Int. J. Radiation Oncology Biol. Phys., Vol. 15, pp. 1085–1090
Printed in the U.S.A. All rights reserved.

0360-3016/88 $3.00 + .00
Copyright © 1988 Pergamon Press plc

File Copy
Pub. # 5021
Study # 8001
Site: hn
Modality: Qrt/NTN
Status: Pub

702238

● *Original Contribution*

NEUTRON VS PHOTON IRRADIATION OF INOPERABLE SALIVARY GLAND TUMORS: RESULTS OF AN RTOG-MRC COOPERATIVE RANDOMIZED STUDY

T. W. GRIFFIN, M.D.,[1] T. F. PAJAK, PH.D.,[2] G. E. LARAMORE, PH.D., M.D.,[1] W. DUNCAN, M.B., CH.B.,[3] M. P. RICHTER, M.D.,[4] F. R. HENDRICKSON, M.D.,[5] AND M. H. MAOR, M.D.[6]

[1]Department of Radiation Oncology, University of Washington Hospital/School of Medicine, Seattle, WA 98195; [2]Division of Statistics, Radiation Therapy Oncology Group, American College of Radiology, Philadelphia, PA 19107; [3]Department of Radiation Oncology, The Princess Margaret Hospital, Toronto, Ontario, M4X 1K9, Canada; [4]American Oncologic Hospital, Fox Chase Cancer Center, Philadelphia, PA 19111; [5]Department of Therapeutic Radiology, Rush-Presbyterian St. Lukes Medical Center, Chicago, IL 60612; and [6]Department of Radiotherapy, MD Anderson Hospital, Houston, TX 77030

A total of 32 patients with inoperable, recurrent or unresectable malignant salivary gland tumors were entered on a randomized RTOG/MRC study comparing fast neutron radiotherapy with conventional photon radiotherapy. Twenty-five patients were entered from the United States and 7 patients were entered from Scotland. Seventeen patients were randomized to receive neutrons and 15 patients were randomized to receive photons. Sixty-one percent of the neutron-treated patients and 75% of the photon-treated patients presented with inoperable or unresectable tumors, while 39% of the neutron-treated and 25% of the photon-treated patients had recurrent disease. Twenty-five patients were study-eligible and analyzable. The minimum follow-up time is 2 years. The complete tumor clearance rates at the primary site were 85% (11/13) for neutrons and 33% (4/12) for photons following protocol treatment ($p = 0.01$). The complete tumor clearance rates in the cervical lymph nodes were 86% (6/7) for neutrons and 25% (1/4) for photons. The overall loco/regional complete tumor response rates were 85% and 33% for neutrons and photons respectively. The loco/regional control rates at 2 years for the 2 groups are 67% for neutrons and 17% for photons ($p < 0.005$). The 2-year survival rates are 62% and 25% for neutrons and photons respectively ($p = 0.10$). These findings are consistent with previously published uncontrolled series.

Salivary gland cancer, Neutrons, Radiation therapy.

INTRODUCTION

Salivary gland tumors are relatively rare. With an incidence of approximately 1:100,000, malignant salivary gland tumors comprise 1–3% of all head and neck malignancies.[6] Conventional treatment can be quite successful, and consists of surgery alone for small, well-differentiated tumors and surgery plus postoperative radiation therapy for larger and more poorly-differentiated tumors. The treatment results with unresectable or inoperable malignancies are less satisfactory.[6]

Treatment of inoperable salivary gland tumors with radiotherapy is often technically difficult, and results reported following low LET irradiation are suboptimal. Reported series tend to be small and difficult to compare with each other. Overall tumor control rates average below 30%.[4,7,10–12,18–20,22,24] Given the combination of a relatively poor outlook[26] with conventional treatment and a generally superficial location, inoperable salivary gland malignancies provided a logical tumor system for study in the early neutron clinical trials.

Neutron irradiation was first used to treat advanced salivary gland tumors by Stone *et al.* using a physics laboratory-based cyclotron in Berkeley, California.[25] More recently, the results of fast neutron clinical trials have been reported from other treatment centers in Great Britain, Europe, the United States, and Japan.[3,5,8,9,13,16,17,21,23] Although instituted on a more-or-less empirical basis, these results have been consistently encouraging, and it has been suggested that salivary gland tumors are much more responsive to neutrons than to photons.[5] The radiobiology results strongly support this conclusion.

