ORIGINAL ARTICLE

Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

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ABSTRACT

BACKGROUND

We compared concomitant cisplatin and irradiation with radiotherapy alone as adjuvant treatment for stage III or IV head and neck cancer.

METHODS

After undergoing surgery with curative intent, 167 patients were randomly assigned to receive radiotherapy alone (66 Gy over a period of 6½ weeks) and 167 to receive the same radiotherapy regimen combined with 100 mg of cisplatin per square meter of body-surface area on days 1, 22, and 43 of the radiotherapy regimen.

RESULTS

After a median follow-up of 60 months, the rate of progression-free survival was significantly higher in the combined-therapy group than in the group given radiotherapy alone (P=0.04 by the log-rank test; hazard ratio for disease progression, 0.75; 95 percent confidence interval, 0.56 to 0.99), with 5-year Kaplan–Meier estimates of progression-free survival of 47 percent and 36 percent, respectively. The overall survival rate was also significantly higher in the combined-therapy group than in the radiotherapy group (P=0.02 by the log-rank test; hazard ratio for death, 0.70; 95 percent confidence interval, 0.52 to 0.95), with five-year Kaplan–Meier estimates of overall survival of 53 percent and 40 percent, respectively. The cumulative incidence of local or regional relapses was significantly lower in the combined-therapy group (P=0.007). The estimated five-year cumulative incidence of local or regional relapses (considering death from other causes as a competing risk) was 31 percent after radiotherapy and 18 percent after combined therapy. Severe (grade 3 or higher) adverse effects were more frequent after combined therapy (41 percent) than after radiotherapy (21 percent, P=0.001); the types of severe mucosal adverse effects were similar in the two groups, as was the incidence of late adverse effects.

CONCLUSIONS

Postoperative concurrent administration of high-dose cisplatin with radiotherapy is more efficacious than radiotherapy alone in patients with locally advanced head and neck cancer and does not cause an undue number of late complications.

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Local or regional recurrences and distant metastases are frequent after surgical treatment of stage III or IV squamous-cell carcinoma of the head and neck. The risk of failure is particularly high in patients with inadequate resection margins, extranodal spread, or multiple involved lymph nodes.[1-4] In patients with such locally advanced tumors, surgery is usually followed by adjuvant radiotherapy. The advantage of postoperative radiotherapy is well documented[2-5] and compares favorably with the benefit afforded by preoperative irradiation.[6,7]

Several studies have demonstrated that concurrent treatment with radiotherapy and chemotherapy is a promising approach for locally advanced squamous-cell carcinoma that is not amenable to surgery,[8,9] justifying tests of the efficacy of chemotherapy plus radiotherapy as postoperative (adjuvant) treatment.[10] Indeed, sequential adjuvant treatment with chemotherapy and radiotherapy significantly reduced the probability of nodal failure and distant metastasis, and this improvement was directly linked to the levels of clinical and pathological risk.[11] Moreover, in early randomized trials, concomitant postoperative radiotherapy and chemotherapy significantly improved local or regional control but had no effect on overall survival.[12,13]

In 1994, the European Organization for Research and Treatment of Cancer (EORTC) began a randomized trial (EORTC trial 22931) to test the hypothesis that adjuvant chemotherapy and radiotherapy improves progression-free survival, overall survival, and local or regional control more than does radiotherapy alone in patients with stage III or IV head and neck cancer.

METHODS

PATIENT POPULATION AND ELIGIBILITY CRITERIA

The main objective of this study was to determine whether the addition of cisplatin to high-dose radiotherapy after radical surgery increases progression-free survival in patients at high risk for recurrent cancer. Secondary end points included overall survival, relapse, and acute and late adverse effects.

In this multicenter study, the stage of the tumor was determined on the basis of the histologic findings and classified according to the criteria of the Union Internationale contre le Cancer.[14] All patients underwent a full endoscopic examination during which a diagram was made of the extent of disease. Chest radiography, serum chemical analyses, and a complete blood count were obtained. Computed tomography of the site of the primary tumor and the neck was highly recommended.

