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PRESENT RESULTS OF NEUTRON THERAPY

The German experience

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Results of fast neutron therapy are reviewed with special reference to the main indications for this type of treatment and the experience of five German centers. Neutron therapy seems beneficial compared to conventional radiotherapy in advanced salivary gland tumors, inoperable or unresectable soft tissue sarcomas, some bone tumors, prostate cancer stage C and some rare low-grade tumors. About 3 000 patients with malignancies have been treated with neutrons at the German centers Berlin/Rossendorf, Essen, Hamburg, Heidelberg and Münster. Treatment results and treatment-related morbidity depend on the treatment techniques and the physical selectivity of the neutron machines. A critical appraisal suggests that fast neutrons are of advantage in about 5% of all radiotherapy patients.

Fast neutrons were first used for cancer treatment by Robert Stone (1) at the Lawrence Berkley Laboratory in 1938. Today neutron therapy is applied at 21 centres throughout the world. More than 18 000 patients have been treated so far with neutrons, either as sole irradiation modality or combined with other types of radiotherapy. Fast neutron therapy is used on the basis of radiobiological arguments and clinical experience. Neutrons have some special radiobiological qualities due to the high linear energy transfer. The relative biological effectiveness (RBE) is 1.5 to 8 times higher for neutrons than for photons (2). This higher RBE is due to lower oxygen enhancement ratio, less repair of sublethal and potentially lethal radiation damage and less variation in radiation sensitivity during the cell cycle phases (3).

All over the world neutron centers have been built since the 1970's. The technical possibilities of the first generation machines were limited. Treatment was applied with a variety of machines—cyclotrons and DT-generators—and due to physical and technical limitations, treatment modalties and results cannot be directly compared with modern photon therapy. In Germany neutron therapy started in 1972 at Berlin/Rossendorf. Five neutron therapy centers (4) exist in Germany: Berlin/Rossendorf, Essen, Hamburg, Heidelberg and Münster. Nearly 3 000 patients have been treated at these centers. The Table shows the diagnoses of the treated patients. Nearly all patients were treated in phase I and II studies and for different reasons only a few patients were treated in randomized trials.

The results of clinical neutron studies are subsequently reviewed with particular reference to the supposed main indications for neutrons and the German experiences.

Salivary gland tumors

Malignant salivary gland tumors are relatively rare in comparison to other malignancies of the head and neck region. They can arise in several different sites and have diverse histologies with varying potential for aggressive local behavior and metastasis. In limited disease the primary treatment has traditionally been surgery alone or surgery plus postoperative radiation therapy for microscopic residuals. Radiotherapy with photons or electrons has had limited success in eradicating gross postoperative

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Table

Tumor diagnoses in patients treated by fast neutrons in Germany (1972–1990)

	Berlin	Essen	Hamburg	Heidelberg	Münster	Total
Soft tissue sarcoma	475	294	314	83	33	1199
Head and neck cancer	41	97	73	45	24	280
Salivary gland tumor	—	35	94	22	30	181
Lung cancer	263	3	10	111	—	387
Rectal cancer	—	—	70	78	40	188
Prostate cancer	—	12	82	7	4	105
Other urologic malignancies	22	—	15	—	—	37
Bone tumors	—	36	39	10	11	96
Brain tumors	—	18	34	—	1	53
Other tumors	189	51	91	85	7	423
Total	990	546	822	441	150	2949

remnants or unresectable tumors. Pooled data (5–16) show local control in only 72 of 281 patients (26%). For that reason malignant salivary gland tumors were natural targets for neutron therapy studies and a large number of patients with advanced salivary gland tumors have been treated with fast neutrons worldwide. The results have been remarkably consistent and pooled data show long-term local and regional tumor control in 234 of 354 irradiated patients (66%) (16–27). A randomized clinical trial was initiated by the RTOG in the United States and the MRC in Great Britain, comparing neutron therapy and photon therapy in advanced salivary gland tumors (16, 28). After inclusion of 32 patients in this study, it was found that the group receiving fast neutron radiotherapy had a significantly better loco-regional tumor control rate and also a better survival during the first years of the follow-up. The study was closed early for ethical reasons and 25 patients could later on be analyzed. The loco-regional control rate was 56% in the neutron group versus 17% in the photon group ($p = 0.09$). However, neutrons gave no improvement of overall survival (15% versus 25%, p = n.s.). Distant metastases accounted for most failures in the neutron arm and loco-regional failures for most failures in the photon arm.

