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● *Clinical Original Contribution*

EVALUATION OF THE DOSE FOR POSTOPERATIVE RADIATION THERAPY OF HEAD AND NECK CANCER: FIRST REPORT OF A PROSPECTIVE RANDOMIZED TRIAL

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Purpose: This study was designed to determine in a prospective randomized trial the optimal dose of conventionally fractionated postoperative radiotherapy for advanced head and neck cancer in relation to clinical and pathologic risk factors.

Methods and Materials: Between January 1983 and March 1991, 302 patients were enrolled on the study. This analysis is based on the first 240 patients entered through September 1989, of whom 221 (92%) had AJC Stage III or IV cancers of the oral cavity, oropharynx, hypopharynx, or larynx. The patients were stratified by postulated risk factors and randomized to one of three dose levels ranging between 52.2 Gy and 68.4 Gy, all given in daily doses of 1.8 Gy. Patients receiving > 57.6 Gy had a field reduction at this dose level such that boosts were only given to sites of increased risk.

Results: The overall crude and actuarial 2-year local-regional recurrence rates were 25.4% and 26%, respectively. Patients who received a dose of ≤ 54 Gy had a significantly higher primary failure rate than those receiving ≥ 57.6 Gy ($p = 0.02$). No significant dose response could be demonstrated above 57.6 Gy except for patients with extracapsular nodal disease in the neck in whom the recurrence rate was significantly higher at 57.6 Gy than at ≥ 63 Gy. Analysis of prognostic factors predictive of local-regional recurrence showed that the only variable of independent significance was extracapsular nodal disease. However, clusters of two or more of the following risk factors were associated with a progressively increased risk of recurrence: oral cavity primary, mucosal margins close or positive, nerve invasion, ≥ 2 positive lymph nodes, largest node > 3 cm, treatment delay greater than 6 weeks, and Zubrod performance status ≥ 2. Moderate to severe complications of combined treatment occurred in 7.1% of patients; these were more frequent in patients who received ≥ 63 Gy.

Conclusion: With daily fractions of 1.8 Gy, a minimum tumor dose of 57.6 Gy to the whole operative bed should be delivered with a boost of 63 Gy being given to sites of increased risk, especially regions of the neck where extracapsular nodal disease is present. Treatment should be started as soon as possible after surgery. Dose escalation above 63 Gy at 1.8 Gy per day does not appear to improve the therapeutic ratio.

Head and neck neoplasms, Postoperative radiotherapy, Dose optimization, Prognostic factors.

INTRODUCTION

The combination of surgery and radiotherapy in the treatment of advanced squamous cell carcinomas of the head and neck developed empirically because of the poor local-regional control rate achieved with either modality alone. The concept of integrated treatment with combined modalities rather than use of one modality as attempted salvage treatment for recurrences after unsuccessful treatment with the other was enunciated by MacComb and

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Fletcher in 1957 (17). Data in support of the combined approach were published in 1970 by Fletcher and Evers (12), who also stressed the importance of irradiating the whole tumor bed rather than just the site(s) of known residual disease after surgery.

During the 1970s and early 1980s, a number of reports of surgical series documented an association between various clinico-pathologic features and the risk of recurrence, including primary disease site (8), surgical margins (16), perineural invasion (6), number and location of positive neck nodes (19), and presence of extracapsular nodal extension (13). At the same time, convincing evidence of the efficacy of adjuvant radiotherapy in substantially reducing the risk of local-regional recurrence from that expected after surgery alone was provided by data from the UT M. D. Anderson Hospital (2, 9), Memorial Hospital, New York (20, 21), the Institut Gustave Roussy (5), the Netherlands Cancer Institute (3) and the University of Florida (18). The issue of the relative efficacy of preoperative versus postoperative radiotherapy was addressed in a prospective randomized trial begun in 1973 by the Radiation Therapy Oncology Group (RTOG) (14). This trial showed a significant superiority of postoperative irradiation in terms of local regional disease control.

