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● *Original Contribution*

NEUTRON THERAPY IN CERVICAL CANCER: RESULTS OF A PHASE III RTOG STUDY

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Between October 1976 and May 1984, 156 patients with locally advanced cervical cancer were entered into a Phase III trial with the participation of five institutions. Patients were randomly assigned to receive photons only (50 Gy in 25 fractions over 5 weeks plus intracavitary applications or external-beam boost) or mixed-beam radiotherapy (2 fractions a week of neutrons, 3 fractions a week of photons to a total RBE-adjusted dose of 50 Gy over 5 weeks plus intracavitary applications or external mixed-beam boost). Only patients with squamous carcinoma of FIGO Stages IIB, III, or IVA with negative para-aortic nodes on lymphangiogram were eligible. Ten patients were excluded from the analysis because of ineligibility or cancellation. Of the 146 patients analyzed, 80 were treated with mixed-beam radiotherapy and 66 with photons. Patients were grouped by stage and institution. The percentage of patients undergoing intracavitary applications was 50% on mixed beam and 75% on photons ($p < 0.01$). Tumor clearance was 52% and 72% for mixed beam and photons, respectively ($p < 0.03$). Local control at 2 years was 45% for mixed beam and 52% for photons. Median survivals were 1.9 years on mixed beam and 2.3 years on photons. Severe complications occurred in 19% and 11% in mixed beam and photons respectively ($p < 0.13$). The inferior outcome with neutron therapy in this study may have resulted from the use of horizontal neutron beams of varying energy and penetration. 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 cancer.

Cervical cancer, Neutron therapy.

INTRODUCTION

Radiation therapy is widely accepted as the preferred treatment for invasive cancer of the uterine cervix. The effectiveness of the treatment is related to the extent of the tumor at presentation. As the local tumor advances, the likelihood of controlling it with radiation diminishes. In an analysis of locoregional failures in 916 patients with squamous carcinoma of the cervix in the intact uterus, Jampolis *et al.*[6] had a 33% (72/218) failure rate within the irradiated volume in patients with Stage III disease. Patients with Stages IB-IIA and IIB had local failure rates of only 7% (34/404) and 18% (37/204) respectively. Because of the poorer results in advanced cervical cancer, the Radiation Therapy Oncology Group (RTOG) initiated a randomized study to compare neutron with photon irradiation in October 1976. For the experimental portion of the study, a combination of neutrons and photons in a mixed schedule was chosen to overcome some limitations of the neutron beams available at that time. The main deficiencies were: restricted access to the neutron-producing physical facility, the inferior depth dose of neutrons when compared to high-energy photons, and the availability of only a fixed horizontal neutron beam in most facilities. Five institutions participated in the study: The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Texas; Université Catholique de Louvain, Brussels, Belgium; University of

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Washington, Seattle, Washington; Cleveland Clinic Foundation, Cleveland, Ohio; and Fermi Laboratories, Chicago, Illinois. Initially only International Federation of Gynecology and Obstrics (FIGO) Stages III and IVA were included in the study. The protocol was revised in July 1979 to include Stage IIB.

METHODS AND MATERIALS

Patient selection

Patients with biopsy-proven squamous cell carcinoma of the uterine cervix, FIGO Stages IIB, III, or IVA were accepted. All patients were required to have a lower-limb lymphangiogram. Those with metastatic para-aortic nodes on lymphangiogram were excluded unless a selective biopsy from the suspect area was negative. Patients were also excluded for any evidence of hematogenous metastasis. A Karnofsky performance status of 60 or greater was required. All patients gave written informed consent prior to entry into the study. Patients were excluded on the bases of previous radiation therapy, chemotherapy, and/or surgery for cancer in the pelvis as well as simultaneous or prior cancer at another site except for controlled skin and lip epithelial carcinoma. Patients were also excluded if they had active, uncontrolled infection in the area of contemplated irradiation, were pregnant or immediately postpartum, or were so obese as to result in a depth-dose distribution of 40% or less.

Pretreatment evaluation

The staging work-up included a history and physical exam, pelvic examination with diagram of pelvic findings, cystoscopy, procto-sigmoidoscopy, and biopsies (4-quadrant, endocervical, and endometrial aspiration biopsies were recommended). Laboratory tests included a complete blood count, urinalysis, and liver function tests. Imaging procedures required were X rays of the chest, lower extremity lymphangiogram, intravenous pyelogram, barium enema, and barium studies for small bowel mobility.

