International Atomic Energy Agency

INDC(NDS)-216/GZ

INDC INTERNATIONAL NUCLEAR DATA COMMITTEE

NUCLEAR DATA NEEDED FOR NEUTRON THERAPY

SUMMARY REPORT

Second Research Co-ordination Meeting

organized by the
International Atomic Energy Agency

Vienna, 24 - 27 January 1989

Prepared by

K. Okamoto
IAEA Nuclear Data Section

March 1989

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Abstract

The Second Research Co-ordination Meeting (RCM) of the IAEA Co-ordinated Research Programme (CRP) on Nuclear Data Needed for Neutron Therapy was convened by the IAEA Nuclear Data Section, in Vienna, from 24 to 27 January 1989. The Summary Report of the First RCM was issued as INDC(NDS)-203/GZ (March 1988). Special emphasis was put on the discussion on the issue of the final publication of this CRP.

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Full Report

1. Introduction

Neutrons are most widely used in radiotherapy among the high LET radiations. Fast neutron therapy is applied today routinely in about 20 centres world-wide. More than 10000 patients have been treated with neutrons, either as the sole irradiation or in combination with other radiotherapy techniques. The available radiobiological and clinical data indicate that the dose response curves for tumor control and normal tissue complications are as steep for neutrons (or high-LET radiations) as for photons (or low-LET radiations). The same accuracy in dose delivery and in physical selectivity is to be achieved. To reach this goal, basic physical data are still missing in the range of the high-energy neutrons which are used at present in neutron therapy. In particular, information is required on the following aspects:

1) Evaluation of Kerma and absorbed dose in different human (or biological) tissues.

2) Determination of the response of different detectors (kerma and absorbed dose in the detector materials).

3) Optimization of the collimation and shielding systems and improvement of the physical selectivity.

This CRP together with the complementary new CRP on Atomic and Molecular Data for Radiotherapy is planned to fulfill the physical data requirements for radiotherapy.

2. Organization of the Meeting

The Second Research Coordination Meeting (RCM) of the participants of the IAEA CRP on Nuclear Data Needed for Neutron Therapy was convened by the IAEA Nuclear Data Section at the IAEA Headquarters in Vienna during the week 24-27 January 1989.

This RCM was chaired by Roger M. White, Lawrence Livermore National Laboratory, USA, and Koichi Okamoto was the Scientific Secretary.

The agenda of the meeting is listed in Appendix I, the nine CRP participants and one observer who attended the meeting are listed in Appendices II and III. This CRP consists of nine Research Agreements. Three participants of this RCM also attended the RCM on Atomic and Molecular Data for Radiotherapy held in the following week.

3. Reports by the Participants of the Second RCM

Nine CRP participants reported on their performance during the period and the proposed programme for the next period; thse reports are summarized in Appendix IV.

In addition to the reports on their performance, a lecture on the "Present status of fast neutron therapy survey of the clinical data and of the clinical research programmes" was given by A. Wambersie. His lecture is a useful presentation on the scope of this CRP and his paper is attached to this interim report.

4. Summary and outline of the final report

There is no need to repeat here the summary described in the previous interim report, INDC(NDS)-203/GZ (March 1988), but if anyone would be interested to read it, to please contact the IAEA Nuclear Data Section.

5. Results of the Second RCM (summarized by the Chairman)

This meeting concentrated on the organization of a Final Technical Report to be issued after the 3rd and final RCM which will be held in 1991 in Belgium. The emphasis of this report will be to provide up-to-date information on the status and needs of nuclear data for neutron therapy. It is intended to be of use to both the radiation therapist who needs this information and to the nuclear physicist who must produce it. As such, this report is intended to help further bridge the gap between the nuclear therapist and nuclear physicist.

The following outline is structured to:

(1) provide the driving force by demonstrating the success of neutron therapy,

(2) provide an overview of the current protocols, and

(3) to demonstrate how the dose delivery to patients can be improved by on-going and new experimental measurements and theoretical calculations of nuclear data.

The outline of Final Report and time frame adopted, including assignments of working groups and dates of rough draft delivery to Koichi Okamoto, IAEA, are as follows:

I. INTRODUCTION: WAMBERSIE, MENZEL, 1 March 1989

- to include brief summary of problems encountered when going from photons to low energy neutrons and then to high energy neutrons.

II. STATUS/SUCCESS of NEUTRON THERAPY: WAMBERSIE, 1 March 1989

III. OVERVIEW OF PROTOCOLS: BROERSE, 1 March 1989

- DIETZE and MENZEL to meet with BROERSE in March 1989 for further discussions

IV. OPTIMIZATION OF DOSE DELIVERY

- to include problems, priorities, new measurements, etc.
- (also Research results of IAEA contracts)

A. Sources of neutrons: p+Be and d+Be
20 MeV to 100 MeV

WHITE, HAIGHT, OLSSON, DELUCA, January 1990

Known information available:

(1) ICRU Report (WAMBERSIE) - complete to OKAMOTO → WHITE
only neutron source part to others - SOON

(2) DATA from DIETZE - SOON

(3) JONES in South Africa via DELUCA - SOON

(4) IAEA report on p+Be - in hand (INDC(NDS)-153/L)

(5) IAEA report on neutron sources - in hand (IAEA-TECDOC410)

B. Collimation and Transport

HAIGHT, OLSSON, DELUCA, WHITE, January 1990

(1) Sources of TRANSPORT codes

Los Alamos, Livermore, DIETZE to inquire with Cierjacks, OLSSON to inquire with the NEA DATA BANK

(2) Status of nuclear data needed for shielding, collimation, and transport calculations

C. Microscopic Data and Kerma

((1) DATA - DIETZE, OLSSON, HAIGHT, WHITE*, January 1990
(
(* Note: Contribution from Howerton on KERMA CALCULATIONS
** (FROM DATA BASE, including energy conservation, etc.
(
((2) KERMA - DELUCA, MENZEL, DIETZE, HIRAOKA (KAWASHIMA),
(ZOETELIEF, with help from Dr. Wambersie's staff

** Note: Include new (n,n), (n,n') data from Dietze, Ohio Univ., also Axton evaluation, J.J. Coyne data?

V. CONCLUSIONS - to be written by a group at the final meeting (3rd RCM) in 1991

APPENDICES: Tables of necessary data, including KERMA FACTORS, etc.

