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Phase III randomised trial

Accelerated radiotherapy and concomitant high dose chemotherapy in non resectable stage IV locally advanced HNSCC: Results of a GORTEC randomized trial

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ABSTRACT

Background: The objective was to evaluate the efficacy of a strong increase of the dose-intensity of concomitant radio-chemotherapy (RT-CT) in patients with far advanced non metastatic HNSCC.
Methods: Eligible patients had N3 disease (UICC 1997) and the primary tumor and/or the node(s) had to be strictly unresectable. Patients with palpable N2B–C were also eligible if massive nodal involvement was present. 109 patients were included, with 53 randomized to RT-CT and 56 to accelerated RT. In the RT-CT arm, the RT regimen consisted of 64 Gy in 5 weeks and the CT regimen consisted of synchronous CDDP 100 mg/m^2 on days 2, 16, and 30 and 5FU 1000 mg/m^2 on days1–5 and 29–33 of the RT course. After RT-CT, two adjuvant cycles of CDDP-5FU were delivered in good responders. A control arm was using a very accelerated RT, delivering 64 Gy in 3 weeks.
Results: The most common tumor sites were oropharynx and hypopharynx. Most of the patients had T4 disease (70%) and 100% had a massive nodal involvement (mainly N3 with a mean nodal size >7 cm in both arms). A significant difference was observed in favor of the RT-CT arm ($p = 0.005$) in terms of cumulative incidence of local regional failure or distant metastases. However, the overall survival and event free survival rates were not significantly different between the two arms ($p = 0.70$ and 0.16, respectively). The lack of survival benefit in favor of the RT-CT was partly due to an excess of initial early treatment related death in the RT-CT arm.
Conclusion: The very intense RT-CT schedule was more efficient on disease control, but was also more toxic than accelerated RT alone, pointing out that there was no clear improvement of the therapeutic index. This study shows the limits of dose-intensification, with regard to concomitant RT-CT.

In the recent decades, the role of chemotherapy (CT) in head and neck squamous cell carcinoma (HNSCC) has been extensively studied [1–4]. It has been used mainly in three ways in the treatment of locally advanced HNSCC: as induction treatment [5–7]; concomitantly with radiotherapy (RT) [1–4,8–11]; as adjuvant treatment after RT and/or surgery [1,2,5]. Based on evidence level 1A and in particular on the MACH-NC meta-analysis [1,2], which analyzed updated individual patients data from 87 randomized trials, concomitant RT-CT has become a standard of care in locally advanced HNSCC. The magnitude of the survival benefit associated with the addition of CT, when given concomitantly with RT was found to be 6.5% at 5 years and higher with platinum based-CT [2]. Adding CT to RT is also associated with a substantial increased of acute and late toxicities [3,12,13], pointing out the need to optimize these therapeutic combinations.

In the past decades, considerable interest has also been raised about non conventional fractionation schedules in RT for HNSCC, either with hyperfractionated and/or accelerated RT [14–19]. The aim of such altered fractionated RT was to increase the dose intensity of RT, either by increasing the total dose of RT (hyperfractionation) or by reducing the overall time of RT (acceleration). In both cases, an improved outcome has generally been observed, as compared to conventional RT and a meta-analysis based on the collection of the individual patients data from more than 6500 patients randomized between conventional and altered fractionated RT concluded to a small but significant improvement, both in local control and survival, in favor of altered fractionated RT [20].

Taking into account the results of randomized studies, a new regimen was designed in an attempt to markedly increase the dose-intensity with the subsequent hypothesis to markedly increase the efficacy of RT-CT. This very intense regimen was tested

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in a series of patients with far locally advanced HNSCC, both at the primary and the nodal sites, carrying both a high risk of local–regional failure, but also a high risk of distant metastases.

The design of this RT-CT regimen took into account three requirements. The first was that the CT had to be given concomitantly to RT in order to use the type of RT-CT timing that has proved to be the most efficient [1,2]. The second requirement was that CT had to be used at conventional high doses, which is a type of CT that had been able to decrease the rate of distant metastases [2]. Finally the proposed RT-CT incorporated an accelerated RT regimen. Accelerated RT has been shown on its own to improve tumor control in HNSCC patients [14–19].