To be eligible, patients had to have previously untreated, histologically proven squamous-cell carcinoma arising from the oral cavity, oropharynx, hypopharynx, or larynx, with a tumor (T) stage of pT3 or pT4 and any nodal stage (N), except T3N0 of the larynx, with negative resection margins, or a tumor stage of 1 or 2 with a nodal stage of 2 or 3 and no distant metastasis (M0). Patients with stage T1 or T2 and N0 or N1 who had unfavorable pathological findings (extranodal spread, positive resection margins, perineural involvement, or vascular tumor embolism) were also eligible, as were those with oral-cavity or oropharyngeal tumors with involved lymph nodes at level IV or V, according to the anatomical lymph-node distribution proposed by Robbins et al.[15]

Patients had to be at least 18 years of age and no older than 70 years, with a performance status of 0, 1, or 2, according to the scale of the World Health Organization; they also had to have a serum creatinine concentration of 1.36 mg per deciliter (120 μmol per liter) or less, a white-cell count of at least 4000 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, and a hemoglobin concentration of at least 11.0 g per deciliter (6.8 mmol per liter). Aminotransferase values and bilirubin values could not exceed twice the upper limit of normal. Patients who had a history of invasive or synchronous cancer (except nonmelanoma skin cancer), had previously received chemotherapy, or had known central nervous system disease were excluded from the study.

The study protocol was accepted by the independent review committee of each participating center. Informed consent was obtained from all patients in accordance with institutional guidelines.

SURGERY

All eligible patients underwent primary surgery performed with curative intent. The extent of surgical resection of the primary tumor and neck-dissection procedures followed accepted criteria for adequate excision, which depend on the volume and location of the tumor. If the tumor was within 5 mm of the surgical margins, the resection margins were considered to be close.

RADIOTHERAPY

All patients received postoperative radiotherapy consisting of conventionally fractionated doses of 2 Gy each in five weekly sessions. Maximal and minimal

target-volume doses and the maximal dose to the spinal cord were recorded. Treatments were conducted on linear accelerators of 4 to 6 MV with the use of isocentric techniques. A large volume encompassing the primary site and all draining lymph nodes at risk received a dose of up to 54 Gy in 27 fractions over a period of 5½ weeks. Regions that were at high risk for malignant dissemination or that had inadequate resection margins received a 12-Gy boost (total, 66 Gy) in 33 fractions over a period of 6½ weeks. The dose to the spinal cord was limited to 45 Gy.

CHEMOTHERAPY

Chemotherapy consisted of 100 mg of cisplatin per square meter of body-surface area on days 1, 22, and 43 of the course of radiotherapy. Patients received prophylactic hydration and antiemetic agents.

FOLLOW-UP

Patients were evaluated every 2 months for the first 6 months, every 4 months for the next 24 months, every 6 months for the next 2 years, and annually thereafter. Adverse effects, weight, performance status, and tumor response were assessed at baseline, weekly for the first eight weeks, and at each follow-up assessment.

STUDY DESIGN

After surgery, patients were randomly assigned to receive radiotherapy alone or radiotherapy combined with chemotherapy. Randomization was centralized, either electronically (by means of the Internet) or by telephone, by the EORTC Data Center. Principal eligibility criteria were checked at the time of randomization. The Pocock minimization technique was used for the randomization; center and tumor site were used as stratification factors.

The trial was designed to detect an absolute increase in progression-free survival of 15 percent (from 40 percent to 55 percent at three years) with a two-sided 5 percent significance level and a statistical power of 80 percent. We planned to recruit 338 patients. Recruitment was stopped as soon as the 178th event occurred, before the final analysis. Although not initially planned, an interim analysis was performed at the end of the recruitment period and interim results were published.[16] The final analysis included 26 additional months of follow-up. According to the intention-to-treat principle, no patient was excluded from the demographic and efficacy analysis. Progression-free survival, the primary end point, was defined as the time from randomization to any type of progression or death from any cause. Overall survival was defined as the time from randomization to death from any cause. Both end points were estimated by means of Kaplan–Meier methods, and comparisons between treatment groups used the log-rank test.[17] The cumulative incidences of local or regional relapses, late reactions, metastases, and second primary tumors were analyzed as secondary end points. The cumulative incidence of each individual event was estimated by the competing-risk method, in which death from other causes was considered a competing risk. Comparisons between treatment groups used Gray's test.[18] All tests were two-sided. Version 2.0 of the Common Toxicity Criteria of the Radiation Therapy Oncology Group was used to grade adverse effects. Likewise, the Late Radiation Morbidity Scoring Scheme of the Radiation Therapy Oncology Group and the EORTC was used to assess late adverse effects.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From February 1994 to October 2000, 334 patients from 23 institutions consented to participate in the trial; 92 percent were men, and 69 percent were more than 50 years of age. Of these 334 patients, 167 were randomly assigned to receive radiotherapy alone and 167 to receive concurrent chemotherapy and radiotherapy. The baseline characteristics of the two groups were similar (Table 1). The median and maximal follow-up times were 60 months and 100 months, respectively (58 and 96, respectively, in the radiotherapy group, and 61 and 100, respectively, in the combined-therapy group).