The names underlined are persons in charge.

PRESENT STATUS OF FAST NEUTRON THERAPY SURVEY OF THE CLINICAL DATA AND OF THE CLINICAL RESEARCH PROGRAMMES

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Abstract

The clinical results reported from the different neutron therapy centres, in USA, Europe and Asia, are reviewed. Fast neutrons were proven to be superior to photons for locally extended inoperable salivary gland tumours. The reported overall local control rates are 67 % and 24 % respectively. Paranasal sinuses and some tumours of the head and neck area, especially extended tumours with large fixed lymph nodes, are also indications for neutrons. By contrast, the results obtained for brain tumours were, in general, disappointing. Neutrons were shown to bring a benefit in the treatment of well differentiated slowly growing soft tissue sarcomas. The reported overall local control rates are 53 % and 38 % after neutron and photon irradiation respectively. Better results, after neutron irradiation, were also reported for bone- and chondrosarcomas. The reported local control rates are 54 % for osteosarcomas and 49 % for chondrosarcomas after neutron irradiation; the corresponding values are 21 % and 33 % respectively after photon irradiation. For locally extended prostatic adenocarcinoma, the superiority of mixed schedule (neutrons + photons) was demonstrated by a RTOG randomized trial (local control rates 77% for mixed schedule compared to 31 % for photons). Neutrons were also shown to be useful for palliative treatment of melanomas. Further studies are needed in order to definitively evaluate the benefit of fast neutrons for other localisations such as uterine cervix, bladder, and rectum. It can be concluded that fast neutrons are superior to photons for at least 10 % to 20 % of the radiotherapy patients. As far as the technical point of view is concerned, it is recognized that the first patient series were treated in "suboptimal" conditions. However, recently, important improvements were made. In particular, several high-energy hospital-based cyclotrons are now fully dedicated to neutron therapy. It is likely that these improved technical conditions will further extend the indications of fast neutrons. Some technical and dosimetric problems still remain to be investigated : they are part of the justifications of the coordinated research programme on "Nuclear data needed for neutron therapy" initiated by the IAEA .

Introduction

Fast neutrons therapy is applied today routinely in 17 centres throughout the world (**Table I**). More than 10 000 patients have been treated so far with neutrons, either as the sole irradiation modality or in combination with other radiotherapy techniques. The available clinical data now enable us to identify some of the best indications of fast neutrons, as well as to discuss other tumour sites for which neutrons could possibly bring a benefit.

TABLE I

THE NEUTRON THERAPY FACILITIES IN THE WORLD		
Centre	Neutron Producing Reaction	Comments
EUROPE		
MRC-Clatterbridge, U.K.	p(62)+Be	rotational gantry variable collimator
Orléans, France	p(34)+Be	vertical beam
UCL- Louvain-la-Neuve, Belgium	p(65)+Be	vertical beam (multileaf collimator and horizontal beam in preparation)
Hamburg, Fed.Rep.Germany	(d + T)	rotational gantry
Heidelberg, Fed.Rep.Germany	(d + T)	"
Munster, Fed.Rep.Germany	(d + T)	"
Essen, Fed.Rep.Germany	d(14)+Be	rotational gantry
UNITED STATES		
M D Anderson- Houston, Texas	p(42)+Be	rotational gantry variable collimator
Cleveland, Ohio	p(43)+Be	horizontal beam
UCLA - Los Angeles	p(46)+Be	rotational gantry variable collimator
Seattle, Washington	p(50)+Be	rotational gantry multileaf collimator
Fermilab	p(66)+Be	horizontal beam
ASIA		
National Institute of Radiological Sciences (NIRS) - Chiba, Japan	d(30)+Be	vertical beam multileaf collimator
Institute for Medical Sciences (IMS) - Tokyo, Japan	d(14)+Be	horizontal beam
Korea Cancer Center Hospital (KCCH) - Seoul, Korea	d(50.5)+Be	rotational gantry
King Faisal Hospital - Riyadh, Saudi Arabia	p(26)+Be	rotational gantry
AFRICA		
National Accelerator Centre (NAC) Faure, Rep.South Africa	p(66)+Be	rotational gantry variable collimator

From ICRU [22] and Tsunemoto et al. [34]

Salivary gland tumours

Locally extended inoperable salivary gland tumours are the first type of tumours for which the superiority of fast neutrons, compared to conventional low-LET radiation, has been recognized.

TABLE II

NEUTRON THERAPY OF SALIVARY GLAND TUMOURS LOCO-REGIONAL CONTROL RATE VERSUS TUMOR HISTOLOGY (minimum one year follow-up)		
Tumor histology	Number of patients	Loco-regional control (%)
Adenoid cystic	17	15
Mucoepidermoid	9	6
Malignant mixed	2	2
Undifferentiated	4	3
Overall	32	26 (81 %)

Modified from Griffin et al. (1988) [16].

Already in 1979, Griffin reported promising results [17].In Europe, the 2 most important series were obtained in Hammersmith [10] and in Amsterdam [4], with persistent local controls of 77 % and
66 % respectively. These results were confirmed by the recent publication of the Seattle data (**Table II**) [16]. A the NIRS, 21 patients with inoperable or recurrent parotid gland tumour were treated with fast neutrons : local control was achieved in 13 cases (62 %). In addition, 14 patients were treated after radical surgery : no local recurrence was observed. On the total number of 35 patients treated with neutrons, 4 complications were scored [34].

A recent review of all the patient series treated worldwide (**Table III**) indicates a overall local control rate of 67 %, while the overall local control rate for "similar" patient series treated with low-LET radiation (photons, electrons, implants) reaches only 24 % [20]. However, such a comparison of historical series is always questionable and only a randomized trial can bring a definite conclusion.

