered had been on the small side.

When treatments were resumed in December of 1956, the doses were increased by 10%, this being the least amount indicated as needed by the RBE studies. The dose to be aimed at thus became 5250 rads in 5 weeks. Such a dose should be the equivalent in energy absorbed to a dose stated as 5470 tissue roentgens. In May, 1957, for various reasons the treatment of patients was stopped for a few months, and those who had been treated were observed. During this period of observation the conclusion was reached that the optimum dose was something still larger than had been given. This decision was made because some of the tumors were not being made to disappear, and most of the patients apparently could have tolerated somewhat more radiation. The plan formulated at this time was to deliver a tumor dose of 5000 rads in 5 weeks, and then judge by the patient's general condition and the reaction of the tissues whether to continue to 6000 rads in 6 weeks. Twenty-seven patients have since then received tumor doses of approximately 6000 rads, including those with carcinomas of the lung, cervix, tongue, and bladder. This plan is still in effect.

To date, the number of patients treated is too small and the elapsed time too short to permit any final conclusions as to the place this tool is to take in the treatment of cancer. By discussing how separate patients were treated, it is proposed to demonstrate the method of planning treatments, the method of taking advantage of the peculiar characteristics of this radiation, and in general the types of patients in which it seems to be of the greatest usefulness.

For each example of treatment presented below, a diagram is given showing the contour outline of the surface of the patient in the region being treated, with superimposed isodose lines. The numbers shown on

the isodose lines differ somewhat from those shown in Fig. 1 because the center of interest shifts from percentage of maximum absorbed dose to percentage of dose planned for the periphery of the tumor. When the region containing the tumor was determined and outlined on the contour diagram, the isodose line nearest to the periphery of this region was labelled 1.00. The figures on the other isodose lines show the respective percentages of this selected dose that would be absorbed at the levels indicated.

Examples of Clinical Procedure

The first patient to be presented demonstrates one of the obvious conditions for which 70-Mv x-rays are superior to conventional beams, i.e., large size. Patient RL 53 was 27 cm. in the anterior-posterior diameter through the lower abdomen and pelvis. The patient had a stage III carcinoma of the cervix. The cervix was replaced by a nodular bleeding tumor that extended to the left fornix. There was extension of the tumor to the right side wall of the pelvis through the parametrium, with involvement of the utero-sacral ligament. On the left side the extension was less marked.

Figure 2 shows the contour through the suprapubic region with a superimposed isodose chart for a field 13.5 cm. in diameter, at a target-skin distance of 190 cm. The radiologists said they wanted to treat a volume of tissue involving a 13.5-cm. cylinder with its lower edge at the lower edge of the symphysis and extending in an anterior-posterior direction from 5 cm. in front of to 5 cm. behind the cervical os. The physicist showed that, by a single field from behind, a volume of this extent could be treated in its periphery to the desired dose (1.00) if the center of the volume could tolerate 7% more (1.07). The fall-off in dose level is shown in the chart. The estimated tumor region was given a minimum of 6000 rads and a maximum of 6420 rads in 6 weeks. Since the cervix and structures close to it received 6420 rads in 6 weeks, it was decided that no additional radium treatment should be given unless later examination showed that it was needed.

Four and one-half months after the beginning of therapy all visual and palpable evidence of the cancer was gone and vaginal smears were negative for cancer cells. This patient was sent to us by a radiologist because he felt that he could not treat her adequately through her fat. The surgeons did not want to operate because of the fat and because the disease was too advanced. With the 70-Mv x-rays there was no problem in delivering the selected dose. The end is not yet – but the patient is comfortable and the disease is at least temporarily controlled.

Patient RL 10 is presented as an example of thorough irradiation of the entire true pelvis by x-rays alone (no radium) in a stout patient with advanced disease. This patient was 78 years old, 24 cm. thick, and had a stage IV squamous cell carcinoma of the uterine cervix. The anterior wall of the vagina was infiltrated down to within 1.5 cm. of the urethral meatus. There was bilateral parametrial involvement

extending to the side walls. By rectal examination a mass had been felt in the cul-de-sac, and by cystoscopy edema of the floor of the bladder was seen, but no actual tumor invasion. Because of the extent of the disease it was decided to treat her by external irradiation alone and, to deliver a thorough dose throughout the pelvic cavity, 70-Mv x-rays were selected. For part of her treatments she was treated through four fields, anterior, posterior, and both laterals, but later it was found that two fields, one anterior and one posterior, would do as well (Fig. 3). She was given 5250 rads to the 1.00 level, with a maximum dose in the tumor of 6020 rads. The level of 5250 or more rads was achieved from 4.5 cm. below the anterior surface to the same distance inside the posterior surface.

