Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial

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Summary

Background Concomitant chemoradiotherapy and accelerated radiotherapy independently improve outcomes for patients with locally advanced head and neck squamous-cell carcinoma (HNSCC). We aimed to assess the efficacy and safety of a combination of these approaches.

Methods In our open-label phase 3 randomised trial, we enrolled patients with locally advanced, stage III and IV (non-metastatic) HNSCC and an Eastern Cooperative Oncology Group performance status of 0–2. We randomly allocated patients centrally with a computer program (with centre, T stage, N stage, and localisation as minimisation factors) in a 1:1:1 ratio to receive conventional chemoradiotherapy (70 Gy in 7 weeks plus three cycles of 4 days' concomitant carboplatin-fluorouracil), accelerated radiotherapy-chemotherapy (70 Gy in 6 weeks plus two cycles of 5 days' concomitant carboplatin-fluorouracil), or very accelerated radiotherapy alone (64·8 Gy [1·8 Gy twice daily] in 3·5 weeks). The primary endpoint, progression-free survival (PFS), was assessed in all enrolled patients. This trial is completed. The trial is registered with ClinicalTrials.gov, number NCT00828386.

Findings Between Feb 29, 2000, and May 9, 2007, we randomly allocated 279 patients to receive conventional chemoradiotherapy, 280 to accelerated radiotherapy-chemotherapy, and 281 to very accelerated radiotherapy. Median follow-up was 5·2 years (IQR 4·9–6·2); rates of chemotherapy and radiotherapy compliance were good in all groups. Accelerated radiotherapy-chemotherapy offered no PFS benefit compared with conventional chemoradiotherapy (HR 1·02, 95% CI 0·84–1·23; p=0·88) or very accelerated radiotherapy (0·83, 0·69–1·01; p=0·060); conventional chemoradiotherapy improved PFS compared with very accelerated radiotherapy (0·82, 0·67–0·99; p=0·041). 3-year PFS was 37·6% (95% CI 32·1–43·4) after conventional chemoradiotherapy, 34·1% (28·7–39·8) after accelerated radiotherapy-chemotherapy, and 32·2% (27·0–37·9) after very accelerated radiotherapy. More patients in the very accelerated radiotherapy group had RTOG grade 3–4 acute mucosal toxicity (226 [84%] of 268 patients) compared with accelerated radiotherapy-chemotherapy (205 [76%] of 271 patients) or conventional chemoradiotherapy (180 [69%] of 262; p=0·0001). 158 (60%) of 265 patients in the conventional chemoradiotherapy group, 176 (64%) of 276 patients in the accelerated radiotherapy-chemotherapy group, and 190 (70%) of 272 patients in the very accelerated radiotherapy group were intubated with feeding tubes during treatment (p=0·045).

Interpretation Chemotherapy has a substantial treatment effect given concomitantly with radiotherapy and acceleration of radiotherapy cannot compensate for the absence of chemotherapy. We noted the most favourable outcomes for conventional chemoradiotherapy, suggesting that acceleration of radiotherapy is probably not beneficial in concomitant chemoradiotherapy schedules.

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Introduction

Chemotherapy has been used widely in locally advanced head and neck squamous-cell carcinoma (HNSCC) as induction treatment,[1–6] concomitantly with radiotherapy,[1,2,7–14] or as adjuvant treatment after radiotherapy or surgery.[1,2,15] The updated meta-analysis of chemotherapy in head and neck cancer (MACH-NC)[1,2] used individual patient data from 93 randomised trials (level 1A evidence) and showed that concomitant chemoradiotherapy is the standard of care in locally advanced HNSCC. By 5 years, addition of concomitant chemotherapy to radiotherapy was associated with an increase in survival of 6·5%, a 12–13% improvement in locoregional control, and about a 3% decrease in distant metastases relative to radiotherapy alone.[2] However, the addition of concomitant chemotherapy was also associated with a substantial increase in acute and late toxic effects,[12] emphasising the need to improve these therapeutic combinations.

Previously, we showed that a regimen of fluorouracil plus carboplatin combined concomitantly with con-

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ventional radiotherapy was better than conventional radiotherapy alone, although the addition of this chemotherapy increased rates of acute and late side-effects significantly.[10,12] However, this increase in toxicity was regarded as acceptable because of the magnitude of benefit noted for locoregional control (25% at 3 years) and overall survival (8% at 5 years). The benefit associated with this carboplatin-fluorouracil regimen was much the same as was that noted for concomitant cisplatin alone in the recent update of the MACH-NC meta-analysis.[2] We used this regimen as the first reference group in our present study.

Non-conventional fractionated radiotherapy for locally advanced HNSCC is an attractive possible treatment, either through use of hyperfractionated radiotherapy[16–19] or accelerated radiotherapy.[19–21] The aim of such modified fractionated radiotherapies is to increase the dose intensity of treatment, either by increasing the total dose (hyperfractionation) or by reduction of the overall treatment time (acceleration). In most cases, a benefit in tumour control probability has been reported by comparison with conventional radiotherapy, and the MARCH meta-analysis[19] (which was based on the collection of updated individual patient data from 15 randomised trials) concluded a small but significant improvement in local control and overall survival after altered fractionated radiotherapy. In this context, we previously showed that a very accelerated regimen was substantially better than was conventional radiotherapy alone in terms of locoregional control (gain of 24% at 3 years), although rates of the acute mucosal toxicity were greatly increased (but late side-effects of radiation were not).[20] We used this regimen as a second reference group in our present study.