A prospective randomized trial for inoperable primary or recurrent malignant salivary gland tumours was initiated by the RTOG in 1980 (**Table IV**).. The loco-regional control rates at 2 years were 67 % for neutrons and 17 % for photons. Although, the numbers of patients were small (13 and 12 respectively), the study was closed in 1986 - for ethical reasons -, when the statistical significance of the difference between treatments became apparent ($p < 0.005$) [20]. One should point out that the local control rates observed in the randomized study are very similar to the average local control rates reported in the historical series

Taken as a whole, the results of the non-random clinical studies and the prospective randomized trial overwhelmingly support the contention that fast neutrons offer a

TABLE III

REVIEW OF THE LOCO-REGIONAL CONTROL RATES FOR MALIGNANT SALIVARY GLAND TUMOURS TREATED DEFINITIVELY WITH RADIATION THERAPY

FAST NEUTRONS

Authors	Number of patients *	Loco-regional control (%)
Saroja et al., 1987	113	71 (63 %)
Catterall and Errington,1987	65	50 (77 %)
Battermann and Mijnheer, 1986	32	21 (66 %)
Griffin et al., 1988	32	26 (81 %)
Duncan et al., 1987	22	12 (55 %)
Tsunemoto et al. (in press)	21	13 (62 %)
Maor et al., 1981	9	6
Ornitz et al., 1979	8	3
Eichhorn, 1981	5	3
Skolyszewski, 1982	3	2
Overall	310	207 (67 %)

LOW-LET RADIOTHERAPY PHOTON AND/OR ELECTRON BEAMS, AND/OR RADIOACTIVE IMPLANTS

Authors	Number of patients *	Loco-regional control (%)
Fitzpatrick and Theriault,1986	50	6 (12 %)
Vikramet et al., 1984	49	2 (4 %)
Borthne et al., 1986	35	8 (23 %)
Rafla, 1977	25	9 (36 %)
Fu et al., 1977	19	6 (32 %)
Stewart et al., 1968	19	9 (47 %)
Dobrowsky et al., 1986	17	7 (41 %)
Shidnia et al., 1980	16	6 (38 %)
Elkon et al., 1978	13	2 (15 %)
Rossman, 1975	11	6 (54 %)
Overall	254	61 (24 %)

* Patients treated de novo and for gross disease after a post-surgical recurrence are included, but not patients who were treated postoperatively for microscopic residual disease.

Updated from B.R.Griffin et al. [16] and T.W. Griffin et al. [20]

TABLE IV

NEUTRON THERAPY OF INOPERABLE SALIVARY GLAND TUMOURS. RESULTS OF A RTOG/MRC PROSPECTIVE RANDOMIZED TRIAL		
	Photons	Neutrons
Number of evaluable patients	12	13
Loco-regional control		
at 1 year	17 % ± 11	67 % ± 14
at 2 year	17 % ± 11	67 % ± 14
Survival		
at 1 year	67 % ± 12	77 % ± 12
at 2 year	25 % ± 14	62 % ±14

Modified from Griffin et al. 1988 [20]

significant advance in the treatment of inoperable and unresectable primary or recurrent malignant salivary gland tumours.

Paranasal sinuses

Remarkably good results have also been observed with neutron therapy for locally extended tumours of the paranasal sinuses. In the series treated at the Hammersmith Hospital, 86 % (37/43) of the patients showed complete remission and relief of symptons was noticed in all cases. Thirty percent of the patients survived at 3 years with a 50 % local control rate [14].

Several factors could explain these interesting results, indicating that paranasal sinuses could be a good indication for neutron therapy :

- the superficial location of these tumours;

- the diversity of differentiated histology : in the Errington's series, there were 14 squamous cell carcinomas, but also 11 adenoid-cystic carcinomas and 8 adenocarcinomas;

- the presence of bone structures, in or near the target volume, which reduces the absorbed dose to the cells located in the osseous cavities [8].

Other head and neck tumours

Conflicting results have been reported, in Europe, for neutron therapy of advanced squamous cell carcinomas of the head and neck. The first study conducted by Catterall [9] showed a highly significant advantage of neutrons over photons with respect to local control and survival. However, these results were not substantiated in a european multi-centre randomly controlled trial. The disease-free survival rate at 12 months was 34 % (34/100) for the neutron- and 38.9 % (37/95) for the photon group. The recurrence rates were 37 % and 39.7 % respectively [11].

In Japan, 13 patients with tumour of the supraglottis were treated with fast neutrons at the NIRS. A local control was reported in 11 cases (84 %), while, with photons for similar patients, local control was achieved in only 25 % of the cases. In the same centre, no difference in local control after neutron or photon irradiation was reported for carcinoma of the glottis and subglottis [34].

In the United States, a RTOG trial with small patient numbers revealed a local control of 52 % (12/23) for the neutron group, compared with 17 % (2/12) for the photon group ($p = 0.035$). The actuarial survival rate at 2 years was 25 % in the neutron group and 0 % in the photon group [18] . Another RTOG trial did not show any difference in the control of the primary tumour and survival rates when comparing photon- and mixed schedule (neutrons and photons) irradiations. Despite this, the persisting local control rate of lymph node metastases was 69 % (115/167) in the mixed schedule group and 55 % (76/139) photon group ($p = 0.024$) [19]. The survival rate in the group of patients with complete clearance of cervical adenopathy was significantly higher than in the group with persisting nodes. A similar difference of 12.5 % in favour of the neutron treated patients was found in the Edinburgh series for the local control of lymph nodes metastases of more than 3 cm in diameter [13].

It seems reasonable to conclude that fast neutrons can bring a significant benefit in well defined patient series with tumours in the head and neck area, especially locally advanced tumours and fixed metastatic lymph nodes. However, there is no argument at present for recommending neutron therapy as a general treatment policy for all tumours of the head and neck area. In particular, it seems reasonable to keep the classical treatments for tumour types which are efficiently controlled with photons (such as T_{1-2} tumours of the larynx).

