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Phase III randomised trial

Randomized phase III trial (GORTEC 98-03) comparing re-irradiation plus chemotherapy versus methotrexate in patients with recurrent or a second primary head and neck squamous cell carcinoma, treated with a palliative intent

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ABSTRACT

Purpose: This randomized phase III trial investigated the potential benefit of concurrent re-irradiation, fluorouracil and hydroxyurea versus methotrexate for patients treated with palliative intent for recurrent or second primary head and neck squamous cell carcinoma (HNSCC) in previously irradiated area.
Patients and methods: Patients with recurrent HNSCC or a second primary not amenable to curative-intent treatment were randomized to the R-RT arm (concurrent re-irradiation, fluorouracil and hydroxyurea) or to the Ch-T arm (methotrexate). The primary endpoint was overall survival (OS). Due to a very slow accrual, the trial was closed after inclusion of 57 patients.
Results: Fifty-seven patients were included. All patients died in the two arms with a maximal follow-up of 5 years. Although four complete responses were achieved in R-RT arm, (none in Ch-T arm) re-irradiation did not improve OS compared with methotrexate (23% versus 22% at 1 year, NS). Sixteen patients experienced clinical grade $\geqslant 3$ late toxicities (>6 months), 11 in R-RT arm and five in Ch-T arm.
Conclusions: Premature discontinuation of the trial did not allow us to draw firm conclusions. However, there was no suggestion that concurrent re-irradiation, fluorouracil and hydroxyurea improved OS compared to methotrexate alone in patients treated with palliative intent for a recurrent or second primary HNSCC.

The therapeutic results of head and neck squamous cell carcinoma (HNSCC) have been improved by combination of surgery and post-operative radiotherapy (RT) with or without concomitant chemotherapy in resectable tumors [1,2]. In the case of locally advanced unresectable HNSCC, concurrent chemo-radiotherapy (CRT) has yielded an absolute benefit of 8% at 5 years compared with RT alone [3–5]. However, loco-regional recurrences may occur up to 50% of patients with locally advanced HNSCC after multi-modality treatment [6]. A loco-regional recurrence or a second primary HNSCC in a previously irradiated area is then a therapeutic challenge [7].

Salvage surgery offers the best chance for long-term disease control and possible cure in patients with a resectable, recurrent or a second primary cancer in a previously irradiated area with 5-year survival rates ranging from 15% to 40% [8,9]. However, salvage surgery is not always feasible. For unresectable disease, the standard treatment is systemic chemotherapy [10]. Response rates with systemic therapy are approximately 30%, with median survival at about 6 months in previously irradiated patients [11]. One of the most commonly used anticancer agent for the palliation of patients with recurrent HNSCC has probably been methotrexate with response rates between 8% and 50% [11,12]. The advantages of methotrexate are its ease of administration in an outpatient setting and the low incidence of severe side effects. Single-agent methotrexate is considered as one of the standard treatments of this disease and a standard comparator for phase III studies [12,13].

The only potentially curative treatment for unresectable recurrent head and neck cancer (HNC) or a second primary is a salvage second course of radiotherapy, with a full dose re-irradiation [10] with or without concurrent chemotherapy. In the 1990s, the University of Chicago demonstrated that full-dose

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re-irradiation with concurrent chemotherapy was feasible in patients with inoperable recurrent HNSCC [14,15]. With the use of re-irradiation, better control of disease has been reported in patients with an unresectable tumor [16–18]. The original treatment schedule combined protracted radiotherapy delivering 60 Gy over 11 weeks and concomitant fluorouracil (5FU) and hydroxyurea ("Vokes" protocol) [15]. This schedule proved to be efficient in some inoperable patients, with long-term disease-free survival in a small proportion of cases [19]. A review of the Institute Gustave-Roussy (IGR) experience found that in 106 patients treated with this "Vokes" protocol, the 2 and 5-year overall survival (OS) rates were 24% and 14%, respectively, with 41% of complete responses at 6 months and median survival duration of 10 months [16].

