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ORIGINAL REPORT

Randomized Trial of Postoperative Reirradiation Combined With Chemotherapy After Salvage Surgery Compared With Salvage Surgery Alone in Head and Neck Carcinoma

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Full-dose reirradiation combined with chemotherapy has been shown to be feasible after salvage surgery with acceptable toxicity. The Groupe d'Etude des Tumeurs de la Tête et du Cou and Groupe d'Oncologie Radiothérapie Tête Et Cou groups performed a randomized study to assess its efficacy.

Patients and Methods
Between 1999 and 2005, 130 patients with head and neck cancer were treated with salvage surgery and randomly assigned to full-dose reirradiation combined with chemotherapy (RT arm) or to observation (a "wait and see" approach; WS arm). Eligibility criteria were recurrence or a second primary tumor in a previously irradiated area, no major sequelae resulting from the first radiotherapy, good general condition, no distant metastasis, and salvage surgery with macroscopic complete resection. Patients in the RT arm received 60 Gy over 11 weeks combined with concomitant fluorouracil and hydroxyurea.

Results
Sixty-five patients were randomly assigned to each arm. There was no imbalance in the distribution of the main tumor and patients characteristics. The most serious acute toxicity in the RT arm was mucositis, attaining grade 3 or 4 in 28% of patients. At 2 years, 39% of patients in the RT arm and 10% in the WS arm experienced grade 3 or 4 late toxicity according to Radiation Therapy Oncology Group criteria ($P = .06$). Disease-free survival (DFS) was significantly improved in the RT arm, with a hazard ratio of 1.68 (95% CI, 1.13 to 2.50; $P = .01$), but overall survival (OS) was not statistically different.

Conclusion
Full-dose reirradiation combined with chemotherapy after salvage surgery significantly improved DFS, but had no significant impact on OS. An increase in both acute and late toxicity was observed.

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INTRODUCTION

Patients with recurrent head and neck squamous cell carcinoma (HNSCC) or a second primary tumor occurring in a previously irradiated area have a poor prognosis. Salvage surgery, when feasible, is the standard of care. However, even in a selected population of operable patients, the results of salvage surgery alone remain poor, with a high rate of locoregional failures.[1]

In the 1990s, the University of Chicago demonstrated that full-dose reirradiation with concurrent chemotherapy was feasible in patients with inoperable recurrent HNSCC.[2] The original treatment schedule combined protracted radiotherapy delivering 60 Gy over 11 weeks and concomitant fluorouracil and hydroxyurea. This schedule proved efficient in inoperable patients, with long-term disease-free survival in a small proportion of cases. This experience also showed that full-dose reirradiation could be delivered without intolerable toxicity, and this was further confirmed in subsequent studies.[3-11] A phase II study, conducted at the Institute Gustave Roussy, showed that concomitant radiation and chemotherapy after salvage surgery was feasible and could potentially improve locoregional control (LRC).[12]

This result prompted the Groupe d'Etude des Tumeurs de la Tête et du Cou and the Groupe d'Oncologie et de Radiothérapie Tête Et Cou to

launch a phase III multicentric trial to evaluate the efficacy of concomitant radiation and chemotherapy after salvage surgery. We report here the first analysis of this randomized trial.

PATIENTS AND METHODS

Patients

Patients who underwent surgery for a recurrence or a second primary tumor in a previously irradiated area were eligible. The tumor target of the initial course of radiotherapy was the first carcinologic event. The tumor operated on by salvage surgery was the second carcinologic event. The term "third carcinologic event" defines carcinologic events occurring after salvage surgery (local and/or nodal recurrence, metastasis, or new primaries). The pretreatment work-up included an endoscopy under general anesthesia, computed tomography scan, and/or magnetic resonance imaging. Assessment of distant metastasis included a chest x-ray with a chest computed tomography scan if needed, liver ultrasound, and a bone scintigraphy, depending on symptoms. Laboratory tests were performed to evaluate hematologic, renal, and hepatic function.

