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● *Original Contribution*

RANDOMIZED STUDY OF PREOPERATIVE VERSUS POSTOPERATIVE RADIATION THERAPY IN ADVANCED HEAD AND NECK CARCINOMA: LONG-TERM FOLLOW-UP OF RTOG STUDY 73-03

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This is a report of a 10-year median follow-up of a randomized, prospective study investigating the optimal sequencing of radiation therapy (RT) in relation to surgery for operable advanced head and neck cancer. In May 1973, the Radiation Therapy Oncology Group (RTOG) began a Phase III study of preoperative radiation therapy (50.0 Gy) versus postoperative radiation therapy (60.0 Gy) for supraglottic larynx and hypopharynx primaries. Of 277 evaluable patients, duration of follow-up is 9–15 years, with 7.6% patients lost to follow-up before 7 years. Loco-regional control was significantly better for 141 postoperative radiation therapy patients than for 136 preoperative radiation therapy patients ($p = 0.04$), but absolute survival was not affected ($p = 0.15$). When the analysis was restricted to supraglottic larynx primaries (60 postoperative radiation therapy patients versus 58 preoperative radiation therapy patients), the difference for loco-regional control was highly significant ($p = .007$), but not for survival ($p = 0.18$). In considering only supraglottic larynx, 78% of loco-regional failures occurred in the first 2 years. Thirty-one percent (18/58) of preoperative patients failed locally within 2 years versus 18% (11/60) of postoperative patients. After 2 years, distant metastases and second primaries became the predominant failure pattern, especially in postoperative radiation therapy patients. This shift in the late failure pattern along with the increased number of unrelated deaths negated any advantage in absolute survival for postoperative radiation therapy patients. The rates of severe surgical and radiation therapy complications were similar between the two arms. Because of an increased incidence of late distant metastases and secondary primaries, additional therapeutic intervention is required beyond surgery and postoperative irradiation to impact significantly upon survival.

Head and neck carcinoma, Squamous cell, Combined modality, Preoperative irradiation, Postoperative irradiation, Supraglottic larynx, Randomized study, Adjuvant therapy, Second primary, Distant metastases.

INTRODUCTION

It is well recognized that the primary problem in patients with advanced head and neck carcinoma is loco-regional control of disease and that combined modality therapy with surgery and radiation therapy is frequently required (2, 4, 7–10, 30, 33). The optimal sequencing of these modalities has long been an unsettled question (2, 9, 20, 21, 23, 24, 29, 30, 33) there being advocates for both preoperative (11, 14) and postoperative radiotherapy (4, 9,

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31). Radiotherapy administered preoperatively may enable or facilitate surgery by shrinking tumor, or may be used alone at radical doses for definitive management. There is no delay in starting irradiation, tumor vascularity is not disturbed, and cells dislodged during surgery are less likely to lead to distant metastases. On the other hand, postoperative radiotherapy leads to less difficulty with healing and can be adjusted to reflect the pathology, especially the presence of residual disease, close margins of resection, or other adverse features which would warrant an increase in the dose of irradiation. There are few randomized comparisons of these two approaches. In a previous randomized, prospective study (29) involving tumors of the hypopharynx, a high rate of fatal complications in the group receiving preoperative radiotherapy led to abandonment of the study. This particular study of hypopharyngeal cancer may have been compromised to some extent by the disease site under investigation, as frequently these patients are chronically malnourished and have impaired healing even when surgery alone is used.

In 1973, the Radiation Therapy Oncology Group (RTOG) undertook a prospective randomized study to compare preoperative radiation plus surgery, surgery plus postoperative radiation (POST-OP RT), and definitive radiation with surgery for residual disease in patients with advanced, operable head and neck carcinoma (RTOG 73-03). Preliminary reports on this study (26, 27) at 1 and 2 years indicated no difference in loco-regional control or survival between POST-OP RT and PRE-OP RT patients. Another interim report presented a significant difference in the loco-regional control rate between PRE-OP RT and POST-OP RT in the subset of patients with supraglottic laryngeal tumors (25). Subsequently, after the close of the study and a minimum follow-up of 3 years (median 5 years), a significant difference was noted in the overall loco-regional control rate between the PRE-OP RT and POST-OP RT patients (13). This report is an analysis of the same series with a minimum follow-up of 7 years (median 10 years) and reclassification of all the cases according to more recent AJCC nomenclature (1). The impact of treatment on survival and the patterns of failure have been analyzed. The results indicate a slight but significant advantage for postoperative radiotherapy for all sites in terms of improved loco-regional control, which, however, does not translate into enhanced survival because of the negative impact of second primary tumors and distant metastases.

