Int. J. Radiation Oncology Biol. Phys., Vol. 37, No. 3, pp. 593–599, 1997

0360-3016/97 $17.00 + .00

ELSEVIER

PII S0360-3016(96)00591-3

● *Clinical Investigation*

A PHASE I/II STUDY OF EXTERNAL BEAM RADIATION, BRACHYTHERAPY AND CONCURRENT CHEMOTHERAPY IN LOCALIZED CANCER OF THE ESOPHAGUS (RTOG 92-07): PRELIMINARY TOXICITY REPORT

LAURIE E. GASPAR, M.D.,* CHUNLIN QIAN, PH.D.,† WALTER I. KOCHA, M.D.,‡ LAWRENCE R. COIA, M.D.,§ ARNOLD HERSKOVIC, M.D.‖ AND MARY GRAHAM¶

*Department of Radiation Oncology, Wayne State University, Detroit, MI; †RTOG Headquarters, Philadelphia, PA; ‡Department of Oncology, University of Western Ontario, London, Ontario, Canada; §Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA; ‖Department of Radiation Oncology, Oakwood Hospital, Dearborn, MI; and ¶Department of Radiation Oncology, Washington University, St. Louis, MO

Purpose: A multi-institutional, prospective study was designed to determine the feasibility and tolerance of external beam irradiation plus concurrent chemotherapy and esophageal brachytherapy (EB) in a potentially curable group of patients with adenocarcinoma or squamous cell carcinoma of the esophagus.

Methods and Materials: Planned treatment was 50 Gy external beam radiation (25 fractions/5 weeks) followed 2 weeks later by EB [either high dose rate (HDR) 5 Gy, weeks 8, 9, and 10, for a total of 15 Gy, or low dose rate (LDR) 20 Gy, week 8]. The protocol was later revised to delete the LDR alternative, owing to poor accrual, and to decrease the HDR dose to 10 Gy (i.e. 5 Gy, weeks 8 and 9). Chemotherapy was given weeks 1, 5, 8, and 11 with cisplatin 75 mg/m^2 and 5-fluorouracil 1000 mg^2/m per 24 h, 96-h infusion. The study closed in January 1995 after 56 patients had been entered on the HDR arm. Six patients were declared ineligible owing to tumor extension to the gastroesophageal junction (three patients) or involved celiac lymph nodes (three patients). Of the 50 eligible patients, the planned EB dose was 15 and 10 Gy in 40 and 10 patients, respectively. Forty-six (92%) of the eligible patients had squamous histology, and three (6%) adenocarcinoma.

Results: Life-threatening toxicity or treatment-related death occurred in 13 (26%) and 4 (8%) of the 50 eligible patients, respectively. Treatment-related esophageal fistulas occurred in three patients (12% overall, 14% of patients starting EB) at 0.5–6.2 months from the first day of brachytherapy, leading to death in three. The fourth death was secondary to renal toxicity and infection attributed to chemotherapy. No correlation was found between the development of fistula and location of primary tumor, brachytherapy active length or applicator diameter. So far, 5 of the 6 treatment-related fistulas have occurred following 15 Gy EB. The other fistula occurred after only 5 Gy of a planned 15 Gy was delivered.

Conclusion: Thirty-five patients (70%) were able to complete external beam, EB, and at least two courses of chemotherapy. Estimated survival rate at 12 months is 48%, with an estimated 11-month median survival rate. Survival following external beam radiation plus concurrent chemotherapy and EB does not appear to be significantly different from survival seen following external beam radiation and chemotherapy only. The development of six fistulas in the 35 patients completing EB is of concern. Based on the high incidence of fistulas, we urge extreme caution in employing EB as a boost following concurrent external beam radiation and chemotherapy. © 1997 Elsevier Science Inc.

Esophagus cancer, Brachytherapy.

INTRODUCTION

Recent advances have been made in the therapy for cancer of the esophagus, because of a prospective randomized trial [Radiation Therapy Oncology Group (RTOG) 8501, Southwest Oncology Group, (SWOG) 8598, North Central Cancer Treatment Group (NCCTG) 88-40-51] demonstrating a statistically significant survival advantage for external beam radiation and concurrent chemotherapy, compared to external beam radiation alone (8). Two-year survival rates are now in the range of 35%, compared to 10% with radiation alone (12). Nevertheless, locoregional tumor control remained a major problem, with 27% having persistence of disease and 16% developing recurrence of locoregional disease following combined modality treatment.