In the German neutron centers a total of 181 patients were treated for advanced malignant salivary gland tumors between 1972 and 1990. Pötter et al. (29–31) published the Münster data on neutron therapy in 27 cases of adenoid-cystic carcinomas, treated from January 1986 to March 1991. Eleven patients had lymph node or distant metastases and 24 patients had been treated with surgery or irradiation before. The mean follow-up time was 14 months, ranging from 2 to 46 months. The overall local control rate was 74%; 7 patients had local relapses. Four patients died from the disease and two patients from other diseases. Pötter et al. (30, 31) demonstrated that judgement of tumor response should be based on modern imaging techniques.

In Hamburg 130 patients with advanced salivary gland tumors were treated with fast neutrons between 1976 and 1993. Adenoid cystic carcinoma was the dominating histology in 101 of the patients. The most frequent locations were the parotid gland, the submandibular gland and the paranasal sinuses. Between July 1977 and December 1988, a group 44 patients were treated for adenoid cystic carcinoma (27). All patients had previously undergone one or more surgical interventions. The local control rate was 78% at one year and 65% at two years after neutron therapy. Based on these results a controlled clinical trial was designed and started in January 1991. In this study standardized comparable methods will be used for diagnostics and therapy. In summary, available data suggest that neutron therapy is superior to conventional radiotherapy for advanced malignant salivary gland tumors.

Soft-tissue sarcomas

Well operable soft-tissue sarcomas are treated by radical resection. For more advanced lesions the treatment will often be a combination of doubtful radical or non-radical resection and preoperative or postoperative radiotherapy, and in some cases supplemented by chemotherapy. A special problem is to obtain local control of inoperable tumors or gross residual tumor mass after surgery. Especially in the extremities fast neutrons have been used to control the tumor and maintain function of the extremities. During the last 30 years data from 349 patients with soft-tissue sarcomas and remaining macroscopic tumor treated with neutrons have been published worldwide (32–43). In 196 of these patients local control was obtained (56%). Similarly, pooled data for photon therapy in soft-tissue sarcomas with macroscopic tumor mass show local control in 45 of 116 patients (39%) (44–49).

A survey has shown that 1 199 patients with soft-tissue sarcomas were treated at the five German neutron centers

from 1972 to 1990. In he largest series reported by Schmitt et al. (32), 220 patients were treated at Essen between 1978 and 1983. The treatment was non-randomized and consisted of neutron irradiation in 94 cases with gross tumor and of neutron boost irradiation after photon irradiation in 127 cases with no gross tumor after resection (R0:23 patients, R1:104 patients). In the group with gross tumor mass local control and survival rates at five years were 56% and 26% respectively. Budach et al (43) reported 40 patients treated with neutrons for soft-tissue sarcomas with microscopic or macroscopic tumor residuals after surgery between 1983 and 1988 at Essen. The median follow-up was 29.3 months. The actuarial three-year local control and survival rates were 69.3% and 91%. However, the rate of grade 3/4 late morbidity according to the RTOG/EORTC score was 28% in the series of Schmidt et al. in the neutron group compared to 7% in the group treated by photons and neutron boost. In Hamburg 337 patients with soft-tissue sarcomas were treated with fast neutrons in the period from 1976 to 1993. Franke (34) published data of 45 patients treated between 1976 and 1980 and reported a local control rate of 60%. Schwarz et al. (50) analyzed 147 patients with soft-tissue sarcomas treated with fast neutrons in Hamburg between 1984 and 1988. The patients had different histologies, such as liposarcoma (23.8%), malignant fibrous histiocytoma (18.4%), fibrosarcoma (17%), leiomyosarcoma (12.2%), malignant schwannoma (9.6%) and other histologies (19%). Tumor grading was available in 135 cases: G1 (n = 32), G2 (n = 37), G3 (n = 66). The most common location (57%) was the extremities. Eleven patients had lymph node metastases and 12 patients distant metastases at the start of neutron therapy. Residual tumor classification was R0 in 56 cases, R1 in 24 cases and R2 in 61 cases. All patients had surgery before irradaition. Grade 3 and 4 acute side-effects (RTOG/EORTC score) occurred in 3 patients and grade 3 and 4 late side-effects (RTOG/EORTC score) in 3 patients. Median follow-up time was 42 months. At the time of analysis 80 patients were alive, whereas 67 patients had died, 42 of them with local control, and 25 of them with local recurrence. Local control rate at five years was 83% in G1, 75% in G2 and 38.6% in G3 tumors. After 5 years 52.5% of all patients were alive. Significant prognostic factors for survival were grade (G1 80.2%, G2 69% and G3 30.4%), and residual tumor stage (R0 71.8%, R1 58.1% and R2 32.3%).

According to the published data neutron therapy seems to be warranted unresectable or recurrent soft-tissue sarcomas. Neutrons may be especially beneficial for low-grade tumors, but this remains to be proven by future studies.