TREATMENT

Thirty-two percent of patients in the combined-therapy group started radiotherapy more than 43 days after the surgical procedure, as compared with 25 percent of those in the radiotherapy group. A total of 21 patients (12 in the radiotherapy group and 9 in the combined-therapy group) started treatment 8 to 10 weeks after surgery. A total of 11 patients never started the radiotherapy protocol (2 in the radiotherapy group and 9 in the combined-therapy group). In addition, 15 patients (4 percent: 7 patients in the radiotherapy group and 8 in the combined-therapy group) received less than 60 Gy, which corresponds to a 10 percent deviation from the total value of 66 Gy listed in the protocol. Among patients who re-

Table 1. Characteristics of Patients and Tumors.

Characteristic	Radiotherapy (N=167)	Combined Therapy (N=167)	Total (N=334)
Sex — no. (%)			
Male	155 (93)	153 (92)	308 (92)
Female	12 (7)	13 (8)	25 (7)
Unknown	0	1 (1)	1 (1)
Age			
18–50 yr — no. (%)	58 (35)	46 (28)	104 (31)
51–70 yr — no. (%)	109 (65)	121 (72)	230 (69)
Median — yr	53	55	54
Tumor stage — no. (%)*			
T1	16 (10)	11 (7)	27 (8)
T2	43 (26)	40 (24)	83 (25)
T3	49 (29)	44 (26)	93 (28)
T4	57 (34)	72 (43)	129 (39)
Unknown	2 (1)	0	2 (1)
Nodal stage — no. (%)*			
N0	42 (25)	37 (22)	79 (24)
N1	29 (17)	35 (21)	64 (19)
N2	84 (50)	83 (50)	167 (50)
N3	12 (7)	12 (7)	24 (7)
Primary tumor site — no. (%)			
Oral cavity	46 (28)	41 (25)	87 (26)
Oropharynx	47 (28)	54 (32)	101 (30)
Hypopharynx	34 (20)	34 (20)	68 (20)
Larynx	38 (23)	37 (22)	75 (22)
Unknown	2 (1)	1 (1)	3 (1)
Resection-margin status — no. (%)			
Positive	43 (26)	52 (31)	95 (28)
Negative	122 (73)	115 (69)	237 (71)
Unknown	2 (1)	0	2 (1)
Histologic differentiation — no. (%)			
Well differentiated	64 (38)	74 (44)	138 (41)
Moderately differentiated	70 (42)	60 (36)	130 (39)
Poorly differentiated	32 (19)	30 (18)	62 (19)
Unknown	1 (1)	3 (2)	4 (1)
Extracapsular spread — no. (%)			
Positive	89 (53)	102 (61)	191 (57)
Negative	78 (47)	65 (39)	143 (43)
Perineural involvement — no. (%)			
Yes	24 (14)	21 (13)	45 (13)
No	140 (84)	143 (86)	283 (85)
Unknown	3 (2)	3 (2)	6 (2)
Vascular embolisms — no. (%)			
Yes	31 (19)	35 (21)	66 (20)
No	135 (81)	131 (78)	266 (80)
Unknown	1 (1)	1 (1)	2 (1)
Lymph-node involvement — no. (%)			
0–1 Positive	73 (44)	72 (43)	145 (43)
≥2 Positive	93 (56)	89 (53)	182 (54)
Unknown	1 (1)	6 (4)	7 (2)

* The tumor (T) and nodal (N) staging system of the Union Internationale contre le Cancer was used.[14]

ceived at least 60 Gy, 81 had treatment interruptions resulting in a total duration of treatment of more than seven weeks (42 in the radiotherapy group and 39 in the combined-therapy group).

The median and the interquartile range of the total dose of radiation were the same in both groups: 66 Gy (interquartile range, 65 to 66). The median duration of treatment was 47 days (interquartile range, 45 to 51) in the radiotherapy group and 47 days (interquartile range, 44 to 50.5) in the combined-therapy group.