In view of suboptimal primary tumor control, intensification of the radiation dose was thought to be reasonable. Esophageal brachytherapy (EB) was proposed as a boost

Presented at American Society of Therapeutic Radiation Oncology, Miami, Florida, October 1995

Reprint requests to: Laurie E. Gaspar, M.D., Department of Radiation Oncology, Harper Hospital, Wayne State University, 3990 John Rd., Detroit, MI 48201.

Accepted for publication 4 November 1996.

Table 1. 1983 TNM staging system

T0	No evidence of primary tumor
T1	Involves ≤5 cm length; no obstruction; not circumferential; confined to esophageal wall
T2	Involves >5 cm length; obstruction; circumferential; confined to esophageal wall
T3	Extra-esophageal spread
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis

to the primary tumor, allowing relative sparing of the surrounding normal tissues. Several retrospective studies had suggested that EB combined with external beam radiation offered improved local control and relief from dysphagia compared to historical controls treated with external beam only (5, 9, 12). Few data were available regarding the outcome of chemoradiation followed by an intracavitary EB boost. Therefore, the purpose of RTOG 9207 was to assess the feasibility, tolerance, and efficacy of external beam irradiation with concurrent chemotherapy and EB.

METHODS AND MATERIALS

Patient selection

All patients had histologically confirmed squamous cell or adenocarcinoma of the thoracic esophagus measuring ≤10 cm in length. The esophageal primary tumor had to be clinically limited to the esophagus with or without the presence of involved regional lymph nodes, i.e., T1-2, NX-N1, and M0 by the 1983 UICC Clinical Staging System (Table 1). To be enrolled, a patient had to have Karnofsky performance status (KPS) ≥60, white blood cell count ≥ 4.0×10^9 cells/liter, platelets ≥ 150×10^9 cells/liter, total serum bilirubin ≤ 1.5 mg%, serum creatinine ≤ 1.5 mg%, and/or creatinine clearance ≥ 65 cc/min. There had to have been no history of prior malignancy other than nonmelanoma cancers of the skin or *in situ* cervical carcinoma within 5 years of entrance to the study. The study protocol was approved by the National Institutes of Health and the review boards at all the participating institutions. All patients gave informed, written consent.

Ineligibility factors included cervical esophageal tumors (upper tumor border < 18 cm from the incisor teeth), extension of tumor to within 1 cm of gastroesophageal junction, radiological or clinical evidence of lymph node metastases to supraclavicular or more distant nodal groups, and invasion of the tracheobronchial tree proven by bronchoscopy.

Pretreatment evaluations

The following were required within 4 weeks preceding registration: complete medical history and physical exam; complete blood count; biochemical screening profile including alkaline phosphatase, total bilirubin, and creatinine; chest radiography; barium contrast esophagogram including proximal stomach, abdominal, and thoracic computed tomography (CT) scan; and esophageal endoscopy with biopsy. Bronchoscopy was required in all patients with primary tumors situated < 29 cm from the incisors. Bone scan was required only if the serum alkaline phosphatase was above normal or the patient reported new bony pain. Swallowing was graded according to the scale in Table 2.

Radiation therapy

External beam. Megavoltage radiation therapy units were used with a minimum source-to-axis distance of 80 cm. The radiation field extended at least 5 cm above and below the tumor, with at least 2 cm lateral margin. The field included the supraclavicular fossa if the tumor originated above the level of the carina. The boost radiation field was the same length. Multifield techniques were used to limit the maximum dose to the spinal cord to ≤ 45 Gy.

The radiation treatments were delivered 5 days/week, 2 Gy/fraction. The initial anterior-posterior parallel-opposed fields received 30 Gy and the off-cord fields received 20 Gy, for a total dose of 50 Gy in 25 fractions in 5 weeks. All doses were calculated without correction for inhomogeneity of tissue. The dose gradient within the volume of tissue treated was not to vary > 10%.