The main inclusion criteria were as follows: (1) Histologically proven HNSCC occurring in an area previously irradiated with at least 45 Gy. The intersection between the first irradiation and the reirradiation fields had to be greater than 65%. (2) Clinical and/or radiologic evidence of deep infiltration ($>$ 1 cm). Laryngeal tumors were included only in case of extra-laryngeal spread (rT4). For all sites, any superficial tumor could only be included if it was associated with a nodal recurrence. An isolated nodal recurrence could only be included if it exceeded 3 cm. (3) No distant metastasis. (4) A Karnofsky performance score of $\geq$ 80 and hematologic and cardiovascular status not contraindicating chemotherapy. (5) Patients with severe sequelae after the initial course of radiotherapy, such as osteoradionecrosis or severe cervical fibrosis, were excluded. (6) An interval of at least 6 months between the initial course of radiotherapy and salvage surgery. (7) Salvage surgery with macroscopically complete resection (debulking surgery was not allowed). (8) Rapid and complete wound healing allowing reirradiation to start no later than 8 weeks after salvage surgery. An interval of 6 weeks between salvage surgery and reirradiation was recommended, and randomization was performed approximately 2 weeks after salvage surgery.

Reirradiation With Concurrent Chemotherapy

In the reirradiation arm (RT arm), patients were to receive six cycles, with each cycle delivering 2 Gy/fraction, 5 days/wk, with concomitant hydroxyurea (1.5 g/d orally) and continuous infusion fluorouracil (800 mg/m^2/d), as previously reported.[2,4,11] There were 9-day rest periods between cycles. Reirradiation was performed using 4 to 6 MV photons, along with a conventional treatment planning system or three-dimensional conformal radiotherapy (no intensity-modulated radiotherapy was available).

A general guideline was to restrict the radiation fields to the tumor bed, as determined by the surgeon and the radiation oncologist, without nodal prophylaxis beyond the first adjacent nodal area. Hence the entire neck was not systematically reirradiated. The margin around the tumor bed was at least 1 cm and could be extended up to 2 cm in some deeply infiltrating tumor and/or nodal relapses.

A smaller margin could be accepted only in case of reirradiation close to the spinal cord. The dose was calculated at the International Commission on Radiation Units and Measurements (report No. 50) intersection point. The spinal cord was systematically excluded from the reirradiation beams. When the posterior cervical nodes had to be treated, electron beams of appropriate energy (8 to 12 MV) or oblique posterior photon beams were used. When surgery required a tracheostomy and/or a nasogastric tube, they were generally maintained during the course of reirradiation.

Quality Assurance

Patient charts were reviewed by a panel consisting of investigators and external experts. The location of the first carcinologic event, the type, location, and TNM classification of the second carcinologic event and the histologic reports were reviewed. In the reirradiation arm, the total dose, the overall time, and the dose per fraction were verified, as were the reirradiation fields, according to tumor and nodal extension. When reviewing the radiotherapy quality assurance for the first 25 patients, adequate coverage was defined as coverage of the entire tumor bed with a minimum margin of 1 cm.

Toxicity

Toxicity was considered acute when occurring within 6 months after randomization. It was scored according to the Radiation Therapy Oncology Group scoring system. Late toxicities were scored according to the European Organisation for Research and Treatmente of Cancer–Radiation Therapy Oncology Group scoring system. Deaths were considered to be treatment-related in two situations: when they occurred during reirradiation or within 6 months of randomization, without evidence of a carcinologic event. When deaths occurred later without a carcinologic event, they were classified as treatment-related if toxicity was the most obvious explanation after discussion with the main investigator (extensive mucosal necrosis and laryngeal edema were the two such examples observed).

Statistical Considerations

Patients were stratified according to the center and tumor site. Disease-free survival (DFS) at 3 years was chosen as the primary end point after approval by the institutional review boards. Additional end points were overall survival (OS) and acute and late toxicity.

Results are expressed as percentages or medians (with range), and the two groups were compared using non parametric tests: χ^2 or Fisher's exact test for qualitative data and the Wilcoxon test for quantitative data.

DFS was calculated as the time from the date of randomization to the date of the first event after randomization, which was documented as a recurrence (local, locoregional, or metastatic, excluding new primaries) or death, or to the date of the last follow-up.