Although re-irradiation is a potentially curative therapy, this modality may cause serious organ injury due to a high cumulative radiation dose. In addition, re-irradiation may be ineffective against an apparently radiation-resistant tumor [10]. The most frequent late toxicities (>6 months after re-irradiation) in the IGR series were grade 2–3 cervical fibrosis (37%), mucosal necrosis (17%), and severe trismus (23%) [16]. In a phase II study by Langer et al. the cumulative incidence of serious (acute plus late) toxicities was 80% at 6 months after treatment initiation [20]. Treatment-related death occurred in approximately 8% of patients, including carotid hemorrhage which occurred in 2–5% of patients. Re-irradiation remains investigational, and the benefits of such aggressive therapy need to be assessed further in clinical randomized trials comparing it with the current standard chemotherapy.

The French Head and Neck Oncology Radiotherapy Group (GORTEC) conducted this phase III trial (GORTEC 98-03) to compare palliatively intended concurrent re-irradiation plus chemotherapy (5FU and hydroxyurea) with a single chemotherapeutic agent, methotrexate, in patients with unresectable recurrent HNSCC or a second primary in a previously irradiated area. The main objective was to assess whether re-irradiation and chemotherapy could yield a better outcome than methotrexate alone for patients selected to receive palliative treatment.

Patients and methods

Patients and eligibility

Patients (18–75 years) with histologically-confirmed recurrent HNSCC or a second primary after one course of radiotherapy delivering at least 50 Gy (as primary treatment or postoperatively, external beam radiotherapy and/or brachytherapy, with or without concomitant platinum-based chemotherapy) unamenable to any curative salvage therapy, were eligible. Other inclusion criteria were as follows: no distant metastasis, Karnofsky performance score of $\geqslant 70$ and laboratory tests with the following results: platelet count >100,000/μl, neutrophil granulocytes >2500/μl, and serum creatinine $\leqslant 120$ μmol/l. Patients with severe sequelae after the initial course of radiotherapy, such as osteoradionecrosis or severe cervical fibrosis, were excluded. Patients with a contraindication for 5FU, methotrexate, and/or hydroxyurea were excluded. The interval since the first course of radiotherapy had to be at least 6 months. All patients were required to sign the informed consent document that was approved by each Institutional Review Board before initiating protocol therapy. All patients were required to undergo an endoscopy under general anesthesia, computed tomography (CT) scan, and/or magnetic resonance imaging (MRI). Assessment of distant metastasis included a chest X-ray with a chest CT scan if needed, liver ultrasound, and a bone scan according to symptoms. Laboratory tests were performed to evaluate hematologic, renal, and hepatic function.

Treatment

In the chemotherapy arm (Ch-T arm), methotrexate was injected weekly as an intravenous push or intramuscularly at 40 mg/m^2 until disease progression or toxicity.

In the re-irradiation arm (R-RT arm), patients were to receive six cycles, with each cycle delivering 2 Gy/fraction/day, with concomitant hydroxyurea (1.5 g/d, 1.0 g 2 h before and 500 mg, 10 h after RT) and continuous infusion 5FU (800 mg/m^2/d) for 5 days, with an overall treatment period of 11 weeks as previously reported [8,16]. There were 9-day rest periods between cycles. Re-irradiation was delivered using cobalt or $\leqslant 10$ MV photons, using a conventional treatment planning system or three-dimensional (3D) conformal radiotherapy. Reproducible immobilization was required. 3D treatment planning using CT-based tumor and normal tissue definition was recommended but not mandatory. A general guideline was to restrict the radiation fields to the gross tumor volume (GTV), without nodal prophylaxis beyond the first adjacent nodal area. Hence, the entire neck was not systematically re-irradiated. The margin around the GTV was at least 2 cm. A smaller margin was acceptable only in case of re-irradiation close to the spinal cord. The dose was calculated at the ICRU intersection point [International Commission on Radiation Units and Measurements (report No. 50)]. The spinal cord was systematically excluded from the re-irradiation beams. The cumulative dose to the spinal cord of two irradiations had to be limited to $\leqslant 50$ Gy. When the posterior cervical nodes required treatment, electron beams of the appropriate energy (8–12 MeV) or oblique posterior photon beams were used.