Brachytherapy. The esophageal brachytherapy could be either low-dose-rate (LDR) or high-dose-rate (HDR) ^{192}Ir, although institutions were required to declare themselves HDR or LDR for the entire duration of the study. The range of acceptable dose rates for HDR and LDR was 0.2–5.0 Gy/min and 0.5–1.0 Gy/h, respectively. The HDR brachytherapy treatment consisted initially of 15 Gy in three fractions of 5 Gy during weeks 8, 9, and 10. The HDR dose was specified at a 1-cm depth from the mid-dwell position. Equal dwell times were to be used. Center-to-center separations of the dwell positions of the stepping source were to be no more than 1 cm. HDR fractions were 6–8 days apart, given concurrently with the 5-fluorouracil (5-FU) in week 8, 24–48 h after starting the 5-FU infusion of the third cycle of chemotherapy. Following the observation of several fistulas in the HDR group, the HDR brachytherapy dose was reduced in December 1994 to 10 Gy in two fractions of 5 Gy, 1 week apart in weeks 8 and 9. The LDR group received 20 Gy during week 8, given concurrently with the 5-FU infusion of the third cycle of chemotherapy. The LDR dose was specified 1 cm from

Table 2. Grading of swallowing status

Grade 1	No dysphagia; able to eat any solids
Grade 2	Mild dysphagia; semisolids and liquids
Grade 3	Moderate dysphagia; liquids only
Grade 4	Complete obstruction; unable to take even liquids

the midsource position. In December 1994, the LDR alternative was discontinued, having accrued only 19 patients in 2.5 years.

The HDR and LDR brachytherapy was delivered with a 10–12-Fr applicator (external diameter 4–6 mm), inserted transnasally or transorally. Center-to-center separations of the ^{192}Ir seeds were no more than 1 cm. The active treatment length, i.e., the distance from the proximal and distal HDR dwell positions or LDR source positions, was the pretreatment esophageal tumor length plus a 1-cm margin proximal and distal margin. The esophageal tumor length was determined from the CT scans, barium swallow, and endoscopy findings, taking the longest of the three available determinations.

Chemotherapy

5-Fluorouracil, 1000 mg/m^2 of body surface area/day, was administered as a continuous intravenous infusionfor the first 4 days of weeks 1, 5, 8, and 11. Cisplatin, 75 mg/m^2, was given at a rate of 1 mg/min on the first day of each course. The dose of 5-FU was reduced by 25% if severe stomatitis or diarrhea developed. The dose of cisplatin was not reduced for transient changes in renal function, but was reduced by 25% or 50% if the granulocyte count fell below 3.0×10^9 cells/liter or 1.0×10^9 cells/liter, respectively, or a platelet count below 75×10^9 cells/liter or 50×10^9 cells/liter. If the renal function did not return to normal by the time of the next scheduled dose of cisplatin, the cisplatin was discontinued.

Follow-up

Patients were seen 3 months posttherapy and then at minimum follow-up intervals of 6 months. Barium swallow, CT scan of the chest and abdomen, chest X ray, complete blood count, serum biochemistry, history, physical exam including assessment of KPS weight, and swallowing status were to be done at each visit. Endoscopy was required 1–3 months following completion of therapy. Posttreatment biopsies were required only if suspicious areas were identified at endoscopy.

Patients with no evidence of tumor upon barium swallow, CT, and endoscopy were considered "responders to therapy." Those with histologically confirmed tumor posttreatment were "failures of therapy." There was no definition of partial response for this clinical trial.

Data collection and statistical analysis

The study end points were (a) patient tolerance to the proposed treatment in terms of life-threatening acute esophagitis and late fistula, (b) the percentage of patients receiving at least 75% of the treatment, (c) local control and patterns of failure, and (d) survival.

In RTOG 85-01, a study of 50 Gy external beam radiation (25 fractions in 5 weeks) and concurrent 5-FU and cisplatin chemotherapy in which the entry criteria were similar to RTOG 92-07, life-threatening esophageal toxicity occurred in 5% of patients. The life-threatening toxicity of RTOG 92-07 was not expected to increase beyond 10%. The 1-year local control was expected to be ≥56%, similar to the local control found in RTOG 85-01 with chemoradiation.