Randomization and stratification

Patients were grouped by stage and institution. Patients were randomly assigned through RTOG headquarters following confirmation of eligibility and after being informed of the investigational nature of this study and giving written consent.

Patients were randomly assigned to receive photons only (50 Gy in 25 fractions over 5 weeks and intracavitary applications or external-beam boost) or to mixed-beam radiotherapy (2 fractions a week of neutrons, 3 fractions a week of photons to a total radiobiological equivalent (RBE) dose of 50 Gy over 5 weeks and intracavitary applications or external mixed-beam boost). Randomization was weighted 3:2 in favor of the mixed-beam regimen to accrue more patients in the experimental arm of the study.

Protocol treatment plans

Treatment was started with external radiation to the whole pelvis. Typically, the anterior and posterior fields measured 15 × 15 cm and extended from the middle of L5 to the mid-obturator foramen. A four-field box arrangement was frequently used. In the photon portion of the study arm, the aim was to deliver 50 Gy in 5 to 5½ weeks, 5 treatments per week with fractions of 1.8 to 2 Gy. In the mixed-beam portion of the study, patients were treated 3 times per week with photons and 2 times per week with neutrons. The neutron daily dose was calculated by dividing the daily photon dose by the RBE factor, which ranged between 3 and 3.3 for the participating institutions. Thus, the number of fractions, the overall time, and the equivalent dose were designed to be the same in both portions of the study. After 5 weeks of treatment, patients in each group were evaluated for further treatment using one or two intracavitary radioactive applications for a total of 4000–5000 mg-hrs (radium equivalent). Patients who received intracavitary irradiation could receive an additional external dose of up to 6 Gy of photons or the equivalent dose in mixed beam to the involved pelvic sidewall if clinically indicated. Patients who could not receive intracavitary irradiation because of poor geometry or inadequate regression of the tumor continued with external radiation, photons, or mixed beam, to a reduced volume confined to the residual disease. The aim of this boost therapy was to deliver 10–16 Gy or its equivalent with the mixed beam.

Study parameters and follow-up

The endpoints evaluated in this study were tumor clearance, local tumor control, survival, patterns of tumor recurrence, and treatment-related toxicity. Tumor clearance was defined as complete disappearance of all visible and palpable tumor. Upon completion of treatment, follow-up was required every 3 months for 3 years, every 6 months for the fourth and fifth years, and annually thereafter. The data were collected and reviewed by the study data manager at the central RTOG Headquarters and by the study chairman.

Statistical methods

Survival was measured from the start of protocol treatment. Survival curves were calculated according to the method of Kaplan and Meier,[8] and survival comparisons were made using the logrank test.[9]

For comparisons of proportions, Fisher's exact test[5] was used when the cell values were sufficiently small; otherwise the Yates corrected Chi-square test[5] was used. p-values reported are two-sided except where noted.

The logistic regression model[2] was used to identify factors related to intracavitary application and tumor clearance. In the model for intracavitary application at 3 months, given survival at that time, factors initially included were assigned treatment, FIGO stage, institution,

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Table 1. Status of case records

	Photons	Mixed beam	Total
ases randomized	68	88	156
Cancelled	0	2	2
Ineligible	2	6	8
Cases analyzed	66	80	146

Karnofsky score, age, and three sites of disease involvement (pelvic sidewalls, parametrium, and vaginal walls). Some levels of certain factors were grouped together, so that sufficient patient numbers were in each category. The model for tumor clearance at 6 months, given survival at that time, initially included all of the above variables plus intracavitary application.

The Cox proportional hazard regression model[3] was used to identify factors prognostically significant for survival. The same baseline patient characteristics initially entered in the logistic regression were also used in the Cox regression. All regression analyses were performed in a step-down fashion.

Table 3. Patient and treatment characteristics

	Photons		Mixed beam		Total	
	No.	%	No.	%	No.	%
FIGO Stage						
IIB	15	22.7	18	22.5	33	22.6
IIIA	3	4.6	2	2.5	5	3.4
IIIB	38	57.6	51	63.8	89	61.0
IVA	10	15.2	9	11.3	19	13.0
Karnofsky Performance Status						
90–100	48	72.7	50	62.5	98	67.1
60–80	18	27.3	30	37.5	48	32.9
Age						
20–29	4	6.1	2	2.5	6	4.1
30–39	5	7.6	10	12.5	15	10.3
40–49	12	18.2	17	21.3	29	19.9
50–59	24	36.4	23	28.8	47	32.2
60–69	16	24.2	22	27.5	38	26.0
≥70	5	7.6	6	7.5	11	7.5
Intracavitary application						
None	18	27.3	39	48.8	57	39.0
One or two	48	72.7	41	51.2	89	61.0

RESULTS

Between October 1976 and May 1984, 156 patients were entered into this study. Sixty-eight patients were randomly selected to receive photons, and 88 patients received mixed-beam radiotherapy. Treatments for two patients assigned to mixed beam were canceled. Eight patients were ineligible, two on photons and six on mixed beam (Table 1). Of the eight ineligible patients, four had adenocarcinomas, two had Stage IIA disease, and two had positive para-aortic nodes.