METHODS AND MATERIALS

Initially, patients with previously untreated primary squamous cell carcinoma of the oral cavity, oropharynx, supraglottic larynx, and hypopharynx were eligible. Patients had to be considered operable at study entry with T3 or T4 primary lesions and nodes of any N stage, except for N3A; in a previous classification system, this stage denoted a patient with any fixed ipsilateral nodes. Patients with T2 lesions of the hypopharynx were also eligible. Subsequently, eligibility was expanded to allow patients with T2 lesions of any of the four regions or with maxillary sinus lesions of any T classification. Patients with distant metastases, two simultaneous tumors, previous radical surgery, radiation therapy, or chemotherapy for head and neck tumors (except skin cancer), poor general condition, or who were unsuitable for immediate surgery were excluded from the study.

The patients were stratified prior to randomization to treatment by sex, region of the tumor, and T and N classification (Table 1). Patients with oral cavity and oropharynx lesions were assigned to PRE-OP RT, POST-OP RT, or definitive radiation with surgery for salvage of residual disease. Patients with supraglottic larynx and hypopharynx lesions were assigned to either PRE-OP RT or POST-OP RT treatment.

Endpoints of the study included loco-regional control, survival, cause of death, and complications of therapy. Patterns of first failure for this analysis were defined as loco-regional failure, distant failure, or unrelated death, whichever occurred first. Patients who never achieved initial loco-regional clearance, whether due to positive surgical margins or gross residual disease, were considered loco-regional failures. Causes of death in each category were further identified and attributed to "treated disease", or to distant metastases, second primary, complications of therapy or unrelated causes, as applicable. With multiple sites of failure, the primary mode of failure was determined as the cause of death. Metastases were distinguished from second primaries on the basis of histology, site, or clinical context. Patients were classified as NED (no evidence of disease) if there was no evidence of loco-regional or distant metastases.

The radiation therapy in the preoperative group consisted of treatment of the primary and regional neck node areas given at the rate of 1.8–2.0 Gy per day for a total tumor dose of 50.0 Gy in 5–5.5 weeks, with treatment of all fields each day. Surgery was performed 4–6 weeks following completion of radiation therapy. Postoperative radiation therapy was commenced within 4 weeks of surgery and was given in the same manner as in the preoperative group. The tumor volume treated was identical in both

Table 1. RTOG 73-03

Stratify	Randomize: Treatment
Sex T-Stage N-Stage	RT (5000 rads) + surgery vs. Surgery + RT (6000 rads) vs. RT* (6500–7000 rads) with surgery for salvage

* A randomization option only for oral cavity and oropharynx. Open: 5/73; Closed: 6/79.

instances and typically used lateral fields with customized lead shielding and a matching yoke field in the first phase of treatment, followed by a boost using reduced lateral fields to the tumor bed. The dose delivered to the primary site was 60.0 Gy, with 50.0 Gy to the rest of the neck. The extent of surgery was the same in both the pre- and postoperative groups, consisting of a radical operation including the primary site with or without a lymph node dissection.

The time events were plotted as step functions using the Kaplan-Meier (12) product-limit method. The corresponding comparison tests were calculated using the log-rank (21) method. From May 1973 to June 1979, 358 patients were entered in the study. The data cut-off for this analysis was June 1988, thus providing minimum follow-up of 9 to 15 years, with median follow-up of 10 years. Only 7.6% of the patients were lost to follow-up before 7 years. Fifty-one percent of the patients accrued into this study were derived from two institutions; 11 institutions contributed fewer than 10 cases each. For this analysis 33 patients were excluded (Table 2): ineligible (17), cancelled (12), not randomized (4). The latter patients were entered from cancer control institutions that were allowed to choose the treatment for each patient.