A sample of 50 patients for each dose rate (LDR and HDR) was planned. With this sample size, the lower bound of the 95% one-sided confidence interval around hypothesized totals of (a) 75% patients receiving the designated protocol treatment would be 65%; (b) 56% local control at 1 year would be 44%; and 51% overall survival rate at 1 year would be 39%. Hypothesized rates for feasibility, local control, and survival were derived from the RTOG 85-01 experience. The target accrual for each dose rate was 55 patients, allowing for an additional 10% of the required sample to guard against ineligible or unevaluable cases.

Interim reports with statistical analyses, including toxicities, were prepared every 6 months. It was predetermined that if the accrual for a particular dose rate was < 12 patients/year, further patient accrual to that dose rate was to be terminated.

RESULTS

Demographic data

Between June 1992 and February 1994, 56 patients were entered on the HDR option and 19 patients on the LDR option. Since accrual was much slower than expected for the LDR arm, new patient entry to the LDR arm was discontinued as of December 1994. Fifty-six patients were entered to the HDR alternative, although six patients were later deemed ineligible for the following reasons: primary tumor extension to the gastroesophageal–esophageal junction (three patients) and suspected tumor involvement of the celiac lymph nodes (three patients). The demographic data and tumor characteristics of the 50 evaluable patients are given in Table 3.

Compliance

Forty-seven patients (94%) completed the planned external beam irradiation concurrent with two courses of chemotherapy. Forty-two patients (84%) received one or more fraction(s) of brachytherapy; 35 (70%) had all fractions, i.e., 15 Gy in three fractions before the protocol change (29 patients) and 10 Gy in two fractions afterward (6 patients). Seven patients had only one of the planned fractions of brachytherapy. Eight patients never started the brachytherapy: 2 were due to refusal, 2 had disease progression, 1 was because of deterioration in medical condition, 1 was due to death, and 2 were for unknown reasons. Forty patients (80%) started the third course of chemotherapy; 29 (58%) started the fourth course. Reasons for not starting or completing the third or fourth cycle of chemotherapy included patient refusal (7 patients), poor general condition (1 patient), disease progression (2 patients), treatment toxicity (3 patients), death (2 patients), or unidentified reason (5 patients). Of the initial 50 eligible

Table 3. Patient/tumor characteristics of the 50 evaluable patients on RTOG 92-07

Characteristic	No. (%) of patients
Age (yr)	
Mean	63.8
Range	40.1–75.7
Gender	
Male	32 (64%)
Female	18 (36%)
Race	
White	33 (66%)
Black	15 (30%)
Hispanic	2 (4%)
KPS	
70–80	23 (46%)
90–100	27 (54%)
Histology	
Squamous	46 (92%)
Adenocarcinoma	4 (8%)
% Weight loss	
Mean	6.4
Range	0–22
≥10%	16 (32%)
<10%	31 (62%)
Missing data	3 (6%)
Current weight (kg)	
Mean	67
Range	40–159
Primary length (cm)	
Mean	6.1
Range	1.5–10
<5 cm	15 (30%)
≥5 cm	35 (70%)
Clinical T stage	
T1	12 (24%)
T2	38 (76%)
Clinical N stage	
N0	39 (78%)
N1	8 (6%)
NX	3 (1%)
Clinical M stage	
M0	50 (100%)

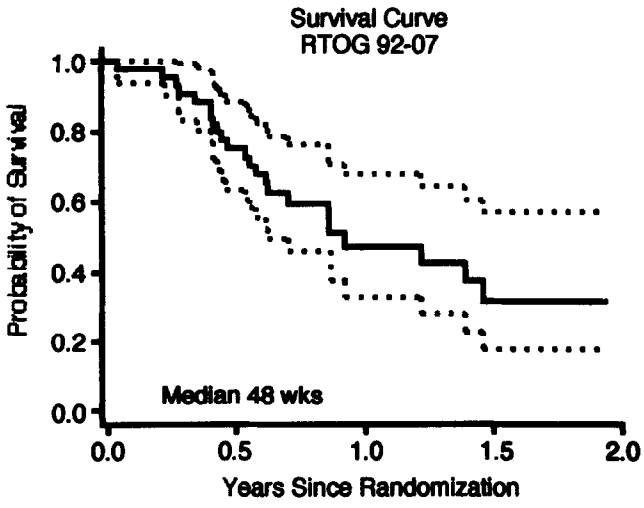

Fig. 1. Kaplan–Meier survival curve, RTOG 92-07.