A sample size of 130 patients was required to detect an absolute difference of 20% in DFS at 3 years, with type I and type II error rates of 0.05 and 0.20 respectively. The study was performed as an intent-to-treat analysis. Univariate analyses of DFS and OS were based on a comparison of Kaplan-Meier curves by the log-rank test. Multivariate analyses were computed through a Cox model and were adjusted for centers, tumor sites, type of second carcinologic event (recurrence *v* second primary), and histologic signs of severity (histologically involved surgical margins and vascular or perineural invasion). All tests are two-sided.

RESULTS

The trial was activated in 1999 and closed in 2005. A total of 130 patients from 16 French and Belgian centers were included, 65 patients in the RT arm, and 65 patients in the "wait and see" approach arm (WS arm; Fig 1).[1]

Patient Population

There was no imbalance between the two arms in the distribution of the sex ratio, age, initial weight, performance status, or of the clinical characteristics of first and second event.

The clinical characteristics of the first and second carcinologic events are presented in the Appendix (online only) and in Table 1, respectively. Ninety-two (71%) of the 130 second carcinologic events were recurrences, and the remaining 38 (29%) of 130 were new primaries. Seventy-seven (59%) of the 130 patients had a pharyngeal tumor and 71 (55%) of 130 lesions were restaged as T3 or T4.

Salvage Surgery

Salvage surgery was performed according to routine practice in each center. Although the majority of the patients had no evidence of nodal involvement, a lymph node dissection was performed in most

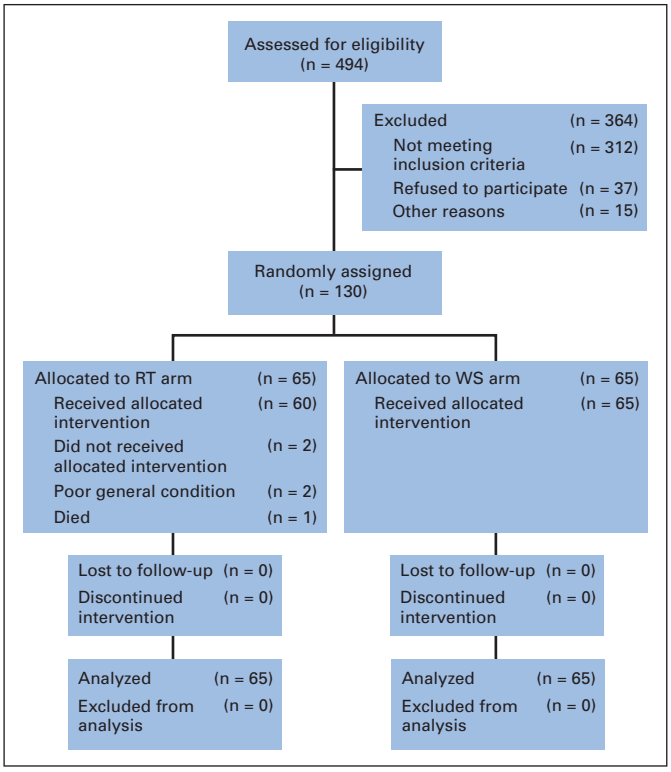

Fig 1. CONSORT diagram. RT, full-dose reirradiation combined with chemotherapy; WS, "wait and see" approach.

Table 1. Characteristics of Second Carcinologic Events (at the time of salvage surgery)

Characteristic	RT Arm (n = 65) No.	RT Arm (n = 65) %	WS Arm (n = 65) No.	WS Arm (n = 65) %	*P*
Progression type					
Local recurrence	25	38	35	54	
Nodal recurrence	10	15	9	14	.32
Local and nodal recurrence	7	11	6	9	
New tumor	23	35	15	23	
Progression type					
Recurrence	42	65	50	77	.12
New tumor	23	35	15	23	
Site					
Oropharynx	22	34	24	37	.93
Larynx	4	6	6	9	
Hypopharynx	17	26	14	22	
Oral cavity	12	18	12	18	
Isolated node	10	15	9	14	
Stage T					
Missing	15	23	18	28	
T1	2	3	2	3	
T2	7	11	15	23	.25
T3	20	31	12	18	
T4	21	32	18	28	
Stage N					
Missing	3	5	4	6	
N0	43	66	44	68	
N1	5	8	8	12	
N2a	4	6	7	11	.20
N2b	7	11	1	2	
N2c	2	3	0	0	
N3	1	2	1	2	
Stage M, M0	65	100	65	100	
Stage TNM, AJCC 2002					
Missing	15	23	19	29	
I	2	3	2	3	
II	7	11	13	20	.39
III	16	25	11	17	
IVA	24	37	20	31	
IVB	1	2	0	0	