Response and toxicity evaluation

The objective evaluation of response was according to the Southwest Oncology Group (SWOG) standard response criteria. The first CT scan was performed 3 months after the beginning of treatment and the second CT at 6 months. Toxicity was considered acute if it occurred within 6 months after randomization. It was scored according to the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria. Late toxicities were scored according to the European Organization for Research and Treatment of Cancer (EORTC) – RTOG late radiation morbidity scoring system. Symptom improvement and quality of life (QOL) were assessed using the Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N) questionnaire (4th version). This questionnaire was proposed to the patients initially and was re-evaluated by the patients every three months.

Quality assurance

Patient charts were reviewed by a panel consisting of investigators and external experts (at least a head and neck surgeon and a radiation oncologist) at regular intervals. Patient selection, radiotherapy (techniques) and chemotherapy (protocol) were reviewed. In the re-irradiation arm, the total dose, the overall treatment time, and the dose per fraction were verified, as were the re-irradiation fields, according to tumor and nodal extension.

Statistical considerations

The primary endpoint was overall survival (OS). Additional endpoints were acute and late toxicity and QOL. The OS rates were expected to be 85% at 6 months, 61% at 9 months and 44% at 1 year for the R-RT arm and 50% at 6 months, 35% at 9 months and 25% at 1 year for the Ch-T arm. The trial was designed to detect a difference of 19% at 1 year. A sample size of 160 patients was required to detect this difference, with α risk of 0.05 and β risk of 0.20. Patients

were stratified according to the hospital and tumor site. OS was calculated as the time from the date of randomization to the date of the first event after randomization. The study was performed as an intent-to-treat analysis. Univariate analyses of OS were based on a comparison of Kaplan–Meier curves by the log-rank test. All tests are two-sided.

Results

The trial was activated in June 1999 and closed in 2005. The trial was closed prematurely after the inclusion of 57 patients due to very slow accrual. A total of 57 patients from 10 GORTEC institutions were enrolled, 30 patients in the re-irradiation arm, and 27 patients in the methotrexate arm. All patients were unamenable to any curative salvage therapy.

Patient population

Pre-treatment clinical characteristics are summarized in Table 1. One patient in the Ch-T arm was erroneously included; this patient had never received any radiotherapy. Ninety percent of the patients enrolled were male with an average age of 58 years. The mean initial Karnofsky performance status was 80. There were 44 loco-regional recurrences and 13 second primary cancers located all in a previously irradiated areas ($\geqslant$50 Gy). Among the different tumor localizations, the most common was the oropharynx (54%), including tonsil, soft palate, base of tongue or vallecula; the oral cavity (18%) and the hypopharynx (18%). Thirty-three percent of patients had two diseased sites and 9% had three sites (Table 2). Forty-one patients (72%) had T3 or T4 disease prior to re-irradiation or methotrexate, 25 of whom (7 with T3 and 18 with T4) were in the R-RT arm (83%) while 16 patients (eight with T3 and eight with T4) were in the Ch-T arm (60%). Sixty-one percent of patients had N0 disease (Table 3).

Prior radiotherapy

All patients had previously received external beam radiotherapy, except for one who had never received radiotherapy and was erroneously included in the Ch-T arm. Two patients had previously received brachytherapy plus external beam radiotherapy. After the initial radiotherapy, 10 patients had late toxicities (five in each arm). Regarding the grade $\geqslant$3 late toxicities, five patients exhibited subcutaneous tissue toxicity (cervical fibrosis), three, xerostomia, three, larynx toxicity and one, toxicity of the mucous membranes before the second treatment.

Table 1
Pretreatment characteristics.