The number of patients and the equipment used to deliver the external radiations by each institution is shown in Table 2.

Patients in the two treatment groups were well balanced with respect to stage, Karnofsky performance status, and age (Table 3). Conditional on survival to 3 months, the percentage of patients undergoing intracavitary applications by this time was unbalanced, with 75% on photons and 50% on mixed beam ($p < 0.01$). The logistic regression showed intracavitary application at 3 months to be significantly related to assigned treatment, Karnofsky score, institution, and two sites of disease involvement (parametrium and vaginal wall). The treatment methods and tumor doses actually received are listed in Table 4. The external doses in both groups are very similar. The neutron doses include a gamma ray contamination of about 10%. Patients who had an intracavitary application in the photon group had a slightly higher dose than their counterparts in the mixed-beam group.

The results of the study chairman's evaluation of radiation therapy are presented in Table 5. Of the cases reviewed, 85% had acceptable delivery of radiotherapy; 11 of the 15 patients with unacceptable major variations to protocol radiotherapy were treated with mixed beam. Two of these 15 patients were selected to receive mixed beam but received photons only; four patients selected to receive mixed beam received less than the minimum required 30% neutron dose. Two patients on photons and three on mixed beam had treatment interruptions resulting in a total treatment time greater than 80 days with no intracavitary application. Four patients, two on each regimen, had midline blocks at 30 Gy in violation of the protocol prescription.

Table 2. Number of patients and delivery of treatment by institution

Institution	No. of pts.	Neutron energy, production and beam orientation		Photon energy and equipment
M. D. Anderson—TAMVEC	74	50 MeV d → Be	horizontal	25 MV Betatron
U. of Washington (Seattle)	26	22 MeV d → Be	horizontal	15 MV Linac
atholique University (Belgium)	25	50 MeV d → Be	horizontal + vertical	18 MV Linac or ^{60}Co
veland Clinical—GLANTA	14	25 MeV d → Be	horizontal + vertical	10 MV or 18 MV Linac
rmilab	7	66 MeV p → Be	horizontal	4 MV Linac

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Table 4. Summary of treatment received

	Whole pelvic irradiation	Reduced volume irradiation		
	Gy ± 1 SD	Intracavitary application mg-hrs	or	External boost Gy ± 1 SD
Mixed beam	51.30 ± 5.75 Eq.	3813 ± 1474		12.61 ± 5.04 Eq.
Photons	50.96 ± 4.30	4413 ± 1248		11.91 ± 4.14

SD = Standard deviation; Eq. = Equivalent dose, calculated by multiplying the neutron dose by the RBE factor and adding this to the photon dose component.

Local tumor clearance and control

The rate of tumor clearance was calculated as the percentage of patients with tumor clearance at 6 months out of the number of patients alive at that time. Tumor clearance was reported in 72% (41/57) of patients receiving photons and 52% (38/73) of patients receiving mixed beam. This difference is significant at $p = .03$ (Yates-corrected Chi-square). Tumor clearance by treatment and prognostic factors is given in Table 6. A better clearance with photon therapy is seen in both earlier (IIB, IIIA) and later FIGO stages (IIIB, IVA). Analysis by pelvic sidewall involvement shows that the advantage of photon therapy is more predominant in patients who had no or only one pelvic wall attachment. In either portion of the study, patients who had intracavitary application had a better tumor clearance than patients who had no intracavitary application. The logistic regression analysis showed two factors to be significantly related to increased tumor clearance at 6 months: photon therapy and intracavitary application (which may include other prognostic information, since it occurs after the start of treatment). The advantage of photon therapy over neutron therapy in achieving tumor clearance is apparent when comparing patients who had only external radiation and patients who received an intracavitary application. The initial better local control with photons was not maintained however. Results of an analysis of local control at 2 years were 52% for photons and 45% for mixed beam.