NOTE. Missing data were taken into account in the comparisons.
Abbreviations: RT, full-dose reirradiation combined with chemotherapy; WS, "wait and see" approach; AJCC, American Joint Committee on Cancer.

cases (109 of 130 patients; 84%). A flap was commonly used (68%) and was a myocutaneous flap in most cases (70 of 89 patients), a free flap in 18 patients, and a gastric pull-up in one patient.

Surgical Specimen

The characteristics of the surgical specimen are detailed in Table 2: 51 (39%) of 130 patients had nodal involvement, with extracapsular rupture in 34 of 51 patients. Tumor margins were histologically analyzed in 119 of 130 patients: 34 (29%) of 119 margins were considered positive or suspicious. Other histologic signs of severity (vascular emboli, perineural invasion, diffuse infiltration) were present in 72 (55%) of 130 patients.

As shown in Tables 1 and 2, patients were well balanced between the two arms: there were no significant differences with respect to modalities used to treat the first carcinologic event, the type of second carcinologic event (recurrence *v* a new primary), site, T and N stage, and the histologic characteristics of the surgical specimen. There were 64 patients who had either a positive or suspicious margins, extracapsular rupture, or more than one invaded nodes; these 64 patients were equally distributed between the two arms (32 patients in each arm).

RT Arm

The median interval between irradiation of the first and second tumor was 3.5 years (range, 0.5 to 30.5 years). Fifty-two (80%) of 65 patients received five or six cycles. Five patients in the RT arm had no reirradiation at all: refusal after randomization (n = 2), patient's poor general condition (n = 2), and death before beginning reirradiation (n = 1). Two patients had reirradiation without concomitant chemotherapy. For the 60 patients who received reirradiation, the median dose was 60 Gy (range, 5 to 60 Gy). The interval between salvage surgery and the beginning of reirradiation was less than 6 weeks in 27 of 60 cases and less than 8 weeks in 48 of 60 cases. For the 58 patients who received reirradiation plus concomitant chemotherapy, chemotherapy was delayed or given at lower doses in eight cases. Forty of 60 patients who received reirradiation were hospitalized for a median cumulative duration of 25 days, (range, 3 to 40 days).

Quality Assurance

To verify consistency between the reirradiation fields and the tumor bed to be irradiated, a review of all the consecutive cases was performed from 1999 to 2001. The irradiation fields were considered appropriate for the first 24 of 25 patients who underwent reirradiation. Subsequently, the following cases were not reviewed, given that the learning curve of the reirradiation technique was considered achieved.

Table 2. Characteristics of Surgical Specimen After Salvage Surgery

Characteristic	RT Arm (n = 65) No.	%	WS Arm (n = 65) No.	%	P
Nodal histology, N+	27		24		.17
Positive nodes*					
Median	2		1		
Range	1-99		1-12		
No. of patients with positive nodes	27		24		
1	10	37	16	67	.07
2	7	26	5	21	
≥ 3	10	37	3	12	
Capsular rupture					
Yes	19	70	15	63	.55
No	8	30	9	37	
Quality of resection					
Missing	4	6	7	11	
Sufficient	47	72	38	58	.43
Suspicious or involved	14	22	20	31	
Histologic signs of severity (vascular emboli, perineural invasion, diffuse infiltration)					
Missing	5	8	7	11	
None	25	38	21	32	.84
Presence	35	54	37	57	

NOTE. Missing data were taken into account in the comparisons.
Abbreviations: RT, full-dose reirradiation combined with chemotherapy; WS, "wait and see" approach.
*Nodal mass, n = 99.