Characteristics	R-RT arm (30)	Ch-T arm (27)	Total (57)
Gender n (%)			
Male	25 (83%)	26 (96%)	51 (90%)
Age (years)			
Mean	57.7	58.9	58.3
Median	60.5	58.3	59.5
Karnofsky performance status			
Mean	82	81	82
Median	80	80	80
Recurrence *n* (%)	24 (80%)	20 (74%)	44 (77%)
Second primary cancer *n* (%)	6 (20%)	7 (26%)	13 (23%)
Tumor site n (%)			
Oral cavity	6 (20%)	4 (15%)	10 (18%)
Oropharynx	16 (53%)	15 (56%)	31 (54%)
Hypopharynx	5 (17%)	5 (19%)	10 (18%)
Larynx	1 (3%)	1 (4%)	2 (4%)
Nodes only	2 (7%)	2 (7%)	4 (7%)
Prior radiotherapy dose (Gy)			
Mean	61.4	63.1	62.2
Median	62.5	65	65

Table 2
Disease sites before treament.

Characteristics	R-RT arm (30)	Ch-T arm (27)	Total (57)
One site *n* (%)	16 (53%)	17 (63%)	33 (58%)
Oral cavity	5	1	6
Oropharynx	7	10	17
Hypopharynx	3	2	5
Larynx	0	2	2
Nodes only	1	2	3
Two sites *n* (%)	12 (40%)	7 (26%)	19 (33%)
Oral cavity/hypopharynx	5	4	9
Oropharynx/hypopharynx	3	1	4
Oropharynx/nodes	1	0	1
Hypopharynx/larynx	1	1	2
Others	2	1	3
Three sites *n* (%)	2 (7%)	3 (11%)	5 (9%)
Oral cavity/oropharynx/ hypopharynx	1	2	3
Oropharynx/hypopharynx/ larynx	1	0	1
Hypopharynx/larynx/other	0	1	1

Table 3
TNM classification before treatment.

Characteristics	R-RT arm (30)	Ch-T arm (27)	Total (57)
T			
Unknown	3 (10%)	6 (22%)	9 (16%)
T1	0	1 (4%)	1 (2%)
T2	2 (7%)	4 (15%)	6 (11%)
T3	7 (23%)	8 (30%)	15 (26%)
T4	18 (60%)	8 (30%)	26 (46%)
N			
Unknown	3 (10%)	0	3 (5%)
N0	18 (60%)	17 (63%)	35 (61%)
N1	3 (10%)	1 (4%)	4 (7%)
N2a	2 (7%)	1 (4%)	3 (5%)
N2b	2 (7%)	2 (7%)	4 (7%)
N2c	1 (3%)	3 (11%)	4 (7%)
N3	1 (3%)	3 (11%)	4 (7%)

Protocol compliance and acute toxicity

In the R-RT arm, 19 of the 30 patients (63%) received six cycles of re-irradiation and five patients received five cycles. The median dose of radiation was 60 Gy. Two patients did not receive re-irradiation at all (one myocardial infarction and one death before the beginning re-irradiation). Eleven of 28 patients (39%) discontinued radiotherapy, nine permanently (two patients because of death, two because of progression, two toxicities, and three due to alteration of general status) and two temporarily. Acute mucositis was observed in seven patients, two of whom exhibited grade $\geqslant$3 (RTOG). Seven patients had acute radio-dermatitis which attained grade $\geqslant$3 (RTOG) in one patient. Regarding the concurrent chemotherapy, 15 patients discontinued 5FU and hydroxyurea (12 permanently, three temporarily). Early chemotherapy-induced hematological toxicities were grade 3 thrombocytopenia (n = 2), grade 3–4 leukopenia (n = 3), grade 3 anemia (n = 1). Other toxicities were nausea, vomiting (n = 2), hand-foot syndrome and skin toxicity (n = 1), grade 4 stomatitis and pulmonary grade 4 adverse event (n = 3), and infectious shock (n = 1). Ten patients were hospitalized because of toxicities (median duration was 10 days). In total, only 12/28 patients (43%) received complete courses of both re-irradiation and concurrent chemotherapy.

Table 4
Clinical response and patterns of failure.