These patients (N = 325) were further restricted to those randomized to PRE-OP RT and POST-OP RT treatment arms in the four initial primary regions; therefore, patients with lesions in the maxillary sinus (5) and those assigned to the definitive radiation arm (43) have been excluded from this analysis. Thus, 277 patients (136 PRE-OP and 141 POST-OP) were used in all subsequent analyses. The treatment arms were examined for balance across pretreatment factors of sex, age, Karnofsky performance scores (KPS), primary site, and T and N stages (Table 3).

Table 2. RTOG 73-03: Exclusions

Total entered	358
Cancelled[1]	12
Ineligible[2]	17
Non randomized	4
Total evaluable	325

[1]Reasons for Cancellation:

(Preop)	(Postop)	(Rad'n)	
	5		Patients refused treatment; unable to follow
1	2	1	Deterioration before treatment
2		1	Other: complications of alveolectomy, change in diagnosis, nervous breakdown

[2]Reasons for Ineligibility:

(Preop)	(Postop)	(Rad'n)	
1	3	3	Nonprotocol site: Upper gingiva, hard palate
3	1		Second primary tumor at study entry
	1	2	N3A—ineligible N-stage
3			Other: Improper randomization, nontumorous lesion, T1 lesion

Table 3. Pretreatment characteristics of patients entered into RTOG protocol 73-03

	Preop RT (N = 136)	Postop RT (N = 141)
	No. (%)	No. (%)
Sex		
Male	109 (80)	116 (82)
Age		
Median	57	58
Range	37–79	29–77
KPS		
<80	27 (20)	29 (21)
>80	109 (80)	112 (79)
Site		
Oral cavity	20 (15)	20 (14)
Oropharynx	23 (17)	23 (16)
Hypopharynx	58 (43)	60 (43)
Supraglottic larynx	35 (26)	38 (27)
AJC Stage		
II	12 (8)	15 (10)
III	62 (46)	63 (45)
IV	62 (46)	63 (45)
T-Stage		
T2	32 (24)	30 (21)
T3	68 (50)	77 (55)
T4	36 (26)	34 (24)
N-Stage		
N0	53 (39)	54 (38)
N1	40 (29)	47 (33)
N2	22 (16)	26 (18)
N3	21 (15)	14 (10)

RESULTS

Analyzable patients were evaluated for loco-regional control. The loco-regional control rates were significantly better for the (N = 141) POST-OP RT patients (70%) than for the (N = 136) PRE-OP RT patients (58%) ($p = 0.04$) (Fig. 1). In the first 2 years, the difference between these groups was slight, but it became more pronounced after 2 years. Tables 4 and 5 demonstrate the patterns of first failure within these two time intervals. Loco-regional failures constituted 59% of all failures within 2 years in the PRE-OP RT patient versus 55% for POST-OP RT. Beyond 2 years it was 27% versus 8%. In this time period, deaths attributable to distant metastases and second primaries were 21/39 in the POST-OP RT group versus 9/33 in the PRE-OP RT. The significant difference between treatment arms with respect to loco-regional control did not translate to survival (Fig. 2). The causes of death reflect the difference that was seen in the loco-regional failure

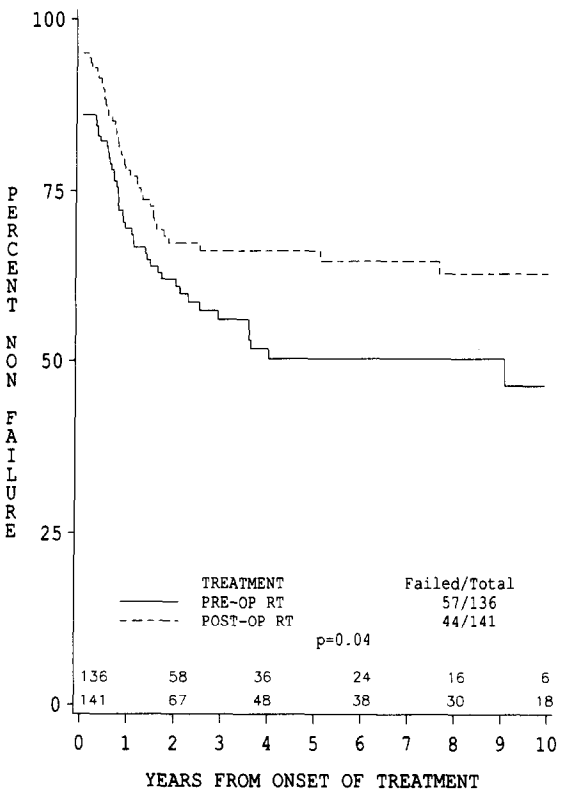

Fig. 1. Loco-regional control of disease in patients receiving PRE-OP RT versus POST-OP RT (all sites), showing significantly increased loco-regional control for POST-OP RT ($p = 0.04$).