In the combined-therapy group, 17 patients (10 percent) never started chemotherapy, whereas 18 patients (11 percent) stopped chemotherapy after one course and 25 patients (15 percent) stopped chemotherapy after two courses. Compliance with chemotherapy also decreased with the number of courses delivered: the first, second, and third cycles were administered on time and without delay in 147 patients (88 percent), 110 patients (66 percent), and 82 patients (49 percent), respectively.

SEVERE ACUTE ADVERSE EFFECTS

Although the cumulative incidence of severe (grade 3 or higher) functional mucosal adverse effects was significantly greater in the combined-therapy group than in the radiation group (incidence, 41 percent vs. 21 percent; P=0.001), the types of mucosal reactions were similar in the two groups (P=0.28). The incidence of muscular fibrosis of grade 3 or higher was greater in the combined-therapy group than in the radiotherapy group (10 percent vs. 5 percent), whereas the incidence of severe xerostomia was lower (14 percent vs. 20 percent). Other severe complications in the radiotherapy and combined-therapy groups were as follows: dysphagia (12 percent and 10 percent, respectively), shoulder syndrome (8 percent and 5 percent, respectively), impaired lymphatic drainage (7 percent and 2 percent, respectively), laryngeal complications (1 percent and 2 percent, respectively), bone complications (1 percent and 2 percent, respectively), mucosal necrosis (1 percent and 2 percent, respectively), and skin and connective-tissue fibrosis (1 percent and 2 percent, respectively).

Severe leukopenia occurred in 16 percent of the patients in the combined-therapy group, and severe granulocytopenia occurred in 13 percent. Severe nausea occurred in 12 percent of the patients receiving concurrent chemotherapy and radiotherapy, and severe vomiting occurred in 11 percent. These were the only severe chemotherapy-related adverse ef-

fects reported in at least 10 percent of the patients in this group. The quality of life was not assessed in this study.

PROGRESSION-FREE SURVIVAL

Progression-free survival was the primary end point of this trial. After a median follow-up of 60 months, a total of 194 treatment failures (103 in the radiotherapy group and 91 in the combined-therapy group) had been recorded. There was a significant (P=0.04 by the log-rank test) difference in progression-free survival in favor of the combined-therapy group over the radiotherapy group (Fig. 1) (hazard ratio for disease progression, 0.75; 95 percent confidence interval, 0.56 to 0.99). The estimated median duration of progression-free survival was 23 months (95 percent confidence interval, 18 to 30) in the radiotherapy group and 55 months (95 percent confidence interval, 33 to 75) in the combined-therapy group, and the Kaplan–Meier estimates of 5-year progression-free survival were 36 percent and 47 percent, respectively. The disease progressed in 159 patients (90 in the radiotherapy group and 69 in the combined-therapy group), and 35 died without reported evidence of disease (13 in the radiotherapy group and 22 in the combined-therapy group).

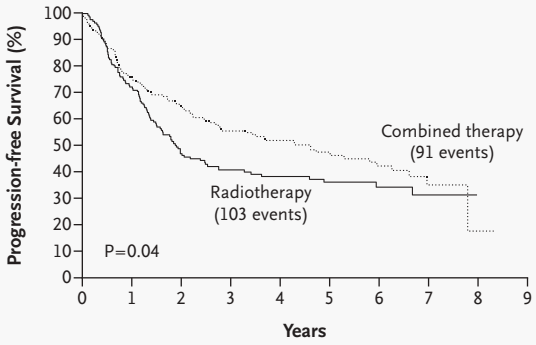


Figure 1. Kaplan–Meier Estimates of Progression-free Survival.
Patients assigned to combined therapy had higher rates of progression-free survival than those assigned to radiotherapy (hazard ratio for progression, 0.75; P=0.02).

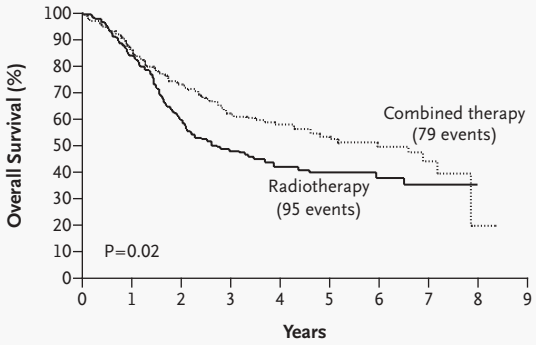


Figure 2. Kaplan–Meier Estimates of Overall Survival.
Patients assigned to combined therapy had higher survival rates than those assigned to radiotherapy (hazard ratio for death, 0.70; P=0.04).