Survival

A comparison of overall survival shows no significant difference between treatments (Logrank test, $p = 0.50$) with median survival times of 2.3 years on photons and 1.9 years on mixed beam (Fig. 1). The Cox regression analysis showed increased survival to be significantly related to high Karnofsky performance score and lower FIGO stage. Although intracavitary application was related to tumor clearance, its prognostic significance did not continue, or it became overshadowed by other factors.

Table 5. Evaluation of radiotherapy delivery, percent

	Photons	Mixed beam	Total
Per protocol	49.2	52.6	51.1
Acceptable minor variation	30.2	14.5	21.6
Acceptable major variation	9.5	14.5	12.2
Unacceptable major variation	6.4	14.5	10.8
Death during RT	4.8	4.0	4.3

Table 6. Tumor clearance at 6 months by patient and treatment characteristics

	Photons		Mixed beam	
	No.	% clear	No.	% clear
Overall*	57	71.9	73	52.1
Clinical Stage (FIGO)				
IIB and IIIA	18	77.8	20	50.0
IIIB and IVA	39	69.2	53	52.8
Pelvic sidewall involvement				
0–1 Side	45	75.6	53	47.2
Both	11	54.5	19	63.2
Karnofsky Performance Status				
60–80	12	41.7	26	50.0
90–100	45	80.0	47	53.2
Age at study entry				
<50	20	60.0	25	48.0
50–59	20	80.0	21	52.4
≥60	17	76.5	27	55.6
Intracavitary application				
None	12	58.3	34	41.2
One or two	45	75.6	39	61.5

* One record of a patient on photons had no information regarding tumor clearance. Records of eight patients on photons and seven on mixed beam were not included in the analysis of tumor clearance since they did not survive at least 6 months.

Patterns of failure

Patterns of failure at unlimited follow-up are presented only for patients who were clear of disease at 6 months. There were 41 patients in the photon group and 38 in the mixed-beam group available for this analysis. The overall rate of tumor progression is similar in the two groups. Patients treated with photons had a lower rate of pelvic failure and a higher rate of metastases compared to the mixed-beam group (Table 7). Beyond 2 years of follow-up, there was only one failure in the photon group compared with six failures in the mixed-beam group.

Complications

Only major complications are listed in Table 8. All bowel complications required surgery. Bladder complications in the mixed-beam group included bladder contracture with hydronephrosis and kidney failure (two patients), hemorrhagic contracted bladder requiring ileoconduit (one patient), neurogenic bladder with recurrent infections (one patient), and rectovesical fistula (one patient). There was one patient with a contracted bladder in the photon group. The overall complication rate was 19% with mixed-beam radiation, compared with 11% with photon radiation ($p = 0.13$, one-sided Fisher exact test).

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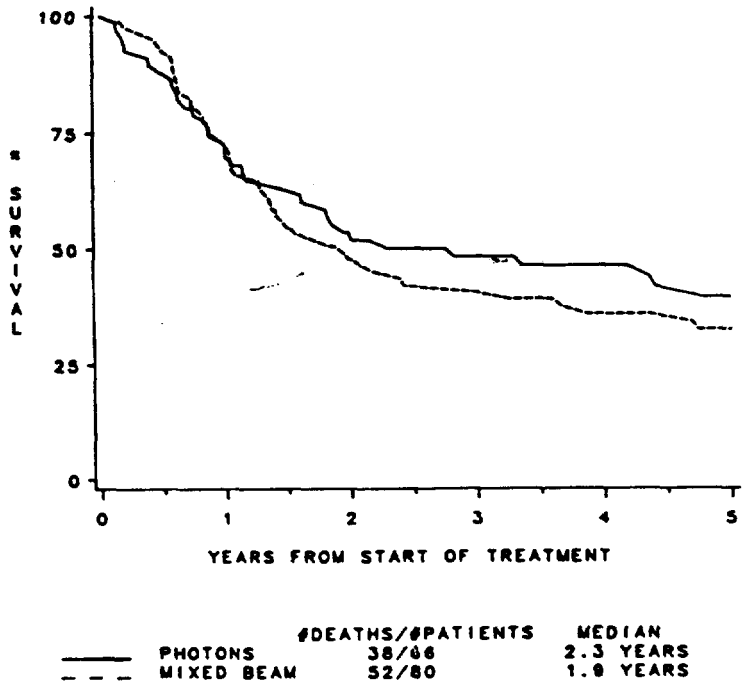

Fig. 1. Survival by treatment.