rate: number of deaths caused by "treated primary" was lower in POST-OP RT 27/141 (25%) patients compared to PRE-OP RT 42/136 (37%) patients, ($0.10 > p > 0.05$). When the analysis was restricted to supraglottic larynx patients, this pattern of failure was found to be even more pronounced. The overall loco-regional failure rate was 25/58 (47%) for PRE-OP RT patients and only 12/60 (23%) for POST-OP RT patients (Fig. 3) ($p = 0.007$). Again, this did not result in a statistically significant difference in survival (Fig. 4). Likewise, the patterns of first failure followed the trend of all the patients. Beyond 2 years, 7/17 (41%) of failures in the PRE-OP RT group were loco-regional, compared to 1/17 (6%) for POST-OP failures during the same period (Table 7). This was also reflected in cause of death; 14/47 (29%) of PRE-OP RT patient deaths were caused by "treated primary" compared to 4/42 (9.5%) of the POST-OP RT deaths (Tables 6 and 7). The incidence of distant metastases and second primary failures increased in step with the decrease in local failure rate. The POST-OP RT failure rate attributed to these two causes was 8/17 (48%) of all failures compared to only 4/17 (24%) for PRE-OP RT in supraglottic carcinoma (Table 7). The rates of severe surgical and radiotherapy complications were similar between the two arms (Table 8). Nineteen patients (7%; 14 surgical and 5 radiotherapeutic) died from complications related to therapy, which all occurred within 2 years of treatment (Table 4). Of these, eight surgical and three radiotherapeutic com-

Table 4. Patterns of first failure and cause of death within 2 years of randomization (RTOG 73-03): all patients

Failure: cause of death	Preop RT (N = 136) No. (%)	Postop RT (N = 141) No. (%)
Loco-regional	48 (59)*	41 (55)
Treated disease	36	26
Distant metastasis	5	5
Second primary	2	1
Complications	1	1
Unrelated	2	3
Unknown	0	1
(Alive)	2	4
Distant metastasis	15 (19)	11 (15)
Distant metastasis	14	10
Complications	1	0
Unrelated	0	1
NED-dead	18 (22)	23 (30)
Second primary	3	3
Complications	9	7
Unrelated	3	3
Unknown	3	5
Total failed or died within 2 years	81	75
NED-alive beyond 2 years	53	65
NED-alive lost to follow-up within 2 years	2	1

* Value in parenthesis: as a percentage of all patients failing or dying.

Table 5. Patterns of first failure and cause of death beyond 2 years after randomization (RTOG 73-03): all patients

Failure: cause of death	Preop RT (N = 53) No. (%)	Postop RT (N = 65) No. (%)
Loco-regional*	9 (27)†	3 (8)
Treated disease	6	1
Distant metastasis	2	1
Unrelated	1	0
(Alive)	0	1
Distant metastasis	2 (6)	8 (20)
Distant metastasis	1	8
(Alive)	1	0
NED-dead	22 (67)	28 (72)
Second primary	8	13
Unrelated	14	12
Unknown	0	3
Total failed or died beyond 2 years	33	39
NED-alive beyond 2 years	20	26

* $p = 0.01$.
† Value in parenthesis: as a percentage of all patients failing or dying.