Nineteen months after the commencement of therapy the patient is without evidence of disease and is very comfortable. This patient had relatively little general reaction throughout the treatment period. The external surfaces showed only mild changes during or after the irradiation. She had some diarrhea and dysuria – but not incapacitating. With only external irradiation, an advanced carcinoma of the cervix has at least temporarily disappeared.

Patient RL 21 (Fig. 4) is presented to demonstrate how the region of maximum absorption can be moved nearer one surface of the body than the other when a two-field technique is used. This patient had a squamous cell carcinoma in the right upper lobe of the lung so close to the mediastinum that a field was selected to include the mediastinal glands centering 2 cm. to the right of the midline. (He had involvement of supraclavicular nodes as proved by biopsy and these were treated separately by single-field radiation from the back.) The patient measured almost 20 cm. from front to back in the region to be treated. By placing 3 cm. of bolus over the anterior field the point of maximum dosage moved to 9 cm. – instead of 12 cm. – behind the anterior wall. Thus the region treated with the planned dose was in front of the bodies of the vertebrae and extended to near the posterior surface of the sternum. The periphery of the tumor area absorbed 5250 rads in 34 days, the maximum absorbed dose being 5420 rads in the center of the tumor region. The supraclavicular lymph nodes were given 5250 rads in 34 days from their separate field.

The patient had no dysphagia. He became very fatigued and somewhat nauseated toward the end of treatment and for a few weeks after treatment stopped. The skin of the anterior field where there had been 3 cm. of bolus developed a dry desquamation. Seventeen months after beginning treatment, he is carrying on his regular occupation as a salesman. He is not as well as before developing cancer, but the lesion appears to be under control temporarily.

The contour and isodose curves for patient RL 41 are presented as Fig. 5 to show how by a single anterior oblique field it was possible to treat the anterior mediastinum and the region of the lingula of the left lung, and yet avoid a large dose to the spinal cord. The patient, a 72-year-old man, had a carcinoma of the lingula diagnosed by roentgenograms plus a positive cytology finding in the sputum examination. He was a poor

surgical risk, with severe dyspnea. The region within the 1.00 line received 6000 rads in 47 days. It is only six months since he started his treatments – but he was considerably relieved by the treatments. It would appear now that the tumor is probably spreading beyond the treated region.

Patient RL 46 (Fig. 6) demonstrates a special use of the ability to deliver large doses to considerable depths. This patient, a 60-year-old woman, had been treated for uterine fibroids in such a way as to cause destruction of the skin over the lower abdomen anteriorly and the sacrum posteriorly. She had had skin grafts placed to cover these areas of destruction. In June of 1955 the patient was found to have an adenocarcinoma of the endocervix. To avoid further irradiation, the surgeons operated on her and removed what they could. In late 1957 she was found to have a recurrence and was told nothing could be done. In January, 1958, her radiation therapist sent her to the Radiological Laboratory to see if we could treat her without affecting the grafted areas anteriorly and posteriorly.

The contour and isodose curves (Fig. 6) show that the planned dose (1.00 = 5200 rads) was delivered to a region 15 cm. wide and 8 cm. deep through the pelvis with less than 10% of this amount to the anterior surface and none to the posterior surface. The dose was delivered in 26 separate sittings in 36 days.

These treatments were finished on March 7, 1958. So far there has been some decrease in the palpable cancerous infiltration but it has not disappeared. This patient, however, would have been given only supportive therapy if it had not been possible to deliver the large dose to the middle of the pelvis through the lateral fields.

The last two patients to be discussed demonstrate two methods of using these multimillion-volt x-rays to treat lesions in the head and neck. Patient RL 38 had an extensive carcinoma involving the junction of the alveolar ridge, tongue, floor of the mouth, and tonsilar pillar on the right side, plus some hard nodes in the right side of the neck. The entire lesion was located on the right side, so it was necessary to deliver a high dose to all tissues beyond the midline. By treating from the left side, the contour and isodose lines (Fig. 7) show that the absorbed dose is built up to a sufficient level just to the left of the midline and this dose level extends out to the right surface. Moreover, the field could be so directed that the spinal cord received only 21% of the tumor dose. Some bolus had to be used anteriorly on the left side to level out the isodose curves in the depth.

