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Expanding Options in Radiation Oncology: Neutron Beam Therapy.

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Summary.

Twelve years experience with neutron beam therapy in Britain, U.S.A., Europe and Japan shows that local control is achievable in late-stage epidermoid cancer somewhat more frequently than with conventional radiotherapy. Tumors reputed to be radioresistant (salivary gland, bladder, rectosigmoid, melanoma, bone and soft-tissue sarcomas) have proved to be particularly responsive to neutrons. Pilot studies in brain and pancreatic tumors suggest promising new approaches to management of cancer in these sites.

The availability of neutron therapy in the clinical environment opens new prospects for irradiation of "radioresistant" tumors, permits more conservative cancer surgery, expands the use of elective chemotherapy and provides a wider range of options for cancer patients.

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Introduction.

In 1920 Dr. Neville S. Finzi addressed the 5th International Congress of Surgery in Paris on "The Treatment of Tumors by Radium and X-rays" (Brit. J. of Surg., 1920, 8:68). At this early stage in the development of radiation oncology, Dr. Finzi identified four clinical applications of the new modality: radical treatment for tumor control by radiation alone, symptomatic relief, elective or prophylactic application of radiation designed to sterilize the operative site which may have been contaminated by cancer cells and radiation as an adjuvant to surgery rendering inoperable tumors resectable. He concluded that "inoperable is no longer synonymous with incurable," thus providing a new option in cancer management. Six decades have passed since these observations were made, and although at no specific point in time has any spectacular "breakthrough" been made, the total cumulative advance in the management of cancer by radiation has indeed been spectacular. Along with the improvements in the physics and engineering of high energy machines, providing more penetration and greater precision in delivery of adequate tumor doses while sparing adjacent normal tissues there has been a concomitant uninterrupted continued improvement in cancer control rates.

In the fifteen year interval between 1955 and 1970 the cure rate for many tumors has virtually doubled (Table I). At the same time the availability of higher energies has made the use of particulate radiations, including electrons and neutrons, feasible in the clinical environment. Apart from our improved understanding of radiobiology, medical physics (treatment planning), and clinical technique, the beam energy available for this purpose has increased by a factor of 1000 during the six decades under review, from some 60-100 kilovolt x-rays in the early days of this era up to 60-70 million electron volts for effective neutron beams with sufficient penetration for treatment of deep seated cancer.

Experience With Neutron Beam Therapy.

It is now 12 years since the first patients were treated with neutrons by Dr. Mary Catterall in London,[2] 7 years since the first patients were treated with neutrons in the United States[5] and 5 years since the high energy (66 MeV) Neutron Therapy Facility commenced its clinical operation,[4] yet the final answer as to the efficacy of this modality remains elusive.

The Fermilab Neutron Therapy Facility.

The Fermilab neutron beam differs in many respects from those available in other centers. The accelerator at Fermilab is primarily designed for research in high energy physics, the 66 MeV neutron beam being a convenient by-product of the operation. In this accelerator protons are accelerator through 5 stages up to a final energy of 1 million MeV (1 TeV). The first stage is the familiar Cockroft-Walton electrostatic generator providing a copious supply of protons at an initial energy of under 1 MeV, directed into a very large (150 meter) linear accelerator in which they are accelerated to an energy of 200 MeV. The 200 MeV proton beam is injected into a booster synchrotron providing an energy of 8 GeV (1 GeV = 1000 MeV), suitable for injection into the large accelerating ring (6 kilometers in circumference) within which they can be accelerated to an eventual energy of 500 GeV. The fifth and final stage of acceleration is still under construction and will entail a cryogenic superconducting magnetic system enabling the proton energy to be doubled providing the 1 TeV proton beam.

At the present time medical interest is confined to the second stage of acceleration (the linear accelerator phase) with protons up to 200 MeV in energy. For neutron beam therapy the protons are deflected by a bending magnet at a point in the accelerator where their momentum corresponds to 66 MeV. The proton beam is transported through the

intervening shielding wall and impinges on a beryllium target providing high energy neutrons suitable for radiation therapy.

The neutrons produced by the impact of high energy protons on beryllium differ in peak energy and spectral distribution from all other neutron beams hitherto used in radiation therapy, which are generally produced by deuterons (15-50 MeV). The Fermilab neutron beam has a higher penetration, better skin sparing, a sharper beam profile and a lower RBE than those employed elsewhere. Many of the newer hospital based cyclotrons planned for future neutron therapy installations will employ the high energy proton-beryllium process. These future beams will resemble the Fermilab neutron beam more closely than those generated by the previously used low energy cyclotrons. For this reason the Fermilab experience in neutron dosimetry, radiobiology and clinical response is likely to have a more immediate clinical application.[3]

International Studies.