Brain tumours

The marked radioresistance of the majority of brain tumours of the adult to photon irradiation was the rationale for treating them with fast neutrons. No prolongation of survival and no benefit in terms of quality of life was observed for the neutron treated patients. This was observed in most of the centres, and underlines the high RBE of normal CNS, which obviously prevents to achieve a sufficient therapeutic gain factor for brain tumours [32].

Recently, using neutron boost, Breteau, in Orleans, observed a slight improvement in survival for grade IV astrocytoma for non-operated patients, and for patients who had incomplete resection [6].

At the NIRS in Japan, grade III (15 patients) and grade IV (22 patients) astrocytomas were treated with fast neutrons either as mixed schedule or as boost. Cumulative 5 year survivals of 36 % and 16 % respectively were reported [34]. The corresponding survival rate for grade IV astrocytoma in the Brain Registry in Japan is 9.8 %. Malignant meningioma is also considered as a good indication for fast neutrons at the NIRS.

As far as differentiated tumours of the spinal cord are concerned, Schmitt reported the result obtained for 10 extensive and inoperable low grade astrocytomas [30]. These patients were treated in Essen between 1980 and 1986 with neutron doses of 8 Gy in 10 fractions. Objective neurological improvements were seen in 6 cases with follow-up periods of 12 - 71 months. Complete remission occured in 2 of them and no change of symptoms in 2 other patients. Two patients deceased from progressive disease. This pilot study will be continued to find out the optimum dose for long term control .

Sarcomas of soft tissues, bone and cartilage

Soft tissue sarcomas were treated in most of the neutron therapy centres, mainly because they are often resistant to X-rays and, also, because of the excellent results reported from Hammersmith [8].When evaluating the results of neutron therapy, comparison with historical series should be made very carefully, since the series could differ by histology, degree of differentiation, local extent, localization, etc.... Furthermore, patient recruitment is influenced by the general treatment policy in a given centre (i.e.the relative place of surgery and/or chemotherapy). Therefore, randomized trials would be needed but were difficult to achieve so far.

The largest patient series were treated in Essen. Neutrons only were used first and a 76.5 % local control rate was achieved. However, a high percentage of complications was observed (22 %), which could be related to the poor beam penetration and the high skin doses. Therefore, later on, neutrons alone were abandoned and neutrons were applied as boost : the local control rate was then 61.9 % and the complication rate was reduced down to 15 %. The results of this study are reported in detail by Schmitt et al. in these proceedings [33].

A review of the results reported from the different centres (**Table V**) indicates an overall local control rate after neutron therapy of 53 % for inoperable soft tissue sarcomas. This value is higher than the value of 38 % currently observed after low-LET radiation for similar patients series [23] [24].

As far as primary bone tumours are concerned, conventional radiotherapy generally fails to control bulky tumours, as appropriate doses inevitably induce osteoradionecrosis. The low neutron kerma in bone reduces the absorbed dose by 25 % or more to cells in osseous cavities [8] and allows to applicate adequate doses with a reduced probability of late normal bone injury. Hence, differentiated primary bone tumours of the adult were part of many clinical neutron programmes.

The review of the published data indicates that for 88 patients with osteosarcoma treated at different institutions, a persisting local control of 54 % (52/97) was achieved [23] [28] . Most of these patients had inoperable tumours or refused amputation (**Table VI**). Due to the large treatment volumes and often preceeding chemotherapy, a complication rate up

TABLE V

REVIEW OF THE LOCAL CONTROL RATES FOR SOFT-TISSUE SARCOMAS TREATED DEFINITIVELY WITH RADIATION THERAPY			
NEUTRONS			
Institutions	Number of patients *	Local control (%)	
Essen + Heidelberg,1983	60	31 (52 %)	
Hammersmith, 1987	50	26 (52 %)	
Hamburg, 1987	45	27 (60 %)	
TAMVEC, 1980	29	18 (62 %)	
Fermilaboratory, 1984	26	13 (50 %)	
Seattle, 1986	21	15 (71 %)	**
Louvain-la-Neuve, 1982	19	4 (21 %)	
Amsterdam, 1981	13	8 (61 %)	
NIRS, 1979	12	7 (58 %)	
Edinburgh, 1986	12	5 (42 %)	
MANTA, 1980	10	4 (40 %)	
Overall	297	158 (53 %)	
PHOTONS/ELECTRONS			
Institutions	Number of patients *	Local control (%)	
Tepper & Suit, 1985	51	17 (33 %)	
Duncan & Dewar, 1985	25	5 (20 %)	
McNeer et al., 1968	25	14 (56 %)	
Windeyer et al., 1966	22	13 (59 %)	
Leibel et al., 1983	5	0 (33 %)	
Overall	128	49 (38 %)	

* Patients treated de novo or for gross disease after surgery are included but not patients treated postoperatively for microscopic residual disease or for limited macroscopic residual disease.

** Two-year actuarial data

Modified from Laramore et al., [23] [24].

TABLE VI

REVIEW OF THE LOCAL CONTROL RATES FOR OSTEOSARCOMAS AFTER NEUTRON- AND PHOTON THERAPY *		
NEUTRONS		
Institutions	Number of patients	Local control (%)
NIRS	41	33 (80 %)
Essen	24	12 (50 %)
Seattle	13	3 (23 %) +
Fermilab	9	2
Edinburgh	5	1 ++
Amsterdam	3	0 ++
MANTA	1	1
M D Anderson Hospital	1	0
Overall	97	52 (54 %)
PHOTONS		
Institutions	Number of patients	Local control (%)
De Moor	43	9 (33 %)
Beck et al.	21	1 (5 %)
Tudway	9	5
Overall	73	15 (21 %)

* Patients treated post-operatively for microscopic residual disease or for limited macroscopic residual disease are not included.

\+ Two year actuarial data.

++ Persistant mass and calcification treated as failure.

Modified from Richter et al., 1984 [28] and Laramore et al., [23].