Supported in part by the National Cancer Institute under core grant #CA-23113 and individual facility grants CA-12441, CA-17465 and CA-18081.

Reprint requests to: Thomas W. Griffin, M.D., Department of Radiation Oncology RC-08, University Hospital, 1959 NE Pacific St., Seattle, WA 98195.

Accepted for publication 18 May 1988.

0016310

BOX No. Binder-Collected & Copied From Shelf RTOG Publish Manuscripts
FOLDER Copied 4-21-94 At FermiLab
REPOSITORY FermiLab NTF
Radiation Therapy Oncology Group
COLLECTION RTOG Published Manuscripts RTOG

The first radiobiological evidence that neutrons should be particularly effective in the treatment of salivary gland tumors came from Batterman *et al.*[2] Batterman and coworkers measured the relative biological effectiveness (RBE) of neutrons produced by a d → T reaction relative to ^{60}Co radiation using human tumors metastatic to the lung. They determined the RBE for growth delay in terms of the time required for tumor mass to return to its preirradiation volume as evaluated on serial radiographs. Patients having 2 or more metastases had lesions simultaneously treated with the 2 types of radiation. The relative biological effectiveness (RBE) for adenoidcystic carcinoma was 5.7 for a single radiation dose and 8.0 for fractionated radiation such as would correspond to clinical treatment schemes. The RBE's for most other tumors were in the range of 2.5 to 4.0.

Based on the encouraging results from earlier non-random clinical trials, and the strong supporting evidence from Dr. Batterman's radiobiology studies, the Radiation Therapy Oncology Group and the Medical Research Council of Great Britain sponsored a prospective, randomized study comparing fast neutron irradiation with low LET photon and/or electron treatment of inoperable malignant salivary gland tumors.

METHODS AND MATERIALS

Thirty-two patients were entered in a prospectively randomized study comparing fast neutron radiation therapy with conventional photon and/or electron radiation therapy for inoperable primary or recurrent malignant salivary gland tumors.

Eligibility criteria included inoperable primary or unresectable recurrent salivary gland malignancies limited to the following histologies: mucoepidermoid carcinoma, acinic cell carcinoma, adenoidcystic carcinoma, adenocarcinoma, squamous cell carcinoma, and malignant mixed tumors. Tumors originating in the parotid gland, submaxillary gland, and minor salivary glands were eligible. Patients must have been between the ages of 18 and 76 inclusive, had no prior malignancies other than non-melanoma skin cancer, had no prior radiation therapy, and had a Karnofsky score greater than or equal to 60.

The study was opened in July 1980, and closed in March 1986. Patients were stratified by surgical status (inoperable primary tumors vs unresectable recurrent tumors), tumor size (<5 cm vs >5 cm), and histology (squamous or malignant mixed vs other). They were then randomized to receive control low LET photon and/or electron treatment or treatment with fast neutrons. Patients with unmeasurable postoperative residual disease were ineligible.

Patients randomized to the control treatment all received supervoltage radiation therapy. Two dose/time/fractionation schedules were used. Patients from the United States were to receive 70 Gy delivered over 7½ weeks. Patients from Scotland were to receive 55 Gy delivered over 4 weeks. These treatment schedules reflected the treatment conventions in the 2 countries and were thought to be clinically equivalent.

Patients randomized to neutron irradiation were treated with 12 neutron fractions, 3 fractions per week, over 4 weeks. The actual neutron dose delivered depended upon the neutron scaling factor for the neutron energies available at the treating institution. Twenty-two neutron Gy was to be delivered at the Fermilab, 17.14 neutron Gy at the University of Pennsylvania facility, 17 neutron Gy at the University of Washington, and 16.5 Gy at Western General Hospital in Edinburgh. These doses were based on radiobiological intercomparison studies and are thought to be clinically equivalent. The protocol schema is illustrated in Figure 1.

Patient work-up and pretreatment evaluation included a complete history and physical examination, a drawing of the primary tumor and regional lymph nodes with centimeter measurements, a photograph of the lesion, chest x-ray, mandible x-ray, and CT scan of the tumor volume. Following treatment, patients were evaluated every 2 months for the first year, every 3 months for the second and third years, every 4 months for the fourth and fifth years, and yearly thereafter.