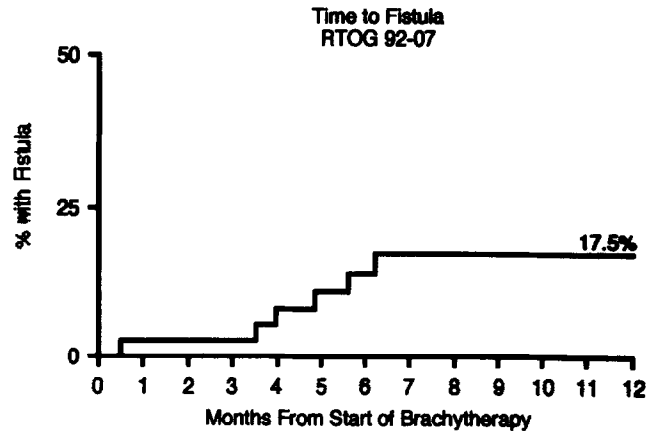

Fig. 2. Cumulative incidence of esophageal fistulas, RTOG 92-07.

patients, 25 (50%) finished the external beam radiation, chemotherapy, and brachytherapy as per protocol.

Survival and sites of failure

With a median follow-up of 11 months, 23 deaths have been reported in the 50 patients eligible for EB with HDR, and the 1-year survival rate is estimated to be 48%, with a log-transformed 95% confidence interval of 34–67%. Figure 1 is the survival curve with log-transformed 95% confidence intervals and censoring marks for 48 patients for whom there is follow-up information available.

Information regarding tumor response and first site of failure was available in 48 patients eligible for EB with HDR (Tables 4 and 5). Persistent disease was found in 19% of patients; complete response was seen in 73%. Of the complete responders, locoregional failure as the site of first relapse occurred in 23%, 13% local failure alone, and 10% combined local and distant failure. Tumor response and site of first failure in the 130 chemoradiation patients on RTOG 85-01 are also presented in Tables 4 and 5. Given the much shorter follow-up for RTOG 92-07, the incidence of locoregional or distant failures may increase. However, at present, complete response and locoregional control rates appear to be comparable between the two studies.

Treatment toxicity

Severe toxicity (RTOG Grade 3) was documented in 29 (58%) of the patients, mostly in the form of hematologic or gastrointestinal side effects. Life-threatening (RTOG Grade 4) or fatal toxicity (RTOG Grade 5) was seen in 13 (26%) and 4 (8%) of patients, respectively. Toxicities are summarized in Table 6. Life-threatening esophageal strictures occurred in two patients. Esophageal fistulas, thought to be treatment-related rather than tumor-related, occurred in 6 patients, leading to death in 3. All patients with fistula had endoscopy and attempted biopsy at time of fistula or had autopsy at death. The fistula was aorto-esophageal in 1 patient, esophageal-bronchotracheal tree in 3, and esophageal-mediastinal in 2. A comparison of

Table 4. Tumor response in RTOG 92-07 and RTOG 85-01

	RTOG 92-07 (n = 48)	RTOG 85-01 (n = 130)
Persistent disease	9 (19%)	34 (26%)
No information	4 (8%)	7 (5%)
Complete response	35 (73%)	89 (68%)

the pretreatment studies and brachytherapy simulation films with the postfistula studies suggested that the fistulas occurred in the region of the brachytherapy. Fistulas occurred in patients with primary tumors in both the middle and lower esophagus (Table 7). The cumulative yearly incidence estimate for fistula was 17.5%/year, as compared with the crude rate of 14.3% (6 of 42) for those patients who had at least one fraction of brachytherapy, or 12% (6 of 50) for all study patients. The interval from first brachytherapy to diagnosis of esophageal fistula ranged from 0.5 to 6.2 months, with a median of 3.9 (Fig. 2). Five of the six patients developing fistulas received 15 Gy brachytherapy dose. The other patient received just one fraction of 5 Gy and developed a fistula within 0.5 months. None of the 10 patients treated after the reduction of brachytherapy dose from 15 to 10 Gy have developed fistulas, although the duration of follow-up available on these patients is more limited.