On the basis of the MARCH[19] and MACH-NC[2] meta-analyses and the previous experience of the Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC),[10,12,20] we aimed to assess the value of combining accelerated radiotherapy with concomitant chemotherapy in patients with locally advanced HNSCC. Our accelerated radiotherapy-chemotherapy groups combined two notable advances in oncology: concomitant chemotherapy and accelerated radiotherapy, which have both been shown to improve the probability of tumour control outcome independently. Before the start of this trial, there were no data for this type of comparison and our hypothesis was that the increase in the dose intensity attributable to the combination of accelerated radiotherapy-chemotherapy would lead to an improvement in progression-free survival (PFS) and disease control, as compared with either very accelerated radiotherapy alone or compared with conventional concomitant chemoradiotherapy.

Methods

Study design and participants

Our randomised phase 3 trial was done by the GORTEC at university hospitals, cancer centres, and private hospitals in France and Belgium. Eligible participants had previously untreated histologically proven squamous-cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx; stage III or IV disease (excluding distant metastases); Eastern Cooperative Oncology Group (ECOG) performance statuses of 0–2; adequate haematological, renal, and liver function; no previous radiotherapy or chemotherapy; no history of other cancer in the previous 5 years; no clinically significant cardiac disease; and no clinically significant impairment that would have contraindicated the use of chemotherapy. We obtained written informed consent from all patients and the protocol was approved by institutional ethic committees.

Randomisation and masking

Patients were randomly assigned in a 1:1:1 ratio to one of three treatment groups (conventional chemoradiotherapy, accelerated radiotherapy-chemotherapy, or very accelerated radiotherapy) with minimisation by centre (22 centres), T stage (three categories: T2–3, T4, or other), N stage (two categories: N0–1, N2–3), and primary localisation (five categories: oropharynx, oral cavity, hypopharynx, larynx, or no primary). To avoid deterministic minimisation and assure allocation concealment, the treatment which minimises the imbalance was assigned with a probability of 0·90 (ie, <1·0). Randomisation was done centrally at the biostatistics unit of the Institut Gustave Roussy (Villejuif, France). Doctors faxed a randomisation form to a data manager who did the randomisation with a computer program. Doctors and patients were not masked to treatment-group assignment.

Procedures

We obtained a full history for all participants, and did a physical examination, blood tests, head and neck CT or MRI, chest CT, and an endoscopy examination after general anaesthesia. We assessed tumours by clinical examination and CT scanning took place at 3, 6, 9, and 12 months after completion of treatment, and every 6 months thereafter. We did not recommend systematic CT-PET to patients on enrolment to the trial.

Participants who were randomly allocated to receive conventional concomitant chemoradiotherapy received radiation doses of 70 Gy in 7 weeks (five fractions of 2 Gy per week) with spinal cord exclusion at 40 Gy and chemotherapy of three cycles of 4 days of carboplatin 70 mg/m² per day plus fluorouracil 600 mg/m² per day from day 1 to 4, day 22 to 25, and day 43 to 46. Patients randomly allocated to receive accelerated radiotherapy-chemotherapy received radiation doses of 70 Gy in 6 weeks: five fractions of 2 Gy per week until 40 Gy (with spinal cord exclusion at 40 Gy) and then 1·5 Gy per fraction twice daily for 5 days per week for the remaining 30 Gy and concomitant chemotherapy of two cycles of 5 days of carboplatin 70 mg/m² per day and fluorouracil 600 mg/m² per day from day 1 to 5 and day 29 to 33. Primary prophylactic recombinant granulocyte colony stimulating factor was not recommended in these two groups, which was in line

with European Organisation for Research and Treatment of Cancer (EORTC), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) guidelines.

Participants who were randomly allocated to receive very accelerated radiotherapy received radiation doses of 64·8 Gy in 3·5 weeks without chemotherapy (1·8 Gy twice daily for five days per week), with spinal cord exclusion at 34·2 Gy.

The interval between twice-daily radiation fractions was at least 8 h. We used a 4–6 MV linac and a conventional three-dimensional treatment planning system (no intensity-modulated radiation therapy was done at the same time). When appropriate, cervical posterior nodes were treated with electron beams (8–12 MeV) or with oblique posterior photon beams. The prophylactic nodal irradiation dose was 45 Gy in the uninvolved neck in the very accelerated radiotherapy group and 50 Gy for the two other groups.

For the purpose of radiotherapy quality assurance, we analysed a sample of participants to ensure that there was no imbalance of the quality of radiotherapy between the three groups. Total doses, duration of radiotherapy, doses per fraction, dose distributions, fields of irradiation, and tumour volume coverage were reviewed by a panel of investigators and external experts.

We graded acute radiation and chemotherapy toxicities according to Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria and the WHO scoring system. Toxicities occurring more than 3 months after the end of treatment were graded according to the RTOG/EORTC scoring system.[12] Because some patients did not receive radiotherapy or chemotherapy and because some data were missing for patients, the toxicity analysis could not be based on all randomly allocated patients but only on assessable patients who received at least one dose of chemotherapy (for chemotherapy toxicity) or one radiotherapy fraction.

Statistical analysis

The primary endpoint was PFS, which was defined as time between randomisation and the first of the following events: locoregional progression or relapse, distant relapse, or death from any cause (or the last follow-up contact for patients who did not have any of these events). Secondary endpoints were locoregional progression (disease progression or relapse above the clavicles), distant metastases, overall survival, and acute and late toxicity.

We estimated that 196 patients per group would be needed to show a hazard ratio (HR) of 0·66 with the accelerated radiotherapy-chemotherapy group compared with the other groups (corresponding to a 15% absolute increase of 3 year PFS from 35% to 50%), with a two-sided type I error of 0·05 and a power of 90%. To allow two by two comparisons of the three treatment groups, we multiplied the required number of patients in all groups by $\sqrt{2}$,[22] leading to a total number of 840 patients (280 per group).