TABLE VII

REVIEW OF THE LOCAL CONTROL RATES FOR CHONDROSARCOMAS AFTER NEUTRON- AND PHOTON THERAPY *		
NEUTRONS		
Institutions	Number of patients	Local control (%)
Fermilab	16	9
MANTA	9	7
Seattle	9	4 +
Amsterdam	6	0 ++
Edinburgh	5	0 ++
M D Anderson Hospital	4	4
NIRS	2	1
Overall	51	25 (49%)
Institutions	Number of patients	Local control (%)
PHOTONS		
Princess Margaret Hospital	20	7 (35 %)
M D Anderson Hospital	10	3 (30 %)
Overall	30	10 (33 %)

* Patients treated post-operatively for microscopic residual disease or for limited macroscopic residual disease are not included.

\+ Two year actuarial data.

++ Persistant mass and calcification treated as failure.

Modified from Richter et al., 1984 [28] and Laramore et al., [23].

to 36 % was registered [31]. An overall local control rate of 21 % after photon irradiation is currently reported for similar patient series.

As far as differentiated chondrosarcomas are concerned, the review of the % results reported from the same institutions indicates a persisting local control after neutron therapy in 49 % (25/51) of the patients [23] [28]. This value compares well with the 33 % (10/30) local control rate achieved after photon irradiation (**Table VII**). Debulking surgery followed by appropriate neutron- or neutron-boost irradiation then may become an alternative to ablative or mutilating surgery.

In conclusion, fast neutrons may be considered the best radiation quality for differentiated, slowly growing, soft tissue sarcomas, and for locally extensive inoperable or recurrent tumours. A similar conclusion applies to osteosarcomas and chondrosarcomas.

Prostatic adenocarcinomas

Prostatic adenocarcinomas, having in general a long doubling time, should be a good indication for neutron therapy taking into account the available radiobiological data [1]. In fact, the benefit of neutron therapy was rapidly recognized in several centres and initially, in Hamburg, by Franke [15]. Excellent results were also achieved at Louvain-la-Neuve using mixed schedule (3 neutron and 2 photon fractions per week) [27]. At NIRS, in Chiba, for prostatic adenocarcinomas Stage A2, B and C, local controls at 3 years of 3/3, 3/5 and 8/14 respectively were reported [34] .

The most convincing data are the result of a randomized trial, inititated by the RTOG, on locally advanced (C,D1) adenocarcinomas of the prostatic gland [29]. The local control rate was 77 % for patients treated with mixed schedule (55 patients) and only 31 % for patients receiving photons alone (36 patients) ($P < 0.01$). Actuarial survival rates at 8 years ("determinental" survivals, i.e. adjusted by exclusion of intercurrent deaths) were 82 % and 54 % respectively ($P=0.02$).

Of course, one has to take into account the slow natural history of prostatic adenocarcinoma and to be careful before deriving definitive conclusions. However, the clinical data at present available indicate a significant benefit for fast neutrons (used in mixed schedule) compared to the current photon irradiation modalities for locally advanced cases. The RTOG is now performing another randomized trial comparing neutrons only to conventional photon treatment.

Pelvic tumours

Neutron therapy of the tumours of the cervix, bladder and rectum has been carried out in several centres. However, the first patients series were in general treated in "suboptimal" conditions as far as the physical selectivity was concerned [2] [3] [12]. This point has to be taken into account when analysing the results and especially the complication rates.

For locally advanced cervical cancers, a randomized trial was carried out by the RTOG comparing mixed schedule (neutrons + photons) and photon only irradiation [26]. A total

number of 146 patients were analysed (stages IIB, III, and IVA with negative para-aortic nodes), 80 patients were treated with mixed schedule and 66 with photons. Tumour clearance was 52 % and 72 % for mixed schedule and photons respectively, local control at 2 years was 45 % and 52 %. Median survival was 1.9 years for mixed schedule and 2.3 years for photons; severe complications occured in 19 % and 11 % of the patients respectively. The inferior outcome with neutrons resulted from "suboptimal" technical conditions, especially the use of fixed horizontal beams. A new randomized trial using high-energy hospital-based cyclotrons with gantry-mounted beam- delivery systems has recently been activated to evaluate more rigorously the role of fast neutron therapy for advanced cervical cancers.

A similar study was performed by Tsunemoto et al. [34] at the NIRS in Japan, where 98 patients with stage IIIB squamous cell carcinoma were randomized between mixed schedule (neutrons + photons) and photons only (45 and 53 patients respectively). The local control rates were 73 % after mixed schedule compared to 66 % after photon irradiation. However, the cumulative 5 year survival was 49 % in both series. This was due, according to the authors, to the frequent involvement of the para-aortic lymph nodes in stage IIIB cancers, which could obscure the effects of the greater efficiency of neutrons for the local control of the pelvic lesions.

As far as bladder and rectal tumours are concerned, the data reported from Amsterdam and Edinburgh give no indication that fast neutrons can produce better results than photons [2] [3] [12] [13]. However, in both cases, the dose distributions achieved with neutrons were much worse than those currently achieved with photons. It could then be expected that the morbidity observed outside the target volume could be reduced in the future by using higher energy neutron beams. Preliminary results of the pilot study recently initiated in Orleans using p(34)+Be neutron beams should be mentioned [7]. For recurrent or inoperable rectal adenocarcinoma, complete tumour regression was observed in 23/31 cases, and at 14 months, persistent local control was achieved in 14/31 cases. Severe pelvic sclerosis was observed in 2 cases.

Melanomas

Although surgery, when feasible, is the treatment of choice for melanomas, radiation therapy may be required for some patients at a given stage or the disease (discussion of the value of adjuvant chemotherapy is outside the scope of this paper). Melanomas are often resistant to photon irradiation; this can be related, from a radiobiological point of view, to the broad shoulder of the survival curves for several cell lines [25] . Therefore neutron therapy could be an alternative.