Just as the use of radiotherapy developed empirically, so did the dose. In the 1960s and 1970s, Fletcher evolved the concept of the treatment of subclinical disease by elective irradiation of undisturbed lymphatic areas potentially harboring clinically undetectable metastases. In this context, it was shown that 50 Gy in 25 fractions over 5 weeks was sufficient to control subclinical disease in over 90% of patients (11). It was clinically recognized, however, that higher doses were necessary to achieve the same control rates in the postoperative setting, and the dose recommended in the 2nd Edition of Fletcher's Textbook of Radiotherapy published in 1973 (10) was 60 Gy in 30 fractions. The need for the extra dose was rationalized on the basis that a surgically dissected area would be less well oxygenated than an undisturbed tumor bed. In a report from the University of Florida in 1979, Marcus *et al.* (18) recommended that the dose be increased even further to 65 Gy at 170–180 cGy per fraction and that oral cavity and oropharyngeal primaries be boosted to 70 Gy, particularly when surgical margins were microscopically positive.

With this clinical experience as a starting point, the head and neck surgeons and radiation oncologists at The University of Texas M. D. Anderson Cancer Center (MDA) decided to mount a prospective randomized study to determine the optimal dose for postoperative radiotherapy of head and neck neoplasms. The specific aims of the study were: (a) to evaluate the clinical and pathologic criteria defining subsets of patients at higher or lower risk of recurrence after treatment by surgery and postoperative radiotherapy, (b) to determine for both risk categories of patients the total radiation dose giving the best trade-off between tumor control and normal tissue complications, and (c) to study the dose-response relationship for normal tissue injury with postoperative radiotherapy. This is the first report of the results of this study.

METHODS AND MATERIAL

Study design

The basic design of the study is illustrated in Figure 1. Patients with primary squamous cell carcinomas arising in the oral cavity, oropharynx, hypopharynx, or larynx, or with neck nodal disease metastatic from a previously excised or unknown primary who were deemed to require combined modality treatment were eligible. Patients were first stratified according to primary site of origin. They were then assigned to notional risk categories, one for the primary site (Table 1) and one for the neck (Table 2) using a separate point system for each. The systems were devised empirically, based on our best estimate, at the time, of the relative importance of different clinicopathologic factors in determining the risk of local and regional recurrence. Within each risk category, patients were then randomized to one of two treatment arms that differed only in the final dose given to the sites of maximum risk. Those in the lower risk category were randomized between dose levels A and B, while those in the higher risk category were randomized between dose levels B and C. Dose level A was initially set at 52.2–54.0 Gy in 29–30 fractions over 6 weeks, but after the first interim analysis showed an increased rate of recurrence in this group of patients, dose A was increased in November 1985 to 57.6 Gy in 32 fractions over $6\frac{1}{2}$ weeks. Dose levels B (63 Gy in 35 fractions over 7 weeks), and C (68.4 Gy in 38 fractions over $7\frac{1}{2}$ weeks) remained constant throughout the course of the study.

The study was designed to establish the dose-response for tumor control within each risk category and for normal tissue injury in all patients. In addition, it permitted a test of the validity of the risk assessment system through dose level B, which was common to both risk categories. The accrual target was 300 patients.

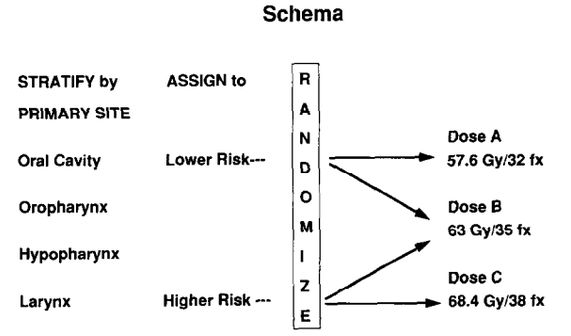

Fig. 1. Study design schema. Note: Prior to November 1985, dose level "A" was set at 52.2–54.0 Gy (see text).

Table 1. Assessment of risk for recurrence at primary site

	Points				
Criterion	0	1	2	3	4
Stage	T1–T2	—	T3	—	T4
Margins*	−ve	—	Mucosa† +ve → −ve	Deep† +ve → −ve	Close final margins (< 5 mm)
Nerve invasion	−ve	—	Minor nerve(s) +ve	Major nerve entrapped‡	Major nerve +ve
Neck nodes	N0	N1	≥ N2	—	—

Point range = 0–14; Low risk = 1–6; High risk = 7–14.
* Any final positive margin automatically connotes high risk.
† +ve → −ve means new negative margins were obtained after frozen section identification of positive margins.
‡ Nerve traverses tumor mass but is not pathologically invaded.