OVERALL SURVIVAL

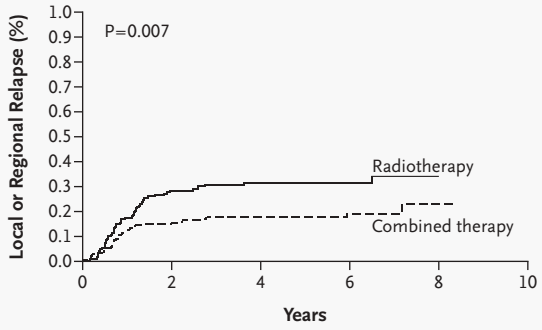
A total of 174 patients (52 percent) died. There was a significant (P=0.02 by the log-rank test) difference in overall survival in favor of the combined-therapy group over the radiotherapy group (Fig. 2) (hazard ratio for death, 0.70; 95 percent confidence interval, 0.52 to 0.95). The estimated median time to death was 32 months (95 percent confidence interval, 25 to 46) in the radiotherapy group and 72 months (95 percent confidence interval, 51 to 94) in the combined-therapy group. The Kaplan–Meier estimates of overall survival at five years were 40 percent in the radiotherapy group and 53 percent in the combined-therapy group. Head and neck cancer was the cause of death in 116 patients — 71 (43 percent) in the radiotherapy group and 45 (27 percent) in the combined-therapy group. Treatment-related adverse effects were the cause of death in one patient in each group. Two patients in the radiotherapy group died of infection.

CUMULATIVE INCIDENCE OF LOCAL AND REGIONAL RELAPSES

There were 83 local or regional failures (52 in the radiotherapy group and 31 in the combined-therapy group). The estimated five-year cumulative incidence of local or regional relapses was 31 percent in the radiotherapy group and 18 percent in the combined-therapy group (Fig. 3). The difference was significant (P=0.007 by Gray's test).

CUMULATIVE INCIDENCE OF METASTASES AND SECOND PRIMARY TUMORS

The estimated five-year cumulative incidence of metastases was 25 percent in the radiotherapy group



No. at Risk					
Radiotherapy	167	126	66	31	9
Combined therapy	167	130	88	47	12

Figure 3. Cumulative Incidence of Local or Regional Relapses.

Patients assigned to combined therapy had higher rates of local or regional control than those assigned to radiotherapy (P=0.007 by Gray's test).

and 21 percent in the combined-therapy group. The difference was not significant (P=0.61 by Gray's test). The estimated five-year cumulative incidence of second primary tumors was 13 percent in the radiotherapy group and 12 percent in the combined-therapy group; the difference was not significant (P=0.83 by Gray's test).

CUMULATIVE INCIDENCE OF LATE COMPLICATIONS

The cumulative incidence of late complications was not significantly different between the two groups (Fig. 4). As was the case with acute functional reactions, the incidence of severe muscular fibrosis was higher in the combined-therapy group than in the radiotherapy group (10 percent vs. 5 percent), but the incidence of severe xerostomia was lower (14 percent vs. 22 percent).

DISCUSSION

Various strategies have been proposed to improve the outcome among patients who have resectable, locally advanced squamous-cell carcinoma of the head and neck with a high risk for recurrence or metastasis. In 1970, Fletcher and Evers reported the first convincing evidence of the benefit of combining radiotherapy with surgery.[5] Since then, the risk of treatment failure above the clavicles has been repeatedly found to be significantly reduced by the use of postoperative radiotherapy,[3,4,19] and it has been clearly demonstrated that patients at high risk for recurrent disease or metastasis should be treated aggressively after surgery.[20]

From the late 1970s to the early 1990s, promising results emerged from the use of various combinations of postoperative chemotherapy and radiotherapy in randomized[10,21,22] and nonrandomized[23-25] studies. Among the former, Intergroup Study 00-34 showed that the sequential addition of cisplatin and fluorouracil to radiotherapy reduced the incidence of nodal and distant failures, but did not improve survival.[10]

Cisplatin has been investigated in the management of squamous-cell carcinomas of the head and neck since the early 1970s. The interest in this compound was due to its presumed radiosensitizing role, whether given in small weekly doses or in higher doses (100 mg per square meter) every three weeks (days 1, 22, and 43 during radiotherapy).[26] We used the latter approach, but when our trial began in 1994, most trials of adjuvant treatment had not demonstrated the superiority of combined therapy over radiotherapy alone in patients with locally advanced carcinoma of the head and neck.