Four institutions participated in the study. Fast neutrons were generated at the Fermilab facility using a 66 MeV proton linear accelerator. Cyclotrons were used for neutron production at the University of Washington and at Edinburgh. Neutrons were produced at the University of Pennsylvania facility from a DT generator. The neutron energies and methods of production are listed in Table 1.

Thirty-two patients were entered on the study. Fifteen patients were randomized to receive low LET treatment and 17 were randomized to receive neutrons. Three low LET randomized patients and 4 neutron randomized patients were ineligible, leaving a total of 25 patients available for analysis. Two patients randomized to photons and one patient randomized to neutrons were excluded because they had no measurable disease at the time of randomization. One patient refused all radiation after randomization to photons. The three remaining ineligible patients were excluded for reasons of benign histol-

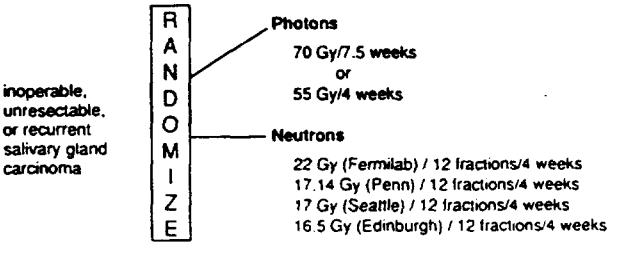

Fig. 1. Randomization schema for inoperable and unresectable primary and recurrent salivary gland tumors. The neutron dose is adjusted for the institutional neutron scaling factors.

0016311

Table 1. Facility-adjusted neutron doses

Facility	Machine	Neutron reaction	Neutron dose
Fermilab	Linac	66 Me Vp ⇒ Be	22 Gy
University of Pennsylvania	DT generator	14 Me Vd ⇒ T	17.14 Gy
University of Washington	Cyclotron	22 Me Vd ⇒ Be	17 Gy
Western General	Cyclotron	15 Me Vd ⇒ Be	16.5 Gy

ogy, a prior malignancy (rectum), and a mucosal carcinoma not of salivary gland origin. The last patient was entered on this study in August 1985.

The male-to-female ratio was 58% to 42% for photons and 54% to 46% for neutrons. Forty-two percent of photon patients and 54% of neutron patients were 70 years old or greater. The parotid gland was the primary site in 83% of photon-treated patients and 69% of neutron-treated patients. Twenty-five percent of photon patients and 39% of neutron patients presented with recurrent disease. The median size of the primary tumor in largest dimension was 7.0 cm (range 3.0–16.0 cm) for patients randomized to photons and 6.0 cm (range 3.0–9.0 cm) for patients randomized to neutrons. Lymph nodes involved with tumor were found in 33% of photon patients and 54% of neutron patients. The pretreatment patient characteristics are listed in Table 2 and the presenting tumor histologies are listed in Table 3.

Differences in the tumor clearance rates were evaluated by Fisher's exact test.[1] The difference in survival was evaluated by the Mantel-Haenszel test.[15] In both instances, one-sided tests of significance were utilized. Time events were plotted as step functions using the Kaplan-Meier method.[14] Time was measured from the start of treatment until the time of the first failure or the time of the last follow-up if the patient did not fail.

Prior to analysis, quality control chart, film and dosimetry reviews were carried out at RTOG Headquarters by the protocol chairman. All cases were reviewed, and major unacceptable protocol violations were discovered in 2 cases. A photon-treated patient discontinued radiation after 16 Gy and refused further treatment. Review of treatment portal films revealed that significant tumor mass extended beyond the treatment margins of a neutron-treated patient. Although both of these patients failed to achieve a complete remission and both ultimately died of their disease, they are included in the result analysis to avoid biasing the study.

RESULTS

Patients were considered to have complete primary tumor clearance if the primary tumor mass both clinically and radiographically totally disappeared following protocol treatment. Complete nodal clearance is similarly defined for patients with initial nodal disease. Patients were considered to achieve a complete response when both complete primary and nodal clearances were achieved.