Patients

The study was opened on January 1, 1983, and was closed with 302 patients enrolled on March 31, 1991. The protocol was approved by the MDA Institutional Review Board, and all patients gave their informed consent to participate. This analysis is based on the first 240 patients entered through September 1989. There were 181 males and 59 females with a median age of 60 years (range 33–84). The distribution of patients by primary site and by T and N stage is shown in Tables 3 and 4. All but 14 patients underwent their major surgical resection at MDA, the remainder having been operated upon by two collaborating outside head and neck surgeons. Patients entered into the trial must have had all gross tumor removed without surgical cut-through, although microscopically positive margins were permitted. The surgical pathology was performed or reviewed at MDA in every case. The presence or absence of the various putative pathologic risk factors was specifically documented. All radiotherapy was delivered at MDA.

Radiotherapy techniques

Patients requiring bilateral treatment were irradiated initially with parallel opposed fields of ^{60}Co γ-rays matched to anterior supraclavicular fields. Treatment was delivered at a rate of 180 cGy per day to the central axis of the large fields until a spinal cord dose of 45 Gy was reached, when a reduction was made off the cord. Treatment was then continued with either ^{60}Co or 6 MV X rays and electron beam supplements to the posterior cervical strips. Total doses were as follows: 54 Gy to surgically undisturbed sites of potential subclinical disease, for example, the undissected contralateral neck or putative sites of an unknown primary; 57.6 Gy to pathologically uninvolved parts of the surgical bed, for example, regions of the neck from which the dissected nodes were histologically negative; and the randomly assigned total dose to the primary site and/or pathologically involved regions of the neck. Final doses to the primary site and neck were determined by separate randomizations. In cases where the primary site randomized to receive a higher dose than the neck, the dose to the primary site took precedence. On the other hand, when the neck randomized to receive a higher dose than the primary site, the neck was boosted with electrons of appropriate energy. Electron doses were specified at the 90% isodose line. In patients where part of the neck received a higher dose than randomly assigned because of the need to boost the primary site, analysis was done on the basis of assigned (not actual) neck dose.

Patients in whom unilateral treatment only was deemed

Table 2. Assessment of risk for recurrence in the neck

	Points				
Criterion	0	1	2	3	4
No. of nodes	0	1	2–3	≥ 4 or matted	—
No. of nodal groups*	0–1	2	3	≥ 4	—
Size/extracapsular extension (ECE)†	—	< 3 cm without ECE	> 3 cm without ECE	< 3 cm with ECE	3–6 cm with ECE
Direct invasion	—	—	—	Muscle; skin; nerve; vein	Carotid; base of skull

Point range = 0–14; Low risk = 1–6; High risk 7–14.
* Large single or matted nodes are scored as involving all groups into which the nodal mass extends.
† Nodes > 6 cm automatically connote high risk.

Table 3. Primary site of origin

Site	No. of pts.
Oral cavity	77
Oropharynx	44
Hypopharynx	40
Larynx	76
Other	3
Total	240

necessary were treated with electrons of appropriate energy, either alone or in a 4:1 mix with megavoltage photons.

Quality control

The plans for all treatments were reviewed in a biweekly planning session attended by all the head and neck radiation oncology staff to ensure uniformity of treatment techniques and compliance with protocol guidelines. Only four patients failed to complete their prescribed courses of treatment; another nine had treatment interruptions exceeding 2 days, the longest being 6 days.

Data management

All patients were followed on a regular schedule at the MDA, and by their referring physicians in the case of out of town patients. After each follow-up appointment, a data form was coded to indicate disease status at the primary site and in the neck, the presence of any complications of treatment, and the development of metastatic or new primary sites of disease. The median follow-up to last contact or death was 22 months with a range of 2 to 95 months. The cut-off for analysis was May 1991. Patients alive at the cut-off date had a median follow-up of 45 months and all but 16 living patients had been followed for a minimum of 2 years.