Studies currently underway at the Fermilab Neutron Therapy Facility are listed in Table II. Our initial experience is comparable with results obtained in other centers. Table III illustrates current international

experience with epidermoid cancer of the head and neck[1,2,9] and comparable data from the Fermilab facility. In this tumor the local control rate obtained with the neutron beam appears somewhat superior to that achieved with a corresponding technique using photons, but the difference is small and statistically marginally significant. This is in sharp contrast with the highly significant results observed at Hammersmith. The exact reason for this difference remains to be determined but is clearly a vitally important question in regard to optimization of neutron beam therapy. Criteria for optimization with neutrons may well be different from those in conventional radiation therapy.

Further international experience is summarized in Table IV for tumors reputed to be radioresistant, at least to conventional radiation therapy. Here the results appear to be considerably more striking than those observed in the case of epidermoid cancer. Local control rates of the order of 70% or higher are obtained consistently in salivary gland tumors,[7] melanoma,[10] bone sarcomas[10] and soft tissue sarcomas.[2,5,10] These observations suggest that it is precisely those tumor types which are resistant to conventional radiation which tend to be most responsive to high LET radiations, in which case the availability of neutron beams could have a very significant impact on radiotherapeutic practice.

Pilot Studies (Pancreas and Brain).

Two other common radioresistant tumors have been studied at Fermilab. Carcinoma of the pancreas has been studied by treating locally advanced non-resectable tumors (without overt metastases), in patients who have had exploratory laparotomy for biopsy and bypass surgery, using 3 intersecting beams (anterior and 2 lateral fields) delivering a dose of 19.5 Gy to the pancreas.[6] Fifty patients treated in this way tolerated the treatment well, all showed immediate symptomatic relief, but survival was not strikingly prolonged except in 5 patients (10% of the total) who are apparently free of tumor 1 to 2 years after irradiation. The majority of the patients have died of metastases or complications attributable either to the disease or to the treatment. In all patients examined by autopsy the tumor had demonstrably regressed and was replaced by a massive fibrosis of the pancreas within which residual microscopic foci of apparently viable tumor could be identified. Whether these foci would have recurred or eventually regressed is not known. In addition many patients showed severe radiation changes in the stomach and adjacent bowel. A further series of patients treated at a higher dose (22.5 Gy) showed a higher incidence of complication but no improvement in survival. It is concluded that a neutron dose of 19.5 Gy delivered in 13 fractions over 6 weeks remains the best available treatment we have to offer for this condition.[8]

A new approach to management of high grade astrocytoma (glioblastoma multiforme) has been developed and 40 patients have been entered on a pilot study. It had previously been shown that neutrons could be effective in ablating malignant brain tumors but did little to improve survival because of the intolerance of normal brain for this form of radiation. In Fermilab we evaluated the combined effect of neutron therapy with reduced fractionation (6 once weekly fractions) together with the hypoxic cell radiosensitizer Misonidazole. Initial observation suggests that survival has been markedly extended with this technique, but the specific contributions of the changed fractionation and the radiosensitizer remain to be evaluated by a controlled clinical trial.

Conclusions.

It seems clear from the results described that neutron beam therapy provides a series of new options in the field of radiation oncology and consequently will have an important role to play in the future of this specialty. In spite of the obvious limitations of all existing equipment, which was primarily designed for research in particle physics rather than for medical applications, the results with neutron beam therapy in almost all tumor sites studied are at least as good if not substantially better than the best obtainable with conventional beams. A wide variety of tumor types, reputed to be "radioresistant" can be ablated without significant side effects by the use of appropriately planned neutron beam therapy. These tumors have hitherto been treated exclusively by surgery or by mixed modality procedures (pre-operative irradiation and wide resection). The availability of neutron beam generators in the clinical environment provides another option in the management of patients with radioresistant tumors.

Neutron beam therapy could provide equally effective local control while avoiding the functional and cosmetic disturbance of cancer surgery. Patients suitable for this approach are those with late stage cancers of the head and

neck, advanced salivary gland tumors, sarcomas of bone and of soft tissue, non-resectable melanoma and locally advanced tumors of the pelvis (carcinomas of uterus, bladder, prostate and rectosigmoid).