The tolerance and efficacy of the resulting very intense RT-CT regimen was tested against a very accelerated RT regimen which was previously reported to be feasible in locally advanced HNSCC and subsequently was able to improve markedly tumor control probability, as compared to conventional RT, as it has been shown more recently in a randomized trial [19].

Material and methods

Inclusion criteria

Patients eligible to enter in the study had unresectable nodes classified as N3 (UICC 1997) biopsy proven HNSCC. Patients with palpable N2-B and -C nodal involvement could also be included, pending they had unresectable disease. The primary tumor and/or the cervical node(s) had to be strictly inoperable due to the local and/or regional extension of the disease. The statement of unresectability was made by at least two head and neck surgeons, one radiation oncologist, and one medical oncologist.

The patients had no previous history of cancer and/or previous RT or CT. A Karnofsky performance status scoring of 70 or more was necessary to enter in the study. An informed consent was signed by each patient before randomization.

The local regional work-up consisted of a CT scanner and/or MRI and a pan-endoscopy under general anesthesia to assess the primary tumor extension and potential second primaries.

A metastatic work up was performed in order to exclude metastatic patients with thoracic radiogram and CT, liver ultrasounds and bone scintigraphy (in case of clinical signs). No PET-CT was available at the time of the trial.

Treatment

Patients were randomized to receive either very accelerated RT delivering 64 Gy in 32 fractions of 2 Gy and 23 days (2 Gy/fraction, BID) or RT-CT delivering 62–64 Gy/5 weeks and 31–32 fractions (with 1 week rest after each treatment week and 2 Gy/fraction, BID). In the concomitant RT-CT arm, the CT regimen used high dose-intensity CT with three cycles of CDDP 100 mg/m^2 on days 2, 16, and 30 of the radiotherapy and two cycles of 5FU 1 g/m^2/day on days 1–5 and 29–33 of radiotherapy. In addition, in patients who achieved a complete CR and who could tolerate additional CT, a further two cycles of CDDP-5FU (CDDP 100 mg/m^2 on day 1 and 5FU, 1 g/m^2/day on days 1–5) was given 28 and 49 days after completion of the concomitant RT-CT.

In both arms, the interval between RT fractions was at least 8 h. A 4–6 MV linac was used along with conventional treatment planning system (no IMRT was performed at that time). The spinal cord exclusion was performed at 34 Gy in both arms, and cervical posterior nodes were treated thereafter with electrons beams of appropriate energy (8–12 MeV) or with oblique posterior photon beam(s), when appropriate. Prophylactic nodal irradiation dose was 45 Gy in the uninvolved neck.

Statistical method

Randomization was done by minimization using center and T(T0–2/T3/T4) as minimization factors. Randomization was performed centrally by phone at the Unit of Biostastistics and Epidemiology of the Institute Gustave Roussy.

The primary end point was the event free survival (EFS), defined as the minimum time between randomization and local–regional progression/relapse or distant relapse or death from any cause or the last follow-up contact for patients who did not experience any event. The secondary endpoints were survival, defined as the time between randomization and death from any cause or the last follow-up contact for patients who were alive.

The inclusion of 60 patients per group would allow detecting a difference of the EFS rates from 30% at 2 years in the very accelerated RT group to 60% in the concomitant RT-CT group, with a 0.05 two-sided type I error rate and a 90% power.

Analyses were carried out on the intent-to-treat principle. Differences between groups were evaluated by χ^2 test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. The survival probabilities were estimated according to the Kaplan–Meier method. The curves carry Rothman's 95% confidence intervals (95%CI). Survival curves were compared by the log-rank test. In order to estimate the respective contribution of disease evolution (local–regional or distant) and of death as first event (without cancer evolution occurring before) in the EFS, the cumulative incidences of each of these two events were calculated according to the competing risk method and compared between the two arms [21].

Results

Characteristics of the patients

Between 1996 and 2000, 109 patients from 3 GORTEC centers (Clermont-Ferrand, Nancy and Villejuif) were included in this study, with 53 randomized to RT-CT and 56 to accelerated RT.

The mean age was 55 years and 92% (RT-CT) and 89% (RT) of the patients were male. As shown in Table 1, the most common tumor

Table 1
Main characteristics of the patients by treatment arms.