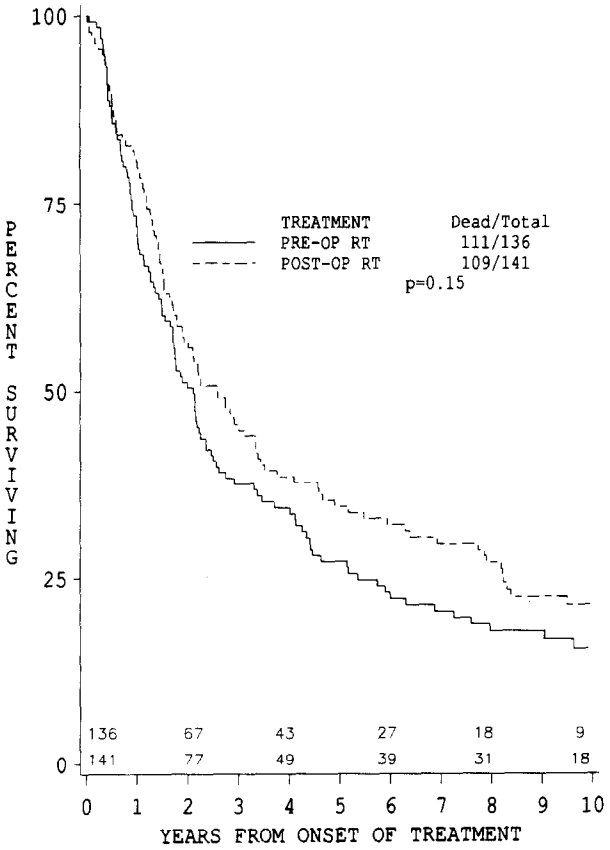

Fig. 2. Actuarial survival rates of patients receiving PRE-OP RT versus POST-OP RT (all sites). No significant difference in survival is seen over 10 years.

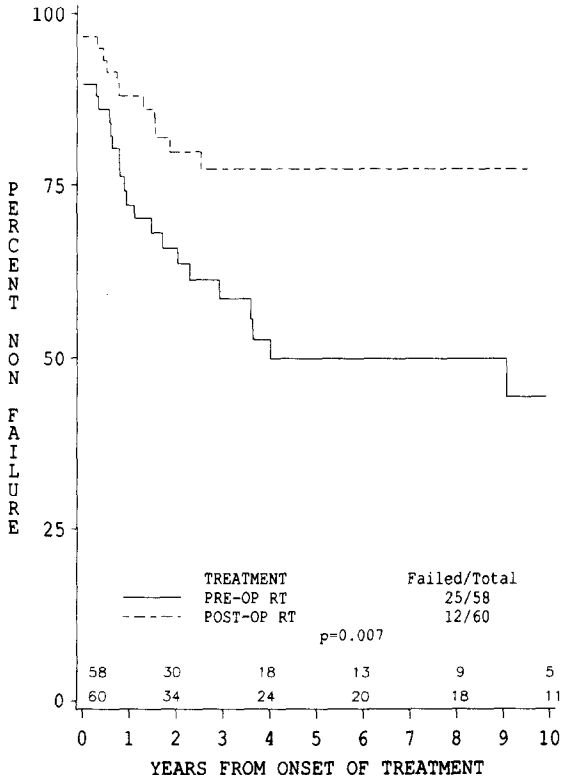

Fig. 3. Loco-regional control in patients with supraglottic carcinoma, showing a significant difference in favor of POST-OP RT ($p = 0.007$).

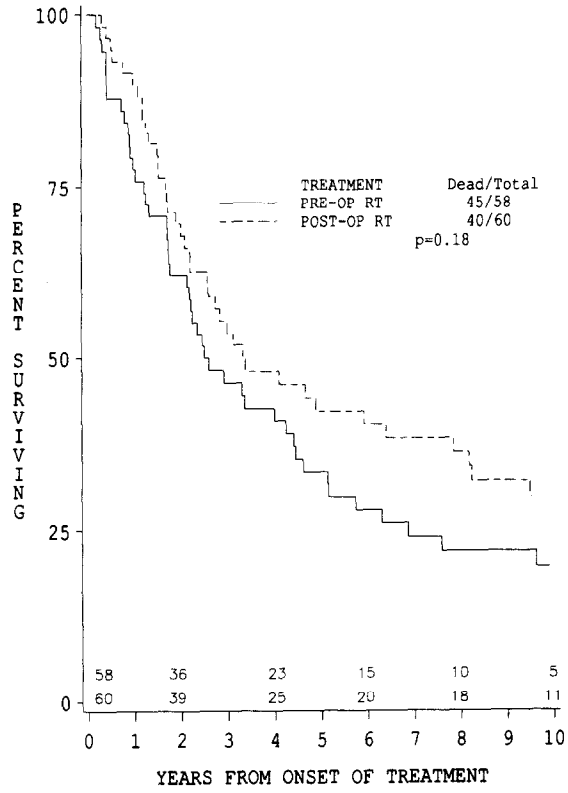

Fig. 4. Actuarial survival of patients with carcinoma of the supraglottic larynx. There is no significant difference between PRE-OP RT and POST-OP RT.