	R-RT (23) *n* (%)	Ch-T (20) *n* (%)	Total (43) *n* (%)
Clinical response			
Complete response (CR)	4 (17%)		4 (9%)
Partial response (PR)	2 (9%)	2 (10%)	4 (9%)
Stable disease	3 (13%)	4 (20%)	7 (16%)
Progression	14 (61%)	14 (70%)	28 (65%)
Overall response (CR + PR)	6 (26)	2 (10%)	8 (18%)
Loco-regional recurrence	14 (61%)	11 (55%)	25 (58%)
Distant metastasis	5 (22%)	5 (25%)	10 (23%)
Second cancer	2 (9%)		2 (5%)

In the Ch-T arm, a minimum of 12 courses of methotrexate were planned in the protocol yet only three patients received ⩾10 courses, 15 patients ⩽3, and eight patients 4–6 courses. Eleven patients definitely discontinued methotrexate for the following reasons: tumor progression (6), death (4), and patient request (1). Mucosal toxicity was observed in five patients with grade 3 in 1, grade 1–2 hematologic toxicity ($n = 9$) and grade 1 renal toxicity in 1. Other toxicities were mild: neuropathy ($n = 3$), alopecia ($n = 1$), fever and dysphagia ($n = 1$), nausea ($n = 2$).

The median Karnofsky index was 60 in both arms at the end of the treatment. Fourteen (61%) patients in the R-RT arm had a feeding tube (nasogastric or medical gastrostomy) during and/or after treatment compared with eight (40%) patients in the Ch-T arm.

Clinical response and patterns of failure

As shown in Table 4, 43 patients were assessable for an objective response at least 3 months after the treatment (12 deaths occurred within 3 months). A complete response was observed in four (17%) patients in the R-RT arm, but none in the Ch-T arm. A partial response was observed in two patients in each arm. Overall response was found in six patients (26%) in the R-RT arm and two patients (10%) in Ch-T arm. However, 14 patients (61%) relapsed or progressed loco-regionally in the R-RT arm and 11 patients (55%) in the Ch-T arm. Distant metastasis was similar in the two arms (five patients each). Two patients developed a second cancer in the R-RT arm, whereas no second cancers occurred in the Ch-T arm.

Late side effects

Sixteen patients experienced clinical grade ⩾3 late toxicities (Table 5), 11 in the R-RT arm [mucous membrane (4), pharynx (3), larynx (1), salivary gland (1) and subcutaneous tissue (2)] and five in Ch-T arm [mucous membrane (1), pharynx (1), larynx (1), and subcutaneous tissue (2)]. Treatment with re-irradiation and chemotherapy appeared to be more toxic than treatment with methotrexate. Trismus occurred in one patient and hemifacial edema in one patient in the R-RT arm.

Table 5
Late toxicities according to RTOG/EORTC criteria.

	R-RT arm		Ch-T arm	
Toxicity	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Mucous membrane	6	4	2	1
Pharynx	7	3	2	1
Larynx	9	1	2	1
Salivary gland	9	1	3	0
Sub-cutaneous	7	2	2	2
Bone	10	0	3	0

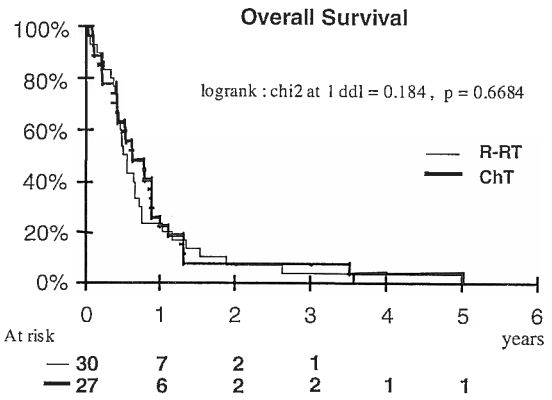

Fig. 1. Overall survival of two arms: re-irradiation and methotrexate.