Table 2. Pretreatment characteristics

	Photon %	Neutron %
Male	58	54
Female	42	46
Age > 70	42	54
Parotid gland	83	69
Other sites	17	31
Median size of primary	7.0 cm	6.0 cm
Per cent lymph node involvement	33	54
Disease status		
Recurrent	25	39
Inoperable/unresectable	75	61

Patients who did not achieve an initial complete response were considered as failures on study day one. Patients who did achieve a complete response were considered a failure to the planned initial treatment on the study day when a recurrence was reported. With respect to survival analysis, death was considered a treatment failure regardless of cause.

All patients had a minimum of 2 years' follow-up at the time of this analysis.

Patients treated with neutrons had a significantly higher primary tumor clearance rate than patients treated with photons. Eighty-five percent of the neutron-irradiated patients (11/13) achieved complete clearance of all primary tumor in contrast to 33% (4/12) of the photon-irradiated patients ($p = 0.01$). Nodal tumor clearance rates similarly favored neutrons (86% for neutrons vs 25% for photons). The loco/regional complete response rates were 85% for neutron-treated patients and 33% for photon-treated patients. Figure 2 illustrates the overall complete response rates for neutrons and photons.

Figure 3 illustrates the loco/regional tumor control rates for the 2 treatment groups. Again, there is a statistically significant advantage favoring the neutron-irradiated patients ($p < 0.005$). This advantage was mainly due to the large difference in complete response rates, and it should be noted that 5 complete responders died without failing locally (1 photon and 4 neutron). The 2-year loco/regional tumor control rates were 67% for neutrons and 17% for photons.

Table 3. Tumor histologies

	Photon %	Neutron %
Mucoepidermoid	17	31
Acinic cell	0	23
Adenoidcystic	25	23
Malignant mixed	8	0
Adenocarcinoma	17	15
Squamous	33	8

0016312

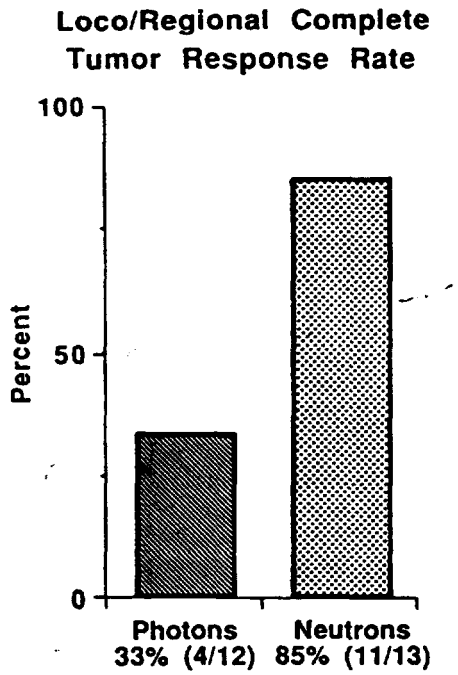

Fig. 2. Complete response rates for neutron-treated and photon-treated patients. The difference is statistically significant at the $p = 0.01$ level.

When absolute survival was examined, the same trend favoring neutrons was seen, but with a significance level of only $p = 0.10$ (Fig. 4). The 2-year survival rates were 62% for neutrons and 25% for photons. There are currently 3 patients alive on the photon arm (23.9, 25.5 and 77.2 months) and 6 patients alive on the neutron arm (24.0, 24.4, 28.9, 29.2, 61.1, and 68.2 months). The main difference in survival between the treatment arms occurs between 12 and 18 months after the start of treatment. There were 2 intercurrent deaths on the photon treatment arm (1 pneumonia and 1 heart disease), and 3 intercurrent deaths on the neutron-treatment arm (2 pneumonia and 1 heart disease). Table 4 summarizes the 2-year study results.

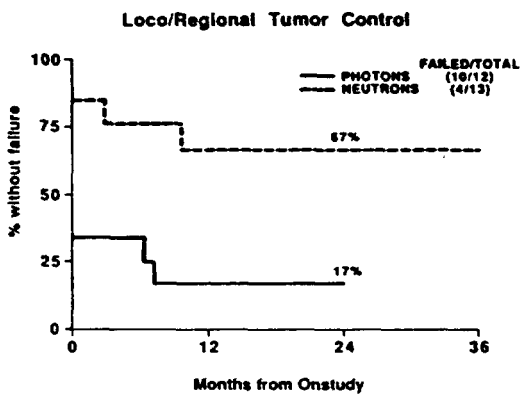

Fig. 3. Loco/regional tumor control rates for neutron-treated and photon-treated patients. The difference is statistically significant at the $p < 0.005$ level.