The impact of the new modality is fourfold: (1) Neutrons expand the scope of radiation therapy to include intrinsically radioresistant tumors hitherto considered unsuitable for irradiation; (2) Where tumor ablation can be accomplished by irradiation alone, new procedures for conservative or corrective surgery become feasible; (3) With improved control of local disease, neutrons expand the role of elective chemotherapy for the prevention or retardation of metastatic growth; and (4) Neutrons expand the range of options available to the cancer patient who may wish to consider conservative treatment with the new modality as a possible alternative to radical surgery.

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Table I

Improved Survival of Several Types of Cancer When Treated With Megavoltage Radiotherapy.
(From Committee on Labor and Public Welfare 1970)

Type of cancer	Representative: With kilovoltage X-rays (1955)		Representative: With megavoltage X-rays (1970)	
Hodgkin's disease	30	35	70	75
Cancer of the cervix	35	45	55	65
Cancer of the prostate	5	15	55	60
Cancer of the nasopharynx	20	25	45	50
Cancer of the bladder	0	5	25	35
Cancer of the ovary	15	20	50	60
Retinoblastoma	30	40	80	85
Seminoma of the testis	65	70	90	95
Embryonal cancer of the testis	20	25	55	70
Cancer of the tonsil	25	30	40	50

Table II

Current Studies (Fermilab)

1. Squamous cell carcinoma of the cervix, stages IIB, IIIA, IIIB, IVA. Para-aortic nodes negative or equivocal on lymphangiogram.

2. Squamous cell carcinoma of the head and neck, stages T2, T3, T4, with any N stage. Inoperable, or pre/post surgery.

3. Adenocarcinoma of the prostate, clinical stage C.

4. Transitional or squamous cell carcinoma of the bladder, stage B1 (grade III or IV), or B2, C, D1 (any grade) to be treated with or without planned surgery.

5. Squamous cell carcinoma of the esophagus, lesions smaller than 15 cm in length, without fistula or sinus track.

6. Non-oat cell cancers of the lung or bronchi. Chemotherapy is optional after neutron therapy.

7. Supratentorial glioma, grade III or IV (with or without misonidazole).

8. Adenocarcinoma of the pancreas. Chemotherapy optional.

9. Salivary gland tumors, inoperable, unresectable, or recurrent, stages I to IV.

10. Metastatic melanoma in skin, subcutaneous tissue or peripheral lymphatics (measurable lesions).

11. Bone sarcomas (osteo- and chondrosarcoma).

12. Soft-tissue sarcoma.

Table III

Local Control in Epidermoid Carcinoma.

HEAD & NECK	PHOTONS			NEUTRONS		
	Treated	Controlled	Complications	Treated	Controlled	Complications
Hammersmith (15 MeV)	63	12	3	70	53	12
Amsterdam (D-T)	13	7	1	41	22	5
Houston (50 MeV)	41	18	3	49	23	10
Fermilab (66 MeV)	73	32	4	51	28	11
TOTAL	190	69	11	211	126	38
Local Control Rate		36%			60%	
Complication Rate		6%			18%	
*Probability of Uncomplicated Control		34%			49%	

* = Prob. Uncompl. Contr.= (Contr. Rate)x(1-Compl. Rate)

Table IV

Local Control in Radioresistant Tumors.

[(a) Local Controls; (b) Cases Studied]

		(a) : (b)
1. SALIVARY TUMORS	Hammersmith	25 : 31
	Houston	8 : 13
	Amsterdam	10 : 11
	Seattle	7 : 11
	Fermilab	11 : 15
	TOTAL	61 : 81 (76%)
2. SARCOMAS OF BONE	MANTA	6 : 7
	Chiba	15 : 18
	Fermilab	5 : 10
	TOTAL	26 : 35 (74%)
3. SOFT TISSUE SARCOMA	Amsterdam	8 : 13
	Houston	20 : 29
	Hammersmith	23 : 28
	MANTA	4 : 7
	Chiba	5 : 7
	Fermilab	7 : 13
	TOTAL	67 : 97 (70%)
4. MELANOMA	Chiba	12 : 14 (86%)
5. RECTOSIGMOID (UNRESECTABLE)	Amsterdam	14 : 25 (56%)
6. BLADDER (UNRESECTABLE)	Amsterdam	11 : 22
	Fermilab	4 : 6
	TOTAL	15 : 28 (54%)

(See Ref. 5)