Overall survival and causes of death

The main objective of this trial was to determine whether re-irradiation combined with chemotherapy according to the Vokes protocol could improve overall survival compared to chemotherapy alone with methotrexate. Overall survival rates at 1 year were identical in both arms ($p = 0.6$). The overall survival rates (50% at 6 months, 30% at 9 months and 23% at 1 year, respectively) observed in the R-RT arm in our study were below those described in the literature. The rates (59%, 48% and 22%, respectively) observed in the Ch-T arm were in fact comparable to or higher than those described in the literature (Fig. 1).

In this trial, all patients died with a maximum follow-up of 5 years. The causes of death are summarized in Table 6. Four patients died of toxicity: three in R-RT arm were due to hemorrhage (1), hematological toxicity with infection (1), and a carotid rupture (1) and in the Ch-T arm, septic syndrome with neutropenia (1). Four patients died of intercurrent disease: two in the R-RT arm [bleeding in a patient with tumor progression (1), lung infection (1)] and two in the Ch-T arm [pneumopathy (1) and infection in addition to the recurrence (1)].

Discussion

This randomized phase III study compared two very different palliatively intended therapeutic options for previously heavily treated HNC patients. In one arm, full dose re-irradiation and concomitant 5FU and hydroxyurea were used and compared to single-agent chemotherapy with methotrexate. Re-irradiation and concomitant 5FU and hydroxyurea initially described by Vokes et al.

Table 6
Causes of death.

	R-RT (30)	Ch-T (27)	Total (57)
Death	30	27	57
Unique causes			
Toxicity	2	1	3
LRP	19	16	35
DM	1	1	2
2nd localization	1	0	1
Unknown cause	1	2	3
Multiple causes			
LRP/DM	3	4	7
LRP/ICD	1	2	3
2nd localization/ICD	1	0	1
LRP/toxicity	1	0	1
Survival at 1 year (Kaplan–Meier)	23% [12; 41]	22% [11; 41]	23% [14; 35]

LRP: loco-regional progression; DM: distant metastasis, ICD: intercurrent disease.

[14,15] can be considered as one of the standard re-irradiation regimens for both post-operative and definitive re-irradiation for a recurrent or a second primary HNSCC. We recently reported the results of a randomized trial of postoperative re-irradiation combined with chemotherapy using this regimen, after salvage surgery compared with salvage surgery alone. This regimen led to a major improvement of local control and also disease-free survival (DFS) in this setting but with no detectable survival advantage [8].

The relatively poor enrollment rate observed in our study led to premature discontinuation of the trial and consequently, no definitive conclusions could be drawn. The expected number of subjects in our study was 160, with 80 patients in each arm. The main reason for this slow enrollment was related to difficulties in randomizing patients between two modalities that were markedly different from each other, and then it was difficult to explain the randomization to the patients. A similar experience was attempted within the RTOG which started a comparable randomized trial aimed at conducting the same type of comparison in HNC patients treated with a palliative intent. However, this randomized trial was closed early after including 17 patients due to lack of recruitment (Ang, K.K. personal communication). Finally, only 57 patients were enrolled in our trial. However, despite this small sample size, this study will be the only randomized study to evaluate the value of re-irradiation versus chemotherapy alone in the palliative treatment of HNC patients. A number of other reasons could also explain the results, and especially the poor outcome following re-irradiation. The main reason to explain this difference is that patients were selected as being very advanced and palliative cases, whereas in the previous series, a significant proportion of patients had less advanced disease and were re-irradiated with a curative intent. Initially, in our study, there were 83% of patients with T3 or T4 disease at the time of recurrence or the second cancer whereas in our previous IGR series, the proportion of T3–4 disease was 62%. This characteristic could probably explain the low complete response rate (17%) in this trial, while a 41% complete response rate was observed in our previous IGR series [16]. Secondly, in the present study, there were 24 patients (80%) with at least two sites of tumor extension (more extensive disease) in the R-RT arm. This could also largely influence the treatment outcomes. We rarely found multi-site tumor extension in other studies. Furthermore, we exclusively enrolled patients unamenable to any type of curative treatment including salvage surgery and brachytherapy [21], but also re-irradiation with a curative intent. Indeed, the possibility to be randomized to methotrexate led us to include patients who could be reevaluated with a potential curative intent. This is contrary to that observed in several other studies such as the Chicago study which yielded better median survival duration (11 months) in 115 patients, 49 of whom received salvage surgery [18]. Another reason could be poor compliance with protocol treatment: two patients did not receive re-irradiation and in the remaining patients, only 12/28 (43%) received full re-irradiation and chemotherapy courses.