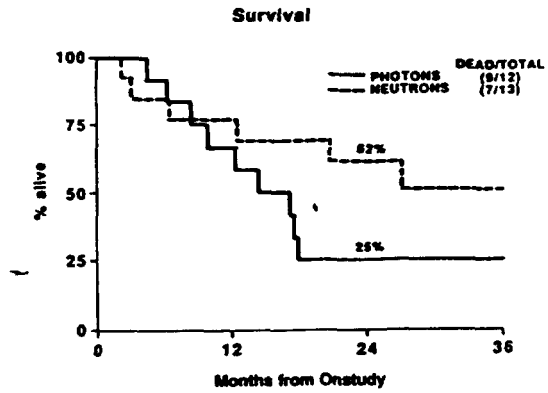

Fig. 4. Survival rates for neutron-treated and photon-treated patients. The difference is significant at the $p = 0.10$ level.

The toxicity associated with treatment is presented in Table 5. Although not statistically significant, the neutron-treated patients tended to show more toxicity than the photon-treated patients. This trend is consistent with other studies using low energy neutron generators.

DISCUSSION

Fast neutron radiotherapy for cancer dates from the 1930's when Stone and coworkers used a neutron beam from an early physics cyclotron in Berkeley, California, to treat patients with advanced malignant disease.[25] While these early clinical studies were conducted on a more-or-less empirical basis, the development of mammalian cell culture techniques in the 1950's later led to a radiobiological rationale for high LET (linear energy transfer) particle irradiation.

Neutron and other high LET radiations offer several potential advantages over low LET photon or electron irradiation. All of these advantages are related to the increased energy deposition from these particles in tissue per unit tract length. This property results in a lower oxygen enhancement ratio (OER) (approximately 1.6 for neutrons compared to 2.5 to 3.0 for photons), a reduced ability to repair sublethal damage, a reduced ability to recover from potentially lethal damage, and less variation in radiosensitivity across the cell cycle for neutron-treated cells compared to photon-treated cells. While the initial impetus for clinical trials with high LET irradiation came from its ability to kill hypoxic cells, the advantages demonstrated for the treatment of salivary gland tumors probably are derived from the other biological factors (most likely reduced potentially lethal damage repair and cell cycle effects). These biological factors resulted in an RBE of 8, as demonstrated by Batterman, for clinically fractionated neutron irradiation of adenoidcystic salivary gland carcinoma.

Prior to this report, the results of neutron treatment of 289 patients with inoperable salivary gland tumors have been published. This number excludes patients who were treated for presumed residual disease following surgery.

0016313

Table 4. Study results

Endpoint	Treatment	Total evaluable	Number still alive and at risk	One year	Two years
Loco-regional tumor control	Photons	12	1	17% (±11)	17% (±11)
	Neutrons	13	5	67% (±14)	67% (±14)
Survival	Photons	12	3	67% (±12)	25% (±14)
	Neutrons	13	6	77% (±12)	62% (±14)

Some of these patients were treated with "mixed beam" treatment; others were treated with neutrons alone. Treatment was delivered in 12–38 fractions over 4–7 weeks. In spite of this variability, the results are remarkably consistent. The largest reported series comes from the Fermilab where 71 of 113 patients treated with fast neutrons achieved permanent local control of their disease. The authors of this report concluded that, "Neutron beam therapy is the treatment of choice for unresectable, residual and recurrent salivary gland tumors."[21] Table 6 lists the reported neutron experience in this tumor system. The composite local control rate is 67% (194/289).[3,5,8–10,13,16,17,21,23]

Local tumor control rates following low LET photon and/or electron irradiation for inoperable salivary gland carcinomas are less satisfactory. Table 7 lists the photon treatment results in this clinical situation. As in Table 6, series reporting patients who were treated for presumed residual disease following surgery are not included. The composite local control rate following photons in these series is 24% (61/254).[4,7,10–12,18–20,22,24,26]

The results of the randomized cooperative study reported in this paper support the data from the prior radiobiological and clinical work. With 2 years minimum follow-up, the loco/regional tumor control advantage of 67% for neutrons vs 17% for photons is statistically significant at the $p < 0.005$ level. There is a strong trend favoring neutrons in terms of survival as well (62% vs 25% at the $p = 0.10$ level). Table 8 compares the results obtained in this study with both low LET and high LET historical experience.