Table 3. Late Toxicity at 1 and 2 Years After Random Assignment

Toxicity	RT Arm (n = 42; 1 missing) No.	%	WS Arm (n = 33; 3 missing) No.	%
Toxicity at 12 and 12.5 months after random assignment, RTOG grade ≥ 3				
Mucositis	4	10	1	3
Skin	0	0	0	0
Subcutaneous tissues	6	14	3	9
Larynx	0	0	0	0
Osteoradionecrosis	1	2		
Trismus	3	7	2	6
Pharyngeal stenosis	1	2	0	0
No. of patients	11	26	3	9
Toxicity at 24 months after random assignment, RTOG grade ≥ 3*				
Mucositis	1	6	0	0
Skin	1	6	0	0
Subcutaneous tissues	4	22	1	5
Larynx	1	6	0	0
Trismus	5	28	2	10
Osteoradionecrosis	3	17	0	0
Pharyngeal stenosis	1	5.5	0	0
No. of patients	7	39	2	11

Abbreviations: RT, full-dose reirradiation combined with chemotherapy; WS, "wait and see" approach; RTOG, Radiation Therapy Oncology Group.
*At 24 months after random assignment, n = 18 (three missing) for RT arm and n = 19 for WS arm.

Acute Toxicity and Treatment-Related Deaths

In the RT arm, 17 (28%) of 60 patients experienced grade 3 or 4 acute toxicity: mucositis/pharyngitis in all cases, with four patients experiencing marked deterioration of their general condition. Two of these four patients died of sepsis during chemoradiation, and these cases were considered as treatment-related deaths. Another patient died of massive hemorrhage 1 month after the end of chemoradiation (treatment-related death). A case of hand-foot syndrome was observed in the RT arm. Three patients experienced grade 3 hematologic toxicity (anemia without neutropenia).

Two other treatment-related deaths were observed more than 6 months after randomization: one patient died of extensive mucosal necrosis and another of laryngeal edema, 10 and 13 months after chemoradiation, respectively.

Late Toxicity in Surviving Patients

At 12 months from randomization, 11 (26%) of 42 patients had grade 3 or 4 late toxicity in the RT arm, compared with three (9%) of 33 patients in the WS arm (Table 3; $P = .06$). One year after randomization, eight (18%) of 42 patients had a nasogastric tube or a gastrostomy in the RT arm, compared with 11 (33%) of 33 in the WS arm ($P = .16$).

At 24 months after randomization seven (39%) of 18 patients had grade 3 or 4 late toxicity in the RT arm, compared with two (10%) of 19 patients in the WS arm (Table 3; $P = .06$). The main grade 3 and 4 late toxicities were sclerosis, trismus, and osteoradionecrosis, which could be associated in the same patient. Two years after randomization, five of 18 patients still had a feeding tube in the RT arm, compared with two of 19 patients in the WS arm ($P = .09$).

Intercurrent Disease

There were two deaths in the RT arm (pulmonary sepsis) and three deaths in the WS arm (pulmonary sepsis, cardiac infraction, gastric hemorrhage).

Third Carcinologic Events and DFS

In the RT arm, 16 local recurrences occurred: nine were isolated and seven were associated with a nodal recurrence (four patients), a metastatic recurrence (two patients), or both (one patient). In the WS arm, 32 local recurrences occurred: 18 were isolated, and 14 were associated with a nodal recurrence (nine patients), a metastatic recurrence (two patients), both (two patients), or a second primary (one patient). Thus there was a significant difference in LRC between the two arms, in favor of the RT arm: hazard ratio, 2.73 (95% CI, 1.66 to 4.51; $P < .0001$; Fig 2). However, isolated distant metastases were more frequent in the RT arm (10 patients) than in the WS arm (two patients).

There was a significant difference in DFS between the two arms in favor of the RT arm (main end point, Fig 3). This significant difference was found in the univariate analysis ($P = .006$), as well as in multivariate analysis after adjustment on centers, the type of carcinologic event (recurrence *v* second primary), and tumor sites: hazard ratio, 1.68 (95% CI, 1.13 to 2.50; $P = .01$).

