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Original article

# Randomized trial comparing two methods of re-irradiation after salvage surgery in head and neck squamous cell carcinoma: Once daily split-course radiotherapy with concomitant chemotherapy or twice daily radiotherapy with cetuximab

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ABSTRACT

*Background:* A previous randomized trial in recurrent Head and Neck squamous-cell carcinoma (HNSCC) has shown re-irradiation combined with chemotherapy after salvage surgery significantly improved disease-free survival (DFS). The objective of this randomized trial was to compare two methods of re-irradiation in terms of toxicity and survival.

*Patients and methods:* Patients with recurrence/second primary in previously irradiated area were randomly allocated to receive either 60 Gy over 11 weeks with concomitant 5FU – hydroxyurea (VP-arm), or 60 Gy (1.2 Gy twice daily) over 5 weeks with cetuximab (HFR-arm). Primary endpoint was treatment interruption >15 days (acute toxicity).

*Results:* Twenty-six patients were included in VP-arm and 27 in HFR-arm. One patient in VP-arm experienced >15 days interruption due to toxicity, and none in HFR-arm. In both arms, all patients received at least 60 Gy. In VP-arm, 8/26 patients had chemotherapy delay and/or dose reduction. In HFR-arm, 4/27 patients had <6 cycles cetuximab. There was no significant difference in overall survival (Median OS: 37.4 months vs 21.9 months, $p = 0.12$). Toxicities and DFS were not different between 2 arms.

*Conclusions:* Twice daily schedule of re-irradiation of 60 Gy/5 weeks with cetuximab was tolerable and no significant difference in treatment delays occurred between two arms.



Patients with recurrent head and neck squamous cell carcinoma (HNSCC), or a second primary, 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 loco-regional failures [1].

The GETTEC (Groupe d'Etude des Tumeurs de la Tête et du Cou) and GORTEC (Groupe d'Oncologie et de Radiothérapie Tête Et Cou) reported the results of a phase III randomized multicentric trial evaluating concomitant chemo-radiotherapy after salvage surgery [2]. Its goal was to compare the "wait and see" attitude to post-operative re-irradiation, using split course radiotherapy delivering 60 Gy over 11 weeks with concomitant 5FU and hydroxyurea [3]. In 130 patients, full-dose re-irradiation combined with chemotherapy after salvage surgery significantly improved disease-free survival (DFS), but had no significant impact on overall survival (OS). However loco-regional failure remained the major cause of death, and an increase in both acute and late toxicity was observed in the re-irradiation arm.

Meta-analysis of altered fractionated radiotherapy in HNSCC with 15 randomized trials showed an improvement in survival, in comparison to conventional radiotherapy. Comparison of different types of altered radiotherapy suggested that hyperfractionation had the greatest benefit [4]. Concomitant cetuximab with radiotherapy improved loco-regional control and survival, without significant increase in toxicity compared with radiotherapy alone in HNSCC [5].

These data prompted us to launch a phase II randomized multicentric trial to compare two regimens of re-irradiation after salvage surgery: mono-fractionated radiotherapy with concomitant chemotherapy [2], and bi-fractionated radiotherapy with

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cetuximab as experimental arm. We report here the results of first analysis of this randomized phase II trial.

## Patients and methods

### Patients

Patients who underwent surgery for a recurrent HNSCC (second tumor at the same zone of head and neck region as the initially treated tumor) or a second primary (second tumor at a different zone of head and neck region with the initially treated tumor) in a previously irradiated head and neck area with at least 50 Gy were eligible.

Randomization was performed after salvage surgery. Doctors or their clinical research assistants faxed (or by internet) randomization form to data manager who did the randomization with a computer program. Doctors and patients were not masked to treatment-group assignment.

The main inclusion criteria were as follows: Histologically proven squamous cell carcinoma (SCC) of oral cavity, pharynx, larynx, or unknown primary; 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; one of these high risk histologic gravity signs on surgical specimen: positive margins, capsular rupture, perineural spread; macroscopic complete resection; >6 months between the initial course of radiotherapy and salvage surgery; sufficient healing for beginning re-irradiation within 8 weeks of salvage surgery; 18–75 years; WHO 0–1; M0; without severe sequelae of initial radiotherapy; >50% of recurrent tumor has received $\geq$50 Gy during previous irradiation.

### Concomitant chemotherapy or cetuximab and re-irradiation

Patients received either once daily radiotherapy with concomitant chemotherapy or hyperfractionated radiotherapy (twice daily) with cetuximab.