Osteosarcoma, Ewing's sarcoma, chondrosarcoma and chordoma

The experience with fast neutron therapy for osteosarcoma, Ewing's sarcoma, chondrosarcoma and chordoma is very limited. In the German centers a total of 96 patients have been treated. The radiobiological reasons for using neutrons are large tumors with a high proportion of hypoxic cells and the fact that chordomas and low-grade chondrosarcomas are well differentiated and slowly proliferating neoplasms. A special advantage of neutrons is the low neutron kerma in bone which reduces the absorbed dose in bone by 25% which may reduce the risk of osteonecrosis. The worldwide published data on 97 patients with osteosarcoma (22, 35, 37, 39, 41, 42, 51, 52) show local control in 52 patients (54%). Schmitt et al. (51) published in 1982 the results of neutron therapy in 24 patients with locally advanced osteosarcomas treated in Essen; 12 of them were locally controlled.

Concerning chondrosarcomas with macroscopic tumor present at the time of neutron therapy, a review of the worldwide data indicates local control in 48% (29/61 patients) (35, 37, 39, 40–43). Harwood et al. (53) and McNaney et al. (54) published a retrospective analysis of chondrosarcomas treated by photons. Only 10 of 30 patients (33%) were locally controlled, Budach et al. (43) published results of neutron therapy for chondrosarcomas at Essen University in 1990. From 1979 to 1988, 18 patients were treated with neutrons alone or neutron boost. The median follow-up period was 36 months. The actuarial 3-year local control and survival rates were 55.6% and 62.9%. The local control rates were 62.5% for microscopic disease and 40% for macroscopic disease. At Hamburg, 13 patients were treated with fast neutrons for advanced chordomas. All patients had macroscopic tumor at the time of treatment, ranging from a diameter of 2 cm in an occipital tumor to 16 cm in a sacral. Eleven patients were treated with neutrons and 2 patients with photons and neutrons. The single dose per fraction was 0.6 Gy–1.3 Gy with 3–5 fractions per week and the total dose 11–16.2 Gy. No serious acute or late side-effects were observed. With a mean follow-up period of 27 months, 8 of the 13 patients were free from local progression. Kaplan-Meier calculation gave a survival rate at four years of 45% and a local control rate of 50%.

These published results indicate that neutrons may be beneficial for subgroups of patients with advanced chondrosarcoma, chordoma and osteosarcoma.

Paranasal sinuses

Good results of neutron therapy have been reported by Errington (55) from Hammersmith Hospital; 86% (37/43) of the patients showed complete remission and relief of symptoms and the 3-year local control rate was 50%. Schwarz & Hübener (56) reported about 20 patients treated at Hamburg between 1977 and 1988. Mean follow-up was 16 months and local control was achieved in 11 patients. Especially patients with adenoid cystic carcinomas, low grade adenocarcinomas and sarcomas may benefit from neutron therapy.

Low-grade 'pencil' gliomas of the spinal cord

Budach et al. (57) published results of neutron therapy at Essen in 10 patients with low-grade spongioblastomas and ependymomas of the spinal cord. Total doses between 7.4 Gy and 10.4 Gy were delivered with 0.7 and 1.33 Gy per fraction. Two complete and six partial remissions of ataxia and motor disturbances were observed. Bladder dysfunction was improved in three of five cases. At 88 months, follow-up complete or partial remission was maintained in four patients. In summary, neutrons seem to be a valuable treatment option for incompletely resected low-grade "pencil" gliomas.

Prostate adenocarcinoma

The 5-year local control rates for locally advanced prostatic cancer after high-dose photon therapy range between 54% and 68% (58–64). Results of neutron therapy has been studied at several centers in the United States and Europe. The most promising data derive from a randomized trial of the RTOG (58, 65, 66). Patients with locally advanced prostate cancer were randomized to receive conventional photon irradiation of neutrons used in a mixed-beam schedule. The 10-year clinically assessed local control rate was 70% in the mixed-beam group versus 58% in the photon group and the corresponding survival rates were 46% and 29% respectively. No significant differences were found in complication rates. An NTCWG study has also been performed comparing neutron and photon therapy but the follow-up is still too short for definite conclusions.

In Germany prostate cancer has been treated with fast neutrons at Hamburg. Franke et al. (67) reported on 12 patients with stage C or D1 prostate cancer treated with neutrons during the pilot phase from 1976 to 1980. A large volume including prostate and pelvic lymph nodes was treated with photons and the prostate was boosted with neutrons. A 4-year survival of 85% was obtained in patients with T3-tumors. A prospective controlled clinical trial is going on at Hamburg, implying 50 Gy with a neutron boost of 4.8 to 6 Gy and 50 Gy photons to the pelvis. Photons to whole pelvis supplemented by a neutron boost with 4.8–6 Gy to the prostate.