We did the analyses on the basis of the intention-to-treat principle, and estimated PFS and survival probabilities according to the Kaplan-Meier method. We estimated probabilities of locoregional progression and metastasis

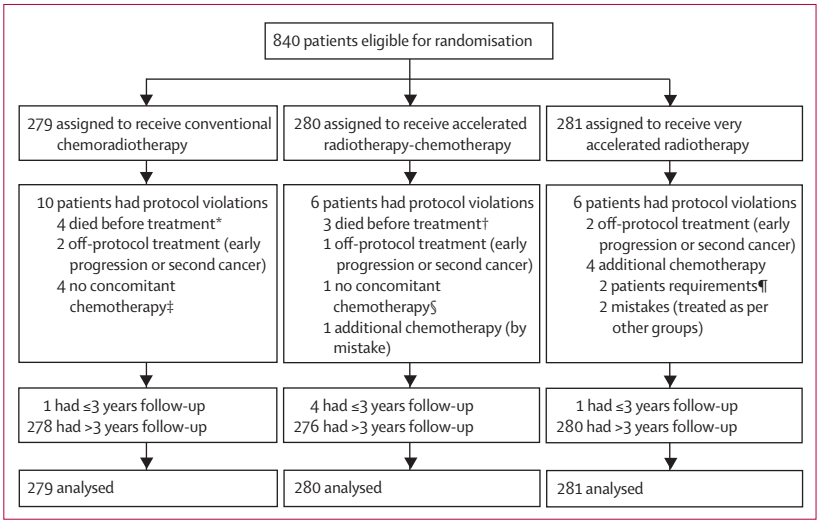

Figure 1: **Trial profile and reasons for protocol violations**
*Pulmonary embolism, respiratory failure (lung metastases), carotid haemorrhage, and accident 4–17 days after randomisation. †Cerebrovascular stroke, pulmonary embolism, and sudden death of unknown cause 4–17 days after randomisation. ‡One deteriorated performance status, one second cancer, one mistake, and one unknown reason. §Thrombocytopenia. ¶Patients declined to receive radiotherapy only and were treated by concomitant chemoradiotherapy.

	Conventional chemoradiotherapy group (n=279)	Accelerated RT-CT group (n=280)	Very accelerated RT group (n=281)
Sex (male)	244 (87%)	245 (88%)	242 (86%)
Mean age, years	56·1 (7·7, 39–74)	56·9 (8·2, 37–75)	56·5 (8·6, 34–74)
Primary localisation			
No primary	2 (<1%)	1 (<1%)	3 (1%)
Oropharynx	183 (66%)	184 (66%)	188 (67%)
Oral cavity	28 (10%)	31 (11%)	27 (10%)
Hypopharynx	49 (18%)	47 (17%)	45 (16%)
Larynx	17 (6%)	17 (6%)	18 (6%)
T stage			
T0	2 (<1%)	2 (<1%)	3 (1%)
T1	0	1 (<1%)	0
T2	23 (8%)	23 (8%)	26 (9%)
T3	94 (34%)	99 (35%)	100 (36%)
T4	160 (57%)	155 (55%)	152 (54%)
N stage			
N0	61 (22%)	56 (20%)	58 (21%)
N1	39 (14%)	46 (16%)	47 (17%)
N2a	29 (10%)	32 (11%)	23 (8%)
N2b	52 (19%)	49 (18%)	53 (19%)
N2c	67 (24%)	68 (24%)	71 (25%)
N3	31 (11%)	29 (10%)	29 (10%)

Data are n (%) or mean (SD, range). RT=radiotherapy. CT=chemotherapy.

Table 1: **Baseline characteristics of patients**

	Progression-free survival		Overall survival		Locoregional failure		Distant metastases	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Accelerated RT-CT *vs* conventional CRT	1·02 (0·84–1·23)	0·88	1·05 (0·86–1·29)	0·60	0·97 (0·74–1·26)	0·81	1·26 (0·90–1·75)	0·18
Accelerated RT-CT *vs* very accelerated CRT	0·83 (0·69–1·01)	0·060	0·87 (0·72–1·06)	0·169	0·76 (0·59–0·98)	0·033	1·16 (0·83–1·63)	0·38
Conventional RT-CT *vs* very accelerated CRT	0·82 (0·67–0·99)	0·041	0·81 (0·67–0·99)	0·040	0·77 (0·59–0·99)	0·045	0·96 (0·68–1·37)	0·82

RT=radiotherapy. CT=chemotherapy. CRT=chemoradiotherapy.