Statistical methods

Actuarial curves for local-regional control, disease-specific survival, and overall survival were generated using the Berkson Gage method (4). The analysis of prognostic factors used a simple statistical model describing the probability of local-regional control and the distribution of times to failure for those not controlled. The probability of control is assumed to vary with the values of the prognostic factors according to a logistic model. Times to failure for patients not controlled are assumed to follow an exponential distribution that does not change with covariate values. Parameters of the model were fit using maximum likelihood methods. Significance of individual variables and model comparisons were assessed by likelihood ratio tests.

Table 4. T and N stage

	Tx	T1	T2	T3	T4	Total
Nx	18	—	—	1	—	19
N0	—	3	16	45	26	90
N1	—	1	13	21	7	42
N2	1	—	10	32	9	52
N3	2	1	3	21	10	37
Total	21	5	42	120	52	240

Table 5. Overall disease status (n = 240)

	Alive	Dead
NED	82	—
Local-regional ± DM	2	56
DM only	4	50
Second primary	7	16
Lost to follow-up	0	3*
Dead: other causes	—	20
Total	95	145

* Presumed dead of disease with local-regional recurrence.
NED = No evidence of disease; DM = Distant metastases.

RESULTS

Overall recurrence and survival data

Of the 240 patients entered through September 1989 and followed through May 1991, 58 had documented recurrences at the primary site and/or neck with or without also developing distant metastases. An additional three patients were lost to follow-up after 2, 7, and 10 months and are assumed for the purpose of analysis to be dead of their head and neck cancers with local-regional recurrences. This gives a crude overall recurrence rate of 25.4% and a 2 year actuarial recurrence rate of 26%. The disease status of all patients as of May 1991 is shown in Table 5. There were 86 patients who died without local regional recurrence, in whom the cause of death was metastatic disease in 50, second primary cancer in 16 and nonneoplastic illness in 20. Actuarial curves for disease control above the clavicles, disease-specific survival, and overall survival are shown in Figure 2.

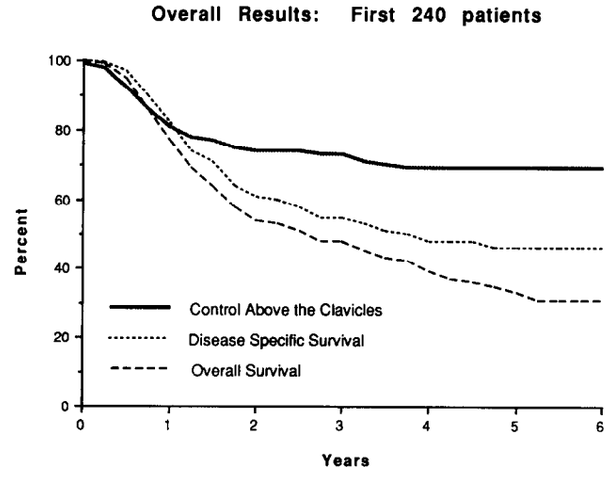

Fig. 2. Actuarial curves for local-regional control, disease-specific and overall survival for the entire group of 240 patients.

Table 6. 2-year actuarial control rates at the primary site and neck by dose

Risk	Dose (Gy)	Primary site No. pts.	Primary site Control rate %	Neck No. pts.	Neck Control rate %
Lower	≤ 54.0	17	63[1]	9	89
	57.6	66	92[2]	65	86
	63.0	51	89	54	89
Higher	63.0	51	89	61	84
	68.4	54	81	51	77

1 vs. 2 $p = 2.34$.

Disease control by risk category and dose

The 2-year actuarial probability of disease control at both the primary site and in the neck according to risk category and randomly assigned dose is shown in Table 6. (The total number of patients in the primary site analysis reflects exclusion of one patient with an unknown primary). Conclusions from these data are that: (a) lower risk patients receiving ≤ 54 Gy had a significantly higher primary failure rate than those receiving ≥ 57.6 Gy ($p = .02$); (b) with doses ≥ 57.6 Gy there was no apparent dose response for tumor control at either the primary site or in the neck; and (c) the pathologic point scoring system we used for risk categorization did not predict accurately for probability of recurrence since there were no significant differences in either primary or neck control rates at the 63 Gy level according to risk category. As shown in Table 7, the overall probability of disease control above the clavicles was reduced in patients having the primary site, neck, or both categorized as higher risk, but this trend was not statistically significant.