While the rate of rectosigmoid complications was similar in the two treatment groups, the rate of small bowel and bladder complication was markedly higher in patients treated with mixed beam. The rate of major complications in patients receiving only external radiation was similar in each treatment group. In contrast, patients who received an intracavitary application had a 27% complication rate after mixed beam treatment compared with 10% after photons.

DISCUSSION

The unfavorable physical characteristics of external neutron beam resulted in only a limited experience of this

Table 7. Patterns of failure in patients who had tumor clearance at 6 months

Treatment	No failure	Pelvis	Pelvis + distant	Distant	Total
Photons	23 (56%)	9 (22%)	2 (5%)	7 (17%)	41
Mixed beam	19 (50%)	15 (40%)	2 (5%)	2 (5%)	38

Table 8. Severe complications by treatment

	Mixed beam		Photons	
	Ext. XRT	Ext. + Intracavitary XRT	Ext. XRT	Ext. + Intracavitary XRT
Total patients	39	41	18	48
Complications				
Rectosigmoid	1	5	2	2
Small Bowel	1	4		1
Bowel, unspecified		1		1
Bladder	2	3*		1
Number of patients with severe complications	4 (10%)	11* (27%)	2 (11%)	5 (10%)
Total	15 (19%)		7 (11%)	

* Two patients on mixed beam had both bowel and bladder complications. XRT = Radiotherapy.

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treatment in cervical cancer. Morita *et al.*[12] reported on 98 patients with Stage IIIB cervical carcinoma treated with either neutrons or photons. Patients were assigned to either treatment according to the availability of the cyclotron at the time of entry into the study. Neutron radiation was mixed with photons, as in this study. After external radiation to 50–55 Gy, all patients received 11–13 Gy to point A by intracavitary radiation. There was no difference between the neutron and photon treatments as shown by local tumor control, rate of complications, and survival. In a retrospective study, Maruyama *et al.*[10] combined external photon radiation with intracavitary californium-252, a neutron emitting radioisotope. Patients with Stages III and IV disease were treated with external photon radiation up to a dose of 60 Gy. Intracavitary radiation was either the conventional cesium-137 following the external treatment, or ^{252}Cf given before or after the external radiation. Better local control and survival were reported