DISCUSSION

Esophageal brachytherapy has long been advocated as a radiotherapeutic technique enabling irradiation of locoregional disease to a high dose with relative sparing of the surrounding normal tissues, potentially increasing tumor control while minimizing acute and chronic toxicity (3, 4, 6). Compared with external beam irradiation dose escalation, other possible advantages include increased speed of relief of dysphagia, shortening of treatment time, and patient convenience (14).

Several retrospective studies (1, 5, 7, 9, 10, 16) and two prospective studies (18, 19) comparing external beam irradiation with or without a brachytherapy boost claim improved survival, local control, and swallowing ability favoring patients treated with HDR, intermediate-dose-rate, or LDR brachytherapy. Concurrent chemotherapy was not an established therapy during the years that these studies were conducted.

Retrospective reports of external beam with or without a brachytherapy boost in large patient numbers have been reported by Hishikawa *et al.*, from Japan, where esophageal cancers are predominantly squamous cell cancers in the upper-middle thoracic esophagus (9–11). A comparison of survival in patients treated with or without a 12-Gy brachytherapy boost following external beam radiation (median external beam dose of 50 Gy) suggested that although 5-year survival was not definitely improved by the addition of a brachytherapy boost, local control at 2 years was significantly improved in the brachytherapy group. The 2-year actuarial local control rate following brachytherapy was 63%, as opposed to 20% with external beam alone. Cause of death following brachytherapy was attributed to local failure in 28% of patients, local failure with distant metastases in 12%, distant metastasis in 29%, and intercurrent disease in 31%. Esophageal ulceration, stricture, and fistula were found in 28%, 10%, and 4% of patients, respectively.

Table 5. First sites of failure in RTOG 92-07 and RTOG 85-01

	RTOG 92-07 (n = 48)	RTOG 85-01 (n = 130)
Locoregional	6 (13%)	23 (18%)
Distant	3 (6%)	14 (11%)
Local/distant simultaneous	5 (10%)	7 (5%)
Failure, not specified	0	5 (4%)
No failure	21 (44%)	40 (31%)

Table 6. Life-threatening and fatal toxicities in RTOG 92-07 (n = 50)

	Life-threatening	Fatal	All (%)
Upper aerodigestive tract excluding fistulas*	6	0	6 (12%)
Fistula	3	3	6 (12%)
Gastrointestinal tract†	1	0	1 (2%)
Hematologic‡	8	1	9 (18%)
Infection	2	0	2 (4%)
Skin§§	0	1	1 (2%)
Renal	0	1	1 (2%)
Other	3	0	3 (6%)

* For the lungs and esophagus, life-threatening effects included ulceration, necrosis, perforation, and formation of a stricture.

† Life-threatening gastrointestinal side effects involved nausea and vomiting for >6 days, requiring hospitalization.

‡ Life-threatening hematologic effects included a leukocyte count below 1.0×10^9 cells/liter, a platelet count below 25×10^9 cells/liter, and a hemoglobin concentration below 50 g/liter.

§ Fatal side effects of skin involved moist desquamation simultaneous with renal toxicity.

Table 7. Patient/tumor characteristics in six patients who developed fistulas

Case no.	Tumor length (cm)	Distant from incisors (cm)	T stage	N stage
1	5.5	25	2	0
2	9.0	25	2	0
3	3.0	26	2	0
4	4.0	19	1	0
5	4.0	36	2	0
6	3.0	25	1	0

Table 8. Clinical results of external beam radiation, brachytherapy boost, and concurrent chemotherapy