In view of these findings and because it was sometimes difficult to distinguish between recurrences at the primary site or immediately adjacent neck, further analysis was based on any failure above the clavicles.

Salvage attempts

Of the 58 patients known to have sustained a failure above the clavicles, 36 underwent attempted salvage therapy consisting of further surgery ± chemotherapy in 11, additional radiotherapy ± chemotherapy in 3, and chemotherapy only in 22. Only one of these patients is a long-term survivor, being free of disease 22 months after salvage surgery.

Table 7. 2-year probability of disease control above clavicles by primary and neck risk category for all patients regardless of dose

Neck risk	Primary risk Lower %	Primary risk Higher %
Lower	84[1]	71[2]
Higher	76[3]	69[4]

1 vs. 2 $p = 0.19$; 1 vs. 3 $p = 0.29$; 1 vs. 4 $p = 0.10$.

Analysis of prognostic factors

To investigate further the relative significance of clinical prognostic factors and radiation dose, we undertook a more detailed analysis of 199 patients (the analytic group) who received at least 57.6 Gy to their site of maximum risk and who were irradiated after their first ablative surgery. This group of patients had a 2-year actuarial rate of disease control above the clavicles of 75%. The characteristics of the analytic group are set out in Table 8. Univariate analysis was then undertaken of the ability to predict for recurrence above the clavicles of each of the following factors: oral cavity primary, close or positive margins, nerve invasion, number of positive nodes ≥ 2, largest node > 3 cm, extracapsular nodal disease present, Zubrod score ≥ 2, and delay in starting radiotherapy > 6 weeks. This showed that the only one of these factors with independent significance in predicting treatment failure was extracapsular nodal extension in the neck ($p = 0.04$). The presence of ≥ 2 pathologically involved nodes was of marginal significance ($p = 0.08$). Although factors other than extracapsular extension were not independently significant, the co-existence of clusters of two or more of these putative adverse prognostic factors did correlate with the risk of recurrence. Figure 3 shows the actuarial probability of remaining disease-free above the clavicles according to risk factor analysis. From this figure it can be seen that patients without extracapsular extension but having ≥ 4 other adverse factors did as poorly as those with extracapsular extension. Table 9 shows the crude recurrence rates by ECE status and the number of other adverse factors. This analysis shows that ECE is a dominant prognostic factor which, when present, overwhelms other prognostic indicators; these have significance only in patients without extracapsular disease in the neck. In the subset of patients with ECE, that is, the worst prognostic group, a dose-response for disease control also became apparent between 57.6 Gy and 63 Gy or greater. The 2-year actuarial control rates were 52%, 74%, and 72% with doses of 57.6 Gy, 63 Gy, and 68.4 Gy, respectively ($p = 0.03$).

Table 8. Characteristics of the analytic group and prognostic factor analysis

Characteristics		Prognostic factor analysis	Crude recurrence rate	%	Actual 2-year control %	p*
Primary site						
Oral cavity	58	Oral cavity†	14/58	24	67	0.80
Oropharynx	43	Other	27/141	19	77	
Hypopharynx	35					
Larynx	63					
Margins						
Negative	93	Negative	18/93	19	75	0.71
Close (+ → −)	89	Close or				
Positive	17	positive†	23/106	22	73	
Nerve invasion						
Absent	152	Absent	30/152	20	78	0.36
Present	47	Present†	11/47	23	64	
No. nodes pos.						
0	34					
1	31	0–1	8/65	12	84	0.08
≥ 2	134	≥ 2†	33/134	25	70	
Size of largest node						
0	34					
< 3 cm	118	< 3 cm	27/118	23	70	0.79
> 3 cm	47	> 3 cm†	10/47	21	77	
Extracapsular nodal disease						
None	89	Absent	12/89	13	81	
Connective tissue	67	Present†	29/110	26	70	0.04
Muscle/vessel/ bone	43					
Treatment delay						
0–4 wks	57					
4–6 wks	105	≤ 6 wks	30/162	19	77	0.35
> 6 wks	37	> 6 wks†	11/37	30	64	
Zubrod score						
0–4 wks						
0–1	173	0–1	35/173	20	75	0.48
≥ 2	26	≥ 2†	6/26	23	73	

† Putative adverse factors.
* Calculated using the model described in "Methods" section.