Table 2: **Treatment efficacy**

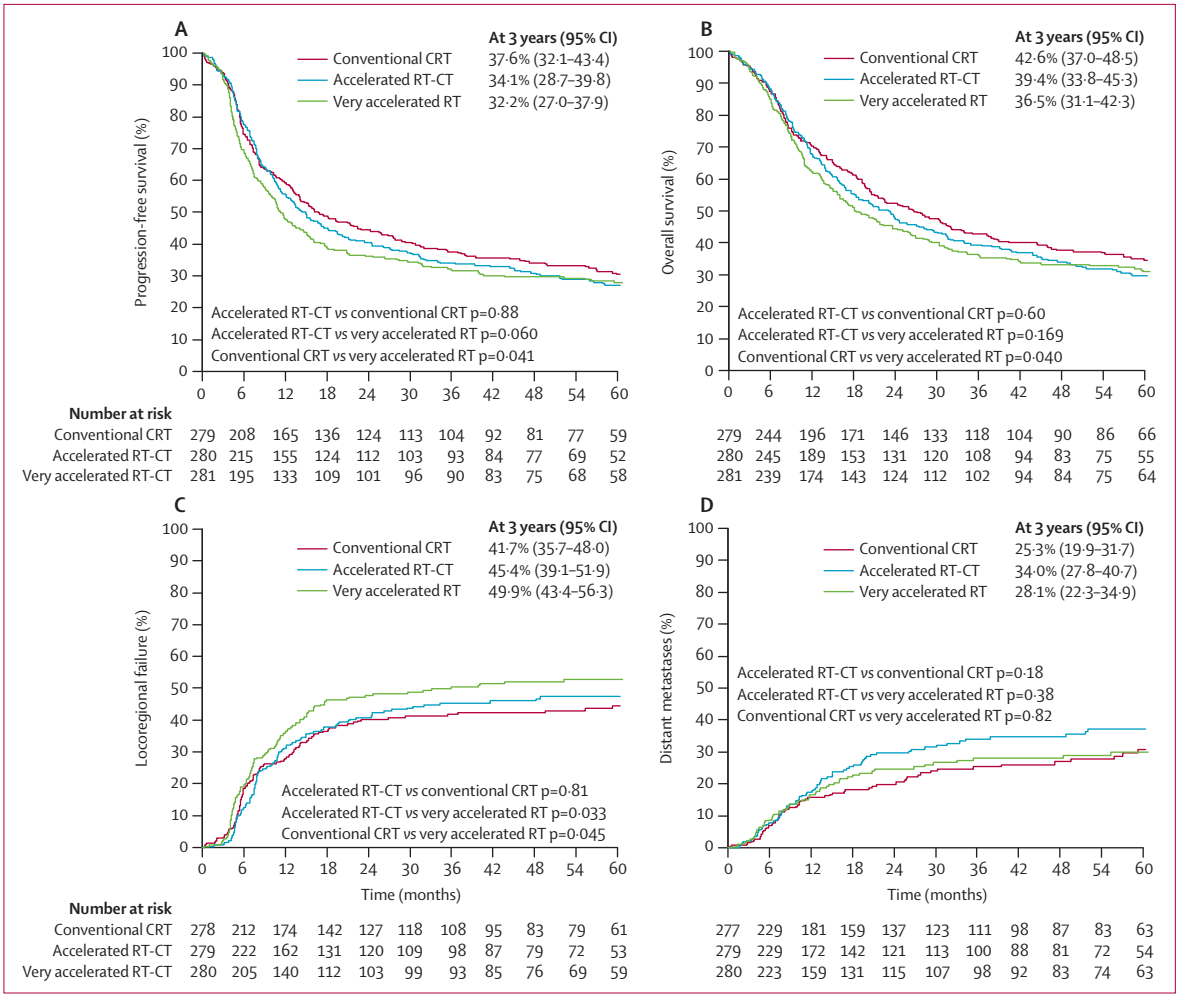

Figure 2: **Probability of progression-free survival (A), overall survival (B), locoregional failure (C), and distant metastases (D)**
p values were calculated after adjustment for tumour stage, node stage, and tumour site. CRT=chemoradiotherapy. RT-CT=radiotherapy-chemotherapy. RT=radiotherapy.

with 1–Kaplan-Meier methods, censoring patients without the studied event at the time of last follow-up or death. We calculated Rothman's 95% CIs. We compared curves between treatment groups with the log-rank test in univariate analysis and used the Cox model to account for minimisation factors. All HRs are adjusted for localisation and T and N stages. We compared use of feeding tubes from 1 year to 5 years after randomisation between treatment groups with a generalised linear model for binomial variables with a logit link. For the late toxicity in three categories (none, grade 1–2, or grade 3–4), we used generalised linear models for multinomial variables with a cumulative logit link. Generalised linear models allow the analysis of correlated data arising from repeated measurements in each patient. All analyses were done with SAS version 9.1.

The trial is registered with ClinicalTrials.gov, number NCT00828386.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled and randomly allocated 840 patients at 22 GORTEC centres between Feb 29, 2000, and May 9, 2007 (figure 1). Table 1 shows baseline characteristics of patients, which were balanced between groups. Most patients had stage IV disease, with 760 (90%) patients presenting with T3–T4 disease and 665 (79%) with N1–N3 disease. Figure 1 shows the trial profile and protocol violations; treatment and toxicity data for one patient who was randomly allocated to receive conventional chemoradiotherapy were missing.

Median follow-up was 5·2 years (range 0·4–9·5, IQR 4·9–6·2) and was much the same between groups. Only six patients were followed up for less than 3 years and all other living patients were followed up between 3 years and 9·5 years. 601 of 840 enrolled patients died and 628 had one or more events of locoregional progression or relapse, metastasis, or death. 350 patients had locoregional progression and 204 had metastatic progression. Table 2 and figure 2 show treatment efficacy in terms of PFS, overall survival, locoregional failure, and rates of distant metastases. PFS did not differ between the accelerated radiotherapy-chemotherapy group and the conventional chemoradiotherapy group (p=0·88; table 2, figure 2). Although not significantly different (p=0·060), accelerated radiotherapy-chemotherapy seemed to improve PFS compared with very accelerated radiotherapy. Conventional chemoradiotherapy improved PFS compared with very accelerated radiotherapy (p=0·041). Conventional chemoradiotherapy improved overall survival compared with very accelerated radiotherapy (p=0·040). However, overall survival did not differ between the accelerated radiotherapy-chemotherapy group and the very accelerated radiotherapy group (p=0·169) or the accelerated radiotherapy-chemotherapy group and conventional chemoradiotherapy group (p=0·60). Incidence of locoregional failures was lower after conventional chemoradiotherapy or accelerated radiotherapy-chemotherapy than it was after very accelerated radiotherapy (p=0·045 and p=0·033, respectively), but incidence did not differ between the chemotherapy groups (p=0·81). Incidence of distant metastases did not differ between any groups (table 2, figure 2, appendix).