Table 5. Treatment complications*

	Photon %		Neutron %	
	Any	Grade > 3	Any	Grade > 3
Mucosal	50	8 (1/12)	62	23 (3/13)
Skin	50	17 (2/12)	85	15 (2/13)
Fibrosis	58	8 (1/12)	62	0
Necrosis	8	0	23	15 (2/13)
Dry mouth	67	17 (2/12)	100	8 (1/13)
Taste impairment	50	8 (1/12)	77	31 (4/13)

* Patients could have more than one complication.

Table 6. Neutron loco/regional tumor control rates for malignant salivary gland tumors

	Number of patients	Loco/regional tumor control
Saroja *et al*[21]	113	63% (71/113)
Catterall & Ellington[5]	65	77% (50/65)
Batterman *et al*[2,3]	32	66% (21/32)
Griffin *et al*[13]	32	81% (26/32)
Duncan *et al*[8]	22	55% (12/22)
Maor *et al*[16]	9	67% (6/9)
Ornitz *et al*[17]	8	38% (3/8)
Eichhorn *et al*[9]	5	60% (3/5)
Skolyszewski *et al*[23]	3	67% (2/3)
Total	289	67% (194/289)

Table 7. Low LET (photon/electron) loco/regional tumor control rates for malignant salivary gland tumors

	Number of patients	Loco/regional tumor control
Fitzpatrick and Thoriault[11]	50	12% (6/50)
Vikram *et al*[26]	49	4% (2/49)
Borthne *et al*[4]	35	23% (8/35)
Rafla[18]	25	36% (9/25)
Fu *et al*[12]	19	32% (6/19)
Stewart *et al*[24]	19	47% (9/19)
Dobrowsky *et al*[7]	17	41% (7/17)
Shidnia *et al*[22]	16	38% (6/16)
Elkon *et al*[10]	13	15% (2/13)
Rossman[20]	11	54% (6/11)
Total	254	24% (61/254)

Table 8. Comparison of the RTOG-MRC study results with historical results

	Number of patients	Loco/regional tumor control %
Low LET		
Low LET historical experience	254	24
RTOG/MRC photon controls	12	17
Neutron		
Historical neutron experience	289	67
RTOG/MRC neutron results	13	67

0016314

The number of patients entered in this study is small, and the original accrual goals were 22 patients per treatment arm based on projected 2-year loco/regional tumor control rates of 20% for photons and 60% for neutrons. As the study progressed and treatment results became obvious, and as more neutron results became available from other institutions, it became very difficult to continue accrual to a randomized study containing a photon treatment. The study was closed when the statistical significance of the difference between treatments became apparent.

Taken as a whole, the data from the radiobiological studies, the non-random clinical studies and the prospective randomized clinical trial reported here overwhelmingly support the contention that fast neutron radiotherapy offers a significant advance in the treatment of inoperable and unresectable primary and recurrent malignant salivary gland tumors.