	Staar *et al.* (15)	Montravadi *et al.* (13)	RTOG 9207
No. patients	32	40	50
Pathology	NS	Adeno Ca (29) Squamous (11)	Adeno Ca (4) Squamous (46)
Extent of disease	Stage II–III		Stage II–III
Chemo	Mito-C 10 mg/m^2 days 2, 29 5FU 1000 mg/m^2 per day × 4 days	Mito-C 10 mg/m^2 i.v., days 1, 29, 5-FU 1000 mg/m^2 per day × 4 days	DDP 75 mg/m^2 day 1, wk 1, 5, 8, 11; 5-FU 1000 mg/m^2 per day × 4 days, wk 1, 5, 8, 11
XRT (Gy/wk)	55.8 Gy/6 wk	40–55 Gy/4–6 wk	50 Gy/5 wk
HDR* dose/fraction	7 Gy	5 Gy	5 Gy
No. fractions	2	2	2–3
Interfraction interval	2 wk	2 wk	1 wk
Applicator diameter	NS	6 cm	4–6 mm
Complication			
Stricture	NS	23%	4%
Fistula	NS	0%	12%
Local control	NS	85% complete response 78% local control	73% complete response 58% local control
Survival	1 yr 48%, 2 yr 2% Median 15 mo	3 yr 40%	1 yr 48%

* All doses specified at 1 cm from mid-dwell position. Chemo = Chemotherapy; 5-FU = 5-fluorouracil; DDP = cisplatinum; HDR = high dose rate; Mito-C = mitomycin C; NS = not stated.

The addition of concurrent (with or without maintenance) chemotherapy to external beam irradiation has been shown to be superior to external beam irradiation alone for medically fit patients with localized cancer of the esophagus (8, 12). The addition of chemotherapy has been shown to improve survival significantly, with corresponding improvements in locoregional control and reduction in incidence of distant metastases. Previous studies claiming benefits to brachytherapy are now of questionable relevance if chemotherapy was not included in the treatment regimen. Tables 4 and 5, in which response rate and sites of first failure are tabulated for RTOG 92-07 and RTOG 85-01, suggest little benefit for the addition of a brachytherapy boost to external beam irradiation and chemotherapy alone. A direct comparison of RTOG 85-01 and RTOG 92-07 is difficult, since response was assessed without endoscopy in RTOG 85-01. Nevertheless, a significant improvement in complete response and locoregional control following brachytherapy boost was not demonstrated.

Prior to this report, published results of external beam radiation, brachytherapy boost, and concurrent chemotherapy in a meaningful number of patients have been few (13, 15). Table 8 summarizes these experiences as well as our own. RTOG 92-07 has documented treatment-related fistulas in 12% of the patients, compared to none reported by Montravadi *et al.*(13) or Staar *et al.*(15). Direct comparison between these clinical series is hampered by the differences in staging, classification, response end points, and duration of follow-up. Differences in treatment regimens or sequencing may account for some of the observed differences in toxicity. Compared to the experience of Montravadi *et al.*, RTOG 92-07 called for (a) more courses of chemotherapy, (b) chemotherapy with a cisplatinum-containing regimen, (c) chemotherapy concurrent with brachytherapy, and (d) a higher brachytherapy dose (initially 15 Gy in three fractions).

The high incidence of esophageal fistulas seen in this study is alarming. Further CT review is ongoing to compare the pretreatment tumor length, esophageal tumor wall thickness, and association of tumor with surrounding normal structures with subsequent fistula formation.

In the absence of clear benefits of brachytherapy boost, in terms of either tumor response, local control, or patient survival rates, there are no plans to take this current treatment regimen to the Phase III setting. Pending the results of other prospective studies, extreme caution is urged in the use of external beam radiation, brachytherapy boost, and concurrent chemotherapy as used in this study.

REFERENCES

1. Al-Sarraf, M.; Pajak, T.; Herskovic, A.; Leichman, L.; Brindle, J. S.; Vaitkevicius, K.; Cooper, J.; Byhardt, R.; Davis, L.; Emami, B. Progress report of combined chemo-radiotherapy (CT-RT) versus radiotherapy (RT) alone in patients with esophageal cancer, an intergroup study. Proc. ASCO 12:197; 1993.
2. Barcat; Guisez, J. Essais de traitement de quelques cas d'epithelioma de l'oesophage par les applications locales directes de radium. Bull. Mem. Soc. Med. Hop. Paris 26:717–712; 1909.
3. Bottrill, D. O.; Plane, J. H.; Newaishy, G. A. A proposed afterloading technique for irradiation of the oesophagus. Br. J. Radiol. 52:573–574; 1979.