Neutron therapy may be beneficial compared to photon therapy in advanced prostatic cancer. An adequate treatment technique is essential for the neutron therapy in order to minimize side-effects in the pelvic organs. Further prospective trials are necessary to evaluate neutron therapy in prostate cancer.

Rectal cancer

Neutrons may have a potential biological advantage in advanced and recurrent rectal carcinomas which are thought to contain a high proportion of hypoxic cells. The published data are ambigious. Duncan et al. (68) have reported data for comparing neutron therapy and photon therapy. The local control rates were unsatisfactory in primary tumors; 10% and 6.3% for neutrons and photons respectively. For recurrences the local control rate was better for neutrons (33.3%) than for photons (18.8%). The 3-year survival was around 10% for both treatment modalities. In the series reported by Battermann & Mijnheer (19) the late morbidity after neutron therapy was high but these authors used low-energy machines which give satisfactory dose distributions. In Germany studies have been performed in Hamburg, Münster and Heidelberg.

Franke et al. (69) reported 60 patients treated at Hamburg with neutrons for advanced primary and recurrent rectal cancer. They observed good results concerning pain relief and local control and the treatment-related morbidity was tolerable. Engenhart et al. (70) published the Heidelberg data for 26 patients with large and unresectable locally recurrent adenocarcinoma of the rectum. The treatment consisted of 40 Gy photons to the pelvis and a neutron boost of 6.6 to 10 Gy to the tumor. All patients were symptomatic with severe pain prior to therapy. The follow-up ranged from 6 to 26 months, with a mean follow-up of 12.8 months. A complete pain relief was observed in 13 patients (50%) and the local tumor control rate at the time of evaluation was 85%. The late radiation damage was moderate.

A benefit of neutron therapy compared to photon therapy cannot be regarded as proven. Especially the data from Heidelberg are promising. Randomised trials are however, necessary to define the role of fast neutrons in comparison to other treatment modalities including combined chemotherapy and radiotherapy.

Non-small cell carcinoma of the lung

Patients with non-small cell carcinoma of the lung have worldwide been entered in different studies evaluating fast neutrons therapy. The results of these studies are inconsistent. Most studies have not shown advantages concerning local control and survival when compared to standard radiation therapy (71–75).

Eichorn et al. (73, 74) have published results from Berlin/Dresden. Neutrons did not seem to improve the survival rates. At autopsy an increased tumor eradication rate with increasing neutron dose was observed in patients treated by a combination of neutrons and photons. The tumor sterilization rate at autopsy was 33% (149/429 patients) in photon treated patients and 48% (45/93 patients) in patients receiving a neutron boost. Schnabel et al. (75) reported the results of a randomized trial involving 115 patients at Heidelberg. Forty-eight patients received a total dose of 18 Gy neutrons. The control patients received a dose of 54 Gy photons. Only 30 patients in the neutron arm and 46 patients in the control arm were eligible. There was no significant difference in survival and local control

between the two groups. Side effects were somewhat worse with neutrons. In both these German studies the applied doses in the photon group were low and the technology of the neutron machines was not optimal. With the used low-energy cyclotrons the radiation morbidity was high. Hitherto published reports do not show a superiority of neutrons compared to photons for treatment of non-small cell lung cancer.

Other tumor types

Neutron therapy has been used for a variety of other tumpr types and sites, such as carcinomas in the head and neck region, esophagus, pancreas, urinary bladder, uterine cervix, and breast and malignant brain tumors. The literature shows no clear benefit of neutrons versus photons for these tumors. Also in Germany, patients with the mentioned tumor types have been treated with neutrons in phase I and phase II studies but no randomised trials have been designed so far.

Conclusions

A critical appraisal of the results until now suggests that for a few tumor types (inoperable or unresectable soft tissue sarcomas, some primary bone tumors, advanced malignant salivary gland tumors, prostate cancer stage C and some rare low-grade tumors) neutron therapy is superior to photon therapy. Neutron therapy plays a role in cancer therapy in Germany with about 3 000 patients treated so far at five centers. During the last years neutron therapy in Germany has been concentrated to the above mentioned of tumors. All treatment machines in Germany are first generation machines with unfavourable technical conditions. In the future these machines have to be replaced by modern high-energy cyclotrons facilitating the application of recent advances in modern radiotherapy like isocentric treatment, 3-D treatment planning, conformal therapy and of multileaf collimators. This seems important for optimizing the treatment results in terms of local control, survival and side effects. At present it can be estimated that about 4–5% of all radiotherapy patients might benefit from neutron treatment.

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