The mean overall radiation dose in patients randomly allocated to receive conventional chemoradiotherapy was 69·0 Gy in 34 fractions over 48 days, compared with 69·3 Gy in 38 fractions over 42 days in the accelerated

	Conventional chemoradiotherapy group	Accelerated RT-CT group	Very accelerated RT group	p value
Radiotherapy not done*	6	4	2	..
Radiotherapy data missing	1	0	1	..
Number of analysed patients	272	276	278	..
Mean dose received, Gy	69·0 (6·5)	69·3 (4·9)	64·3 (5·1)	..
Mean radiotherapy duration, days	48·2 (6·4)	41·8 (4·0)	25·6 (5·1)	..
Definite stop of radiotherapy	11 (4%)	10 (4%)	10 (4%)	0·95
Toxic effects	2	4	1	..
Death†	5	1	7	..
Other	4	5	2	..
Received dose before stopping				
≤50 Gy	6	3	6	..
>50 Gy	5	7	4	..
Temporary stop of radiotherapy	76 (28%)	68 (25%)	48 (17%)	0·010
Mean duration, days	3·7 (3·5)	2·8 (2·5)	3·5 (4·7)	0·28
≤3 days	48	50	39	..
>3 days	28	18	9	..
Number of files reviewed for RT-QA	42	48	48	..
Scored as per protocol for the volume§	33/37 (89%)	44/48 (92%)	46/46 (100%)	0·06
No deviation for dose	34/42 (81%)	40/48 (83%)	41/48 (85%)	0·85
No deviation for duration	35/39 (90%)	42/45 (93%)	44/47 (94%)	0·78

Data are n, n (%), mean (SD), or number of files meeting criteria/number of files assessed (%). RT=radiotherapy. CT=chemotherapy. QA=quality assurance. *Reasons shown in figure 1. †Causes of deaths are described in the appendix. §≤10% of the planned target volume receiving <95% of the dose.

Table 3: **Radiotherapy compliance and quality assurance**

	Conventional chemoradiotherapy group (n=279)	Accelerated RT-CT (n=280)
Cycles received		
Unknown	1 (<1%)	0
None	10 (4%)	5 (2%)
Cycle 1	267 (96%)	275 (98%)
Cycle 2	256 (92%)	258 (92%)
Cycle 3	203 (73%)	1 (<1%)
Correct number received*	198 (71%)	257 (92%)
Doses received		
Cycle 1†		
≥95%	257 (96%)	261 (95%)
<95%	10 (4%)	13 (5%)
Cycle 2‡		
≥95%	238 (93%)	229 (89%)
<95%	18 (7%)	27 (10%)
Cycle 3§		
≥95%	186 (92%)	..
<95%	16 (8%)	..

RT=radiotherapy. CT=chemotherapy. *p<0·0001. †Data missing for one participant in the accelerated RT-CT group. ‡Data missing for two participants in the accelerated RT-CT group. §Data missing for one participant in the conventional chemoradiotherapy group.

Table 4: **Chemotherapy compliance**

See Online for appendix

	Conventional chemoradiotherapy group	Accelerated RT-CT group	Very accelerated RT group	p value
Mucositis (RTOG grading)				0·0001
0–2	82 (31%)	66 (24%)	42 (16%)	..
3–4	180 (69%)	205 (76%)	226 (84%)	..
Mucositis (WHO grading)				0·016
0–2	57 (22%)	43 (16%)	30 (11%)	..
3	98 (37%)	103 (38%)	99 (37%)	..
4	108 (41%)	125 (46%)	138 (52%)	..
Feeding tube	158/265 (60%)	176/276 (64%)	190/272 (70%)	0·045
Skin toxicity (RTOG grading)				0·24
0–2	152 (58%)	150 (56%)	161 (63%)	..
3–4	108 (42%)	118 (44%)	104 (37%)	..
Haematological toxicity during chemotherapy				
Haemoglobin				0·48
Grade 0–2	253 (96%)	268 (97%)	..	..
Grade 3	8 (3%)	6 (2%)	..	..
Grade 4	3 (1%)	1 (<1%)	..	..
Leucocyte				0·55
Grade 0–2	236 (89%)	237 (86%)	..	..
Grade 3	24 (9%)	32 (12%)	..	..
Grade 4	4 (2%)	6 (2%)	..	..
Platelet				0·90
Grade 0–2	254 (96%)	262 (95%)	..	..
Grade 3	6 (2%)	8 (3%)	..	..
Grade 4	4 (2%)	5 (2%)	..	..
All haematological				0·57
Grade 0–2	228 (86%)	230 (84%)	..	..
Grade 3	26 (10%)	35 (13%)	..	..
Grade 4	10 (4%)	10 (4%)	..	..
At least one toxic effect*				0·07
Grade 0–2	44 (17%)	33 (12%)	31 (11%)	..
Grade 3	186 (70%)	214 (78%)	220 (80%)	..
Grade 4	36 (14%)	29 (10%)	23 (8%)	..
Hospitalisation because of toxic effects	71/265 (27%)	89/276 (32%)	76/272 (28%)	0·34
Mean duration of hospitalisation, days	17 (13)	18 (16)	19 (19)	0·60

Data are n (%) or mean (SD). RT=radiotherapy. CT=chemotherapy. RTOG=Radiotherapy Oncology Group. *Eg, mucositis (Radiation Therapy Oncology Group grading), skin, haematological, renal, and other toxic effects.