Encouraging results were obtained at the Hammersmith Hospital (Catterall, personal communication) where 87 tumour sites, in 48 patients, were treated with fast neutrons. They consist of metastatic tumours, recurrences after surgery or sites unsuitable for surgery. Permanent local control was achieved in 62 % of the sites (the minimum follow-up was 3 months). In addition, in 20 of the 25 patients good palliation was otained. These results, as well as others (e.g. from Edinburgh), indicate that fast neutron therapy can be an alternative in the treatment of some melanomas, especially where surgery can not be performed, and for metastatic tumours.

Other tumour sites or types

The value of fast neutrons has been assessed in other tumour types or sites, such as bronchus or oesophagus carcinoma. No general and definitive conclusions can be drawn yet, but some of the results are promising [5] [21] [32] [34] [35] [36].

Encouraging results for Pancoast tumours were obtained at the NIRS in Chiba were the cumulative survival rate at 5 years of 21 patients stage III or IV was 24 %. It was 36 % and 10 % for stages III and IV respectively [34].

As far as the oesophagus is concerned, 34 patients were irradiated at the NIRS with fast neutrons given either as boost or in mixed schedule. Local control was achieved in 15 of them (44 %). In a comparable group of 81 patients treated with photons, the local control rate was 30 % (24/81). For small lesions (< 8 cm in length) the local control rate after neutron irradiation was somewhat better than after photon irradiation i.e. 50 % (13/26) compared to 41 % (17/41). The superiority of fast neutrons was less apparent for a small group of patients with large tumours (> 8 cm in length) where the local control rate was 29 % (2/7) compared to 26 % (7/27) for photons [34].

Discussion and conclusions

The general conclusions which emerge from the review of the clinical results are in agreement with what one could expect from the radiobiological data : replacement of X-rays by neutrons - or more generally of low-LET by high-LET radiation - brings a benefit for some types of tumours and, on the contrary, a loss for other tumours. As a matter of fact, the available clinical data enable us to identify :

- tumours for which indeed fast neutrons were found to be superior to the conventional X-rays. They are listed in Table VIII.
- tumours for which conflicting or incomplete results have been reported and for which additional studies are necesssary.
- tumours for which no benefit, or even worse results, were observed with fast neutrons.

As far as the first group of tumours is concerned, they are, in general, slowly growing and well differentiated. The benefit observed for fast neutrons could to some extent be expected from the observations reported by Battermann [1].

In the second group, there are several tumour types for which further studies are necessary. However, when evaluating the results, at least 2 factors need to be taken into account :

a) some of the conflicting results which were reported could be related to differences in patient recruitment, and to the fact that in some studies the patients "subgroups" for which neutrons could bring a benefit were not identified.

b) in many centres, neutron treatments were applied in the past in "sub-optimal" technical conditions (e.g.: beam penetration, skin sparing, fixed beams, etc...). These technical factors could bias the conclusions that one would derive concerning the value of fast neutrons. For example, one cannot derive valid conclusions from bladder tumours irradiated with d(16)+Be beams [12]. Similarly, the difficulty of treating cervix tumours with a fixed horizontal beam was stressed at TAMVEC [26].

TABLE VIII

CLINICAL INDICATIONS FOR NEUTRON THERAPY (SUMMARY)
1. SALIVARY GLAND TUMOURS locally extended, well differentiated
2. PARANASAL SINUSES adenocarcinomas, adenoid cystic carcinomas, other histology (?)
3. SOME TUMOURS OF THE HEAD AND NECK AREA locally extended, metastatic adenopathies
4. SOFT TISSUE SARCOMAS, OSTEOSARCOMAS, CHONDROSARCOMAS especially slowly growing/well differentiated
5. PROSTATIC ADENOCARCINOMAS locally extended
6. MELANOMAS inoperable/recurrent.

From Wambersie et al., [36]

Negative results for brain tumours were reported from most of the centres. Such conclusions are in agreement with the radiobiological data and especially the high RBE value observed for CNS. However, a possible benefit for neutron boost should be further investigated [6].

Finally, neutrons should not be used for tumours showing an exquisite radiosensitivity to X-rays (e.g. seminomas, lymphomas, or in general poorly differentiated rapidly growing tumours). Neutrons would then reduce a differential effect which selectively protects the normal tissues.

As far as the proportion of patients, suitable for neutron therapy is concerned, figures ranging from 10 to 20 % have been suggested. They correspond to the percentages of radiotherapy patients for which neutrons were shown to be superior than conventional X-rays. These percentages are probably at the lower limit since they were often obtained with low energy cyclotrons and poor physical selectivity. It is likely that with high-energy, hospital based modern cyclotrons, neutron therapy will be found to be used for a larger proportion of patients. In addition, neutrons could extend the field of the indications of radiation therapy by allowing to envisage the treatment of groups of tumours "traditionally" considered to be radioresistant (e.g. adenocarcinomas).

Selection of the patients remains one of the main problems in clinical neutron therapy, since inappropriate application of neutrons, will worsen the clinical results. In that respect, the development of individual predictive tests is essential. If,in a given group of patients, the subgroup suitable of neutron therapy has not been identified and if the whole group has been treated by neutrons, the benefit obtained for the subgroup suitable for neutrons will be diluted or counterbalanced by the worse results obtained in the other subgroup for which photons would have done better. This could explain, at least partly, some of the discrepancies which seem to exist between the published data [36].

Further and improved collaboration between the neutron therapy centres is essential in order to pool the available clinical information and to provide the centres, as quickly as possible, with sufficient data in order to allow them to select the patients for neutron therapy and to apply the best treatment modality (i.e. clinical RBE, fraction size, overall time). This is the goal which is aimed at, in the United States, by the Neutron Therapy Section of the RTOG (Radiation Therapy Oncology Group) and, in Europe, by the Heavy-Particle Therapy Group of the EORTC (European Organization for Research on Treatment of Cancer).