In mono-fractionated arm (Vokes' protocol, VP), 60 Gy in 11 weeks, patients received six cycles, with each cycle delivering 2 Gy/fraction, 5 days/week, with concomitant hydroxyurea (1.5 g/d orally) and continuous infusion fluorouracil (800 mg/m2/day), as previously reported [2], with 9-day rest periods between cycles (split course).

In hyperfractionated radiotherapy arm (HFR), patients received a total dose of 60 Gy in 50 fractions, 1.2 Gy/fraction, 2 fractions/-day, 5 days/week during 5 weeks consecutively. Cetuximab was initiated one week before radiotherapy at a loading dose of 400 mg/m$^2$, followed by weekly 250 mg/m$^2$ during radiotherapy.

The re-irradiation was performed using 4 to 6 MV photons, along with a 3D conformal radiotherapy with or without intensity-modulation. A general guideline was to restrict the radiation fields to primary tumor bed or recurrent neck nodes, without prophylactic irradiation of neck nodal region beyond the first adjacent nodal area. The clinical target volume (CTV) included the margin around tumor bed at least 1 cm (up to 2 cm in some deeply infiltrating tumor). Smaller margin could be accepted only in case of re-irradiation close to critical organs at risk such as spinal cord. The planned target volume (PTV) was obtained by adding additional margin of 3–5 mm to CTV taking into account interfraction set-up uncertainties. The spinal cord was systematically excluded from the reirradiation beams with maximum dose of 10 Gy according to initial irradiation dose.

The evaluation of the quality of radiotherapy treatment plan has been carried out by GORTEC quality assurance team. Treatment plan would be considered as major deviation if >10% of the PTV receiving less than 95% of prescribed dose.

### Toxicity

Toxicity was considered as acute when occurring within 6 months after randomization. Patients were evaluated according to the NCI Common Terminology Criteria for Adverse Events v3.0 (NCI-CTCAE v3) for acute and late toxicity.

### Statistical considerations

Patients were stratified according to the center and tumor site. Using Simon's two-stage design, with alpha = 10% and beta = 10%, 28 subjects were expected in each arm (stage 1 = 9 patients, stage 2 = 19 patients). After inclusion and evaluation of the 9 first patients, if the number of patients which experienced toxicities was superior or equal to 3, the study had to be stopped. If this number was inferior or equal to 2, 19 additional patients would be included in each arm.

Chi-square tests were used to compare proportions for categorical variables. Fisher's exact test was used for categorical variables when one or more values were below 5.

The primary endpoint was the comparison between both arms of the number of patients with a treatment interruption for more than 15 days, due to acute toxicity. It was evaluated using the exact test of Fisher. Additional endpoints were toxicity, DFS and OS. DFS was to be 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, loco-regional or metastatic, excluding new primaries) or death, or to the date of the last follow-up.

Survival was estimated using the Kaplan–Meier method. Survival rates are presented with their 95% CI, and were estimated with a univariate Cox proportional hazards regression model.

All statistical analyses were performed with SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA).

## Results

From June, 2010 to February, 2014, 60 patients were randomized in seven French centers, 31 in VP arm and 29 in HFR arm. Seven enrolled patients could not be treated: 3 early deaths before treatment (sepsis, cardiac arrest, disease progression), 2 poor general conditions, and 2 withdrawals of consent. Fifty-three patients started treatments and are included in the analysis set, 26 in VP arm and 27 in HFR arm (Fig. 1). Follow-up of patients were registered during 3 years after randomization. The median follow-up was 36 months (95% CI: 31–43) with no difference between the two arms (log-rank test: $p = 0.70$).

### Patient population

There was no imbalance between the 2 arms in clinical characteristics of operated tumor (Table 1). Forty-five of the 53 (85%) operated tumors were recurrences, and the remaining 8/53 (15%) were new primaries. Thirty-three of 53 patients (62%) had a pharyngeal tumor, 37/53 (70%) lesions were restaged as T3 or T4, and 40/53 (75%) as N0.

Salvage surgery was performed according to routine practice in each center. The lymph node dissection was performed in most cases (48/53 patients; 91%). A flap was commonly used: myocutaneous flap in 23/53 (43%) patients, and free flap in 25/53 (47%) patients.

Detailed surgical specimen characteristics (Table 2): 21/48 (44%) patients had nodal involvement, with extracapsular rupture in 10/21 (48%). Tumor margins were analyzed in 50/53 patients:

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