	RT-CT (n = 53)	RT (n = 56)	p
Tumor site			
Oropharynx	36 (68%)	32 (57%)	
Hypopharynx	12 (23%)	17 (30%)	
Other	5 (9%)	7 (13%)	0.51
Tumor stage			
⩽T2	8 (15%)	12 (21%)	
T3	6 (11%)	6 (11%)	
T4	39 (74%)	38 (68%)	0.69
Bone/cartilage invasion (two missing data)	14 (27%)	7 (13%)	0.07
Extension beyond the midline (one missing data)	32 (60%)	38 (69%)	0.34
Para and/or retropharyngeal space (one missing data)	25 (47%)	26 (47%)	0.99
Nodal extension			
Palpable N2B–C	7 (13%)	13 (23%)	
N3	46 (87%)	43 (77%)	0.18
Number of nodes (mean (sd))	2.9 (2.1)	3 (2.2)	0.80
Bilateral	26 (49%)	34 (61%)	0.22
Supra-clavicular	7 (13%)	10 (18%)	0.50
Ulceration/skin	7 (13%)	6 (11%)	0.69
Deep fixicity (three missing data)	41 (79%)	38 (70%)	0.32
Retropharyngeal space	8 (15%)	7 (13%)	0.69
Diameter of the largest node (cm) (mean (sd))	7.8 (2.5)	7.1 (3.2)	0.26

sites were the oropharynx and hypopharynx. The distribution of the patients according to the tumor and nodal stages is shown in Tables 1 and 2. Most of the patients had T4 disease (70%) and a massive nodal involvement was present in all cases, mainly classified as N3 disease (87% in the RT-CT arm and 77% in the RT arm). The mean nodal size was 7.8 cm in the RT-CT arm and 7.1 cm in the RT arm ($p = 0.26$) with a deep fixicity in more than 70% of the cases, in the two arms. The distribution of the main tumor characteristics was well balanced between both arms, as shown in Table 1.

Radiotherapy

Three patients of the RT-CT arm did not receive RT. Among the other patients, the median total dose was 62 Gy in 31 fractions in both arms, with a median overall time of 37 and 24 days, in the RT-CT and RT, respectively. Interruption of RT was observed in nine cases (18%) in the RT-CT arm, and six cases (11%) in the RT arm ($p = 0.28$). In the RT-CT arm, the interruptions were temporarily in four cases and definitive in the remaining five patients (range 4–40 Gy). In this arm, the causes of definitive interruption were death (2), toxicity (2) and ischemia (1). In the RT arm, four interruptions were temporarily and only one was definitive due to a concurrent pulmonary failure.

Quality assurance for radiotherapy

The characteristics of the treatment delivered to the patients were reviewed by a panel consisting of investigators and external experts who examined the medical charts twice a year throughout the period of time of the trial. The total dose, the duration of radiotherapy, the dose per fraction, and the dose distributions were also checked as well as along with the verification of the fields of irradiation and adequate tumor coverage. The tumor and nodal involvement were also re-staged.

For the purpose of the RT quality assurance (QA), a sample of the patients were analyzed to ensure that there was no imbalance of the quality between the two arms. Ninety-three radiotherapy charts were reviewed, 44 in the RT-CT arm and 49 in the RT arm. A major deviation on the total dose as defined by a dose variation higher than 10% was found in 12% and 10% for the RT-CT and RT arm, respectively ($p = 1$). A major deviation on the overall treatment time (>42 days for RT-CT and >28 days for RT) was found in 19% for the RT-CT arm and 10% for the RT arm ($p = 0.21$). A deviation on the gross tumor volume coverage was found in three cases (7%) for the RT-CT arm (minor deviations) and one case (2%) in the RT arm (major deviation).

Table 2
Distribution of the patients according to the TNM classification (UICC 1997).

	N2B-C	N3
T0	–	8
T1	–	3
T2	–	9
T3	2	10
T4	18	59

Table 3
Distribution of the percentage of the theoretical CT dose received by patients during the first three concomitant CT courses.