The importance of the technical factors has been stressed. Although important progress have been recently achieved, especially with the introduction of new high-energy cyclotrons fully dedicated to the therapy applications, some further improvements are needed before reaching with fast neutrons the same level of physical selectivity, reliability, and accuracy on dose delivery as that currently achieved with modern electron linear accelerators.

The available radiobiological and clinical data indicate that the dose response curves for tumour control and normal tissue complications are as steep for neutrons (or high-LET radiations) as for photons (or low-LET radiations). The same accuracy in dose delivery and in physical selectivity should then be aimed at. To reach this goal, some basic physical data are still missing in the range of the high-energy neutrons at present used in therapy. They are needed in particular :

- to evaluate the kerma, and the absorbed dose, in the different human (or biological) tissues;
- to determine the response of the different detectors (kerma and absorbed dose in the detector materials);
- to optimize the collimation and shielding systems, and thus improve the physical selectivity.

This justifies the Coordinated Research Programme on "Nuclear data needed for neutron therapy" initiated by IAEA.

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Appendix I

Second Research Co-ordination Meeting on
NUCLEAR DATA NEEDED FOR NEUTRON THERAPY

IAEA Headquarters, Vienna
24-27 January 1989

AGENDA

Tuesday, 24 January, 9:30 hrs

Opening, Introduction by Chairman (R.M. White), Adoption of Agenda
Short comments by the Scientific Secretary on the final issue of the CRP activities

SESSION I Reports by participants

- activities completed/being done
- special problems encountered
- plans for the last year's programme

I-1 Neutron Cross Section & Kerma Factors

1) R.C. Haight
2) N. Olsson
3) P.M. DeLuca Jr.
4) R.M. White
5) G. Dietze

I-2 Measurements/Calculations of other physical (mainly nuclear) parameters for neutron therapy

1) T. Hiraoka
2) J.J. Broerse
3) A. Wambersie

Wednesday, 25 January, 9:00 hrs

SESSION II Reports by participants (cont.)

II-1 Neutron Cross Section & Kerma Factors (cont.)

6) H.G. Menzel

SESSION III Presentation of Current Activities (Lecture)

A. Wambersie: Present status of fast neutron therapy: Survey of the clinical research programmes

SESSION IV Discussions on the Intercomparison and on the Final Report of the CRP

SESSION V Working Group discussions

SESSION VI The first Plenary Session on the outline of the final report

Thursday, 26 January, 9:00 hrs

SESSION VII Working Group discussions

SESSION VIII The second Plenary Session on the workload sharing of the chapters for the final report

Friday, 27 January, 9:00 hrs

SESSION IX Conclusions and recommendations (Plenary Session)

Second Research Co-ordination Meeting on
NUCLEAR DATA NEEDED FOR NEUTRON THERAPY

IAEA Headquarters, Vienna
24-27 January 1989

LIST OF CRP PARTICIPANTS

Name	Title of Project
1. Takeshi HIRAOKA (4706/CF; CSI: K. Kawashima) Nat. Inst. of Radiological Sciences	"The measurements of physical parameters and related quantities for neutron dosimetry"
2. Günther DIETZE (4750/CF) Physikalisch-Technische Bundesanstalt	"Investigation of neutron producing and neutron induced reactions relevant for neutron therapy"
3. Hans-Georg MENZEL (4751/CF) Univ. des Saarlandes	"Measurements of kerma factors of A-150 and carbon for neutrons with energies between 20 and 60 MeV using low pressure proportional counter"
4. Paul M. DELUCA Jr. (4752/CF; CSI: H. Barschall)	"Measurements of kerma factors for neutrons of energies above 14 MeV"
5. Roger M. WHITE (4753/CF) Lawrence Livermore Nat. Lab.	"Calculation of kerma factors"
6. Johannes J. BROERSE (4779/CF) Radiobiological Inst. TNO	"Physical and biological data needed for nuclear particle therapy"
7. André WAMBERSIE (4806/CF) Univ. Catholique de Louvain	"RBE, Microdosimetry and physical characteristics of neutron beams of different energy used in therapy"
8. Nils OLSSON (4837/CF; CSI: H. Condé) Uppsala University	"Measurements of neutron induced cross section for C, O and N in the 20-100 MeV energy range"
9. Robert HAIGHT (4910/CF) Los Alamos Nat. Lab.	"White-source measurements of neutron nuclear data for radiotherapy"

Second Research Co-ordination Meeting on
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Coordinated Research Programme on NUCLEAR DATA NEEDED FOR NEUTRON THERAPY

Institute Chief Sci. Investigator Research Agreement No.	Proposed Programme for the next period	Report at Second RCM
Lawrence Livermore National Laboratory (USA) Roger M. White 4753/CF	Updating kerma factors on new measurements or/and dependable theoretical calculation of secondary particle spectra for neutron induced reactions.	- Monte Carlo transport calculations; All Particle Method (APM) includes transport of n,γ,e and light charged-particles and coupling between all species, e.g. (n,p) or (p,n), photon induced electron emissions. - Nuclear and atomic data bases: ENDL: periodically updated, ECPL: currently being updated, EGDL: currently being updated, EEDL: (Evaluated Electron Data Library) - New; contains data for Z=1 to 100 over energy range 10 eV to 100 GeV EADL: (Evaluated Atomic Data Library) - New; contains data for Z=1 to 100, and for each sub-shell will include data for number of electrons, binding energy and radiative and non-radiative transition probabilities per initial vacancy as well as their widths and whole atom data.
University of Wisconsin (USA) Paul M. DeLuca Jr. (CSI: H.H. Barschall) 4752/CF	Measurements of kerma factors on O,Mg,Al,Si and Fe at neutron energies between 14 and 20 MeV.	- Studies on the estimate of gas contribution (direct n-interaction with counting gas) in measurement of kerma factors of Mg,Al,Si and Fe. - Survey of Kerma factors for C,O,Al,Si and Fe.