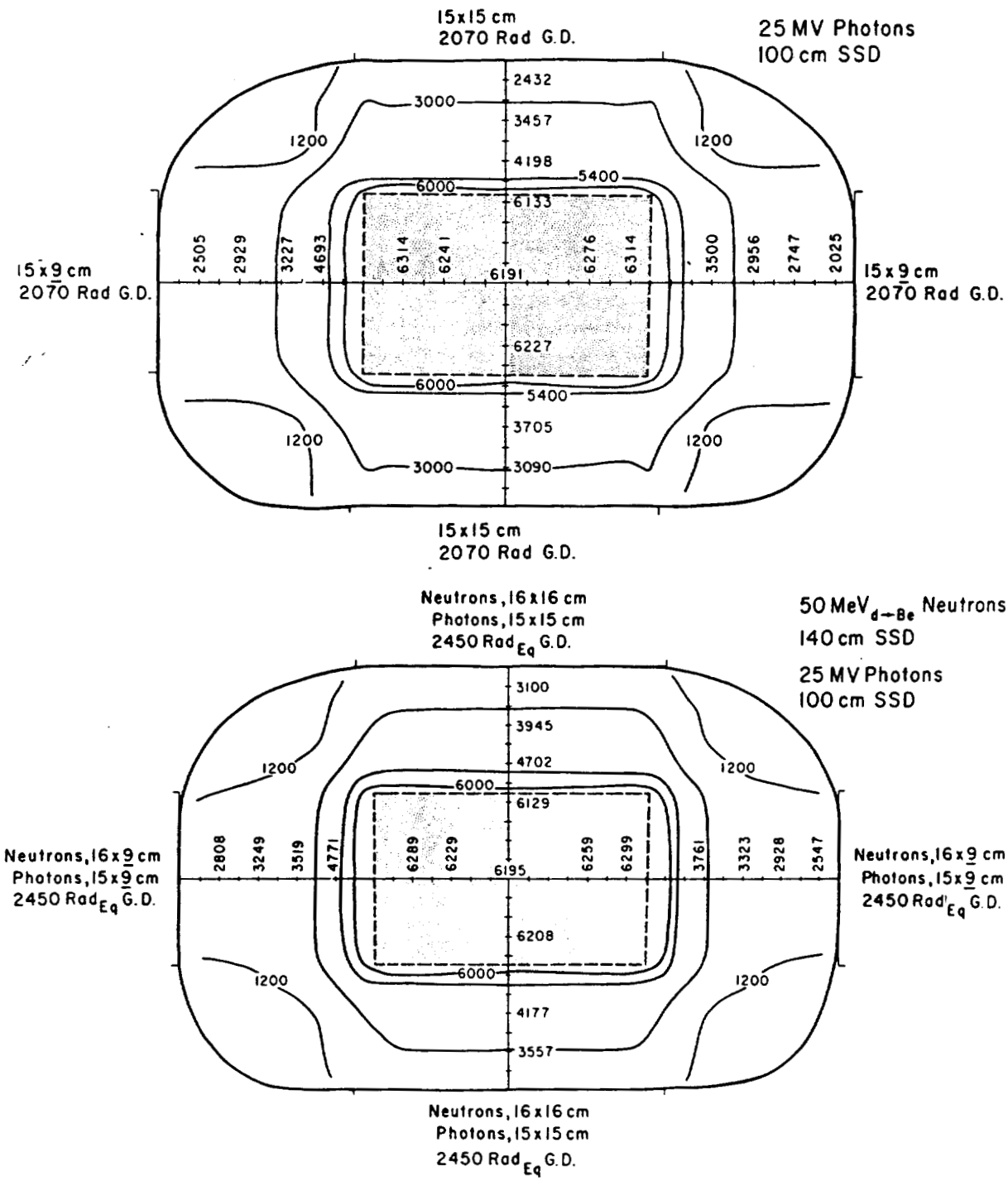

Fig. 2. Isodose distribution for four field pelvis irradiation. Top—25 MV photons. Bottom—mixed beam combining 25 MV photons and 50 MeV d → Be neutrons.

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for the patients who received intracavitary ^{252}Cf prior to the external radiation. The results were given, however, only for patients who had Stage IIIB disease. While administering the neutron component early in the treatment makes sense based on radiobiological considerations,[4] intracavitary radiation is more effective if applied after the external radiation, when the tumor is smaller and receives a higher, more homogenous dose.

A preliminary report on the patients who were treated at UT M. D. Anderson Hospital and participated in the current study was published in 1981.[11] The analysis revealed no difference between the neutron mixed-beam and photon groups with regard to local tumor control, frequency of complications, or survival. A significantly higher number of patients treated with photons received intracavitary radiation compared to the mixed-beam group.

In the present analysis, photon-therapy patients again had a significantly higher rate of intracavitary placement compared with patients treated with mixed beam. The logistic regression demonstrated that this difference could not be explained by an imbalance in other baseline factors. Moreover, photon therapy resulted in a significantly higher clearance of the pelvic tumor. This treatment effect was demonstrated in the logistic regression to be in addition to the effect of the intracavitary application on clearance. However, the Cox regression demonstrated that the early advantage of photon therapy was not maintained.

The higher rate of complications in the bladder and small bowel in patients treated with mixed beam can be ascribed to the fixed horizontal neutron beam with which most patients were treated. A horizontal beam requires that patients be treated in an upright position for the anterior and posterior portals. This position increases the diameter of the patient, resulting in a higher dose to the urinary bladder. The upright position also allows more bowel to descend into the irradiated pelvis. These deficiencies are further accentuated by the inferior depth dose of neutrons when compared with high energy photons. For the same tumor doses delivered to the target, higher doses to the surrounding normal tissues are delivered with a mixed beam containing neutrons compared to high energy photons alone (Fig. 2).

Results in locally advanced cervical cancer are better with high-energy photons than with ^{60}Co irradiation. This was shown in a randomized trial by Allt,[1] and later with more patients and longer follow-up, by Johns.[7] High-energy beams result in a superior dose distribution to the tumor and sparing of surrounding normal tissues. Therefore, it is logical to assume that the constraints of the neutron beam as given in this study resulted in inferior dose distribution that adversely affected local control.

If there is a real advantage to external radiation with neutrons in the treatment of advanced cervical cancer, it was masked by the significant shortcomings of the equipment used in this study. It would be unfair to evaluate neutron therapy for advanced cervical cancer solely on the basis of these results. Thus, in July 1986, a new randomized trial for evaluation of neutron therapy in cervical cancer was started by the RTOG. The four participating institutions all possess multi-angle high-energy hospital-based neutron-therapy facilities.

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