Stability analysis of prognostic factors

In testing the predictive value of clusters of factors that were not individually significant, changes in the number of factors sometimes led to model estimates that failed to yield a lower local control rate for patients with a greater number of poor prognostic factors. These occurrences led to a concern that the findings might be unstable in that a replication of the current study might not yield the same monotonicity. The bootstrap method (7) was used to examine this issue.

The bootstrap uses repeated random samples with replacement from the data to estimate the distribution of outcomes were the study to be replicated. One hundred such samples were generated. In 83 of these samples, the model indicated an increasing proportion of recurrence with the number of grouped risk factors. Of the reversals observed in the other 17 samples, 12 were between the first and second group (0–1 vs. 2–3 adverse factors), four between the second and third (2–3 vs. ≥ 4 adverse factors), and one between the first and third group. We conclude, therefore, that using the groupings reported here, there is a greater than 80% probability that the estimated proportion of recurrences would increase with the number of unfavorable signs if a repeat of the trial were to be undertaken.

Normal tissue reactions

Acute reactions were generally well tolerated. Of the total 240 patients, only nine (3.8%) required interruption of treatment exceeding 2 days for acute reactions. The maximum treatment interruption was 6 days. Average weight loss during therapy was 2.6 kg.

A total of 17 (7.1%) patients sustained one or more moderate to severe late complications (Grade 3–4 on the

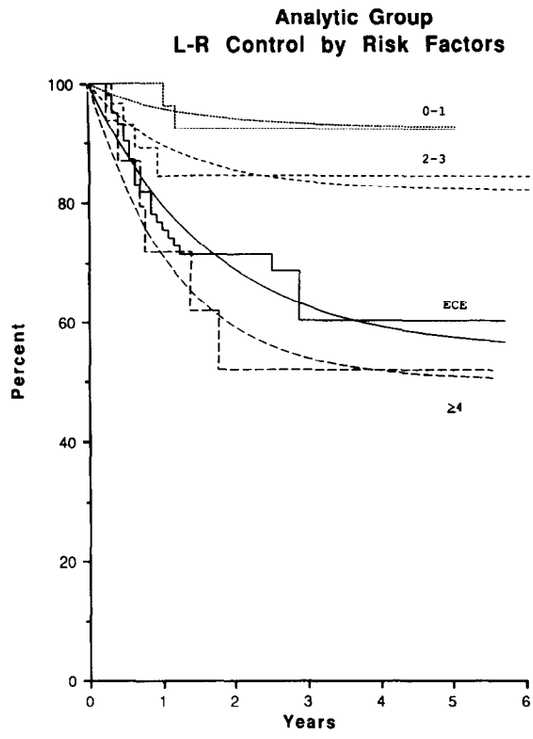

Fig. 3. Actuarial curves for local-regional control in the analytic group according to presence of extracapsular nodal extension (ECE) or clusters of other adverse prognostic variables. In patients with ECE, the control rate was dose dependent: 52% at 2 years with a dose of 57.6 Gy vs. 74% at 63 Gy and 72% at 68.4 Gy ($p = 0.03$). See text.

modified RTOG scale). There were no lethal complications of treatment. A listing of the late complications along with the doses to the primary site and neck is provided in Table 10. The most frequent complication was pharyngo-esophageal stricture which occurred in 10 patients after laryngectomy, and partial pharyngectomy, necessitating gastrostomy in three. In seven patients, there was bone exposure or necrosis, requiring surgery in two. The remaining complications were fistulae in two, and severe neck edema and fibrosis in one.