We found that concurrent chemotherapy and radiotherapy significantly increased progression-free survival. The five-year actuarial estimates of progression-free survival were 47 percent in the combined-therapy group and 36 percent in the radiotherapy group, and the respective values for overall survival were 53 percent and 40 percent. These differences are in line with those reported in other trials and meta-analyses, showing that locally advanced tumors respond better to concurrent chemotherapy and radiotherapy than to radiotherapy alone.[27-33]

Apart from a significant effect on survival indexes, adjuvant chemotherapy and radiotherapy were also associated with a pattern of failure that differed from that associated with radiotherapy. The estimated five-year rate of death from head and neck cancer was reduced from 43 percent to 27 percent by the concomitant addition of cisplatin to radiotherapy. Combined therapy did not, however, reduce the probability of distant relapse. Two thirds of the patients received at least two full cycles of chemotherapy, and 49 percent received the planned three courses without any delay or dose reduction. Notwithstanding the more aggressive treatment in the combined-therapy group, the incidence of acute ad-

verse effects after cisplatin and radiotherapy was acceptable, and the incidence of severe late adverse effects was similar in the two groups (Fig. 4).

The interim analysis,[16] performed after a median follow-up of 34 months, demonstrated a significant advantage of combined therapy over radiotherapy alone, according to an O'Brien–Fleming sequential design, with respect to both progression-free survival (143 events; P=0.0096; estimated hazard ratio, 0.56) and overall survival (115 events; P=0.0057; estimated hazard ratio, 0.65). The shape of the progression-free survival curve (Fig. 1) suggests that the effect of chemotherapy decreases over time (the hazard is nonproportional).

Our results must be interpreted in the light of various factors that can influence the magnitude of the effect of combined chemotherapy and radiotherapy, as demonstrated by the results of the Radiation Therapy Oncology Group 95-01 trial.[34] In that trial, primary tumor sites were evenly distributed among the oral cavity, larynx, hypopharynx, and oropharynx, although there were slightly more oropharyngeal cancers. The design of our study did not include a subgroup analysis on this basis. Thus, the extent of benefit from combined chemotherapy and radiotherapy at particular sites cannot be reliably assessed. Likewise, the selection of patients in our study was based on both pathological factors (resection-margin status and the presence or absence of extranodal spread, perineural involvement, and vascular embolisms) and clinical factors (tumor and nodal volume and nodal site). Therefore, the participants can be considered at high risk for both local or regional failure and distant metastasis. It is important to note that resection margins were positive in about 30 percent of our patients, with no significant imbalance in this variable between the two groups. It seems unwise to extrapolate the magnitude of the effect we observed to studies based on pathological risk criteria alone.

In conclusion, after surgery with curative intent, adjuvant treatment with high-dose cisplatin plus radiotherapy is more efficacious than radiotherapy alone in patients with squamous-cell carcinoma of the head and neck with unfavorable clinical or pathological factors or both. The addition of chemotherapy to radiotherapy significantly increased the rates of local control, disease-specific survival, and overall survival, without a high incidence of late adverse effects. The effect of the postoperative administration of concurrent chemotherapy and radiotherapy on outcome is likely to be influenced by the criteria used to select patients.

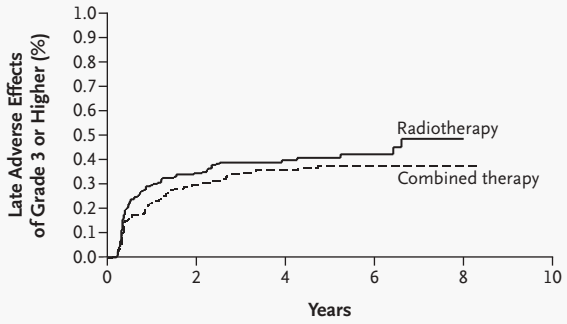


Figure 4. Cumulative Incidence of Late Adverse Effects of at Least Grade 3.
The following severe late adverse effects were included in the analysis: xerostomia, dysphagia, muscular fibrosis, shoulder syndrome, impairment of lymphatic drainage, laryngeal complications, bone complications, mucosal necrosis, and skin and connective-tissue fibrosis.

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