plications occurred in the PRE-OP RT group versus six and two, respectively, in the POST-OP RT group. The number of major deviations in treatment from the protocol prescription in both groups of patients after randomization was equivalent (31% versus 29%). If these patients are excluded from analysis, the differences are not erased but are actually strengthened.

DISCUSSION

This study is unique in that it is one of few prospective randomized studies that have compared the utility of preoperative versus postoperative radiotherapy in advanced head and neck squamous cell carcinoma. It is also distinctive in being the largest of these studies with the longest follow-up. The advantage of combined modality therapy in the optimal management of advanced head and neck carcinoma has been well established in a number of reports (2, 7, 9, 30). Historically, preoperative radiotherapy was favored, as surgery was often facilitated by the regression of tumor and loco-regional control increased. However, the morbidity of such an approach (3, 4, 5, 14, 16, 18) has led to a greater emphasis on POST-OP RT, which allows doses to be altered to control areas at higher risk of disease recurrence (15, 17). Taking into account all the patients randomized between PRE and POST-OP RT in this study regardless of site, there was a significant advantage for those receiving POST-OP RT because of contin-

Table 6. Patterns of first failure and cause of death within 2 years of randomization: supraglottic larynx patients

Failure: cause of death	Preop RT (N = 58) No. (%)	Postop RT (N = 60) No. (%)
Loco-regional	18 (60)*	11 (44)
Treated disease	10	3
Distant metastasis	4	2
Second primary	1	1
Complications	0	1
Unrelated	1	2
(Alive)	2	2
Distant metastases	6 (20)	4 (16)
Distant metastasis	6	4
NED-dead	6 (20)	10 (40)
Second primary	0	1
Complications	5	1
Unrelated	1	6
Unknown	0	2
Total failed or died within 2 years	30	25
NED-alive at 2 years	28	34
NED-alive lost to follow-up within 2 years	0	1

* Value in parenthesis: as a percentage of all patients failing or dying.

ued loco-regional relapses in the PRE-OP group ($p = 0.04$). In the supraglottic larynx these differences were even more pronounced and were significant to the $p < 0.007$ level.

Table 7. Patterns of first failure and cause of death beyond 2 years after randomization: supraglottic larynx patients

Failure: cause of death	Preop RT (N = 28) No. (%)	Postop RT (N = 34) No. (%)
Loco-regional*	7 (41)†	1 (6)
Treated disease	4	1
Distant metastasis	2	0
Unrelated	1	0
Distant metastasis	0 (0)	4 (24)
Distant metastasis	0	4
NED-dead	10 (59)	12 (70)
Second primary	4	4
Unrelated	6	6
Unknown	0	2
Total failed or died beyond 2 years	17	17
NED-alive beyond 2 years	11	17

* $p = 0.02$.

† Value in parenthesis: as a percentage of all patients failing or dying.

Table 8. RTOG 73-03: treatment complications

	Preop RT (N = 136)	Postop RT (N = 141)
Overall complication rate	67% (91)	76% (107)
Severe complications	24% (33)	27% (38)
Surgical complication rate	43% (59)	42% (59)
Severe surgical complications	18% (25)	14% (20)
Radiation reaction rate	53% (72)	67% (95)
Severe radiation reactions	14% (26)	20% (28)

Note that the superiority of POST-OP RT was only clearly established after prolonged follow-up and was reflected mainly in improved loco-regional control. However, loco-regional failure is still the major problem, especially within the first 2 years, accounting for nearly 60% of failures. This pattern of failure remains prominent in the PRE-OP RT patients after 2 years, with failure in the primary or regional nodes comprising 30% of the failures compared to only 6% in those receiving POST-OP RT. However, the advantage of lower loco-regional failure in patients randomized to POST-OP RT is not reflected in significantly improved overall survival. The actuarial survival at 7 years was 20% and 29% for the PRE-OP RT and POST-OP RT groups, respectively. This is markedly decreased from the expected 85% survival rate for an average healthy 58-year-old in the United States (28) (the median age of patients in this study) during the same 7-year period. In other non-randomized studies, greater benefit for POST-OP RT as compared to PRE-OP RT (2, 24) has also been reported. In a sequential study, Seiden *et al.* 1984 (24) reported a significant difference in local control rate in operable advanced supraglottic carcinoma (71% vs. 48%) as well as improved disease-free 5-year survival (55% vs. 35%) in patients receiving postoperative radiotherapy.