There was a dose response for complications when analyzed in terms of the maximum target dose delivered: 1/36 (2.8%) for ≤ 57.6 Gy; 9/117 (7.7%) for 63 Gy; and 7/87 (8.0%) to 68.4 Gy. However, this may be coincidental since there was no dose response in terms of dose to the primary site which was where the majority of complications occurred.

Table 9. Crude recurrence rates by ECE status and number of other adverse factors

Number of adverse factors	ECE+ (%)	ECE− (%)
0–1	2/5	2/41 (5)
2–3	8/37 (22)	4/32 (13)
4–5	16/58 (28)	6/16 (38)
≥ 6	3/10 (30)	—

DISCUSSION

This report is based on a preliminary analysis of the trial and it is possible that some of the conclusions may change when the entire data base matures. Nonetheless, the results obtained thus far challenge some aspects of conventional wisdom regarding postoperative radiotherapy and suggest possible ways in which the results of treatment might be improved.

A surprising result of the trial was the absence of a significant dose-response function for tumor control with total doses ≥ 57.6 Gy. (However, in the subset of patients with extracapsular nodal disease, there was better local-regional control with doses ≥ 63 Gy than at lower doses). There are several possible explanations for the lack of a clear dose-response for tumor control. First, the theoretical slope of the tumor cure probability curve for postoperative irradiation is inherently shallower than that for radiotherapy alone, since a certain proportion of patients receiving postoperative treatment would have been cured by surgery alone. With a shallow theoretical slope, it could be that the number of patients at each dose level and the spread of dose levels was simply insufficient to detect the dose-response function. A second possible explanation is that there was sufficient heterogeneity in the residual tumor burden of patients across the three dose levels to obfuscate a dose response function. This interpretation is supported by fact that in the more homogeneous group of patients with extracapsular extension, there was a significant difference in recurrence rates between those receiving 57.6 Gy or ≥ 63 Gy. The purpose of the risk assessment stratification in this trial was to reduce the heterogeneity within each dose randomization. However, the lack of discrimination of the risk assessment point system at dose level B suggests that this stratification was inadequate and that considerable heterogeneity existed, both within and between the dose randomization strata.

A third possibility is that a significant number of recurrences might have occurred outside the boost volume, making any analysis in terms of the final total dose irrelevant. Although the exact site of recurrence was not sufficiently well documented in most patients to be precisely correlated with radiation portals, we believe this explanation to be unlikely, based on the patterns of recurrence most commonly observed.

A final possibility, and one that lends itself to experimental inquiry, is that the effect on tumor control of dose increments above 57.6 Gy was offset by tumor cell regeneration occurring during the additional time taken to deliver the higher doses at 1.8 Gy per day. Several recent analyses have been published in which the dose equivalent of tumor cell regeneration during treatment has been estimated to be approximately 60 cGy per day (22). Thus, in this trial, each dose step of 5.4 Gy would have to be

Table 10. Listing of moderate/severe late complications

Case no.	Maximum doses (Gy)		Complication	Resolved
	Primary site	Neck		
1	54.0	54.0	Pharyngeal stricture	No (gastrostomy)
2	57.6	63.0	Pharyngeal stricture	Yes
3	57.6	68.4	Pharyngeal stricture	No
4	63.0	63.0	Pharyngeal stricture	No
5	63.0	68.4	Pharyngeal stricture	Yes
6	63.0	63.0	Pharyngeal stricture	No
7	68.4	65.6	Pharyngeal stricture	No
8	64.8	69.0	Pharyngeal stricture	No
9	68.4	63.0	Pharyngeal stricture	No (gastrostomy)
10	63.0	63.0	Bone exposure	Yes
11	63.0	56.0	Bone exposure	Yes
12	68.3	63.0	Bone exposure	Yes
13	63.0	63.0	Bone exposure	Yes (HBO)
14	66.9	68.0	Fractured mandible	No (surgery)
15	63.0	63.0	Bone exposure	Yes
			Fistula	Yes
16	63.0	63.0	Stricture	No (gastrostomy)
			Bone necrosis	No (surgery)
			Fistula	No (surgery)
17	57.6	63.0	Neck fibrosis/edema	No

discounted by 1.8–3.0 Gy because of the extra time taken to deliver the dose (3–5 days according to whether or not treatment extended over a week-end). The effective dose increments could, therefore, be too small to be resolvable.