Institute Chief Sci. Investigator Research Agreement No.	Proposed Programme for the next period	Report at Second RCM
Los Alamos National Laboratory (USA) Robert C. Haight 4910/CF	After preliminary measurements of (n,p),(n,d) and (n,α) on carbon from threshold to 250 MeV at a few angles, extension of range of these measurements is planned. 1) For neutron energies below 50 MeV, new detectors to cover a large solid angle and to detect alpha particles to below 1 MeV are used. 2) For neutron energies above 50 MeV, the data with better statistics are expected.	Description on the white spallation neutron source at LAMPF (800 MeV p on tungsten target, 1 MeV<E_n<500 MeV) 1) E_n: 50-500 MeV, with 90m TOF path at 15° (n-prod. angle). Detector telescopes, multiwire drift chamber, a bending magnet, CSI(Tl) "Wall". (15cm thick). 2) E_n: 1-50 MeV, with 9m TOF path. Detector telescope (3 silicon surface barriers) Initial measurements on carbon show good separation between p,d and α with low BG.
Uppsala Universitet (Sweden) Nils Olsson (CSI: H. Condé) 4837/CF	1) Analysis of the results of elastic and inelastic neutron scattering cross-section measurements from nitrogen and oxygen at 21.6 MeV. 2) Determination of differential cross sections and partial kerma factors, as well as model calculations for nitrogen and oxygen at 21.6 MeV. 3) Initial measurements of (n,p) cross section data for tissue materials in the energy range around 100 MeV (long term).	- Final results of differential neutron scattering cross sections and partial kerma factors for carbon at energies from 16.5 to 22.0 MeV (completed). - Preliminary results of differential neutron scattering cross sections for nitrogen and oxygen at 21.6 MeV (in progress). - Description of the Uppsala (n,p) facility for neutron energies < 200 MeV. - Plans for a beam swinger in Uppsala for neutron scattering measurements in the energy region < 100 MeV.

Institute Chief Sci. Investigator Research Agreement No.	Proposed Programme for the next period	Report at Second RCM
Universität des Saarlandes (FRG) Hans-Georg Menzel 4751/CF	1) Kerma factor measurements for A-150, carbon and aluminium with monoenergetic neutrons (30 and 40 MeV) using low pressure proportional counters and time-of-flight techniques. In collaboration with PTB, Braunschweig). 2) Detailed analysis of the results and of former results obtained in 1987 applying most recent atomic data (stopping powers, W-values) and using the spectral information provided by the proportional counters.	- Measurements of ionization yield spectra and kerma with low pressure proportional counters (A-150, graphite) with monoenergetic neutrons (20-60 MeV, SIN (now PSI), 5-19 MeV, PTB). - Development of new approaches to evaluate absorbed dose and kerma via cavity chamber principles using the combination of measured spectra for A-150 and graphite. Derivation of effective W-values and gas-to-wall absorbed dose conversion factors. - Measurements with proportional counters with broad neutron energy spectra (neutron therapy facilities).
Physikalisch-Technische Bundesanstalt (FRG) Günther Dietze 4750/CF	Study on $^{9}Be(\alpha,n)^{12}C$ Cross-section and angular distribution of emitted neutrons, E_α = 6 - 18 MeV in order to obtain data of $^{12}C(n,\alpha)^{9}Be$ using the reciprocity theorem	- Investigations on C at the PTB: $^{12}C(n,n)^{12}C$, $^{12}C(n,n')^{12}C^{*}_{4.4}$ - $6<E_n<14$ MeV; $^{12}C(n,\alpha)^{9}Be$ - $7<E_n<11$ MeV; $^{12}C(n,n'3\alpha)$ - $11<E_n<19$ MeV. Carbon kerma factors $13<E_n<19$ MeV. - Comparison of the results with ENDF/B-V and Axton's evaluation.

Institute Chief Sci. Investigator Research Agreement No.	Proposed Programme for the next period	Report at Second RCM
National Institute of Radiological Sciences (NIRS) (Japan) Katsuhiro Kawashima (CSI) Takeshi Hiraoka 4706/CF	1) Measurements of neutron response of Al ionization chamber with gases of air, CO_2 and Ar using modified attenuation method. 2) Measurement of stopping powers of various dosimetric materials for 70 MeV proton beam. 3) Determination of absorbed dose in an inhomogeneous lung phantom. 4) Measurements of microdosimetric quantity of lineal energy distribution for neutron beam in radiotherapy.	- Measurement of differential w-values for p,d,^{3}He, neutron and ^{60}Co-γ by eight ionization chambers for air Argon Nitrogen Carbon-dioxide Methane Methane based TE gas.
TNO Radiobiological Inst. (Netherlands) Johannes J. Broerse (CSI) Johannes Zoetelief 4779/CF	1) Further studies on characteristics of Mg/Ar ionization chambers used as photon dosemeters in mixed neutron-gamma ray fields (in cooperation with PTB). 2) Determination of radiation quality and cavity size effects with high pressure ionization chambers in mixed field. 3) Biological implications of the disturbance of secondary charged particle equilibrium at interfaces of materials of different elementary composition (in cooperation with UCL, Louvain-la-Neuve, Belgium).	- Summary of the preliminary results on relative responses of four Mg/Ar chambers of the same design for neutron energies from 5 to 19 MeV. - Studies on high pressure ionization carried out at neutron energies of 0.9 to 15 MeV, with several filling gases. Ref. J. Zoetelief et al., Rad. Prot. Dosimetry 23 (1988) 451.

Institute Chief Sci. Investigator Research Agreement No.	Proposed Programme for the next period	Report at Second RCM
Université Catholique de Louvain (Belgium) André Wambersie 4806/CF	1) Continuous work on systematic RBE determination for the different neutron spectra. 2) Absorbed dose determination at interfaces of soft tissues with A-150 plastics, water, air, bone and others. 3) Check on measurement of kerma and kerma ratios in tissue substitutes, bone, air, and others. 4) Studies on correlation of physical data with systematic RBE determination for different neutron beams and biological systems, and dose ranges relevant to neutron therapy.	- Systematic evaluation of the RBE of different neutron spectra used at several (now 20) therapeutical centers.