Percentage of theoretical dose (%)	CDDP	5FU
0	4 (8%)	3 (6%)
<50	5 (9%)	8 (15%)
50–74	11 (21%)	7 (13%)
75–89	2 (4%)	3 (6%)
⩾90	31 (58%)	32 (60%)

Chemotherapy

Out of the 53 patients in the RT-CT arm, three did not receive chemotherapy and one received only 1 day of 5FU. The distribution of the theoretical CT dose is presented in Table 3. The mean percentage of the theoretical dose received was 77% for CDDP and 5FU. Out of the 50 patients who received CT, 15 had definitive interruption of CT during the course of RT: eight for toxicity (six hematological, one renal and one mucosal), two for early death, and five for severe inter-current medical problems. Out of the 35 patients who completed the three cycles of CT, five had a dose reduction of CDDP, two of 5FU, and two of both because of toxicity.

After RT, the intent was to add a further two cycles of adjuvant CDDP-5FU, in selected patients who could tolerate it and who achieved a rapid CR. Only 26 patients could receive this adjuvant CT, including four who had previously interrupted CT during the course of RT. A definitive interruption of the adjuvant part of the CT was observed in four patients.

Altogether, considering both the concomitant RT-CT and the adjuvant CT part, only 15/53 (28%) patients received full dose with no delay of the planned CT.

Early deaths

Early deaths, occurring during the course of treatment and within the first 3 months of randomization were more frequent in the RT-CT arm (nine versus two cases). This imbalance in the occurrence of early death was the cause of the early interruption of the trial. In the RT-CT arm, the causes of early death were respiratory infection (five cases) vascular failure (two cases) other intercurrent disease in one case and unknown in one case. In the RT arm, there was one tumor related hemorrhage and one unknown reason.

Acute and late toxicity

The main acute toxicity was related to mucosal reactions. In order to assess these acute mucositis, both the WHO and the RTOG scoring systems were used. A more severe and more prolonged mucositis (with confluent mucosal reactions in most cases) was seen in the accelerated RT arm, as shown in Table 4.

The other acute toxicities of radiotherapy and especially the skin toxicity were equivalent in both arms (Table 4).

Despite the very high dose intensity of CDDP (100 mg/m^2 every 2 weeks), only one grade 2 renal toxicity was observed.

A feeding tube (essentially a medical gastrostomy or rarely a nasogastric tube) was used in 94% of the patients in the RT-CT arm, and also in 94% in the accelerated RT arm, with a mean duration of 173 days (from 18 days to 20 months) and 136 days (from 41 days to 21 months), respectively ($p = 0.39$). The main reasons for having a feeding tube was tumor bulk related swallowing difficulties and severe acute mucosal reactions. Six months after randomization, 42 patients were still carrying a feeding tube, 19 in

Table 4
Mucosal and skin acute toxicities by treatment arms.

Toxicity ⩾ grade 3	RT-CT (%)	RT (%)	p
Mucosa (WHO scoring system)	83	96	0.04
Mucosa (RTOG scoring system)	64	87	0.008
Skin (RTOG scoring system)	44	37	0.57

the RT-CT arms and 23 in the RT arm. Other specific chemotherapy related toxicities are presented in Table 5.

The median survival was very short in this study, and hence the comparison of long term side effects between arms was limited to a few number of patients. At 10 months this was evaluable in about half of the patients randomized (54 patients) and no difference between the two arms was observed as shown in Table 6 (EORTC-RTOG scoring system). No subsequent difference was observed with longer follow-up but number of patients remaining at risk throughout the time was more and more limited to allow a reliable comparison (<40 evaluable patients after 1 year).

Table 5
Specific chemotherapy related renal and hematological toxicities (⩾grade 3) by cycle (RT-CT arm).

Grade ⩾3	Cycle 1 (%)	Cycle 2 (%)	Cycle 3 (%)	Cycle 4 (%)	Cycle 5 (%)
Renal	0	2	0	0	6
Platelets	4	8	3	5	12
Leukocytes	15	10	24	11	6
Hemoglobin	6	8	18	20	0

Table 6
Toxicities (⩾grade 3) by treatment arms between 6 and 10 months after randomization.

	RT-CT (%)	RT (%)	*p*
Mucosa	17	13	0.71
Neck Fibrosis	18	12	0.69
Larynx	19	18	1
Renal	7	0	0.44

Hospitalization

Planned initial hospitalization was significantly more frequent in the RT-CT arm (100% versus 87%; $p < 0.01$), but was also significantly longer in the RT-CT arm (mean duration 34 versus 23 days, $p = 0.008$). Initial hospitalization was either due to treatment realization, poor general condition or more frequently to living far from the hospital, or combined reasons.