Table 5: **Acute toxic effects**

radiotherapy-chemotherapy group and 64·3 Gy in 35 fractions over 26 days in the very accelerated radiotherapy group. Radiotherapy was definitively stopped before the planned end in 4% of the patients in each group (table 3). Rates of temporary interruptions of radiotherapy were highest in the conventional chemoradiotherapy group and lowest in the very accelerated radiotherapy group, lasting for an overall mean duration of 3·3 days (SD 3·6; table 3). Table 3 also shows results of the quality assurance review of 138 radiotherapy charts, which seemed balanced across groups. For all patients, according to the data received from the centre, the radiotherapy doses and overall time were as per protocol without deviation (ie, no dose modification of >2 Gy or time >9 days off schedule) in 248 (91%) of 272 treated and assessed patients in the conventional chemoradiotherapy group, compared with 252 (91%) of 276 in the accelerated radiotherapy-chemotherapy group, and 242 (87%) of 278 in the very accelerated radiotherapy group (p=0·31).

Ten patients in the conventional chemoradiotherapy group and five in the accelerated radiotherapy-chemotherapy group did not receive concomitant chemotherapy (table 4). Compliance to cycle 1 and cycle 2 of chemotherapy was good (542 [97%] of 559 patients received cycle 1 and 514 [92%] patients received cycle 2), and compliance to cycles 1 and 2 did not differ between groups (table 4). However, probably because there was a third cycle only in the conventional chemoradiotherapy group and compliance to this cycle was low (203 [73%] of 279), the administration of the correct number of chemotherapy cycles was better in the accelerated radiotherapy-chemotherapy group (p<0·0001; table 4). There was good compliance between the distribution of the theoretical chemotherapy doses and the planned doses in both groups; rates of compliance did not differ between groups (table 4).

The number of deaths within the 3 first months after randomisation did not differ between groups (13 deaths in the conventional chemoradiotherapy group, 14 deaths in the accelerated radiotherapy-chemotherapy group, and 16 deaths in the very accelerated radiotherapy group). During the first 3 months in conventional chemoradiotherapy group, four deaths occurred before the start of treatment (figure 1), five deaths occurred during treatment (table 3), and four deaths occurred after end of treatment, compared with three deaths, one death, and ten deaths, respectively, in the accelerated radiotherapy-chemotherapy group, and no deaths, seven deaths, and nine deaths, respectively, in the very accelerated radiotherapy group.

Haematological toxicity in patients given chemotherapy did not differ between 264 patients assessed in the conventional chemoradiotherapy group and 275 patients assessed in the accelerated radiotherapy-chemotherapy group (26 [10%] grade 3 and ten [4%] grade 4 in the conventional chemoradiotherapy group and 35 [13%] grade 3 and ten [4%] grade 4 in the accelerated radiotherapy-chemotherapy group; table 5). In the three groups, the main acute toxic effects were mucosal reactions. Severe mucositis was more commonly noted in the very accelerated radiotherapy group than in the other two groups (table 5). Other acute toxic effects did not differ between groups (table 5). Overall, the rate of grade 3–4 acute toxicity seemed lower in the conventional chemoradiotherapy group (222 [83%] of 266 assessed patients) than it was in the accelerated radiotherapy-chemotherapy group (243 [88%] of 276 assessable patients) and the very accelerated radiotherapy group (243 [89%] of 274 assessable patients; p=0·07). Rate and duration of hospital admission owing to toxic effects (during treatment or in the 3 months after the end of treatment) did not differ between groups (table 5).

The rate of patients with a feeding tube (medical gastrostomy or naso-oesophageal tube) differed between the three groups (p=0·045), and was highest in the very accelerated radiotherapy group (table 5). The main reasons for having a feeding tube were tumour-bulk related swallowing difficulties or severe acute mucosal reactions. In the 5 years after treatment, the rate of patients having a feeding tube was higher in the very accelerated radiotherapy group than it was in the conventional chemoradiotherapy group (p=0·027; figure 3). Rates of late neck fibrosis, late mucosal toxicity, late xerostomia, and late laryngeal toxicity 1–5 years after randomisation did not differ between groups (figure 4). Rates of late bone toxicity also did not differ between groups in this time (data not shown).