In case of a local recurrence in the RT arm, only palliative chemotherapy was administered in eight of 16 cases. In the WS arm, 16 of 32

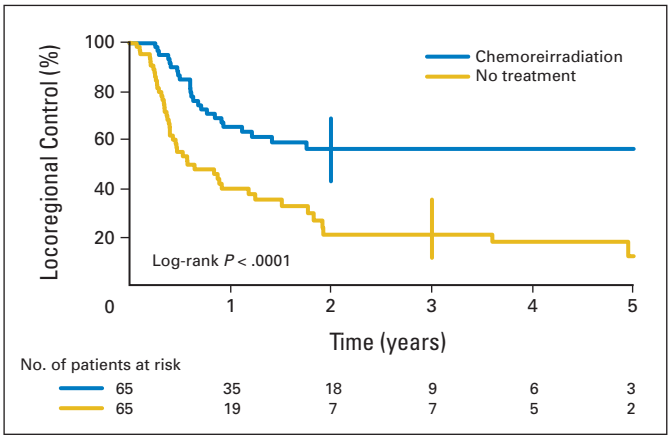

Fig 2. Locoregional control. Large tick marks represent the 95% CI of the point estimates. Chemoirradiation, reirradiation plus concomitant chemotherapy.

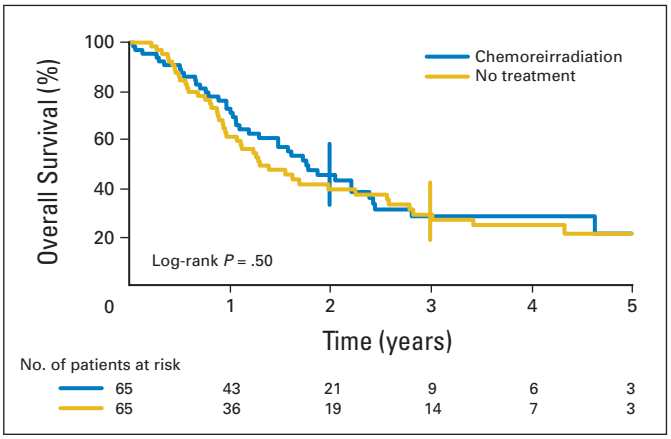

Fig 4. Overall survival. Large tick marks represent the 95% CI of the point estimates. Chemoirradiation, reirradiation plus concomitant chemotherapy.

local recurrences were treated with reirradiation and concomitant chemotherapy, using the same protocol used in the RT arm. Only three of these 16 patients achieved a complete response.

Causes of Death and OS

Deaths related to a locoregional recurrence were less frequent in the RT arm than in the WS arm (21 *v* 34 patients). However, deaths related to treatment (five *v* zero), distant metastases (six *v* three), or second primary (four *v* one) were more frequent in the RT arm than in the WS arm. There was no significant difference in OS between the two arms ($P = .50$; Fig 4).

DISCUSSION

It is noteworthy that inclusion criteria were strict for this randomized trial: each patient had to be examined by a surgeon and a radiation oncologist before randomization to ensure that patients with major sequelae after initial radiotherapy were excluded (patients with osteoradionecrosis or major neck fibrosis were not eligible). Only patients in good general condition could be included. In addition, only patients with total wound healing could be randomly assigned, and wound healing had to be achieved within 4 weeks of surgery so postoperative treatment could begin within 8 weeks of surgery. The resection technique was at the surgeon's discretion. There was a high rate of nodal dissection (84% of patients), although the majority of patients had no evidence of nodal involvement. Flaps were widely used to protect the carotid (68% of patients). Patients with free-flap reconstructions underwent irradiation without specific dose or volume constraints, and no complications were seen concerning the long-term viability of free flaps. Patients with gross residual disease after surgery were excluded because of the poor results of reirradiation in these patients, as observed in our experience[12] and as reported by Machtay et al.[13]