REFERENCES

1. Armitage, P.: *Statistical Methods in Medical Research.* New York, John Wiley & Sons, Inc. 1973, pp. 135–136.
2. Batterman, J.J., Breur, K., Hart, G.A.M., van Peperzeel, H.A.: Observations on pulmonary metastases in patients after single doses and multiple fractions of fast neutrons and cobalt-60 gamma rays. *Europ. J. Cancer* **17**: 539–548, 1981.
3. Batterman, J.J., Mijnheer, B.J.: The Amsterdam fast neutron radiotherapy project: a final report. *Int. J. Radiat. Oncol. Biol. Phys.* **12**: 2093–2099, 1986.
4. Borthne, A., Kjellevold, K., Kaalhus, O., Vermund, H.: Salivary gland malignant neoplasms: treatment and prognosis. *Int. J. Radiat. Oncol. Biol. Phys.* **12**: 747–754, 1986.
5. Catterall, M., Errington, R.D.: The implications of improved treatment of malignant salivary gland tumors by fast neutron radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* **13**: 1313–1318, 1987.
6. Conley, J., Baker, D.G.: Cancer of the salivary glands. In *Cancer of the Head and Neck.* New York, Churchill Livingstone. 1981, pp. 524–556.
7. Dobrowsky, W., Schlappack, O., Karcher, K.H., Pavelka, R., Kment, G.: Electron beam therapy in treatment of parotid neoplasm. *Radiother. Oncol.* **6**: 293–299, 1986.
8. Duncan, W., Orr, J.A., Arnott, S.J., Jack, W.J.C.: Neutron therapy for malignant tumors of the salivary glands. A report of the Edinburgh experience. *Radiother. Oncol.* **8**: 97–104, 1987.
9. Eichhorn, H.J.: Pilot study on the applicability of neutron radiotherapy. *Radiobiol. Radiother.* 3: 262–292, 1981.
10. Elkon, D., Colman, J., Hendrickson, F.R.: Radiation therapy in the treatment of malignant salivary gland tumors. *Cancer* **41**: 502–506, 1978.
11. Fitzpatrick, P.J., Theriault, C.: Malignant salivary gland tumors. *Int. J. Radiat. Oncol. Biol. Phys.* **12**: 1743–1747, 1986.
12. Fu, K.K., Leibel, S.A., Levine, M.L., Friedlander, L.M., Boles, R., Phillips, T.L.: Carcinoma of the major and minor salivary glands: analysis of treatment results and sites and causes of failures. *Cancer* **40**: 2882–2890, 1977.
13. Griffin, B.R., Laramore, G.E., Griffin, T.W., Eenmaa, J.: Fast neutron radiotherapy for advanced malignant salivary gland tumors. *Radiol. Oncol.* **12**: 105–111, 1988.
14. Kaplan, E.L., Meier, P.: Non parametric estimation from incomplete observations. *J. Amer. Statist. Assoc.* **53**: 457–481, 1958.
15. Mantel, N.: Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chem. Rep.* **5**: 163–170, 1966.
16. Maor, M.H., Hussey, D.H., Fletcher, G.H., Jesse, R.H.: Fast neutron radiotherapy for locally advanced head and neck tumors. *Int. J. Radiat. Oncol. Biol. Phys.* **7**: 155–163, 1981, and private communication.
17. Ornitz, R., Herskovic, A., Bradley, E., Deyeand, J.A., Rogers, C.C.: Clinical observations of early and late normal tissue injury and tumor control in patients receiving fast neutron irradiation. In *High LET Radiations in Clinical Radiotherapy,* Barendsen, G.W., Broerse, J., Breur, K. (Eds.). New York, Pergamon Press. 1979, pp. 43–50.
18. Rafla, S.: Malignant parotid tumors: Natural history and treatment. *Cancer* **40**: 136–144, 1977.
19. Reddy, E.K., Mansfield, C.W., Hartman, G.V., Rouby, E.: Malignant salivary gland tumors: role of radiation therapy. *JAMA* **71**: 959–961, 1979.
20. Rossman, K.J.: The role of radiation therapy in the treatment of parotid carcinomas. *Am. J. Radiol.* **123**: 492–499, 1975.
21. Saroja, K.R., Mansell, J., Hendrickson, R.R., Cohen, L., Lennox, A.: An update on malignant salivary gland tumors treated with neutrons at Fermilab. *Int. J. Radiat. Oncol. Biol. Phys.* **13**: 1319–1325, 1987.
22. Shidnia, H., Hornback, N.B., Hamaker, R., Lingeman, R.: Carcinoma of major salivary glands. *Cancer* **45**: 693–697, 1980.
23. Skolyszewski, J., Byrski, E., Chrzanowska, A., Gasinska, A., Reinfuss, M., Huczkowski, J., Lazarska, B., Michalowski, A., Meder, J.: A preliminary report on the clinical application of fast neutrons in Krakow. *Int. J. Radiat. Oncol. Biol. Phys.* **8**: 1781–1786, 1982.
24. Stewart, J.G., Jackson, A.W., Chew, M.K.: The role of radiation therapy in the management of malignant tumors of salivary glands. *Am. J. Roentgenol.* **102**: 100–108, 1968.
25. Stone, R.S.: Neutron therapy and specific ionization. *Am. J. Roentgenol.* **59**: 77–85, 1948.
26. Vikram, B., Strong, E.W., Shah, J.P., Spiro, R.H.: Radiation therapy in adenoid-cystic carcinoma. *Int. J. Radiat. Oncol. Biol. Phys.* **10**: 221–223, 1984.

0016315