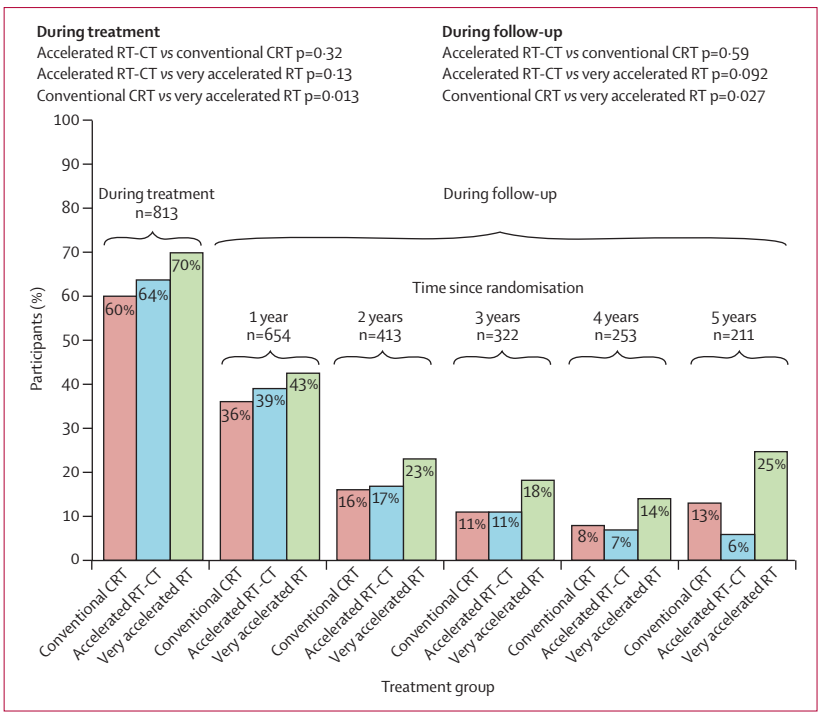

Figure 3: **Participants with feeding tubes during treatment and during 5-year follow-up**
CRT=chemoradiotherapy. RT-CT=radiotherapy-chemotherapy. RT=radiotherapy.

Discussion

The hypothesis of our study was that a combination of acceleration of radiotherapy and concomitant use of chemotherapy would result in a gain of 15% in PFS by 3 years. We showed that there was no such benefit and that acceleration of radiotherapy by 1 week, concomitant to chemotherapy, did not add any benefit when compared with conventional concomitant chemoradiotherapy. However, we could not rule out differences in planned doses of chemotherapy between conventional chemoradiotherapy and accelerated radiotherapy-chemotherapy groups that might partly mask a potential effect of acceleration. Notably, the planned total dose of concomitant chemotherapy was three cycles of 4 days in the conventional chemoradiotherapy group compared with only two cycles of 5 days in the accelerated radiotherapy-chemotherapy group (ie, 17% higher in the conventional chemoradiotherapy group).

Our findings are in agreement with the results of the only other phase 3 randomised trial[17] that specifically addressed this issue (panel). That trial, by the Radiotherapy Oncology Group (RTOG 0129),[17] compared two cycles of concomitant chemotherapy plus 72 Gy radiotherapy in 6 weeks with three cycles of cisplatin chemotherapy plus conventional 70 Gy radiotherapy in 7 weeks. No benefit was reported with a 1 week acceleration of radiotherapy, and the trial suggested that a third cycle of concomitant chemotherapy might compensate for the noted absence in acceleration. A subgroup analysis of the trial[17] that stratified for presence of human papillomavirus was done for the subsite of oropharyngeal tumours and showed a favourable prognostic significance of P16 immunostaining as a surrogate for human papillomavirus positivity. However, the analysis of human papillomavirus status did not change the overall conclusions of the study.[17] We did not assess the prognostic significance of human papillomavirus because the value of this measure had not been widely described at the time we designed our study.[23]

The second notable finding from our study was that very accelerated radiotherapy alone was inferior to the two chemotherapy regimens assessed in terms of locoregional control, and also in terms of PFS and overall survival when compared with conventional chemoradiotherapy. This finding was unexpected because the accelerated radiotherapy regimen that we used is one of the most intense altered fractionated regimens reported so far, and was substantially better than was conventional radiotherapy alone in terms of tumour control probability in a previous phase 3 randomised trial.[20] We expected very accelerated radiotherapy to be at least as good as conventional chemoradiotherapy for tumour control. Despite the strong acceleration associated with this very intense radiotherapy regimen, we did not note the expected relation and our data also add new insights to the long list of randomised trials[2,7–9,13] that have shown that a combination of concomitant chemoradiotherapy is better than radiotherapy alone in locally advanced HNSCC. Even a very intense acceleration of radiotherapy seems unable to compensate for the absence of concomitant chemotherapy.

The overall rate of early deaths in our trial was fairly high (5% in the first 3 months), and was possibly linked to the poor health of patients with locally advanced disease who had tobacco-related and alcohol-related comorbidities. In terms of other toxic effects, as expected, acute mucosal toxicity was an important issue in the three groups, being more pronounced in the very accelerated radiotherapy group. However, there were no general toxic effects caused by systemic chemotherapy in patients treated in the very accelerated radiotherapy group. Regarding the use of feeding tubes, the incidence was higher in the very accelerated radiotherapy group, both during treatment and during long term follow-up.