4. Dickson, R. J. Radiation therapy in carcinoma of the esophagus—A review. Am. J. Med. Sci. 241:662–677; 1971.
5. Flores, A. D.; Nelems, B.; Evans, K. G.; Evans, H; Evans, J. H.; Stoller, J. L.; Jackson, S. M. Impact of new radiotherapy modalities on the surgical management of cancer of the esophagus and cardia. Int. J. Radiat. Oncol. Biol. Phys. 17:937–944; 1989.
6. Guisez, J. Malignant tumors of the esophagus. J. Laryngol. Otol. 40:213–232; 1925.
7. Hareyama, M.; Nishio, M.; Kagami, Y.; Narimatsu, N.; Saito, A.; Sakurai, T. Intracavitary brachytherapy combined with external beam irradiation for squamous cell carcinoma of the thoracic esophagus. Int. J. Radiat. Oncol. Biol. Phys. 24:235–240; 1992.
8. Herskovic, A.; Martz, K.; Al-Sarraf, M.; Leichman, L.; Brindle, J.; Vaitkevicius, V.; Cooper, J.; Byhardt, R.; Davis, L.; Emami, B. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N. Engl. J. Med. 326:1593–1598; 1992.
9. Hishikawa, Y.; Kurisu, K.; Taniguchi, M.; Kamikonya, N.; Miura, T. High dose-rate intraluminal brachytherapy for esophageal cancer: 10 years experience in Hyogo College of Medicine. Radiother. Oncol. 21:107–114; 1991.
10. Hishikawa, Y.; Kurisu, K.; Taniguchi, M.; Kamikonya, N.; Miura, T. High-dose-rate intraluminal brachytherapy (HDRIBT) for esophageal cancer. Int. J. Radiat. Oncol. Biol. Phys. 21:1133–1135; 1991.
11. Hishikawa, Y.; Kamikonya, N.; Tanaka, S.; Miura, T. Radiotherapy of esophageal carcinoma: Role of high-dose-rate intracavitary irradiation. Radiother. Oncol. 9:13–20; 1987.
12. Hyden, E.C.; Langholz, B.; Tilden, T.; Lam, K.; Luxton, G.; Astrahan, M.; Jepson, J.; Petrovich, Z. External beam and intraluminal radiotherapy in the treatment of carcinoma of the esophagus. Thorac. Cardiovasc. Surg. 96:237–241; 1988.
13. Montravadi, R. V. P.; Gates, J. O.; Bajpai, D.; Crawford, J. N.; Trenkner, J. D.; Trenkner, D. A. Combined chemotherapy and external radiation therapy plus intraluminal boost with high dose rate brachytherapy for carcinoma of the esophagus. Endocurietherapy/Hyperthermia Oncol. 11:223–233; 1995.
14. Nori, D.; Allison, R. Prospects for improved treatment results with radiation dose escalation in esophageal cancer. Endocuriether/Hyperthermia Oncol. 9:63–67; 1993.
15. Staar, S.; Mueller, R. P.; Achterrath, W. Intensified treatment for inoperable esophagus cancer: simultaneous radiochemotherapy combined with HDR intraluminal brachytherapy: results of a phase II trial. Proc. ASCO (Abstr) 12:223; 1993.
16. Sur, R. K.; Kochhar, R.; Negi, P. S.; Gupta, B. D. High dose rate intraluminal brachytherapy in palliation of esophageal carcinoma. Endocuriether. Hyperthermia Oncol. 10:25–29; 1994.
17. Wang, R. Z.; Zhao, R. O. Combined intracavitary and external radiotherapy for esophageal carcinoma: a prospective randomized clinical trial on 128 patients. Chin. J. Radiat. Oncol. 1:41–43; 1987.
18. Yin, W. Brachytherapy of carcinoma of the esophagus in China, 1970–1974 and 1982–1984. Proc. Remote Afterloading. Brachytherapy Meeting. 34–35; 1989 .