The overall crude and actuarial recurrence rates above the clavicles in this trial (25.4% and 26% at 2 years, respectively) are comparable to those reported by others (3, 5, 14, 18, 20, 21). From this trial, we can conclude with reasonable confidence that a recurrence rate of this order cannot be substantially reduced by further dose escalation using daily fractions of 1.8 Gy. In fact, the therapeutic ratio would most likely decrease with doses > 68.4 Gy because of the increased risk of treatment complications. On the basis of our data, we currently recommend that when treatment is given at 1.8 Gy per fraction, the dissected tumor bed receive a minimum dose of 57.6 Gy, with sites of increased risk being boosted to 63 Gy in patients with extracapsular nodal disease, or clusters of two or more other adverse prognostic factors.

Two large cooperative group studies incorporating postoperative radiotherapy have recently been published (15, 23) in which somewhat lower minimum doses were specified: 50 Gy to "low risk" areas and 60 Gy to areas of "high risk" (extracapsular nodal disease, primary margins < 5 mm, or carcinoma in situ at the mucosal margins). The reported recurrence rates in these trials are similar to ours when allowance is made for differences in primary site of origin and stage distribution. However, it is impossible to compare the absolute results meaningfully without taking account of all the prognostic factors influencing outcome. Furthermore, neither of the cooperative group studies was designed to *test* for a dose response relationship, so there is no way of concluding that the doses chosen were optimal.

In addition to its primary goal of defining the dose-response for tumor control and complications, our trial has provided a unique opportunity to assess the weight of various putative prognostic factors in a prospective fashion with uniform surgery, pathology, and tight quality control of radiation dose and technique. The finding that extracapsular nodal disease in the neck was a powerful, independently significant prognostic factor came as no surprise, since it has been well recognized as the most significant factor determining the risk of recurrence after surgery alone (13). However, the lack of independent significance of other factors, such as microscopically positive mucosal margins or perineural invasion, was unexpected. We interpret this result as indicating that a minimum dose of 57.6 Gy was sufficient to sterilize the residual tumor in the majority of patients with these findings.

Although none of the putative risk factors other than ECE was independently significant for the risk of recurrences, the coexistence of clusters of the factors was found to be so. Thus, patients with ≥ 4 individually insignificant risk factors had the same probability of recurrence as those with extracapsular extension (Fig. 3). Bootstrap methods were used to estimate the probability that, were the study to be replicated using the current grouping of the numbers of bad prognostic factions, the risk of recurrence would increase with the number of factors. The method produces an estimate of this probability that is greater than 80%. To the best of our knowledge, this is the first use of cluster analysis of clinical prognostic factors in the context of assessment of risk of recurrence. The closest approxi-

mation is perhaps the analysis of Amdur *et al.* (1) where patients were stratified according to the number of "indications" for postoperative radiotherapy.

In spite of an overall 2-year 74% rate of freedom of recurrence above the clavicles, survival in this series of patients was only 53% at 2 years, and 31% at 5 years, as a result of additional mortality from metastases, second primary cancers, and intercurrent illnesses. This is an inherent limitation to improved survival through better control of disease above the clavicles. Nonetheless, there is ample room for improvement in local-regional control, and any such improvement is of major significance for quality of life. For this reason, we have recently opened a new protocol to evaluate accelerated fractionation in relation to the best current standard therapy derived from this trial, namely 63 Gy at 1.8 Gy per fraction.

CONCLUSION AND RECOMMENDATION

On the basis of the initial results of this prospective trial, we presently recommend that patients being treated postoperatively off-protocol for head and neck cancer, using daily fractions of 1.8 Gy, receive a minimum of 57.6 Gy to the whole operative bed. Sites of increased risk, especially regions of the neck where extracapsular extension was present, should be boosted to 63 Gy. Undissected areas potentially harboring subclinical disease can safely be treated with 54 Gy at 1.8 Gy per fraction (or 50 Gy at 2 Gy per fraction). Treatment should be started as soon as possible after surgery to minimize the amount of tumor cell proliferation allowed to occur before treatment begins. However, there is no arbitrary time limit in which irradiation must begin.

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