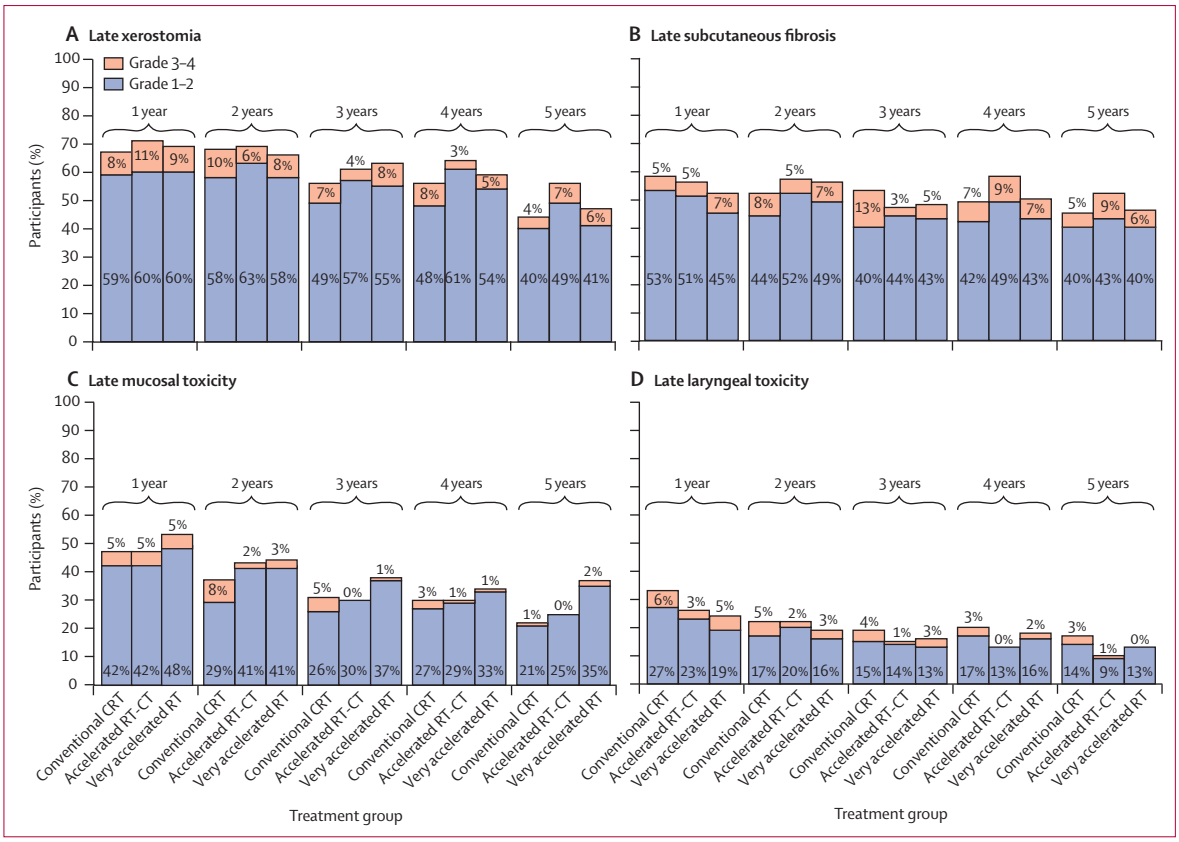

Figure 4: **Participants with late toxicity**
Data for 560 participants were available 1 year after randomisation (194 in the conventional chemoradiotherapy group, 188 in the accelerated radiotherapy-chemotherapy group, and 178 in the very accelerated radiotherapy group), 390 participants at 2 years (146, 128, and 116), 302 participants at 3 years (110, 97, and 95), 247 participants at 4 years (89, 77, and 81), and 207 participants at 5 years (77, 67, and 63). RT-CT=radiotherapy-chemotherapy. RT=radiotherapy.

Although the other late effects did not differ between groups, analysis of our data suggests that very accelerated radiotherapy is less effective and slightly more toxic than is conventional chemoradiotherapy.

We did not record data for rates of salvage surgery; however, we believe the probability of such surgery was low in all three treatment groups, because most of the patients had inoperable disease at initial work-up and could not subsequently be proposed for salvage surgery at the time of post-treatment tumour progression or relapse.

In conclusion, we show the limitations of dose intensification of radiotherapy and chemotherapy in locally advanced HNSCC, and suggest that the acceleration of radiotherapy cannot fully compensate for a missed dose of chemotherapy. Thus, conventional radiotherapy plus three cycles of concomitant chemotherapy remains the standard of care within the GORTEC group. The concomitant use of molecularly targeted drugs that could add some anti-tumour efficacy, with low increases in toxicity,[24] might be a promising avenue for exploration. However, a randomised study by the GORTEC group[25] of larynx preservation suggested that radiotherapy plus cetuximab was not superior to cisplatin-based chemoradiotherapy in terms of tumour control, and that concomitant chemoradiotherapy remains the best approach in this type of cancer. This finding was supported by a reported absence of benefit of addition of cetuximab to concomitant chemoradiotherapy when compared with concomitant chemoradiotherapy alone in a randomised trial of

Panel: **Research in context**

Systematic review
The rationale for combining accelerated radiotherapy and concomitant chemotherapy in locally advanced head and neck squamous-cell carcinomas (HNSCCs) was strong, based on the data from the updated Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC)[1,2] and from the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH).[19] The potential added value of combining both approaches together was not known.

Interpretation
We showed that acceleration of radiotherapy cannot compensate for the absence of concomitant chemotherapy in HNSCC, and that there is no justification to intensify radiotherapy in concomitant chemoradiotherapy. Both messages are important in routine practice and in understanding the behaviour of these cancers when treated with radiotherapy and chemotherapy. Our findings concur with the results of the only other phase 3 randomised trial[17] that specifically addressed this issue.

940 patients.[18] New induction chemotherapy approaches with cisplatin-docetaxel-fluorouracil are underway.[3–6] In particular, future randomised trials should assess the value of addition of induction docetaxel-cisplatin-fluorouracil before concomitant chemoradiotherapy, as compared with concomitant chemoradiotherapy alone. The value of potentially more efficient radiotherapy, such as carbon ion therapy, should also be tested for radioresistant tumours.[26]

Contributors

JB, CS, PG, VG, PM, GC, BG, LM, MA, PD, TP, EB, MR, ND-S, SS, CT, OD, SG, ML, VF, MH, LG, AL, ST, and AA designed the study. All authors participated in data collection. VG, MA, GC, TP, EB, OD, ML, AL, PM, CT, SG, MR, JB, VF, PG, MH, LM, PD, and CS reviewed radiotherapy charts. AA, JB, and AP did the statistical analysis. All authors participated in data interpretation, writing of the manuscript, and gave final approval for publication.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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