This patient's tumor region was given a dose of 6000 rads in 43 days (peak dose of 6185 rads in center of tumor). The treatments were finished on January 28, 1958. In April, the review clinic of radiologists, rhinolaryngologist, and surgeons felt that, while there was much less infiltration, there was still tumor present. Hence a very radical surgical removal was performed. Extensive pathological study of the material removed revealed only a small "carcinoma in situ" in the tongue. The original lesion was classed as a squamous cell carcinoma, right tonsil.

The last patient to be considered, RL 36, had a squamous cell carcinoma of the hard palate that extended across the midline, involving both tonsilar regions. Hence it was necessary to give a "tumor dose" throughout the whole posterior two-thirds of the palate and both lateral walls of the pharynx. Figure 8 shows that this was accomplished by using two lateral fields and by placing 7 cm. of bolus on both sides. The patient was given 5242 rads throughout the "tumor region" in 39 days, ending eight months ago. At the present time the tumor seems to have disappeared and the central ulcerated area has healed. This is a remarkable result even should it be only temporary.

Discussion

The number of patients treated on the synchrotron is not large enough and the time since starting treatments is not long enough to permit any statistical study of results. However, Table I does give some indication of what is happening. Of the 67 patients who have been treated, 25 have already died – within two years of starting treatment. This high figure is to be expected when advanced cases are accepted for treatment.

Much has been learned about how the patients and their tissues react to this quality of radiation, and some individual patients, whose treatments were described above, have shown remarkably good results. RL 53, a very stout woman with advanced uterine carcinoma, is one of these. Four months after treatment her vaginal smears were negative for cancer and all physical evidence of the neoplasm had disappeared. This remarkable immediate result from external x-rays alone surprised everyone. RL 10, another woman with advanced carcinoma of the cervix, is living and well, and without detectable evidence of cancer 19 months after treatment. This result of treatment by external irradiation, without any intra-uterine radium, has surprised both the radiologists and the gynecologists. A third patient with carcinoma of the uterus, RL 46, could not have been given a real therapeutic dose by lower energy units, as mentioned above.

Some of the patients with lesions about the head and neck have also shown gratifying early results. RL 36 had an ulcerated lesion of the posterior part of the hard palate on the left side. The infiltration from this extended to both tonsils and, on the left side, to the anterior tonsillar pillar and the posterior third of the lower alveolar ridge. Six months later all evidence of the tumor was gone except for the scar over the area that had been ulcerated. RL 38 had a unilateral lesion of the region of the junction of the tongue, anterior tonsillar pillar, lower alveolar ridge, and posterior pharyngeal wall. Three months later a radical operation was performed because it was believed that, in spite of remarkable shrinkage, there was still tumor present. Pathological examination of the removed specimen showed no active malignant cells – except for one area described as "carcinoma in situ" on the surface of the tongue. The disappearance of such an extensive lesion is truly remarkable.

The recovery of the patient who has survived the longest since the start of her treatment, RL 46, is another remarkable result. She had an extensive epidermoid carcinoma of the left antrum and ethmoid sinuses, with invasive destruction of the bony walls. She was treated with a single port from the front with wax bolus over the front. She was given 4800 rads in 35 days, throughout the antral and ethmoid regions. One year after treatment, removal of the mucosa of the antrum showed some

carcinoma cells, and therefore a radical surgical procedure was undertaken – but no cancer was found in the additional material removed. It is now a year since the surgery, and she continues to be free of cancer and is very well.

While there have been many failures among the patients treated, it is believed by those observing the patients that some remarkable results are being obtained – probably the result of thorough irradiation of the whole region involved by the tumor.

Table I. Mortality Data as of July 31, 1958

Region of Cancer	Number Treated	Number Dead	Number Living	Survival Time* of Those Alive		
				> 1 yr.	6–12 mos.	< 6 mos.
Head and Neck	16	5	11	2	3	6
Lung	15	10	5	1	4	0
Urinary Bladder	10	4	6	1	1	4
Uterus–Body	4	1	3	2	1	0
Uterus–Cervix	9	1	8	1	2	5
Miscellaneous	13	4	9	1	4	4
Total:	67	25	42	8	15	19

*Time from the beginning of treatment with 70-Mv x-rays from the synchrotron.