In the present study, however, there was no suggestion of an improvement of overall survival with re-irradiation and concomitant 5FU and hydroxyurea. In fact, the median overall survival duration (7.6 months) observed with methotrexate alone was in the range of previously reported results of other phase III studies [10–12]. However, the median survival duration (6 months) and 1 year survival rate (23%) with re-irradiation and chemotherapy in our study were lower compared to previously reported studies, such as 8.2 months and 41.7% in the RTOG 96-10 study [17]; 12.1 months and 50.2% in the RTOG 99-11 study [20]; 10 months and 40% in our previous IGR experience [16]. These poor results are likely explained by the fact that our patient population was selected for palliative therapy.

Toxicity-related deaths could also impair the outcome of re-irradiated patients. In the present study, there were three toxicity-related deaths in the R-RT arm compared with only one in the Ch-T arm. These results are comparable to those of other studies.

In the present study, the first cause of death was loco-regional failure (23/30) and this was also the case in a recent study [22]. Thus, improving loco-regional control is still an important issue. As in the primary treatment of HNSCC, dose-escalation with hyperfractionated regimens could yield higher loco-regional control rates without a significant increase in late radiation-induced morbidity [23]. These hyperfractionated re-irradiation regimens have been increasingly used in other studies and could be considered in future studies [20,24–26]. Dose escalation in the target volume is essential for improving the efficacy of radiation with maximum protection of normal tissues. Intensity-modulated radiation therapy (IMRT) which was not used in this study could be another way to achieve dose-escalation [27–29]. Most patients were treated with 3D conformal or even 2D conventional techniques. This could be another reason for poor loco-regional control. Lee et al. [30] used IMRT for re-irradiation in 74 patients with recurrent HNC. Patients who had undergone IMRT had a better 2-year loco-regional progression-free survival rate (52% vs. 20%) compared to those who had not.

Several other therapeutic agents have been considered to further circumvent the radio-resistance of recurrent HNSCC. Taxanes have been shown to be effective when added to cisplatin and 5FU followed by radiotherapy in the primary setting [31,32]. Taxanes could be an alternative option in recurrent HNSCC, as shown in the RTOG 99-11 study [20]. Other phase I/II studies using taxanes and cisplatin have also demonstrated promising results [25,33]. EGFR targeted therapy especially by cetuximab has shown its survival benefit in locally advanced [34] or recurrent/metastatic [35] HNSCC last recent years. Vermorken et al. [35] showed recently in the phase III EXTREME study that adding cetuximab to platinum-based chemotherapy with fluorouracil significantly prolonged the median OS from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab in the first-line treatment of patients with recurrent and/or metastatic HNSCC. This is the first time that improved overall survival has been shown in patients with recurrent and/or metastatic HNSCC since the introduction of cisplatin. However, we started the present trial before the EXTREME study, and no other chemotherapy regimens had showed survival benefit compared to Methotrexate alone at that time. Our results with median survival of 7 months compare favorably to EXTREME study, since our selection is more heavily treated patients (all re-irradiated) and no first-line treatment are included. We are conducting a phase II trial to introduce cetuximab with re-irradiation for this population of patients with recurrent HNSCC or second primary in previously irradiated area.

In conclusion, the premature discontinuation of this randomized phase III trial did not allow us to draw firm conclusions. However, there was no suggestion that concurrent re-irradiation, 5FU and hydroxyurea improved overall survival compared to methotrexate alone for the palliative treatment of patients with recurrent HNSCC or a second primary in a previously irradiated area.

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