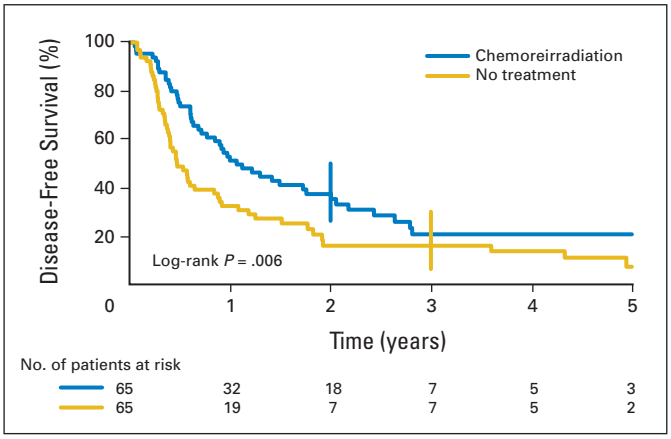

Fig 3. Disease-free survival. Large tick marks represent the 95% CI of the point estimates. Chemoirradiation, reirradiation plus concomitant chemotherapy.

In our selected population of patients, postoperative reirradiation combined with chemotherapy after salvage surgery markedly improved LRC and DFS. However, this schedule increased acute and late toxicity and did not significantly improve OS. LRC and DFS were improved, suggesting that chemotherapy combined with reirradiation is efficient against microscopic residual disease, as evidenced by the description of the third carcinologic events in the two arms: in the RT arm, local recurrences were reduced by a factor of 2, as compared with the WS arm. However, reirradiation plus concomitant chemotherapy mainly had a local effect: indeed, the rate of nodal recurrences was only slightly reduced in the RT arm. This could be due to the fact that reirradiation was performed with smaller fields than the initial course of radiotherapy, which did not treat the entire neck. The rate of isolated distant metastasis was higher in the RT arm, which suggests that patients surviving longer without locoregional recurrences remain exposed to the risk of distant metastases over a longer period of time. The high rate of distant metastases could also be linked to the extent of nodal involvement in the RT arm (Table 2, number of positive nodes, $P = .07$). Furthermore, the contribution of treatment-related deaths as well as deaths related to second primaries was higher in the RT arm. Finally, at the date of the analysis, 40 deaths had occurred in the RT arm, compared with 45 deaths in the WS arm. However, the trial was not powered to detect differences in OS, and one third of the patients were still being observed at the date of analysis.

A treatment that increases LRC without significantly increasing OS raises the issue of toxicity. We observed five treatment-related deaths, which were not observed in our previous feasibility trial.[12] At 1 and 2 years, there was a higher rate of complications (mucosal and subcutaneous sclerosis, osteoradionecrosis, trismus, and pharyngeal

stenosis) in the RT arm. At 2 years, approximately 40% of surviving patients experienced grade 3 or 4 late toxicity in the RT arm, versus 10% in the WS arm. This did not take into account salivary toxicity, which was not documented by the investigators. This acute and late toxicity is in accordance with what has been described in other reirradiation series for operable[12,13] or inoperable disease[4-10] (see Appendix).

In summary, the trial demonstrated that small-field reirradiation with concomitant chemotherapy efficiently eradicated microscopic disease and markedly reduced the rate of local recurrences. It should be noted that this novel therapeutic concept was applied to a population of strictly selected patients. Considering the increased toxicity observed in this series, it is essential for future studies to incorporate new radiotherapy techniques. Indeed, intensity-modulated radiotherapy[14,15] can more accurately target the operative bed and spare adjacent normal tissues; a second possibility would be to use hyperfractionation, with small doses per fraction that could spare normal tissues[16] and reduce late toxicity. A third promising approach could be to combine reirradiation with less cytotoxic drugs, such as molecularly targeted therapies.[17] It was recently shown that targeting the epidermal growth factor receptor with the monoclonal antibody cetuximab did not increase the incidence of in-field radiation mucositis.[18]

It is, however, unlikely that these new therapeutic approaches will have a dramatic impact on the survival of patients undergoing salvage surgery. Moreover, only half of the patients with locoregional recurrences are amenable to salvage surgery. For these reasons, locoregional control must remain a major goal when choosing front-line treatment for patients with HNSCC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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