The rate and duration of secondary hospitalizations (after the end of the treatment) was not different between the two arms (rate 40% versus 33%, mean duration 22 versus 30 days).

Tumor control and survival

The median follow-up was 11.9 years, not different between the two arms. Among the 14 patients alive at the time of analysis, six (three in each arm) were lost to follow-up before 5 years (two during the second month after randomization, one at 7 months and three between 1 and 3 years). The other patients were followed for 5–13 years.

The event free survival (EFS) rates were not significantly different between the two arms ($p = 0.16$), the 2-year rates (95%CI) were 31.8% (21–45%) in the RT-CT arm and 20.0% (12–32%) in the RT

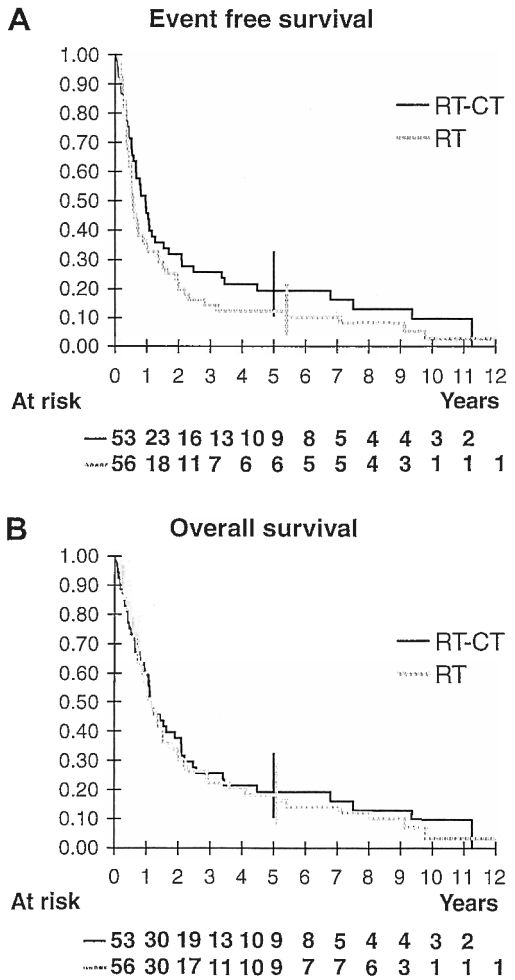

Fig. 1. Kaplan–Meier curves for event-free survival (1A) and survival (1B). Vertical bars denote 95% confidence interval of the actuarial rates.

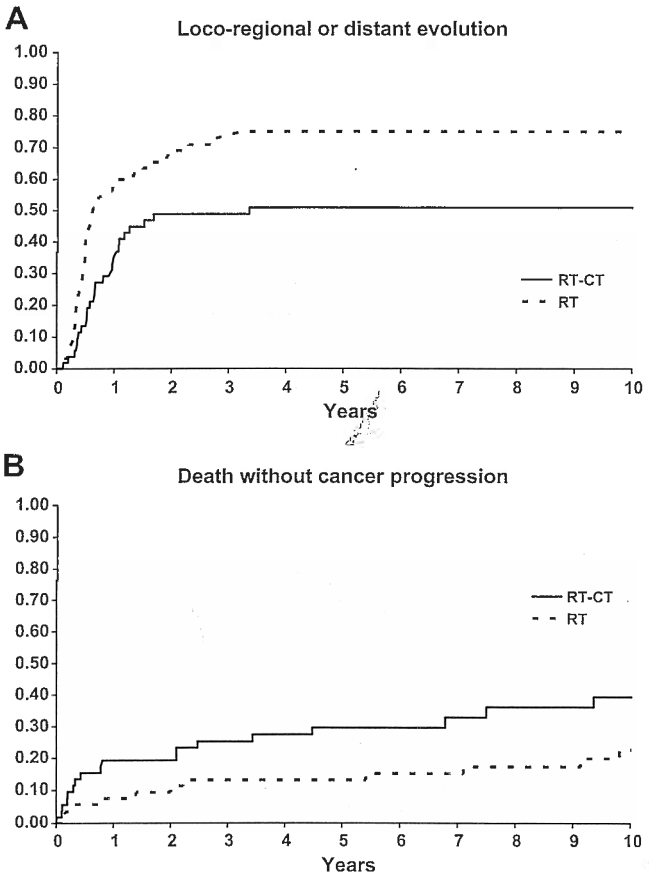

Fig. 2. Cumulative incidence of loco-regional or distant evolution (2A) and of death without cancer progression (2B).