A possible criticism of this study is the different radiation dose used in both arms of the study. The dose of 50 Gy in 5 weeks was selected for preoperative radiation to produce a control rate of greater than 90% for subclinical disease (6, 8) and to limit complications that would arise with surgery. When this study was designed, it was considered that this was equivalent to a postoperative dose of 60 Gy. When radiation is delivered postoperatively, a higher dose is generally considered necessary because of increased tumor resistance as a result of hypoxia, induced by surgical disruption of vascularity and scarring (17). Since the complications of the two groups were similar in this study, a higher preoperative dose would undoubtedly have caused greater morbidity and adversely affected the results in this arm (18). This study serves as a valid randomized comparison of two approaches to combined modality therapy in common use at that time. However, it is clearly impossible to determine if the main advantage of postoperative radiation therapy relates to the timing or dose of radiation administered.

With longer follow-up, there has been a distinct shift to a pattern of distant metastases and second primaries in all patients, but particularly in the POST-OP RT group, eliminating any possible advantage derived from the improved loco-regional control. This shift does not appear to be caused by improved survival but may be related to lifestyle and continued tobacco and alcohol use, which maintain the patient's susceptibility to developing further lesions. Second malignancies, most commonly in the aerodigestive tract, are well-recognized in patients with head and neck carcinoma (32) and necessitate indefinite follow-up. Latent distant metastases may be present that have hitherto been overshadowed by the problem of loco-regional control, and assume prominence with increasing survival. Since the incidence of distant metastases was similar in both the PRE-OP RT and POST-OP RT groups in the first 2 years, this is unlikely to be caused by delays in instituting radiotherapy. Distant metastases alone were responsible for approximately 20% of all the deaths and were not decreased by preoperative radiotherapy. The relative increase in the rate of distant metastases has been noted by other authors (2, 3, 19) and needs to be addressed if an impact on overall survival of advanced head and neck cancer is to be made.

Treatment-related complications were the direct cause of death in 7% of cases. The rate of complications was similar in both groups, despite the higher dose in the POST-OP RT group which was reflected in a slightly higher acute radiation reaction rate. All treatment-related deaths occurred in the first 2 years following therapy, and there has been no increase in the rate and severity of complications since the previous reports of this study (13, 25). The complication rate was significant in both groups and was severe in a quarter of the patients. Therefore, improvement in loco-regional control probably cannot be achieved merely by increased intensity of treatment, and additional therapy is required.

In the subset of patients with carcinoma of supraglottic larynx, the cause of death was loco-regional in 10% of those receiving POST-OP RT and 30% in those receiving PRE-OP RT ($p = 0.007$). Overall loco-regional control was approximately 80% versus 50% for PRE-OP RT, but the 10-year survival rate was only 30% and was similar for the two groups of patients. The patterns of first failure were again significant for loco-regional failure in the first 2 years, constituting 44–60% of all failures. Beyond this period, the POST-OP RT patients remained locally controlled, but distant metastases continued to occur. Second primaries and unrelated causes were also responsible for a high attrition rate and ultimately caused half the deaths in this group.

In summary, long term follow-up of a randomized prospective study indicates an advantage for POST-OP RT for all sites of head and neck carcinoma, but especially so for patients with supraglottic carcinoma. However, the continued attrition related to unrelated deaths, second primaries, and distant metastases after 2 years does not allow the benefits of this treatment to be translated into statistically significant better overall survival. Psychosocial and/or nutritional measures to counter the problem of lifestyle and other factors putting the patients at risk of such failure require consideration. Furthermore, the increasing prominence of distant metastases will need to be countered by additional therapeutic intervention.

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