arm, and the 5-year EFS rates were, respectively, 19.5% (11–33%) and 12.3% (6–24%) (Fig. 1a). The overall survival was not statistically different in the two arms ($p = 0.70$), the 5-year survival rates (95%CI) were 19.3% (11–32%) in the RT-CT arm and 18.3% (10–31%) in the RT arm (Fig. 1b). The cumulative incidence of local–regional failure or distant metastasis was significantly lower in the RT-CT arm than in the RT arm ($p = 0.005$) with 5-year rates of, respectively, 50.9% (36–64%) and 75.0% (61–85%) (Fig. 2a). However, the cumulative incidence of death occurring without previous cancer progression was significantly higher in the RT-CT arm than in the RT arm ($p = 0.025$) with 5-year rates of, respectively, 29.6% (18–44%) and 12.7% (5–23%) (Fig. 2b). The lack of survival benefit in favor of the RT-CT arm was mainly due to the excess of early non cancer related death in the RT-CT arm, as shown in Fig. 2.

Among the 10 patients who died after 5 years, the cause of death was the evolution of the treated cancer for two patients of the RT arm, for the eight other patients (four in each arm) the causes of death were second malignancies (three patients) or other diseases or unknown (five patients without cancer evolution).

Discussion

The aim of the study was to test a very intense RT-CT regimen, designed to increase the dose intensity and subsequently the anti-tumor efficacy in far advanced HNSCC patients, having both a high risk of LR and distant failure. Based on the progress in the field of RT and CT for locally advanced HNC, the characteristics of this regimen has firstly to combine CT concomitant to accelerated RT and secondly to use a high dose of CT with a resulting regimen likely to be one of the most intense RT-CT regimens, reported so far in this type of cancer. In order to have a reference arm to be compared with, a very accelerated RT regimen was used, which had been shown to provide better anti-tumor efficacy, as compared to conventional RT alone [20]. As expected, acute toxicity was a major concern in both arms with confluent mucositis in most cases, associated with prolonged time for healing. The use of a feeding tube is almost mandatory when such an intense regimen is envisaged, and was used in 94% of the patients. Additional toxicities were seen in the RT-CT, which overall proved to be more poorly tolerated. The early deaths, including some cases directly related to the treatment were also more common in the RT-CT arm, justifying the definitive interruption of the study.

However, despite the increased initial toxicity, and although no difference in overall survival could be detected, the final carcinological results were in favor of the RT-CT arm, in which less failures were seen, both at the primary site, in the neck and distantly (Fig. 2a). Such a benefit of adding CT concomitant with altered fractionated RT, as compared to altered fractionated RT alone has already been reported by few authors [8–10,15] and is consistent with our results.

This RT-CT regimen was more efficient on disease control, but also more toxic, pointing out that no real improvement of the therapeutic index could be achieved. Within the GORTEC group, this regimen was hence abandoned for better tolerated RT-CT regimen [11,12].The patients entered in the present study had far locally advanced disease, and for many cases could have been candidate for up-front palliative treatment. Interestingly there were some long term disease free survivors (about 19% in both arms at 5 years), suggesting that indeed a curative intent must be proposed for this type of patients. However, the relatively poor results also suggest that the outcome of these very advanced, strictly unresectable patients can not be improved by markedly increasing the dose intensity of RT-CT. This study clearly shows that the limits of such dose-intensification are reached, and suggest that alternative solutions are needed. In this population, the use of new molecular targeted drugs that may add some efficiency, with more limited toxicity [13,22] is one of the possibilities. New effective induction chemotherapy regimen with cisplatin-taxotere-5FU could also be considered [23–25], or alternative more efficient radiotherapy techniques [26].

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